Australian Government
Department of Health
Therapeutic Goods Administration

Efficacy Evaluation Report

Complementary Medicines Evaluation Section

ProstateEZE Max – Caruso's Natural Health Pty Ltd

Remainder of document redacted on the basis of irrelevant information
Section 22 Freedom of Information Act 1982

Complementary and OTC Medicines Branch

Evaluators: [redacted]

Personal information - Section 47F Freedom of Information Act 1982

Date of report: 19 May 2021

Verified by: [redacted] **19 May 2021**

Personal information - Section 47F Freedom of Information Act 1982

TRIM reference: D20-3523337

This report contains confidential information in Section 25.

TGA Health Safety Regulation

[redacted]

[redacted]

24. References

24.1. References provided for assessment

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Natural Medicines Professional Monograph (2019d) – Database – Saw Palmetto.

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TGA Advertising Code (No. 2), 2018.

Wilt, TJ., Ishani, A. (2011). Pygeum africanum for benign prostatic hyperplasia (Review). The Cochrane Collaboration, The Cochrane Library 9.

24.2. References sourced by the evaluator

EMA Assessment reports and herbal monographs

Assessment report on *Prunus africana* (Hook f.) Kalkm., cortex

Assessment report on *Serenoa repens* (W. Bartram) Small, fructus

Assessment report on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba

Assessment report on *Cucurbita pepo* L., semen

Community herbal monograph on *Cucurbita pepo* L., semen

European Union herbal monograph on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba

Cochrane Reviews

Ilic D, Forbes KM, Hassed C. (2011). Lycopene for the prevention of prostate cancer. *Cochrane Database of Systematic Reviews.*

Tacklind J, MacDonald R, Rutks I, Stanke JU, Wilt TJ. (2012). *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews.*

Other

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2011). Scientific Opinion on the substantiation of health claims related to lycopene and protection of DNA, proteins and lipids from oxidative damage (ID 1608, 1609, 1611, 1662, 1663, 1664, 1899, 1942, 2081, 2082, 2142, 2374), protection of the skin from UV-induced (including photo-oxidative) damage (ID

1259, 1607, 1665, 2143, 2262, 2373), contribution to normal cardiac function (ID 1610, 2372), and maintenance of normal vision (ID 1827) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2031

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Module 2.5.7 - Literature references

(010) - Braun, L. & Cohen, M (2014a)., Herbs & Natural Supplements: An Evidence-based Guide: Volume 2, Pygeum, *Churchill Livingstone.*

(011) - Braun, L. & Cohen, M (2014b)., Herbs & Natural Supplements: An Evidence-based Guide: Volume 2, Saw palmetto – liposterolic extract, *Churchill Livingstone.*

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(022) – Health Canada Monographs – Lycopene (2019 viewed in 2020).

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(024) – Montvale, NJ. (2007)., PDR for Herbal Medicines, Pumpkin, Thompsons Healthcare.

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(013) - Ross, AB., Vuong, LT., Ruckle, J., Synal, HA., Schulze-Koing, T., Wertz, K., Rumbeli, R., Liberman, RG., Skipper, PL., Tannenbaum, SR., Bourgeois, A., Guy, PA., Enslen, M., Nielsen, ILF., Kochhar, S., Richelle, M., Fay, LB., Williamson, G. (2011). Lycopene bioavailability and metabolism in humans: an accelerator mass spectrometry study. *American Journal of Clinical Nutrition*, Vol 93, pp 1263-73.

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(005) - Simoes, GF., Sakuramoto, P., Santos, CB., dos, Furlan, NKC. & Augusto, TM (2018)., An Overview on Prostate Pathophysiology: New Insights into Prostate Cancer Clinical Diagnosis. *Pathophysiology – Altered Physiological States*, Chapter 10, pp 183-202. DOI: 10.5772/intechopen.74269.

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(016) – Wilt, TJ., Ishani, A. (2011)., Pygeum africanum for benign prostatic hyperplasia (Review). *The Cochrane Collaboration, The Cochrane Library 9*.

Submission ID: L[redacted]
TGA Reference: [redacted]
Revised due date for response 17 December 2020
(as per email correspondence with [redacted])

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Senior Evaluator, CMES
Delegate of the Secretary
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Attention: [redacted]

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I refer to the recent Notice under Section 31 of the Therapeutic Goods Act 1989 requiring further information for the AUSTL(A) application for Caruso's ProstateEZE Max (AUSTL 231578). Attachment A of the notice raised 11 questions. Please see the responses to each of the questions below.

Question 1. GCP

The Assessed listed medicines evidence guidelines state in section 5.4.2 that all studies should be conducted according to Good Clinical Practice (GCP) principles and have appropriate ethical certification. GCP is about ensuring good assurance and record-keeping practices, which allow for accurate reporting, interpretation and verification. [redacted]

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Please clarify if the trial was conducted to GCP, and if so, please provide the supporting evidence.
Alternatively, **please comment on how the trial maintained good assurance and record-keeping practices to allow for accurate reporting, interpretation and verification**

Answer

The trial was conducted to TGA GCP guidelines.

[redacted]

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All researchers are trained and aware of GCP guidelines.

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Question 2. Plant part used for *Serenoa repens* extract (p174)

The study states that the investigational product, ProstateEZE Max contains Serenoa repens (equivalent to 660 mg of dry leaf per capsule). Module 2.5.4 states that the clinical study (Coulson et al., 2013) was performed on the actual finished product. The plant part used for the S. repens extract in the proposed product is listed as 'seed' in the application form (module 1.2.1b) and the draft label (Module 1.3.3b). [redacted]

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Please clarify this discrepancy (S. repens, leaf vs seed) and comment on what impact this may have on the extrapolation of the outcomes of the clinical trial to the proposed product.

Please also confirm whether the extract in the proposed product is from 'fruit' or 'seed

Answer

This was addressed initially in Module 1.2.5 and Appendix E of our submission. The TGA also looked at this discrepancy when the previous restricted representation was applied for and approved in 2015.

There was an error in the clinical paper relating to the plant part used in the study. The actual plant part used in the formula was the seed. I have attached the specification for the product used in the trial as attachment A to this email.

The extract in the proposed product is identical to that used in the clinical trial.

Question 3. Participant demographics (p 174)

Results were provided for participant demographics at baseline. It was stated that there were no significant differences between the active and placebo groups in age, weight, body mass index and PSA score. It was also stated that there were no significant correlations between symptom severity and these demographic parameters in the active and placebo groups. However, it is not clear what statistical tests were conducted to reach these conclusions, as the 'Statistics' section of the paper does not mention baseline analysis.

Please clarify what statistical tests were used for these baseline analyses and provide the results (if available), so that the significance of the results can be ascertained.

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[redacted]

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Question 4. Total prostate function results (p 174 & 175)

On page 174 of the paper it is stated that "The total IPSS median (25th, 75th percentiles) scores were not significantly different at baseline between the active and placebo groups 3 (1,4) and 3.5 (1.25, 4.75) respectively (Table 1)". These values appear to be incorrect, as the results in Table 1 for the active and placebo groups are 19.5 and 18, respectively, not 3 and 3.5.

Please provide the correct values for the total IPPS median (25th, 75th percentiles) scores at baseline and the statistical result.

Answer

There is an error in the text in the paper, instead of referring to total IPSS it is referring to Question 1 results "had a sensation of not emptying your bladder completely after urination"

Table 1 total score is the correct data 19.5 and 18

Question 5. Individual BPH symptoms (p 174-175)

With respect to individual BPH symptom scores (as measured by the IPSS), the paper states that "The results for the active group showed a significant percentage decrease in mean severity for all questions, except weak urinary stream after 1 month of treatment. There was a significant improvement in urinary stream by month 2 and all symptoms remained significant at month 3". The paper also states "Of interest was that observation that, the placebo group experienced significant reduction in night-time urinary frequency at month 1 but reverted to baseline levels by month 2 and 3". There were no statistical results (p-values) presented highlighting the significant decrease for all symptoms in the active group.

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Please provide the statistical results (p-values) for all the individual BPH symptom analyses, including those that were not statistically significant.
Please clarify whether the stated correlations between less night-time urinary frequency and 'pushing and straining' and 'stopping and starting' were statistical correlations, and if so, provide details of the statistical tests.

Answer

Test statistic (p-value)

[redacted]

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Question 6. Baseline symptom score for nocturia (p 175)

In Table 1 of the paper, the baseline symptom score for nocturia for the active treatment group is missing in the first column of results (printing error?); the 1-month, 2-month and 3-month results are provided.
Please provide the baseline value so that the baseline severity of nocturia for the active treatment group can be ascertained.

Answer

Baseline symptom score for IPSS in table 1 appears to be a printing error. The value is "3"

Question 7. Baseline day-time urinary frequency (p 176)

The paper states that the average day-time urinary frequencies at baseline were similar for active and placebo groups, however p-values were not provided to support this statement. In Figure 1A the day-time urinary frequencies at time 0 do not appear similar.
Please comment on the apparent difference in the baseline day-time urinary frequencies between groups in Figure 1A.
Please provide the between group statistical results (p-values) for baseline daytime urinary frequency if tested, so that similarity at baseline can be ascertained

Answer

The daytime urinary frequencies are provided in the table below Figure 1. The graph looks like there is a difference as the axis is only from 5.8 to 7. The p-value for difference between groups at baseline is as per question 3 and calculated using a 2-tail t-test [redacted].

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Question 8. Baseline night-time urinary frequency (p 176)

The average baseline night-time urinary frequencies for the active and placebo groups were provided, however it is unclear whether these were statistically analysed.
Please provide the between group statistical results (p-values) for baseline night time urinary frequency, if tested, so that similarity at baseline can be ascertained.

[redacted]

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Question 9. Missing urinary frequency statistical results for months 1 to 3 (p 176)

No statistical results (p-values) have been provided for paired *t*-tests conducted for day-time urinary frequency in the placebo group for months 1, 2 and 3; for night-time urinary frequency in the placebo group for months 1, 2 and 3; and for the active group for night-time urinary frequency at 3 months.

Please provide the p-values from these paired t-tests, so that the statistical significance can be ascertained

Answer

[redacted]

[redacted]

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[redacted]

[redacted]

Question 10. Day-time and night-time urinary frequencies ANOVA (p 172 & 176)

Day-time and night-time urinary frequencies were also statistically analysed using a mixed design repeated-measures analysis of variance (ANOVA), which confirmed a statistically significant trend that active treatment significantly reduced frequencies over placebo. The F statistic and p-values were provided, however it was not clear which effects were included in the model and to which effect(s) these statistics relate to. For example, the model may have assessed group, time and time x group effects.

Please confirm which effects were assessed and provide the results, so that the effects of treatment can be confirmed

Answer

The ANOVA assessed a time, treatment and time vs treatment effect

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Question 11. Clinical significance of reduction in nocturia (p 176)

The published trial states "...the reduction in nocturia from 2.9 times to 1.8 times was also a clinically significant outcome".

Please comment on this conclusion, as the criteria for determining clinical significance were not mentioned in the 'Materials and Methods' section therefore it is unclear on what basis clinical significance has been determined (e.g. whether it is based on documented clinical practice information/evidence), so that the clinical significance of this outcome can be ascertained

Answer

Nocturia (night frequency) increases as both men and women age, however getting up more than 2 times per night is not considered normal as per the American Urological Association guidelines. (https://www.urologyhealth.org/urology-a-z/n/nocturia). [redacted]

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Please do not hesitate to contact me should you require any further information.

Kind regards,

[redacted]

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Attachment A **Document 13**

Submission ID: [redacted] Irrelevant - Section 22 Freedom of Information Act 1982
TGA Reference: [redacted]
Due date for response 15 March 2021
(as per email correspondence with [redacted]) Personal information - Section 47F Freedom of Information Act 1982

Senior Evaluator, CMES
Delegate of the Secretary
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Attention: [redacted] Personal information - Section 47F Freedom of Information Act 1982

I refer to the recent Notice under Section 31 of the Therapeutic Goods Act 1989 requiring further information for the AUSTL(A) application for Caruso's ProstateEZE Max (AUSTL 231578). Your email dated 12th February raised some requests for outstanding information. Please see the responses to each of the questions below.

Question 1. Literature search strategy

The literature search strategy appears unclear and incomplete.
Please comment on the literature search strategy and please address the identified inconsistencies.

Answer

We have updated the information provided within the dossier to be complete and clear. **Attachment A** is an update to the Module 1.5.1 Literature based submission documents – Literature review methodology which has been updated to be clearer on the exclusion criteria. This includes studies that were not relevant to the subject, animal, in vitro and in vivo studies, studies on irrelevant dosage forms or where the dosage was higher than that used in Caruso's Prostate Eze Max.
Attachment B is a clearer and complete list of the result list from the search terms used with notes as to their inclusion or exclusion. This is a more complete list as there were a lot of exclusions that were not provided on the list previously as they were mostly irrelevant exclusions.
Attachment C is an additional table with the numerical result list per search term for the pubmed search.

Question 2. Pivotal trial – IPPS scores (p 174-175)

Please clarify which Wilcoxon statistical test was used to determine the statistical significance between groups at 3 months.
Also, please provide the absolute p-values for the results that were statistically significant.

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[redacted]

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Question 3. Pivotal trial – Day time and night-time urinary frequencies ANOVA (p 172-176)

Please provide the data on the Tests of Between-subjects effects for the ANOVA analysis, and any other post-hoc analysis that might have been conducted if this was significant e.g. tests for significance between groups at each time point.

[redacted]

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[redacted]

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Question 4. GCP

Thank you for clarifying in your previous response to the first round section 31 Request for Information that the trial was conducted to GCP guidelines and that all researchers are trained and aware of GCP guidelines. As requested in the first round section 31 Request for Information, please provide the supporting evidence if possible, e.g. certificate of GCP training.

Answer

[redacted] the Principal Investigators on the study and were experienced at conducting clinical studies to GCP requirements. [redacted] and [redacted] were PhD candidates at this time and were given training in GCP as part of the induction process. As this study was conducted in 2011/12 we don't have supporting evidence for any GCP certificates relevant to this period.

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Indications – interim outcome of assessment

Please comment on the individual interim outcomes and/or please advise of any errors of omission or fact. Please note that additional data is not being requested at this stage of evaluation.

Question 5.

May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.

For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.

In the pivotal trial with ProstateEze Max, only one of the IPSS subscores for symptoms (night time urinary frequency) was statistically significant between groups at 3 months. [redacted]

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[redacted]

[redacted]

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Answer

[redacted]

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Reference #14 Health Canada Monograph for Pygeum Prunus Africana matches our material dosage and form and supports the claim 'Helps reduce the urologic symptoms (such as weak urine flow, incomplete voiding, frequent daytime and nighttime urination) associated with benign prostatic hyperplasia. [redacted]

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The primary source referenced from this monograph was also included to support these symptoms reference #16 Wilt, TJ. Et al, Pygeum africanum for benign prostatic hyperplasia (review). Reference #15 Natural Medicines Monograph (and its primary source study) also refers to Pygeum decreasing nocturia by 19%, increasing peak urine flow by 23% and reducing residual urine volume by 24%. [redacted]

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Question 6.

Pygeum africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.

[redacted]

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[redacted]

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[redacted]

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Answer

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Question 7. Secondary indications

Help maintain/support healthy prostate function
Helps enhance/promote prostate health
Helps maintain/support prostate health

[redacted]

The prostate performs a number of functions including secreting enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa, and metabolising testosterone. [redacted]

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Prostate health can be ascertained by several means including, but not limited to, determining size via imaging, digital rectal examination (size and regularity) and PSA test. [redacted]

In table 4 (Module 2), Ref #10 (Braun & Cohen, textbook) is provided as evidence of phytosterols inhibiting the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms of BPH. [redacted]

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Ref #22 (Health Canada monograph for lycopene) permits the statement 'Helps to support prostate health' for lycopene [all-trans)-Lycopene (USP) and psi, psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose of 6.5-30mg/day. [redacted]

The remaining evidence provided in Table 4 (Module 2) to support these indications relates to the improvement in urinary symptoms of BPH. [redacted].

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[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Answer

[redacted] BPH is a medically diagnosed condition of the prostate. As there is evidence to support the use of ProstateEze for assisting with a symptom(s) of BPH (Question 5) would it therefore be suitable to apply a qualifier to the claim 'Helps support prostate health for men with medically diagnosed benign prostatic hypertrophy'.

Question 8. Secondary indications

Relieve symptoms of urinary frequency

This indication is supported by the night-time and day-time urinary frequency results in the pivotal trial.

Interim outcome: The acceptability of this indication is dependent on satisfactory resolution of issues relating to the urinary frequency results in the pivotal trial (Questions 2 and 3, above).

Answer

[redacted]

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Question 9.

Reduce free radicals that are formed in the body
Helps reduce/decrease free radical damage to body cells

[redacted].

Irrelevant - Section 22 Freedom of Information Act 1982

- Ref #1 (pivotal trial with ProstateEze Max) did not investigate free radical formulation in the body or damage to body cells, [redacted].
- Ref #22 (Health Canada monograph for lycopene) permits the statement 'Provides antioxidants for the maintenance of good health' for lycopene [all-trans)-Lycopene (USP) and psi,psi-Carotene (USP) from Solanum lycopersicum (fruit flesh) or synthetic] when given orally at a dose not to exceed 30mg/day. ProstateEze Max provides 2.1mg/day of lycopene, which is within this range. [redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

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- Ref #23 (Story et al.) notes that lycopene can be a potent antioxidant molecule, effective at scavenging the ROS singlet oxygen. [redacted] Irrelevant - Section 22 Freedom of Information Act 1982
- Ref #9 (Natural medicines monograph – lycopene) reports under 'Antineoplastic effects' that lycopene has antioxidant effects and might reduce cancer risk by scavenging free radicals and quenching singlet oxygen, which prevents oxidative damage to DNA. A dose is not reported, although Table 4 (Module 2) states that 6mg/day has been used. ProstateEze Max provides 2.1mg/day, which is below the reported amount. [redacted] Irrelevant - Section 22 Freedom of Information Act 1982
- Ref #8 (Hevesi et al.) describes an *in vitro* study investigating the antioxidant and anti-inflammatory effects of Epilobium parviflorum. The aqueous acetone extract of E.parviflorum showed higher antioxidant effect in the DPPH assay than well-known antioxidants; inhibited the lipid peroxidation determined by the TBA assay; and possessed a protective effect against oxidative damage, generated in fibroblast cells. In the COX inhibition assay, E. parviflorum decreased the PGE2 release, so showing inhibition of the COX-enzyme. [redacted] Irrelevant - Section 22 Freedom of Information Act 1982

[redacted] Irrelevant - Section 22 Freedom of Information Act 1982

Answer

Thank you for the feedback. We would like to explore the option of amending the claim to be Contains Antioxidants rather than linking the condition to the function of antioxidants. Lycopene is a known antioxidant Kumar et al, Mascio, PD.

Questions relating to the label

Question 10.

[redacted] Irrelevant - Section 22 Freedom of Information Act 1982

DREAM • CREATE • INSPIRE

[redacted]

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Question 11.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Question 12.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

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[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Question 13.

[redacted]

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

Question 14.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

[redacted]

Question 15.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

[redacted]

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Question 16.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

[redacted]

Question 17.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

[redacted]

Question 18.

[redacted]

Irrelevant - Section 22 Freedom of Information Act 1982

[redacted]

Please do not hesitate to contact me should you require any further information.

Kind regards,

[redacted]

Personal information - Section 47F Freedom of Information Act 1982

Caruso's Natural Health

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Module 2.5.4 - Overview of Efficacy

Here is the link to the Evidence Table to support the permitted indications and the proposed medium level claims for the AUST L(A) application. As per the TGA's Guidelines on the evidence required to support indications for listed complementary medicines. The following table is the systematic review process for the search strategy and details on inclusions or exclusions from the evidence table.

The main piece of evidence for the claims table to support the products' efficacy is a clinical study (Coulson, et al, 2013) performed on the actual finished product Caruso's ProstateEze Max Capsules, a phase II randomised double-blind placebo controlled clinical trial evaluated the efficacy and safety of ProstateEze Max in the management of symptoms of medically diagnosed benign prostate hypertrophy (BPH). The results of the study were favourable with significant reductions in day time and night time urinary frequency. The below from the published study documents the IPSS symptoms severity scores in the active and placebo groups. The results for the active group showed a significant percentage decrease in mean severity for all questions, except weak urinary stream after 1 month of treatment. There was a significant improvement in urinary stream by month 2 and all symptoms remained significant at month 3. The most positive improvements were observed in the questions relating to pushing, straining, stopping and starting that were correlated with less night time urinary frequency.

Table. 3. IPSS symptom severity scores in active and placebo groups (Coulson, et al, 2013).

Table 1 Individual IPSS symptom severity scores in the active and placebo groups over the 3-month intervention.

IPSS symptom severity item.	Active treatment group ($n=32$)			Median IPSS scores	Placebo treatment group ($n=25$)			Median IPSS scores	Significance between groups at 3-month[a]
	Baseline	1-Month	2-Months	3-Months	Baseline	1-Month	2-Months	3-Months	
Had a sensation of not emptying your bladder completely after you finished urinating?	3	2.5	2	1.5	3.5	3	3	3	$p=0.06$
Had to urinate again less than two hours after you finished urinating?	4	3.5	3	3	3	3.5	3	3	$p=0.29$
Stopped and started again several times when you urinated?	2	2	1	1	3	2	2	2	$p=0.06$
Found it difficult to postpone urination?	3	3	3	3	3.5	3	2	3.5	$p=0.07$
Had a weak urinary stream?	3	3	3	3	4	3	2	3.5	$p=0.1$
Had to push or strain to begin urination?	2	1	1	1	1	1	1	1	$p=0.2$
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?		2	2	2	2	2	2	2.5	$p<0.05$
Total score	19.5	15.5	14	12.5	18	16.5	16.5	16.5	$p<0.05$

[a] Wilcoxon signed ranks test.

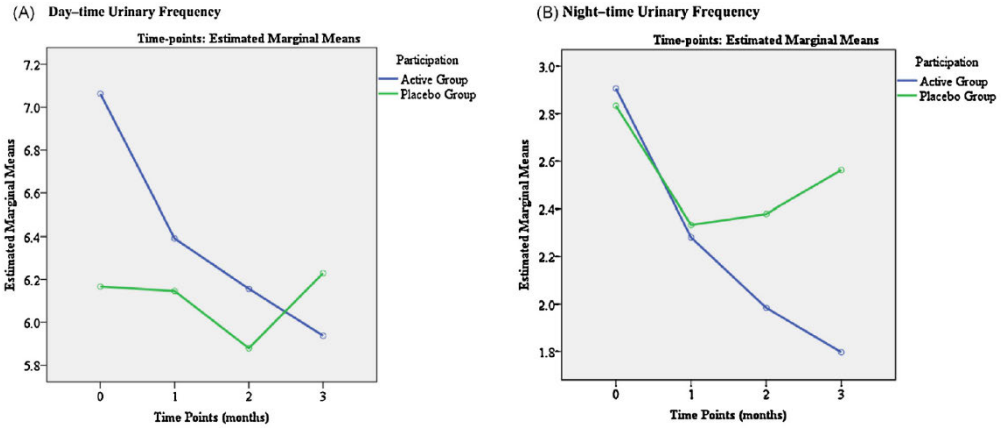

Figure. 4. Day-time and night-time urinary frequency (Coulson, et al, 2013).

Table. 4. Evidence Table for ProstateEze Max Capsule

Product Ingredients	Per soft Capsule - 1 per day Prunus africana (Pygeum) stem bark 15g (75mg input) (sitosterol & sitosterol glycosides calculated as sitosterol 9.75mg) Serenoa repens (Saw Palmetto) dry seed 660mg (fatty acids 39.6mg) Epilobium parviflorum (Willow herb) dry herb 300mg Cucurbita pepo seed oil fixed (Pumpkin seed oil) 180mg Lycopene 2.1mg
Indication List	Permitted indications
1	Help maintain/support healthy prostate function
2	Helps enhance/promote prostate health
3	Maintain/support prostate health
4	Relieve urinary frequency
5	Reduce free radicals that are formed in the body
6	Helps reduce/decrease free radical damage to body cells
Indication List	Higher level assessed indications
7	May assist in the management of symptoms of medically diagnosed benign prostatic hypertrophy.
8	For the symptomatic relief of medically diagnosed benign prostatic hypertrophy.
9	Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation and interruption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.
Required warning	* As per ARTG listing
Search Date	[redacted]
Publication dates	[redacted]
Search strategy use	[redacted]
Inclusion criteria	[redacted]
Exclusion criteria	[redacted]
List of studies included in the inclusion criteria	[redacted]

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Permitted Indication	Author	Source title and Publisher	Impact factor	Year	Substance used	Dosage	Size of Study	Summary of findings/Health benefit	Balance of evidence
		(Such as title of pharmacopoeia or textbook. Include page numbers and edition number)			Preparation	Daily dosage, frequency & method		Include enough information to demonstrate relevance and study outcomes	Primary supporting (PS); Secondary
[redacted]									

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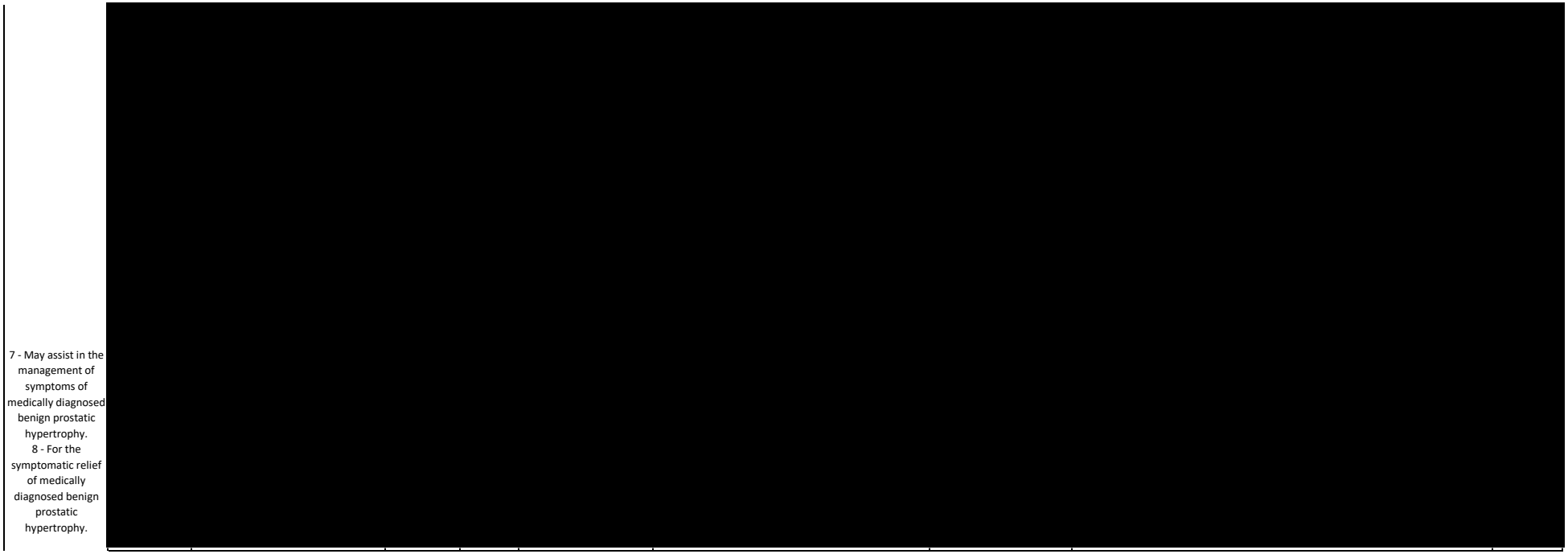

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	[redacted]
9 - Pygeum Africana may provide support for the symptomatic relief [of] nocturia, nocturnal frequency, weak stream, after-dribbling, hesitation	[redacted]

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and interuption of flow when such symptoms are associated with medically diagnosed benign prostatic hypertrophy.	[redacted]
5 - Reduce free radicals that are formed in the body 6 - Helps reduce/decrease	

free radical damage to body cells	[redacted]
1 - Help maintain/support healthy prostate function 2 - Helps enhance/promote prostate health 3 - Maintain/support protstate health	
4 - Relieve urinary frequency	

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Complementary Therapies in Medicine (2013) 21, 172—179

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A phase II randomised double-blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: A herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy

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Available online 23 February 2013

KEYWORDS
Benign prostate hypertrophy;
Herbal medicines;
Urological health;
Male health

Summary
Objective: The aim of the clinical trial was to evaluate the efficacy and safety of ProstateEZE Max, an orally dosed herbal preparation containing *Cucurbita pepo*, *Epilobium parviflorum*, lycopene, *Pygeum africanum* and *Serenoa repens* in the management of symptoms of medically diagnosed benign prostate hypertrophy (BPH).
Design: This was a short-term phase II randomized double-blind placebo controlled clinical trial.
Setting: The trial was conducted on 57 otherwise healthy males aged 40—80 years that presented with medically diagnosed BPH.
Intervention: The trial participants were assigned to receive 3 months of treatment (1 capsule per day) with either the herbal preparation ($n = 32$) or a matched placebo capsule ($n = 25$).
Outcome measures: The primary outcome measure was the international prostate specific score (IPSS) measured at baseline, 1, 2 and 3 months. The secondary outcomes were the specific questions of the IPSS and day-time and night-time urinary frequency.
Results: There was a significant reduction in IPSS total median score in the active group of 36% as compared to 8% for the placebo group, during the 3-months intervention ($p < 0.05$). The day-time urinary frequency in the active group also showed a significant reduction over the 3-months intervention (7.0—5.9 times per day, a reduction of 15.6% compared to no significant reduction change for the placebo group (6.2—6.3 times per day) ($p < 0.03$). The night-time urinary frequency was also significantly reduced in the active group (2.9—1.8, 39.3% compared to placebo (2.8—2.6 times, 7%) ($p < 0.004$).

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0965-2299/$ — see front matter
http://dx.doi.org/10.1016/j.ctim.2013.01.007

Conclusion: The herbal preparation (ProstateEZE Max) was shown to be well tolerated and have a significant positive effect on physical symptoms of BPH when taken over 3 months, a clinically significant outcome in otherwise healthy men.

Introduction

Benign prostatic hyperplasia (BPH) (also known as hypertrophy) is the non-malignant enlargement of the prostate gland characterized by the proliferation of both the stromal and epithelial elements within the periurethral and transition zone of the prostate, resulting in obstructive and irritative symptoms of the lower urinary tract in men.[1–3] BPH is present in more than 50% of men aged over 60 years with 15% to 30% of these men reporting lower urinary tract symptoms (LUTS). However, not all symptoms are caused by the hyperplasia, and many are attributable to various types of dysfunction of smooth muscle (detrusor) in the bladder.[4] Clinical evaluation for BPH includes the presence of LUTS such as hesitancy in initiation of micturition, straining, weak force of stream, stopping and re-starting or interruption of the stream, a feeling of incomplete voiding, terminal dribbling, dysuria (painful urination) and increased nocturia (night-time urination).[3,5] However, it is reported that up to one third of men with low flow rates do not have bladder outflow obstruction but have detrusor underactivity that results in reduced stream.[3,6]

Although nearly all men develop histological BPH, the degree of prostatic enlargement resulting from hyperplasia is highly variable.[1] Frequency of symptoms and prostate enlargement naturally increases with age. At 30 years of age, the prostate weighs approximately 20 g and remains so unless BPH develops. By 40 years, hyperplasia is present in 8% of men, increasing to 60% in their seventies and 90% in those aged over 80 years.[4,7,8] About 25% of men experience moderate to severe LUTS, which greatly affects their quality of life and potential risk of complications such as recurrent urinary tract infections, bladder calculi (stones) and haematuria (blood in urine).[4,9]

The management of BPH is typically multi-modal comprising pharmacotherapy, herbal medicines, life-style modifications and in severe cases, surgery. Pharmacotherapy treatment utilises α1-adrenergic receptor antagonists and 5α-reductase inhibitors. These α1 agonists block the α1adrenoreceptors at the bladder neck and in prostatic smooth muscle causing muscle relaxation, however, about 15% of patients have mild side-effects such as headache, dizziness, drowsiness, postural hypotension, and rarely syncope (<1%).[4] The 5α-reductase inhibitors have anti-androgenic activity by suppressing the formation of dihydrotestosterone from testosterone. Dihydrotestosterone is ten times more active than testosterone and plays a central role in the development of the prostate, but the biochemical factors underlying prostate enlargement remain unclear.[4,5,10] Adverse effects associated with 5α-reductase inhibitors (i.e. finasteride) include ejaculatory dysfunction, loss of libido and impotence.[4,11]

Over the last two decades there has been a strong interest in the use of herbal medicine extracts to treat BPH, and these have included *Seronoa repens* (Saw Palmetto), *Equisitum* (Field or Common Horsetail) and *Epilobium* (Fireweed).[12–14] In Europe, particularly Germany, Austria, Italy and France, phytotherapy is often the first line treatment administered for the management of symptoms of BPH.[14] The earliest commonly prescribed botanical extracts were derived from *S. repens*[15] and *Epilobium parviflorum*. The German commission E monograph also provides documentation on the traditional use of the oil from *Cucurbita pepo* (Pumpkin seed) for the treatment of prostate enlargement in Europe.[16] In Africa, *Pygeum africanum* (African prune tree) was used traditionally to treat bladder problems and *Old man's disease* before being introduced to Western medicine.[17] The benefits of lycopene in prostate health have had a more recent history. Early epidemiological studies reported that diets rich in tomato (*Solanum lycopersicum*) were correlated with a lower incidence of prostate cancer.[18,19] There is now a growing body of clinical evidence attributing these benefits for treatment of prostate problems to the lycopene content of the fruit.[20]

This study was designed to evaluate the effect of an herbal preparation (ProstateEZE Max) containing *C. pepo*, *E. parviflorum*, lycopene, *P. africanum* and *Serenoa repens* for the management of LUTS symptoms in men medically diagnosed with BPH.

Materials and methods

Recruitment and randomization: The participants were recruited through local media advertising and clinical trial databases. Participants that met the inclusion criteria were healthy males aged between 40 and 80 years of age with medically diagnosed (histologically) BPH, having a minimum score of 8 on the international prostate symptom score (IPSS) questionnaire.

Potential participants were excluded if they had used a pharmaceutical or natural therapy for BPH or other urological symptoms within the last 30 days. Men were ineligible if they had recently started a bladder-training program; had urogenital surgery within the last 6 months; had bladder biopsy and/or cystoscopy and biopsy within the past 30 days; had an indwelling catheter or practiced self-catheterisation. Men were also ineligible if they had been medically diagnosed with chronic persistent local pathology (i.e. interstitial cystitis, bladder stones), were receiving/prescribed anticoagulation therapy; had been diagnosed with severe renal and/or hepatic insufficiency; and had been diagnosed with genital anatomical deformities. Men were also ineligible to participate if they had uncontrolled diabetes mellitus, a history of spinal cord injury, an uncontrolled psychiatric disorder and/or abnormal secondary sexual characteristics, had diagnosed prostatic cancer, had current or a history of chronic alcohol and/or illicit drug abuse, or had participated in any other clinical trial during last 30 days.

The randomization of participants to the active treatment or placebo was performed independently to the investigators, using the Random Allocation Software. The randomization was based on 70 participants randomly allocated into 2 arms of equal numbers (n= 35). The trial was granted ethical approval by the Endeavour College of Natural Wellness Ethics Committee.

Interventions: The investigational product, ProstateEZE Max is a commercially available capsule-form herbal formulation containing *C. pepo* seed oil (160 mg), *E. parviflorum extract (equivalent to 500 mg dry herb)*, lycopene (2.1 mg), *Prunus Africana* (equivalent to 15 g dry stem, standardized to β-sitosterol) and *S. repens (equivalent to 660 mg of dry leaf per capsule)* with the excipents lecithin, hydrogenated vegetable oil and beeswax and soya oil in a blue softgel capsule. The placebo product contained the same amounts of lecithin, hydrogenated vegetable oil, beeswax and but had higher levels of soya oil in the same soft gel capsule. The investigational product and the placebo capsules were both non-marked blue coloured, oblong shaped soft gelatin capsules. The study product and placebo capsules were identical in capsule odour, texture, hardness and packaging. The ProstateEZE and placebo capsules were administered as 1 capsule per day with food.

Primary and secondary outcomes: The primary outcome was the validated international prostate symptom score (IPSS). The IPSS consists of seven (7) questions regarding specific symptoms associated with BPH.[21] All participants enrolled in the study reported a baseline total IPSS of ≥8, to run statistical analysis if improvements were observed by the participants. The ratings were: 0: not at all; 1: less than 1 time in 5; 2: less than half the time, 3: about half the time; 4: more than half the time; 5: almost always. The IPSS uses the following rating system: 0—8 (mild symptoms), 9—19 (moderate symptoms), 20—35 (severe symptoms). The symptom index for BPH was developed and validated by a multidisciplinary measurement committee of the American Urological Association (AUA).[21] The index was internally consistent (Cronbach's α = 0.86) and had an excellent test—retest reliability (r = 0.92). Scores were highly correlated with subjects' global ratings of the magnitude of their urinary problem (r = 0.65—0.72) and powerfully discriminated between BPH and control subjects (receiver operating characteristic area 0.85). The index was sensitive to change and is considered practical for use in practice and for inclusion in research protocols.[21]

The secondary outcomes were individual symptoms of BPH (as measured by the IPSS) and changes in day-time and night-time frequency of micturition. The day-time and night-time frequency were measured by a daily record in a patient diary and the frequency averaged over each month at 1-month, 2-months and 3-months.

Participant plasma electrolytes (PE), liver function tests (LFT) and the Prostate Specific Antigen (PSA) was also recorded at baseline and at 3-months (±14 days). The participants provided fasting blood sample, after rising, at a QML Pathology collection centre. QML pathology was responsible for collection, transport, analysis, and reporting of findings in accordance with applicable guidelines.

Participant compliance (full use of medications 95%) was monitored during the monthly interviews and the dose compliance was monitored by the return of the product containers at completion of the study.

Statistics: A minimum number of 23 participants per group was required to achieve a statistical power of 80% on the basis of a 25% reduction in average symptoms severity as measured by the total IPSS score. The data was analysed according to an intention-to-treat approach. Kolmogorov-Smirnoff test for normality confirmed that IPSS variables were not normally distributed, while day-time and night-time urinary frequency were normally distributed across the study time period. Non-parametric tests (Wilcoxon signed rank test) were performed on the IPSS individual questions and IPSS total score. Paired t-tests were performed on day-time and night-time urinary frequency to compare baseline data with 1, 2 and 3 month data. Furthermore, a repeated measures analysis, mixed-design (Split-Plot) ANOVA was carried out on the data specifically the day-time and night-time urinary frequency employing the SPSS software (version 20) package. Statistical significance for this clinical study was set at $p < 0.05$.

Results

Participant demographics: The clinical study enrolled 60 eligible participants. There were 3 withdrawals immediately after randomization due to an unwillingness to further participate and these men were excluded from the final analysis. There was no statistical difference between participants in the active group (n= 32) and placebo group (n= 25) in age (mean ± SD, 63.0 ± 10.1 years, and 64.9 ± 9.6 years respectively), weight (85.7 ± 11.6 kg and 88.9 ± 15.5 Kg), body mass index (27.8 ± 3.6 and 27.0 ± 6.1), and PSA score (2.8 ± 2.0 and 3.3 ± 2.5). There were no significant correlations between symptom severity (using the total IPSS for severity rating) and the parameters, age, weight, body mass index or PSA score in either the active or placebo groups.

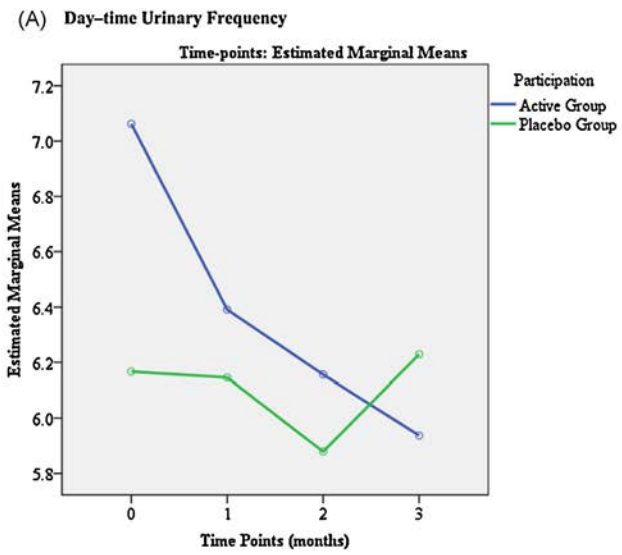
Total prostate function: The total IPSS median (25th, 75th percentiles) scores were not significantly different at baseline between the active and placebo groups 3 (1, 4) and 3.5 (1.25, 4.75), respectively (Table 1). There was a progressive reduction in the IPSS scores for the active group over placebo after 1-month, 2-months and through to 3-months of the intervention. At the end of the clinical study period (3-months), the total IPSS median score recorded was reduced by 35.9% for the active intervention over placebo (8.3%) a significantly different trend ($p < 0.05$). There was no significant difference in total prostate function in the placebo group at months 2 and 3.

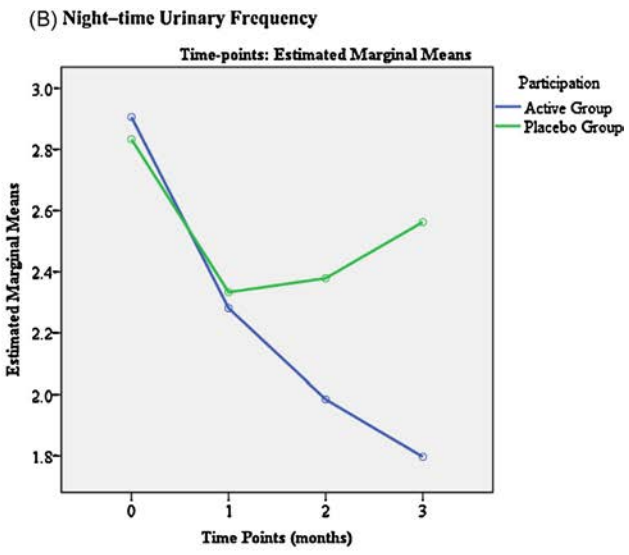
Individual BPH symptoms: The results for the active group showed a significant percentage decrease in mean severity for all questions, except *weak urinary stream* after 1 month of treatment. There was a significant improvement in *urinary stream* by month 2 and all symptoms remained significant at month 3. The most positive improvements were observed in the questions relating to *pushing and straining* and *stopping and starting* that were correlated with less night-time urinary frequency. Of interest was the observation that, the placebo group experienced significant reduction in night-time urinary frequency at month 1 but reverted to baseline levels by month 2 and month 3. This was perhaps due to participants paying more attention to the

Table 1 Individual IPSS symptom severity scores in the active and placebo groups over the 3-month intervention.

IPSS symptom severity item.	Active treatment group ($n = 32$)			Median IPSS scores	Placebo treatment group ($n = 25$)			Median IPSS scores	Significance between groups at 3-month[a]
	Baseline	1-Month	2-Months	3-Months	Baseline	1-Month	2-Months	3-Months	
Had a sensation of not emptying your bladder completely after you finished urinating?	3	2.5	2	1.5	3.5	3	3	3	$p = 0.06$
Had to urinate again less than two hours after you finished urinating?	4	3.5	3	3	3	3.5	3	3	$p = 0.29$
Stopped and started again several times when you urinated?	2	2	1	1	3	2	2	2	$p = 0.06$
Found it difficult to postpone urination?	3	3	3	3	3.5	3	2	3.5	$p = 0.07$
Had a weak urinary stream?	3	3	3	3	4	3	2	3.5	$p = 0.1$
Had to push or strain to begin urination?	2	1	1	1	1	1	1	1	$p = 0.2$
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?		2	2	2	2	2	2	2.5	$p < 0.05$
Total score	19.5	15.5	14	12.5	18	16.5	16.5	16.5	$p < 0.05$

[a] Wilcoxon signed ranks test.





Time Point Intervention Day–time	Treatment Group			Placebo Group		
	Mean	95%CI Lower Bound	95%CI Upper Bound	Mean	95%CI Lower Bound	95%CI Upper Bound
Baseline	7.1	6.1	8.1	6.2	5.0	7.3
1–month	6.4	5.5	7.3	6.2	5.2	7.2
2–month	6.2	5.3	6.9	5.9	4.9	6.9
3–month	5.9	5.0	6.9	6.3	5.2	7.3

Time Point Intervention Day–time	Treatment Group			Placebo Group		
	Mean	95 %CI Lower Bound	95% CI Upper Bound	Mean	95 %CI Lower Bound	95% CI Upper Bound
Baseline	2.9	2.5	3.4	2.8	2.3	3.4
1–month	2.3	1.8	2.8	2.3	1.8	2.9
2–month	2.0	1.5	2.5	2.4	1.8	2.9
3–month	1.8	1.4	2.2	2.6	2.1	3.1

Fig. 1 Day-time (A) and night-time (B) trends in urinary frequency for the active group over the placebo group during the 3-month intervention period.

life-style factors such as reducing coffee and water intake in the evenings. The individual questions *weak urinary stream* and *sensation of not emptying fully* were also reduced at month 1 and 2 but reverted to baseline levels by month 3. The placebo participants reported greater severity to the question *had to push and strain* over the trial period.

Urinary frequency: Paired *t*-tests were performed on day-time and night-time urinary frequency data to compare baseline with month 1—3. At baseline, the average day-time urinary frequencies were similar for active and placebo groups [mean ± SD, 7.0 ± 3.2, and 6.2 ± 2.0], respectively. There was a significant trend toward reduced day-time urinary frequency in the active group to 6.4 ± 2.8 times (9.1% reduction, $p < 0.018$), which continued to progressively decrease after two months to 6.1 ± 2.7 times (a 12.6% reduction, $p < 0.003$) and to 5.9 ± 2.5 times (15.6% reduction, $p = 0.016$) by 3-months. The placebo group also experienced reductions in day-time frequency at 1-month and 2-months but were returning to baseline levels by 3-months. A repeated measures analysis with a mixed design ANOVA confirmed the statistically significant trend that the active treatment significantly reduced urinary frequency over placebo during the day-time ($F = 3.052$, $p < 0.03$) and night-time ($F = 4.601$. $p < 0.004$).

The average baseline night-time urinary frequency for the active and placebo group were 3.0 ± 1.2 and 2.8 ± 1.3 times, respectively. There was a significant reduction in night-time urinary frequency after 1 month in the active group to 2.4 ± 1.4 times (20.4% reduction, $p < 0.001$) to 2.0 ± 1.3 times by 2 months (36.7% reduction, $p < 0.001$). After 3 months of treatment, the active group participants recorded an average night-time urinary frequency of 1.8 ± 1.0 times, corresponding to a 39.3% reduction compared to baseline. This is comparable to the results for Question 7 in the IPSS. There was a slight reduction in night—time urinary frequency in the placebo group at months 1 and 2 but it returned to baseline levels by month 3 (Fig. 1A and B)

Safety profiles: There were no significant changes to the PE or LFTs in either group after 3 months of treatment. The PSA levels for each participant remained in the healthy reference range for all participants in the active and placebo groups (mean ± SD, 2.7 ± 2.0 and 4.0 ± 3.9, respectively). The ProstateEZE Max product was well tolerated and there were no adverse reactions reported in this clinical trial.

Discussion

The results of this phase II double-blinded, clinical trial indicate that daily administration of the herbal preparation ProstateEZE Max had a significant positive effect on the management of LUTS symptoms of BPH in otherwise healthy adult men. Specifically the trend for all IPSS symptom severity items was reduced from baseline to 3-months with the active treatment as compared to placebo. Day-time urinary frequency reduced from 7.1 times to an average of 5.9 times per day, a urinary frequency rate that is consistent with normal urinary voiding function. At night it is expected that a person can sleep 6—8 h without the need for urination.[1,4] therefore the reduction in nocturia from 2.9 times to 1.8 times was also a clinically significant outcome.

A significant strength of this clinical trial is that the herbal components are well-characterised standardized

extracts. The doses of the extracts used were also in the higher end of the therapeutic doses. Namely, the *S. repens* dose was 660 mg/day. While there are studies on each of the herbal components in the formula that we investigated, this is the only study that has evaluated the efficacy of this herbal medicine combination. Therefore, the results of this study may not be directly comparable to other, single herbal component efficacy studies for BPH. The duration of the study was 12 weeks, which was sufficient to observe any changes in BPH symptom severity but also short enough to have excellent compliance that was observed in this particular study group. The group of men used in the study were also generally healthy without any other concomitant disease or on other medications. This may be different from many other studies. There was a high adherence rate (95%) with use of the study medications with appropriate blinding of participants and researchers. The primary outcome measure, namely the IPSS score is a valid tool utilized by clinicians and researchers. This is a clinically sensible, reliable, valid and responsive measure for BPH. However, the major limitation of this preliminary clinical study is the relatively low sample size and the lack of comparative studies that have investigated the herbal combination. Hence further clinical studies on a larger sample cohort with the addition of more objective outcomes such as flow rate, are required. A further weakness is the absence of a flow rate measurement. Given that this study was a preliminary investigation only, the aim of the study was mostly to assess if the herbal medicine combination could improve symptom relief, particularly day and night-time urinary frequency. Moreover, all men enrolled in the study had been medically diagnosed with BPH. As such, appropriate medical testing had been performed that included flow rate that confirmed that there was urinary flow obstruction and thus a positive diagnosis of BPH.

There is supportive scientific literature for the positive effects of each of the individual extracts in this preparation. Small trials have indicated that, compared with placebo, *S. repens* can improve urinary symptom scores and flow measures.[5] These results were not supported by a large-scale efficacy study of *S. repens*.[22] However, on review of methodology, it is not possible to make comparisons due to 2 distinct design differences. Firstly, the dose used 320 mg (<50% of the dose in this study) and secondly, the sample group consisted of moderate to severe cases, rather than the mild to moderate cases used in this study. It should also be noted that recently, a larger trial that investigated *S. repens* using daily doses from 320—980 mg did not demonstrate efficacy in BPH.[23] As pointed out earlier, the combining of this extract with other herbal components makes it difficult to make a direct comparison of the results between studies. In addition, although the age group was comparable, there was a complete exclusion of all other conditions requiring medication in the present study to reduce any potential drug interactions that might occur.

In a comparative study using finasteride (5α-reductase inhibitor), *S. repens* produced similar improvements in urinary symptom scores and peak urine flow.[15] The major constituents of *S. repens* are free fatty acids and corresponding ethyl esters, sterols and lipids. Anti-gonadotropic effects of the lipophilic extracts have been studied in both animal models and human cell lines. Hence, it is postulated that a lipidosterolic extract of the fruit that may explain *S. repens* activty. This fraction has demonstrated 5α-reductase inhibition activity in the rat ventral prostate by 50%, and reduced conversion of testosterone into dihydrotestosterone in human foreskin fibroblasts by 90%. A fruit extract has also demonstrated the inhibition activity of both 5α-reductase and 17β-hydroxysteroid dehydrogenase in cultures of epithelial cells and fibroblast cells, obtained from the prostates of patients with BPH.[24]

A recent study of the combination of *S. repens* and *C. pepo* demonstrated a positive effect on symptomatic BHP in Korean men.[16] *C. pepo* seed is rich in lignans and phytosterols that have a direct enzymatic action to reduce production of dihydrotestosterone, thereby reducing symptoms of BPH.[16]

There has been extensive research dedicated to *P. africanum* for male health. In 2002, a Cochrane review indicated 18 of 31 studies carried out between 1966 and 2000 involving 1562 men, demonstrate that *Prunus africanum* significantly improves the combined outcome of urological symptoms and flow parameters.[25] Patients administered *P. africanum* were twice as likely to have an overall improvement in symptoms. Nocturia was reduced by 19%, residual urine volume decreased by 24% and peak urine flow increased by 23%. Overall the results showed a statistically significant benefit for the use of *P. africanum* over placebo. Currently the WHO Monograph for *P. africanum* supports the therapeutic benefits of the extract as a treatment of urinary tract symptoms of BHP stages I and II for cases where diagnosis of prostate cancer is negative. Ten studies cited by the Monograph also demonstrated significant improvements in the symptoms of nocturia, daytime polyuria, dysuria, and the hesitancy and urgency of micturition, as compared with placebo in men with BPH.[26]

In a recent study, the effect of *P. africanum* on prostate cell growth concluded that oral intake of *P. africanum* resulted in serum levels of active substances that were sufficient to inhibit the proliferation of cultured myofibroblasts prostatic cells.[27] Another recent study using primary prostate cells obtained from BPH/LUTS patients being treated with *P. africanum*, suggested that the herb has anti-proliferative and apoptotic activity on proliferative prostate fibroblasts and myofibroblasts.[28]

Earlier cell research has demonstrated that extracts of *Epilobium* species can inhibit the proliferation of human prostate cells, with those with the highest concentration of the constituent, oenothein B, a dimeric hydrolysable tannin, having the greatest anti—proliferative effect.[29] More recent cell research with COX inhibition assays has shown *E. parviflorum* has significant beneficial intracellular metabolic activity and decreases PGE(2).[30]

Epidemiological evidence strongly suggests that lycopene consumption reduces prostate cancer risk.[31—33] Pre-clinical studies show that lycopene acts via various mechanisms that have the potential to cooperate in reducing the proliferation of normal and cancerous prostate epithelial cells, in reducing DNA damage and in improving intracellular metabolism. The novel finding that lycopene reduces local androgen signalling in the prostate suggests also efficacy in prevention of BPH.[20]

There are a number of implications that can be gained from these studies to date. They indicate, firstly, that some

men may not respond to particular herbal medicines, as is the case for the pharmaceutical therapies. Therefore a mixture of herbal extracts for BPH is a plausible alternative for reducing lower urinary tract symptoms in men diagnosed with BPH. Secondly, there is a need for more comprehensive dosing studies on individual/combination products. Thirdly, direct comparison of trial results should only be conducted if the herbal extracts have similar chromatographic profiles. Unfortunately, this data is not available and the differences in the extracts used in the above studies may also be partly responsible for the conflicting results in these trials. Fourthly, it is important to consider the sample group being tested, as it appears likely that herbal medicines are far more effective in treating mild to moderate symptoms, rather then severe cases. Finally, studies should be conducted on individuals who are not using concomitant medication, as there is a lack of research on the potential drug-herbal interactions between the commonly prescribed drugs (used in the 60 plus age-groups) and these herbal medicines.

In conclusion, the results of this study indicate that this herbal medicine preparation was effective for management of histologically diagnosed BPH in otherwise healthy adult males. Based on the knowledge of the active constituents in the individual extracts, it is likely that there are interactive mechanisms of action underlying the therapeutic effect of the herbal medicine preparation. This study also demonstrated that there were no adverse reactions associated with the use of ProstateEZE Max for an extended period of time.

Author contributions

Conducted clinical trial recruitment: SC, SB, AR, ES. Participant assessments: SC, SB, ES, AR. Analyzed the data: HG, ES, LV. Wrote the manuscript: SC, ES, LV. Critically reviewed the manuscript: SC, SB, AR, ES, LV. SC, AR, ES, LV approved the final version of the manuscript.

Ethical approval and clinical trial registration

The study was carried out according to the principles expressed in the declaration of Helsinki and was approved by the Human Research Ethics Committees [ACNM HREC Number 023]. The clinical trial was registered with the Australia/New Zealand Clinical Trial Registry with Number ACTRN 12610000168055.

Conflicts of interest

Funding and study medication for the project was received from the clinical trial sponsor Totally Natural Products, Sydney, Australia. The sponsor had no involvement in the collection, analysis or interpretation of the data; writing the report; or the decision to submit the paper for publication.

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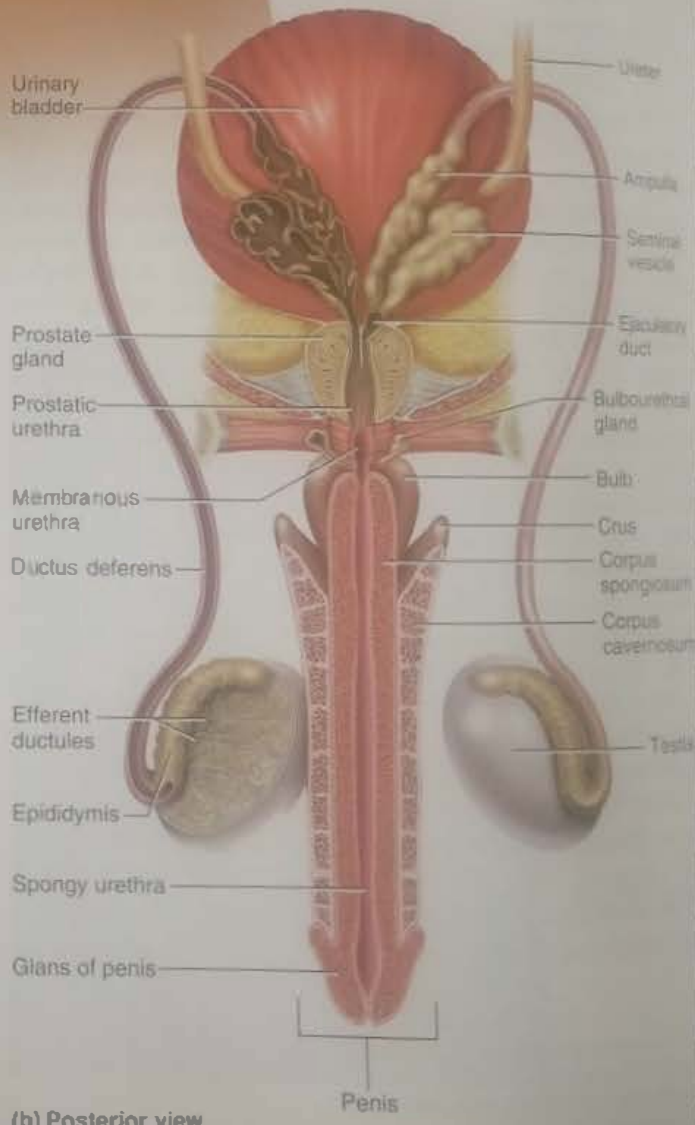
FIGURE 27.11 The Male Reproductive Tract.

Why does enlargement of the prostate gland interfere with urination?

(a) Sagittal section



(b) Posterior view

THE ACCESSORY GLANDS

There are three sets of *accessory glands* in the male reproductive system: the seminal vesicles, prostate gland, and bulbourethral glands:

1. The **seminal vesicles** are a pair of glands posterior to the urinary bladder; one is associated with each ductus deferens. A seminal vesicle is about 5 cm long, or approximately the dimensions of the little finger. It has a connective tissue capsule and underlying layer of smooth muscle. The secretory portion is a very convoluted duct with numerous branches that form a complex labyrinth. The duct empties into the ejaculatory duct. The yellowish secretion of the seminal vesicles constitutes about 60% of the semen; its composition and functions are discussed later.
2. The **prostate**[23] (PROSS-tate) **gland** surrounds the urethra and ejaculatory duct immediately inferior to the urinary bladder. It measures about 2 by 4 by 3 cm and is an aggregate of 30 to 50 compound tubuloacinar glands enclosed in a single fibrous capsule. These glands empty through about 20 pores in the urethral

[23] *pro* = before + *stat* = to stand; commonly misspelled and mispronounced "prostrate"

INSIGHT 27.2 Clinical Application

Prostate Diseases

The prostate gland weighs about 20 g by age 20, remains at that weight until age 45 or so, and then begins to grow slowly again. By age 70, over 90% of men show some degree of *benign prostatic hyperplasia*—noncancerous enlargement of the gland. The major complication of this is that it compresses the urethra, obstructs the flow of urine, and may promote bladder and kidney infections.

Prostate cancer is the second most common cancer in men (after lung cancer), affecting about 9% of men over the age of 50. Prostate tumors tend to form near the periphery of the gland, where they do not obstruct urine flow; therefore, they often go unnoticed until they cause pain. Prostate cancer often metastasizes to nearby lymph nodes and then to the lungs and other organs. It is more common among American blacks than whites and very uncommon among Japanese. It is diagnosed by digital rectal examination and by detecting *prostate specific antigen (PSA)* and *acid phosphatase* (a prostatic enzyme) in the blood. Up to 80% of men with prostate cancer survive when it is detected and treated early, but only 10% to 50% survive if it spreads beyond the prostatic capsule.

wall. The stroma of the prostate consists of connective tissue and smooth muscle, like that of the seminal vesicles. The thin, milky secretion of the prostate constitutes about 30% of the semen. Its functions, too, are considered later. The position of the prostate immediately anterior to the rectum allows it to be palpated through the rectal wall to check for lumps suggestive of prostate cancer. This procedure is known as *digital rectal examination (DRE)* (Insight 27.2).

3. The **bulbourethral (Cowper[24]) glands** are named for their position near a dilated bulb at the inner end of the penis and their short (2.5 cm) ducts leading into the penile urethra. They are brownish, spherical glands about 1 cm in diameter. During sexual arousal, they produce a clear slippery fluid that lubricates the head of the penis in preparation for intercourse. Perhaps more importantly, though, it neutralizes the acidity of residual urine in the urethra, which would be harmful to the sperm.

THE PENIS

The **penis**[25] serves to deposit semen in the vagina. Half of it is an internal **root** and half is the externally visible **shaft** and **glans**[26] (figs. 27.11 and 27.12). The external portion is

[24]William Cowper (1666–1709), British anatomist
[25]*penis* = tail
[26]*glans* = acorn

Dorsal vein

J. Frick, W. Aulitzky

Physiology of the Prostate

Summary: The presence of the prostate is universal in mammals; when compared among species the prostate is marked by variations in its anatomy, biochemistry and pathology. The epithelial cells provide secretions that empty through ducts into the urethra to form a major component of the seminal plasma of the ejaculate. The prostate is stimulated to grow and is maintained in size and function by the presence of serum testosterone. Several protein-type growth factors, such as urogastrone and prostatropin, may also affect prostatic growth. After testosterone from the plasma has entered the prostatic cell through diffusion it is metabolized to other steroids by a series of enzymes. Over 95% of testosterone is converted to the most important prostatic androgen dihydrotestosterone. DHT then binds to the activated androgen receptor. The hormone receptor complex undergoes transformation and translocation into the nucleus. In the nucleus RNA-polymerase is activated followed by the synthesis of mRNA. The noncellular stroma and connective tissue compose the extracellular matrix. The extracellular matrix plays an important role in development and control of cellular functions.

Zusammenfassung: *Physiologie der Prostata.* Die Prostata findet man bei allen Säugern, wobei jedoch innerhalb der einzelnen Arten die Anatomie, die Biochemie und Pathologie der Drüse sehr unterschiedlich ausgeprägt ist. Die Epithelzellen produzieren ein Sekret, das über die Drüsenschläuche in die hintere Harnröhre abgegeben wird und einen wesentlichen Teil des Seminalplasma ausmacht. Wachstum und Funktion der Prostata wird primär durch Testosteron gesteuert, was wiederum eine normal funktionierende Hormonachse, beginnend im Hypothalamus über die Hypophyse und den Hoden, voraussetzt. Wachstumsfaktoren wie Urgogastron und Prostatropin beeinflussen ebenfalls das Wachstum der Prostata. Testosteron gelangt durch Diffusion in die Prostatazelle und wird dort durch Enzyme in andere Steroide transformiert. Über 95% des Testosterons wird zu Dihydrotestosteron (DHT), dem wichtigsten prostatischen Androgen, metabolisiert und bildet den Androgen-Rezeptorenkomplex, der innerhalb des Zellkerns die entsprechenden Proteinsynthesen induziert. Die extrazelluläre Matrix umfaßt Stroma und Bindegewebe. Diese Matrix steht jedoch in enger Verbindung mit den zellulären Funktionen.

Introduction

The presence of the prostate is universal in mammals, and when comparisons are made between species the prostate is marked by variations in its anatomy, biochemistry and pathology. The rat prostate is characterized by distinct and separate anatomical lobes, such as the dorsal, ventral, and lateral, each with its own function; however, in the human and dog the corresponding anatomical lobes are not apparent but may exist only as zones in what anatomically appears to be a single uniform prostate.

In humans the prostate weights about 25 g and is located at the base of the bladder. The epithelial cells provide secretions that empty through ducts into the urethra to form a major component of the seminal plasma of the ejaculate. The prostate is stimulated to grow and is maintained in size and function by the presence of serum testosterone. The effect of the endocrine glands on the prostate is demonstrated in Figure 1. A normal function of the hormonal axis beginning with a rhythmic release of LHRH by the hypothalamus followed by a pulsatile secretion of LH and FSH from the pituitary maintains a normal testosterone secretion from the testes and is responsible for normal prostate growth and function. Other factors stimulating prostate growth include adrenal androgens. Estrogens do not block androgen action on the prostate. The role of prolactin on prostatic growth is not fully understood yet. Several protein-type growth factors may also affect prostate growth [1–3].

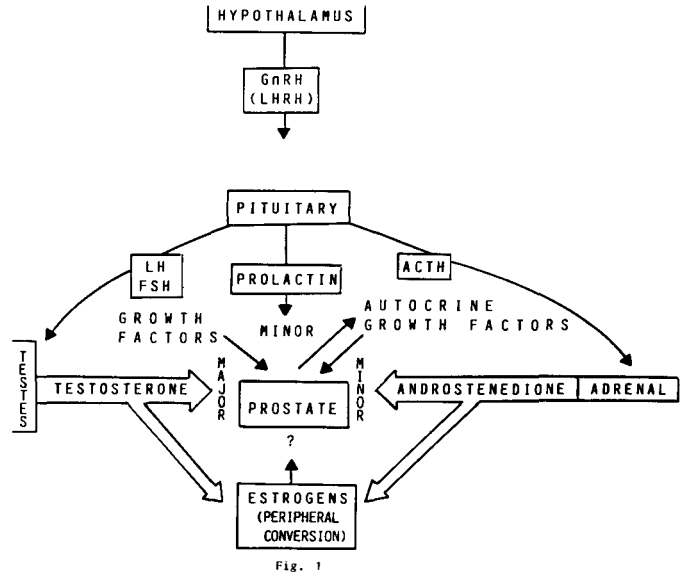


Figure 1: Schematic demonstration of factors affecting prostate growth.

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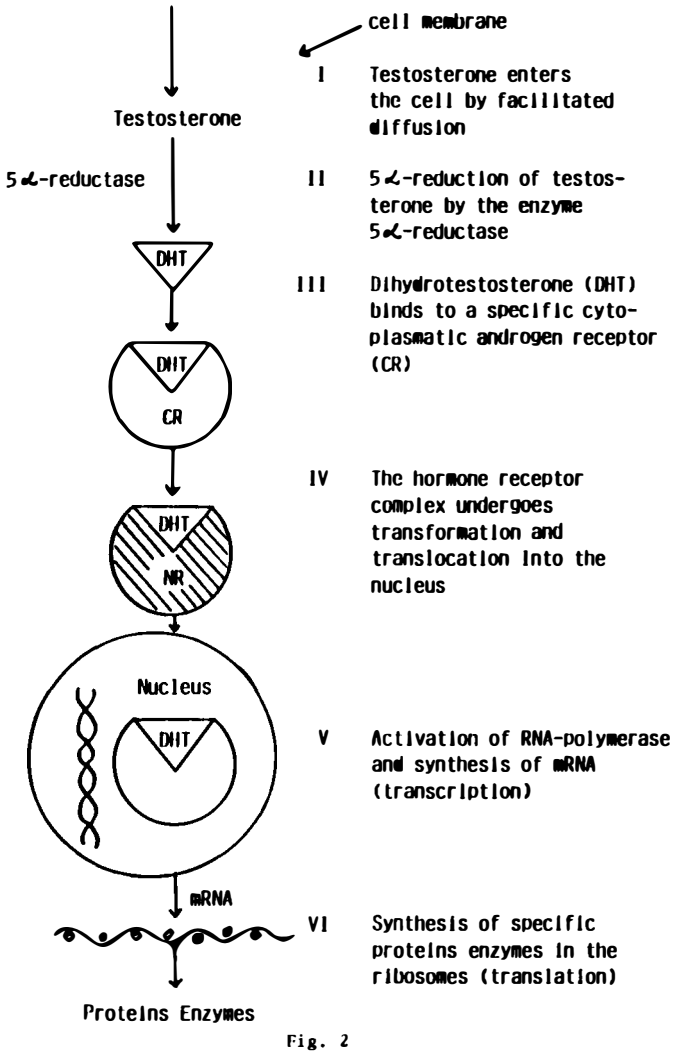

Figure 2: Mechanism of action of androgens in the prostatic cells.

Androgen Metabolism of the Prostate

After testosterone from the plasma has entered the prostatic cell through diffusion it is metabolized into other steroids by a series of enzymes [4, 5]. Over 95% of testosterone is converted into the most important prostatic androgen-dihydrotestosterone (DHT). This conversion takes place under the influence of 5 α-reductase. DHT then binds to the activated androgen receptor [6]. The hormone receptor complex undergoes transformation and translocation into the nucleus. In the nucleus RNA-polymerase is activated followed by the synthesis of mRNA. This process is followed by transportation of mRNA into the cytoplasmic compartment and is translated to secretory proteins. These proteins are secreted into the lumen on neurological command during the process of ejaculation (Figure 2).

Other Factors Modifying Testosterone's Effect on the Cell

Estrogen/Androgen Synergism in Prostate Growth

Estrogens do not block androgen-induced growth of the prostate cell but, on the contrary, can synergize androgen effects. Castrated dogs receiving estrogens and DHT produced a tremendous enhancement in the size of the prostate (estradiol doubled the androgen induced growth). This synergistic effect does not, however, occur in the rat. Whether this species difference occurs because the rat does not develop benign prostatic hypertrophy (BPH) and the dog does, is still a matter for discussion.

Growth Factors

In 1979 *Jacobs* et al. demonstrated a growth factor in crude extracts of normal, BPH and cancerous human prostates [7]. There are some identified growth factors that originate in the prostate. One of these growth factors is urogastrone (which belongs to the same family as mouse epidermal growth factor) and one is prostatropin which is a prostate epithelial growth factor. There is little doubt that most tissues are susceptible to stimulation by growth factors and to inhibition of growth by tissue chalones. The balance between cell growth and cell death appears to be under the same hormonal and growth factor control.

Structure of the Prostate

The human prostate is organized analogously to a bunch of grapes immersed in a fibrous gelatin. Each of these grapes is equivalent to the alveoli which are lined with tall columnar secretory epithelial cells that drain by a system of branching ducts into the prostatic urethra. This permits the secretions of the prostate to be added to the seminal plasma [1].

Cell Types

The prostatic epithelium is composed of three types of cells: the secretory epithelial cells, the basal cells and/or the stem cells. There is a flow of cells from reserve quiescent stem cells to a more rapidly dividing transient proliferating population and finally to the formation of the fully mature non-dividing differentiated secretory cell that will then die off [8]. The tall columnar epithelial cells are terminally differentiated and are easily distinguished by their morphology and enzymes that stain with acid phosphatase and prostatic specific antigen [9].

Stroma and Tissue Matrix

The noncellular stroma and connective tissue compose the extra-cellular matrix. A matrix system is defined as a residual skeleton structure that organizes cells as well as subcellular particles. The extracellular matrix plays an important role in development and control of cellular functions. It is

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believed that communication through these structural matrix elements may play a central role in controlling prostatic developments and functions [10, 11].

Substances and Compounds Which Originate from the Prostate

These substances and compounds are as follows: zinc, citric acid, spermine, prostaglandins, cholesterol, seminin, acid phosphatase, prostatic acid phosphatase, and prostatic-specific antigen.

Zinc: The human prostate has the highest content of zinc (50 mg/100 g dry weight). Zinc binds many proteins and *Heathcote* et al. described a zinc-binding protein in BPH. Zinc was also found to be a prostatic antibacterial factor [12, 13].

Citric acid: In the human the prostate is the major source for citrate in seminal plasma. The seminal plasma citric acid content is 376 mg/100 ml. Citrate is a potent binder of metal ions. Citric acid seminal plasma levels cannot be equated directly to plasma testosterone levels [14, 15].

Spermine: The prostate is the main source of this protein and the content in human seminal plasma is between 50 mg and 350 mg/100 ml. Spermine metabolism should interact with growth, but the biological role of this peptide has not been resolved at present. It is further believed that this compound may protect the genitourinary tract from infective agents. [16].

Prostaglandins: Regarding these compounds there is a historical curiosity. In 1959 *Eliasson* found the primary source in the seminal vesicles and not in the prostate as *von Euler,* who discovered the prostaglandins in 1934, believed. Although the original name has survived, these compounds should be named "Seminoglandins" [17–19].

For discussion of this topic see page S 178

Cholesterol: The prostate may be a partial source of cholesterol in the seminal plasma. The cholesterol content of seminal plasma is about 100 mg/100 ml and that of phospholipids 85 mg/100 ml. The cholesterol/phospholipids ratio should stabilize the spermatozoa against temperature and environmental shock.

Seminin: Seminin is a proteolytic enzyme with a molecular weight of 30,000. It is believed that this compound originates from the prostate as it appears in the first fraction of the split ejaculate. Seminin might influence the coagulation and liquefaction of the seminal plasma [15].

Acid phosphatase (AP) and prostatic acid phosphatase (PAP): PAP is a 102,000 dalton glycoprotein. AP and PAP originate from the secretion of the prostate, the seminal plasma content of AP is about 800–1500 U/ml. Both enzymes have been used for a long time to monitor the course of prostatic cancer disease in advanced stages [14].

Prostatic specific antigen (PSA): Wang and co-workers reported on human PSA in 1979 for the first time. It is a 33,000 dalton glycoprotein. This protein is only detected in the epithelial cells of the prostatic ductal elements. PSA has been shown to be clinically important for the detection and monitoring of prostate cancer [20].

Transport of Compounds into Prostatic Secretion

Transport mechanisms into prostatic secretion are of great interest because of the prevalence of prostatitis and the need for new modalities of chemotherapy. There are compounds reaching concentrations in the prostatic secretion that approach their concentration in blood. In general, some compounds are assumed to pass across the membrane by non-ionic diffusion, possibly by lipid solubility through the membrane. To summarize, the prostate has a tremendous transport power and the prostatic transport systems may function under hormonal influence; induction by testosterone and inhibition by estrogens.

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Prostate Gland: Structure, Functions and Regulation

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The prostate gland plays an important role in male reproduction. It secretes enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa. Development, differentiation and maintenance of the prostate gland depend on steroid and peptide hormones. Beside hormones growth factors also regulate the prostate gland. This review will focus on the structure, functions and mode of regulation of the prostate gland.

Introduction

The prostate, the largest male accessory gland, surrounds the urethra at the neck of the urinary bladder. In an axial view the gland appears round, elliptical or triangular in shape. It weighs only a few grams at birth and approximates 20 g by the age of 20 years. Thereafter its weight and histology are stable for another 25 years.

Structure. It is encapsulated by a thin fibroelastic tissue layer which gives it an unlobulated appearance. However, the fibroelastic capsule gives rise to septa which extend inward and subdivide the prostate into five lobes: an anterior, a posterior, a medial and two laterals [1]. These lobes lodge 30–50 branched tubuloalveolar or saccular glands, 16–32 excretory ducts, dense stroma, blood vessels, lymphatics and nerves [2]. Although the normal prostate cannot be divided into lobes, there is a tendency towards lobulation as benign prostatic hyperplasia progresses [1].

Histologically, the prostate is divided into two major zones: a central and a peripheral. The two zones have distinct features, as shown in Table 1 [3]. In addition a transitional zone, an anterior segment and a preprostatic sphincteric zone have also been identified [4].

The normal human prostate gland of the young adult has five types of acinar cells [5].

1. Microvillar cells have numerous microvilli on the apical surface.
2. Secretory cells show active secretion and bulging of the apical cell membrane.
3. Holey cells possess one to several small holes on the apical cell surface.

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Table 1
Features of central and peripheral zones of the prostate

Feature	Central zone	Peripheral zone
Branching of duct system	Elaborate	Simple
Size of terminal sacculations	Large	Small
Stroma	Dense, collagen rich	Loose, delicate
Acini arrangement	Lobular	Evenly distributed

4. Crater cells have broken apical cell membrane.
5. Bare cells have fairly smooth apical surface with scant microvilli at the periphery.

Besides these cell types basal cells, stem cells and neuroendocrine cells are also found in the prostate [1].

Prostatic secretion is a homogeneous, serous and slightly acidic (pH 6.6) milky fluid with low (<1%) protein content. It constitutes nearly 0.5 ml of average 3–3.5 ml of the normal human ejaculate. The constituents of prostatic secretion include various enzymes, lipids, metal ions and amines, as shown in Table 2.

Table 2
Constituents of prostatic secretion

Acid phosphatase	Fibrinolytic enzymes
Albumin	Inositol
a-Amylase	Magnesium, zinc, sodium
β-Glucuronidase	Plasminogen activator
Cephalin	Phospholipids
Cholesterol	Seminin
Choline	Proteolytic enzymes
Citric acid	Spermine
Dermatan	Spermidine
Diastase	

Embryology and development. The prostate makes its appearance at the 11th week of gestation as multiple solid outgrowths of the urethral epithelium both above and below the entrance of mesonephric duct. The epithelial buds branch and rebranch to form the complex ductal system of the prostate. Five distinct groups of epithelial buds are formed which develop into five internal lobes of the prostate. The anterior lobar tubules shrink, lose their branches, lumen and appear as small, solid embryonic epithelial outgrowths at birth. The mesenchymal cells which are present around the ductal systems, become denser at the periphery and form the prostatic capsule. By the 22nd week, a muscular stroma is considerably developed which continues to progressively

increase until birth [6]. Postnatal development of the human prostate proceeds in the following phases: (i) a regression period after birth; (ii) a quiescent period up to 12–14 years and (iii) a maturation period between 14 and 18 years. No lobe formation is observed during postnatal development [7].

Functions

The prostate gland has various useful functions:

1. Physically, through its mass and musculature, it participates in the control of urine output from the bladder and in the transmission of seminal fluid during ejaculation [8].
2. As an exocrine gland, it contributes to the seminal plasma a spectrum of small molecules and enzymes like fibrinolysin, coagulase and other coagulum lysing enzymes which facilitate fertility and are involved in coagulation [1].
3. Prostatic fluid safeguards sperm viability by reducing the acidity of the urethra. It facilitates and enhances sperm motility by contributing a certain factor (albumin) to seminal plasma that stimulates the motility of epididymal and washed ejaculated spermatozoa [1].
4. Prostatic acid phosphatase, by hydrolysing phosphorylcholine to choline is directly involved in the nutrition of spermatozoa [1].
5. As an endocrine gland, it helps rapid metabolism of testosterone to more potent androgen dihydrotestosterone (DHT) and thus also influences both hypothalamic and hypophyseal functions [8].
6. The high level of zinc in human seminal plasma appears to originate primarily from the secretion of prostate gland which acts as an antibacterial agent [9].

Regulation by hormones

The majority of our current understanding of the regulation of prostate has been derived from studies carried out on rat ventral prostate.

Morphology and ultrastructure

Steroid hormones: The prostate is one of the target organs for the action of androgens. Besides androgens other steroids like oestrogen and progesterone also regulate the growth of the prostate [10].

Androgens: The dependence of the prostate gland on the presence of testicular hormones for maintenance of its structural and functional integrity is well known [11, 12]. Withdrawal of this hormonal support, as by orchiectomy, results in drastic metabolic changes and an accelerated rate of tissue involution in the prostate – a process known as autophagia [13]. At the subcellular level, testosterone or androstenedione maintain the prostatic epithelium, preserve microvilli, the Golgi apparatus and the endoplasmic reticulum [14]. The ventral prostate of

the rat when cultured without androgens shows a marked involution of the components of the Golgi apparatus, disappearance of secretory granules, microvilli and regression of the rough endoplasmic reticulum [14]. Ribosomes also decrease in number and tend to become isolated instead of being associated in polyribosomes. Nuclei shrink and become irregular with deep invaginations. Nuclei decrease in size and the perichromatin granules are reduced in number. Immunization with testosterone too leads to reduction of weight of the prostate [15].

Testosterone and its principal metabolite, DHT, can suppress stromal growth and foster increase in epithelial height and secretory activity. DHT, being five times more potent than testosterone, evokes extensive hyperplasia at higher doses. Adrenal steroids have also been implicated in maintaining the prostate gland [16].

Oestrogens cause a regression of the sex accessory glands in male rats [17]. However, the ultrastructure of the prostate from oestrogen-treated males is generally indistinguishable from castrates [18]. Oestradiol is believed to affect the prostate both directly at cellular level and indirectly via gonadotropin inhibition at the level of the hypothalamus or pituitary gland [19]. Oestradiol exerts its antiandrogenic effect on the epithelium of intact animals resulting in lower epithelial height and reduction in the number of cell organelles and secretory bodies and has no discernible effect upon the glandular epithelium in castrates. Testosterone alone can restore glandular morphology to normal in these animals. Oestrogen in combination with testosterone can prevent regeneration of the rough endoplasmic reticulum and elicits the formation of large lipid like inclusions and the accumulation of secretory bodies in the apical zone of many cells [20]. Brief administration of oestrogen to newborn rats results in permanent suppression of prostate growth and reduces prostatic responsiveness to testosterone in adulthood [21].

In castrates, the prostatic stroma becomes thickened with a large increase in fibrous material between and surrounding each acinus, although smooth muscle cells retain their normal cytology. In response to oestradiol treatment, alone or in combination with testosterone, smooth muscle cells increase in size and number. The organelles decrease in number, the cytoplasm becomes more electron dense and the nuclei turn more heterochromatic. Surface vesicles are profuse in smooth muscle cells in animals treated with oestradiol alone. Large phagocytic vacuoles are characteristic of the glands of animals treated with oestrogen and testosterone in combination [20].

Gestagens: Besides testosterone and oestrogens, progesterone also regulates the prostate gland by virtue of its androgenic activity. When given to castrated male rats progesterone and progestins maintain or stimulate the weight, cytology and secretory functions of the prostate [22].

Peptide hormones

Prolactin, a hypophyseal hormone, has synergistic action on androgen induced weight gain and citric acid secretion by the lateral prostate of the rat,

and also has a direct effect on the growth of the latter [23]. It increases prostatic accumulation of both testosterone and DHT [24], while antiprolactin, bromocriptine suppress the uptake of testosterone [25]. Hypophysectomy causes a more profound atrophy of the rat prostate than does castration. Immunization with prolactin and injection of prolactin antiserum inhibit prostate growth [26].

Insulin, a peptide hormone regulating blood glucose, is also required for normal growth of the prostate. Severe diabetes results in castrate-type accessory organs [27]. Insulin treatment of diabetic rats is necessary to obtain prostatic response to testosterone [28]. In diabetic animals the prostatic epithelium shows a lower cell height, a diminution in secretory granules and the presence of autophagic vacuoles [28].

Proteins and nucleic acid synthesis

The net tissue contents of DNA, protein and mRNA coding for these proteins decrease after castration and are restored to normal by replacement of androgen [29–33]. The enhancement of DNA synthesis by androgens is organ specific and both nuclear and mitochondrial DNA syntheses increase [34]. Similarly, the transcription machinery is also switched on which is evident by increased rRNA synthesis, nucleolar RNA polymerase activity and polyribosome formation [35, 36]. The protein content of the prostate decreases during castration as a result of a combined effect of an accelerated rate of protein degradation and a reduced rate of protein synthesis. On the other hand, several intracellular proteins whose functions are unknown increase in the prostate after castration [37]. The effect of androgen supplementation is preceded by an increase in nuclear RNA synthesis [38, 39]. The androgenic effects appear to be directed towards unwinding of DNA or movement of the enzyme along the template [40]. Androgens also regulate the translational machinery. The effect of androgens on the activity of protein initiation factors occurs immediately after it enters the target cell [41]. The ^{35}Met-tRNA$_f$Met binding to prostate ribosomes is enhanced within 10 minutes of androgen injection in castrated rats [42, 43]. Androgens induce aldolase mRNA and the synthesis of poly (A)-enriched 6–15 S mRNA fraction in a highly tissue and steroid specific manner [44, 45]. Androgens also regulate the transcriptional capacity of the C_1, C_2 and C_3 prostatic binding protein genes and are known to play a major role in determining mRNA stability in the rat ventral prostate [46]. The expression of mRNA for dorsal protein 1 is androgen dependent [47]. Prolactin is known to synergize the action of androgens. Simultaneous injection of DHT and prolactin to mature castrated rats augments the level of DNA, RNA and proteins to normal levels [48, 49]. Likewise, prolactin injection to intact mature male rats significantly increases both DNA and RNA in the ventral prostate gland [48]. A direct, auxiliary action on prostatic protein synthesis has also been reported for insulin [50, 51].

Enzyme activities

The stimulation of prostatic DNA-dependent RNA polymerase by androgens has been well documented [31, 52, 53]. Both nucleolar and extra-nucleolar RNA polymerase activities can be stimulated by androgens [54]. The association of steroid-receptor complexes with chromatin causes enhanced template activity resulting in increased transcription by exogenous and endogenous RNA polymerase B [55]. The stimulation of RNA polymerase activity by DHT is effectively inhibited by diethylstilboesterol [52, 56].

DNA polymerase and DNA lipase activities are remarkably enhanced by androgenic stimulation [57]. Nicking closing enzyme activity decreases after castration. However, its activity can be maintained or returned to normal values by the administration of DHT [58]. DNA unwinding activity and prostatic thymidine kinase activity are also regulated by androgens in a highly steroid and tissue specific manner [57].

Testosterone by producing an inhibitory modulator of phosphodiesterase brings down the levels of cAMP and phosphodiesterase to normal in castrated rats. This regulation of cAMP considerably influences several prostatic enzymes that are involved in carbohydrate metabolism [59, 60].

The activities of L-ornithine decarboxylase and S-adenosyl-L-methionine decarboxylase are dramatically enhanced in the ventral prostate of castrated rats in response to androgenic stimulation [61, 62]. Orchiectomy results in significant decline in methylthioadenosine phosphorylase and chromatin associated protein phosphokinase activities in the rat ventral prostate which is reversed by testosterone treatment [63]. The decrease in activities appears to precede measurable changes in the protein and RNA contents [64].

Steroid receptor

All of the steroids mediate their biological effects through an interaction with steroid-specific intracellular receptors. Receptors for androgen (AR) [65], oestrogen (ER) [66], progesterone (PR) [67] and glucocorticoids (GR) [68] have been demonstrated in the human prostate. Regulation of these receptor sites by hormones is well established and has been studied in rat models [69–72]. Prostatic AR gradually increases during the early postnatal period to a peak around the time when the rat attains sexual maturity [73]. Upon ageing there is a diminution in the androgen binding sites [74, 75]. Treatment with exogenous testosterone increases AR content in aged rats to values identical to those of young mature rat prostates [75]. The concentration of AR in the cytoplasm of the prostatic cell undergoes a rapid increase within 24 hours after castration [76]. This is matched by a concomitant decrease in the concentration of free androgen in the nucleus and in the nuclear receptor [77]. However, the net concentration of receptor in a cell remains constant [77, 78]. The nuclear receptor is replenished within minutes after a single intravenous injection of androgens to castrated rats [75, 77, 79]. If the period of androgen withdrawal

in these castrated animals extends to 4–7 days, there is a progressive decline in the pool of cytoplasmic receptors which could be due to an increased proteolytic activity in the prostate [77, 80–82]. Although the level of AR declines after castration, the level of mRNA for AR is high [83]. Oestrogens also increase cytosolic and nuclear AR content of the prostate in castrated dogs either alone or in synergism with androgens [84–86]. A similar effect is also observed in normal as well as experimental prostatic carcinoma of rats [70, 87]. Oestrogen-dependent positive regulation of AR has been reported for both human and canine prostates [71, 88]. Oestrogens have also been shown to induce the PR content of dog prostate [71]. The oestrogen-mediated upregulation of AR content has been postulated to be mediated via the ERs [70]. ER, although present in the prostate of intact male rats, are undetected after 3 days postcastration and the levels recover 15 days after castration [89]. This matches with a rise in mRNA for ER over normal levels [90].

Steroid hormones have also been reported to elicit their effect through regulation of growth factors, their receptors or both in their respective target tissues.

Regulation by growth factors and growth suppressors

Growth factors along with a number of growth modulators present within the prostate gland are involved in intracellular signalling. There is a balance between factors that activate and factors that suppress growth. The inhibitory elements are called suppressors. Both stromal and epithelial cells of the prostate themselves can synthesize and respond to growth factors in a reciprocal and interactive manner. Many of these growth factors appear to be under hormonal regulation particularly in response to androgens, oestrogens and other endocrine factors. Androgens and growth factors can also stimulate the synthesis and degradation of extracellular matrix components that can alter cellular responses to steroids and growth factors [91, 92]. Growth factors can work internally in the cell (intracrine) or can be secreted extracellularly to serve as signals to its own cell in which it was synthesized (autocrine) or stimulate a nearby cell (paracrine) [1]. After being secreted the growth factors bind to specific growth factor receptors that reside on the plasma membrane of the target cell. This in turn activates a series of second messenger signals that involve protein kinases, membrane phospholipases or G protein pathways [92].

Growth factors reported to be present in the prostate include fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF) and nerve growth factor (NGF).

FGF is of two types, basic and acidic [93]. It is the basic FGF (bFGF) which plays an important role in the prostate and is a broad-spectrum mitogen that can stimulate angiogenesis [93]. EGF and its receptor (EGF-R) have been localized in the prostate [94] and the EGF-R can be regulated by androgens [95]. TGF-a, a structural analogue of EGF, has been shown to stimulate the

growth of cancer cells of the human prostate in culture and to produce epithelial hyperplasia in the prostatic lobe of male mice [96].

TGF-β has two genes: TGF-β 1 and TGF-β 2. Both of these factors are present in the prostate [97]. TGF-β has a negative regulatory effect on epithelial cell growth while it is a positive factor for stromal growth [97, 98]. In addition, TGF-β is also an angiogenetic factor and can regulate neovascularization [1]. Two other factors related to TGF-β are Mullerian inhibitory substance and inhibin. The synthesis of inhibin in the prostate is regulated by hormones [99, 100].

IGFs (somatomedin) occur in two closely related forms, type I and type II, and are single chain polypeptides that share sequence homology with proinsulin. Insulin-like substances have also been detected in the prostate [101]. PDGF, a strong mitogen, has also been shown to be expressed in prostatic tumour models and cells in culture [102, 103].

NGF-like protein is localized predominantly to the stromal components of normal, benign prostatic hyperplasia and adenocarcinomatous prostate; while NGF-R is localized predominantly to the epithelial cells of the prostate thereby mediating paracrine interactive growth modulation of the human prostate [104].

The combination of steroid hormones and different growth factors and their sequence of action on different cells of the prostate at various stages of development are quite complex. Their exact mechanism of action still remains an important area in understanding the biology and pathology of the prostate.

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Chapter 10

An Overview on Prostate Pathophysiology: New Insights into Prostate Cancer Clinical Diagnosis

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Abstract

The prostate is an accessory gland of the male reproductive tract, and its presence is universal in mammals. It is committed to the prostatic fluid production and storage, which is released with other semen components during ejaculation. Such fluid contributes to increasing motility and fertility of the spermatozoa, and the neutralization of the vagina, thus playing an important role in fertilization. Few pathological complications, often progressively aggravated with age, can affect this gland (i.e. benign and malignant proliferative changes; all to be described next in this chapter). Nowadays, the neoplastic expansion is the main motivator and contributor for studies on enlightening of growth regulation mechanisms and physiology of the prostate.

Keywords: physiology, pathology, benign prostatic hyperplasia, prostate cancer, biomarkers

1. Prostate anatomy

The human prostate is a pelvic gland located under the urinary bladder and in front of the rectum, and it is composed by glandular and non-glandular structures surrounded by one same capsule [1–3]. It consists mainly of muscular-fibrous tissue, which it is subdivided into about 50 tubule-alveolar glands [4], at the lateral and posterior segment of the urethra, which drain to 20–30 small prostatic ductules opening in the prostate, or close to the posterior wall of the prostatic urethra [5–8]. The prostatic secretion, which accounts for approximately 20% of

the seminal fluid, confers a characteristic odor of this flowing, and participates in the activation of spermatozoa [8]. The ducts of the prostatic glands open into a sulcus located on each side of the urethral ridge, called the prostatic sinus. The prostate is traversed throughout the prostatic portion of the urethra, from the base to the apex, with a slightly curved course in the anterior-posterior direction, and closer to its anterior face [5–8].

The prostate is anatomically described as an inverted pyramid whose apex is the lowest portion, and which is located about 1.5 cm behind the lower border of the pubic symphysis and is directly related to the upper face of the urogenital diaphragm. The base of the prostate gland is in a horizontal plane that passes through the middle part of the pubic symphysis, and it is directly related to the cervix of the bladder and the inner ostium of the urethra. Inferior-lateral surfaces are convex and are separated from the superior fascia of the pelvic diaphragm by a venous plexus, and are related to the pubococcygeal muscles [6–9]. The posterior surface is flattened and triangular, and it is related to the bladder of the rectum. The anterior surface is narrow and separated from the pubic symphysis by retropubic fat tissue. The upper part is related to the seminal glands and to the lower extremities of the vas deferens, and near its base presents small depressions for the entrance of the ejaculatory ducts [6].

Despite not being clearly distinguished anatomically, the following prostate lobes are traditionally defined: right, left and a middle lobe [5–8]. In pathology, the prostate is described in different zones (peripheral zone, central zone, transition zone and anterior fibro-muscular zone) [9]. The right and left lobes are not isolated from each other, being connected, prior to the urethra, by the isthmus of the prostate, constituted by fibromuscular tissue. Their muscular fibers represent the superior continuation of the external sphincter muscle of the urethra to the cervix of the bladder, and it is devoid of glandular tissue. The middle lobe, of variable size, is the part of the prostate that protrudes internally from the upper part of the posterior face of the organ, between the ejaculatory duct and the urethra [5–8]. However, structurally, the middle lobe is indeed inseparable from the right and left lobes. In each prostate lobe we can identify four lobules: (I) Posterior-Inferior, located posterior to the urethra, and inferior to the ejaculatory ducts. It constitutes the face of the prostate, palpable to digital rectal examination; (II) Lateral-Inferior, directly lateral to the urethra, forming the major part of the right or left lobe; (III) Superomedial, deeply to the inferoposterior lobe, surrounding the ipsilateral ejaculatory duct; (IV) Anteromedial, deeply to the inferolateral lobe, directly lateral to the proximal portion of the prostatic urethra.

The superior fascia of the pelvic diaphragm reflects in the superior direction from the visceral fascia of the pelvis to envelop the prostate, and then continues superiorly over the bladder. The portion covering the prostate is dense and fibrous, being called the fascia of the prostate. It is located externally to the prostate capsule and is separated from it, laterally and anteriorly, by the loose connective tissue harboring the prostatic venous plexus. The fascia of the prostate fuses anteriorly with the tendinous arch of the pelvic fascia, which at the level of the pube is called the medial puboprostatic ligament [5–7]. Smooth muscle fibers fulfill this ligament, and it is called the puboprostatic muscle. The lateral puboprostatic ligament extends from the fascia of the prostate to the tendon arch of the pelvic fascia. Inferior to the puboprostatic ligaments, the prostate associates with the medial borders of the pubococcygeus muscle, and

from this point the muscle fibers extend in the superior direction to fuse with the fascia of the prostate, forming the prostate lifting muscle. Later, the fascia of the prostate is separated from the tunica of the rectum by the rectovesical septum [6, 10].

The prostatic arteries are usually direct branches of the inferior bladder artery from one of the branches of the internal iliac artery. In some cases, it may be a branch of the internal pudendal artery, or the medial rectal artery [5–7, 10]. The veins draining the prostate girdle, to form the prostatic venous plexus, located in the fascia of the prostate. The prostatic venous plexus continuous superiorly with the bladder venous plexus, and communicates posteriorly with the internal vertebral venous plexus. The lymphatic vessels of the prostate drain into the internal iliac lymph nodes [5–7, 10]. Finally, the prostate is innervated by sympathetic fibers from the lower hypogastric plexus. These fibers innervate smooth muscle fibers and blood vessels [5–7, 10].

2. Prostate gland hormonal regulation

There are considerable variations related to the prostate anatomy, biochemistry and pathology of several mammal species. In humans, the sexual accessory tissues (or glands) produce high concentration of several biologically active substances, such as fructose, citric acid, spermine, prostaglandins, zinc, proteins including immunoglobulins, and specific enzymes (i.e. esterases and phosphatases) [11].

The growth, differentiation and maintenance of the activity of the prostate gland [12] are mainly controlled by androgens, which is the basis of the anti-androgenic therapies for the treatment of primary prostate cancer. The development and physiology of the prostate is also directly modulated by somatothrophic hormones (such as insulin, prolactin and growth hormone), retinoic acid and estrogen [13, 14], as well as a biomolecular scenario of complex interactions between the epithelium and stroma [15], which sum up to a complicated and poorly understood regulatory mechanism.

Receptors type androgen receptor (AR) and estrogen receptor (ER) are responsible for mediating the physiological effects of androgens and estrogens, respectively [16, 17]. Briefly, the receptor located in the cytoplasm binds to testosterone or dihydrotestosterone, dissociates a heat shock protein (HSP), dimerizes, and it is translocated to the nucleus, where, together with a variety of co-activators and co-repressors, activates or inactivates different sets of genes [18]. The classic AR has 110 kDa and several features in common with members of the nuclear receptor family, such as estrogen receptors, progesterone, thyroid hormones, and peroxisome proliferator-activated receptors (PPARs) [19].

Testosterone and dihydrotestosterone (DHT) act through AR. The AR primarily functions as a transcription factor. It is an extremely important molecule, responsible for the primary male sex differentiation (formation of gonads and external genitalia), and for the pubertal acquisition of the male secondary characteristics (events associated with puberty and adolescence) [20]. It is also liable for most cases of complete androgen insensitivity (resulting in infertile XY

karyotype female) [21], and it is deeply associated with the origin of prostate tumors and, particularly, with the recurrence of androgen independent cancer [22–24].

The most striking androgen dependence of the prostate gland is observed by hormonal or surgical castration. In a rat model, removal of the testes results in prostate involution to approximately 10% of its original size after 21 days. Epithelial cells death and stroma reorganization are responsible by such event [25]. Similar to AR, estrogen receptors (ERs) belong to the family of nuclear receptors. The two subtypes, ERα and ERβ, have different physiological roles. They share homology with each other, but are the products of different genes [26]. Both ERα and ERβ are expressed in the prostate. In adults, ERα and ERβ are preferentially found in the stroma and in the epithelium, respectively [27]. Similarly to the AR, ER expression might be suppressed by methylation of its promoters, and this epigenetic alteration was suggested to be involved in both benign prostatic hyperplasia and prostate cancer development [28, 33].

The action of estrogens on prostatic ductal morphogenesis and cell differentiation is complex [14]. However, a brief exposure of rodents to estrogens during neonatal development causes irreversible and dose-dependent effects on morphology, cellular organization and function of the gland [29, 30]. Reduced prostate size at adulthood was associated with decreased responsiveness at puberty due to reduced AR content [31]. The reduced AR levels were justified by increased proteasomal degradation of AR protein at postnatal day 10 [32].

Estrogen exposure to occasional doses during the gestation period causes increased concentrations of androgen receptor in mice, ductal budding and prostate weight later in the adulthood [34]; whereas the neonatal exposure to high doses compromises the growth epithelial differentiation, and accounts for changes in the secretory function, as well as for incidence of prostatic intraepithelial neoplasia (PIN) and prostatitis [14, 29]. The effect of high doses of estrogens on the neonatal prostate is due not only to the changes in the androgen concentrations, via permanent actions on the hypothalamic-gonadal pituitary gland, but also due to direct effects on the prostate gland, since the administration of testosterone is not able to reverse those effects [35]; this phenomena is known as estrogenic *imprinting*.

High doses of estrogen administered in adult animals function as castration, resulting in the inhibition of the hypothalamic-pituitary-gonadal axis, by suppression of the gonadotrophin releasing hormone, and consequent blockage of the hormone testosterone by the testes [36, 37]. Nonetheless, such effects can be reversed (contrary to those observed in neonates), by replacing testosterone or dihydrotestosterone hormones.

It is well established that some of the circulating androgens are converted into estrogens in various peripheral tissues by the enzyme aromatase [38]. The aromatase was also identified in the human prostate, suggesting that this gland is able to perform the aromatization reaction and it is a feasible local source of estrogen production [39]. Estrogens acts in target cells all over the body and in addition to sexual organs they influence growth, health and cell activity. Despite early work of estrogens used as therapy for androgen-resistant prostate cancer, it can be critical in predisposing prostate cancer.

Estrogens also participate in several pathological changes in the prostate; among the very well described pathologies is the induction of chronic inflammation [40, 41], squamous metaplasia reported in several species of mammals [42–44], and human prostate cancer [45].

There are several pathological complications, including benign and malign proliferative alterations, often aging escalate-associated, that affect prostate gland. So, studies focusing on the growth regulation and physiology of the prostate are very precious to understand the origin and progression of these pathologies.

3. Benign prostate hyperplasia (BPH)

Benign prostate hyperplasia (BPH) is a common urological issue that causes prostate enlargement in men after 40-years-old. It is a noncancerous augmentation of the prostate gland size, with stromal and glandular epithelial hyperplasia in the transition zone. It is estimated that 50% of 50 year old, and 75% of 80 year old men could have some lower urinary tract symptom (LUTS). In such condition the urethra can be partially or totally blocked, resulting in urinary retention, weak urination stream, incomplete bladder emptying and hesitancy; and so carrying secondary problems as urinary tract infections, bladder stones and chronic kidney disease, culminating in kidney failure. The LUTS is reflection of the hormonal changes rising with age, and resulting in abnormal stromal and epithelial cell proliferation (hyperplasia) in the transition zone of the prostate. The molecular etiology of these events remains unclear, but few studies attempt to correlate it to sex steroids hormones [46], also known as gonadocorticoids and gonadal steroids, that interact with vertebrate androgen and estrogen receptors. It is important to mention that the BPH is generally not a precursor lesion to a prostate cancer (PCa) condition.

Some animal models studies, including dogs and chimpanzees, have been performed in order to understand the prostate conditions. Chimpanzees sporadically suffer from age-associated BPH, and are the closest match to human prostate gland. Throughout the time, dogs are like human counterpart because they develop BPH containing distinct nodules of hyperplasia with diffuse areas of compression of the rectum producing constipation, a symptom opposed to the urinary retention in men [47, 48]. In order to supply these deficiencies, some transgenic animal models using other normal mammal species were developed. Prostate-specific 15-LOX-2 transgenic mouse and PPARð knockdown mice naturally develop increased prostate size with age, in addition to epithelial-hyperplasia, and prostatic intraepithelial neoplasia progression [49, 50].

4. Prostate cancer

Nearly 14 million new cases of cancer occurred worldwide during 2012 [51], generating around 8.2 million deaths. More than a half of cancer deaths arose in countries of medium or low human development index (HDI). The four most common types, in this order were lung, female breast, bowel and PCa. Among malignant neoplasms that affect men, PCa is the most common, after non-melanoma skin tumors, especially in the male population from the sixth decade of life. This is a recognized public health problem, since according to data from the Mortality Information System (MIS), 13,773 deaths were caused by PCa in Brazil in 2013 [52].

Considering the statistics worldwide, PCa prevalence is only beaten by lung cancer in men. Unlike some types of tumors, the incidence of PCa has increased over the years. There are two

main factors for this association: the improvement of diagnostic methods and the extended life expectancy of men over the years; since PCa has slow growth and its incidence is age-associated, it is very comprehensible the increased detection of this malignant neoplasia lately in the years. The origin of PCa and the several processes giving direction to PCa carcinogenesis are still unclear, but often are assumed that several components may influence it, among which stands out: diet, genetic, hormonal, and environmental factors; all currently being widely investigated in the literature.

The treatment of PCa can be very controversial because there are many variables, such as the patient's age, prostatic specific antigen (PSA) concentrations and the stage of the tumor. Patients in inoperable conditions, due to age, are treated with hormone therapy or radiation. The most common hormone therapy for PCa is the androgen deprivation, since the prostate gland is a highly androgen dependent gland, and because the majority of prostate tumors originate from androgen-dependent glandular epithelial cells of the prostate [53]. The therapies in use for PCa will be best addressed later in this chapter.

5. Clinical diagnosis and biomarkers for PCa

The diagnosis and follow-up of PCa patients are often difficult because of the absence of specific markers that could change accordingly to the status of disease, the best therapy, and the existence of future complications caused by the chosen treatment.

For several decades many researchers joined efforts to study biomarkers of prognosis and treatment for PCa. Almost 50-years, PSA measurement represented the best marker for PCa. The primary idea was to substitute the digital rectal examination by PSA screening; nevertheless this was not possible despite the low specificity and false positive rate, as it is also observed in BPH [54]. No significant progress in the use of PSA as a precise biomarker of PCa was achieved during the past years.

Beyond this scenario, advances in genetic testing for PCa risk and new molecular diagnostic assays have been designed to improve diagnostic accuracy and treatment decision beyond prostate-specific antigen (PSA) testing. PSA is a protein of the kallikrein family synthesized in the prostatic epithelium and secreted in the seminal fluid. From its discovery in 1970 to the present day, it is a diagnostic tool used as a tumor marker for early diagnosis, treatment and monitoring of patients with neoplasia in conjunction with the rectal examination. However, many studies have questioned the use of this biomarker for a diagnosis, due to the exponential increase in the diagnosis of PCa and, consequently, the increase of unnecessary hormonal, radiotherapeutic, chemotherapeutic and surgical treatments such as radical prostatectomy [55, 56]. PSA evaluation is performed by its measurement in serum using immunoassay (34 kDa). Normal values vary according to the method used. In most tests, values of up to 2.5 ng/mL are allowed as normal. If this value is higher, it is indicated to request the dosage of fractionated PSA, which relates total PSA to free PSA (fPSA). The result is expected to be equal to or greater than 20%; if it is lower, there is a probability that it is a PCa [57]. However, this test does not have 100% of specificity or sensitivity, insofar as there is PCa whose PSA is not altered, and there are other transient factors that can raise serum PSA levels, such as prostatitis

[58], benign prostatic hyperplasia [59], prostatic biopsies [60] and trauma, due to prostatic cell lysis releasing PSA into the bloodstream [61].

Despite results enhancing detection at earlier stage and decreasing the number of metastatic patients, the use of prostate-specific antigen (PSA) to detect PCa has low specificity, unnecessary biopsies and frequently mistaken diagnoses. Also, PCa has various features so prognosis following diagnosis is greatly variable. Hence, there is a requirement for new prognostic biomarkers, particularly to differentiate between inactive and aggressive forms of the disease, to improve clinical management of PCa patients. Research continues into finding additional markers that may allow this goal to be attained.

In order to improve the specificity of PSA as a tumor biomarker, tests called PHI (Prostatic Health Index), that predicts the risk of having PCa and 4 K score™ (predicts the risk of having high-risk of PCa) were launched on the American and European markets [62]. 4 K score™ blood test combines 4 prostatic biomarkers (total PSA, fPSA, intact PSA, and human kallekrein 2(hK2)) with the age of the patient, the digital rectal exam (DRE) findings (presence of a nodule or not), and the result of previous biopsies [63]. The higher the score, the greater the probability of finding tumor cells in a biopsy (Gleason ≥ 7). This test combination is interesting because it does not allow unnecessary biopsies to be performed, whereas post-operative, as well as any surgery, has risks and can lead to future complications for the patient, affecting his quality of life.

Another non-invasive test available is the ExoDxTM Prostate (IntelliScore) Test18, which, through urinalysis, assesses the risk of developing invasive PCa, and thereby target the best treatment by molecular analysis of three specific genes in exosome and microvesic RNAs released by tumor cells, called extracellular vesicles (further discussed in this chapter) [64]. These related genes (*ERG*, *PCA3* and *SPDEF*) are most commonly related to tumor progression and, consequently, its aggressiveness and invasion [65].

It is important to note that these tests are not accessible to the entire population, either because of the high cost of the technology, or because some countries have still not approved it. Thus, the main diagnostic method used nowadays for the screening and detection of the PCa remains PSA testing and rectal examination (DRE). If the results of these exams are altered, a biopsy is necessary to confirm the diagnosis, and determine the aggressiveness and prognosis of the cancer. This is done by histological analysis of the biopsied tissue, following classification according to the Gleason Scale. This system consists of the sum of 2 values that represent the degree of the tumor, and that determine the dominant cellular pattern and the most frequent cellular pattern, respectively. Tumor grades range from 1 to 5, the former representing more differentiated and prostate restricted tumors, while the latter represents totally undifferentiated tumors that have normally infiltrated the glandular stoma. The score, therefore, ranges from 2 (1 + 1) to 10 (5 + 5), and values below 4 on the Gleason Scale represent a well differentiated PCa; between 5 and 7, an intermediate PCa; and between 8 and 10, advanced PCa [66]. The determination of the degree and stage of cancer allows classification into high, intermediate and low risk categories.

The clinical picture of castrated-resistant prostate cancer (CRPC) is quite heterogeneous, ranging from the asymptomatic increase in the PSA indices to the distant metastasis (commonly bone metastasis), with an important impairment of the patient's quality of life [66]. This is a

reflection of the complexity and diversity of biomolecular alterations already found in biopsies. Tumor progression is related to a number of genetic changes that can affect AR, signaling cascades, apoptosis mechanisms and cell regulation, or, as in many cases, a combination of all of them [67].

Biomolecular techniques, such as fluorescent *in situ* hybridization (FISH) and Microarray, for example, have identified a variety of key factors genes, oncogenes and tumor suppressor genes, related to the development and progression of PCa [68, 69]. The use of molecular techniques also allowed the identification of some genes related to the suppressive function of metastasis, opening a new perspective for researching the phenomenon of tumor invasion to other tissues and, with that, to identify and elucidate new indicators of prognosis, or even PCa target therapies. As example, some studies have focused attention on the CDH1 gene and its protein expression, located on chromosome 16q22, which encodes the E-cadherin, a glycoprotein responsible for cell-cell adhesion, an important cellular function that prevents EMT in tumor progression [70].

The Metastatic prostate adenocarcinoma (metPA) is diagnosed by immunohistochemistry. Nowadays very promising biomarkers have been used to determine prostatic origin of metPA, such as prostate specific membrane antigen (PSMA) and NKX3.1 [71]. PSMA is a type II membrane protein not secreted and is expressed in all forms of prostate tissue, but it is expressed at high levels on malignant prostate cells with limited extraprostatic expression [72]. Many approaches to target PSMA include DNA-based vaccines, as well as passive administration of monoclonal antibodies (PSMA-mAb), including 7E11.C5.3, that has already been approved by USA FDA (Food and Drug Administration); the medication is commercially available as ProstaScint® [72, 73].

Compared to PSA, PSMA is upregulated with androgen deprivation, and its expression was correlated with cancer aggressiveness and poor prognosis, while PSA decreases with androgen deprivation [72]. PSMA was also evaluated in PCa using PET molecular imaging system. After all, PSMA is not specific only to prostate gland; it is expressed in other normal tissues (such as salivary glands, duodenal mucosa, renal tubular cells, and neuroendocrine cells in the colon), and in malignant cells (renal cell carcinomas, colon carcinomas, and endothelial cells that surround or are into the tumors) [74].

Although multiple independent studies sought to demonstrate evidence that genetic variations may be independent predictors of PCa risk in addition to family history and serum PSA levels, the challenge in the years to come will be to introduce these new gene-based diagnostic and prognostic tests in algorithms integrating the other known risk factors including age, ethnicity, family history and PSA level to better tailor diagnostic and therapeutic strategies for PCa.

5.1. The extracellular vesicles (exosomes) and PCa: beyond classical biomarkers

Several studies have related to novel PCa biomarkers that can precisely detect, and treat, types of aggressive cancer by headlining circulating tumor cells (CTCs) and circulating extracellular vesicles (EVs) **(Figure 1)**. Notably, EVs are released by almost all the cells, and brings lots of molecular information. The study based on EVs provides lots of information about its content,

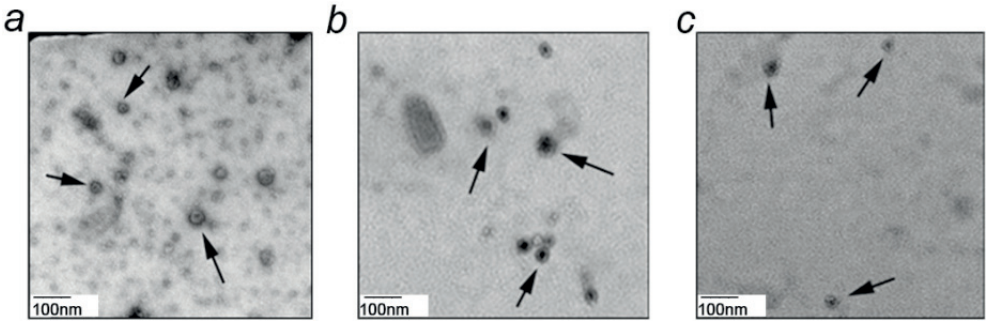

Figure 1. Representative TEM images of exosomes derived from (a) C42 PCa cell line, (b) LNCaP xenograft serum and (c) patient plasma by ultracentrifugation method. Exosomes were negatively stained with 2% uracyl acetate after removal of moisture. Arrows indicate cup-shaped structures which are identified as exosomes (30–100 nm in diameter). From: Kharmate et al. [86]. Online available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0154967.

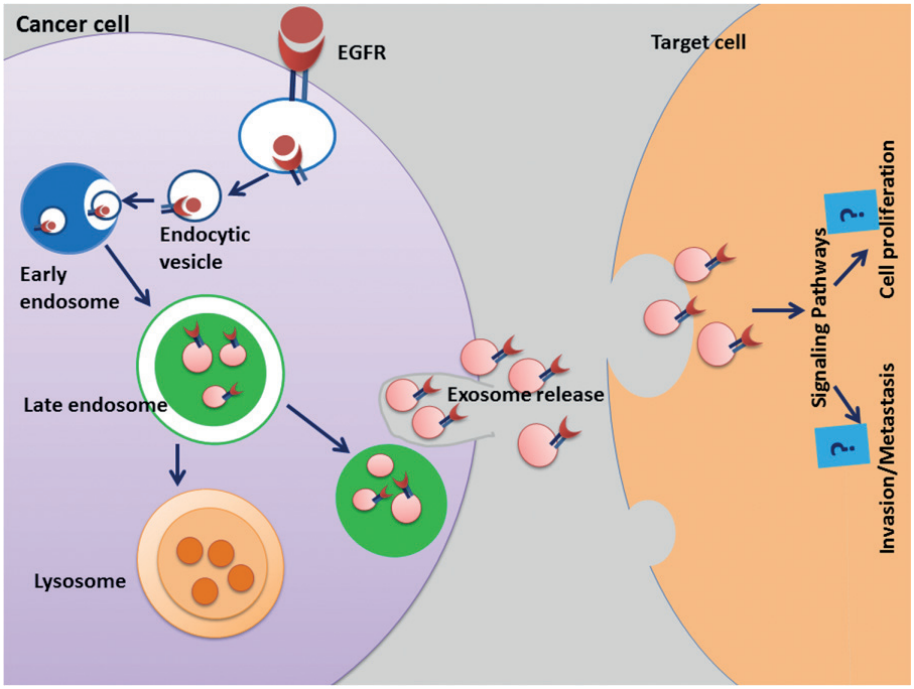

Figure 2. *Schematic representation of possible role of EGFR-exosomes in cancer progression.* Ligand binding induces rapid activation and internalization of EGFR and endocytosis. Whether EGFR escapes lysosomal degradation and is released extracellularly via exosomes is unknown. The transfer of EGFR via exosomes may significantly alter the tumor microenvironment and could be relevant to progression of an aggressive PCa. From: Kharmate et al. [86]. Online available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0154967.

such as: lipids, proteins, nucleic acids and metabolites [75, 76]. All of each can be isolated in small volumes from body fluids, just by using some steps of ultracentrifugation, as a non-invasive method to monitor disease progression, and are proposed to function as tumor-specific molecular signatures. They are small structures (50–150 nm) that carry genetic and/or nongenetic materials from tumor cells. Recent study analyzed the presence of CD9 and CD63 (a housekeeping exosome marker) positive EVs, demonstrating that patients with metastatic cancer and detectable CTCs have higher CD9 detectable in plasma [77]. The CD9 positive EVs were found higher in plasma of PCa patients compared to HPB patients, and were related to paracrine signaling that contributes to PCa progression [77]. *In silico* reanalysis of genes involved in vesicular trafficking demonstrated that the expression of required well-known endosomal sorting complexes, such as *RAB27A*, *RAB27B* and *VPS36*, are downregulated in patients with advanced PCa [78].

Other studies suggest possible micro-RNAs roles in PCa [79] due to their recruitment to EVs present in various human body fluids; they are miR-2909 and miR-615-3p, which was detected in urinary-exosomal of PCa patients [80, 81]. Also EVs was useful to monitor the response to radiation therapy, in the search for a personalized treatment according to different profiling levels [82].

Biomarkers	Biomarkers Measurement	Sample	Recommendation
Prostate Health Index (PHI)	PSA, fPSA, [−2]proPSA	serum	Approved by the Food and Drug Administration (FDA) * Related to PCa aggressiveness
4K*score*	PSA, fPSA, iPSA, hK2	serum	The test provides information about the probability of having a high-risk PCa * Related to PCa aggressiveness
PCA3 *score*	*m*RNA *PCA3* in relation to *m*RNA *PSA*	urine obtained after prostate massage	Approved by the Food and Drug Administration (FDA) * Inconclusive results about its relationship with PCa aggressiveness
*mi*RNAs and other exosomal biomarkers	No standardized methodology	blood and urine	Directly related to development and progression of cancer No standardized methodology Preliminary results

Table 1. Biomarkers in PCa detection and prognosis.

Additionally to androgens (as described in Section 3), prostate physiology is, in part, regulated by the epidermal growth factor (EGF), whose action is mediated by its receptor (EGFR). EGFR is one of the mediators of cell proliferation, and its overexpression has been associated with aggressiveness and invasion of PCa. It has been described and identified as an important anti-PCa target, and some inhibitors of EGFR were tested with limited effectiveness in prostate cancer patients; they are Gefitinib, Lapatinib, and Erlotinib [83–85]. Recently, EGFR was also observed in EVs (**Figure 2**) of PCa patients [86].

Previous studies have demonstrated that PSA can be detectable in plasma and urine derived EV's [87]. Logozzi et al. [88] demonstrated that an acid microenvironment (such as the tumor microenvironment), functions as a key factor for the exosomal releasing, and determines the quality and quantity of released vesicles, including the ones containing PSA, an enzyme that needs an acidic microenvironment for full activation, in PCa.

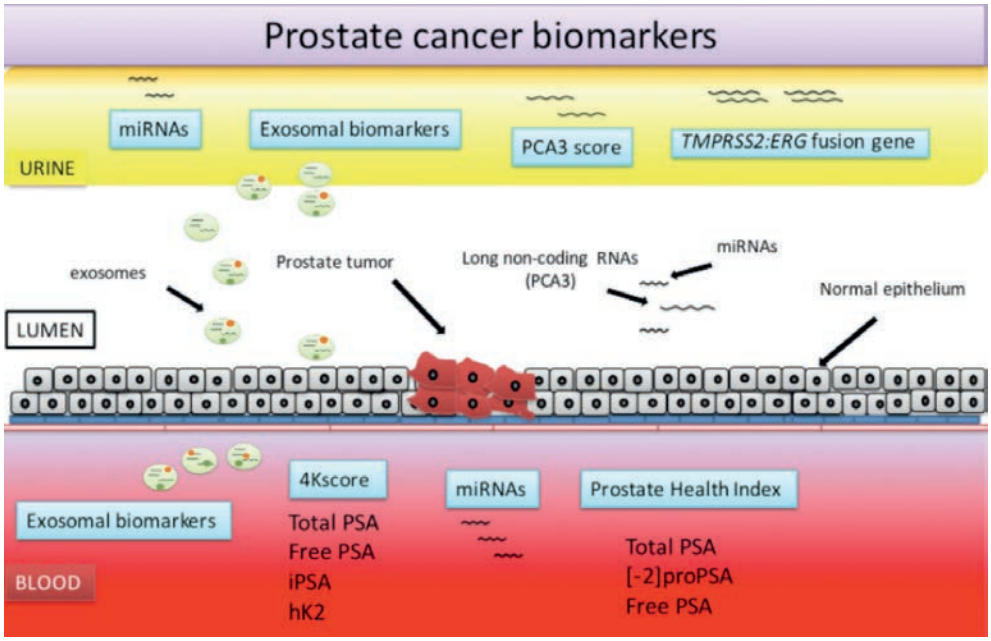

Figure 3. The prostate specific antigen (PSA) remains the most used biomarker in the management of early prostate cancer (PCa), in spite of the problems related to false positive results and overdiagnosis. New biomarkers have been proposed in recent years with the aim of increasing specificity and distinguishing aggressive from non-aggressive PCa. The emerging role of the prostate health index and the 4Kscore: both are blood-based tests related to the aggressiveness of the tumor, which provide the risk of suffering PCa and avoiding negative biopsies. Furthermore, the use of urine has emerged as a non-invasive way to identify new biomarkers in recent years, including the *PCA3* and *TMPRSS2: ERG* fusion gene. Available results showed PCA3 score usefulness to decide the repetition of biopsy in patients with a previous negative result, although its relationship with the aggressiveness of the tumor is controversial. More recently, aberrant the microRNA expression in PCa has been reported by different authors. The utility of circulating and urinary microRNAs in the detection and prognosis of PCa has also been explored. Although several of these new biomarkers have been recommended by different guidelines, large prospective and comparative studies are necessary to establish their value in PCa detection and prognosis. From: Filella and Foj [69]. Online available at: http://www.mdpi.com/1422-0067/17/11/1784.

To summarize, in recent years, many new promising PCa biomarkers have been identified **(Table 1) (Figure 3)**, and found to be associated with tumor aggressiveness. Multiplied studies showed the utility of the PHI, the 4Kscore™ and the PCA3 score to reduce the number of unnecessary prostate biopsies in PSA tested men. Actually, these biomarkers have been recommended for different guidelines. Still, large prospective studies, avoiding bias due to selection of patients according to PSA serum levels, are necessary to compare the value of these biomarkers. Also, new efforts are necessary to standardize the methodology for the measurement of exosomal and non-exosomal miRNAs, in order to analyze accurately their usefulness in the management of patients with early PCa. Finally, the combined role of these biomarkers together with magnetic resonance imaging data should be elucidated [89].

Adapted from: Filella and Foj [69]. (*Recommended by the National Comprehensive Cancer Network).

6. Treatment modalities for PCa

PCa treatment is variable, and it is chosen according to the staging of the cancer and, mainly, according to the patient's own preference. Since this type of cancer has slow growth, the presence of low-risk groups, where tumor is diagnosed still *in situ*, is indicative of an active surveillance treatment in which the patient only accompanies the tumor through regular PSA testing, and digital touch every 3–6 months [90]. During this follow-up period, if the existence of a tumor progression is observed, radiotherapy or surgery is indicated by total removal of the prostate gland (radical prostatectomy).

Radical prostatectomy may be the first choice of the patient who opts for complete removal of the gland, by caution of future metastasis. It is an effective procedure, however, just like any surgical procedure, there may be complications and compromise the patient's quality of life. For this procedure, the most common complications are the urinary incontinence, erectile dysfunction, and inguinal hernia; anyhow, the prognosis tends to be positive and long-lasting [91]. Nonetheless, some tumors may recur over time even after radical prostatectomy. In such cases, it is important to evaluate whether the recurrence was local or occurred at a distance (lymph nodes or other organs, such as liver, bone, or lung).

Hormone therapy is usually used in patients with lymph node involvement or distant metastasis. It consists of reducing androgen concentrations to the level of castration. This can be done by surgical method through bilateral orchiectomy, or through drugs that act on the androgen receptor (AR) pathways; the latter being more commonly used nowadays. At first, hormone deprivation therapy has great effects on the control of advanced PCa. However, it is known that part of the cases evolves to the state of CRPC. The mechanisms responsible for progression of tumor growth, despite hormonal blockade, have not been fully elucidated yet. Current studies have shown that molecular changes in the androgen receptor (AR) are related to such progression. Among these changes, it is relevant to mention the overexpression of AR, mutations in the

AR gene that allow its activation by other endogenous steroids, increased production of growth factors activating AR even in the absence of androgen, changes in co-regulatory proteins and upregulation of enzymes related to androgen synthesis [92].

There are two drug lines for hormone therapy; the first line accounts for the central blockers that constitute the agonists of gonadotrophin-releasing hormone (GnRH agonists), and the peripheral androgen receptor blockers. Usually they are used in a comminuted way, since the central blockers, for example, Leuprolide (Lupron) and Gosserelin Acetate (Zoladex), acts through the interruption of the pituitary feedback mechanism, inhibiting LH realizing by the pituitary gland, and leading to a decreased testoterone production [63]. However, because these drugs initially boosted testosterone production, the combination with peripheral androgen receptor blockers, such as Bicalutamide (Casodex), Flutamide (Flutamide) and Androcur (Androcur), shall be indicated due to their binding capacity to the ARs in a way that inhibits androgenic stimulation, deactivating their genetic expression [93].

The second line of therapy is most commonly used when PCa is resistant to the first-line hormonal therapies stage. Abiraterone Acetate (Zytiga) is a drug that primarily acts on the adrenal gland through the inhibition of the 17α-hydroxylase/C17, 20-lyase (CYP17) enzyme, essential for androgen biosynthesis in tissues [94, 95]. Enzalutamide (Xtandi) is another drug of this therapeutic line that works by inhibiting androgen receptors, their signaling pathways, and is able to act on anti-androgen-resistant tumor cells.

It is important to emphasize that hormonal therapy is a palliative treatment, in that it acts to contain the progression of advanced PCa, and not its elimination. In this context, given the scarcity of effective treatments for these types of tumors, it is promising to still search for new biomarkers capable of not only diagnosing PCa early, but also being able to evaluate its aggressiveness and prognosis.

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CME

Benign prostatic hyperplasia: A clinical review

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ABSTRACT

Benign prostatic hyperplasia (BPH) is an increasingly common diagnosis seen in men over age 50 years. Primary care providers must be aware of patient presentation, diagnostic tests, appropriate lifestyle modifications, treatment options, and potential complications in order to properly manage and educate patients with BPH. If left untreated, BPH can significantly decrease a man's quality of life; however, many pharmacologic and surgical treatments are available to control the symptoms.

Keywords: benign prostatic hyperplasia, alpha-adrenergic antagonists, 5-alpha-reductase inhibitors, transurethral resection of the prostate, TURP, urinary retention

Learning objectives

- Discuss the cause, pathophysiology, and risk factors for developing BPH.
- Explain the clinical presentation of BPH and the screening methods and diagnostic tests used in its evaluation.
- Discuss management options for patients with BPH.

Benign prostatic hyperplasia (BPH) is one of the leading diagnoses affecting men of increasing age. By age 50 years, about 50% of men are diagnosed with BPH; by 80 years, 90% of men are diagnosed, and the greatest prevalence occurs among men ages 70 to 79 years.[1,2] In BPH, a proliferation of prostatic cells leads to an increase in prostate size, urethral obstruction, and lower urinary tract symptoms.[2,3] Men with BPH can experience great discomfort with urination and may develop complications including recurrent urinary tract infections (UTIs) and renal failure.[2] Given the aging population, healthcare providers can expect an overall increase in the rates of BPH diagnoses, and must be able to recognize and treat the disorder.

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PATHOPHYSIOLOGY

BPH occurs in the prostate's transitional zone, where stromal and epithelial cells interact. The growth of these cells is affected by sex hormones and cytokine responses.[2]

Dihydrotestosterone (DHT) Within the prostate, testosterone is converted to DHT, the androgen thought to be the main mediator of prostatic hyperplasia. The clinical importance of DHT became clear when patients treated with orchiectomy and 5-alpha-reductase inhibitors (which stop conversion of testosterone to DHT) showed decreases in BPH symptomatology. The role of DHT was further

Key points

- BPH is a common diagnosis in men age 50 years and older.
- Men with BPH suffer from storage and voiding symptoms.
- IPSS is used to assess severity of BPH and guide treatment decisions.
- Alpha-adrenergic antagonists and 5-alpha-reductase inhibitors are first-line medications for patients suffering from BPH.
- TURP is the gold-standard surgical treatment.

demonstrated when men with BPH were found to have significantly higher DHT levels within prostate tissue compared with men whose prostates were of normal size.[4]

Age Because plasma androgen levels decrease with age, more data are needed to specify why BPH occurs as men get older. Estrogens may play a role in BPH, targeting stromal cells through an estrogen receptor mechanism. The ratio of estrogens to androgens increases with age, and this may explain why BPH occurs among men as they get older; however, more evidence is needed to reach a definitive conclusion.[4]

Cytokines Cytokines contribute to prostate enlargement by inciting an inflammatory response and by inducing epithelial growth factors. As the prostate enlarges due to hyperplasia, the portion of the urethra that passes through the prostate is compressed, ultimately compromising urinary outflow and leading to obstructive symptoms. The patient develops bladder hyperactivity, inflammation, and distension as bladder smooth muscle cells enlarge to maintain urine flow in response to resistance from prostatic obstruction. These changes cause oxidative stress and free radical formation, as well as alterations to the alpha-adrenergic nerves of the bladder, resulting in storage symptoms (**Table 1**). When bladder smooth muscle cells can no longer grow and thereby counteract this resistance, smooth muscle contractions become impaired and voiding symptoms dominate.[2]

TABLE 1. Symptoms of BPH[5]

Storage symptoms
• Urinary frequency
• Urinary urgency
• Urinary incontinence
• Nocturia
• Dysuria
Voiding symptoms
• Difficulty initiating urinary stream
• Urinary hesitancy
• Straining to void
• Decreased urinary flow
• Intermittency
• Dribbling
• Incomplete bladder emptying

RISK FACTORS

Common risk factors for BPH include increasing age, functioning testicles, metabolic syndrome, family history of BPH, obesity, history of diabetes, and black race.[2,5]

A patient's diet, smoking, and exercise can influence BPH progression.[2,6,7] Patients who consume a diet rich in vegetables appear to have less severe BPH symptoms than those who do not, although the consumption of fruit has not been shown to have a similar significant relationship to BPH severity. A diet high in starches and meat has been linked to an increased risk of developing BPH. Studies have also shown that excessive alcohol intake can increase BPH risk and progression.[2] Although smoking may be a risk factor for BPH, conflicting evidence precludes the establishment of such a relationship.[7]

Studies demonstrate that a sedentary lifestyle can increase the risk of developing BPH or intensify the severity of lower urinary tract symptoms in patients who already have the condition.[6] Incorporating exercise and physical activity into the daily routine are important, because activity can help prevent BPH as well as metabolic syndrome, which is strongly linked to BPH. Being physically active is also more cost-effective than using pharmacologic or surgical interventions for treating BPH.[6]

Once a patient is diagnosed with BPH, clinicians and patients must be aware of factors associated with worsening disease progression, including increased age, severe lower urinary tract symptoms, increased prostate size, and high prostate-specific antigen (PSA) levels.[5]

CLINICAL MANIFESTATIONS

The symptoms of BPH can be grouped into two main categories: storage and voiding (**Table 1**). Men may have few of these symptoms initially, but with increasing age and disease progression, symptoms can become more prevalent.[3] Patients with BPH often report that the symptoms are distressing and bothersome, and impair their quality of life.[8]

DIAGNOSIS

Practically speaking, BPH is a diagnosis of exclusion. When men over age 50 years complain of lower urinary tract symptoms, the following tests can be used to rule out all other possible causes before arriving at a BPH diagnosis.[1]

History Healthcare providers must ask specific questions about storage and voiding symptoms, and should be aware of excessive water consumption or diuretic use that may account for a patient's symptoms.[5] The American Urological Association Symptom Index (AUASI) and the International Prostate Symptom Score (IPSS) are subjective questionnaires that can be used to help evaluate lower urinary tract symptoms and their effect on patients suffering from BPH.[3,5] These questionnaires have patients rate symptoms of incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia on scales from 0 (not at all) to 5 (almost always). The scores

TABLE 2. BPH medications and adverse reactions[5,8]

Drug	Recommendation	Adverse reactions
Alpha-adrenergic antagonists (terazosin, alfuzosin, doxazosin, silodosin, tamsulosin)	First-line	Fatigue, headache, dizziness, hypotension, syncope, dry eyes, dry mouth, nasal congestion, erectile dysfunction, ejaculatory dysfunction
5-alpha-reductase inhibitors (finasteride, dutasteride)	First-line or adjunct	Erectile dysfunction, ejaculatory dysfunction, loss of libido, gynecomastia
PDE-5 inhibitor (tadalafil)	First-line for concomitant BPH and erectile dysfunction; shown efficacious as BPH monotherapy	Headache, flushing, nasal congestion, indigestion, back pain
Anticholinergics (darifenacin, solifenacin, trospium chloride, oxybutynin, tolterodine, fesoterodine)	Adjunct therapy	Headache, dry eyes, dry mouth, dyspepsia, constipation

are then tallied, and classified as mild (0-7), moderate (8-19), or severe (20-35).[9] These rankings help to guide treatment decisions and responses.[3] The IPSS contains identical questions to that of AUASI, but includes an additional quality of life measure, asking patients to classify their feelings if they had to live with their urinary symptoms for the rest of their lives on a scale of 0 (delighted) to 6 (terrible).[9,10]

Digital rectal examination (DRE) Perform a DRE to assess the size, shape, and consistency of the prostate gland.[3] An enlarged prostate often presents on examination as soft, smooth, boggy, mobile, and with an obscured sulcus. Note any nodules or indurations, which may suggest prostate cancer.

Prostate-specific antigen (PSA) level Given the challenges of evaluating true prostate size in primary care offices by DRE, obtaining a PSA level makes it easier to diagnose BPH. PSA levels often correlate with prostate size; therefore, a PSA level of 1.5 ng/mL is often indicative of BPH.[1] However, this value is highly variable and may fluctuate based on the patient's age, race, medications, or comorbid urinary conditions. Due to the nonspecific nature of PSA, a diagnosis of BPH cannot be made from PSA levels alone. Yet in the presence of other positive diagnostic outcomes, an elevated PSA level can help a primary care provider arrive at a BPH diagnosis.[1]

Urinalysis Ordering a urinalysis is recommended as a primary step in order to exclude UTI, prostatitis, cystolithiasis, nephrolithiasis, renal cancer, and prostate cancer as causes of lower urinary tract symptoms.[5]

Voiding diaries Documenting the time voided, volume voided, and associated activities (such as fluid intake) in a voiding diary may help in BPH diagnosis, especially in patients with urinary frequency. The primary care provider can differentiate if symptoms are BPH-related or due to polyuria, overactive bladder, or behavioral causes. Patients should keep a voiding diary for at least 24 hours, although many primary care providers suggest keeping it for 3 to 7 days so that they can evaluate trends.[2,11] Voiding diaries also can be used to evaluate treatment efficacy.

Measuring postvoid residual volume A postvoid residual volume measurement is recommended for patients with moderate or severe symptoms, defined by an AUASI/IPSS score of 8 or greater.[11] Symptoms of BPH can be associated with urinary retention, and a large residual volume in combination with other tests may indicate BPH.[5]

Prostatic ultrasound Transabdominal or transrectal prostatic ultrasound also may be considered to accurately evaluate the size, shape, anatomy, and potential pathology of the prostate in a minimally invasive, cost-effective, and reproducible way.[2,12] A transabdominal ultrasound also can assess the bladder and postvoid residual urine, which may be contributing to a patient's symptoms.[2]

Blood urea nitrogen (BUN) and creatinine Serum BUN and creatinine levels may be used in diagnosing and monitoring BPH, although the use of these levels in initial BPH assessment is controversial. The European Association of Urology (EAU) recommends obtaining baseline BUN and creatinine measurements and watching for potential renal failure complications associated with BPH.[2] The American Urological Association (AUA) does not suggest obtaining these baseline levels because preliminary renal insufficiency tends to be equal among men of similar ages regardless of whether they have BPH.[11] However, measuring the patient's BUN and creatinine levels may help evaluate progressive obstruction and impaired renal function.

Refer the patient to a urologist if his symptoms are too severe or complicated to evaluate and treat in a primary care setting.[5] Increasing PSA levels, persistent hematuria, urinary retention, recurrent urinary tract infections, possible prostate cancer, renal failure, or inadequate pharmacologic treatment are indications for a urology consult.[3]

TREATMENT

Many pharmacologic (**Table 3**) and surgical interventions have been approved for treating BPH, with the goals of improving patient symptoms and quality of life while slowing disease progression and reducing complications.[9] Treatment decisions are based on the severity of the condition.

Watchful waiting For men with mild BPH symptoms (IPSS less than 8), watchful waiting is recommended. This includes yearly follow-up appointments with history and physical examination to determine the progression of the disorder and

reevaluate treatment options.[5] During this time period, various behavioral modifications, such as avoiding antihistamines, reducing fluid intake in the evening, and decreasing alcohol and caffeine consumption can provide symptom relief.[11]

Men suffering from moderate to severe symptoms (IPSS of 8 and greater) may consider lifestyle changes, but will likely require pharmacologic treatment or surgery if pharmacologic treatment fails.[2,11] Patients on medication should be evaluated at least twice a year in the office to discuss the efficacy of the medication and potential dose adjustment. They also should undergo DRE and PSA screening at least annually.

Alpha-adrenergic receptor antagonists The mainstay of BPH treatment, these medications inhibit sympathetic adrenergic receptors, causing prostatic and bladder smooth muscle cell relaxation.[5] The resultant reduced urethral constriction and improved urinary flow lessen obstructive BPH symptoms.[3]

Alpha-adrenergic receptor antagonists are further subclassified according to their extent of selectivity for certain alpha-1 receptors. Doxazosin, terazosin, and alfuzosin are considered nonselective, blocking all alpha-1 receptors equally; silodosin and tamsulosin are selective for alpha-1A receptors that are mainly located in the urogenital tract.[5] Selective agents are associated with fewer systemic adverse reactions (such as hypotension, dizziness, and fatigue) than nonselective agents.[3,9] Clinicians should avoid prescribing nonselective alpha-blockers to older adults because these drugs can cause orthostatic hypotension and syncope.[13] However, a patient with BPH and hypertension may be a candidate for a nonselective agent because it would treat both conditions.

Both types of alpha-adrenergic receptor antagonists cause clinically significant decreases in BPH symptoms after 1 week of therapy, as reflected by AUASI score decreases; however, 2 to 4 weeks of treatment is recommended to achieve the full effect of the medication.

Alpha-adrenergic receptor antagonists should not be prescribed to patients planning to have cataract surgery due to the risk of floppy iris syndrome.[5] Because this class of medications does not reduce prostate size, patients are still at risk for urinary retention, associated complications, and disease progression.[3]

5-alpha-reductase inhibitors Another first-line drug option is a 5-alpha-reductase inhibitor, which blocks the conversion of testosterone to DHT, inhibiting prostatic hyperplasia, reducing prostate size, and slowing disease progression. Treatment with a 5-alpha-reductase inhibitor reduces urinary retention and the need for future BPH surgeries, and should be started in patients with PSA levels greater than 1.5 ng/mL, as long as patients have no contraindications. Within 2 to 6 months, men taking 5-alpha-reductase inhibitors for BPH treatment should experience a 25% decrease in prostate size and an improvement in BPH symptoms.[5] These drugs can be used as monotherapy or adjunct therapy to alpha-adrenergic receptor antagonists. Combination therapy is more successful than monotherapy but is associated with more adverse reactions.[5]

Tadalafil This drug, mainly used to treat erectile dysfunction, is the phosphodiesterase-5 inhibitor approved for BPH treatment. Tadalafil causes smooth muscle relaxation of the detrusor muscle, prostate, and vascular cells of the urinary tract, and decreases prostatic and bladder hyperplasia.[5] After 4 weeks of use, tadalafil improves lower urinary tract symptoms and quality of life, and is an option for men suffering from concomitant BPH and erectile dysfunction.[5,8]

Anticholinergic agents This class of medication has been approved as add-on therapy when alpha-adrenergic antagonists fail to control BPH symptoms. Anticholinergics block muscarinic receptors on the detrusor muscle and improve storage symptoms after fewer than 12 weeks of therapy.[5] However, anticholinergics may exacerbate constipation, cognitive impairment, and dementia in older adults, and should be avoided or closely monitored if used in these patients.[13]

Saw palmetto This herb has been used to reduce lower urinary tract symptoms; however, recent data propose that symptom improvement may be solely a placebo effect.[14]

Surgery Surgical treatment for BPH is indicated when medical treatment fails to elicit a sufficient response, when symptoms are severe, if there is concern for complications, or if the patient has renal failure, refractory gross hematuria, recurrent UTIs, or bladder stones.[11] Recommended options include open surgery, transurethral resection of the prostate (TURP), and transurethral holmium laser enucleation of the prostate (HoLEP).[2]

Open surgery involves removing the prostatic adenoma from the adjacent prostate tissue. With the enlarged prostate no longer compressing the urethra, voiding symptoms improve postoperatively. This procedure carries the risk of several complications including wound infection, hemorrhage, UTI, and sepsis.

TURP is the gold standard for BPH treatment and is the most commonly performed procedure for men suffering from BPH.[1,2] During TURP, an endoscope is inserted through the urethra and the prostatic adenoma is removed via loop electrode. TURP is effective for improving BPH symptoms but may cause complications such as hemorrhage, hyponatremia, and retrograde ejaculation.

Bipolar TURP uses bipolar current and is a minimally invasive procedure associated with fewer complications and a shorter hospital stay. Because 0.9% sodium chloride solution can be used for irrigation instead of nonconducting glycine as in monopolar TURP, the procedure can be longer and complications are reduced.

HoLEP, another minimally invasive procedure, involves removal of the prostate adenoma by laser irradiation, and can be considered in men who do not qualify for TURP due to prostate size. Although HoLEP is a longer surgical procedure than TURP, it is less commonly associated with complications and requires a shorter hospital stay.[2,9]

Temporary and permanent urethral stents are also used to treat BPH in high-risk patients who are unable to undergo

invasive surgery. The minimally invasive procedure involves endoscopic stent placement into the prostatic urethra, improving BPH symptoms and minimizing complications because of the smaller incision and reduced trauma to the surrounding tissue.[2]

Botulinum toxin is another potential treatment option that has been explored but is not approved. Injecting the toxin into the prostate inhibits acetylcholine release, resulting in smooth muscle paralysis and tissue atrophy.[2] Acute inflammation is followed by scarring and shrinkage of the prostate.

COMPLICATIONS

Recurring urinary retention is a common complication of BPH. Men at greater risk for urinary retention are those with PSA levels above 1.6 ng/mL or prostate volumes over 31 mL. Other complications include bladder calculi as a result of urinary stasis and UTIs from increased postvoid residual urine. Macroscopic hematuria and renal failure have also been observed.[2]

Patients also may develop sexual dysfunction as a result of pharmacologic or surgical interventions. Erectile dysfunction has been reported in patients taking 5-alpha-reductase inhibitors, and men taking these medications or alpha-adrenergic antagonists have reported ejaculatory dysfunction. Ejaculatory dysfunction also is a complication in 80% of men undergoing open surgery and 65% to 80% of men undergoing TURP.[2]

PATIENT EDUCATION

Patients with BPH or at risk for the condition should be told about the symptoms, preventive measures that can be integrated into daily life, diagnostic tests, treatments, possible complications, and when to schedule follow-up appointments with their primary care providers.

Clinicians should encourage patient lifestyle modifications to decrease the risk of developing BPH or to help control preexisting symptoms. Such lifestyle modifications include diet and exercise to maintain a healthful weight, limiting excessive water intake, limiting or avoiding coffee and alcoholic beverages, and bladder training (including urinating at least once every 3 hours).[2]

Patients also should be aware of the symptoms of BPH complications so they can seek adequate medical attention if necessary. Encourage patients to return to the primary care office if their symptoms worsen or they develop dysuria, pelvic pain, urinary retention, or hematuria.

Patients with mild symptoms who are otherwise healthy should see their primary care provider annually. Those taking alpha-adrenergic receptor antagonists should follow up every 2 to 4 weeks for the first year of therapy and then yearly thereafter if symptoms are controlled. Patients taking a 5-alpha-reductase inhibitor should see their primary care provider every 3 months during the first year of therapy, and then annually.[11] Patients who have had TURP should follow up with their providers on an individual basis.

CONCLUSION

As the US population ages, the prevalence of BPH is bound to increase. Primary care providers must be well-versed on the definition, pathophysiology, associated risk factors, evaluation, diagnosis, treatment, prevention, and complications of BPH. Providers must ask patients about lower urinary tract symptoms when taking a health history of older men, so they can manage patients optimally and refer them to a specialist when indicated. **JAAPA**

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Pumpkin

View 1861 Products Containing: Pumpkin

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Scientific Name

Cucurbita pepo, synonyms Cucumis pepo, Cucurbita galeottii, Cucurbita mammeata.

Family: Cucurbitaceae.

Background

Pumpkin is a plant native to South America. It is now grown worldwide. Pumpkin seed and its oil are used as a medicine. The fruit and seed are used in a variety of culinary dishes and desserts (92380,92384).

Also known as: Calabaza, Citrouille, Cucurbitea Peponis Semen, Field Pumpkin, Graine de Citrouille, Great Pumpkin, Huile de Graines de Citrouille, Pepo, Pumpkin Seed Oil, Styrian Pumpkin.

History

People Use This For

Orally, pumpkin is used for symptoms of benign prostatic hyperplasia (BPH), bladder irritation, overactive bladder, pyelonephritis, intestinal worms, and androgenic alopecia.

Roasted pumpkin seeds are considered a snack food.

Safety

LIKELY SAFE ...when used orally and appropriately in amounts commonly found in foods.

POSSIBLY SAFE ...when used orally and appropriately in medicinal amounts for up to one year (2,7,18,5093,92378,92383).

PREGNANCY AND LACTATION: Insufficient reliable information available; avoid using amounts greater than those found in food.

Effectiveness

See detailed evidence summary

POSSIBLY EFFECTIVE

Androgenic alopecia. Clinical research suggests taking pumpkin seed oil (Octa Sabal Plus, Dreamplus Co. Ltd.) 400 mg daily in divided doses for 24 weeks increases hair count by 30% compared to placebo in men with mild to moderate hair loss. Self-rated improvement and satisfaction scores were 62% and 52% higher with pumpkin seed oil vs. placebo, respectively (92378).

Benign prostatic hyperplasia (BPH). Taking pumpkin seed oil or pumpkin seed alone or with saw palmetto and other ingredients may improve symptoms of BPH (5093,6777,11231,92379,92382,92383). One study shows that taking pumpkin seed 5 grams twice daily for 12 months may be more effective than taking pumpkin seed extract 1000 mg twice daily in terms of overall symptoms and response to therapy (92383). Some preliminary clinical research also suggests that taking pumpkin seed oil (Prostafit, EuRho Vital) daily for 6 months may be as effective as the BPH medication prazosin (92382).

Dosing & Administration

- Adult

  Oral:

  Androgenic alopecia (alopecia areata): Pumpkin seed oil (Octa Sabal Plus) 400 mg daily in divided doses for 24 weeks has been used (92378).

  Benign prostatic hyperplasia (BPH): Pumpkin seed 5 grams twice daily for 12 months has been used (92383). Pumpkin seed oil (Prostafit, EurRho Vital) two tablets daily for 6 months has been used (92382). Pumpkin seed extract (Prosta Pink Forte) 1-2 capsules daily for 12 weeks has been used (11231). Pumpkin seed oil 480 mg per day in 3 divided doses in combination with saw palmetto has been used (6777). An herbal combination product containing pumpkin seed oil extract 160 mg, saw palmetto lipoidal extract 106 mg, nettle root extract 80 mg, lemon bioflavonoid extract 33 mg, and vitamin A (100% as beta-carotene) 190 IU three times daily for 6 months has been used (5093). Another herbal product (ProstateEZE, Totally Natural Products), containing pumpkin seed oil 160 mg, small-flowered willow herb extract equivalent to 500 mg dry herb, lycopene 2.1 mg, pygeum equivalent to 15 grams dry stem, and saw palmetto equivalent to 660 mg dry leaf, daily for 3 months has been used (92379).

- Standardization & Formulation

  There is insufficient reliable information about the standardization of pumpkin products.

Adverse Effects

Report an Adverse Reaction to Pumpkin

General: Pumpkin products are generally well tolerated, and adverse effects to pumpkin seed or its oil are rare. In clinical trials, mild abdominal discomfort and decreased ejaculatory volume have been reported in one person each (5093,92378).

- ⊞ Gastrointestinal
- ⊞ Genitourinary

Toxicology

There is insufficient reliable information about the toxic effects of pumpkin.

Interactions with Drugs

LITHIUM

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Pumpkin is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, pumpkin might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

Interactions with Herbs & Supplements

None known.

Interactions with Foods

None known.

Interactions with Lab Tests

None known.

Interactions with Diseases

None known.

Mechanism of Action

General: The applicable part of pumpkin is the seed. Pumpkin seeds can contain as much as 50% fatty oil, 38% protein, and 37% carbohydrates, depending on the growing and processing conditions (8257,92382). Pumpkin seeds are also rich in cucurbitin and carotenoids, including lutein, carotene, and beta-carotene (515). The seed oil is rich in unsaturated fatty acids, including 47% linoleic acid, 29% oleic acid, 14% palmitic acid, and 8% stearic acid (8257). The oil is also rich in vitamin E, including both gamma-tocopherol and alpha-tocopherol (3 mg/100 grams) (8257). The enzyme acyl-coenzyme A oxidase (ACOX) is present in the pumpkin seed. The ACOX enzyme catalyzes fatty acid oxidation, specifically the oxidation of fatty acid CoA esters with 4 to 10 carbon atoms (8256). Pumpkin seeds also contain delta-5- and delta-7-sterols (92383)

Anthelmintic effects: Cucurbitin, a constituent in pumpkin seeds, has anthelmintic effects. The concentration of cucurbitin varies significantly among pumpkin species (515).

Anticancer effects: In vitro research shows that pumpkin seed extract or cucurbitin can inhibit the growth of various types of cancer cells. The growth inhibition does not appear to be related to steroid hormone receptor activation (92380).

Diuretic effects: Pumpkin seed oil appears to exhibit a diuretic effect, which can relieve bladder discomfort, causing the perception of reduced prostate gland swelling without reducing the gland size. The phytosterol constituents are also believed to affect urine flow (515). Delta-7 sterols, thought to be mainly responsible for these effects, are detected only in certain strains of pumpkin (92383).

Prostate effects: Animal research suggests that pumpkin seed and seed oil might improve bladder and urethral function, reduce prostate weight, and have anti-inflammatory effects, which might help BPH symptoms (11233,92383).

Pharmacokinetics

There is insufficient reliable information available about the pharmacokinetics of pumpkin.

Classifications

5-Alpha Reductase Inhibitors, Diuretics

References

See Monograph References

This monograph was last reviewed on 7/8/2019 and last updated on 5/9/2019. Monographs are reviewed at least once per year. If you have comments or suggestions on something that should be reviewed or included, please tell the editors. For details about our evidence-based approach, see our Editorial Principles and Process.

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Antioxidant and Antiinflammatory Effect of *Epilobium parviflorum* Schreb.

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***Epilobium parviflorum* Schreb. (Onagraceae) is used for the treatment of benign prostatic hyperplasia (BPH), but its biological action is not entirely identified. This paper aims to report data on *E. parviflorum* with respect to its antioxidant and antiinflammatory effects. The aqueous acetone extract of *E. parviflorum* showed higher antioxidant effect in the DPPH assay than well known antioxidants and inhibited the lipid peroxidation determined by the TBA assay (IC_{50} = 2.37 ± 0.12 mg/mL). In concentrations of 0.2–15.0 µg/mL the extract possessed a protective effect, comparable to catalase (250 IU/mL), against oxidative damage, generated in fibroblast cells. In the COX inhibition assay *E. parviflorum* decreased the PGE_2 release, so showing inhibition of the COX-enzyme (IC_{50} = 1.4 ± 0.1 µg/mL). Copyright © 2008 John Wiley & Sons, Ltd.**

Keywords: Epilobium parviflorum; BPH; DPPH; TBA; fibroblast; COX-enzyme.

INTRODUCTION

Epilobium species have been used commonly as herbal remedies, particularly in central Europe. *Epilobium parviflorum* Schreb. (Onagraceae), known as 'small flowered willow-herb' is a perennial, flowering plant, growing wild across Europe. It has been utilized in the treatment of prostatic disorders and its application has been recommended especially for patients suffering from benign prostatic hyperplasia (BPH) (Hostettmann and Hamburger, 1990; Steenkamp, 2003; Vitalone *et al.*, 2003). Due to the similar external habit of different *Epilobium* species and their widespread use in traditional medicine, the name 'willow-herb' is given to other commonly applied *Epilobium* species, especially *Epilobium angustifolium* L. It has to be noted that all 'willow-herb' designations mentioned in present paper refer exclusively to *Epilobium parviflorum*.

The above-ground part of willow-herb contains phytosterol-esters, phytosterol-glycosides and remarkable amounts of various phenolic compounds. Based on our previous experiments, approx. 0.13 g total phytosterol, 34.8 g total polyphenol, 25.8 g tannin and 0.9 g flavonoid content was determined per 100 g plant material (method described in European Pharmacopoeia Supplement 5.0, 2005). The LC-MS/MS investigations support that the main tannin component of *E. parviflorum* is a macrocyclic tannin, oenothein B, and the main flavonoid component is myricitrin (myricetin-3-O-rhamnoside). The presence of caffeic and chlorogenic acids, derivatives of gallic- and ellagic acids, myricetin, quercetin, kaempferol and their various glycosides is also characteristic of *E. parviflorum* (Hevesi *et al.*, 2006; Ducrey *et al.*, 1995).

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However, the comprehensive biological action of willow-herb is not entirely known, the literature reports its antimicrobial and antiinflammatory properties. The main tannin component of *E. parviflorum*, oenothein B, is proved to inhibit the 5α-reductase enzyme, one of the main targets in the search for drug treatment of BPH (Vitalone *et al.*, 2003; Steenkamp *et al.*, 2006; Lesuisse *et al.*, 1996).

Benign prostatic hyperplasia (BPH) is maintained by complex pathological factors, so it can be linked to several clinical symptoms of the lower urinary tract. BPH is regarded as an endocrine disorder caused by age-related hormone imbalance and increased oxidative damage, but elevated levels of prostaglandins and leukotrienes may also be involved in the maintenance of BPH (Ekman, 1998; Aydin *et al.*, 2006). These facts suggest that substances with antiandrogenic, antioxidant and antiinflammatory actions may be effective in treatment of BPH patients.

The present study aimed to display different aspects of the antioxidant activity and antiinflammatory effect of *E. parviflorum* as well as comparing these results with those that have been reported previously by Steenkamp *et al.* (2006).

MATERIALS AND METHODS

The solvents used in the extraction and in the DPPH assay (acetone, methanol) were of reagent or HP-3D-CE quality, purchased from Reanal, Hungary. DPPH (2,2-diphenyl-1-picrylhydrazyl), Trolox ((±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) and ascorbic acid were acquired from Sigma, Hungary. Most of the chemicals (methanol, butanol, dimethyl sulfoxide (DMSO), hydrochloric acid, bovine brain extract, thiobarbituric acid (TBA), phosphate

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buffered saline (PBS), hydrogen-peroxide, minimum essential medium (MEM), Dulbecco's modified Eagle's medium (DMEM), fetal calf serum (FCS), neutral red solution, trypsine, catalase, RPMI 1640 medium, lipopolysaccharide (LPS), indomethacin) used in the lipid peroxidation assay, in the *in vitro* antioxidant test and in the COX-inhibition assay were purchased from Sigma, United Kingdom. The butylated hydroxytoluene (BHT) was purchased from Aldrich, propyl gallate from Fluka, the alamarBlue reagent from AbD Serotec and the PGE2 assay kit from R&D Systems, United Kingdom.

Epilobium parviflorum was cultivated in 2005 and 2006 in Budapest, Hungary. The aerial parts of flowering plants were collected and dried in the shade at room temperature. Plant material was identified macroscopically and microscopically in the Department of Pharmacognosy, Semmelweis University, Budapest, where the herbarium specimen are deposited (voucher number: EPP0507/S and EPP0607/S).

Aqueous acetone (80% v/v) was used for extraction. Dried, powdered herb (500 g) was extracted in a sonicator with 3 × 2000 mL of solvent, for 2 h. The combined extracts were evaporated to dryness at 50 °C, under reduced pressure. The yield of dried extract was 1.86 ± 0.06% (m/m) of the dried plant material.

DPPH assay. DPPH assay is a simple, colorimetric assay, commonly used for examination of the antioxidant capacity of natural compounds. An ethanol solution of the free radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH) has a deep violet colour, characterized by an absorption maximum of 517 ± 2 nm. In the presence of a hydrogen-donor, DPPH is reduced and the colour of the solution is converted to yellow. The degree of decolorization induced by samples was related to that induced by well-known antioxidant compounds, Trolox and ascorbic acid (Kim and Lee, 2004; Molyneux, 2004; Brand-Williams *et al.*, 1995). Free radical stock solution (30 mM) was freshly prepared by dissolving DPPH in methanol. The stock solution was diluted by methanol to a final absorbance of 0.8 ± 0.02 at 517 nm. Dried *E. parviflorum* extract was redissolved and adjusted to exact concentrations (10, 20, 30, 40 and 50 µg/mL) with 70% (v/v) methanol. Seven different concentrations (10–250 µM) of reference substances, Trolox and ascorbic acid, were prepared with 70% (v/v) methanol. Based on previous observations, 70% (v/v) methanol is appropriate for clear resolution of the extract and reference compounds and does not interfere with the measurement in the volume applied. Spectrophotometric data were acquired using a Hitachi U-2000 spectrophotometer. The absorbance of the free radical solution was measured before every single measurement (A_0). Afterwards 100 µL of sample was added to 2400 µL of radical solution, homogenized and the reduction of absorbance was observed between 30 s and 10 min (A_{10}), until the reaction was complete and reached a plateau rate. The percentage reduction of DPPH was calculated by the following equation:

$$\% = 100(A_0 - A_{10})/A_0$$

The concentration of free radicals was calculated by means of absorbance-inhibition ratio $A = \varepsilon cL$, where ε is the extinction coefficient (1.09×10^4), c is the concentration (M) and L is the path length (1 cm)).

The antioxidant capacity of samples was defined as the mass (µg) of extract equivalent to DPPH, as recommended for plant extracts which do not have defined molar mass (Molyneux, 2004).

Lipid peroxidation assay. Measurement of the end products of lipid peroxidation (mainly malondialdehyde) is one of the most widely used assays for oxidative damage. In a lipid peroxidation model system liposomes are oxidized using an iron source ($FeCl_3$) and ascorbic acid, the Fenton reaction. The genesis of hydroxyl radicals induces damage to liposomes, whereas addition of an antioxidant scavenges free radicals and thus prevents damage. The reduction in the extent of peroxidation was characterized by a lower yield of the coloured chromogenic product, the adduct of thiobarbituric acid (TBA) and malondialdehyde. Decolorization was observed by spectrophotometry (532 nm) (Buege and Aust, 1978; Caillet *et al.*, 2007).

Bovine brain extract was suspended in cool phosphate buffered saline (PBS) at a concentration of 5 mg/mL. The suspension was sonicated for 2 h in an ice-water bath, until the lipid dissolved and the suspension appeared homogenious and milky. 10–15 glass balls were put into the suspension to aid the process. While using the suspension it was kept cool and shaken every 20 min to avoid lipid degradation and to encourage separation.

A 10 mg/mL concentration of *Epilobium* extract was prepared with 70% (*v/v*) methanol. This stock solution was used to make seven serial three-fold dilutions (1 mL of extract and 2 mL of solvent). 70% (v/v) methanol has been found to have no significant effect on the assay. The experiment was set up to include four kinds of control: blank, extract alone, 1×10^{-4} M propyl gallate (antioxidant positive control) and a full reaction mixture (negative control). The full reaction mixture (FRM) contained exact volume of the solvent, liposomes and accelerators of the Fenton reaction ($FeCl_3$, ascorbic acid). The layout of sample preparation is shown in Table 1.

The Fenton reaction had already been generated during sample preparation. After 20 min incubation 0.1 mL of 2% (v/v) ethanol solution of butylated

Table 1. Lay-out of the experiment (TBA assay)

Sample	PBS (mL)	Water (mL)	Solvent[a] (mL)	Extract (mL)	PG (mL)	Liposome (mL)	$FeCl_3$ (mL)	AA (mL)
Blank	0.5	0.3	–	–	–	0.2	–	–
FRM	0.5	–	0.1	–	–	0.2	0.1	0.1
PG	0.5	–	–	–	0.1	0.2	0.1	0.1
E. p.	0.5	–	–	0.1	–	0.2	0.1	0.1
E. p. alone	0.5	0.4	–	0.1	–	–	–	–

[a] 70% (v/v) methanol; PG, propyl gallate; AA, ascorbic acid.
FRM, full reaction mixture; E. p., seven concentrations of *E. parviflorum* extract.

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hydroxytoluene (BHT) was added. BHT is an antioxidant compound, which prevents early unwanted peroxidation of the lipids. 0.5 mL of 1% (w/v) TBA and 0.5 mL of 1% (v/v) hydrochloric acid were then added and the system was heated at 90 °C for 30 min. It was then allowed to cool, leaving thiobarbituric acid to form a red complex with released malondialdehyde. Afterwards the chromogen formed was extracted into 2.5 mL of *n*-butanol. The absorbance of the butanol phase was measured at 532 nm.

The % inhibition of lipid peroxidation can be assessed by comparing the absorbance of full reaction mixture (*FRM*) with that of the extracts (*E*), taking into account the absorbances of blank (*B*) and the extract alone (*Ea*):

$$\text{Inhibition } \% = (FRM - B)(E - Ea - B)/(FRM - B)$$

The inhibition ratio was plotted against concentration in order to determine IC_{50}, the concentration of extracts that achieved 50% of the maximum activity.

***In vitro* test for protection fibroblast cells against free radical induced oxidative damage.** The antioxidant assay described by Murrell *et al.* (1990), Yamasaki *et al.* (1994) and applied by Mensah *et al.* (2001) was used. A prolonged, elevated level of oxygen free radicals can cause oxidative injury to fibroblast cells, which undergo deformation, and indeed may be destroyed. The viability of cultured, human fibroblast cells was measured after pro-oxidant treatment, with hydrogen peroxide, in the absence and presence of *E. parviflorum* extract.

1 mL of dimethyl sulfoxide (DMSO) was added to 80 mg of *E. parviflorum* extract and left overnight to aid the solution in water. Afterwards the extract was dissolved in 100 mL of distilled water. The stock solution was sterilized by filtration through a 0.2 µm membrane. Serial dilutions of extract were prepared by diluting the stock in minimum essential medium (MEM) and then used for the assay. Sterile solutions were prepared freshly for each experiment. Eleventh passage fibroblast cells (143RB cell-line) were trypsinized, centrifuged and resuspended in Dulbecco's modified Eagle's medium (DMEM)/0.5% fetal calf serum (FCS) and diluted in the same mixture to give a standardized suspension of 4×10^4 cells/mL. Fibroblast cells were seeded at a density of 4×10^3 cells/well into 96-well plates, maintained at 37 °C in a humidified incubator of 5% CO_2: 95% air atmosphere and were grown in DMEM/0.5% FCS medium until almost confluent. Based on previous measurements and literature data, 1×10^{-4} M hydrogen peroxide (H_2O_2) was applied as pro-oxidant, suitable to induce recoverable damage on fibroblast cells (4×10^3 cells/well) (Mensah *et al.*, 2001).

Three assay protocols were employed: (1) prior to exposure to H_2O_2, the cells were pretrearted overnight with the extract; (2) extract was added simultaneously with H_2O_2 to the cells; (3) after pretreatment overnight the extract was also added simultaneously with H_2O_2. Five doses of extract were examined in triplicate between 0.185 and 15 µg/mL (final concentration in wells). Cells treated with H_2O_2 only were the negative control, while cells treated with catalase (250 IU/mL), a natural H_2O_2 scavenger enzyme, indicated the positive control of the study. Cells were exposed to pro-oxidant treatment for 4 h, afterwards the neutral red assay was used to assess the protection offered by willow-herb extract (Lee *et al.*, 2000; Babich and Visioli, 2003). Fibroblast cells were also examined visually to observe any damage, such as changes in shape, vacuolization, detachment from wells, caused by the pro-oxidant treatment. The experiment was repeated three times.

COX-inhibition assay (PGE_2 assay). Cyclooxygenase (COX-1 and COX-2) enzymes have a key role in metabolism of arachidonic acid to prostanoid fatty acids, such as prostaglandins (PG), including PGE_2. Increased levels of PGE_2 are associated with several pathological conditions, most notably inflammation. Compounds with COX-inhibitory action can decrease the amount of released PGE_2, thus producing an antiinflammatory effect (Jabbour *et al.*, 2002; Attar and Bulun, 2005).

The assay was carried out on RAW 264.7 macrophage cells, using a PGE_2 assay kit (R&D Systems, UK). Macrophages were stimulated by lipopolysaccharide (LPS, 1 µg/mL/well) to produce PGE_2. The COX inhibition assay applied was based on a competitive binding technique in which PGE_2, released into the medium, competes with a fixed amount of horseradish peroxidase (HRP)-labeled PGE_2 for sites on a mouse monoclonal antibody.

The cytotoxicity of *E. parviflorum* extract was tested in a microplate fluorometric assay using alamarBlue reagent (AbD Serotec, 2007; Nakayama *et al.*, 1997). The extract did not show significant cytotoxic effect on macrophages in the concentration range examined.

E. parviflorum extract was studied for its COX inhibitory effect in the concentration range between 0.45 and 25 µg/mL (final concentration in wells). As a positive control, the effect of a known antiinflammatory agent, indomethacin, was also evaluated. One mL of dimethyl sulfoxide (DMSO) was added to 50 mg of *E. parviflorum* extract and left overnight to aid the solution in water, and then the solution was diluted to 100 mL of distilled water. Stock solution was sterilized by filtration through 0.2 µm membrane. Serial dilutions of extract were prepared by diluting the stock in RPMI 1640 Medium and then used for the assay. Sterile solutions were prepared freshly for each experiment. Seventh passage macrophage cells (RAW 264.7 cell-line) were detached from the culture flask using a cell scaper, resuspended in RPMI 1640 medium and diluted to give a standardized suspension of 1×10^6 cells/mL. RAW 264.7 cells were seeded at a density of 1×10^5 cells/well into 96-well plates, maintained overnight at 37 °C in a humidified incubator of 5% CO_2: 95% air atmosphere. Different doses of extract in triplicate determinations were then added to the culture plates in the presence and absence of LPS. After 24 h of further incubation, the level of PGE_2 in culture supernatants was measured in accordance with the description attached to R&D Systems PGE_2 assay kit (R&D Systems, 2007).

RESULTS AND DISCUSSION

The antioxidant capacity of *E. parviflorum* has been investigated from various angles with three distinct methods. The high radical scavenger activity of willow-herb has been reported before by Steenkamp *et al.* (2006) and Arrodendo *et al.* (2004), however, its protective effect against lipid-peroxidation and oxidative damage on fibroblast cells were not investigated before.

Table 2. Antioxidant capacity of *E. parviflorum* and references

Sample	Equivalency with 10 μM	DPPH
Trolox	992 μg	4 μM
Ascorbic acid	880 μg	5 μM
E. parviflorum	728 μg	(2 μM)[a]

[a] Calculated by the average molecular weight of the extracts components (MW 331.07).

E. parviflorum is rich in phenolic compounds, which due to their redox properties, act as reducing agents, hydrogen donors or singlet oxygen quenchers (Javanmardi *et al.*, 2003). Therefore it was expectable that willow-herb showed a remarkable, concentration-dependent antioxidant activity in DPPH assay (Table 2). Comparing the molar concentration of samples examined, based on the average molecular weight of its main components, willow-herb extract possessed a stronger antioxidant activity than Trolox or ascorbic acid. However, it is necessary to remark that this calculation most probably does not give very accurate results, but it enables a rough estimation to be made and a comparison of scavenging antioxidant effects.

In the TBA assay willow-herb extract showed concentration-dependent inhibition of lipid peroxidation at doses over 0.20 mg/mL (IC_{50} = 2.37 ± 0.12 mg/mL) but at lower concentrations, it seemed to be prooxidant (Fig. 1). It may be presumed that in lower concentrations, while the extracts components react with reagents of the measurement, prooxidant intermediates or end-products release. Hence, the higher concentration of extract that is applied, the stronger antioxidant activity of the components becomes prevalent. The positive control, propyl gallate (10^{-4} M) showed 50% inhibition under the same conditions.

In the concentration range examined, the willow-herb extract exerted protective effect against oxidative damage generated on fibroblast cells (Fig. 2). The

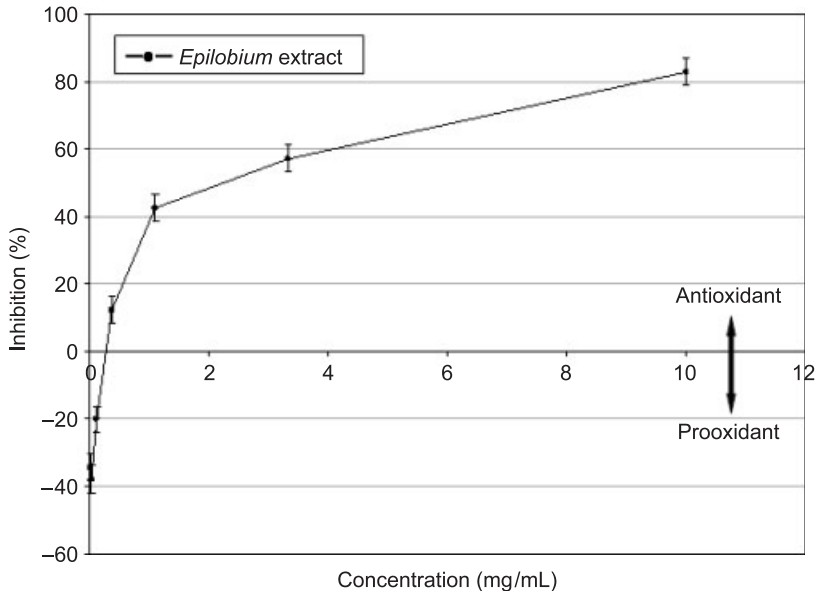

Figure 1. Concentration dependent inhibition (%) of lipid peroxidation exerted by *E. parviflorum* extract. The positive control, propyl gallate (10^{-4} M) showed 50% inhibition under the same conditions.

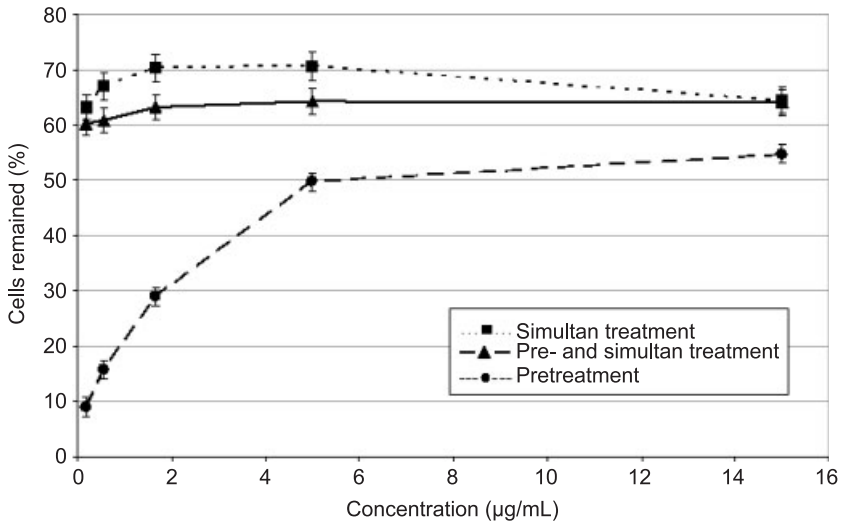

Figure 2. Protection against oxidative damage on fibroblast cells, exerted by *E. parviflorum*, in terms of remained cells (%). Pretreatment: extract alone (overnight); Simultaneous treatment: extract + H_2O_2; Pre- and simultaneous treatment: extract alone (overnight) afterwards extract + H_2O_2; The positive control, catalase (250 IU/mL) protected 64% of cells under the same conditions.

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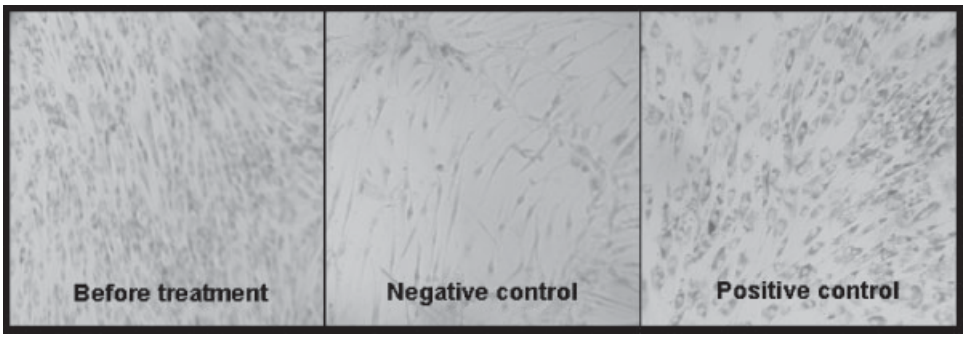

Figure 3. Visual observation of fibroblast cells before and after pro-oxidant treatment. Before treatment: confluent fibroblast cells observed before the treatment. Negative control: cells after a 4 h long exposure to H_2O_2 (10^{-4} M). Positive control: cells treated with catalase (250 IU/mL) and exposed to H_2O_2 (10^{-4} M).

effect was steady and concentration-dependent and the protective action was comparable to that of catalase 250 IU/mL, which protected 64% of the cells under the same conditions. Pretreatment only seemed to be less efficient than simultaneous treatment with extract and peroxide or than pre- and simultaneous treatment together. Visual observations of destruction caused by pro-oxidant treatment, as well as the protective effect of catalase, are presented in Fig. 3.

In the COX-inhibition assay, the positive control indomethacin suppressed the LPS-stimulated PGE_2 release on macrophages (RAW 264.7) with an IC_{50} value of 21 ± 3 μM (n = 4). Under similar experimental conditions *E. parviflorum* extract decreased the PGE_2 release, thus showing concentration-dependent COX-enzyme inhibitory action (IC_{50} = 1.4 ± 0.1 μg/mL), comparable to that of indomethacin.

The results support the findings of Steenkamp *et al.* (2006), namely that, the extract of *E. parviflorum* possesses a COX-enzyme inhibitory effect, however the selectivity between the two isoenzymes could not be determined. The willow-herb extract showed inhibition of COX-enzymes in a scale lower concentration range than reported, with respect to the ethanol extract examined by Steenkamp *et al.* (2006). Based on our previous analytical experience with *E. parviflorum* it can be stated that the occurence of significant differences between the composition of ethanol and acetone (80% (*v/v*)) extracts is highly improbable, henceforth, the inequality between the results is very likely due to the use of distinct examination methods.

These results suggest that the extract of *E. parviflorum* possesses antioxidant and antiinflammatory properties which are likely to contribute to its beneficial effect in BPH.

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Lycopene

View 3983 Products Containing: Lycopene

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View 176 Canadian Licensed Products Containing: Lycopene

Scientific Name

All-Trans Lycopene; Psi-Psi-Carotene, (6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-octamethyldotriaconta-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene.

Background

Lycopene is an unsaturated hydrocarbon carotenoid similar in structure to beta-carotene, but without provitamin A activity (7896). It is a fat-soluble red pigment synthesized by plants and microorganisms and is found in foods such as tomatoes, guava, pink grapefruit, red oranges, apricots, rosehips, and water melon (7896,60484,60523,92173). In the US, more than 80% of dietary lycopene comes from tomatoes and processed tomato products including sauces, juice, ketchup, paste, and soups (92173). A 130 gram serving of fresh tomatoes contains between 4 mg and 10 mg of lycopene, depending on variety, growing conditions, and ripeness (92175). Spaghetti sauce contains about 22 mg lycopene per 125 gram serving, ketchup contains 3.3 mg per tablespoon, and tomato juice contains about 20 mg per 240 mL serving (92175).

Also known as: All-Trans Lycopène, Cis-Lycopène, Licopeno, Lycopène, Lycopenes, Lycopènes, Psi-Psi-Carotène.

History

People Use This For

Orally, lycopene is used for preventing atherosclerosis, cardiovascular disease, cancer, cataracts, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), age-related macular degeneration (AMD), Parkinson's disease, and sunburn. Lycopene is also used for treating prostate cancer, benign prostatic hyperplasia (BPH), prostatitis, male infertility, human papilloma virus (HPV) infection, Helicobacter pylori, asthma, hypertension, hyperlipidemia, congestive heart failure (CHF), gingivitis, oral submucous fibrosis, polymorphous light eruption, pre-eclampsia, and menopausal symptoms.

Safety

LIKELY SAFE ...when used orally and appropriately in amounts commonly found in foods (2406,7772,7773). Lycopene supplements have been used safely in doses of 15 mg to 45 mg daily for 4 to 6 months (60389,60399,60482). Some limited evidence suggests that 120 mg daily is safe for up to one year (60372).

PREGNANCY: **LIKELY SAFE** ...when consumed in amounts commonly found in foods. **POSSIBLY UNSAFE** ... when taken as a supplement during pregnancy. Data are conflicting. In one study, taking a specific oral lycopene supplement (LycoRed, Jagsonpal Pharmaceuticals, India) 2 mg orally daily, starting between weeks 12 and 20 of pregnancy and continuing until delivery, was associated with an increase in rates of preterm labor and low birth weight (60428). However, in another study, taking 2 mg of the same product orally twice daily, starting between weeks 16 and 20 of pregnancy and continuing until delivery, appeared to be safe (60337).

LACTATION: **LIKELY SAFE** ...when consumed in amounts commonly found in foods. There is insufficient reliable information available about the safety of lycopene supplements used during lactation; avoid using in amounts greater than those typically found in foods.

Effectiveness

See detailed evidence summary

POSSIBLY INEFFECTIVE

Bladder cancer. Epidemiological research and population studies have not established a link between dietary intake of lycopene or lycopene serum levels and the risk of bladder cancer (2407,60411,60496,60533).

Diabetes. Population research suggests that increasing intake of dietary lycopene does not significantly decrease the risk of developing type 2 diabetes (14004,14361).

Parkinson's disease. A meta-analysis of epidemiological studies suggests that there is no link between dietary intake or blood levels of carotenoids, including lycopene, and the risk of developing Parkinson's disease (91164).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Age-related macular degeneration (AMD). Epidemiological evidence on the role of lycopene in age-related maculopathy, the precursor of AMD, is contradictory. Some evidence suggests that people with serum levels of lycopene in the lowest quintile are almost twice as likely to develop age-related maculopathy as those with levels in the highest quintile (6110). However, other population studies found no association between lycopene serum levels or dietary lycopene intake and the risk of developing age-related maculopathy (5922,10902,14007,60585).

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). A pooled analysis of population research suggests that people in the highest quintile of total dietary carotenoid intake have a 25% lower risk of ALS than those in the lowest quintile. However, no association was found for lycopene intake alone (90412).

Asthma. Some preliminary clinical research shows that taking a specific tomato extract product (Lyc-O-Mato, LycoRed Natural Products Industries, Ltd.) providing lycopene 15 mg three times daily orally for up to 14 weeks does not reduce asthma exacerbations when compared with

placebo in adults with stable asthma (60482).

In patients with exercise-induced asthma or bronchoconstriction, however, research on the effects of lycopene is conflicting. In one clinical trial, taking this same tomato extract product providing lycopene 30 mg daily for 1 week seems to improve post-exercise lung function, but not FEV1, in some children and adults with a history of exercise-induced asthma exacerbations (7898). However, in adolescent athletes without asthma, but with a history of exercise-induced bronchoconstriction, taking the same product and dose for 1 week did not improve post-exercise lung function (60358). The authors state that the study was likely underpowered to detect a difference in the FEV1 reduction, and the intensity of the exercise challenge may need to be higher for trained athletes.

Atherosclerosis. There is epidemiological evidence that higher serum lycopene levels are associated with a lesser degree of aortic or carotid atherosclerosis (1446,60329,60463). There is also preliminary evidence that higher serum lycopene levels are associated with a lower risk of coronary heart disease and myocardial infarction in people with atherosclerosis (7897,60538). However, there does not seem to be a link between serum lycopene levels and the risk of ischemic stroke (1449).

Benign prostatic hyperplasia (BPH). While some epidemiological evidence shows no link between dietary lycopene intake and the development of BPH (60365), some preliminary clinical research suggests that taking lycopene alone or as a combination product might improve BPH-related symptoms (60374,60399,92164,90354). One preliminary clinical study shows that taking lycopene (LycoVit powder, BASF) 15 mg daily for 6 months slows the progression of BPH and improves symptom scores compared to baseline (60399). Consuming 50 grams of tomato paste daily for 10 weeks decreased prostate specific antigen (PSA) levels by about 11% in patients with BPH in another study (60374). Additional clinical research shows that taking a combination of lycopene 2.1 mg, pumpkin seed oil 160 mg, small-flowered willow herb 500 mg, pygeum 15 grams, and saw palmetto 660 mg (ProstateEZE Max, Caruso's Natural Health) once daily for 3 months reduces the international prostate specific score (IPSS) by 36% compared to 8% with placebo in patients with BPH (92164). In another study, taking a combination of lycopene 5 mg, saw palmetto 320 mg and selenium 50 mcg (Profluss, KonPharma) orally daily for 1 year produced similar IPSS reductions compared to tamsulosin 0.4 mg daily. Taking both the combination supplement and tamsulosin reduced IPSS to a larger degree than either treatment alone (90354).

Breast cancer. There is contradictory evidence about the role of lycopene in breast cancer. Some epidemiological evidence suggests that higher levels of lycopene in the blood and breast adipose tissue are associated with reduced breast cancer risk (10132,34634,60549,60555). However, other epidemiological research shows that neither dietary lycopene intake nor lycopene serum levels are associated with breast cancer risk (10823,15751,60344,60468,60541). Also, some population research suggests that there is a possible relationship between low serum lycopene levels and an increased risk of breast cancer in African American women, but not in Caucasians (60325).

Cardiovascular disease. Some epidemiological research found that higher serum levels of lycopene are associated with a reduced risk of cardiovascular disease, including coronary heart disease and myocardial infarction (7897,15749,60538). However, other epidemiologic research found no association between dietary lycopene intake and the risk of myocardial infarction, stroke, and other cardiovascular events in women or men at low risk for heart disease (9594,10418).

Evidence from intervention trials shows that lycopene does not significantly improve most risk

factors for cardiovascular disease. An analysis of clinical research shows that taking lycopene 4-30 mg orally daily along with usual diet does not improve diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, endothelial function, or inflammatory factors compared to usual diet alone in healthy patients; however, lycopene supplementation seems to reduce systolic blood pressure by about 6 mmHg (95777). It is unclear if lycopene supplementation reduces the risk of cardiovascular events such as myocardial infarction or stroke.

Cataracts. One epidemiological study suggests that serum lycopene levels are inversely associated with the risk of developing cataracts (60203). However other population studies have found no association between lycopene serum levels or dietary intake of lycopene and the development of cataracts (3219,3220,60299).

Cervical cancer. There is contradictory evidence about the effect of lycopene on cervical cancer risk. Some epidemiological evidence suggests that higher serum levels or dietary lycopene intake are associated with a reduced risk of cervical intraepithelial neoplasia and invasive cervical cancer (60429,60430,60439,60566). Other studies have not shown this association (60388,60517,60521).

Colorectal cancer. There is contradictory evidence about the role of lycopene in colorectal cancer. Some population research suggests that people in the highest tertile of dietary lycopene intake are half as likely to develop colorectal cancer as those in the lowest tertile (2407,38845). However, other epidemiological research shows no association between dietary lycopene intake and the risk of colorectal cancer, regardless of smoking status, drinking status, geographical location, gender, and tumor location (3962,34542,95778).

Esophageal cancer. A pooled analysis of population research found that high dietary intake of lycopene is associated with a 25% reduced odds of developing esophageal squamous cell carcinoma compared to low dietary intake of lycopene (91159).

Exercise-induced muscle damage. Preliminary clinical research in adult long-distance runners shows that taking a combination of lycopene, other carotenoids, folic acid, tocopherols, and rosemary extract orally once daily for 4 weeks reduces muscle damage associated with a 2-hour run when compared with placebo (98825).

Glioma. Preliminary clinical research shows that taking lycopene 8 mg orally daily for 3 months does not improve the response to radiotherapy and paclitaxel in people with glioblastoma multiforme or anaplastic astrocytoma (60441).

Helicobacter pylori (H pylori). Preliminary clinical research shows that adding lycopene 30 mg orally daily for one month to a combination of metronidazole, amoxicillin, omeprazole, and bismuth does not significantly increase the rate of H. pylori elimination compared to the combination drug therapy alone (60480).

Human papilloma virus (HPV). Epidemiological research suggests that women with higher plasma levels of lycopene have a faster rate of oncogenic HPV clearance compared to women with lower levels of plasma lycopene. Women with higher levels of lycopene cleared oncogenic HPV in an average of 8.5 months compared to 11-12 months in women with lower levels (12177).

Hyperlipidemia. Preliminary clinical research shows that taking a specific oral lycopene supplement (LycoRed, Jagsonpal Pharmaceuticals, India) 4 mg daily for 6 months reduces total cholesterol by 24% and low-density lipoprotein (LDL) cholesterol by 15% and increases high-density lipoprotein (HDL) cholesterol by 26% compared to baseline in postmenopausal women

(60371). In other studies, increased lycopene intake in the form of tomatoes and increased lycopene serum levels were associated with decreases in LDL cholesterol and triglycerides and increases in HDL cholesterol (60390,60391) However, contradictory evidence exists. In some studies, increased lycopene intake as watermelon or tomato juice did not have any effect on lipid levels in healthy adults (60352) or in people with heart disease (60386).

Hypertension. While preliminary epidemiological evidence shows no link between serum lycopene levels and development of hypertension (60419), some clinical research shows that lycopene can improve blood pressure in patients with hypertension (14287,60415). Taking lycopene 15 mg daily for 6-8 weeks, as a specific tomato extract product (Lyc-O-Mato, LycoRed Natural Products Industries, Ltd.), seems to reduce systolic blood pressure by 10-13.5 mmHg and diastolic blood pressure by 4-6 mmHg when compared to baseline in patients with hypertension (14287,60415). The validity of this finding is limited by the lack of a control group. Furthermore, this lycopene product did not improve blood pressure in patients with pre-hypertension (42079).

Lung cancer. There is contradictory evidence about the role of lycopene in lung cancer. Some epidemiological research has shown that lower dietary lycopene intake or serum levels are linked to an increased risk of lung cancer (2595,60332,60363,60550). In male smokers, for instance, some research shows that high dietary intake of lycopene is associated with a 28% decreased risk of lung cancer compared to low intake of lycopene (60332). Some research in women shows that high dietary intake of lycopene is associated with a 55% decreased risk of lung cancer compared to low intake of lycopene (60550). However, other epidemiological research has found no link between dietary intake of lycopene and the risk of lung cancer (60316,60520,60522), or between serum levels of lycopene and the risk of lung cancer (60554).

Male infertility. Preliminary clinical research shows that taking lycopene 2 mg orally twice daily for 3 months improves sperm concentration, motility, and morphology in some men with idiopathic infertility (60340).

Menopausal symptoms. Preliminary clinical research shows that taking a specific oral combination of lycopene with calcium, vitamin D3, astaxanthin, and citrus bioflavonoids (Cor.Con. International) daily for 8 weeks reduces hot flashes, incontinence, joint pain, anxiety, and depression when compared with no treatment in women with menopause symptoms (19198).

Oral leukoplakia.Preliminary clinical research shows that taking a specific lycopene supplement (LycoRed, Jagsonpal Pharmaceuticals) 2 mg to 4 mg orally twice daily for 3 months improves clinical and histological signs of oral leukoplakia in a dose-dependent manner when compared with placebo (15748).

Oral submucous fibrosis. Preliminary clinical research shows that taking a specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals), providing lycopene 8 mg orally twice daily for 2 months, or 4 mg orally daily for 3 months, improves measures of mouth opening when compared with placebo in men with oral submucous fibrosis associated with a history of chewing betel nuts. The average increase in mouth-opening with lycopene was 3.5 mm, compared to no change with placebo (60381,98823). In one study, taking lycopene eliminated the burning sensation in the mouth that is associated with this condition (98823).

Ovarian cancer. There is contradictory evidence about the role of lycopene in ovarian cancer risk. Some epidemiological evidence shows that a diet rich in carotenoids, including lycopene, is associated with a decreased risk of ovarian cancer in premenopausal women (10133). However, other epidemiological research shows that the risk of developing ovarian cancer is not linked to serum levels of lycopene (60534), or the level of dietary lycopene intake (60373).

Pancreatic cancer. Preliminary epidemiological research shows that high dietary intake of lycopene is associated with a reduced risk of pancreatic cancer. Intake in the highest quartile was associated with a 31% reduction in risk compared with the lowest quartile in one study (15750).

Periodontal disease. Preliminary clinical research shows that taking a specific oral lycopene supplement (LycoRed, Jagsonpal Pharmaceuticals) 8 mg daily for 2 weeks, or receiving a single injection of lycopene gel 2 mg into the gums reduces gingivitis (60400,60473). However, using a combination product (Lycotas, Intas Pharmaceuticals) containing lycopene 2 mg, vitamin C 50 mg, vitamin A 2500 units, zinc sulfate 20.6 mg, and chromium picolinate 75 mcg orally twice daily for 2 weeks does not improve moderate gingivitis or mild to moderate periodontitis when compared with placebo in people who have also undergone scaling and root planning (92172).

Polymorphous light eruption (PMLE). Preliminary clinical research shows that taking a combination of lycopene 2.5 mg, beta-carotene 4.7 mg, and Lactobacillus johnsonii 500 million CFU (Inneov Sun Sensitivity, Laboratoires Innéov) daily for 12 weeks reduces skin lesion severity after a single exposure to light when compared with placebo in patients with polymorphous light eruption (90276). It is not clear if this effect is due to lycopene, other ingredients, or the combination.

Pre-eclampsia. Evidence on the use of lycopene to prevent pre-eclampsia is conflicting. Some clinical research shows that healthy primigravidae who take a specific oral lycopene supplement (LycoRed, Jagsonpal Pharmaceuticals) 2 mg twice daily, starting between weeks 16 and 20 of pregnancy and continuing until delivery, have lower mean diastolic blood pressure and a reduced incidence of pre-eclampsia, intra-uterine growth retardation, and preterm labor when compared with placebo (60337). However, taking this same lycopene supplement once daily does not reduce the incidence of pre-eclampsia when compared with placebo; furthermore, the rates of preterm labor and low birth weight seem to increase (60428).

Prostate cancer. Epidemiological evidence on the role of lycopene for preventing prostate cancer is contradictory. Some research suggests that increased dietary lycopene intake from tomatoes and tomato products, or higher serum levels of lycopene, are associated with a lower risk of developing prostate cancer (1447,1496,2405,2406,7772,7773,7895,12878,60304,60448,98824). A meta-analysis of 42 studies shows that the risk of developing prostate cancer decreases by 1% for each additional 2 mg of daily dietary lycopene intake, and decreases by 3.5% for each 10 mcg/dL increase in the circulating lycopene level (98824). However, other epidemiological studies show no association between dietary lycopene intake or serum lycopene levels and prostate cancer risk (4777,14125,34635,60334,60449,60457,60547,92171), although in one of these studies, dietary lycopene intake was associated with a lower risk in a subgroup of men with a family history of prostate cancer (14125).

Some research has evaluated lycopene for delaying the progression to prostate cancer. Preliminary clinical research in men with high-grade prostate intraepithelial neoplasia shows that taking oral lycopene supplements 4 mg twice daily for one year might delay or prevent progression to prostate cancer (14126). Other preliminary clinical research shows that taking a specific oral tomato extract product (Lyc-O-Mato, LycoRed Natural Products Industries, Ltd.), 30 mg daily for 4 months reduces serum prostate specific antigen (PSA) levels after one month in men at high risk for developing prostate cancer; however, PSA levels seem to return to baseline by 4 months. Furthermore, a similar effect was observed in this study for patients treated with placebo, indicating that this temporary effect is not specific to lycopene (60389).

The evidence on the use of lycopene for treating prostate cancer is conflicting. Taking lycopene

orally 30 mg daily for 3 weeks prior to radical prostatectomy for localized cancer increases serum and prostate lycopene levels and seems to slow tumor growth (7771,60328). In men with relapsed, metastatic prostate cancer, taking lycopene orally 10 mg to 30 mg daily, or tomato products providing a mean of 43 mg of lycopene per day, for 3-6 months stabilizes PSA levels in 29% to 95% of cases (7774,60353,60361,60397,60403,60417). However in other studies, taking lycopene 15 mg to 120 mg daily for up to one year does not seem to affect PSA levels (60372,60384). Other clinical research in men post-orchiectomy for metastatic prostate cancer shows that taking lycopene 2 mg orally twice daily for 6 months increases the rate of normalization of PSA levels from 40% to 78% and reduces death rates from 22% to 13% when compared with placebo (60342).

Prostatitis. Preliminary clinical research shows that a specific combination of lycopene 5 mg with selenium 50 mcg and saw palmetto 320 mg (Profluss, KonPharma), taken orally for 8 weeks, reduces pain scores in men with prostatitis and chronic pelvic pain syndrome by 52% compared to a 26% reduction with saw palmetto alone (60442). It is not clear if this effect is due to lycopene, the other ingredients, or the combination.

Renal cell carcinoma. Preliminary clinical research shows no association between dietary lycopene intake and the risk of developing renal cell cancer (60379).

Sunburn. Preliminary clinical research shows that taking lycopene 10 mg to 16 mg orally daily for 12 weeks, in the form of tomato paste or a tomato extract (Lyc-O-Mato), may provide some protection against sunburn (23012,60324,60452).

More evidence is needed to rate lycopene for these uses.

Dosing & Administration

- Adult

  Oral:

  Asthma: To prevent exercise-induced asthma, a specific tomato extract (Lyc-O-Mato, LycoRed Natural Product Industries Ltd.) providing lycopene 30 mg daily for one week has been used (7898).

  Benign prostatic hyperplasia (BPH): Lycopene (LycoVit powder, BASF) 15 mg daily for 6 months has been used (60399). A combination of lycopene 2.1 mg, pumpkin seed oil 160 mg, small-flowered willow herb 500 mg, pygeum 15 grams, and saw palmetto 660 mg (ProstateEZE Max, Caruso's Natural Health) once daily for 3 months has been used (92164). A combination of lycopene 5 mg, saw palmetto 320 mg and selenium 50 mcg (Profluss, KonPharma) daily for 1 year has been used (90354).

  Exercise-induced muscle damage: A combination product (Lycored Ltd.) containing lycopene 5 mg, other carotenoids 4 mg, folic acid 0.1 mg, tocopherols 4 mg, and rosemary extract once daily for 4 weeks has been used (98825).

  Hyperlipidemia: A specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals, India) providing lycopene 4 mg daily for 6 months has been used (60371).

  Hypertension: A specific tomato extract (Lyc-O-Mato, LycoRed Natural Products

Industries, Ltd.) providing lycopene 15 mg daily has been used for 6 weeks to 8 weeks (14287,60415).

Male infertility: Lycopene 2 mg twice daily for 3 months has been used (60340).

Oral leukoplakia: A specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals) providing lycopene 2 mg to 4 mg twice daily for 3 months has been used (15748).

Oral submucous fibrosis: A specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals), providing lycopene 8 mg orally twice daily for 2 months has been used (60381). A lower dose of the same product, 4 mg orally daily for 3 months, has also been used (98823).

Periodontal disease: A specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals) providing lycopene 8 mg daily for 2 weeks has been used for gingivitis (60400).

Polymorphous light eruption: A combination of lycopene 2.5 mg, beta-carotene 4.7 mg, and Lactobacillus johnsonii 500 million CFU (Inneov Sun Sensitivity, Laboratoires Innéov) has been used daily for 12 weeks (90276).

Pre-eclampsia: A specific tomato extract (LycoRed, Jagsonpal Pharmaceuticals) providing lycopene 2 mg twice daily has been used starting between week 12 and week 20 of pregnancy and continuing until delivery (60337,60428).

Prostate cancer: For preventing progression of high-grade prostate intraepithelial neoplasia to cancer, a specific tomato extract (Lyc-O-Mato, LycoRed Natural Product Industries Ltd.) providing lycopene 4 mg has been used twice daily for 1 year (14126). For treating prostate cancer, specific tomato extract products (LycoRed, Jagsonpal Pharmaceuticals; Lyc-O-Mato, LycoRed Natural Product Industries Ltd.) providing lycopene 10 mg to 30 mg daily as a single dose or divided twice daily for between 3 weeks and 6 months have been used (7771,60353,60397,60458). Lycopene (Puritans Pride) 15 mg daily for 6 months has been used (60417). Lycopene 30 mg daily from tomato pasta sauce products has also been used for 3 weeks prior to prostate cancer surgery (60328).

Prostatitis and chronic pelvic pain syndrome: A specific combination of lycopene 5 mg with selenium 50 mcg and saw palmetto 320 mg (Profluss, KonPharma), has been used for 8 weeks (60442).

Sunburn: Lycopene 10 mg to 16 mg daily for 12 weeks in the form of tomato paste or a tomato extract (Lyc-O-Mato, LycoRed Natural Product Industries, Ltd.) has been used (23012,60324,60452).

Injection:

Periodontal disease: Lycopene 2 mg in a gel formulation has been injected into the gums (60473).

- Standardization & Formulation

There is insufficient reliable information available about the standardization of lycopene.

Adverse Effects

Report an Adverse Reaction to Lycopene

General: Lycopene supplements are generally well tolerated, with the most common adverse effects being mild gastrointestinal complaints (60372,60384,60417,60433,60464).

- ⊞ Dermatologic
- ⊞ Gastrointestinal
- ⊞ Cardiovascular

Toxicology

Insufficient information available.

Interactions with Drugs

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **D**

Lycopene has antiplatelet effects in-vitro (60360,60375,92177). Theoretically, taking lycopene supplements with anticoagulant or antiplatelet drugs might increase the risk of bruising and bleeding.

Some of these drugs include aspirin; clopidogrel (Plavix); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), and naproxen (Anaprox, Naprosyn, others); dalteparin (Fragmin); enoxaparin (Lovenox); heparin; warfarin (Coumadin); and others.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Lycopene has antiplatelet effects in vitro (60360,60375,92177). Theoretically, concomitant use of lycopene supplements with herbs that have anticoagulant or antiplatelet activity could increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, feverfew, garlic, ginger, ginkgo, ginseng Panax, horse chestnut, red clover, turmeric, and others.

BETA-CAROTENE: There is some evidence that taking beta-carotene supplements 20-60 mg daily increases the absorption of lycopene from supplements and from the diet (2403,23015). However, other studies have reported that beta-carotene supplements have no effect on lycopene serum levels (23017,23018), or that they decrease lycopene serum levels (23016). These differences may be due to other factors affecting absorption, such as whether the supplements

were taken with or between meals, and how much fat was present, which increases absorption (94226).

CALCIUM: Calcium supplements can decrease the absorption of dietary lycopene. One small clinical study shows that taking a specific calcium carbonate supplement (Cacit 500, Warner Chilcott) 500 mg while eating a meal containing 19 mg of lycopene reduces the bioavailability of lycopene by 83% compared to only eating the meal containing lycopene 19 mg. The mechanism of this effect is not known; however, it is suspected that calcium inhibits the uptake of lycopene in the gastrointestinal tract (95578).

LUTEIN: There is some evidence that taking a single 24 mg oral dose of lutein decreases the absorption of lycopene from supplements and from the diet, possibly due to competition for transport in chylomicrons. However, taking lutein 12 mg orally daily for 3 weeks does not affect plasma levels of lycopene (92165,94227).

Interactions with Foods

OLESTRA (fat substitute): Olestra may interfere with lycopene absorption. Olestra lowers serum lycopene levels in healthy people by around 30% (23019). If consuming both olestra and lycopene, separate them by several hours.

Interactions with Lab Tests

None known.

Interactions with Diseases

SURGERY: Lycopene has antiplatelet effects in-vitro (60360,60375,92177). Lycopene supplements might cause excessive bleeding if used perioperatively. Tell patients to discontinue lycopene supplements at least 2 weeks before elective surgical procedures.

Mechanism of Action

General: Lycopene is a carotenoid, but it is not a precursor of vitamin A. It is synthesized by plants and microorganisms and is found in foods such as tomatoes, guava, pink grapefruit, red oranges, apricots, rosehips, and water melon (7896,60484,60523,92173). Concentrations of lycopene are often higher in processed versions of these foods due to water loss. For example, fresh tomatoes contain from 0.88 mg to 7.74 mg per 100 grams, while ketchup contains from 9.9 mg to 13.44 mg per 100 grams (92165). Daily dietary lycopene intake varies from about 1 mg/day to 10.5 mg/day (92165). Lycopene from plants is primarily in the all-trans configuration which is poorly absorbed, but its high degree of unsaturation allows cis-trans isomerization to occur in response to light, thermal energy, and chemical reactions (1928,92173). In human plasma, lycopene is present as an isomeric mixture, with 50% as cis-isomers (92173,92175). Lycopene makes up about half of the carotenoids in human serum, concentrating in the low-density and very-low-density lipoprotein fractions. It also concentrates in the adrenal gland, testes, prostate,

lungs, and skin (60488,60536,92173).

Anti-inflammatory effects: Early clinical research shows that taking lycopene in the form of V8 low-sodium 100% vegetable juice (Campbell Soup Co.) daily for 30 days decreases C-reactive protein (CRP) levels by 1.4 mg/dL in women, but not in men, with congestive heart failure. The clinical significance of this finding is unclear (92170).

Antineoplastic effects: Lycopene has antioxidant effects and might reduce cancer risk by scavenging free radicals and quenching singlet oxygen, which prevent oxidative damage to DNA (2401,7773). Lycopene is also thought to suppress carcinogen-induced phosphorylation of regulatory proteins, such as p53 and Rb antioncogenes, and to stop cell division at the G0-G1 cell cycle phase (60303,92173). Lycopene may be protective against carcinogen-induced pre-neoplastic lesions in rat liver by acting on cytochrome P450-2E1 (92173). It also reduces cellular proliferation induced by insulin-like growth factors (60486,60579,92173).

Antiplatelet effects: Lycopene and a tomato extract containing lycopene inhibit platelet activation, including that induced by adenosine diphosphate (ADP) and collagen, in vitro (60360,60375,92177). Suggested mechanisms include inhibition of thromboxane B2 formation, and activation of formation of cyclic GMP and nitrate in platelets (60360).

Lipid-lowering effects: Lycopene's cholesterol-lowering effects may be due to inhibition of macrophage hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (60543,92173) and enhancement of LDL degradation and removal from the circulation (7896,60543).

Sunburn prevention: Lycopene may help prevent UV light-induced skin damage by scavenging reactive oxygen species and absorbing UVA and UVB wavelengths (60487). The lycopene molecule is changed by these processes, resulting in reduced skin lycopene levels (60510).

Pharmacokinetics

Absorption: Lycopene absorption from tomatoes increases when they are cooked, and when they are ingested with fat (1497,2401,7896,60311,60573,92165). Heating and other processing releases lycopene from the food matrix and induces trans- to cis-isomerization of the molecule, which is found primarily in the all-trans configuration in plants (7896,60311,60530,60561,60562,92173). Over half of the total lycopene in human serum is in the form of cis-isomers, suggesting they are more bioavailable (1497,7896,60311,60382,60385,92175).

Lycopene is fat soluble and is incorporated into micelles containing bile salts, cholesterol, and fatty acids in the intestine. These are carried to the intestinal wall, where lycopene is absorbed into the enterocytes by passive diffusion or with the aid of a cholesterol membrane transporter (92165,92175). In the enterocytes, lycopene is packaged into chylomicrons with other lipids, then transported in the lymphatic system before release into the blood (92165).

In healthy volunteers, peak serum concentrations of lycopene were reached 4 hours to 6 hours after ingestion of lycopene 38 mg in a capsule formulation (Makhleshim, Beer-Sheva, Israel) with a meal (60559). After ingesting raw tomatoes or tomato puree containing approximately 16.5 mg of lycopene, serum levels peaked at 6 hours to 12 hours (60573).

Distribution: Average plasma lycopene levels are reported to be 0.22 to 1.06 mcM/L (60518,60536). Levels are inversely correlated with age, with the lowest levels found in patients over 80 years of age (60509,60527,60552).

Lycopene is transported in the blood primarily by low-density lipoproteins (LDL) (39733,60530).

Lycopene is found in high concentrations in the adrenal glands, testes, liver, and prostate, and in lower concentrations in the kidneys, lungs, and ovaries (60394,60534,60539,60562,92175).

Lycopene isomers have been isolated from human breast milk (60542,92175). In one report, levels were 10% of serum concentrations (60558).

Metabolism: Information on the metabolism on lycopene is limited, but it is thought to undergo oxidation and enzymatic cleavage (60488,60526,92175).

Elimination: The half-life of lycopene in adult females fed controlled diets for 10 weeks was determined to be 26 days, and lycopene was eliminated by first-order kinetics (34467). In another study, the half-life of elimination in six adults ingesting processed tomato juice was determined to be 2 days to 3 days (60345). The large discrepancy between these results warrants additional research.

Classifications

Antiplatelet Agents, Carotenoids

References

See Monograph References

This monograph was last reviewed on 3/15/2019 and last updated on 9/3/2019. Monographs are reviewed at least once per year. If you have comments or suggestions on something that should be reviewed or included, please tell the editors. For details about our evidence-based approach, see our Editorial Principles and Process.

Pygeum Download PDF

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Historical Note

Pygeum africanum is a large, evergreen tree native to Africa. Its bark has been used medicinally for thousands of years by traditional African healers to treat bladder disorders, kidney disease, prostate disorders and malaria, as well as male baldness, and to enhance sexual functioning. Since the late 1960s, the extract has been used in clinical practice in Europe; however, because of overharvesting, the plant is now considered an endangered species and efforts are under way to protect it.

CLINICAL NOTE — POPULAR TO THE POINT OF EXTINCTION?

For the past 35 years, pygeum has been used in Europe for the treatment of benign prostatic hyperplasia (BPH) and other disorders. The bark is entirely wild-collected, mainly from Cameroon, Madagascar, Equatorial Guinea and Kenya, and exported principally to Europe for production into commercial medicinal extracts (Stewart 2003). Since 1995, it has been considered an endangered species, so attempts at cultivation are under way to protect the plant from extinction. Prior to 1966, when it was discovered to have significant medicinal effects, *P. africana* was a relatively common, but never abundant, species. The reasons for its demise include economic, social and ecological factors. Currently, wildcrafting is no longer commercially viable in Cameroon, and harvest has ceased in both Uganda and Kenya.

Common Name

Pygeum

Other Names

African plum tree, African prune tree, *Pygeum africanum* , alumty, iluo, kirah, Natal tree, Pignil, Pronitol, Tanaden

Botanical Name/Family

Prunus africana (Hook. f.) KalRm (family Rosaceae)

Plant Part Used

Bark

Chemical Components

Phytosterols (beta-sitosterol, beta-sitostenone), pentacyclic triterpenes (oleanolic and ursolic acids) and ferulic esters (*n* -docosanol and *n* -tetracosanol) (Stewart

2003), atraric acid (AA) and *N* -butylbenzene sulfonamide (NBBS) (Daniela & Baniahmad 2011 , Papaioannou et al 2010).

Main Actions

Pygeum has demonstrated several different pharmacological effects according to in vitro and in vivo data. The majority of initial studies conducted on *P. africanum* were investigating its role in the symptomatic relief of BPH. More recent research is seeking to elucidate pygeum's pharmacological capacity in the modulation and restoration of bladder function, androgen receptor modification and attenuating prostatic cancer cell line replication.

Hormonal effects

In vivo studies have shown that orally administered pygeum extract has a significant effect on dihydrotestosterone (DHT)-induced prostatic enlargement (Choo et al 2000 , Yoshimura et al 2003). Pretreatment with pygeum extract counteracted the effect of DHT-induced prostate enlargement (Choo et al 2000), and the more recent study found that oral administration of pygeum extract suppressed the effects of DHT on micturition (Yoshimura et al 2003) and effectively suppressed prostatic growth when coadministered with DHT; however, it did not reverse established prostatic growth when administered after DHT. A comparative study found that pygeum exerted only a weak inhibition of 5-alpha reductase compared to that of finasteride (Rhodes et al 1993). Phyto-oestrogens isolated in pygeum can exert a dose-dependent oestrogenic or antioestrogenic effect, according to other in vivo tests (Mathe et al 1995), and may also contribute to its effects in the prostate.

Antiandrogenic

Recent in vitro investigations have confirmed the antiandrogenic activity of pygeum. When compared to *Serenoa repens* and *Cucurbita pepo* , pygeum exhibited the highest androgen antagonistic activity (Schleich et al 2006). AA and NBBS, isolated from pygeum, has been shown to selectively competitively inhibit transactivation-mediated ligand-activated human androgen receptor, inhibiting the expression of endogenous prostate-specific antigen. Its effects have proved more potent than currently used clinical antiandrogens such as flutamide and do not display the molecular mechanisms of current antiandrogens associated with resistance. Therefore not only might AA and NBBS be useful novel antiandrogens, but they may also increase the effectiveness of current treatments (Daniela & Baniahmad 2011 , Papaioannou et al 2010 , Quiles et al 2010).

Anti-inflammatory

Phytosterols (beta-sitosterol, beta-sitostenone) reportedly inhibit the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms associated with BPH and chronic prostatitis. The pentacyclic triterpenes (oleanolic and ursolic acids) are believed to inhibit the activity of glucosyltransferase, an enzyme involved in the inflammation process (Stewart 2003).

Studies with pygeum extract confirm that it decreases production of leukotrienes and other 5-lipoxygenase metabolites (Cristoni et al 2000).

Bladder effects

Pygeum protects the bladder from contractile dysfunction induced by ischaemia and reperfusion according to in vivo animal studies (Chen et al 1999). Pretreatment with pygeum prior to induced partial outlet obstruction in animal models prevents the development of contractile dysfunction, possibly by protecting the bladder from ischaemic injury (Levin et al 2005). Administration of pygeum was found to reverse already ischaemic compromised bladder function in a dose-dependent manner (Levin et al 2002).

Inhibition of fibroblast proliferation and apoptosis

Pygeum is a potent inhibitor of prostatic growth factor-mediated fibroblast proliferation, as demonstrated in animal models (Szolnoki et al 2001 , Yablonsky et al 1997). A dose-dependent inhibition of fibroblastic growth was exerted in human stromal cells treated with pygeum extract (Boulbes et al 2006).

Further study comparing cell lines harvested from prostatic tissue with or without BPH and treated with pygeum extract demonstrated apoptosis via alpha-smooth-muscle actin, found in greater amounts in those with BPH. Transforming growth factor-beta $_1$ and fibroblast growth factor 2 were both downregulated. Smooth-muscle tissue was unaffected (Quiles et al 2010).

Chemopreventive

Recent investigations have focused primarily upon *P. africanum* regulation of cancer cell growth in vitro and in vivo. Treatment with pygeum extract exhibited a significant and dose-dependent inhibition of human prostate cancer cell lines and BPH-derived epithelial cells. Pygeum also exerted a potent antimitogenic action in this study (Santa Maria Margalef et al 2003). Pygeum-treated mice displayed a significant reduction in prostate cancer incidence (35%) in comparison to the casein-fed mice (62.5%) (Shenouda et al 2007).

Other Actions

Ferulic esters (*n* -docosanol and *n* -tetracosanol) reportedly lower blood levels of cholesterol, from which testosterone is produced (Stewart 2003).

New metabolomics studies may soon shed further light on the action of pygeum on the prostate. Cornu et al (2012) compared the urine of 15 newly diagnosed men with BPH pre- and posttreatment with pygeum. The result was the identification of three novel compounds that were increased and one that was reduced in the urine samples treated with pygeum only.

Clinical Use

The most commonly investigated form of *P. africanum* is Tanenan (DEBAT Pharmaceuticals, France), which is a lipophilic extract standardised to contain 13% total plant sterols. One capsule of Tadenan contains 50 mg of standardised extract.

Benign prostatic hyperplasia

Clinical trials since the late 1970s have been encouraging, most reporting improvement in BPH symptoms.

A Cochrane systematic review analysed the results of 18 clinical trials that involved a total of 1562 participants (Wilt et al 2002). Seventeen studies were double-blinded, and the mean treatment duration was 61 ± 21 days (range 30–122 days). Most studies used a standardised extract of *P. africanum* in doses ranging from 75 to 200 mg/day.

The overall summary effect size indicated a large and statistically significant improvement with *P. africanum* . More specifically, active treatment increased peak urine flow by 23% and reduced residual urine volume by 24%, and doctors were twice as likely to report that their patients were experiencing an overall improvement in symptoms when pygeum was being used. The authors report that these findings are similar to other widely used treatment options and that treatment was well tolerated.

An observational study (TRIUMPH trial) in six European countries including 2559 newly-presented BPH patients compared treatment with either *P. africanum* , *Serenoa repens* , finasteride or alpha-blocker drugs (tamsulosin etc.) to untreated men (watchful waiters). Follow-up was at 1 year, with significant improvement (IPSS change >4) seen in all categories for the treatments: *P. africanum* 43.3%, *S. repens* 42.7%, finasteride 57% and alpha-blockers 68%, when compared to watchful waiters (Hutchison et al 2007).

IN COMBINATION

In 2013, a randomised, double-blind placebo-controlled trial was published which investigated the effects of a combination supplement ProstateEZE Max — *Cucurbita pepo* seed oil (160 mg), *Epilobium parviflorum* extract (equivalent to 500 mg dry herb), lycopene (2.1 mg), *Prunus africana* (equivalent to 15 g dry stem, standardised to β-sitosterol) and *S. repens* (equivalent to 660 mg dry leaf) on 57 patients with newly medically diagnosed BPH. At the end of 3 months, active treatment resulted in a symptom reduction in the median score (IPSS) of 36% compared to placebo 8% ($P < 0.05$). Daytime frequency of urination was reduced by 15.5% compared to no significant reduction in placebo group ($P < 0.03$) and nighttime frequency was reduced by 39.3% compared to placebo 7% ($P < 0.004$) (Coulsen et al 2013).

Other Uses

Fertility disorders

Pygeum extract was used experimentally in the treatment of 22 men with reduced fertility and diminished prostatic secretion and proved to have a beneficial effect (Lucchetta et al 1984). Treatment was administered every day over 2 months and was most effective in men who did not have prostatitis.

Dosage Range

According to clinical studies:

- •

BPH: 50–100 mg of extract twice daily standardised to 12–13% total sterols.

Adverse Reactions

Pygeum is well tolerated, with side effects similar to placebo (Wilt et al 2002). Mild gastrointestinal discomfort has been reported.

Significant Interactions

None known.

CONTRAINDICATIONS AND PRECAUTIONS

People with known allergies should avoid use.

PREGNANCY USE

Safety not scientifically established; however, it is not used for any indication that would cause a pregnant woman to use it.

PRACTICE POINTS/PATIENT COUNSELLING

- •

Pygeum is a popular treatment in Europe for BPH.

- •

A systematic review of 18 clinical studies found that it has significant effects in BPH, such as increasing peak urine, reducing residual urine volume and producing an overall improvement in symptoms.

- •

Several different mechanisms of action have been identified using animal models, which would explain its effectiveness in BPH.

- •

According to clinical studies, the dose used is 50–100 mg of standardised extract twice daily for BPH and the treatment is well tolerated.

- •

Overharvesting has meant the tree is now considered endangered and efforts are being made to protect it from extinction.

PATIENTS' FAQS

What will this herb do for me?

Standardised pygeum extract is an effective treatment in benign prostate enlargement or inflammation and improves several symptoms.

When will it start to work?

Some men will notice an improvement in symptoms after 4 weeks; however, others will require a long-term treatment.

Are there any safety issues?

It is a well-tolerated treatment but should not be used by people with a known allergy to the plant. If symptoms worsen, seek professional advice.

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Saw palmetto Download PDF

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Herbs and Natural Supplements, Volume 2, 875-880

Historical Note

Saw palmetto was used traditionally as a treatment for urogenital irritations, impotence and male infertility, among other conditions, and was described by the American Eclectic physicians as the 'old man's friend'. Between 1906 and 1917 saw palmetto was listed in the US Pharmacopoeia and between 1926 and 1950 it was in the National Formulary as a treatment for urogenital ailments; however, it fell out of favour for several decades as pharmaceutical medicines came to the forefront of mainstream medicine. Not so in Europe where, in the 1960s, French researchers began to chemically analyse the saw palmetto berry, and a breakthrough lipophilic preparation was eventually developed and subjected to countless clinical trials.

Common Name

Serenoa or saw palmetto

Other Names

American dwarf palm tree, cabbage palm, dwarf palmetto, fan palm, sabal fructus, sabal, serenoa

Botanical Name/Family

Sabal serrulata, Serenoa repens (family Arecaceae or Palmaceae)

Plant Part Used

Dried ripe fruit

Chemical Components

An ethanol extract of the berry contains free fatty acids rich in shorter-chain-length fatty acids, such as capric, caprylic, lauric and myristic acids (Nemecz 2003). Palmitic, stearic, oleic, linoleic and linolenic acids are also present in the extract. There are also lesser amounts of phytosterols (such as beta-sitosterol, stigmasterol, ampesterol and cycloartenol), aliphatic alcohols and polyprenic compounds. The lipophilic extract is used medicinally.

Main Actions

The mechanism of action is not fully elucidated; however, it appears that several mechanisms are at work.

Inhibition of 5-alpha reductase

In different cell systems, the lipid-sterolic extract acts as a non-competitive inhibitor of both type 1 and type 2 5-alpha reductase activity, thereby preventing the conversion of testosterone to dihydrotestosterone (Bayne et al 2000 , Raynaud et al 2002 , Sultan et al 1984). However, it is currently unclear whether the effect is apparent in humans, as contradictory evidence exists. Raynaud et al (2002) explained that the discrepancies found by different authors were due to different experimental conditions and selectivity for fatty acids, as only specific aliphatic unsaturated fatty acids have been shown to inhibit 5-alpha reductase activity.

One study that analysed and compared benign prostatic hyperplasia (BPH) samples taken from both untreated and treated subjects (320 mg saw palmetto extract taken for 3 months) found that local levels of testosterone were raised, whereas dihydrotestosterone levels were reduced, suggestive of local 5-alpha reductase inhibition (Di Silverio et al 1998). An earlier short-term study found that a dose of 160 mg of a liposterolic extract (Permixon) produced no changes to serum dihydrotestosterone levels, whereas finasteride 5 mg induced a significant reduction (Strauch et al 1994). Since prostate levels were untested in this study, it is not known whether a local effect occurred, even though serum levels remained unchanged.

Unlike other 5-alpha reductase inhibitors, there is no interference with the cell's capacity to secrete prostate-specific antigens (PSAs) because it does not affect the transcription of the gene for PSA, as demonstrated both in vitro and in vivo (Maccagnano et al 2006). Although having an obvious clinical advantage with regard to PSA screening for prostate cancer, this also suggests that 5-alpha reductase inhibition is not a major mechanism of action.

Inhibits binding of dihydrotestosterone and testosterone to androgen receptors

Saw palmetto reduces receptor binding of dihydrotestosterone and testosterone by an average of 41%, as tested in 11 different tissue specimens from BPH patients (el Sheikh et al 1988). In 2003, results from two animal studies showed that saw palmetto (whole berry and extract) influenced prostatic hyperplasia via effects on androgen metabolism (Talpur et al 2003).

Inhibits prolactin

In vivo research has identified an inhibitory effect not only on androgens, but also on the trophic effect of prolactin in the rat prostate (Van Coppenolle et al 2000). The inhibitory effect on prolactin activity appears to be due to inhibition of several steps in prolactin receptor signal transduction, according to one animal model (Vacher et al 1995).

Anti-inflammatory

Saw palmetto is a dual inhibitor of the cyclooxygenase (COX) and 5-lipoxygenase pathways, according to in vitro research (Breu et al 1992 , Paubert-Braquet et al 1997). Decreased expression of COX-2 has also been identified, providing a further explanation for the observed anti-inflammatory activity (Goldmann et al 2001).

Antispasmodic

Both the lipid and the saponifiable fractions have demonstrated antispasmodic activity in several in vitro studies (WHO 2003).

Cytochromes

Saw palmetto failed to have a significant effect on CYP3A4 or CYP2D6 when tested in healthy individuals (Markowitz et al 2003).

Antiproliferative effects

In recent years, there has been interest in determining whether saw palmetto may have a role in prostate cancer, as an inhibitory activity has been observed in several test tube studies for prostatic cancer cell lines (Goldmann et al 2001 , Ishii et al 2001 , Scholtysek et al 2009).

In 2009, results of an in vitro study were published which tested a saw palmetto ethanolic berry extract (SPBE) and compared its activity on prostatic cancer cells (DU-145) to individual fatty sterol components β-sitosterol, stigmasterol and cholesterol. Most significant findings included an increased expression of nuclear protein p53, and a reduced expression of p27 and p21, with resulting inhibition of tumour cell growth greatest in SPBE, followed by β-sitosterol and β-stigmasterol respectively. It was also observed that p53 had a mechanical effect of binding to F-actin, increasing adhesive properties of cells, reducing the likelihood of cellular migratory effects. This may in the future have an impact on the knowledge and treatment of tumour invasion (Scholtysek et al 2009).

Other Actions

Although alpha-1 adrenoreceptor activity has been reported in vitro, a clinical study found no evidence of this activity (Goepel et al 19992001). Saw palmetto does not affect platelet function in vivo (Beckert et al 2007).

Traditionally, saw palmetto is believed to act as a mild diuretic, urinary antiseptic and expectorant.

Clinical Use

The most studied saw palmetto preparation is a commercial product known as Permixon (Pierre Fabre Médicament, France), which is a liposterolic extract consisting of 80% free (e.g. 94 g/100 g extract) and 7% esterified fatty acids, as well as small amounts of sterols (beta-sitosterol, campesterol, stigmasterol, cycloartenol), and a minimum percentage of polyprenic compounds, arabinose, glucose, galactose, uronic acid and flavonoids. More recently, some other saw palmetto extracts have also been studied; however, there is concern that variations in chemical constituents may be a key factor behind the inconsistent results sometimes seen. In particular, in the United States, common saw palmetto products include ethanol and CO_2 extracts, whereas in Germany, fruit extracts obtained with 90% ethanol are very popular, and contain a hexane extract. A study comparing saw palmetto extracts produced using 90% ethanol versus under an optimised CO_2 condition found that levels of free fatty

acids differed and the ethanolic extract contained a large amount of ethyl esters that were not present in the CO_2-produced extract (Bombardelli & Morazzoni 1997).

Benign prostatic hypertrophy

Saw palmetto extracts are extremely popular in Europe where herbal preparations represent approximately one-third of total sales of all therapeutic agents sold for the treatment of BPH (Levin & Das 2000). In Germany, for instance, more than 30 different preparations containing saw palmetto are on the market. By far the most intensively studied product of this group is an *n* -hexane-liposterol-extract (Permixon), which is very popular in France and Italy. It is a complex mixture of free fatty acids and their esters, phytosterols, aliphatic alcohols and various polyprenic compounds (Madersbacher et al 2007).

Many clinical studies demonstrate mild to moderate improvements in several common urinary symptoms associated with BPH and with fewer side effects than alpha-blocker and 5-reductase inhibitor drugs. Some more recent study results are less consistent than previously, which is suspected to be mainly due to differences in chemical composition of test products. This is apparent when reviewing the Cochrane systematic reviews and other literature published in the last decade. In particular, differences in test dosages, treatment time frames, severity of disease and, importantly, herbal extract are likely to be contributing factors making the interpretation of results difficult. The possibility of inadequate blinding in some previous studies is yet another factor.

A 2002 Cochrane review assessing the results from 21 randomised controlled trials (RCTs) involving 3139 men concluded that saw palmetto improves urinary scores, symptoms and urinary flow measures compared with placebo, with effects on symptom scores and peak urine flow similar to the pharmaceutical drug finasteride (Wilt et al 2002). Additionally, its use is associated with fewer adverse effects compared with finasteride and, typically, symptomatic relief is reported more quickly.

In 2004, an updated meta-analysis of 14 RCTs and three open-label studies was published (Boyle et al 2004). The analysis used data from 4280 patients derived from clinical studies that had used Permixon. Three randomised trials had a study period of 6 months or longer. Peak urinary flow rate and nocturia were the two common end-points. Active treatment was associated with a mean reduction in the International Prostate Symptom Score (IPSS) of 4.78, and a significant improvement in peak flow rate and reduction in nocturia were also reported.

In contrast to previous systematic reviews, a 2012 Cochrane review of 32 RCTs (27 double-blinded) concluded that saw palmetto was no better than placebo in the control of urinary symptoms, peak urine flow and nocturia (Wilt et al 2012). The review analysed results obtained from 5666 men. The negative CAMUS study had a substantial influence on the results. It involved 369 men and compared standardised saw palmetto extract (Prosta-Urgenin Uro) at three different daily doses (320 mg, 640 mg and 960 mg) over 72 weeks. In the CAMUS study, herbal treatment had no significant effect on the American Urological Association Symptom Index (AUASI) or secondary outcomes, including nocturia, peak urine flow and prostate size as compared to placebo (Barry et al 2011). Similarly, an earlier double-blind study of 1

year of continuous treatment with saw palmetto extract (160 mg twice daily containing 92.1% total fatty acids) failed to produce significant differences compared with placebo measured by AUASI, maximal urinary flow rate, prostate size, residual volume after voiding, quality of life or serum PSA levels in subjects with moderate to severe BPH (Bent et al 2006).

IN COMBINATION

In 2013, positive results were demonstrated for a combination product in a randomised, double-blind placebo-controlled trial of 57 men between the ages of 40 and 80 years with medically-diagnosed BPH (Coulsen et al 2013). The product tested was ProstateEze Max, a herbal formulation containing *Cucurbita pepo* seed oil (160 mg), *Epilobium parviflorum* extract (equivalent to 500 mg dry herb), lycopene (2.1 mg), *Prunus africana* (equivalent to 15 g dry stem, standardised to β-sitosterol) and *Serenoa repens* (equivalent to 660 mg dry leaf). At the end of the 12-week trial period the active treatment group had 35% symptom reduction in the median score (IPSS) of 36% compared to placebo (8%: $P < 0.05$). Daytime frequency of urination was reduced by 15.5% compared to no significant reduction in placebo group ($P < 0.03$) and night frequency was reduced by 39% compared to placebo 7% ($P < 0.004$).

CLINICAL NOTE — BPH

BPH occurs in more than 50% of men over the age of 50 years. It is a slow, progressive enlargement of the fibromuscular and epithelial structures of the prostate gland, which can lead to obstruction of the ureter and urine retention. Symptoms such as frequent and/or painful urination, painful perineal stress and a decrease in urine volume and flow can develop. The condition has four stages, with stage 1 considered mild, stages 2 and 3 more severe and often requiring pharmacological treatment, and stage 4 severe and necessitating surgery.

Comparisons with alpha-adrenoreceptor antagonists

Although several comparative trials have been undertaken with finasteride, only a few have compared it with alpha-adrenoreceptor antagonist drugs, which are also commonly used in BPH (Adriazola et al 1992 , Debruyne et al 2002).

A large, randomised, double-blind study involving 811 men with symptomatic BPH, who were recruited from 11 European countries, showed that Permixon 320 mg/day produced similar results to tamsulosin 0.4 mg/day (Omnic) (Debruyne et al 2002). More specifically, both treatments reduced the IPSS by an average of 4.4 in 80% of subjects. Those patients with the most severe disease experienced the greatest improvement in IPSS total score, with mean changes greater in the Permixon group than in the tamsulosin group (–8.0 and –6.8, respectively). With regard to safety, both treatments were considered well tolerated; however, ejaculation disorders were significantly more frequent with tamsulosin (4.2%) than with Permixon (0.6%). Although these results are promising, this study has been criticised for not including a placebo group as a comparator.

In a short 3-week study, Grasso et al (1995) compared the effects of alfuzosin (7.5 mg/day) with saw palmetto (320 mg/day) in 63 BPH subjects under double-blind test conditions. Both treatments were found to be equally effective with regard to improving irritative score and with maximum and mean urine flow; however,

alfuzosin was shown to more rapidly reduce symptoms of obstruction. Considering most studies have shown that 4–8 weeks' treatment with the herb is required to produce maximal effects, the effect seen at 3 weeks is encouraging.

An earlier study compared the effects of prazosin with saw palmetto in 45 patients with BPH over a 12-week period (Adriazola et al 1992). This study found that, although both treatments reduced symptoms, prazosin was slightly more effective.

In the TRIUMPH study, an observational study across six European countries involving 2351 men with newly diagnosed lower urinary tract symptoms suggestive of BPH, significant improvements were seen in 43% of patients taking *Serenoa repens* , 68% of people taking alpha blockers (tamsulosin), and 58% taking 5-alpha reductase (Hutchison et al 2007).

Changes to prostate size

It is still open to speculation as to whether saw palmetto affects prostate size, because studies have produced contradictory results (Aliaev et al 2002 , Barry et al 2011 , Bent et al 2006 , Pytel et al 2002). One open study of 155 men tested the effectiveness and tolerability of Permixon (160 mg twice daily) over 2 years (Pytel et al 2002) and not only detected a significant improvement in the IPSS and quality of life marker, but also a decrease in prostate size and significant improvement in sexual function after the first year of treatment.

A longer 5-year study using Permixon in 26 subjects with BPH showed that a total daily dose of 320 mg twice daily also significantly reduced disease symptoms and improved quality of life, while reducing prostate size by an average of 30% (Aliaev et al 2002). In 2003, results from animal models showed that saw palmetto (whole berry and extract) significantly diminished prostatic hyperplasia (Talpur et al 2003). In contrast, two previous studies from 2006 and 2011 failed to detect a significant effect on prostate size (Barry et al 2011 , Bent et al 2006).

Androgenetic alopecia

The idea of using saw palmetto for androgenetic alopecia arose from the observation that finasteride appears to have some effect on this condition. One double-blind study has investigated the effects of saw palmetto as a potential therapeutic option, finding a highly positive response in 60% of subjects (Prager et al 2002). A second double-blind study of 48 men and women with androgenetic alopecia noted that mean hair density increased by 17% after 10 weeks of treatment with a topical lotion containing saw palmetto and by 27% after 50 weeks of treatment compared to baseline (Morganti et al, as reported in Linde et al 2006 , Ulbricht & Basch 2006).

Chronic prostatitis and pelvic pain

Evidence to support the herb's use in prostatitis is scarce. However, in April 2003, positive findings from a preliminary study using Permixon to treat symptoms of chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS) were presented at the annual meeting of the American Urological Association (AUA 2003). The RCT involving 61 patients with category IIIB CP/CPPS found that 75% receiving active treatment experienced at least mild improvement in symptoms, compared with 20% of the control group. Furthermore, 55% of patients receiving Permixon reported

moderate or marked improvement, compared with 16% of the control group. In contrast, results from a 2004 prospective, randomised, open-label study failed to find benefits for saw palmetto (325 mg daily) in men diagnosed with category III CP/CPPS (Kaplan et al 2004). After 1 year, the mean total National Institutes of Health Chronic Prostatitis Symptom Index score decreased from 24.7 to 24.6 (*P* = 0.41) and no benefits were seen for quality of life or pain with saw palmetto treatment.

IN COMBINATION

More promising is a 2009 trial of 143 patients with chronic bacterial prostatitis which had two treatment arms, group A receiving the antibiotic prulifloxacin 600 mg, while group B were given the antibiotic plus saw palmetto 160 mg, nettle 120 mg, curcumin 200 mg and quercetin 100 mg extracts for 14 days. After 1 month 87% of group B had no further symptoms compared to 27% of group A (Cai et al 2009).

PRACTICE POINTS/PATIENT COUNSELLING

- •

Many clinical studies demonstrate mild to moderate improvements in several common urinary symptoms associated with BPH, but the effect is most consistent for European preparations. Due to its good safety profile, a trial of treatment is still worthwhile for patients with mild to moderate BPH who have been advised to watch and wait with regard to conventional treatment.

- •

Typically, if symptom reduction is experienced, this develops within 1–2 months' treatment. It is well tolerated and associated with fewer side effects than finasteride and tamsulosin.

- •

The herb does not affect PSA levels; therefore PSA test results will be unaffected.

- •

If symptoms worsen, blood is detected in the urine or acute urinary retention occurs, patients should be advised to seek professional advice.

- •

If the patient is receiving radiotherapy for prostate cancer, saw palmetto supplementation should be ceased.

Other Uses

Traditionally, saw palmetto has been used to treat a variety of urogenital conditions, such as impotence, male infertility and also as an aphrodisiac. It has also been used in female hirsutism, although its effectiveness in this condition is unknown.

Dosage Range

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  Liposterolic extract: 320–960 mg/day in divided doses has been proved safe in a clinical trial (Barry et al 2011).

- •

  Dried berry: 2–4 g.

- •

  Liquid extract (1 : 2): 2–4.5 mL/day.

According to clinical studies

- •

  160 mg twice daily of liposterolic extract taken long term.

Adverse Reactions

The herb is generally well tolerated, with only non-specific symptoms reported, such as gastrointestinal upset, constipation, nausea, abdominal pain and diarrhoea. These minor complaints are generally resolved by taking the herb in association with meals (Agbabiaka et al 2009 , Maccagnano et al 2006).

The 1-year STEP study provided a detailed assessment of the potential toxicity of saw palmetto, including both symptomatic adverse effects as well as asymptomatic laboratory abnormalities (Avins & Bent 2006). It found no evidence that consumption of saw palmetto extract (160 mg twice daily) over a period of 1 year was associated with any clinically important adverse effects. Relatively few participants suffered serious adverse events, and these were more common in the placebo-allocated participants. Additionally, no statistically significant differences were observed between the saw palmetto and placebo groups in the measured domains of sexual functioning, with the exception of the perception-of-sexual-problems domain, which showed a small but significantly greater improvement in the placebo group.

A 74-week trial which used doses up to 960 mg of a standardised extract daily produced no evidence of toxicity (Avins et al 2012).

Significant Interactions

No controlled studies are available and theoretical interactions are difficult to predict, due to the poorly understood nature of the herb's mechanism of action.

Finasteride (and other 5-alpha reductase inhibitor agents)

Additive effect theoretically possible — potential beneficial effect, although the clinical significance is unknown.

Androgenic drugs

Theoretically, saw palmetto may reduce the effectiveness of therapeutic androgens such as testosterone — observe patient for lack of drug effect.

CONTRAINDICATIONS AND PRECAUTIONS

If symptoms of BPH worsen, blood is detected in the urine or acute urinary retention occurs, professional reassessment is required.

Avoid saw palmetto products if undergoing radiotherapy for prostate cancer as preliminary in vitro studies suggest they may radiosensitise normal prostatic cells by inhibiting normal DNA repair (Hasan et al 2009).

PREGNANCY USE

Use of saw palmetto during pregnancy is contraindicated due to the herb's hormonal effects. In clinical practice, it is not used in pregnancy.

PATIENTS' FAQS

What will this herb do for me?

Saw palmetto has been extensively investigated as a treatment to relieve symptoms in BPH (enlarged prostate). Overall, it is more effective than placebo and most consistent results have been obtained for European preparations. There is some research suggesting that it may be useful in some forms of hair loss and prostatitis.

When will it start to work?

Symptom relief for enlarged prostate, if achieved, is generally experienced within 4–8 weeks.

Are there any safety issues?

Saw palmetto is well tolerated; however, occasionally mild gastrointestinal disturbances, headaches and rhinitis have been reported.

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Bioavailability of β-sitosterol from *Pygeum africanum* extract in humans

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Abstract. Although β-sitosterol (BSS) is the active agent in several oral pharmaceutical preparations used for the treatment of benign prostate hypertrophy, including those based on *Pygeum africanum* (PA) bark extract, no explicit bioavailability of BSS was published for humans. In the present work the rate and extent of absorption of BSS was determined in humans by administration of PA extract formulated in two different marketed capsules (reference and test Products). The study was a comparative bioavailability conducted in 18 healthy volunteers, where each Product was given in a single dose of 150 mg dry PA extract, equivalent to 18 mg BSS, in a cross-over design. BSS serum concentrations were analyzed by a validated HPLC-method. The results indicated that PA-based BSS possessed a C_{max} of 9.8 and 8.64 $\mu g.ml^{-1}$, t_{max} of 2.86 and 2.92 h, AUC_{0-8} of 26.7 and 27.24 $\mu g.ml^{-1}.h$, $AUC_{0-\infty}$ of 42.35 and 46.53 $\mu g.ml^{-1}.h$, MRT = 3.08 and 3.22 h, $t_{1/2}$ of 2.53 and 3.41 h, in reference and test Products, respectively. The relative bioavailability based on C_{max} is 88.16 %, and the overall bioavailability judged from AUC_{0-8} = 102.02 %. The results are discussed together with the published data on BSS pharmacokinetics in beagle dog.

Introduction

β-sitosterol (BSS), a phytosterol present in the lipid fraction of plants, is the bioactive agent of several European pharmaceutical products available worldwide [1]. Some of the BSS preparations are indicated for the management of benign prostatic hyperplasia [2,3]. Patients receiving oral doses in the range of 60-130 mg BSS daily for 6 months showed considerable inhibition of prostatic adenoma [2,3]. Also the extract of *Pygeum africanum* bark (PA) is used as an effectual therapy for benign prostatic hyperplasia, based mainly on its content of BSS [1,4,5]. A standardized dry extract of PA contains a minimum of 12 % BSS [5]. Other BSS formulations are claimed to possess hypolipidaemic activity by delivering larger doses of 2-6 g BSS orally per day [1,6,7].

In spite of these important medicinal uses, no explicit bioavailability study with therapeutic doses of BSS or PA extract was published. The only parameter reported in humans is the absorbability of BSS from the gastrointestinal tract after intake of dietary fat, which was amounted to about 5 % or less of the daily intake [8,9,10]. Beagle dog, however, is the only species for which BSS pharmacokinetics have been reported, where its absolute bioavailability was estimated as 9 % upon *p.o.* administration [11].

Accordingly, the present work was initiated to characterize the pharmacokinetics of BSS in man upon oral administration of PA extract. Two different commercially available oral preparations containing equal labeled doses of PA extract were examined for BSS and subjected to a comparative bioavailability study.

The development of a sensitive HPLC method applicable for studying BSS bioavailability lies within the scope of the present work, as sterols are difficult to be analyzed in biological fluids [12]. This is due to the range of their detection with UV (205-210 nm), which limits the number of solvents that can be used in the HPLC mobile phase. Moreover, published HPLC and GLC methods [9, 10, 13, 14] for bioanalysis of BSS are complicated by lengthy procedures of derivatization and sample preparation.

Materials and Methods

Preparations. Two marketed formulations containing *Pygeum africanum* (PA) extract were studied and designated as: Product I (Tadenan®, soft gelatin capsules of Laboratoires Debat. Group Fournier, France, manufactured by Sedico, Egypt; a brand innovator product) used as a reference preparation, and Product II (Prostacure®, hard gelatin capsules, manufactured by October Pharma, Egypt) as a test preparation. Both contain 50 mg PA extract per capsule, but only Product II is labeled to contain an amount of 6 mg of β-sitosterol (BSS) in the extract per capsule. Accordingly, Products I and II were assayed for BSS *in vitro* to ensure their pharmaceutical equivalence, before carrying out the comparative bioavailability study.

Chemicals. Authentic BSS, free of isomeric campesterol, was purchased from E. Merck, Darmstadt, Germany (P/N 103739). Solvents used for bioanalysis were of chromatographic grade. All other chemicals were of analytical grade.

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Estimation of potency of Products I and II in vitro. The contents of 5 capsules of each product were extracted in chloroform-methanol (5:95 ml) with sonication. Test samples of the extract were filtered through Millipore filter (Millix 0.45 um), and 10 µl aliquots injected onto the HPLC, and assayed by adopting the chromatographic parameters described below. Standard concentrations of authentic BSS in the range of 1.0-40.0 µg/ml were similarly analyzed.

Bioavailability study:

Protocol. The Products were subjected to a comparative bioavailability study. The study design was a single-dose, fasting, two-treatment, two-period, two-sequence crossover, comparing equal doses of the test and reference Products, with a two-week washout period between the two phases of the study. An equal number of subjects were randomly assigned to the two dosing sequences The healthy volunteers were selected and the study was conducted according to the internationally accepted guidelines and recommendations [15, 16], and in the spirit of the revised Helsinki Declaration (Hong Kong, 1989) [17]. Before the study began, the proposed protocol has been ethically approved by the Committee of the Medical Unit, National Research Center, Egypt.

Subjects. Eighteen healthy volunteers (17 males and one female) aged 18-42 years were selected on the basis of acceptable medical history, and a comprehensive checkup, including medical examination and clinical chemistry evaluation, which revealed no evidence of cardiac, respiratory, hepatic, or renal disease. Subjects were randomly allocated to each dosing sequence. Each subject gave his signed informed consent.

Treatment. Three capsules [equivalent to 18 mg β-sitosterol, in 150 mg PA extract] of the test or reference preparations were administered, as a single dose to the 12 h fasting subjects. The subjects were given the treatment orally with 240 ml water, and then continued fasting for 4 h, followed by a standard tea/toast breakfast, devoid of phytosterols. Oral fluid supplements (240 ml of water) were given at hourly intervals after treatment.

Blood sampling. Venous blood samples were taken by direct vein puncture at 0, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h, and placed in evacuated blood collection tubes. Following centrifugation, the serum samples were immediately frozen and stored in the deep-freeze at –20 °C until assayed.

Bioanalytical method:

Standard concentrations. A stock solution of the authentic BSS was prepared in methanol at a concentration of 10 mg/100 ml. The stock solution was then diluted fiuther to yield appropriate standard solutions. Standard serum samples were prepared by spiking 20µl of a suitable standard solution into a drug-free serum to obtain BSS concentrations of 1.0, 2.5, 5.0, 10.0, 15.0, and 20.0 µg/ml.

Sample treatment. Each of the unknown or standard serum sample was extracted with 5 ml chloroform by vortex mixer for 1 min, and phase separation was achieved by centrifugation. From each sample, 3.5 ml of the organic layer was transferred to a test tube for removal of solvent by evaporation using temperature regulated sand bath adjusted to 90 °C. Each sample residue is recostituted in 0.2 ml methanol then vortex for 1 min and sonicated for 15 min before injected onto the HPLC-system .

HPLC-equipment. Waters 600E Multisolvent Delivery System -High Performance Liquid Chromatograph was used, equipped with 484 Waters tunable absorbance detector, U6K injector, and TCM temperature control module (Waters Assoc., Milford, MA,USA).

HPLC-evaluation. The chromatographic process was controlled, and peak areas, and regression analysis were determined by the computer program Baseline ®-810 (Waters Assoc., Milford, MA, USA).

Chromatographic parameters. Column used was Lichrosorb 5 RP-18, 250 mm x 4.6 mm and 5µ particle size (Phenomenex, USA), with temperature controlled at 50 °C, and guard pak pre-column module with Bondapak C18 inserts (Waters Assoc., Milford, MA,USA). The mobile phase was 3.5 % water in methanol solution, with a flow rate of 2ml / min. Detector wave length adjusted to 205 nm. Injection volume was 100 µl.

Validation. The HPLC-based bioanalytical method was validated according to internationally accepted criteria [18] for determination of linearity, accuracy, precision, selectivity, and sample stability.

Pharmacokinetic analysis of data. The individual pharmacokinetic parameters of BSS were derived by noncompartmental analysis [19] using WinNonLin-Pro 2.1 computer program (Pharsight, NC, USA). The following parameters were derived: the peak serum concentration C_{max}, the time to reach peak serum concentration t_{max}, the apparent elimination half-life of BSS $t_{1/2}$, as determined by log-linear regression analysis of the terminal portion of the serum concentration-time curve of BSS, and AUC_{0-8} and $AUC_{0-\infty}$ by the linear trapezoidal rule and extrapolation to infinity, respectively. Mean residence time (MRT) of the drug in the systemic circulation was calculated by : MRT = AUMC/AUC (where AUMC is the area under the moment curve).

Results

Potency

The *in vitro* standard curve possessed correlation coefficient = 0.9997, and percentage recoveries ranged 94.21-98.7 %. The results proved that Products I and II contain 6.18 mg and 5.88 mg of BSS per capsule, respectively, confirming their pharmaceutical equivalency.

Bioanalysis and method validation

An acceptable linear relation was established between BSS standard concentrations and the HPLC-peak areas in the range of 1-20 µg/ml. Linear least square regression line of the constructed standard curve was computed, and the correlation coefficient was 0.9985. The percentage recoveries (±SD) were found to be 87.3 % (± 7.8), 92 % (± 8.9), and 96.2 % (± 6.3) for 1, 5, and 20 µg/ml, respectively. The HPLC method proved to be sensitive enough to detect precisely a lower limit of 1.0 µg BSS /ml serum, and was used to quantify the drug in serum up to 8 h after dosing. Precision values varied between -0.57 and 1.73 RSD %. Spiked BSS serum samples were stable when stored at –20 °C for 12 weeks.

HPLC chromatograms

Chromatograms of the fasting serum samples, the standard serum samples spiked with BSS, and a volunteer sample 3 h post dosing (*cf.* Fig. 1.) revealed a good resolution of BSS peak under the selected chromatographic conditions, with no endogenous peaks that would interfere with the determination of BSS. The retention time of BSS-peak (Rt value) =11.15 min. On testing the BSS isomeric compound campesterol, under these HPLC parameters, it was eluted at Rt = 9.75 min, which ensures selectivity and accuracy. Campesterol, if present in the extract, might overlap with BSS peak if no efficient resolution is achieved.

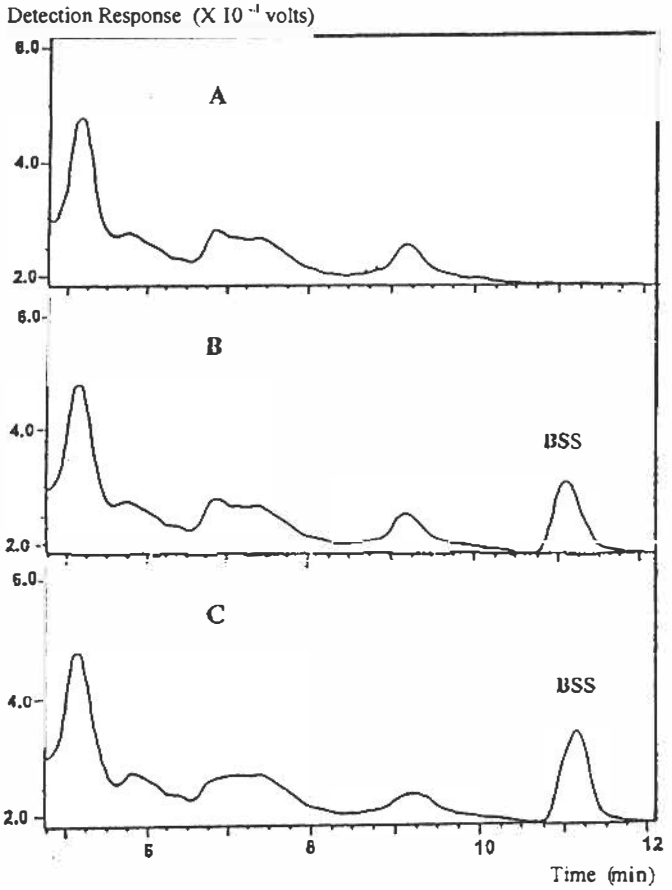

Fig. 1. HPLC chromatogram of serum samples: (A) fasting, (B) standard spiked with BSS, and (C) volunteer after 3 h dosing.

Bioavailability

The mean serum concentrations of BSS after oral administration of the Products to the 18 subjects are listed in Table I, and the mean BSS serum concentrations versus time profiles for the two treatments are shown in Fig. 2. The results of pharmacokinetic data are recorded in Table 2.

Following administration of Product I, the mean maximum BSS serum concentration (C_{max}) was 9.80 µg/ml (range 3.81-16.20 µg/ml). Following Product II administration, the values were significantly the same ($p \leq 0.05$) with a mean C_{max} of 8.64 µg/ml (range 2.21- 14.01µg/ml). The relative bioavailability based on C_{max} was found to be 88.16 %. There was no significant difference in time to maximum concentration, t_{max} = 2.8 h (range 2.0-4.0 h), and 2.92 h (range 1.5-5.0 h), for Product I and II, respectively. The overall bioavailability judged from AUC_{0-8} was found to be 102.02 %. The mean residence time (MRT) was 3.08, and 3.22 h for Products I and II, respectively.

Discussion

The pharmacokinetic data obtained in this study clarify for the first time the bioavailability profile of a therapeutic oral dose of BSS in man, by administration of a standardized extract of PA.

Table 1. Mean serum β-sitosterol (BSS) concentrations (µg.ml^{-1} ± standard error) after oral administration of the two Products in humans (n =18).

Time (h)	Product I	Product II
1	2.052 ± 0.550	1.840 ± 2.030
1.5	3.475 ± 0.478	3.925 ±2.154
2	6.260 ± 0.894	5.300 ± 2.640
2. 5	8.951 ± 1.011	7.878 ± 3.677
3	8.130 ± 0.739	7.687 ± 3.677
4	5.852 ± 0.783	6.064 ± 2.802
5	3.586 ± 0.480	4.225 ± 3.311
6	1.301 ± 0.357	1.610 ± 1.913
8	0.129 ± 0.129	0.284 ± 0.540

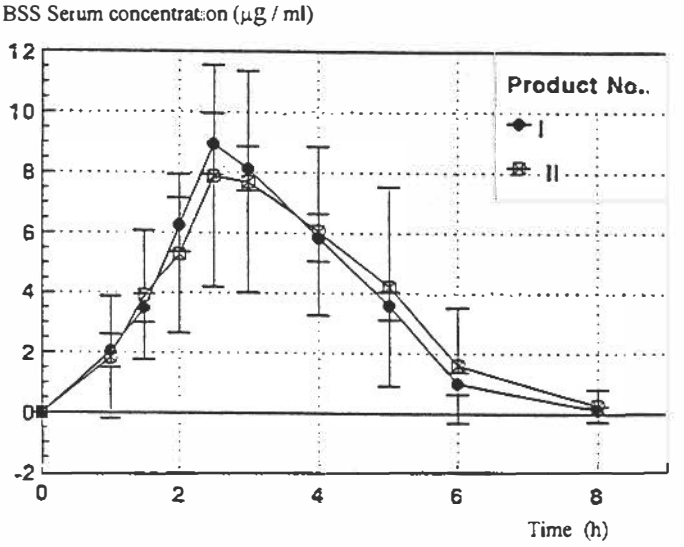

Fig. 2. The mean β-sitosterol (BSS) serum concentration-time profiles for the two treatments. (n = 18, ± SE).

Table 2. Pharmacokinetic data of β-sitosterol (BSS) in *Pygeum africanum* (PA) Products

Parameter	Product I	Product II
Dose (mg)	18	18
C_{max} (µg.ml^{-1})	9.80 (±3.73)	8.64 (±3.53)
T_{max} (h)	2.86 (± 0.72)	2.92 (± 0.81)
AUC_{0-8}(µg.ml^{-1}.h)	26.70 (± 11.09)	27.24 (± 12.34)
$AUC_{0-\infty}$(µg.ml^{-1}.h)	42.35 (± 21.94)	46.53 (± 20.39)
MRT (h)	3.08 (± 0.33)	3.22 (± 0.38)
$T_{1/2}$ (hr)	2.53 (±2.28)	3.41 (± 3.58)

Each value is a mean ± SD (n =18).

The published human data represent studies carried-out only to answer the question of the absorbability of dietary BSS [8-10], and have clarified the following points. When BSS was administered in a 50 mg single oral dose [*cf.* 8], or as 250 mg in dietary daily intake [10], the highest BSS-level in plasma of healthy volunteers was determined as 0.15 and 4 µg/ml, respectively; and the absorbability was estimated as 1.4 and 4 %, respectively. Even on providing 242-415 mg BSS, as a daily fat intake typical of American diet, to hypercholesterolemic patients, the highest concen-

tration determined for BSS ranged 3-10 μg/ml plasma, and the absorption amounted to 5 % or less [9]. On the contrary, it is known that cholesterol, although belonging with BSS to the same class of sterols, is much more efficiently absorbed (45-54 %) from dietary fats [9].

No direct comparison could be assessed between these data and the present results, because the previous studies [*cf.* ref. 8-10] have estimated BSS in blood at daily intervals rather than at hourly intervals, as required for pharmacokinetic determinations. Also, the use of radioisotopic measurements only [*cf.* ref. 8], without distinction between the drug and its metabolites, does not allow a specific measurement of the unchanged drug.

Previously, BSS pharmacokinetics were reported only in the beagle dog [11], where two experimental formulations, administered orally in a dose of about 0.6 mg/Kg body weight, possessed C_{max} values of 0.148 and 0.171 μg/ml blood, and t_{max} values of 0.71 and 0.96 h, respectively. In the present work, BSS behaved differently in man, where in a much smaller dose of approximately 0.25 mg/kg body weight of adults, it produced a pronouncedly higher C_{max} (9.0 μg/ml). On the other hand, BSS absorption in humans tends to be much slower as evidenced from the time for maximum absorption (t_{max}), which was pronouncedly delayed (*ca* 3 h).

The reason for the high C_{max} value of BSS determined in the present work might be due to the species variability and/or the effect of PA-extract on its bioavailability. To assess the influence of PA-extract on the rate and extent of BSS absorption, another study that is designed to compare the bioavailability of pure BSS devoid of PA extract, would be needed. More over, to increase the extent of intestinal absorption of BSS is a challenge that would be the object of future research studies.

Although the active substance of PA extract is termed BSS, the lipophilic mixture contains the following variety of compounds: triterpenic phytosterols, mainly β-sitosterol, with smaller amounts of campesterol, and other sterols along with their glucosides, and β-sitostenone; pentacyclic triterpenoids, present mainly as ursolic, oleanolic, and crataegolic acid, along with their derivatives; linear long chain fatty alcohols, e.g. n-docosanol and n-tetracosanol, present in the extract mainly as ferulic acid esters; and several fatty acids, mainly linoleic, oleic, palmitic, stearic, and behenic acids [4-5].

It is also not proved yet the exact mechanism of action of BSS and other PA constituent(s) against benign prostatic hyperplasia [3]. However, BSS has been recently found to possess some other promising biological activities, namely: an immunomodulatory effect by stimulating the human lymphocyte proliferation *in vitro* and in man [20], and antitumor activity against HT-29 human colon cancer cells *in vitro* [21].

The present work is underlining the necessity for evaluation of the pharmacokinetics of other medicinally active agents, that are administered in dosage forms containing plant extracts.

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Lycopene bioavailability and metabolism in humans: an accelerator mass spectrometry study[1–3]

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ABSTRACT

Background: To our knowledge, there is no direct information on lycopene metabolism in humans.

Objective: The objective of this study was to quantify the long-term human bioavailability of lycopene in plasma and skin after a single dose of ^{14}C-lycopene and to profile the metabolites formed.

Design: We preselected 2 male subjects as lycopene absorbers and gave them an oral dose of 10 mg synthetic lycopene combined with ≈6 μg [6,6′,7,7′-^{14}C]lycopene (≈30,000 Bq; 92% *trans* lycopene). The appearance of ^{14}C in plasma, plasma triacylglycerol–rich lipoprotein (TRL) fraction, urine, expired breath carbon dioxide, and skin biopsies was measured over 42 d. The ^{14}C in lycopene-isomer fractions from plasma and TRL fraction was measured to assess the isomerization of lycopene in vivo.

Results: We quantified ^{14}C from ^{14}C-lycopene in plasma, the plasma TRL fraction, expired carbon dioxide, urine, and skin. The time to maximum concentration (t_{max}) of total ^{14}C-lycopene in plasma was 6 h, and the elimination half-life ($t_{1/2}$) was 5 d, which were different from the t_{max} and $t_{1/2}$ of unlabeled lycopene (0.5 and 48 d, respectively). ^{14}C-Lycopene was extensively isomerized after dosing as a 92% all-*trans* isomer at dosing but changed to 50% *trans*, 38% 5 *cis*, 1% 9 *cis*, and 11% other *cis* isomers after 24 h. A similar pattern of isomerization was seen in plasma TRL fractions.

Conclusions: Lycopene was extensively isomerized after dosing and rapidly metabolized into polar metabolites excreted into urine with the rapid peak of $^{14}CO_2$ after dosing, which implies that β-oxidation was involved in the lycopene metabolism. Lycopene or its metabolites were detected in skin for up to 42 d. *Am J Clin Nutr* 2011;93:1263–73.

INTRODUCTION

Lycopene is the most abundant carotenoid present in tomatoes and one of the main carotenoids present in the human diet (1). Lycopene has been of nutritional interest since it was first suggested as having a role in the prevention of prostate cancer (2) and has subsequently been suggested to play a role in the prevention of cardiovascular disease (3–5) and skin cancer (6) and the reduction of oxidative stress (7, 8). These effects have been suggested to be mediated by the antioxidant capacity of the lycopene molecule via signaling effects of lycopene metabolites (1, 9).

The study of lycopene's role in human nutrition is complicated because the all-*trans* isomer predominates in the main dietary source of lycopene (ie, tomatoes), but blood, plasma, and tissues contain relatively greater concentrations of *cis* isomers (10). The processing of tomatoes by heating converts the all-*trans* lycopene to various *cis* isomers. *cis*-Lycopene isomers are regarded as being more bioavailable because they are more soluble and better absorbed from the intestinal lumen than is the all-*trans* isomer (11), although the isomerization may also take place in vivo. The gastrointestinal lumen (12, 13), liver (14), and enterocytes (15) were identified as potential sites of lycopene isomerization in vivo.

The use of accelerator mass spectrometry (AMS) to detect an ultralow dose of the ^{14}C-labeled lycopene tracer could help answer some of the questions surrounding lycopene bioavailability. AMS instruments measure the ratio or abundance of rare isotopes and have only been used to a limited extent in nutritional science (16–24). AMS can accurately measure ratios at 1% of the natural ^{14}C abundance ("modern carbon": the ratio of ^{14}C:^{12}C before 1950 or 9.8×10^{-16} mol ^{14}C/g carbon) (25). This sensitivity [the low attomole (10^{-18}) range of ^{14}C] makes AMS useful in studies on micronutrients in which a few micrograms of tracer can be used rather than the larger amounts (milligrams) often required for ^{13}C-labeled tracers. Sample sizes required for measurements are very low [eg, a few microliters of blood or a few milligrams of tissue (24)]. The whole-body radiation exposure from nutritional ^{14}C-microdosing experiments that used 3700 Bq ^{14}C ranged from 1.3 to 5.2 μSv compared with 20 μSv exposure from a 4-h airline flight (26), which confirmed that the risk from radiation ^{14}C-microdosing studies was negligible.

Labeled lycopene, in addition to the study of plasma bioavailability, makes it possible to follow the kinetics of excretion in urine and study the changes in the isomer pattern postabsorption

[1] From the Nestlé Research Centre, Lausanne, Switzerland (ABR, AB, PAG, ME, ILFN, SK, MR, LBF, and GW); Vitalea Science, Davis, CA (LTV); the Covance Clinical Research Unit Inc, Honolulu, HI (JR); the Department of Ion Beam Physics, Swiss Federal Institute of Technology, Zurich, Switzerland (HAS and TS-K); DSM Nutritional Products Ltd, Kaiseraugst, Switzerland (KW and RR); and the Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA (RGL, PLS, and SRT).

[2] This study was funded by the Nestlé Research Center, which is part of the Nestlé company. [6,6′,7,7′-^{14}C] lycopene (^{14}C-lycopene) and synthetic unlabeled lycopene were provided by DSM (Kaiseraugst, Switzerland).

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as well as to gain information about metabolism. It also enables the determination of pharmacokinetic variables for lycopene without the possible confounding of endogenous stores of the carotenoid. In this article, we described a study that used ^{14}C-labeled lycopene and AMS to gain a new understanding of the lycopene bioavailability and metabolism in humans and evaluated the use of different AMS instruments for nutrition research.

SUBJECTS AND METHODS

Chemicals and reagents

[6,6′,7,7′-^{14}C]Lycopene (^{14}C-lycopene) was provided by DSM (Kaiseraugst, Switzerland) and was purified before use with a 97.2% radiopurity (by radio-HPLC) and >96% chemical purity by nuclear magnetic resonance spectroscopy (Selcia, Essex, United Kingdom). The specific activity was 6.26 MBq/mg. ^{14}C-lycopene was stored in amber bottles under nitrogen gas at −20°C. The isomeric composition of the ^{14}C-lycopene was 92% all-*trans* and 8% *cis* (predominantly 5-*cis*) determined by HPLC and liquid scintillation counting (LSC) (*see* below). Synthetic unlabeled lycopene was provided by DSM (27) and had a similar isomeric composition of 90% all-*trans* and 10% 5-*cis* isomers. The ^{14}C-lycopene was formulated for human consumption through the mixture of it with 10 mg unlabeled lycopene, dissolution in dichloromethane before homogenization in a gelatin and sucrose matrix, and removal of dichloromethane under a reduced pressure at 40°C. The exact amount of ^{14}C present in the dose was determined by LSC. The doses were flushed with argon, kept away from light, and stored at −20°C. All solvents used were of HPLC grade (Merck, Darmstadt, Germany). Standard lycopene (95% all-*trans*) was from Sigma (Buchs, Switzerland). Mixed *cis*-lycopene-isomer tomato oleoresin (28) was used to identify the retention time of *cis*-lycopene isomers.

Subject selection

This was a proof-of-concept study that used AMS to determine the bioavailability and metabolism of lycopene in humans. Because it is known that some people absorb lycopene poorly, subjects were prescreened to ensure that they had a good postprandial absorption of lycopene before starting the study. Healthy males subjects were recruited who were normolipidemic (fasting plasma triglyceride concentrations <200 mg/dL) and had an age range of 40–50 y, a body mass index (in kg/m^2) of 20–27, and skin type II or III (white, fair to brown hair, and skin that gets sunburned easily). These skin types were selected because they were the most commonly used in previous studies on lycopene concentrations in skin (29, 30). Exclusion criteria were smoking, the regular consumption of alcohol, use of medication, regular use of vitamin, mineral, or antioxidant supplements, gastrointestinal surgery (including appendectomy) or disturbances, exposure to artificial ultraviolet or greater than regular exposure to sunlight, participation in a previous ^{14}C-tracer study, an allergy to fish or peanut products, and an aversion to tomatoes and tomato-based products. Subjects were asked to avoid all lycopene-rich foods, including tomatoes and tomato-based products, during the prescreening and study periods to increase the proportional lycopene bioavailability.

Four male subjects were recruited for prescreening to ensure that they were lycopene absorbers. After donating a fasting blood sample they were given a standardized meal that contained 25 g fat in 2.93 MJ (700 kcal) and 33 g tomato paste (25 mg lycopene). Three hours later, another blood sample was taken. The blood was separated into plasma, and the triacylglycerol-rich lipoprotein (TRL) fraction was isolated by using the method of van Vliet et al (31) and analyzed for lycopene (*see* section entitled "Separation of lycopene isomers"). Two subjects were selected on the basis of a >100% increase in lycopene in both plasma and the TRL fraction 3 h after consumption of the tomato paste. Written informed consent was obtained from volunteers, and the study was approved by the Aspire Independent Review Board LLC (San Diego, CA). The clinical study was carried out at the Covance Clinical Research Unit (Honolulu, HI) in 2006.

Dosing, specimen collection, and sample preparation

The 2 selected male subjects (40 and 60 y of age with a body mass index of 26.2 and 26.7, respectively) were asked to abstain from lycopene-containing foods for 1 wk before the start of the study and then for the duration of the study (6 wk) to obtain conditions similar to a previous study (32). On the test day, the subjects came to the metabolic unit after an overnight fast. Baseline samples of urine (overnight), fasting blood, expired air, and a 4-mm diameter skin-punch biopsy (lower back below the beltline) were taken. The subjects were given an oral dose of 37 kBq ^{14}C-lycopene in 10 mg unlabeled lycopene with a meal (a milkshake that comprised 300 g banana, 100 mL skim milk, 25 g olive oil, and 12.6 g sucrose; 573 kcal, 7 g protein, 86 g carbohydrates, and 8 g fiber). Blood samples were taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 9, and 12 h postdose. Urine and expired air were collected at 4 and 12 h postdose. Fasting blood, 24-h urine, and expired air were collected daily on days 2–7 postdose and subsequently on days 13, 21, 28, 35, and 42 postdose. Skin biopsies were taken on days 0, 4, 7, and 14 for subject 1 and on days 0, 14, 28, and 42 for subject 2 (*see* supplemental Figure 1 under "Supplemental data" in the online issue for an overview of the analyses).

Blood plasma

Blood was collected in lithium-heparin coated tubes and centrifuged for 10 min at 3000 × *g*. Samples were protected from light as far as possible and stored at −40°C. Plasma samples were either directly analyzed for ^{14}C by AMS (both types of AMS instrument) or extracted and individual lycopene isomers separated and collected for AMS analysis by using HPLC (*see* below).

Urine

Subjects were given bottles with which to store their urine and requested to keep samples at 4°C. All urine from subjects was collected during the first week and then spot urine samples were taken at all time points afterward. Urine samples were analyzed directly by AMS (Newton Scientific Inc [NSI (Cambridge, MA)] and Massachusetts Institute of Technology [MIT (Cambridge, MA)] (NSI-MIT) system; *see* below for details).

Breath carbon dioxide

Two methods for breath carbon dioxide collection were used. One method was adapted from the method of Gunnarsson et al

(33) by using 2 perspex tubes; the first tube was filled with Drierite (Sigma), which is a material that traps water, and the second tube was filled with Ascarite II (Sigma), which is a material that traps carbon dioxide. Silica tubing attached the 2 perspex tubes together, and subjects were instructed to blow into the tubes through a plastic drinking straw. The second method for the collection of expired air for the AMS analysis has been described by Schulze-König et al (34). In this method, the carbon dioxide of the exhaled breath was captured on a trap with type 13× zeolite followed by analyses in which the carbon dioxide was directly released into the hybrid ion source of the MIni radioCArbon DAting System (MICADAS) AMS system [Swiss Federal Institute of Technology, Zürich (ETHZ), Switzerland] via the controlled heating of the trap while flushing with helium gas.

Skin biopsies

Four-millimeter-diameter full-thickness punch biopsies were taken from the lower back, just below the beltline, weighed, washed with 0.9% saline solution to remove any contaminating blood and adipose tissue, and stored at −70°C before being shipped for analysis by AMS (bio-MICADAS system; ETHZ).

TRL fraction

The TRL fraction of plasma mainly contained chylomicrons and a small amount of VLDL. This fraction was isolated from plasma by ultracentrifugation by using the method of van Vliet et al (31): Four milliliters of plasma was overlaid with 4 mL sodium bromide solution with a density of 1.006 g/mL, and TRL was separated by ultracentrifugation for 30 min at 100,000 × *g* at 15°C. Samples were extracted by using the same method as plasma, and TRL lycopene isomers were separated by HPLC before gas-fed AMS analysis. Care was taken to protect the samples from light during the procedure, and samples were stored at −40°C before analysis.

Separation of lycopene isomers

The ^{14}C in lycopene isomers and TRL was measured at the following time points: 0, 3, 6, 9, 12, 24, 48, 72, 96, 144, and 336 h. Lycopene isomers in the test dose, plasma, and TRL were isolated by HPLC by using the method of Schierle et al (35). Briefly, 200 μL plasma or 400 μL TRL solution was made up to 1120 μL with distilled water in an amber tube, 1200 μL ethanol was added to denature the proteins, and the sample was mixed by vortex. The sample was extracted 3 times by using 0.05% butylated hydroxytoluene in hexane, and the extracts were evaporated and dissolved in 10 μL dichloromethane and 90 μL hexane. Lycopene isomers were separated by normal-phase HPLC as follows: 50 μL of extracted sample was injected onto a 90-cm Nucleosil HPLC column (3, 300 × 4.6-mm, 5-μm particle-size columns in a series; Machery-Nagel, Düren, Germany) with a Nucleosil precolumn (Machery-Nagel), and lycopene was eluted with an isocratic flow of *n*-hexane with 0.1% *n*-ethyldiisopropylamine at 1 mL/min. A Hewlett-Packard 1050 HPLC (Hewlett-Packard, Santa Clara, CA) with a variable wavelength detector (quantification) and diode-array detector (spectral confirmation) was used. Fractions were collected with a FRAC-100 fraction collector (Pharmacia, Uppsala, Sweden). Lycopene isomers were quantified at 470 nm on the basis of a standard curve determined by using all-*trans* lycopene, with the assumption of a similar absorption coefficient for all lycopene isomers (35). Standard curves were repeated twice a week to ensure repeatability. Lycopene isomers were determined on the basis of previously published chromatograms (35), and a tomato-oleoresin sample was enriched with *cis* isomers of lycopene (28), with isomers confirmed by mass spectrometry/mass spectrometry (MS/MS) analysis (15).

HPLC eluent was collected every minute, and peaks were matched to each appropriate fraction. Because some of the lycopene-isomer peaks were spread out over more than one fraction, ^{14}C counts for the relevant fractions were summed for each isomer. 13- and 15-*cis* Lycopene isomers that were not fully separated by the method were reported together as the sum of the 2 peaks.

Separation of lycopene metabolites

A total of 10 mL urine collected between 12 and 24 h (the greatest enrichment of ^{14}C) from both subjects was treated with β-glucuronidase and sulphatase (25 kU and 250 U, respectively) (Sigma) in 5 mL 50 mmol/L phosphate-buffered solution (pH 7), and incubated overnight at 37°C to deconjugate any possible lycopene metabolites. Urine was lyophilized to near dryness and 1 mL 5% methanol was added. The deconjugated urine sample was passed through a 0.2-μm filter, and 50 μL of the sample was injected into a Hewlett-Packard 1050 HPLC under the following conditions: 0–5 min, 100% solvent A (100% water), followed by a gradient to 100% solvent B (100% methanol) over 25 min, and then 100% solvent B for 10 min. The system was returned to 100% solvent A over 10 min, and the column re-equilibrated with 100% solvent A for a further 10 min. The flow rate was 1 mL/min, and the column used was a 250 × 4.6-mm, 5-μm particle size Zorbax SB-Aq C_{18} column (Agilent). The absorbance was monitored with a photodiode-array detector that measured between 210 and 500 nm, and fractions were collected every 1 min for analysis by liquid scintillation.

Fractions with a greater than background radioactivity were further analyzed with a nanospray full scan and tandem mass experiments (MS/MS in product-ion mode by selecting relevant deprotonated and protonated ions). Analyses were carried out on a TSQ Quantum 7000 triple-quadrupole instrument (ThermoFisher, San Jose, CA) equipped with a static-nanospray interface. Dried fractions of interest were resuspended in 50 μL H_2O/methanol (1:1, vol:vol) that contained 0.1% formic acid. A total of 2 μL was loaded into the nanospray needle and manually centrifuged to allow the droplets to reach the tip of the needle. From the full-scan mass measurements (*m/z* 50–800 in a scan time of 1 s while applying a spray voltage between 700 and 1200 V) in both positive- and negative-ionization modes, ions that corresponded to known lycopene metabolites (36–41) and potential products that resulted from β-oxidation of lycopene were submitted to subsequent MS/MS analyses.

AMS

Bio-AMS is fundamentally a technique for the determination of the radiocarbon content of a biological sample. This is typically accomplished by measuring the ratio of ^{14}C to either of the

2 stable carbon isotopes (^{12}C or ^{13}C). Less typically, it can be accomplished by counting ^{14}C atoms with quantification by comparison with standards run under the same conditions. Each approach for determining the ^{14}C content in a sample has advantages and disadvantages compared with the other; the isotope ratio (IR) approach is far more sensitive and accurate but requires rigorous contamination control, whereas the ^{14}C counting methodology is less sensitive and prone to greater variability but has better throughput, and contamination is less problematic. Because these 2 approaches to the quantification of minute quantities of ^{14}C have never, to our knowledge, been compared for a biological dataset, an ancillary objective was to compare pharmacokinetic results of the 2 bio-AMS methods in plasma.

The following 2 types of AMS instruments were used in this study: the MIT AMS system and the MICADAS AMS system (ETHZ). At MIT, an instrument designed and constructed by the NSI was used. Samples analyzed at MIT included whole blood, plasma, urine, expired air carbon dioxide, TRL, and lycopene isomers in plasma and TRL. At ETHZ, IR AMS analyses were conducted with a MICADAS instrument, and comprised plasma, skin samples, and samples of exhaled air carbon dioxide.

Gas-fed ^{14}C-counting AMS measurements

The NSI-MIT system incorporates a laser-induced combustion interface that produces carbon dioxide directly from samples for online introduction into the gas-fed ion source of the AMS instrument. This system and its operation have been described in detail in previous publications (42, 43). Expired carbon dioxide that was trapped on Ascarite (Sigma) was analyzed after its release by treatment with concentrated sulfuric acid within a septum-sealed vial and released carbon dioxide was introduced directly into the AMS source without laser combustion. The quantification of combusted liquid-phase samples was based on the radioisotope abundance rather than the IR, whereas the quantification of breath samples was made by the IR that was calibrated by using identically treated $Na_2[^{14}C]CO_2$ reference samples.

IR AMS measurements

IR AMS measurements were carried out on a MICADAS instrument (ETHZ) that has been described elsewhere (44, 45). Liquid and solid samples were combusted to carbon dioxide before reduction to a fullerene solid and analysis by IR AMS. Samples of expired breath carbon dioxide were directly introduced in the gas-accepting ion source of the MICADAS instrument (ETH Zurich). Details of the procedure have been previously published (34). Because of the lower limit of quantification of the AMS instrument (ETH Zurich) (≈10% of background ^{14}C; 0.1 modern) and high precision (46), this was used for skin biopsy samples when a low enrichment of ^{14}C was anticipated.

LSC

LSC was performed with a Packard Tri-Carb 2100 TR Liquid Scintillation Analyzer (Packard, Waltham, MA). Samples were mixed with 10 mL liquid scintillation cocktail (Ultima Gold; Perkin Elmer, Shelton, CT), and counts were measured for 10 min.

Pharmacokinetics and data analysis

The incremental area under the curve (AUC) was determined by a mixed log-linear trapezoidal model. The mixed log-linear trapezoidal model performed the AUC calculation in the following way: the linear rule (trapezoidal) was applied when the concentration was ascending and the log linear rule was applied when the concentration was descending. Noncompartmental analyses were performed per Gustin et al (32). The AUC, maximum concentration (C_{max}), time to the C_{max} (t_{max}), and elimination half-life ($t_{1/2}$) were calculated with Kinetica (version 5.0; ThermoFisher Scientific, Billerica, MA).

Samples for lycopene analysis were extracted in duplicate, and AMS analysis of fractions from each replicate, along with total ^{14}C analyses, were analyzed in triplicate. When appropriate, analytic data were reported as means (±SDs). No statistical comparisons were performed because only 2 subjects were studied.

RESULTS

Prestudy

Three of the 4 subjects in the prestudy had an increase (>100%) in lycopene in the plasma TRL fraction. The baseline plasma sample for the fourth subject was visibly fatty, and had high baseline TRL lycopene indicating that the subject had not fasted as requested and therefore, was not considered for the study. Two subjects were selected for participation in the study. Baseline characteristics of the subjects are presented in **Table 1**.

AMS analysis of ^{14}C in plasma, whole blood, skin, expired air carbon dioxide, and urine

^{14}C in plasma appeared rapidly and was present even at 30 min, with a C_{max} of 153–177 Bq/L, t_{max} of 3–6 h, and $t_{1/2}$ of 380–899 h (**Table 2**; **Figure 1**). Generally, pharmacokinetic variables measured for total ^{14}C in plasma were similar for both AMS instruments used. ^{14}C from the oral lycopene dose was still measurable in plasma 42 d after intake with both AMS instruments, although below the limit of quantification for the NSI-MIT AMS instrument. ^{14}C measured in lycopene accounted

TABLE 1
Baseline characteristics of the 2 subjects at the start of the study[1]

	Age	BMI	Fasting plasma lycopene	Fasting plasma TRL lycopene	Total cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides
	y	*kg/m²*	*μmol/L*	*μmol/mmol TG*	*mmol/L*	*mmol/L*	*mmol/L*	*mmol/L*
Subject 1	40	26.2	0.147	0.15	4.59	1.50	2.95	0.84
Subject 2	60	26.7	0.237	0.16	5.10	1.12	3.57	1.49

[1] TRL, triacylglycerol-rich lipoprotein; TG, triglycerides.

for 6 and 10% of the total ^{14}C AUC and between 10% and 30% of the total ^{14}C measured in plasma for subjects 1 and 2, respectively.

^{14}C could be quantitatively measured in urine by AMS for ≤14 d and detected ≤21 d after dosing, with the peak excretion of ^{14}C from lycopene occurring around 24 h (**Figure 2**). The average C_{max}, t_{max}, $t_{1/2}$, and $AUC_{0–1008\ h}$ were 2138 Bq, 24 h, 16.25 h, and 5,588,965 Bq · h, respectively. The recovery of ^{14}C in urine was 19% for subject 1 and 17% for subject 2.

^{14}C in breath carbon dioxide could be detected 4 h after dosing, with values that fell below detection limits at 144 h (**Figure 3**). The average C_{max}, t_{max}, $t_{1/2}$, and $AUC_{0–144\ h}$ were 60 Bq/h, 4 h, 27.8 h, and 932 Bq · h, respectively. The recovery of ^{14}C in breath carbon dioxide was 3.6% and 2.4% for subjects 1 and 2, respectively.

An increase in ^{14}C could be measured in skin biopsies after 4 d and remained elevated over the baseline sample after 42 d (**Figure 4**), with the C_{max} observed at 4–7 d. This amount of ^{14}C corresponded to an increase of ≈2.1 fmol ^{14}C-lycopene/g skin at 144 h, with the assumption that all ^{14}C measured in skin was lycopene. The use of the same ratio of intake to response in skin for a dose of 10 mg lycopene would lead to an increase of 4.3 pmol lycopene/g skin.

Analysis of lycopene isomers in plasma and TRLs

The analysis of isolated lycopene isomers in plasma and TRL fractions indicated that all-*trans* ^{14}C-lycopene was converted to *cis* isomers because ^{14}C was present in 9-, 13-, and 15-*cis* fractions, although these isomers were not present in the lycopene fed to subjects. 5-*cis* Lycopene was also a major ^{14}C-lycopene isomer in plasma (on average, 34% of total ^{14}C-lycopene) when only 8% of the fed ^{14}C-lycopene was present as this isomer. Between 3 and 96 h, ≈50% of the ^{14}C in lycopene was present as all-*trans* isomer in both subjects. At 144 and 336 h in one subject, this amount fell to 40% of the total ^{14}C-lycopene, whereas for the second subject, the ^{14}C in all-lycopene isomers was below the limit of quantification after 96 h. In both subjects, the amount of ^{14}C in 13- + 15-*cis* isomers increased over time, with the average percentage of 4.3% between 3 and 24 h and 12.7% between 48 and 336 h.

The t_{max} for all unlabeled lycopene isomers was higher (12 h) than those measured as ^{14}C-lycopene, whereas the t_{max} and $t_{1/2}$ of total ^{14}C were shorter than both unlabeled and ^{14}C-lycopene (Table 2). The ^{14}C specifically detected as lycopene by HPLC separation and offline AMS detection accounted for 10–30% of the total ^{14}C detected at the same time points in plasma.

The pattern of lycopene isomers in the TRL fraction differed between the 2 subjects, with one subject always having >50% *cis* isomers in the TRL between 3 and 96 h, whereas between 3 and 12 h, the other subject had <40% *cis* isomers in their TRL fraction, which increased to >50% between 24 and 48 h (**Table 3**). Both subjects had similar total ^{14}C-lycopene and total lycopene in their TRL fractions. The plasma unlabeled lycopene-isomer distribution did not change during the study for either subject.

Urinary lycopene metabolites

The HPLC analysis of deconjugated urinary metabolites after the ^{14}C-lycopene dose showed 2 peaks with ^{14}C above background amounts (**Figure 5**). The first peak occurred between 2 and 5 min with minimal retention on a C_{18} column with 100%

TABLE 2
Noncompartmental pharmacokinetic variables for total ^{14}C, ^{14}C-lycopene, and unlabeled lycopene in plasma in 2 subjects (S1 and S2) after a single dose of ^{14}C-labeled lycopene[1]

	C_{max}		t_{max}		$t_{1/2}$		$AUC_{0–last\ sample}$		C_{max}		$AUC_{0–336\ h}$	
	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
	Bq/L		*h*		*h*		*Bq/L · h*		*μmol/L*		*μmol/h*	
Total ^{14}C												
Total plasma ^{14}C[2]	153	172	6	4	380	514	45,311	39,999	—	—	—	—
Total plasma ^{14}C[3]	177	174	5	3	—[4]	899	53,628	45,763	—	—	—	—
^{14}C-Lycopene												
Total plasma lycopene	43.8	47	6	6	131	110	4494	2260	—	—	—	—
All-*trans* lycopene	17.3	19.9	6	6	115	99.6	2018	1178	—	—	—	—
5-*cis* Lycopene	21.6	19.9	6	6	159	69.8	1546	622	—	—	—	—
9-*cis* Lycopene	0.59	0.60	6	6	249	—[4]	49.9	25.6	—	—	—	—
13- and 15-*cis* Lycopene	2.24	3.81	144	72	—[4]	—[4]	507	244	—	—	—	—
Other lycopene isomers	2.31	3.62	6	6	147	—[4]	362	176	—	—	—	—
Unlabeled lycopene												
Total plasma lycopene	—	—	12	12	—[4]	956	—	—	1.01	1.26	31,124	36,279
All-*trans* lycopene	—	—	12	12	—[4]	1264	—	—	0.582	0.757	17,815	21,420
5-*cis* Lycopene	—	—	12	12	—[4]	981	—	—	0.153	0.166	5131	5232
9-*cis* Lycopene	—	—	12	12	—[4]	776	—	—	0.061	0.068	1820	1943
13- and 15-*cis* Lycopene	—	—	12	12	—[4]	391	—	—	0.079	0.112	2390	2751
Other lycopene isomers	—	—	12	12	—[4]	825	—	—	0.132	0.159	3975	4924

[1] C_{max}, maximum concentration; t_{max}, time to the maximum concentration; $t_{1/2}$, elimination half-life; AUC, area under the curve; —, no value was calculated for this parameter.
[2] Obtained by using the MICADAS accelerator mass spectrometry system (Swiss Federal Institute of Technology Zürich, Zurich, Switzerland).
[3] Obtained by using the ^{14}C counting accelerator mass spectrometry system (Massachusetts Institute of Technology, Cambridge, MA)
[4] Not possible to calculate because of the shape of the curve.

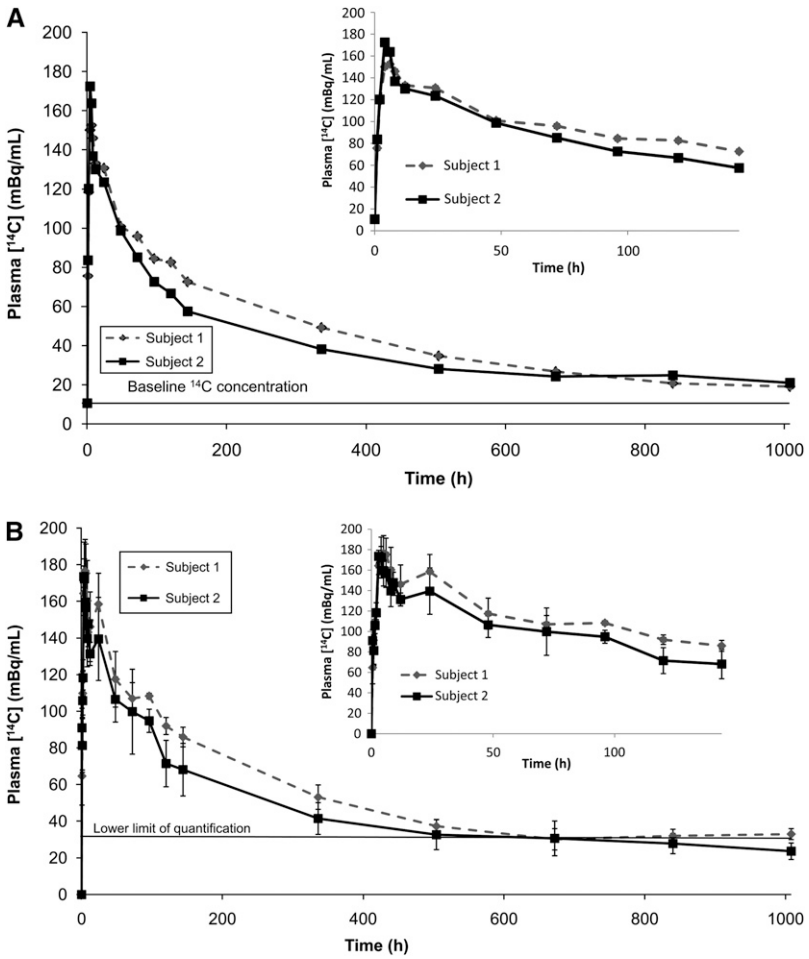


FIGURE 1. Detection of ^{14}C in plasma by using isotope-ratio (A) and ^{14}C-counting (B) accelerator mass spectrometry analysis after a single dose of 30 kBq ^{14}C-lycopene. The inset graphs show the curves between 0 and 144 h. Error bars represent SD from triplicate measurements. Isotope-ratio measurements (MICADAS instrument; ETH Zurich, Zurich, Switzerland) typically have a precision of ≈1%, and thus corresponding error bars are not visible.

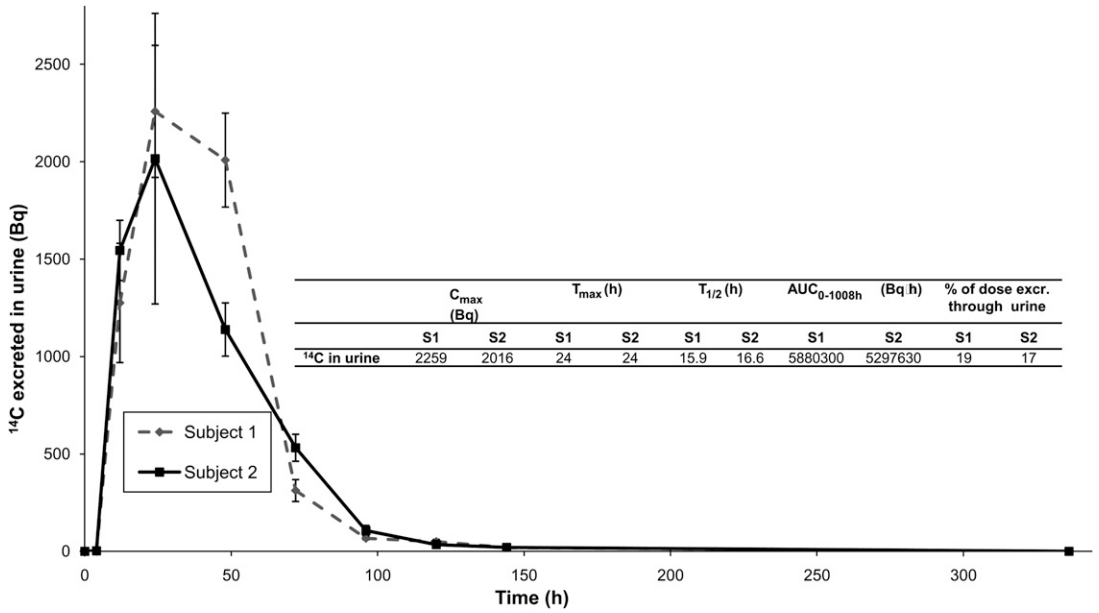
water, which indicated that these metabolites were highly polar and probably had a low molecular weight. A second peak was observed at 22–23 min, which indicated more hydrophobic metabolites. The analysis of these fractions by full-scan nanospray mass spectrometry and MS/MS to confirm the presence of known or potential β-oxidation metabolite masses did not provide or confirm that previously published or potential metabolites were present.

DISCUSSION

Although many studies have examined at the bioavailability of lycopene, particularly by focusing on the differences between various sources of lycopene (eg, natural compared with synthetic) and its metabolism, it has remained difficult to absolutely prove the fate of oral lycopene in humans beyond the appearance in plasma. In this study, we used AMS to show the first in-human proof that oral all-*trans* lycopene was converted into *cis* isomers after ingestion, lycopene and/or postabsorption lycopene metabolites were transported to skin, lycopene was probably, at least in part, metabolized by β-oxidation into carbon dioxide, and polar metabolites were excreted in urine.

Both ^{14}C-lycopene and unlabeled lycopene in plasma followed first-order kinetics overall. Absolute pharmacokinetic results generally differed from previous studies, although the C_{max} was similar to that in a study with a similar study design and dose of lycopene (32) with the diverse range of study designs, doses, and matrices used being the likely reason for differences in lycopene kinetics (47–49). The finding of ^{14}C from lycopene in plasma 1004 h after the dose was unexpected, although there was evidence for a slow-turnover tissue compartment that may have explained this finding (50). Pharmacokinetic variables from the TRL-rich fraction of plasma also differed between ^{14}C- and unlabeled-lycopene, although this result was less conclusive because the baseline for unlabeled lycopene was not reached in one subject.

The presence of mainly *cis* rather than all-*trans* lycopene isomers in plasma and tissue was suggested to be due to the preferential absorption of *cis*-lycopene isomers and/or isomerization of all-*trans* lycopene in the intestinal lumen (12, 13), enterocytes (15), or liver (14). The results from this study supported the idea that all-*trans* lycopene is extensively isomerized in vivo because labeled 5-, 9-, 13-, and 15-*cis* lycopene isomers were detected in plasma, even though the starting ^{14}C-labeled lycopene was 92% all-*trans* and 8% 5-*cis* isomers. Although these results did not rule out the possibility that *cis* lycopene was preferentially absorbed, the results provided further evidence



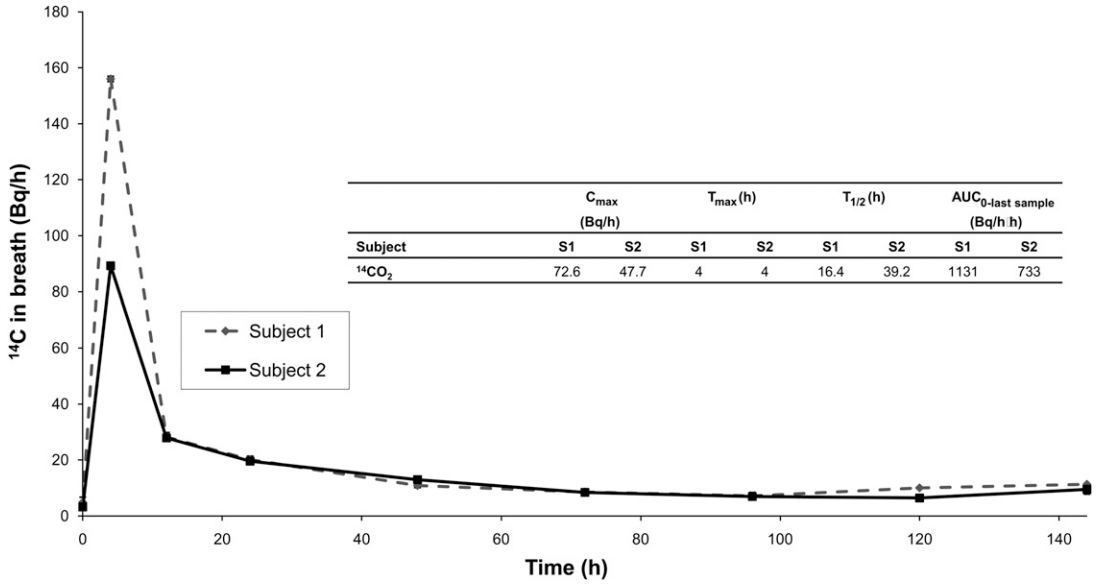
	C_{max} (Bq)		T_{max} (h)		$T_{1/2}$ (h)		$AUC_{0\text{-}1008h}$ (Bq·h)		% of dose excr. through urine	
	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
^{14}C in urine	2259	2016	24	24	15.9	16.6	5880300	5297630	19	17

FIGURE 2. Detection of ^{14}C in urine in 2 subjects (S1 and S2) after a single dose of ^{14}C-labeled lycopene, measured by using ^{14}C-counting accelerator mass spectrometry. All ^{14}C in urine was assumed to be in the form of lycopene metabolites. Error bars represent SD from triplicate measurements. C_{max}, maximum concentration; T_{max}, time to the C_{max}; $T_{1/2}$, elimination half-life; AUC, area under the curve; excr., excreted.

that the in vivo isomerization of all-*trans* lycopene occurs in humans, most notably to 13- and 15-*cis* isomers.

In rats, ≈55% of an absorbed ^{14}C-lycopene dose was present in tissues in the form of undefined polar metabolites, and ≤92% of an absorbed ^{14}C-lycopene dose was present in some tissues after 3 h, which suggested that lycopene was extensively metabolized (36) and possibly explained a large proportion of the 70–90% difference between total ^{14}C and ^{14}C-lycopene observed in this study. The shorter kinetics for total ^{14}C compared with ^{14}C-lycopene suggested that this metabolism occurred rapidly. Some losses may have occurred during the extraction and analysis, although the recovery with pure ^{14}C-lycopene on the HPLC was determined to be 90%, and thus, with the assumption of a similar recovery for other isomers (35), the analytic error unlikely explained the observed difference.

Approximately 18% of the total ^{14}C dose was excreted via the urine in this study. In studies in rats, this figure has been much lower (ie, ≈2% of the total dose over 168 h) (36). To our knowledge, no previous studies have reported the presence of lycopene metabolites in human urine, and the results obtained confirmed that lycopene was metabolized to polar metabolites in mammals (36, 37). Given the difference between total ^{14}C and



	C_{max} (Bq/h)		T_{max} (h)		$T_{1/2}$ (h)		$AUC_{0\text{-last sample}}$ (Bq/h·h)	
Subject	S1	S2	S1	S2	S1	S2	S1	S2
$^{14}CO_2$	72.6	47.7	4	4	16.4	39.2	1131	733

FIGURE 3. Detection of ^{14}C in breath samples as $^{14}CO_2$ in 2 subjects (S1 and S2) after a single dose of ^{14}C-labeled lycopene measured by using ^{14}C-counting accelerator mass spectrometry. Error bars that represented SDs from triplicate measurements were not visible due to the low relative error. C_{max}, maximum concentration; T_{max}, time to the C_{max}; $T_{1/2}$, elimination half-life; AUC, area under the curve.

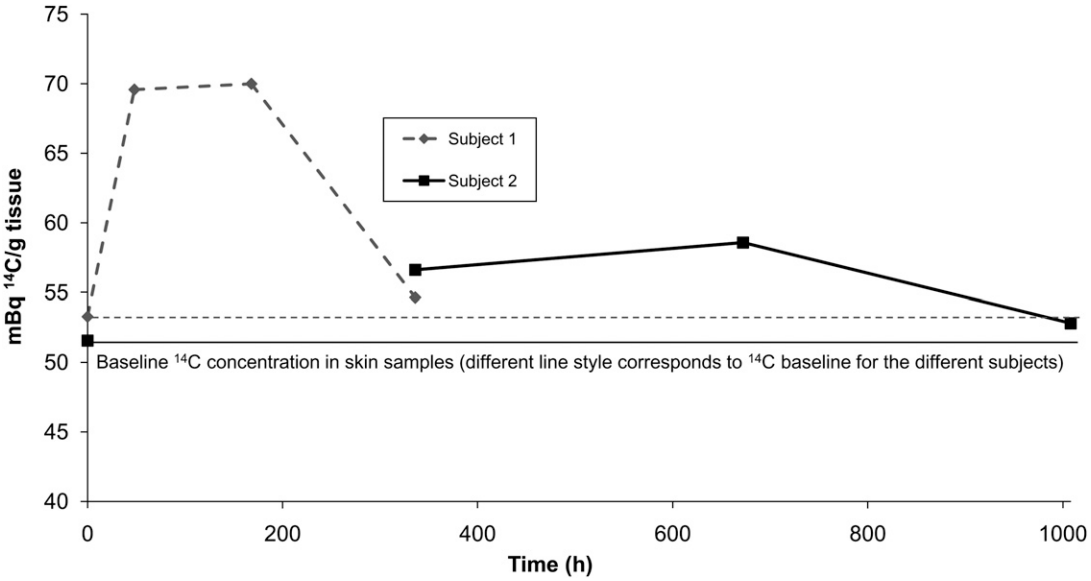


FIGURE 4. Detection of ^{14}C in skin biopsy samples in 2 subjects after a single dose of 30 kBq ^{14}C-labeled lycopene measured by using isotope-ratio accelerator mass spectrometry. The limited number of biopsies that could be taken from each subject precluded the sampling of each subject at all time points. Error bars that represented SDs from triplicate measurements were not visible due to the low relative error.

^{14}C-lycopene in plasma and the rapid peak of $^{14}CO_2$ in expired breath (4 h), it appeared that at least part of the absorbed lycopene was rapidly metabolized. Several metabolite products of lycopene have been proposed and detected in plasma, with some because of the oxidation of lycopene [2,6-cyclolycopene-1,5-diol A (51)], as well as products from the eccentric cleavage of acetate from lycopene (apo-lycopenals) (52). The overall dose of lycopene fed in this study (10 mg) was relatively low, and we did not expect to see large peaks in urine derived from lycopene metabolites. The separation by one HPLC step was not sufficient to obtain a semipure fraction because of the number of highly polar metabolites in urine. Because the ^{14}C enrichment of the urine samples was low, the detection of purified metabolites after repeated purification steps with LSC would not have been possible. In rat studies that used ^{14}C-lycopene to study the lycopene distribution and metabolism, metabolites present in tissues were apparently mostly highly polar metabolites (36, 37), which fit with finding the major peak of ^{14}C extracted from urine eluting in water. The acetate cleavage of lycopene via β-oxidation was the most likely metabolic route because of the finding of lycopenals in plasma (52) and the detection of a rapid peak of breath $^{14}CO_2$ in this study. The future discovery of human lycopene metabolites is of importance because several studies attributed biological activities to proposed metabolites (53).

The finding of elevated ^{14}C concentrations in skin indicated that lycopene or lycopene metabolites reached the skin after a single oral dose. Other studies that used unlabeled lycopene have shown that chronic supplementation with lycopene did elevate skin lycopene concentrations (54), and lycopene contributed to skin color and protection against skin photodamage (29, 55). Because skin biopsies were taken from the lower

TABLE 3
Noncompartmental pharmacokinetic variables for ^{14}C-lycopene and unlabeled lycopene in the plasma triacylglycerol-rich lipoprotein (TRL) fraction in 2 subjects (S1 and S2) after a single dose of ^{14}C-labeled lycopene[1]

	C_{max}		t_{max}		$t_{1/2}$		$AUC_{0–96\ h}$		C_{max}		$AUC_{0–96\ h}$	
	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
	mBq/mmol TG		*h*		*h*		*mBq/mmol TG · h*		*μmol/mmol TG*		*μmol/mmol TG · h*	
^{14}C-Lycopene												
Total TRL lycopene	17.5	10.0	3	3	299	614	525	601	—	—	—	—
All-*trans* lycopene	5.96	7.11	3	3	111	—[2]	164	303	—	—	—	—
5-*cis* Lycopene	8.15	2.84	3	24	190	124	218	154	—	—	—	—
Other lycopene isomers	—[2]	1.99	—[2]	9	—[2]	78.5	140	135	—	—	—	—
Unlabeled lycopene												
Total TRL lycopene	—[2]	1.85	—[2]	9	—[2]	—[2]	128	113	—[2]	1.85	128	113
All-*trans* lycopene	—[2]	1.19	—[2]	9	—[2]	166	65.5	62.6	—[2]	1.19	65.5	62.6
5-*cis* Lycopene	—[2]	0.73	—[2]	0	—[2]	—[2]	63.5	50.6	—[2]	0.73	63.5	50.6
Other lycopene isomers	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]	—[2]

[1] C_{max}, maximum concentration; t_{max}, time to the maximum concentration; $t_{1/2}$, elimination half-life; AUC, area under the curve; TG, triglycerides.
[2] Not possible to calculate because of the shape of the curve.

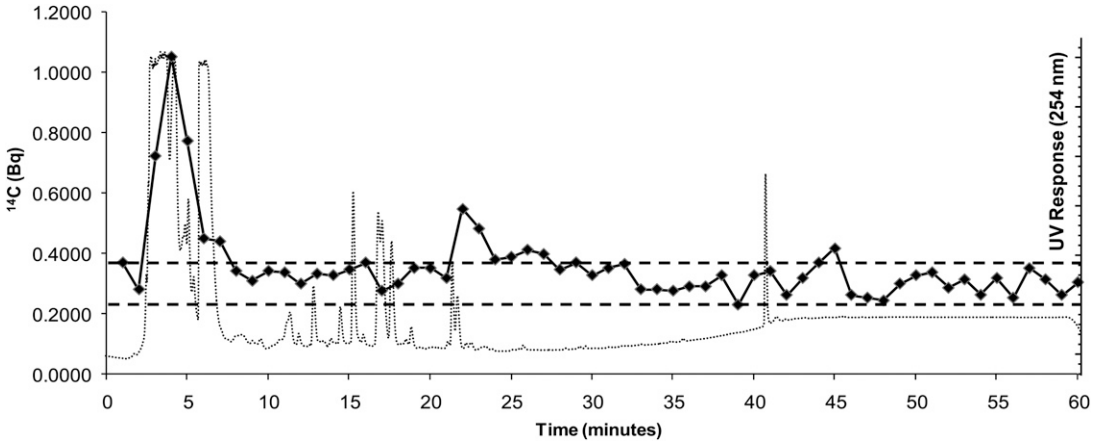


FIGURE 5. Representative chromatogram of the detection of ^{14}C in an extract of deconjugated urine metabolites 12 h after a single dose of ^{14}C-lycopene. The dotted line is the ultraviolet detector response at 254 nm, whereas the solid line is the amount of ^{14}C detected in fractions collected every 30 s. The 2 dashed lines are the range for background ^{14}C. The HPLC gradient was from 100% water through to 100% methanol. Two major peaks of ^{14}C were observed at 5 and 22.5 min. The ^{14}C measurements were made by using liquid scintillation counting. UV, ultraviolet.

lumbar region, which is an area that is generally not exposed to sunlight, it is probable that concentrations would have been higher had biopsies been taken in other regions such as the forehead or hand (54), although this was not practicable for ethical and cosmetic purposes. Skin concentrations of lycopene have been reported to be between 0.13 and 0.22 pmol/mg wet weight (30, 56–58), and supplementation with lycopene for up to 7 weeks has been shown to increase tissue skin lycopene concentrations in humans by 150% (59), and thus, it is probable that the ^{14}C detected in skin biopsy samples was at least partly present as lycopene.

To our knowledge, this study is the first in which ^{14}C-counting and IR AMS instruments were used to analyze a common sample set. Results from measurements of plasma with both instruments were comparable, although the greater sensitivity of the IR AMS instrument meant that measurements at 42 d were still well above the lower limit of quantification (LLOQ), whereas these measurements were below the LLOQ (but above the lower limit of detection) for the ^{14}C-counting AMS instrument. Results for the calculated pharmacokinetic variables were similar; between-instrument differences were no greater than the difference between the 2 subjects. These results highlight the comparability of the 2 types of instruments for measurements over the same range of ^{14}C. For most samples in this study, the sensitivity of the ^{14}C-counting AMS instrument was sufficient, which meant that it was possible to take advantage of the higher throughput and less sample preparation required for this type of AMS. For tissue samples, time points distant to the time of dosing, and other biological samples in which the dilution of the radioisotope by the abundance of stable isotope in the sample pushed the IR closer to the background ^{14}C, the greater IR precision of IR-AMS was an advantage. These results suggested that the 2 types of AMS instruments can be considered complimentary in the context of this type of research study.

With the use of an appropriate AMS instrumentation, it was possible to successfully follow the fate of a microdose of ^{14}C-lycopene in humans, even in tissue samples (skin). This underlined the potential of this instrumentation in further micronutrient research (24). Furthermore, as the size (60), sensitivity (61) and hyphenation (62) of AMS instruments are improved, the possibilities for application of AMS in nutrition research will expand.

In conclusion, this work presents the first use of AMS applied to measuring lycopene kinetics in humans and demonstrates the power of this technique to understand what happens in the body to compounds that are present at low concentrations in food. From this study, it is evident that lycopene was, to some extent, isomerized after ingestion and is rapidly metabolized. Lycopene or its metabolites are transported to skin and may remain there for several days before being turned over. AMS has an enormous potential for furthering the knowledge of the bioavailability of nutrient compounds, especially with the availability of smaller and dedicated bio-AMS instruments.

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The authors' responsibilities were as follows—GW, SK, and LBF: conceived the study, MR, GW, and ABR: designed the study, KW and RR: provided and prepared essential material; LTV and JR: performed the clinical trial; ABR, AB, HAS, TS-K, RGL, PLS, SRT, and PAG: performed analyses; ME and ILFN: performed data analyses; and ABR and LTV: wrote the manuscript. All authors: read and approved the final manuscript. ABR, AB, PAG, ME, ILFN, SK, MR, LBF, and GW are employees of Nestlé, which is a food company that sells products enriched in lycopene. KW and RR are employees of DSM, which is a supplier of nutrient ingredients, including lycopene. Nestlé Research Center employees were involved in the instigation, design, execution, analysis, and interpretation of the results. None of the other authors declared a conflict of interest concerning the results of this study.

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PYGEUM - *PRUNUS AFRICANA*

Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the alternate format help section.

(PDF Version - 53 KB)

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date

August 5, 2019

Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)		
		Proper name(s)	Part(s)	Prepar
Prunus africana	• Pygeum • Red stinkwood	*Prunus africana*	• Stem bark • Trunk bark	Dried

References: Proper name: USDA 2019; Common names: USDA 2019, Godfrey et al. 2010; Source materials: Godfrey et al. 2010, Mills and Bone 2005.

Route of Administration

Oral

Dosage Form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for any age category listed in this monograph for the specified route of administration are listed in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

Standardized extracts

Helps reduce the urologic symptoms (such as weak urine flow, incomplete voiding, frequent daytime and nighttime urination) associated with benign prostatic hyperplasia (Wilt et al. 2002; Ishani et al. 2000; Chatelain et al. 1999; Breza et al. 1998; Carani et al. 1991; Barlet et al. 1990).

Non-standardized preparations

No claim (safety only)

Dose(s)

Subpopulation(s)

Standardized extracts making a claim for symptoms of benign prostatic hyperplasia

Adult Males 18 years and older

Non-standardized preparations

Adults 18 years and older

Quantity(ies)

Symptoms of benign prostatic hyperplasia

Methods of preparation: Standardized extracts

75 - 200 milligrams of extract per day, standardized to 12-14% of phytosterols (Wilt et al. 2002; Ishani et al. 2000; Chatelain et al. 1999; Breza et al. 1998; Carani et al. 1991; Barlet et al. 1990).

No claim (safety only)

Methods of preparation: Dry, Powder, Non-Standardized Extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)

Not to exceed 4 grams of dried stem bark and/or trunk bark, per day.[1]

[1]Note
Maximum daily dose of the crude material is based on a conservative extrapolation of the dose supported in the available evidence.

Direction(s) for use

No statement required.

Duration(s) of Use

No statement required.

Risk Information

Caution(s) and warning(s)

Standardized extracts making a claim for symptoms of benign prostatic hyperplasia (adult males)

- Consult a health care practitioner/health care provider/health care professional/doctor/ physician if symptoms persist or worsen.
- Consult a health care practitioner/health care provider/health care professional/doctor/ physician prior to use to exclude the diagnosis of prostate cancer (Goldman and Ausiello 2004).

Non-standardized preparations for adults (i.e. including women) (safety only)

Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding.

Contraindication(s)

No statement required.

Known adverse reaction(s)

No statement required.

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

No statement required.

Specifications

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.
- Please note that this organism, one of its parts, or the organism or part from which this ingredient is derived, is considered at risk and is listed in Appendix II of CITES. Details are available from the following reference(s): http://www.ec.gc.ca/cites/default.asp?lang=En&n=C5F64D6F-1#_004.

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Pygeum

View 777 Products Containing: Pygeum

View 35 Canadian Licensed Products Containing: Pygeum

Scientific Name

Prunus africana, synonym Pygeum africanum.

Family: Rosaceae.

Background

Pygeum is the name given to extracts, teas, and supplements derived from the bark of the African plum tree *(Pygeum africanum)*, which is native to tropical Africa (10425,10426,70215,70222).

Also known as: African Plum Tree, African Prune, African Pygeum, Amande Amère, Ciruelo Africano, Prunier d'Afrique, Pygeum Africanus.

History

People Use This For

Orally, pygeum is used for treating functional symptoms of benign prostatic hyperplasia (BPH) and prostatic adenoma. It is also used orally for pain, kidney disease, urinary disorders, malaria, dyspepsia, fever, dysuria, psychosis, and sexual desire.

Safety

LIKELY SAFE ...when used orally and appropriately (3902,3903,6368,10425,10426).

PREGNANCY AND LACTATION: Insufficient reliable information available; avoid using.

Effectiveness

See detailed evidence summary

LIKELY EFFECTIVE
Benign prostatic hyperplasia (BPH). Taking pygeum orally reduces the functional symptoms of BPH. Pygeum decreases nocturia by 19%, increases peak urine flow by 23%, and reduces

residual urine volume by 24% in men with BPH (3902,3903,3904,4302,6368,10425,10426). Specific commercial products used in clinical research include Tadenan (Laboratoires DEBAT), Pronitol (Inofarma), and Pigenil (Inverni Della Beffa). Also, taking a specific combination product (ProstateEZE Max, Caruso's Natural Health) containing pygeum, pumpkin seed oil, Epilobium parviflorum, lycopene, and saw palmetto 1 capsule daily for 3 months decreases daytime urinary frequency by an additional 16% and nighttime urinary frequency by an additional 32% when compared with placebo in men with BPH (92164). However, taking a combination of pygeum and stinging nettle does not appear to improve urinary symptoms or quality of life in men with BPH (70219).

More evidence is needed to rate pygeum for this use.

Dosing & Administration

- Adult

  Oral:

  Benign prostatic hyperplasia (BPH): Standardized pygeum extract 75-200 mg daily as a single dose or two divided doses has been used (3902,3903,3904,10425,10426). Specific pygeum extracts used in clinical research have included Tadenan (Laboratoires DEBAT), Pronitol (Inofarma), and Pigenil (Inverni Della Beffa). The duration of pygeum treatment has ranged from 15 days to 120 days (10426). Some research suggests once or twice daily dosing is equally effective (6368). A specific combination product (ProstateEZE Max, Caruso's Natural Health - formerly Totally Natural Products) containing pygeum 15 grams dry stem equivalent, pumpkin seed oil 160 mg, Epilobium parviflorum extract 500 mg, lycopene 2.1 mg, and saw palmetto 660 mg once daily for 3 months has been used (92164).

- Standardization & Formulation

  Standardized pygeum extracts have been clinically evaluated. In most cases, details on the amount of sterols, triterpines, and other constituents contained in each extract are lacking. One specific pygeum extract (Tadenan, Laboratories DEBAT) is standardized to contain 14% triterpenes and 0.5% n-docosanol (10425,10426).

Adverse Effects

Report an Adverse Reaction to Pygeum

General: Orally, pygeum is well tolerated in most clinical research. Nausea and abdominal pain have been reported in some patients, but the rate of these events are similar to placebo treatment (10425,10426,70238).

- ⊞ Gastrointestinal

Toxicology

No adverse hematologic, biochemical, or pathological effects were seen in dogs taking pygeum 375 mg/kg daily or in rats taking pygeum 750 mg/kg daily for up to 6 months (70238). Additionally, pygeum extract in a dosage of 50-100 mg/kg daily for 52 days in rats had no toxic effect on blood chemistry, testes function, prostate function, adrenal function, or kidney function (70236). Taking pygeum at doses up to 80 mg/kg daily did not adversely affect fertility in rats and rabbits in another study (70238).

Interactions with Drugs

None known.

Interactions with Herbs & Supplements

None known.

Interactions with Foods

None known.

Interactions with Lab Tests

None known.

Interactions with Diseases

None known.

Mechanism of Action

General: The applicable part of pygeum is the bark. Pygeum bark contains a variety of constituents, including sterols such as beta-sitosterol, beta-sitosterone, and campesterol, ferulic acid esters such as N-docosanol and N-tetracosanol, triterpines such as oleanic acid, crateagolic acid, and ursolic acid, terpenic acids, aliphatic alcohols, and acidic phenols including atraric acid (70215,70225,70238).

Antiandrogenic effects: In vitro research shows that atraric acid, a constituent of pygeum, has antiandrogenic activity via inhibition of the ligand-induced transactivation of the human androgen receptor and ligand-induced nuclear localization. Glucocorticoid or progesterone receptors are not inhibited by atraric acid (70225). Other in vitro research shows that a selective

dichloromethane extract from pygeum has antiandrogenic effects. Bioactivity-directed fractionation of this extract led to the isolation of N-butylbenzenesulfonamide (NBBS) (70220).

Anticancer effects: The anticancer potential of pygeum has been demonstrated in both *in vitro* (PC-3 and LNCaP cells) and *in vivo* (TRAMP mouse model). In vitro, ethanolic extracts of pygeum inhibited the growth of cancer cell lines through induction of apoptosis, interference with cellular kinetics, and down regulation of ERalpa and PKC-alpha proteins. In animals, pygeum showed a significant reduction in prostate cancer incidence (35%) compared to casein-fed mice (62.5%) (70222). There is evidence that pygeum extracts have antiproliferative effects on prostatic fibroblasts and epithelial cells. Pygeum might inhibit growth factors such as basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF), which might inhibit prostate growth and cellular hyperplasia (4301,6769,11226).

Anti-inflammatory effects: In vitro research shows that pygeum decreases production of leukotrienes and other 5-lipoxygenase metabolites, which suggests possible anti-inflammatory activity (6769,10425,10426,70231,70239). In vitro, pygeum appears to inhibit fibroblast proliferation induced by epidermal growth factor, insulin-like growth factor type I, and basic fibroblast growth factor (4301).

Estrogenic effects: Pygeum contains phytoestrogens, some of which are similar in structure to estradiol. Preliminary animal research shows that pygeum extract increases uterus weight of ovariectomized and adrenalectomized mice, suggesting that pygeum has estrogenic activity (70233).

Genitourinary effects: Multiple mechanisms have been proposed for the genitourinary effects of pygeum, including 5-alpha reductase inhibition, modulation of bladder contractility, decreased leukotriene production, enhanced estrogenic effects, inhibition of fibroblast production, and anti-inflammatory properties (10425,10426). Pygeum extract appears to inhibit human prostatic 5-alpha-reductase, but much less powerfully than finasteride (70232). Reduction of urethral obstruction and improvement of bladder function have been observed (6769). Most studies of pygeum extract have addressed outcomes related to the obstructive component. In rats, pygeum inhibits dihydrotestosterone-induced prostate hyperplasia (70240), with a mechanism that appears unrelated to androgen receptor blockade (70232). In rats and men, pygeum extract has been shown to stimulate secretory activity of the prostate and seminal vesicles (70236,70241). Reduction of contractile dysfunction of the bladder caused by partial outlet obstruction has been observed with pretreatment of rabbits with pygeum extract 1-100 mg/kg daily (70235).

Pharmacokinetics

There is insufficient reliable information available about the pharmacokinetics of pygeum.

Classifications

5-Alpha Reductase Inhibitors

References

See Monograph References

This monograph was last reviewed on 2/8/2019 and last updated on 2/8/2019. Monographs are reviewed at least once per year. If you have comments or suggestions on something that should be reviewed or included, please tell the editors. For details about our evidence-based approach, see our Editorial Principles and Process.

Pygeum africanum for benign prostatic hyperplasia (Review)

Wilt TJ, Ishani A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 9

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Pygeum africanum for benign prostatic hyperplasia

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. The extract of the African prune tree, *Pygeum africanum*, is one of the several phytotherapeutic agents available for the treatment of BPH.

Objectives

To investigate the evidence whether extracts of *Pygeum africanum* (1) are more effective than placebo in the treatment of Benign Prostatic Hyperplasia (BPH), (2) are as effective as standard pharmacologic BPH treatments, and (3) have less side effects compared to standard BPH drugs.

Search strategy

Trials were searched in computerized general and specialized databases (MEDLINE (1966 to 2000), EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting relevant manufacturers and researchers.

Selection criteria

Trials were eligible if they (1) were randomized (2) included men with BPH (3) compared preparations of *Pygeum africanum* (alone or in combination) with placebo or other BPH medications (4) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements. Eligibility was assessed by at least two independent observers.

Data collection and analysis

Information on patients, interventions, and outcomes were extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of *Pygeum africanum* with placebo and standard BPH medications was the change in urologic symptoms scale scores. Secondary outcomes included change in urologic symptoms including nocturia and urodynamic measures (peak and mean urine flow, prostate size). The main outcome measure for adverse effects was the number of men reporting adverse effects.

Main results

A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was 64 days (range, 30 to 122 days). Many studies did not report results in a method that permitted meta-analysis. Compared to men receiving placebo, *Pygeum africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4 to -0.3 (n = 6 studies)]). Men using *Pygeum africanum* were more than twice as likely to report an improvement in overall symptoms (RR=2.1, 95% CI = 1.4 to 3.1). Nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23%. Adverse effects due to *Pygeum Africanum* were mild and comparable to placebo. The overall dropout rate was 12% and was similar between *Pygeum Africanum* (13%), placebo (11%) and other controls (8%).

Authors' conclusions

A standardized preparation of *Pygeum africanum* may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were small in size, were of short duration, used varied doses and preparations and rarely reported outcomes using standardized validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. These trials should be of sufficient size and duration to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

PLAIN LANGUAGE SUMMARY

Extracts from the African prune tree (*Pygeum africanum*) may be able to help relieve urinary symptoms caused by enlarged prostate (benign prostatic hyperplasia)

Benign prostatic hyperplasia (BPH), enlargement of the prostate gland, is common in older men. An enlarged prostate can interfere with urination, increasing the frequency and urge, or causing problems emptying the bladder. Both surgery and drugs are used to try to treat BPH. However, using herbal medicines to try to relieve the symptoms of BPH is becoming common. *Pygeum africanum* is one of several popular herbal remedies for BPH. The review found that *pygeum africanum* is well tolerated, cheaper than many prescription medicines used for BPH, and provides moderate relief from the urinary problems caused by an enlarged prostate.

BACKGROUND

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate. Symptoms related to BPH are one of the most common problems in older men. Histological evidence of BPH is found in more than 40% of men in their fifties and nearly 90% of men in their eighties (Berry 1984). The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH. In the United States treatment of BPH accounts for approximately 1.7 million physician office visits (Guess 1992) and results in more than 300,000 prostatectomies annually (McConnell 1994). The proliferative disorder resulting in BPH affects both the stromal and the epithelial portions of the prostate. The enlarging prostate results in the progressive occlusion of the proximal urethra and can result in both obstructive and irritative urinary tract symptoms. The obstructive symptoms of BPH include weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining (Christensen 1990; Caine 1987). The irritative symptoms include urinary frequency, urgency and nocturia. The treatment goal in the vast majority of patients with BPH is to relieve these bothersome symptoms.

The use of plants and herbs for medicinal purposes (phytotherapy) including treatment of BPH symptoms has been growing steadily in most countries. Usage of plant extracts is common in Europe and is increasing in the United States. Phytotherapeutic

agents represent nearly half of the medications dispensed for BPH in Italy, compared with 5% for alpha blockers and 5% for 5-alpha reductase inhibitors (Di Silverio 1993). In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate urinary obstructive symptoms and represents > 90% of all drugs prescribed for the treatment of BPH (Buck 1996). In the United States their use has also markedly increased, they are readily available as nonprescription dietary supplements and are often recommended in "natural health food stores or books" for self treatment of BPH symptoms.

Pygeum africanum, an extract from the bark of the African prune tree, has been utilized in Europe since 1969 for the treatment of mild to moderate symptomatic benign prostatic hyperplasia. The mechanism of action of *Pygeum africanum* remains unclear. In animal models, *Pygeum africanum* has been shown to have pharmacologic properties that may be beneficial in the treatment of benign prostatic hyperplasia. These include modulation of bladder contractility, anti-inflammatory activity, decreased production of leukotrienes and other 5-lipoxygenase metabolites (Sidoti 1993; Paubert-Braquet 1994), inhibition of fibroblast production (Yablonsky 1997; Paubert-Braquet 1993) effects on adrenal androgens (Thieblot 1977), and restoration of secretory activity of prostate epithelium.

Despite the wide-spread use of *Pygeum africanum* uncertainty remains regarding treatment effectiveness and tolerability. A previous qualitative summary did not meet criteria for a systematic review (Andro 1995). This review included results from open-labelled uncontrolled studies, did not assess study quality nor conduct a quantitative meta-analysis to estimate the magnitude or statistical significance of treatment efficacy and was sponsored by a manufacturer of *Pygeum africanum* extract. We conducted a systematic review including a quantitative meta-analysis, where possible, of the evidence from randomized controlled trials to determine the therapeutic efficacy and tolerability of *Pygeum africanum*, alone or in combination with other herbal agents, for men with symptomatic benign prostatic hyperplasia.

OBJECTIVES

The aim of our review was to provide a comprehensive overview including a quantitative meta-analysis of the existing evidence to determine the therapeutic efficacy and the adverse effects of the plant extract *Pygeum africanum*. Specifically, was *Pygeum africanum* more effective than placebo in improving the symptoms and/or urodynamics of BPH and as effective as current medical therapies.

Main comparison

Determine if *Pygeum africanum* was more efficacious than placebo in improving validated and standardized urologic symptom scores in men with symptomatic BPH.

Secondary comparisons

1. Determine if *Pygeum africanum* is more efficacious than placebo in improving urodynamic measurements and urinary symptoms including peak urine flow, mean urine flow, residual urine, prostate size, nocturia, dysuria, and urinary frequency.

2. Determine if *Pygeum africanum* is as efficacious as active controls in improving urologic symptom scores and urodynamic measures.

3. Determine the adverse effects of *Pygeum africanum*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials.

Types of participants

Men with symptomatic benign prostatic hyperplasia

Types of interventions

Comparison of preparations of *Pygeum africanum* with placebo or medical therapies for BPH with a treatment duration of at least 30 days.

Types of outcome measures

Urologic symptom scores (Boyarsky, American Urologic Association Score, International Prostate Symptom Score:IPSS); Urodynamic measures (defined as change in peak urine flow (PUF), mean urine flow (MUF), residual urine volume; changes in prostate size (measured in cc); urinary frequency, nocturia (times/per evening); quality of life score (QOL); and overall physician/patient health assessment.

Search methods for identification of studies

We searched MEDLINE for 1966 to 2000 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the MeSH headings "prostatic hyperplasia," "phytotherapy," "plant extracts," "Pygeum africanum," "Tadenan", "Docosonal", and "Pigenil" including all subheadings (Dickersin 1994). A search of EMBASE, years 1974 to 1999 was done by using a similar approach to that for Medline. We also searched the private database Phytodok, Munich Germany, and the Cochrane Library, including the database of the

Cochrane Prostate Diseases and Urologic Malignancies Review Group and the Cochrane Field for Complementary Medicine. Reference lists of all identified trials and previous reviews were searched for additional trials. The manufacturer and authors were contacted for missing data or additional trials. There were no language restrictions.

Data collection and analysis

Eligibility:
Two investigators (AI and RM) independently determined if identified studies met inclusion criteria.
Extraction:
The following data were extracted from each included study: study characteristics, demographics of patients, enrollment criteria, outcomes, adverse effects, and number and reasons for dropout. Missing or additional information was sought from authors/sponsors. Included and excluded studies as well as extracted data were reviewed and discrepancies resolved by discussion and consensus.
Assessment of methodological quality:
Study quality was assessed using the method outlined by Schulz and colleagues (Schulz 1995) assigning 1 to poorest quality and 3 to best quality: 1 = trials in which concealment was inadequate (e.g. alteration or reference to case record numbers or to dates of birth); 2 = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and 3 = trials deemed to have adequate measures to conceal allocations (e.g. central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes etc. that contained elements convincing of concealment).
Summarizing results of primary studies:
Outcomes:
The mean urologic symptom score (points), peak and mean urine flow (mL/sec), residual urine volume (mL), prostate size (cc), frequency (% men reporting), urgency (% men reporting), dysuria (% men reporting) and nocturia (# times). The number and percent of men reporting specific side effects and/or withdrawing from the study.
Meta-analysis:
Because no common outcome measure was available from all eighteen studies we utilized two methods for combining data. One method, reported by Saint 1995, assesses treatment effect size for continuous variables by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome when trials report different outcome measures of effectiveness (e.g. symptom scale scores, nocturia, peak urine flow rate). The second method calculates a summary measure for individual outcomes using studies that provide similar outcome measures and utilizes standard meta-analytic techniques described below.
For determining effect size we utilized the outcome that was determined a priori to be most clinically significant (order of clinical importance: symptom scale score > nocturia > peak urine flow > residual urine volume). One outcome from each study was then transformed into units of standard deviations (SD), giving a comparable effect size for each study. The study-specific overall effect size was the difference in mean outcome for the *Pygeum africanum* and placebo groups, divided by the pooled SD of the outcome measure. The summary effect size across studies was calculated as the weighted average of the study-specific effect size, with weights equal to the inverse of the estimated variance of each using standard meta-analytic methodology as developed by DerSimonian and Laird (DerSimonian 1986; Laird 1990). We used the same definition of standardized effect sizes to look at individual and comparable continuous outcomes when available (nocturia and peak urine flow). The statistical significance of the summary effect size was assessed by comparing it with the standard normal distribution. A scale for effect size suggested by Cohen 1988 was used with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect.
Additional meta-analyses considered the difference between *Pygeum africanum* treatment and the control treatment in the mean change from baseline to end of follow-up for each separate continuous outcome. For those studies not reporting mean change scores and the corresponding standard errors, the standard errors for the mean change scores were approximated using the standard errors of the outcomes at baseline and followup. The approximation used the methodology reported by Laird 1990 and Lau 1996 based on the correlation between outcomes. Analyses were conducted for three different assumed values for this correlation (0.25, 0.50, 0.75). This approach was taken to examine the sensitivity of the results to the value of this unknown parameter. Weighted mean differences were calculated using the methodology outlined above. There were no qualitative differences between the meta-analysis results for the three assumed correlation values; we present here the results for the assumed correlation of 0.50. For categorical outcome measures weighted relative risks and 95% CI were calculated using standard meta-analytic techniques.
Chi squared tests were used for analysis of bivariate comparisons (adverse events and dropouts) using simple pooling of data. To assess the percentage of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (i.e., men who dropped out or were lost to follow-up were considered to have had worsening symptoms) (Lavori 1992). The denominator for the modified intention-to-treat analysis included the number randomized to treatment at baseline, and the numerator included the number completing the trial and showing improvement. A test for heterogeneity was calculated according to standard formulas (DerSimonian 1986; Saint 1995) and a random effects model utilized for all summary estimates.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The combined search strategies identified 31 trials; 18 met inclusion criteria. None were conducted in the United States and 12 were reported in a non-English language [German (1), Italian (10), French (2)]. Fourteen trials were excluded because they did not include a control group (Anonymous 1973; Breza 1998; Diz 1973; Grasset 1974; Greiner 1970; Grévy 1970; Guilland-Vallée 1970; Guillemin 1970; Huet 1970; Lange 1970; Lhez 1970; Martínez-Piñeiro '73; Robineau 1976; Rometti 1970). The majority of studies examined *Pygeum Africanum* alone versus placebo alone (n = 11) (Barlet 1990; Bassi 1987; Blitz 1985; Bongi 1972; Donkervoort 1977; Dufour 1984; Frasseto 1986; Maver 1972; Ranno 1986; Rizzo 1985). Two trials comparing *Pygeum africanum* against an anti-inflammatory drug (Gagliardi 1983; Rigatti 1983). One study comparing *Pygeum Africanum* to placebo included an additional treatment arm of *Pygeum africanum* in combination with a steroid (Giacobini 1986). Two studies compared *Pygeum africanum* alone to one or more herbal agents and versus placebo (Barth 1981; Mandressi 1983), one trial compared *Pygeum africanum* to another herbal agent (Dutkiewicz 1996), one trial compared different daily dosage forms of *Pygeum africanum* (Chatelain 1999), and one trial compared two different doses of *Pygeum africanum* in combination with another herbal extract (Krzeski 1993). None of the "active comparison" arms have been conclusively demonstrated to be effective in treating symptomatic benign prostatic hyperplasia.

A total of 1562 participants were randomized in the 18 trials. The mean treatment duration was 64 ± 21.1 days and ranged from 30 to 122 days. The majority of the studies (n = 14; participants = 1103) utilized a standardized extract of *Pygeum africanum*. The doses of *Pygeum africanum* ranged between 75 to 200 mg per day. Of the placebo controlled trials 1 utilized a dose of *Pygeum africanum* equal to 75 mg per day, 7 utilized a dose of 100 mg per day, 4 utilized a dose of 200 mg/day and one did not report the dosage (Dutkiewicz 1996). For studies that provided baseline data, results did not vary between treatment arms and were consistent with men typically presenting with moderate benign prostatic hyperplasia. The mean age was 66.± 6.9 years (9 studies, n = 845, range 42 to 89); nocturia = 3 ± 0.7 times per evening (4 studies, n = 413); peak urine flow = 12 ± 3.6 mL/sec (5 studies, n = 416); residual urine volume = 40 ± 25.6 mL (2 studies, n = 284). Not all studies could be pooled because of differences in reporting methods. Of the 13 trials of *Pygeum africanum* versus placebo identified, 12 reported a beneficial effect of *Pygeum africanum* on at least one measure of effectiveness: overall symptoms, nocturia, peak urine flow or residual volume. Only one trial demonstrated no difference between *Pygeum africanum* and placebo (Rizzo 1985). This trial assessed the effect of *Pygeum africanum* on nocturia, peak urine flow and overall symptom change in 20 men over 12 weeks. None of the trials showed an effect of *Pygeum africanum* worse then placebo or "active control."

Risk of bias in included studies

Only one of the studies reported a method for concealment of treatment allocation (score = 2) but 17 of the 18 studies were double-blinded. Most studies did not provide baseline patient information nor provide clinically relevant baseline or outcomes data in a standardized fashion. No placebo-controlled studies utilized standardized, validated symptom scales (the outcome measure of greatest clinical significance). There was no information on patient race, comorbid conditions, prostate size or standardized/validated urologic symptom scale scores. All studies were of short treatment duration with none having a follow up greater than four months.

Effects of interventions

Summary Effect Sizes:

Six studies involving 474 participants (54% of all participants enrolled in placebo controlled trials) could be pooled to provide a weighted estimate of effectiveness (Barlet 1990; Bongi 1972; Giacobini 1986; Mandressi 1983; Maver 1972; Rizzo 1985). All involved *Pygeum africanum* alone versus placebo, and five utilized a standardized preparation of *Pygeum africanum*. The overall summary effect size was -0.8 SD (95% CI -1.4 to -0.3) indicating a statistically significant large improvement with *Pygeum africanum*. The summary effect size from three studies that provided data on nocturia was -0.8 SD (95% CI -1.4 to -0.1) (Barlet 1990; Bongi 1972; Mandressi 1983). This indicates that *Pygeum africanum* resulted in a statistically significant moderate to large improvement in nocturia. Summary results from the four studies providing data on peak urine flow demonstrated a mean effect size of 0.7 SD (95% CI 1.3 to 0.0) indicating a moderate effect on peak urine flow (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985).

Urinary symptoms and flow measures:

Consistent with the results seen in the summary effect sizes, *Pygeum africanum* improved specific urinary symptoms and flow measures. In 5 double-blind trials involving 430 participants, men receiving *Pygeum africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared to men taking placebo (65% vs. 30%; RR = 2.1; 95% CI = 1.4 to 3.1) (Barlet 1990; Blitz 1985; Bongi 1972; Donkervoort 1977; Mandressi 1983). *Pygeum africanum* reduced nocturia compared to placebo by 19% (weighted mean difference (WMD) = - 0.9 times per evening; 95% CI = -2.0 to 0.1) though this did not reach statistical significance (Barlet 1990; Bongi 1972; Mandressi 1983). *Pygeum africanum* also increased peak urine flow compared to placebo by 23%, WMD = 2.5 mL/sec (95% CI = 0.3 to 4.7) (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985). *Pygeum africanum* reduced residual urine volume by 24% (WMD = -13 mL; 95% CI = -23.3 to -3.0) (Barlet 1990; Giacobini 1986).

To assess for publication bias we constructed funnel plots from published trials providing data for calculation of summary effect size, overall symptom improvement, nocturia and peak urine flown. The few studies available for funnel plot analysis make assessment difficult and do not provide clear evidence for or against publication bias.

Adverse Events:

All studies provided information on the percentage of men who dropped-out or were lost to follow up, potentially the most reliable indicator of tolerability. The mean percentage of participants who dropped out was 12% (n = 179), ranged from 0% to 45% and did not differ between *Pygeum africanum* (13%), placebo (11%) and other controls (8%) (P = 0.4 vs placebo and P=0.5 vs other control). Three studies (two placebo controlled) had drop out rates > 20%. The reason for the high drop out rate was not reported but two of the trials (Barth 1981; Chatelain 1999) indicated that adverse effects were "infrequent and mild" in participants completing the trial. None of these three trials reported outcome data in a method suitable for incorporation into the effect size analyses. Thirteen of the eighteen studies provided information on specific adverse events. Adverse events due to *Pygeum africanum* were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among seven men in five trials.

DISCUSSION

This systematic review summarizes the available evidence from randomized controlled trials regarding the efficacy and tolerability of *Pygeum africanum* for the treatment of lower urinary tract symptoms attributable to benign prostatic hyperplasia. Our results suggest that *Pygeum africanum* improves urinary symptoms and flow measures and that the point estimate for the effect size is moderate in magnitude. Because of the diversity of outcome measures, a summary estimate of the effect of *Pygeum africanum* was based on units of SD available from 6 studies involving 474 participants. This method is useful for determining if an overall benefit exists but only indicates whether the overall effect is of small, moderate or large magnitude. Our analyses of individual effect sizes for nocturia and peak urinary flow indicate that improvement of comparable magnitude occurred in both urinary symptoms and flow measures.

Summary risk ratios and weighted mean differences comparing *Pygeum africanum* to placebo for overall symptoms, peak urine flow, and residual urine volume demonstrated a statistically significant improvement as well as a trend towards improvement for nocturia. These findings are considered clinically significant, comparable to other widely used treatment options and consistent with the results obtained utilizing effect sizes. The results from individual trials demonstrated that all but one study noted an improvement with *Pygeum africanum* for symptoms attributable to benign prostatic hyperplasia. Additionally, *Pygeum africanum* was well tolerated with the drop out rate for men receiving *Pygeum africanum* not different than for men receiving placebo.

While studies utilized different quantities, dosing intervals and preparations of *Pygeum africanum* the majority of studies utilized a standardized extract of *Pygeum africanum* at a dose of 100 to 200 mg per day. Five of the six studies providing data for summary estimates of effect size utilized the standardized extract of *Pygeum africanum*. All summary efficacy data were derived from placebo-controlled, double blind studies utilizing a "noncombination" source of *Pygeum africanum*. This suggests that a standardized preparation of *Pygeum africanum* is associated with the observed improvement in symptoms and flow measures.

No study was conducted in the United States and many studies did not report means and standard deviations making completion of a quantitative review difficult. There was no information provided to determine if *Pygeum africanum* prevented long-term complications of benign prostatic hyperplasia such as acute urinary retention, renal insufficiency or the need for surgical intervention. No studies compared *Pygeum africanum* with medical interventions of demonstrated effectiveness including alpha adrenergic blockers and 5-alpha reductase inhibitors. The "active controls" used in the studies have not been convincingly demonstrated to have beneficial effects.

A possible source of bias is that outcomes included in the effect size calculation could have been selected to favor *Pygeum africanum*. However, we ranked outcome measures for inclusion in the effect size calculation prior to data abstraction and analysis. Furthermore, effectiveness was consistently observed in all but one of the studies and regardless of whether the results were reported as physician rating of patient's global symptom improvement (n = 6 trials; 430 patients); nocturia (n = 3 trials; 325 participants); peak urine flow (n = 4 trials; 363 participants); or residual volume (n = 4 trials; 264 participants). An additional source of bias could result from failure to publish small negative studies (publication bias) or outcomes that were not favorably affected. This would enhance the summary effect size estimates and could contribute to our finding that only one out of seventeen reported studies was negative. Funnel plots were constructed to assess for publication bias, however few studies could be included in the plot construction.

AUTHORS' CONCLUSIONS

Implications for practice

The overall standardized effect size and the summary improvement in global symptoms, nocturia, peak urine flow and residual urine volume suggests that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of mod-

est size and appears to be clinically significant. *Pygeum africanum* is well tolerated and costs less than most prescription medications. A standardized preparation of *Pygeum africanum*, may be a useful treatment option, at least in the short term, for men with lower urinary symptoms consistent with benign prostatic hyperplasia.

Implications for research

Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. Future trials should be of sufficient size and duration (e.g. > 6 months) to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barlet 1990

Methods	Multicentre study. Double blinded: yes.	
Participants	N=263 European men with symptomatic BPH, age > 50. Age range 50-85, mean 67. Lost to follow-up: 8 (3%).	
Interventions	Control: placebo (n=132). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=131). Treatment duration: 60 days.	
Outcomes	Overall improvement in symptoms (MD/subject - rating); Nocturia; peak urine flow; residual volume. Adverse events.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Barth 1981

Methods	Double blinded: yes.
Participants	N=215 European men with symptomatic BPH, age > 50. Lost to follow-up: 67 (31%).
Interventions	Control 1: placebo (n=46). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=50). Control 2: Sitosterin 30 mg (n=34). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=37). Control 3: ERU* 300 mg (n=24). Treatment 3: P. africanum extract (Docosanol) 100 mg daily (n=24). Treatment duration: 8 weeks.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.
Notes	
Risk of bias	

Barth 1981 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bassi 1987

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Mean age: 67 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Pigenil) 100 mg daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Blitz 1985

Methods	Double blinded: yes.
Participants	N=57 French men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 100 mg daily Treatment duration: 60 days.
Outcomes	Overall improvement in symptoms.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Blitz 1985 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bongi 1972

Methods	Double blinded: yes.
Participants	N=50 Italian men with symptomatic BPH, residual volume < 200 ml. Age range: 49-84. Lost to follow-up: 0.
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 60 days
Outcomes	Nocturia; residual volume.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Chatelain 1999

Methods	Double blinded: yes.
Participants	N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF < 15 ml/s, residual volume < 150 ml. Mean age: 66 years. Lost to follow-up: 26 (11.1%).
Interventions	Treatment 1: P. africanum extract (Tadenan) 50 mg x 2 daily (n=101). Treatment 2: P. africanum extract (Tadenan) 100 mg daily (n=108). Treatment duration: 60 days.
Outcomes	Symptom score (IPSS); peak urine flow. Adverse events.
Notes	235 men were randomized, 223 completed the comparative phase, but only 209 men were valid for per-protocol analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Chatelain 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Donkervoort 1977

Methods	Double blinded: yes.
Participants	N=20 Dutch men with symptomatic BPH. Lost to follow-up: 4 (20%).
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 12 weeks.
Outcomes	Overall improvement in symptoms; Nocturia; peak urine flow.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dufour 1984

Methods	Double blinded: yes.
Participants	N=120 French men with symptomatic BPH not in need of surgery. Lost to follow-up: 56 (47%).
Interventions	Control: placebo (n=60). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=60). Treatment duration: 6 weeks.
Outcomes	Nocturia.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dutkiewicz 1996

Methods	Single-site study. Double blinded: no. Randomization: unclear Patients not blinded: Providers not blinded: Lost to follow-up: none
Participants	N=89 Polish men with symptomatic BPH. Age range: 50-68. Lost to follow-up: 0.
Interventions	Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months (n=51). Treatment: Tadenan 2 tablets twice daily (38). Treatment duration: 24 weeks.
Outcomes	Obstructive symptom score Irritative symptom score; peak urine flow; residual volume; prostate volume. Adverse events.
Notes	Exclusions: No details provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Frasseto 1986

Methods	Double blinded: yes.
Participants	N=20 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=10). Treatment: P. africanum extract (Tadenan) 75 mg daily (n=10). Treatment duration: 60 days
Outcomes	"Dysuric symptoms" (nocturia, pollachiuria, reduced strenght of flux). Adverse events.
Notes	Prostate size evaluated by ultrasonography.

Frasseto 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gagliardi 1983

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years. Lost to follow-up: 1 (2.5%).
Interventions	Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 30 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Giacobini 1986

Methods	Double blinded: yes.
Participants	N=21 Italian men with symptomatic BPH. Age range: 48-70. Lost to follow-up: 0.
Interventions	Control: placebo (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily + medroxyprogesterone acetate (Farlutal) (n=7). Treatment duration: 90 days.
Outcomes	Peak flow rate; residual volume. Adverse events.
Notes	

Giacobini 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Krzeski 1993

Methods	Double blinded: yes.
Participants	N=134 Polish men with symptomatic BPH (> 1 symptom). Age range: 53-84, mean 64 years. Lost to follow-up: 14.2%.
Interventions	Treatment 1: P. africanum 25 mg + Urtica dioica 300 mg (n=67). Treatment 2: half dose of above (n=67). Treatment duration: 8 weeks.
Outcomes	Overall improvement in symptoms; nocturia; peak flow rate; residual volume. Adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mandressi 1983

Methods	Double blinded: yes. Randomization: Identical packaging
Participants	N=60 Italian men with symptomatic BPH. Age range: 50-80.
Interventions	Control 1: placebo (n=20). Control 2: Permixon 320mg daily (n=20). Treatment: Pygeum africanum extract Average (n=20). Treatment duration: 30 days. Lost to follow-up: unclear

Mandressi 1983 (*Continued*)

Outcomes	Patient self-rating of "Dysuric symptoms" (pain on voiding) Nocturia. Adverse events. Dropouts due to side effects: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Maver 1972

Methods	Double blinded: yes.
Participants	N=60 Italian men with symptomatic BPH. Age range: 55-85, mean 66 years.
Interventions	Control: placebo (n=30). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=30). Treatment duration: 60 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ranno 1986

Methods	Double blinded: yes.
Participants	N=39 Italian men with symptomatic BPH. Mean age: 70 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=19). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 2 months.
Outcomes	Nocturia; peak urine flow. Adverse events.

Ranno 1986 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rigatti 1983

Methods	Double blinded: yes.
Participants	N=49 Italian men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: NSAID (n=25). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=24). Treatment duration: 60 days.
Outcomes	Residual volume. Adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rizzo 1985

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 42-74, mean 62 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.
Notes	

Risk of bias

Rizzo 1985 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

* Extract of Rad. urticae

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1973	No control group.
Breza 1998	No control group.
Diz 1973	No control group.
Grasset 1974	No control group.
Greiner 1970	No control group.
Grévy 1970	No control group.
Guilland-Vallée 1970	No control group.
Guillemin 1970	No control group.
Huet 1970	No control group.
Lange 1970	No control group.
Lhez 1970	No control group.
Martínez-Piñeiro '73	No control group.
Robineau 1976	No control group.
Rometti 1970	No control group.

DATA AND ANALYSES

Comparison 1. Pygeum africanum vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptoms improvement: Overall improvement/Global assessment/MD rating	5	430	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.40, 3.06]
2 Nocturia (times per evening)	3	325	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.95, 0.14]
3 Peak urine flow (mL/sec)	4	363	Mean Difference (IV, Random, 95% CI)	2.50 [0.29, 4.71]
4 Residual volume (mL)	2	264	Mean Difference (IV, Random, 95% CI)	-13.17 [-23.34, -2.99]

WHAT'S NEW

Last assessed as up-to-date: 25 November 1997.

Date	Event	Description
28 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2002

Date	Event	Description
26 November 1997	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Veterans Affairs Health Services Research and Development (HSRD) Office, USA.
- Minneapolis/VISN-13 Center for Chronic Diseases Outcomes Research (CCDOR), USA.

External sources

- No sources of support supplied

NOTES

This review is out of date and has been withdrawn.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Plant Bark [chemistry]; Plant Extracts [therapeutic use]; Prostatic Hyperplasia [*drug therapy]; Randomized Controlled Trials as Topic; Urination Disorders [drug therapy]

MeSH check words

Humans; Male

SAW PALMETTO, LIPOSTEROLIC EXTRACT

Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the alternate format help section.

(PDF Version - 89 KB)

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date

September 25,2018

Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)		
		Proper name(s)	Part(s)	Prepara
• *Serenoa repens*	• Saw palmetto • liposterolic extract	*Serenoa repens*	Fruit	Dried

References: Proper name: USDA 2018; Common name: USDA 2018, McGuffin et al. 2000; Source material: USP 32 2009, Blumenthal et al. 2000, Mills and Bone 2000.

Route of Administration

Oral

Dosage Form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for any age category listed in this monograph for the specified route of administration are listed in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

Used in Herbal Medicine to help relieve the urologic symptoms (e.g. weak urine flow/incomplete voiding/frequent daytime/night time urination) associated with mild to moderate benign prostatic hyperplasia (BPH) (Croom and Chan 2010; USP 32 2009; Bradley 2006; Wilt et al. 2002; Blumenthal et al. 2000).

Dose(s)

Subpopulation(s)

Adult males 18 years and older

Quantity(ies)

Methods of preparation: Standardized extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)
100 - 400 milligrams of liposterolic extract of dried fruit standardized to 70 - 95 % fatty acids, per day (Croom and Chan 2010; derMarderosian and Beutler 2009; USP 32 2009).

Direction(s) for use

Take with food to minimize gastric disturbance (derMarderosian and Beutler 2009; USP 32 2009).

Duration(s) of Use

No statement required.

Risk Information

Caution(s) and warning(s)

- Consult a healthcare practitioner/health care provider/health care professional/ doctor/ physician if symptoms persist or worsen.
- Consult a health care practitioner/health care provider/health care professional/ doctor/ physician prior to use to exclude a diagnosis of prostate cancer (USP 32 2009; Mills and Bone 2005).

Contraindication(s)

No statement required.

Known adverse reaction(s)

No statement required.

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

Store in a tightly closed, light-resistant container in a cool, dry place (USP 32 2009; WHO 2002).

Specifications

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.

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Wild Yam is used industrially as an active agent in the half-synthesis of steroid hormones and for the manufacture of homeopathic preparations.

PRECAUTIONS AND ADVERSE REACTIONS

General: Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded.

Drug Interactions: There is evidence that the diosgenin componant of Wild Yam may decrease the anti-inflammatory effect of indomethacin by increasing the elimination constant and reducing plasma levels of indomethacin (Yamada et al, 1997). Wild Yam may have an additive estrogenic effect when administered with estrogen containing drugs.

OVERDOSAGE

Poisoning is conceivable with overdosages because of the picrotoxin-like effect of dioscorin (see Cocculi fructus).

DOSAGE

Mode of Administration: Liquid extract.

How Supplied:

Capsules—200 mg, 400 mg, 505 mg, 535 mg

Liquid—1:1; 1:2; 250 mg/ml

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Willow Herb

Epilobium species

DESCRIPTION

Medicinal Parts: The medicinal parts are the herb and the roots of the drug containing Epilobium varieties.

Flower and Fruit: The flowers are arranged in long clusters of crimson flowers. The receptacle extends over the ovary. There are 4 sepals that are often colored and 8 stamens. The petals are purple to pink seldom white or yellow. The style is erect or curved downwards. The stigma is capitual or club-like and has 4 grooves or is divided into 4. The fruit is long, linear capsule-like, quadrangular, 4-valved and opens with 4 bending valves. The seeds are numerous and smooth or they may be covered in tiny warts with a white, often short-stemmed, tuft of hair.

Leaves, Stem and Root: The species includes perennial herbs and occasionally up to 2 m high sub-shrubs with underground creeping rhizomes. The stems are erect, glabrous or covered with simple hairs or glandular hairs. The leaves are entire-margined or dentate. They are alternate or opposite and in whorls of 3, which are flat or occasionally with a turned-back border.

Habitat: The plant is found all over Europe, Asia, Africa and America. Australia, Tasmania and New Zealand.

Production: Willow Herb is the aerial part of Epilobium parviflorum and other small-blossomed Willow Herbs. The herb is dried in the open air in the shade.

Other Names: Blood Vine, Blooming Sally, Rose Bay Willow Herb, Willow-Herb

ACTIONS AND PHARMACOLOGY

COMPOUNDS: ANGUSTIFOLIUM VARIETY

Flavonoids: in particular myricitrin, isoquercitrin, quercitrin, guaiaverin, quercetin-3-O-beta-D-glucuronide

Palmitate

Steroids: in particular beta-sitosterol and its ester, including among others beta-sitosterol caproate

Tannins

COMPOUNDS: HIRSUTUM VARIETY

Flavonoids: in particular guaiaverin, hyperoside, myricitrin, quercetin-3-0-beta-D-glucuronide,quercetin-3-0-alpha-L-arabinofuranoside

Steroids: in particular beta-sitosterol

Tannins

COMPOUNDS: PARVIFLORUM VARIETY

Flavonoids: in particular guaiaverin, quercetin-3-O-beta-D-glucuronide, quercitrin

Palmitate

Steroids: in particular beta-sitosterol and its ester, including among others beta-sitosterol caproate

Tannins

EFFECTS

Willow Herb is reported to have antiphlogistic and antiexudative effects. A watery infusion revealed a significant inhibitory effect on edema in rat paws. The methanol infusion had a distinctly weaker effect.

Antimicrobial effects have also been demonstrated. A suspension of the fresh drug in ethanol stunts the growth of the bacteria of *Pseudomonas pyocyanea.* Tincture and the liquid extract showed anti-microbial effect against *Candida albicans, Staphylococcus albus* and *Staphylococcus aureus.*

The dried residue of a maceration, which is fixed on filter paper, shows a weak effect against *Bacillus subtilis, Escherichia coli, Mycobacterium smegmatis, Shigella flexneri, Shigella sonnei* and *Staphylococcus aureus.* An extra fraction of the drug (insufficiently chemically defined) showed a tumor-inhibiting effect on transplanted tumors in mice and rats. The drug was helpful in treating benign prostate hyperplasia and certain micturition disorders.

INDICATIONS AND USAGE

Unproven Uses: Willow Herb is used internally for micturition problems associated with prostatic hyperplasia (Stages I to II), and for gastrointestinal disorders and mucous membrane lesions of the mouth. Native Americans use the drug for rectal bleeding; the Chinese use it for menstrual disorders. The watery extract is used externally to improve the healing of wounds.

PRECAUTIONS AND ADVERSE REACTIONS

Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded.

DOSAGE

Mode of Administration: The drug is not available as a ready made medicinal preparation; only as a tea, watery extract or as a vegetable.

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Winter Cherry

Physalis alkekengi

DESCRIPTION

Medicinal Parts: The medicinal parts are the ripe fruit and the leaves.

Flower and Fruit: The whitish, long-pedicled flowers are solitary and nodding. The calyx is fused and 5-tipped. The corolla is fused with a slightly 5-tipped margin. There are 5 stamens and 1 superior ovary. The fruit is a cherry-sized, globular, scarlet berry, enclosed in the swollen, orange-red calyx. It contains numerous flat, reniform seeds.

Leaves, Stem and Root: The plant is a perennial and grows from 30 to 60 cm. The stems are erect or ascending and angular with opposite, long-petioled, entire-margined leaves.

Characteristics: Winter Cherry has a lantern-like, enlarged calyx when the fruit is ripe.

Habitat: The plant is indigenous to central and southern Europe, China and Indochina and is naturalized in the U.S.

Production: Winter Cherry fruits are the ripe fruits of Physalis alkekengi.

Other Names: Cape Gooseberry, Coqueret, Strawberry Tomato

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Whitasteroids: among others physalines A-C, F, L-0

Carotinoids: including zeaxanthine dipalmitic acid ester (red)

EFFECTS

No information is available.

INDICATIONS AND USAGE

Unproven Uses: Winter Cherry is used as a diuretic in kidney and bladder conditions and in the treatment of gout and rheumatism.

PRECAUTIONS AND ADVERSE REACTIONS

The ripe fruit is edible, but unripe fruit can cause poisoning in animals. ;

DOSAGE

Mode of Administration: The drug is administered in a ground form and as an extract.

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thujon acting as the principal ingredient, along with containing podophyllotoxin and other lignans.

A diuretic effect has been described for the essential oil and the drug is also said to be emmenagogic and hemostyptic.

The use of the drug on viral warts seems justified because of the podophyllotoxin content.

INDICATIONS AND USAGE

Unproven Uses: For external use only, in the treatment of fig warts.

Homeopathic Uses: Juniperus sabina is used for metrorrhagia, gout, inflammation of the urogenital tract, rheumatism and warts.

PRECAUTIONS AND ADVERSE REACTIONS

The drug is severely toxic. External administration, in particular of the volatile oil, can lead to severe skin irritation, blister formation, necroses and resorbent poisonings.

OVERDOSAGE

One is cautioned against internal administration of the drug and of the volatile oil. Fatal poisonings have occurred repeatedly following administration of the drug in either powder form or infusion as an abortient. Symptoms include, among others, queasiness, cardiac rhythm disorders, spasm, kidney damage and hematuria. Death finds the patient in a state of central paralysis and deep unconsciousness. The internal administration of 6 drops of the volatile oil is life-threatening for humans.

Following gastrointestinal emptying, (inducement of vomiting, gastric lavage, sodium sulfate) and instillation of activated charcoal, the therapy for poisonings consists of treating spasms with diazepam (I.V.), colic with atropine, electrolyte substitution and treating possible cases of acidosis with sodium bicarbonate infusions. Monitoring of kidney function, blood coagulation and liver values is essential. Intubation and oxygen respiration may also be necessary. The level of danger depends upon the age of the drug of the volatile oil, as the toxicity probably develops chiefly through the formation of terpene peroxides during storage. The fresh tips of the branches contain presumably very little toxicity.

DOSAGE

Mode of Administration: For external use, as a powdered drug. Internal application is obsolete because of the danger of intoxication.

Daily Dosage: maximum 1 gm externally.

Savin Tops powder - Powder twice daily, put bandages into the folds of skin.

Skin ointment - Average content: 50% drug.

Homeopathic Dosage: 5 drops, 1 tablet or 10 globules every 30 to 60 minutes (acute) or 1 to 3 times daily (chronic); parenterally: 1 to 2 ml sc acute, 3 times daily; chronic: once a day (HAB1).

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Saw Palmetto

Serenoa repens

TRADE NAMES

Saw Palmetto (available from numerous manafacturers), Saw Palmetto Berries, Saw Palmetto Standardized, Centrum Saw Palmetto, Proactive Saw Palmetto, Standardized Saw Palmetto ExtractCap, Saw Palmetto Extract, Saw Palmetto Power, Premium Blend. Saw Palmetto, Herbal Sure Saw Palmetto, Quanterra Prostate, Super Saw Palmetto Plus

DESCRIPTION

Medicinal Parts: The medicinal parts are the partially dried ripe fruit, the ripe fresh fruit and the ripe dried fruit.

Flower and Fruit: The inconspicuous cream flowers are in short, densely pubescent, paniculately branched inflorescences. The fruit is deep purple to almost black. It is an ovate, 3 cm long, 1-seeded berry. It has a hard but fragile pericarp that covers a pale brown, spongy pulp. The endocarp is thin and papery. The fruit is slightly wrinkled,

1.25 to 2.5 cm long and 1.25 cm in diameter. The hard seed is pale brown, oval or globular, and has a hilum near the base. The whole panicle can weigh up to 4 kg.

Leaves, Stem and Root: The plant is a bushy palm with a maximum height of 6 m. The large, yellow-green leaves have up to 20 segments and form a crown.

Characteristics: The taste of the seeds is soapy and unpleasant.

Habitat: The plant is indigenous to the coastal regions of the southern states of the U.S., from South Carolina to Florida and southern California.

Other Names: Sabal, Shrub Palmetto

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Steroids: Sterols, including beta-sitosterol, beta-sitosterol-3-O-glucosides, beta-sitosterol-3-O-diglucoside, beta-si tosterol-fatty acid esters and their glucosides, for example beta-sitosterol-3-O-myristate, beta-sitosterol-3-O-(6-0-myristyl-beta-glucosides)

Flavonoids: including isoquercitrin, kaempferol-3-O-gIucosides, rhoifolin

Water-soluble polysaccharides (galactoarabane with uronic acid)

Fatty oil: free fatty acids

The lipophilic components (fatty oil with phytosterines) can be found in ethanolic and hexane-extracts. The anti-exudative components (polysaccharides) are found in aqueous extracts. Ethanolic extracts contain both component groups.

EFFECTS

Anti-Androgenic Effects

The lipophilic extract of the herb inhibits binding of dihydrotestosterone (DHT) to the cytosolic androgenic receptor and alpha 1-adrenoceptor in the prostate, thus preventing accumulation of the steroid, which may lead to prostate hyperplasia (Carilla, 1984; Goepel, 1999). Anti-androgenic effects of the lipophilic extract also consist of 5-alpha-reductase and 3- ketosteroid reductase inhibition. These enzymes are responsible for the conversion of testosterone to DHT and for conversion of DHT to an androgen compound, respectively (Sultan, 1984).

Anti-Estrogenic Effects

The herb lowers cytosol and nuclear receptor values for estrogen which result in an anti-estrogen effect since progesterone receptor content is linked to estrogenic activity. Anti-estrogenic agents inhibit stromatic prostate mass growth in patients with benign prostate hypertrophy (DiSilverio, 1992). There is also some evidence with inhibition of several steps involved in prolactin receptor signal transduction in ovary cells (Vacher, 1995).

Anti-Inflammatory Effects

The hexane extracts of the herb have demonstrated anti-inflammatory activity (Champault, 1984). Inhibition of the synthesis of arachidonic acid inflammatory metabolites, through a double blocking of cyclooxygenas and 5-lipoxygenase pathways results in anti-inflammatory properties. (Breu, 1992). The drug also contains anti-spasmodic properties by inhibiting calcium influx and activation of the sodium/calcium ion exchanger. Induction of-protein synthesis plays a role in the antispasmotic effect with cyclic AMP as a possible mediator. Extracts of the drug may also antagonize the contracting effect of acetylcholine on urinary bladders. (Gutierrez, 1996).

CLINICAL TRIALS

Benign Prostatic Hyperplasia

The effect of Saw Palmetto on voiding symptoms and urodynamic parameters was determined in men with lower urinary tract symptoms (LUTS) presumed secondary to benign prostatic hyperplasia (BPH). The study was conducted over a 6-month period with Saw Palmetto 160 mg given twice daily. Parameters evaluated included peak urinary flow rate, postvoid residual urine volume, pressure-flow study and serum prostate-specific antigen. The herb was well-tolerated and significantly improved urinary tract symptoms. There was no significant improvement in objective measures of bladder outlet obstruction (Gerber, 1998).

A 6-month, double-blind, randomized equivalence study was conducted to compare the effects of a Saw Palmetto extract (320 mg Permixon) with those of a 5 alpha-reductase inhibitor (5 mg finasteride). The study included 1098 men with moderate benign prostate hypertrophy (BPH) using the International Prostate Symptom Score (IPSS) as the primary end-point. The finasteride and Permixon treatment groups relieved the symptoms of BPH including a decrease in IPSS, improved quality of life and increased peak urinary flow rate. There was no statistical difference in improvement between the two treatment groups. Finasteride markedly decreased serum PSA levels and prostate volume while Permixon had little effect on androgen-dependent parameters. This conclusion suggests that other pathways might also be involved in the symptomatology of BPH (Carraro, 1996).

Serenoa repens given 160 mg twice daily was compared to alfuzosin 2.5 mg three times daily to determine the effect on 63 benign prostatic hyperplasia. The double-blind, comparative, parallel-groups study determined efficacy by assessment of clinical symptoms (Boyarsky's nscale, visual

analogue scale, clinical global impression), urinary flow rates (uroflowmetry) and residual urinary volume (transabdominal ultrasound). The Serenoa repens treatment group had similar improvement to that of the alfuzosin treatment group, but significant effects were in favor of the alfuzosin treatment group with overall clinical impression and visual analogue scale (Grasso, 1995).

INDICATIONS AND USAGE

Approved by Commission E:

- Prostate complaints
- Irritable bladder

Saw Palmetto is used for urination problems in benign prostate hyperplasia stages I and II. This medication relieves only the difficulties associated with an enlarged prostate without reducing the enlargement.

Unproven Uses: In folk medicine, Saw Palmetto is used for inflammation of the urinary trnct, bladder, testicles and mammary glands. It has been used for nocturnal enuresis, persistant cough, eczema and improvement of libido.

Homeopathic Uses: The herb is used for micturation problems and inflammation of the urinary tract.

PRECAUTIONS AND ADVERSE REACTIONS

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. Stomach complaints following intake have been observed in rare cases. Patients with hormone-dependent cancers should observe caution and speak to a physician regarding the use of Saw Palmetto because of its anti-estrogenic, estrogenic and anti-androgenic effects. The use of Saw Palmetto with pregnancy and breast feeding is not recommended due to its potential hormonal effects.

Drug Interactions: Saw Palmetto is believed to exert estrogen, androgen and alpha-adrenergic blocking effects. Because of this, the use of hormones, hormone-like drugs or adrenergic drugs concomitantly may need to be adjusted.

DOSAGE

Mode of Administration: Comminuted herb and other galenic preparations for oral use.

How Supplied:

Capsule—80 mg, 125 mg, 160 mg, 227 mg, 250 mg, 320 mg 450 mg, 500 mg, 565 mg, 570 mg, 585 mg, 600 mg, 1000 mg

Liquid—1:1

Daily Dosage: The average daily dose is 1 to 2 gm of the drug or 320 mg of the lipophilic extract (hexane or ethanol 90% v/v). Dosages used in studies demonstrated efficacy at 160 mg given twice daily or 320 mg given once daily (Carraro, 1996; Gerber, 1998; Grasso, 1995).

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COMPARISON OF ONCE AND TWICE DAILY DOSAGE FORMS OF *Pygeum africanum* EXTRACT IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A RANDOMIZED, DOUBLE-BLIND STUDY, WITH LONG-TERM OPEN LABEL EXTENSION

C. CHATELAIN, W. AUTET, AND F. BRACKMAN

ABSTRACT

Objectives. To compare the efficacy and safety of *Pygeum africanum* extract, 50 mg twice daily and 100 mg once daily.

Methods. Patients with symptomatic benign prostatic hyperplasia (BPH) entered a 2-month randomized, parallel-group, double-blind, comparative phase (group A, 50 mg twice daily; group B, 100 mg once daily), followed by a 10-month, open phase (100 mg once daily). Main efficacy assessment parameters included International Prostate Symptom Score (IPSS), quality of life (QOL), and maximum urinary flow rate (Qmax).

Results. Two hundred nine patients completed the comparative phase in compliance with the protocol; 174 were included in the open phase. Both treatments had similar efficacy. IPSS (baseline 17 in both groups) improved by 38% in group A and 35% in group B. QOL improved by 28% in both groups. Qmax increased by 1.63 mL/s (16%) in group A and 2.02 mL/s (19%) in group B. After 12 months, the IPSS fell from 16 (baseline) to 9 (−46%). Half of the patients had an IPSS below 8. Mean Qmax increased by 1.65 mL/s (15%). The safety profile was similar between groups and study phases.

Conclusions. *P. africanum* extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at 2 months. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months. UROLOGY **54:** 473–478, 1999.

Phytotherapeutic drugs are widely used[1,2] as medical treatment for benign prostatic hyperplasia (BPH).[3–6] This study compared the efficacy and safety of two dosage regimens of *Pygeum africanum* (Tadenan) extract (either 50 mg twice daily or 100 mg once daily). The long-term maintenance of the effects and the safety of the 100-mg once daily dose were also investigated for a total duration of 12 months.

MATERIAL AND METHODS

The study featured three phases: after a 1-month run-in phase without treatment, patients still meeting the inclusion criteria were randomized into a 2-month double-blind, double-placebo, parallel-group phase and received *P. africanum* 100 mg/day either once daily (one 100-mg capsule in the evening, group B) or twice daily (one 50-mg capsule morning and evening, group A). All patients continuing beyond the 2-month period received *P. africanum* 100 mg once daily for 10 additional months.

Visits took place at inclusion, after the run-in period (randomization visit), after 1 and 2 months of treatment (comparative phase), and after 5, 8, and 12 months for the extension phase (follow-up visits).

The medical history, physical examination, vital signs, routine blood tests, and urinalysis, as well as the main inclusion and noninclusion criteria, were confirmed at the randomization visit. The International Prostate Symptom Score (IPSS), quality of life (QOL), vital signs, and side effects were assessed at all follow-up visits. Investigations performed at entry and after 2 and 12 months included digital rectal examination, maximum urinary flow rate (Qmax) and voided volume (flowmeter), postvoid residual volume (transabdominal ultrasound), and sexual function (qualitative assessment of

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TABLE I. ***Demographic and baseline data of the 209 patients completing the 2-month double-blind comparative phase***

	Pygeum africanum Extract	
	50 mg BID (n = 101)	**100 mg OD (n = 108)**
Age (yr)	65.7 ± 7.2	66.2 ± 7.5
Urinary symptoms (mo)	60.4 ± 49.5	54.4 ± 43.6
IPSS	17.18 ± 4.89	16.65 ± 4.50
QOL	4.32 ± 0.96	4.08 ± 0.83
Qmax (mL/s)	10.17 ± 2.75	10.89 ± 2.66
Voided volume (mL)	261.5 ± 92.5	272.6 ± 120.9
Residual volume (mL)	48.3 ± 42.9	50.2 ± 37.2
Prostate volume (cm^3)	45.1 ± 16.6	45.1 ± 13.5

KEY: BID = twice daily; OD = once daily; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = maximum urinary flow rate.
Data presented as mean value ± SD at randomization.
No comparisons between groups were statistically different.

changes, three-item questionnaire). Prostate volume and prostate-specific antigen (PSA) serum level were assessed at entry into the study and after 12 months.

The main inclusion criteria were age 50 years or older; clinical symptoms of BPH (urinary symptoms, IPSS 10 or greater, and QOL 3 or greater), confirmed by digital rectal examination and transrectal ultrasound (prostate volume 30 cm^3 or greater); Qmax 15 mL/s or less (voided volume 140 mL or greater); residual volume 150 mL or less; PSA less than 10 ng/mL; and serum creatinine less than 160 μmol/L. The main noninclusion criteria included indication for or previous prostate or bladder surgery, prostate and/or bladder cancer, urinary symptoms due to other causes, and treatment during the 3 months preceding inclusion with finasteride, *P. africanum*, or *Serenoa repens* or with any alpha-blocker during 1 month before inclusion.

The IPSS[7–10] was the primary efficacy parameter. A clinically significant improvement was prospectively defined[11,12] as a 40% or greater reduction of mean IPSS from baseline (randomization visit); the main efficacy end point was the percentage of patients reaching this goal. Secondary outcome measures included global IPSS, nocturia (IPSS item 7), QOL, Qmax, residual volume, and prostate volume. Safety was assessed on side effects, vital signs, clinical biology, serum PSA at 12 months, and patients' satisfaction with their sexual function. The study was conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation and the French legislation. The protocol was approved by the Ethics Committee of the Pitié-Salpétrière Hospital (Paris, France). All patients gave their written consent.

Statistical Analysis

The primary criterion was analyzed using a simultaneous testing of two one-sided hypotheses[13]: the first hypothesis tested for one-sided equivalence; the second tested whether the 100-mg once daily dose had a greater efficacy than 50 mg twice daily dose. The limit of equivalence was 20%. For all efficacy and safety parameters, the 90% confidence interval (CI) for the difference between treatment groups was calculated. Analyses of efficacy at 2 months were performed both on the per-protocol population and as an intention-to-treat; results being both quantitatively and statistically comparable, the results presented are those obtained on the per-protocol population. Efficacy and safety analyses at long term were performed on the intention-to-treat populations.

RESULTS

Patient Population

Two hundred thirty-five patients were randomized into the comparative phase, 12 patients (5.1%) dropped out, 11 (4.7%) because of an adverse event and 1 (0.4%) for a nonmedical reason; of the 223 patients who completed this phase, 209 patients (101 in group A and 108 in group B) were valid for the per-protocol analysis, and 14 were not (poor compliance, interruption of treatment, visit performed outside the accepted time frame). The two groups were homogenous for all the demographic and baseline characteristics (Table I).

As defined by the protocol, only the first 174 patients completing the comparative phase entered the open-label extension; 151 patients completed this phase, and 23 patients dropped out: 8 (4.6%) because of an adverse event and 15 (8.6%) for nonmedical reasons. The baseline characteristics of this subgroup of patients and of the patients who participated in the comparative phase were similar.

Efficacy Results

Comparative Phase. The IPSS decreased similarly in both groups. The percentage of patients reaching the therapeutic goal was 42.6% (95% CI 33% to 53%) and 40.7% (95% CI 31% to 51%) in groups A and B, respectively. The 90% CI of the difference between treatments was −13%, +9% ($P = 0.004$ for the one-sided demonstration of equivalence and $P = 0.606$ for the testing of superiority).

Secondary outcome measures (Table II) underwent similar changes in both groups. The mean IPSS was significantly reduced from 17.2 (group A) and 16.7 (group B) to 10.7 (−37.6%) and 10.9 (−34.6%), respectively. The 95% CI of the before-after differences did not include zero, confirming a

TABLE II. *Analysis of changes in secondary outcome measures from baseline to final visit at 2 months*

Group	n	Baseline Mean	Mean Within-Group Change from Baseline (95% CI)	Mean Between-Group Comparison (90% CI)
IPSS				
Pa 50 mg BID	101	17.18	−6.46 (−7.44, −5.47)	−0.70 (−1.75, 0.36)
Pa 100 mg OD	108	16.65	−5.76 (−6.55, −4.96)	
QOL				
Pa 50 mg BID	101	4.32	−1.19 (−1.44, −0.93)	−0.06 (−0.34, 0.22)
Pa 100 mg OD	108	4.08	−1.13 (−1.35, −0.91)	
Qmax (mL/s)				
Pa 50 mg BID	87	10.20	1.63 (0.68, 2.57)	0.40 (−0.82, 1.62)
Pa 100 mg OD	95	10.89	2.02 (0.92, 3.12)	
Residual volume (mL)				
Pa 50 mg BID	87	49.9	0.3 (−12.4, 12.9)	3.0 (−11.5, 17.5)
Pa 100 mg OD	94	52.8	3.3 (−8.8, 15.3)	

KEY: Pa = Pygeum africanum *extract; CI = confidence interval; other abbreviations as in Table I.*

TABLE III. *Secondary efficacy parameters (baseline mean values and per visit results), long-term phase*

Visit	IPSS (n = 174)	QOL (n = 174)	Nocturia (n = 174)	Qmax (mL/s)	Residual Volume (mL)	Prostate Volume (cm^3)
Baseline	16.2	4.1	2.3	10.87 (n = 168)	53.3 (n = 168)	42.0 (n = 174)
1 month	12.3	3.4	1.7	—	—	—
2 months	10.5	3.1	1.5	13.26 (n = 141)	60.0 (n = 140)	—
5 months	9.5	2.6	1.5	—	—	—
8 months	8.7	2.3	1.4	—	—	—
12 months	8.7	2.4	1.4	12.58 (n = 123)	57.9 (n = 123)	39.9 (n = 145)

KEY: Abbreviations as in Table I.

significant reduction of IPSS in each group. The difference of the IPSS reduction between groups was −0.7 and the limit of the 90% CI was less than 2 points, confirming the equivalence of treatments.

All individual items of the IPSS decreased similarly in both groups. Nocturia improved equally in both groups, from 2.3 to 1.5 in both groups. QOL improved in both groups, from 4.3 (group A) and from 4.1 (group B) at baseline to 3.1 and 3.0, respectively. The 90% CI of the difference of the means between the two groups was centered on zero (−0.34, +0.22). Qmax increased by 1.63 mL/s (16.0%) in group A and by 2.02 mL/s (18.6%) in group B. The changes from baseline were statistically and clinically significant in each group, but not different between groups. Residual volume did not vary significantly.

Open Label Extension Phase. Given the equivalence in efficacy during the comparative phase between groups, patients from group A (n = 83) and from group B (n = 91) were pooled for the long-term analysis. Analyses by initial treatment groups showed similar evolutions over the long-term period.

The percentage of patients reaching the therapeutic goal increased with time: 20.1% at 1 month, 42.0% at 2 months, 57.1% at 5 months, 65.4% at 8 months, and 62.8% at 12 months.

The mean IPSS fell from 16.2 at baseline to 8.7 (−46.3%) (Table III). All individual items of the IPSS improved with time. Nocturia decreased from 2.3 to 1.4 after 12 months. QOL improved from 4.1 at baseline to 2.4 (−41.5%). Although no patient scored 2 or lower (mostly satisfied, pleased, or delighted) at baseline, after 12 months, 58.1% of patients had a QOL of 2 or lower; 31.6% of patients scored 5 (unhappy) or 6 (terrible) at entry compared with 10.9% after 12 months. Qmax and other urinary parameters improved significantly after the first 2 months of treatment, and this improvement was maintained after 12 months (Table III). Prostate volume was slightly but significantly reduced at the end of the study, from 42.0 to 39.9 cm^3 (−6.8%).

SAFETY ASSESSMENT

Side effects had similar distributions between groups during the comparative phase and were comparable for both phases of the trial. Few side effects (Table IV) led to patient withdrawal (4.7%

TABLE IV. *Safety profile of side effects leading to premature withdrawal and treatment-emergent serious side effects: 2-month comparative and 12-month long-term phases*

	Two Months (n = 235)				Twelve Months (n = 174)	
	Pa 50 mg BID		Pa 100 mg OD		Pa 100 mg OD	
	SE (n)	SSE (n)	SE (n)	SSE (n)	SE (n)	SSE (n)
Nausea, dizziness	1					
Dyspepsia			1		1	
Constipation	2					
Epistaxis						1
Cardiac arrhythmia						1
Inguinal hernia		1		1		1
Stenosis of colon						1
Joint prosthesis		1				2
Muscular and joint pain			1*	1	1*	1
Back pain						1
Pelvic pain			1			
Increase in urinary symptoms	1					
Dysuria	1*	1	1*	1	3*	3
Urinary retention		1	1*	1	1*	1
Bladder polyp ablation						1
Renal disorder						1
Hematuria					1*	1
Subcutaneous abscess						1
Cataract						1
Phlebitis						1
Headache/migraine						1
Meningeal carcinoma			1*	1		
Subdural hematoma					1*	1
Total	5	4	6	5	8	20

KEY: SE = side effect leading to premature withdrawal; SSE = treatment-emergent serious side effect; other abbreviations as in Table II.
** SE considered by the investigator as an SSE at the same time.*

of patients during the comparative phase and 4.6% of patients during the long-term phase). Treatment-emergent side effects were mostly gastrointestinal; most were not treatment related. Side effects that were possibly drug related were observed in 2.6% of patients in the comparative phase and 2.9% in the 12-month phase. Most serious side effects (Table IV) involved the urogenital system (1.3% and 4.0% of patients in, respectively, the comparative and the long-term phases).

No significant changes were noted in blood or urinalyses in either group or during the study. There was no significant variation of the PSA level at 12 months. Sexual activity was not significantly affected after either 2 or 12 months.

COMMENT

One of the first aims of treatment in BPH is the alleviation of the symptoms, which impair the patients' QOL[14–16] and are usually the initial reason for seeking treatment. The existing clinical evidence[17] confirms the efficacy and safety of *P. africanum* for this indication. Results reported with *P. africanum* administered most often as a 50-mg twice daily dose in open and placebo-controlled clinical trials showed a rapid and significant improvement both in clinical symptoms and in objective parameters. Clinical studies and postmarketing safety data show that the drug is well tolerated, with only mild to moderate side effects, mostly gastrointestinal.

Patients' compliance with the treatment may be improved by a simple dosage regimen (single versus multiple intake per day). A 100-mg capsule was therefore developed; the present study compared the efficacy and safety of the two dosage regimens after 2 months of treatment, as well as the long-term effects of the 100-mg once daily regimen.

The IPSS was chosen both as the main inclusion and evaluation criterion. The strict entry criterion of an IPSS of 10 or greater (and QOL of 3 or greater) ensured the enrollment of patients with symptomatic BPH and impaired QOL, who are the most appropriate candidates for pharmacologic

treatment.[18] The success criterion, arbitrarily defined as a reduction in IPSS of 40% or more from baseline, can be considered as high; this criterion is justified by the absence of a placebo arm in the study and the aim of identifying only those patients whose response was markedly greater than the usually accepted placebo response (Hansen *et al.*[11] estimated this response to reach 24% reduction of the score at 2 months). The percentage of patients who reached this target in the present study was significant (40% at 2 months and 63% at 12 months). Simultaneously, the decrease in the IPSS seen in the present study (6 units after 2 months and 8 units after 12 months) significantly exceeded that usually reported on placebo in randomized studies, which averages approximately 3 points.[4,12] This symptomatic response to *P. africanum* after both 2 and 12 months can be considered favorably in comparison with that observed in randomized trials with alpha-blockers[1,12,19] or 5-alpha reductase inhibitors.[3,20] The absence of a placebo arm in our study limited the evaluation of the net effect of the product tested, and the observed effects must be considered as the aggregate of the drug and placebo effects. However, this study was designed with the objective to compare two daily regimens of the same drug, the efficacy versus placebo having been documented in the past.[17] The clinical effects and the safety profile were similar between the two groups and two treatment periods. There were no significant changes either in the PSA levels or in sexual function of studied patients.

CONCLUSIONS

The results of this study confirm those previously obtained in randomized double-blind, placebo-controlled and open trials.[17] It can be concluded that *P. africanum* extract offers an alternative for the treatment of patients with mild to moderate symptoms of BPH; the effects of once daily administration of 100 mg of *P. africanum* extract are similar to those of the currently recommended dosage regimen of 50 mg twice daily.

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Efficacy and Acceptability of Tadenan®(Pygeum africanum Extract) in the Treatment of Benign Prostatic Hyperplasia (BPH): A Multicentre Trial in Central Europe

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Key words: Pygeum africanum *extract – Benign prostatic hyperplasia – Phytotherapy*

Summary

Pygeum africanum *extract is available as Tadenan® in many countries, including those in central and eastern Europe, for the treatment of mild to moderate BPH. Its efficacy and acceptability have been demonstrated in numerous open and placebo-controlled studies in large populations. The present open three-centre efficacy and safety study was conducted according to common protocol at urology clinics in the Czech and Slovak Republics and in Poland, in order to confirm the therapeutic profile of* Pygeum africanum *in conditions of daily practice, using International Prostate Symptom Score (IPSS) and flowmetry assessments.*

Men aged 50–75 years and in compliance with the selection criteria (including IPSS ≥ 12, quality of life (QoL) score ≥ 3, and maximum urinary flow ≤ 15 ml/s) were first examined then recalled after two weeks during which no treatment was provided (washout and check of stability). If still compliant, they were entered at this point into a two-month period of treatment with Pygeum africanum *extract 50 mg twice daily. There followed a further one-month period without treatment, the objective being to evaluate the persistence of any effects observed during the previous two months of* Pygeum africanum *administration.*

The primary efficacy parameter investigated was IPSS; the other efficacy parameters were QoL, nocturnal frequency, maximum urinary flow, average urinary flow, post-voiding residual volume and prostatic volume, after one and two months of Pygeum africanum *treatment and one month after stopping treatment. A total of 85 patients were evenly distributed between the three centres and completed the entire study. At inclusion their mean IPSS was 16.17, QoL was 3.60 and nocturia was 2.6 times per night.*

The changes in subjective scores, IPSS and QoL after the two-month treatment period were highly statistically significant with mean improvements of 40% and 31%, respectively. Nocturnal frequency was reduced by 32% and the mean reduction was again highly statistically significant. Mean maximum urinary flow, average urinary flow and urine volume were also statistically significantly improved, but the modest improvement in post-voiding volume did not reach statistical significance. The improvements, which exceeded those observed with placebo in earlier studies, were maintained after one month without treatment indicating an interesting persistence of clinically useful activity. Prostatic volume and quality of sexual life remained unchanged throughout. No treatment-related adverse effects were observed.

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In conclusion, under conditions of daily practice, Pygeum africanum *extract induces significant improvement in IPSS and uroflowmetry parameters. These positive effects are accompanied by a very satisfactory safety profile with the overall result of a substantial improvement in QoL.*

Introduction

Benign prostatic hyperplasia (BPH) is a common debilitating and embarrassing disease of men approaching 50 years and increases with age. By the age of 60, histological evidence of BPH is present in approximately 50% of men and this proportion increases to 85% in men of 80 years or more[6]. The associated clinical symptomatology includes all or some of the following signs:

- Urinary frequency (during the day and/or at night).
- Difficulty in postponing urination (urgency).
- Need to strain to commence urination.
- Weak urinary stream/dribbling.
- Sensation of incomplete emptying of bladder.

When symptoms become severe or complications arise, surgery of the prostate, most often by transurethral resection, remains the cornerstone of treatment. However, in the early stages drugs have come to play an important role in recent years, particularly in patients with mild to moderate symptoms or those unwilling or unable to undergo surgery. Since testicular hormones are necessary for the development of BPH, androgen-suppressing drugs, such as gonadotrophin-releasing hormone agonists (or analogues), progestogens and non-steroidal anti-androgens, have been used to treat BPH, but, although they substantially reduce prostate volume, their acceptance is limited by impotence and loss of libido which is particularly marked with the progestogens[14]. Finasteride, a 5α-reductase inhibitor, is better tolerated than other anti-androgens, but the onset of full activity appears to be slow (6–12 months), is uncertain and there is a marked residual effect of impairment of sexual function affecting 10–12% of patients[18]. Another approach is the blockade of α_1-adrenoceptors, which should decrease bladder outlet resistance without affecting detrusor muscle contractility. Currently available drugs in this category include terazosin, alfuzosin, doxazosin and tamsulosin, and all to varying degrees increase urinary flow rate and improve symptoms in men with symptomatic BPH. However, their use is occasionally associated with side-effects due to peripheral vasodilatation, such as postural hypotension, dizziness and headache[12,13]. Finally, a number of drugs derived from plants have a long tradition in the treatment of BPH, especially in Europe, among which *Pygeum africanum* is one of the best known and is the subject of the present report.

An extract of the bark of the African plum tree, *Pygeum africanum* (Tadenan®), has been used successfully in Europe and elsewhere for the treatment of BPH symptoms since the first registration by Debat Laboratories, France, in 1969. Its efficacy has been demonstrated in several controlled clinical trials, especially in a European multicentre double-blind and placebo-controlled study[4]. The extensive literature covering other controlled and open studies was reviewed recently by Andro and Riffaud[2].

Recent *in vitro* studies have shown that *Pygeum africanum* in low concentrations inhibits fibroblast proliferation induced by human fibroblastic growth factor (bFGF), which is believed to play an important part in the development of BPH[8,19]. A reduction

of prostatic fibroblast proliferation may therefore be an important contributing element to the established efficacy of *Pygeum africanum*.

The present open three-centre efficacy and safety study was conducted according to identical protocols at urology clinics in the Czech and Slovak Republics and in Poland, in order to confirm the therapeutic profile of *Pygeum africanum* in conditions of daily practice, using the International Prostate Symptom Score (IPSS) and a Quality of Life (QoL) score for the subjective assessments with urine flowmetry for objective evaluations. The duration of the effect of *Pygeum africanum*, once treatment is stopped, has seldom been documented and the present trial was intended to address this point after one month of follow up.

The objectives of the trial were thus to:

- Assess the efficacy of *Pygeum africanum* extract, given as capsules containing 50 mg of the extract, morning and evening for a period of two months, on subjective and objective symptoms of BPH.
- Explore the duration of the above effects by reassessment one month after stopping treatment.
- Confirm the safety profile of the product.

Patients and Methods

This was an open uncontrolled study in patients suffering from symptoms of BPH who, if complying with the selection criteria at the first visit (V1), were again evaluated after a two-week wash-out period with no treatment (V2) to check the stability of their condition. If still suitable, they were entered into the treatment phase of the study and prescribed *Pygeum africanum* extract 50 mg twice daily for two months. Trial visits took place after one month (V3) and two months (V4) of treatment, followed by reassessment after a further month without treatment (V5).

The study design is shown schematically in Figure 1.

A sufficient number of patients were recruited to ensure approximately 30 fully completed cases in each of the three centres.

Study Population

After approval of the protocol by the three local ethics committees, ambulatory male patients aged 50 to 75 years, mentally alert and in otherwise good physical health, were recruited into the study after giving their informed and signed consent, if presenting with moderate symptomatic BPH diagnosed on the following criteria:

Questionnaire

- Micturitional problems, such as nocturnal frequency, established for at least six months.
- A score at the inclusion visit (V1) of ≥ 12 on the IPSS scale[5].
- A QoL score at visit V1 of ≥ 3 on the QoL scale of Mebust *et al.*[15].

Digital Rectal Examination

- Prostatic hyperplasia characteristic of an 'adenomatous' lesion.

Uroflowmetry

- Maximal urinary flow rate ≤ 15 ml/s.
- Voiding volume (urine volume) ≥ 150 ml.

Transabdominal Ultrasonography

- Residual urinary volume < 100 ml.
- Prostate volume < 100 ml.

The Biochemical Criteria for Inclusion were :

- Serum creatinine < 160 µmol/l.
- Serum prostate specific antigen (PSA) ≤ 4 ng/ml or PSA density < 0.15.
- Urine bacterial count < 10^5/ml.

Patients were excluded if suffering from any associated disease or history such as surgical intervention on the prostate or bladder, micturitional problems associated with an identified bladder pathology (e.g. neurogenic bladder, bladder neck stenosis, lithiasis, bladder cancer, etc), known urethral stricture, diagnosed prostatic cancer, recurrent urinary infections, known renal, hepatic or cardiac insufficiency, or known sensitivity to *Pygeum africanum* extract.

In addition, patients unable to understand or to follow the study protocol or participating or having participated in another clinical trial during the past three months, were excluded as were those with BPH judged by the investigating urologist to require surgical treatment.

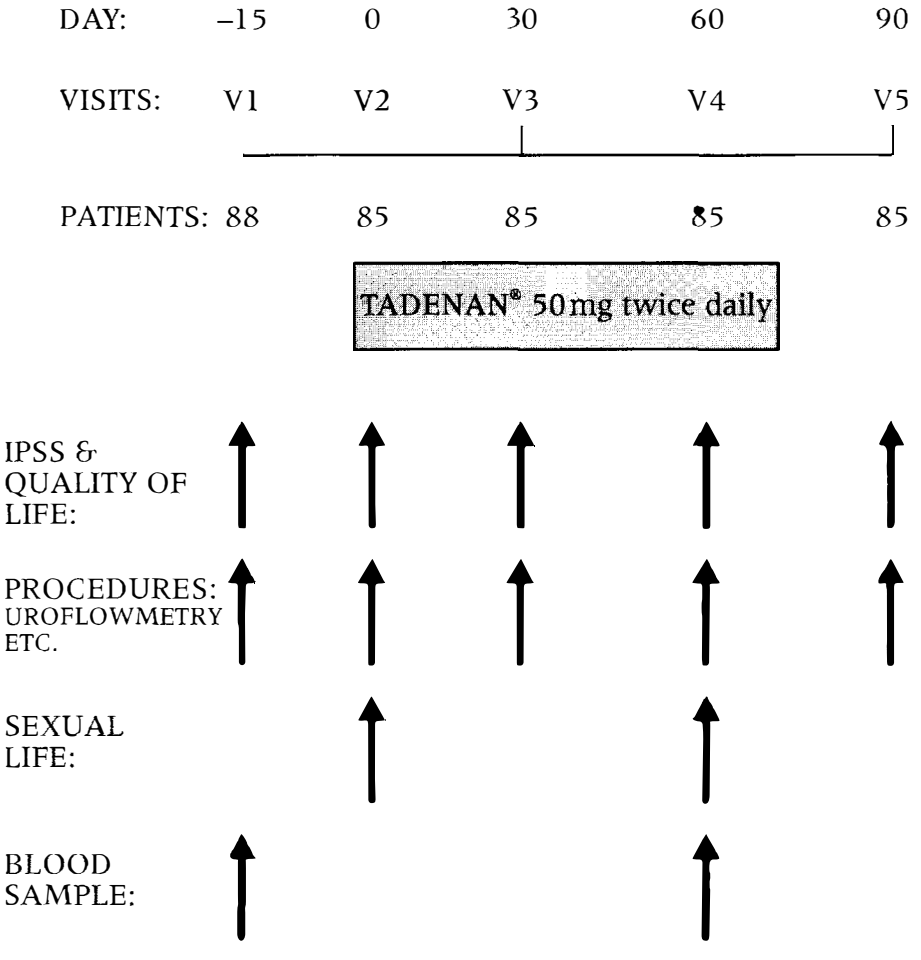

Figure 1. Schema of study

Previous Therapy

Patients for whom *Pygeum africanum*, *Serenoa repens*, finasteride or any other treatment aimed specifically at the symptoms of BPH had been prescribed during the preceding three months were not included, as were also those prescribed vasoactive α-blockers, diuretics, calcium channel blockers, β-blockers or anticholinergic agents during the past three months. Those taking α-blockers prescribed for their urological condition during the preceding month were also excluded.

Evaluation of Efficacy

The principal criterion of efficacy was the mean change in IPSS score (scale 0–35) from baseline visit V2 to visit V4 after two months of active treatment.

The secondary criteria were primarily changes from baseline V2 to V4 for nocturnal urinary frequency (IPSS Question 7) and the Quality of Life score (QoL). Maximum urinary flow rate, average urinary flow rate, urinary volume, the changes in post-micturitional residual volume and prostatic volume were also evaluated.

Changes in the efficacy variables were also examined pre-treatment between baselines V1 and V2, on-treatment between V2 and V3, and post-treatment between V4 and V5.

Evaluation of Safety

Clinical safety assessment, and follow-up of any unexpected events reported spontaneously, were made at every one of the five study visits for each patient. Biochemical and haematological safety was assessed at selection (V1) and after the two-month treatment period (V4) by conventional laboratory tests (differential blood count, platelets, creatinine, ASAT, ALAT, γ-GT and alkaline phosphatase).

At the second visit (V2, before the start of *Pygeum africanum*) and at the end of the active treatment period (V4), patients were asked to complete (if need be with the advice of the investigator) a simplified sexual life questionnaire ('improved', 'remained unchanged' or 'got worse').

Statistical Analysis

The patient data set analysed for efficacy was the treated patients who received the active treatment from visit V2.

The baseline characteristics were described for the pre-treatment period at visits V1 and V2 by centre and by pooled centres.

The treatment effect was analysed on data pooled over centres.

For efficacy variables, changes from baseline (V2) were tested using the paired *t*-test. A Wilcoxon signed rank-sum test was used to confirm statistical conclusions for total IPSS, QoL score and nocturia. Pre- and post-treatment changes were tested similarly.

The *p*-values are quoted without any adjustment for multiple testing, but the subjective efficacy parameters, including the principal criterion on total IPSS, were interpreted using the Bonferroni correction for the four paired comparisons at the global significance level of 5%[3].

Results

Recruitment, Baseline Characteristics and Withdrawals

Thirty men entered the study in Bratislava but three dropped out for personal reasons

before beginning *Pygeum africanum* treatment. Twenty-nine patients were entered in Warsaw and another twenty-nine in Prague, and these all completed the study. Thus, the trial yielded 85 evaluable patients (Table 1). The mean ages were 64.42 years in Warsaw, 64.63 years in Bratislava and 61.02 years in Prague. The overall mean age was 63.35 ± 6.28 years (mean ± S.D.).

The mean duration of the disease from first diagnosis of BPH to selection for the study was 35.38 ± 42.23 months.

Two pre-treatment assessments were made, one at the selection visit V1 and another at the inclusion visit V2, two weeks later.

The average total IPSS was similar at the selection visit V1 in all three participating centres with mean values of 16.45 ± 4.02 (Warsaw), 16.82 ± 4.51 (Bratislava) and 15.62 ± 2.62 (Prague), giving a mean over all centres of 16.29 ± 3.79 (Table 1). At the inclusion visit (V2), the mean IPSS over all centres was 16.17 ± 3.68 (Table 2). The stability of the patients' conditions during the two-week washout period were confirmed by the comparison of the means at V1 and V2. No statistically significant difference was found between these two means. Visit V2 was the reference point for comparison with values obtained during visits V3 and V4 and after treatment (visit V5) with *Pygeum africanum*.

The QoL score was also similar in all three centres at the first visit (V1), with mean values of 3.71 ± 0.76 for Warsaw, 3.68 ± 0.82 for Bratislava and 3.59 ± 0.73 for Prague, giving a mean over all three centres of 3.66 ± 0.76. At V2 the mean QoL over all centres was 3.60 ± 0.74. The mean change in QoL after two weeks of washout was again not statistically significant.

Nocturia, as documented in the IPSS questionnaire, showed only little variation between centres and was stable between the selection and the inclusion visits with a mean at V2 over all centres of approximately 2.6 times per night (Table 2). The mean change between these two pre-treatment visits again lacked statistical significance.

Treatment Outcomes

The homogeneity of the pre-treatment values from the three centres at V1 and V2 was such that it was feasible to pool the data as shown in Table 2. From hereon reference is made to overall means, except where specified.

Table 1. Demographic and baseline characteristics at selection (V1) in each participating centre and pooled data (mean ± S.D.)

	Warsaw	Bratislava	Prague	All centres pooled
Number of patients selected	29	30	29	88
Withdrawals	0	3	0	3
Number of patients treated	29	27	29	85
Age (years)	64.42 ± 4.43	64.63 ± 7.00	61.02 ± 6.66	63.35 ± 6.28
Body weight (kg)	80.75 ± 8.44	80.75 ± 12.92	81.83 ± 8.49	81.12 ± 10.04
Duration of BPH (months)	32.17 ± 37.07	56.33 ± 58.17	19.07 ± 11.07	35.38 ± 42.23
IPSS	16.45 ± 4.02	16.82 ± 4.51	15.62 ± 2.62	16.29 ± 3.79
QoL	3.71 ± 0.76	3.68 ± 0.82	3.59 ± 0.73	3.66 ± 0.76
Nocturia (urinations/night)	2.52 ± 1.06	2.64 ± 1.10	2.79 ± 0.86	2.65 ± 1.00
Maximum urinary flow (ml/s)	9.18 ± 4.03	11.00 ± 2.87	11.54 ± 2.51	10.57 ± 3.33
Average urinary flow (ml/s)	4.68 ± 2.54	5.66 ± 1.60	6.27 ± 1.92	5.53 ± 2.14
Urine volume (ml)	205.66 ± 80.43	214.25 ± 90.26	258.00 ± 82.41	226.10 ± 86.55
Urination time (s)	45.52 ± 19.54	39.79 ± 15.49	46.34 ± 24.80	43.93 ± 20.32
Post-voiding residual volume (ml)	64.14 ± 45.95	24.04 ± 25.91	26.38 ± 26.11	38.05 ± 38.22
Prostatic volume (ml)	41.54 ± 27.33	34.24 ± 18.92	35.55 ± 12.42	37.15 ± 20.51

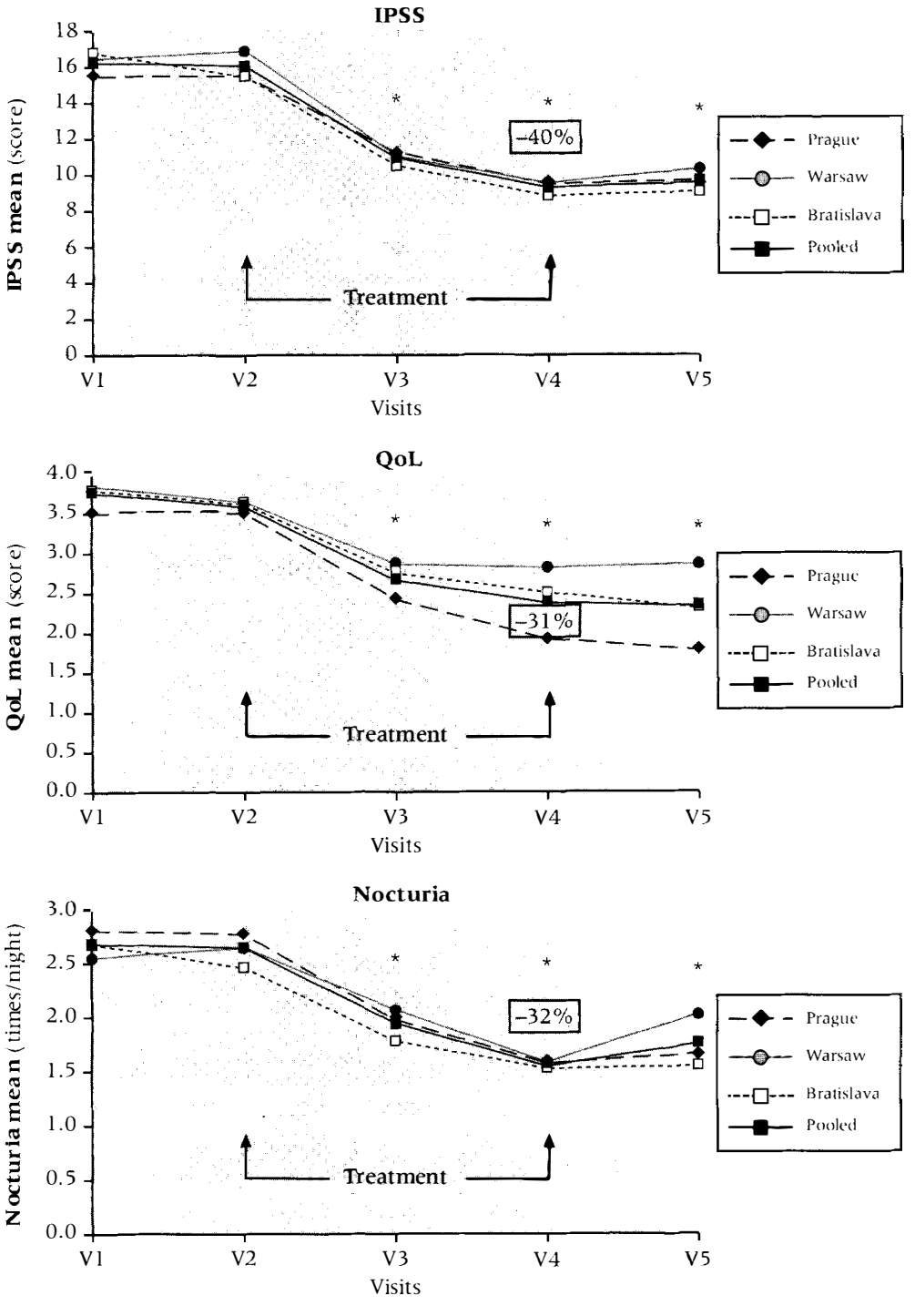

Figure 2. Mean IPSS, QoL and nocturia values before, during and after treatment. *$p < 0.001$ at V3, V4 and V5 for all mean differences from baseline V2; the differences are significant under the Bonferroni correction

Table 2. Effect of treatment compared to baseline (V2) values on IPSS, QoL and nocturia: pooled data from all three centres

	Pre-treatment baseline	On treatment		One month after treatment stopped	Mean change	Mean percentage change*
	V2	V3	V4	V5	V4 vs. V2	V4 vs. V2
IPSS						
• No. of patients	86	85	85	85	84	84
• **Mean**	**16.17**	**11.18**	**9.71**	**10.10**	**6.40**	**−40.17**
• S.D.	±3.68	±4.73	±4.57	±4.96	±4.05	±24.35
Quality of life score						
• No. of patients	86	85	85	85	85	85
• **Mean**	**3.60**	**2.73**	**2.44**	**2.39**	**−1.16**	**−31.31**
• S.D.	±0.74	±0.89	±0.93	±0.90	±0.96	±24.78
Nocturia						
• No. of patients	86	85	85	85	85	85
• **Mean**	**2.62**	**1.95**	**1.66**	**1.78**	**−0.95**	**−31.80**
• S.D.	±0.91	±0.97	±0.92	±0.90	±1.03	±40.69

All changes are significant at level $\alpha = 0.0125$ after the Bonferroni correction
*Calculated from individual percentage changes

Table 3. Nocturia re-examined: pooled results (means) from all three centres

	Number of men getting up to urinate three or more times per night				
Visit	V1	V2	V3*	V4*	V5
Number of men	45	47	25	16	20
Percentage of all patients	51	54	29	19	24

*Tadenan treatment

After one month's treatment (V3) there was a highly significant reduction in IPSS relative to V2 (31%); IPSS was further improved at the end of the second treatment month (40%) and also at one month after stopping treatment, with $p < 0.001$ at each time point (Figure 2). For the principal criterion, after two months of treatment the mean reduction in total IPSS of 6.40 ± 4.05 points was statistically significant when interpreted using the Bonferroni correction.

QoL changes during and after treatment with *Pygeum africanum* largely paralleled those of the IPSS, with an improvement and the same high level of statistical significance ($p < 0.001$) and were of 31% after two months and maintained (approximately 34%) at one month after the end of treatment (Table 2 and Figure 2).

The mean frequency of nocturia had decreased after one month of treatment to 1.95 times per night (V3) and again improved to 1.66 times per night after another month at V4 (Figure 2). The mean change between baseline (V2) and end of treatment (V4) of 32% was highly statistically significant ($p < 0.001$). In order to better estimate the individual impact of IPSS Question 7 (nocturia) improvement, the analysis was completed by an assessment of the actual number of patients getting up to urinate three times or more (Table 3 and Figure 4). It is seen that slightly more than half of them were in this category according to their V1 and V2 pre-treatment IPSS, but that by the end of the two-month *Pygeum africanum* treatment period (V4) this number of men was reduced to 16. Thus, globally speaking, two out of three men (66%) initially getting up three times or more were urinating at least one time less per night while on treatment, with persistence of this

Table 4. Effect of treatment compared to baseline (V2) on maximum urinary flow, average urinary flow, urine volume, urination time, post-voiding residual volume and prostatic volume: pooled data from all three centres

	Pre treatment baseline	On treatment		One month after treatment stopped	Mean change
	V2	V3	V4	V5	V4 vs. V2
Maximum urinary flow (ml/s):					
• No. of patients	85	85	85	84	84
• **Mean**	**10.97**	**12.65**†	**13.07**‡	**13.41**‡	**+2.00**
• S.D.	±3.58	±5.58	±5.56	±6.09	±5.07
Average urinary flow (ml/s):					
• No. of patients	85	85	85	84	84
• **Mean**	**5.94**	**6.65***	**6.93**†	**7.05**‡	**+1.00**
• S.D.	±1.95	±3.11	±2.93	±3.05	±2.80
Urine volume (ml):					
• No. of patients	85	85	85	84	83
• **Mean**	**218.63**	**243.64 n.s.**	**264.04**†	**257.36**†	**+44.52**
• S.D.	±89.47	±122.44	±133.44	±110.17	±156.35
Urination time (s):					
• No. of patients	85	84	84	82	83
• **Mean**	**39.15**	**42.98 n.s.**	**41.68 n.s.**	**41.65 n.s.**	**+2.13**
• S.D.	±18.14	±22.98	±20.42	±22.68	±24.53
Post-voiding residual volume (ml):					
• No. of patients	85	85	85	84	84
• **Mean**	**32.60**	**28.22 n.s.**	**29.62 n.s.**	**28.46 n.s.**	**−3.19**
• S.D.	±42.22	±39.42	±51.94	±45.88	±35.73
Prostatic volume (ml):					
• No. of patients	85	85	85	85	84
• **Mean**	**36.03**	**35.81 n.s.**	**35.96 n.s.**	**35.03 n.s.**	**+0.01**
• S.D.	±15.13	±15.81	±16.32	±15.40	±10.78

Significant changes from V2 baseline (*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$)
n.s. = change not statistically significant

effect one month after discontinuation of *Pygeum africanum*.

Among the objective parameters and taking into account all treated patients, mean maximal urinary flow and average urinary flow were all statistically significantly increased from baseline after one month of *Pygeum africanum* treatment ($p < 0.001$) with additional improvement at the end of the treatment period (V4). The trend to an increase in urinary volume after one month of treatment (V3) did not reach statistical significance but did so by the end of treatment at V4 ($p < 0.01$). Thus, maximum urinary flow increased from a baseline of 10.97 ml/s to 13.07 ml/s, average urinary flow from 5.94 ml/s to 6.93 ml/s and urine volume from 218.63 ml to 264.04 ml at V4. There was a tendency to further increases in maximal and average urinary flow during the final non-treatment month (Table 4 and Figure 3), while the increase in urinary volume was lessened. The change in post-micturitional residual volume was more modest (from 32.60 ml at baseline to 29.62 ml at the end of treatment (V4) visit), and lacked statistical significance. Urination time was not significantly affected by the treatment.

Prostatic volume (Table 4) was unaffected by treatment with *Pygeum africanum*.

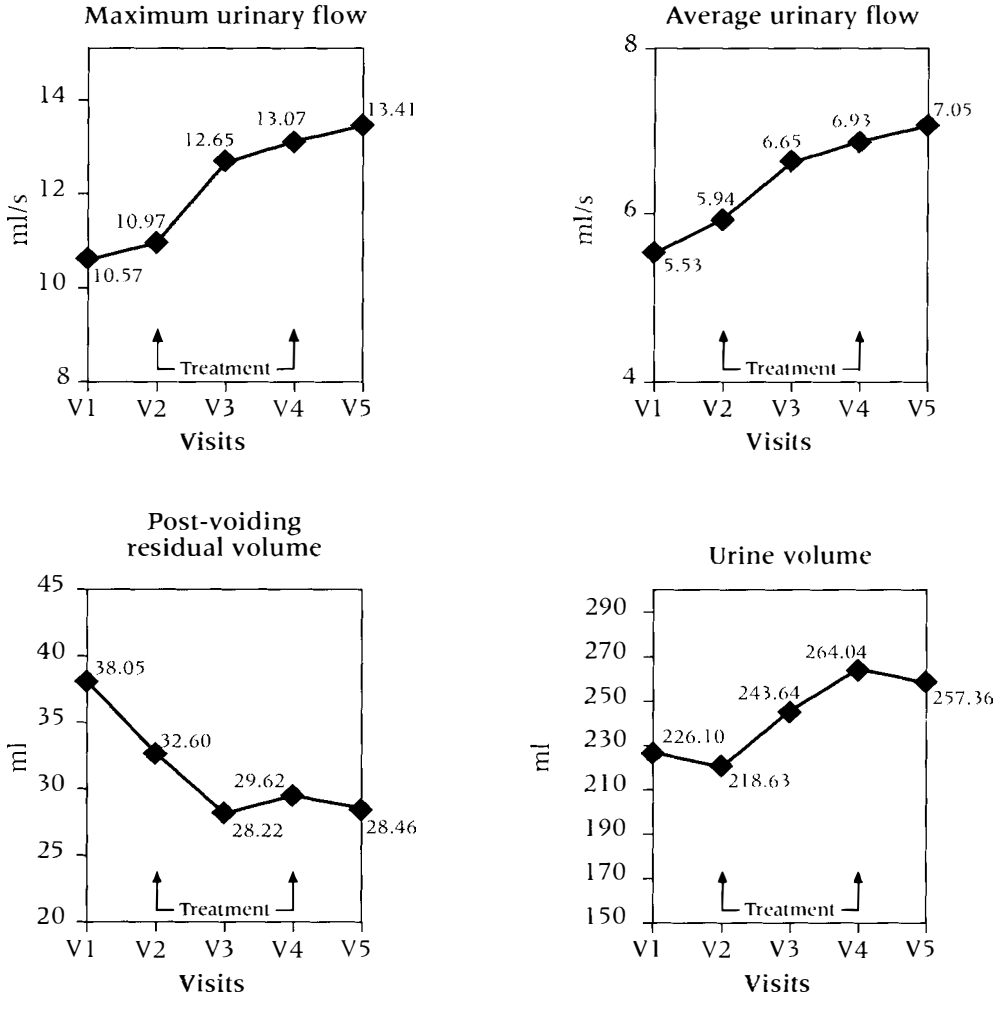

Figure 3. Mean objective urine values before, during and after treatment (pooled data from all three centres)

Sexual Function and Intercurrent Clinical Events

Seventy-six of the 85 patients in the study (89%) reported their sexual life to be satisfactory at entry (V2). Of these, four claimed an improvement at the end of treatment with *Pygeum africanum* (V4). A further three patients, who had reported their sexual life at entry as unsatisfactory, also claimed an improvement for a total of seven improved on *Pygeum africanum* treatment (8.2%). On the other hand, three patients who had been 'satisfactory', claimed that their sexual life was worse at the end of treatment (3.5%), and one, who had been impotent for several years, remained impotent.

No adverse events or clinically relevant changes in biochemical safety parameters were observed, other than three increased PSA values in Warsaw, which were not

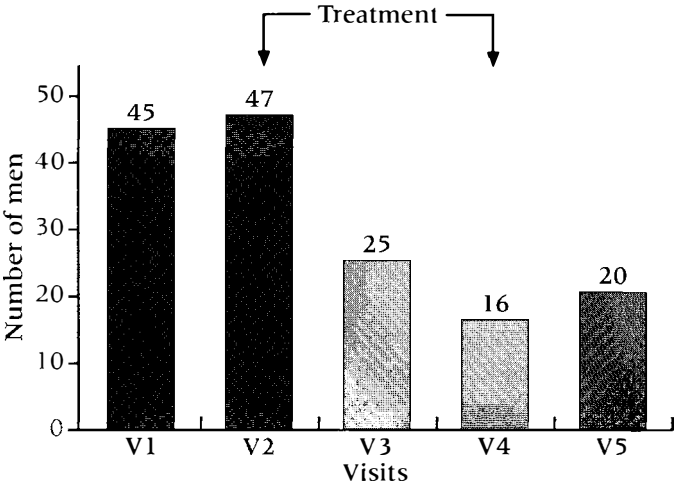

Figure 4. Number of men getting up to urinate three or more times per night (pooled data from all three centres)

associated with development of prostatic carcinoma.

Discussion

Uncontrolled clinical studies provide confirmation and further validation of the findings previously proved and documented with controlled and randomised trials. Such trials permit a general view of the activity of the test-product as it is likely to be observed by the average prescriber and his patient, and play an important role in piloting the design of more ambitious protocols. The present study, using contemporary efficacy criteria, is situated in this context, knowing that earlier double-blind, controlled trials of *Pygeum africanum* have established its efficacy in the treatment of classical BPH symptoms relative to placebo over periods of 6–8 weeks of administration[4,10,16].

In the present study, recall of 88 men compliant with the selection criteria for a second set of subjective and objective tests after 15 days without treatment showed that presence in the study environment without any treatment with *Pygeum africanum* had no influence on the assessed parameters. In contrast, after only one month of treatment with *Pygeum africanum*, the IPSS was statistically significantly reduced, with some progression of this trend after the second month, at which time the reduction compared to baseline as a mean for all three centres was 40%. This value may be compared with the 24% reduction in symptom score on placebo reported by Hansen[11]. After a further month in the study, but with no treatment, the mean IPSS value was still low compared with baseline, but showing some trend to increase compared with the end of treatment.

As might be expected, QoL scores followed the same pattern as mean IPSS, with a distinct improvement apparent after one month of *Pygeum africanum* treatment, again improved after the second month and fully maintained one month after stopping treatment. All these changes from baseline (V2) were highly statistically significant.

Nocturia is perhaps the most annoying of symptoms for mild BPH patients, resulting as it does in a broken sleep pattern and a consequent feeling in the morning of being unrested. Treatment with *Pygeum africanum* was effective on this parameter, resulting in a reduction in the number of urinations per night by an overall mean for the three centres of approximately 32%. It is noteworthy that Barlet *et al.*[4] record a mean reduction of 31% in their 116 men after two months of *Pygeum africanum* treatment, while placebo in their study was responsible for only a 19% reduction. Of the 85 men included in the present study, 47 (54%) were getting up in the night to urinate more than three times before treatment with *Pygeum africanum* began, but by the end of the two-month treatment period only 16 patients (19%) fell into this category. In other words, on average men got up to urinate once less on treatment than before. As for total IPSS, one month later but with no treatment, these figures were tending to rise, but a residual effect of treatment was still apparent.

Of the objective parameters studied by flowmetry, changes from the V2 baseline to the V4 end of treatment visit were for maximum urinary flow (+19%), average urinary flow (+17%) and urinary volume (+21%), all favourably affected by treatment with *Pygeum africanum*. These results are comparable to those reported by Barlet *et al.*[4], while their placebo group changed very little.

For the other objective parameters, the very large variability of changes from V2 influenced the lack of detection of effects as statistically significant. In particular, the overall mean reduction in post-micturitional residual volumes from baseline to the end of treatment was 3.19 ml (approximately 9%) with a large standard deviation of 35.73 ml, and was not statistically significant. This observation differs from that of Barlet *et al.*[4] who found a significant decrease in residual volumes with *Pygeum africanum* relative to placebo.

Prostate volume was unaffected by treatment, thus confirming the observations of others[4,9].

The absence of specific adverse events is further confirmation of the findings of previous studies with *Pygeum africanum*[2].

Comparison with recent studies on other drugs similarly indicated for symptomatic treatment of mild to moderate BPH provides an interesting, although necessarily imprecise, perspective on the results reported here for *Pygeum africanum*[1,7,12–14].

Conclusion

Pygeum africanum treatment has been shown to be usefully effective and safe under the open-label conditions of the study. The evidence suggests that the beneficial effects are well developed after one month of treatment with a slight tendency to further improvement by the end of a second month. The presence of substantial residual activity one month after stopping treatment tends to confirm much clinical observation that, although no explanation can yet be offered, the effects of the product outlive the strict period of administration.

As far as any conclusions can be drawn from the literature for comparison with other products having the same indication, *Pygeum africanum* seems to compare favourably with other medical treatments available, with a satisfactory efficacy:acceptability profile.

Although all the plant extracts have a good safety record, the other treatments for BPH are associated with a certain incidence of adverse events – dizziness, asthenia and hypotension for the α-blockers, decreased libido and impotence for finasteride which, though most often mild and tolerable, limit

nonetheless their usefulness. The virtual absence of any treatment-related adverse events with *Pygeum africanum* may be seen as a substantial advantage by patients whose disease is at this stage provoking only moderate discomfort and is in no way life-threatening. Future studies, and in particular a large on-going international randomised, double-blind, placebo-controlled trial with *Pygeum africanum*, should bring additional evidence to confirm the therapeutic interest of this drug in BPH treatment.

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Lycopene

This abbreviated labelling standard is intended to serve as a guide to industry for the preparation of a Product Licence Applications (PLAs) and labels for natural health product market authorization. It includes generalized claims and is not intended to be a comprehensive review of the medicinal ingredient. Wording of the claim on the PLA and label must therefore be identical to this labelling standard.

Date

2009-09-04

NHPID Name

Lycopene (O'Neil et al. 2012)

Proper Name(s)

- (all-trans)-Lycopene (USP 2009, O'Neil et al. 2006)
- psi,psi-Carotene (USP 2009, O'Neil et al. 2006)

Common Name(s)

Lycopene (USP 2009)

Source Material(s)

- Solanum lycopersicum (Fruit flesh) (USP 2009)
- Synthetic

Route(s) of Administration

Oral

Dosage Form(s)

The acceptable pharmaceutical dosage forms suited to oral administration include, but are not limited to, chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons. This

labelling standard is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s)

Statement(s) to the effect of:

- Provides antioxidants for the maintenance of good health (Silaste et al. 2007, Porrini et al. 2005, Matos et al. 2001)
- Helps to support prostate health (Erdman et al. 2009, Kristal et al. 2008, Schwarz et al. 2008, Mohanty et al. 2005, Giovannucci et al. 2002, Kucuk et al. 2002, Kucuk et al. 2001, Gann et al. 1999)

Dose(s)

Adults:

Antioxidant

Dose(s): not to exceed 30 Milligrams per day (Silaste et al. 2007, Porrini et al. 2005, Kucuk et al. 2002)

Prostate

Dose(s): 6.5 - 30 Milligrams per day(Kristal et al. 2008, Giovannucci et al. 2002, Gann et al. 1999, Giovannucci et al. 1995)

Products must contain more than 95% lycopene (USP 32).

Duration of use

No statement is required

Risk Information

Statement(s) to the effect of:

Caution(s) and Warning(s)

No statement is required

Contraindication(s)

No statement is required

Known Adverse Reaction(s)

No statement is required

Non-medicinal Ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Specifications

- .A Finished Product Specifications Form must accompany the application. The product must comply with the requirements of the most recent published version of the "Evidence for Quality of Finished Natural Health Products" guidance document.
- .The medicinal ingredient may comply with the specifications outlined in the 'Lycopene' and 'Lycopene Preparation' pharmacopoeial monographs in the U.S. Pharmacopoeia (USP).

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An Update on the Health Effects of Tomato Lycopene

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Key Words

lycopene, carotenoids, lycopenoids, bioavailability, cancer, cardiovascular disease

Abstract

Lycopene is a non-provitamin A carotenoid that is responsible for the red to pink colors seen in tomatoes, pink grapefruit, and other foods. Processed tomato products are the primary dietary lycopene source in the United States. Unlike many other natural compounds, lycopene is generally stable to processing when present in the plant tissue matrix. Recently, lycopene has also been studied in relation to its potential health effects. Although promising data from epidemiological, as well as cell culture and animal, studies suggest that lycopene and the consumption of lycopene containing foods may affect cancer or cardiovascular disease risk, more clinical trial data is needed to support this hypothesis. In addition, future studies are required to understand the mechanism(s) whereby lycopene or its metabolites are proven to possess biological activity in humans.

INTRODUCTION

CVD: cardiovascular disease

Isoprenoid: refers to an unsaturated, branched 5-carbon structure

Epidemiological research indicates that diets rich in fruits and vegetables are associated with a decreased risk of chronic diseases such as cardiovascular disease (CVD) (Ignarro et al. 2007) and cancer (Block et al. 1992). It is estimated that approximately 50% of cancer cases and 35% of cancer deaths in the United States can be attributed to poor diet (Williams et al. 1999). Epidemiological studies have associated tomato consumption with a decreased risk of prostate cancer (Jain et al. 1999, Giovannucci et al. 2002) and CVD (Arab & Steck 2000). Despite this evidence, it is not clear which individual compounds present in tomato, such as lycopene, impart these potential benefits or whether other constituents of tomatoes and tomato products produce beneficial effects.

Lycopene, a naturally occurring red carotenoid pigment found in tomatoes, pink grapefruit, watermelon, papaya, guava, and other fruits, has been extensively studied for more than 70 years, with more than 2000 articles published in peer-reviewed journals and 4000 other publications (scientific and otherwise) written on the subject. Most of these articles have focused on lycopene derived from tomatoes. Given the vast amount of information already published about lycopene, we focus on the recent literature (1999–2009) related to the health effects of tomato lycopene in humans. Although in vitro and animal studies are vitally important to understanding the mechanisms behind potential health effects, human studies, specifically clinical trials, are ultimately used to determine the effect of dietary constituents on health, as well as to set nutrition and food labeling policy. For more information on in vitro and animal studies related to the potential health effects of lycopene, please see the reviews by Rao et al. (2006) and Cohen (2002). Over the past decade, lycopene-containing foods (primarily tomato products) and lycopene supplements have been reported to affect diseases ranging from cancer to heart disease to asthma (Dahan et al. 2008, Riccioni et al. 2008, Wood et al. 2008). Most recently, researchers have begun to investigate lycopenoids, oxidative metabolites of lycopene, based on the possibility that these lycopenoids may produce biological effects (Erdman et al. 2009).

Given the scope of literature published on the potential health benefits of this carotenoid in the diet, herein we review publications related to lycopene chemistry, sources, intake, and bioavailability. In addition, we summarize the literature on the presence and formation of lycopenoids, and discuss the most promising directions for future lycopene research.

LYCOPENE CHEMISTRY

Lycopene is one pigment in a large family of plant pigments known as carotenoids. Carotenoids produce colors ranging from the yellow color of squash, to the orange color of pumpkins, to the red color of tomatoes. Carotenoids also contribute to some plant food aromas (Rodriguez-Bustamante & Sanchez 2007). Some carotenoids also possess provitamin A activity and have shown potent antioxidant activity. To date, more than 700 carotenoids have been identified (Britton et al. 2004). There are two primary types of carotenoids: hydrocarbon carotenoids and xanthophylls. Hydrocarbon carotenoids, such as lycopene, are composed entirely of hydrogen and carbon. In contrast, xanthophylls, such as lutein, contain oxygen in addition to carbon and hydrogen (Furr & Clark 1997). Some hydrocarbon carotenoids, such as β-carotene and α-carotene, can be enzymatically cleaved to form vitamin A. Lycopene lacks provitamin A activity because of the absence of a terminal beta ionone ring (Rao & Rao 2007). Carotenoids typically contain 40 carbons. Apo-carotenoids contain less than 40 carbons. The prefix apo is used to identify carotenoids that have been shortened in length by one or more carbons (Britton et al. 2004). Regardless of the number of carbons, all carotenoids possess an isoprenoid backbone (Britton et al. 2004).

The chemical formula for lycopene is $C_{40}H_{56}$. The 11 conjugated and 2 unconjugated double bonds present in lycopene allow for extensive isomerization, resulting in 1056 theoretical *cis-trans* configurations (Zechmeister 1944). Only a few isomers are actually found in nature, however, (**Figure 1**) with the all-*trans* configuration of lycopene being the most common isomer found in foods (Nguyen & Schwartz 2000). The thermodynamic stabilities of the common lycopene isomers have been determined relative to the all-*trans* isomer. The 5-*cis* isomer was found to be the most stable followed by all-*trans*, 9-*cis*, 13-*cis*, 15-*cis*, 7-*cis*, and 11-*cis* (Chasse et al. 2001). The lycopene isomers found in human blood plasma, breastmilk, and human tissues are mainly of the *cis*-isomer type (Hadley et al. 2003, Allen et al. 2002, Ferruzzi et al. 2001, Boileau et al. 2002). The color of lycopene is directly related to its isomeric form. The all-*trans* isomer and most other isomers of lycopene are red, whereas tetra-*cis*-lycopene possesses an orange hue (Nguyen & Schwartz 2000, Zechmeister 1944).

Reactive oxygen species (ROS) are oxygen-containing molecules that either are or have the potential to generate free radicals. Overproduction of ROS results in a condition known as oxidative stress, which has been linked to both cancer and cardiovascular disease (Halliwell 1994). Carotenoids, including lycopene, can be potent antioxidant molecules and are especially effective at scavenging the ROS singlet oxygen. Of the carotenoids, lycopene is the most effective singlet oxygen scavenger in vitro (Sies & Stahl 1995). This antioxidant activity has been proposed as a mechanism for the potential health benefits of carotenoids (Sies & Stahl 1995, Agarwal & Rao 2000). Recently, this antioxidant mechanism has been called into question given the low concentration of lycopene in the body relative to other antioxidant molecules, such as vitamin E (Erdman et al. 2009). This has led to speculation that observed health benefits may be due to the effect of lycopene or oxidative metabolites on gene expression (Erdman et al. 2009).

Reactive oxygen species (ROS): oxygen-containing molecules that either are or have the potential to generate free radicals

Oxidative stress: an imbalance between the oxidative and reductive reactions in living systems favoring oxidation to the extent that damage may result

LYCOPENE SOURCES, INTAKE, AND BIOAVAILABILITY

More than 80% of dietary lycopene intake in the U.S. is derived from processed tomato products such as ketchup, tomato juice, spaghetti sauce, and pizza sauce (Clinton 1998). The amount of lycopene present in processed foods is often much higher than that found in fresh foods given that processing often involves concentration via water loss. For example, ketchup contains 9.9–13.44 mg lycopene/100 g, whereas fresh tomatoes contain anywhere from 0.88–7.74 mg lycopene/100 g wet weight (Rao et al. 1998, Nguyen & Schwartz 1998).

Dietary intake of lycopene varies greatly depending upon the studied population. The average Italian consumes 14.3 mg/day of total carotenoids (Lucarini et al. 2006). Lycopene makes up the largest proportion of carotenoids in the Italian diet, with an average intake of 7.4 mg/day (Lucarini et al. 2006). The average daily intake of lycopene in the United States ranges from 6.6–10.5 mg/day for men and from 5.7–10.4 mg/day for women (Porrini & Riso 2005). The average reported daily lycopene intake is 1.1 mg/day in the United Kingdom, 1.6 mg/day in Spain, 3.8 mg/day in Australia, 4.8 mg/day in France, and 4.9 mg/day in the Netherlands (Porrini & Riso 2005).

Lycopene bioavailability can be affected by a number of factors, including food processing and dietary composition. Lycopene can occur in several forms in fresh plant foods, including carotenoid-protein complexes in chloroplasts or in crystalline form inside chromoplasts (Parada & Aguilera 2007). The effects of processing and storage on lycopene structure and stability are of interest for a number of reasons. Improper processing and storage (i.e., exposure to light and oxygen) may alter the ratio of lycopene isomers or degrade lycopene entirely, making these food products less desirable to the consumer (Xianquan et al. 2005). Traditional commercial processing methods do not have a significant effect on lycopene levels or on *cis/trans* isomerization

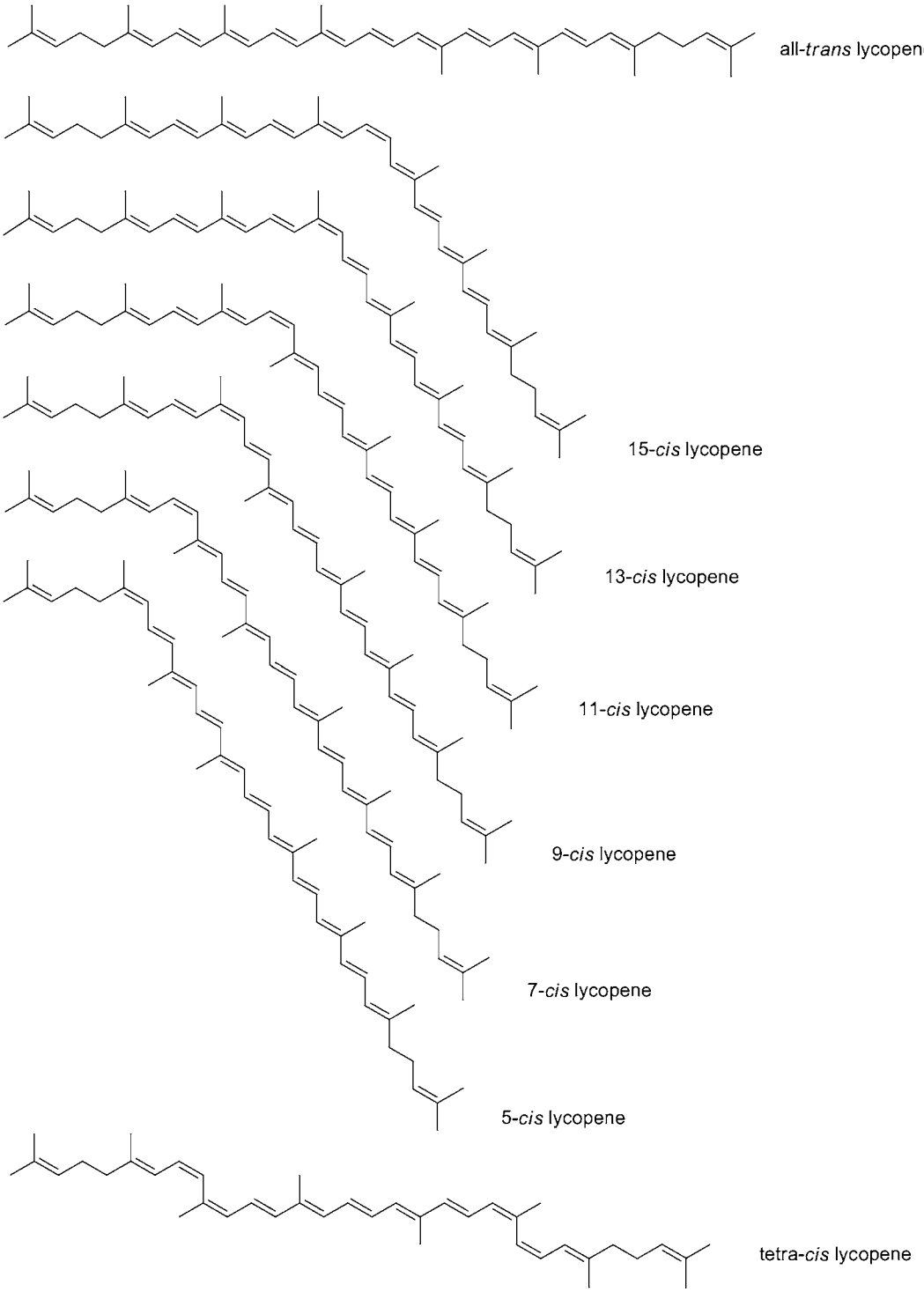

Figure 1

Structure of lycopene and several isomers.

(Nguyen & Schwartz 1998). In fact, thermal processing generally improves lycopene bioavailability by disrupting cellular membranes, which allows lycopene to be released from the tissue matrix (Nguyen et al. 2001). Multiple studies have shown that lycopene from thermally processed tomato products is more bioavailable than lycopene from fresh tomatoes (Gärnter et al. 1997, Stahl & Sies 1992, Allen et al. 2002).

The absolute amount of lycopene absorbed does not appear to vary greatly with dose. A study performed in men observed lycopene absorption after consumption of one serving of tomato juice (Diwadkar-Navsariwala et al. 2003). Different volumes of tomato juice, with a constant percent fat, were administered to deliver 10 mg to 120 mg of lycopene. The range of lycopene absorbed, independent of dose, was between 1.8 mg and 14.3 mg, with an average of 4.7 mg. The amount of lycopene absorbed by the men consuming juice containing 120 mg lycopene was not significantly different from that absorbed by the men consuming juice containing 10 mg lycopene. These authors suggested that inter-individual differences, not dose, has the greatest impact on the amount of lycopene absorbed (Diwadkar-Navsariwala et al. 2003).

Lycopene bioavailability is greatly affected by dietary composition. Given that lycopene is a lipid-soluble compound, consuming it with fat increases its bioavailability. For example, consuming salads with full-fat dressing results in higher blood carotenoid levels than eating salads with reduced fat dressing. When salads were consumed without fat in the same study, no measurable lycopene uptake occurred (Brown et al. 2004). A study by Unlu et al. (2005) showed a similar result, whereby the consumption of tomato salsa with avocado (as lipid source) led to a 4.4-fold increase in lycopene absorption as compared with salsa without avocado.

A schematic of lycopene digestion and absorption is shown in **Figure 2**. Once ingested, lycopene must first be released from the food matrix before it is incorporated into mixed micelles. Micelles contain bile salts, cholesterol, and fatty acids from the meal, and the amphiphilic nature of the micelle structure helps to keep the lipophilic nutrients soluble in the aqueous digesta (During & Harrison 2004). The micelles approach the unstirred water layer of the apical side of the intestinal cells (enterocytes), and lycopene passively diffuses across the apical membrane (During & Harrison 2004). Historically, researchers believed that lycopene was absorbed by the same route as dietary lipids, i.e., passive diffusion (Furr & Clark 1997), and this is still believed to be at least partially true. However, in the past five years, investigators have discovered that lycopene absorption can be facilitated by a cholesterol membrane transporter known as scavenger receptor class B type I (SR-BI) (During et al. 2005, Moussa et al. 2008). Research has also suggested that lycopene absorption may be facilitated by other transporters, but this has not yet been confirmed (During et al. 2005, Moussa et al. 2008). Once inside the enterocyte, lycopene is packaged with other dietary lipids into chylomicrons (During & Harrison 2004). Chylomicrons are then transported across the basolateral membrane and make their way into the lymphatic system, which eventually releases chylomicrons into the blood.

Competition by other carotenoids or cholesterol may also influence lycopene absorption. One post-prandial human study demonstrated that co-consumption of tomato puree (30 mg lycopene) + spinach lutein (30 mg) or encapsulated lutein (30 mg) reduced chylomicron lycopene levels by 70% and 61% respectively, as compared with lycopene levels observed after consumption of tomato puree alone (Tyssandier et al. 2002). However, when subjects consumed these foods daily for three weeks at half of the previous dose (15 mg of lycopene + 15 mg lutein), no difference was observed in steady-state plasma levels of lycopene (Tyssandier et al. 2002). A human study by Johnson et al. (1997) observed that co-administration of β-carotene crystals in oil (60 mg) with lycopene crystals in oil (60 mg) increased the 24-hour postprandial serum area under the curve (AUC) of lycopene by four-fold as compared with the administration of lycopene alone. It is unclear whether absorption of lycopene as part of a food product would increase if co-consumed

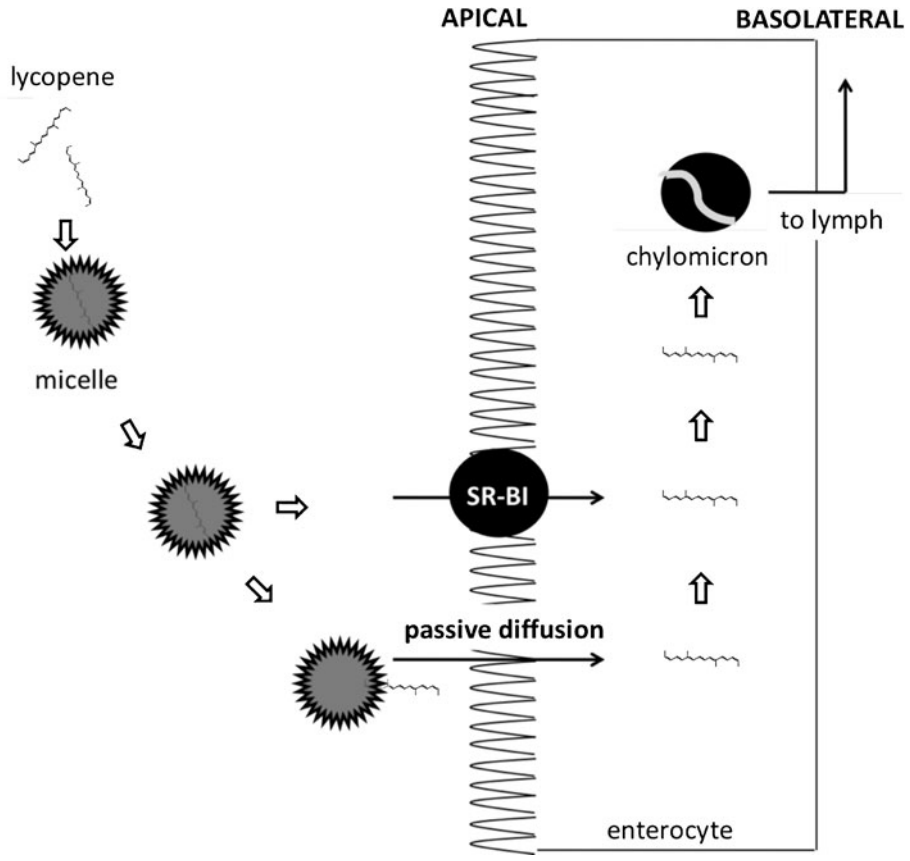

Figure 2

Digestion and absorption of lycopene in the small intestine. Data adapted from During & Harrison (2004) and During et al. (2005).

with a β-carotene–containing food product. Considering the recent research demonstrating the transport of lycopene by cholesterol transporter SR-BI, it is likely that genetic differences in SR-BI expression may also affect the absorption of lycopene. However, no studies have yet been published on this topic.

In addition, lycopene absorption may be affected by other factors such as probiotics and single nucleotide polymorphisms (SNPs). Consumption of a probiotic-containing yogurt versus a regular yogurt lowered blood lycopene levels in a group of 17 women who consumed probiotics for a total of 4 weeks (Fabian & Emaldfa 2007). This study suggests that probiotics may affect lycopene bioavailability or metabolism (Fabian & Emaldfa 2007). Borel et al. (2007) reported that human blood carotenoid levels are influenced by SNPs in apolipoproteins A-IV and B, which are associated with lipid transport.

Single nucleotide polymorphisms (SNPs): variations in a single DNA base pair in a gene that can affect the function of proteins produced from the gene

Greater than 90% of the lycopene found in processed tomato products is in the all-*trans* conformation (Nguyen & Schwartz 1998, Nguyen et al. 2001, Boileau et al. 2002). In vivo studies demonstrate that the *cis*-isomers of lycopene appear to be more bioavailable than the all-*trans* isomer (Stahl & Sies 1992, Unlu et al. 2007). In vitro experiments support the conclusion that increased bioavailability of lycopene *cis*-isomers is at least partially due to increased micellarization and increased uptake by the enterocyte relative to all-*trans* lycopene (Failla et al. 2008).

Human organs store lycopene to varying degrees. Lycopene is found in the highest concentrations in the liver, testes, adrenal glands, and adipose tissues (Kun et al. 2006). It is found in lower concentrations in the kidney, ovary, lung, and prostate (Kun et al. 2006).

BPH: benign prostatic hyperplasia

FFQ: food frequency questionnaire

RR: relative risk

OR: odds ratio

Prostate specific antigen (PSA): a biomarker commonly used to monitor the risk or progression of prostate cancer

POTENTIAL HEALTH BENEFITS OF LYCOPENE

Over the past decade, the effects of lycopene have been studied with respect to a wide range of diseases (various cancers, CVD) (Dahan et al. 2008, Riccioni et al. 2008). Here we summarize data from recent human studies examining lycopene's biological effects on these disease processes.

Cancer

Cancer is the second leading cause of death in the United States, with approximately 1.5 million new cases of cancer diagnosed in 2008 (American Cancer Society 2008). The consumption of tomatoes and tomato products has been associated with a reduced incidence of a number of different types of cancers, most notably prostate, lung, and stomach (Giovannucci 1999).

Of the diseases studied in relation to lycopene, prostate cancer is one of the most well-researched. In addition to prostate cancer, benign prostatic hyperplasia (BPH), the age-related non-cancerous overgrowth of the prostate gland, also negatively affects men's health. Some of the strongest epidemiological evidence to support an association between tomato product consumption and a reduced incidence of prostate cancer has come from the Health Professionals Follow-Up Study (HFPS). Most recently, a prospective observational study by Giovannucci et al. (2002) collected food frequency questionnaire (FFQ) data from the HPFS group of 47,365 men in 1986, 1990, and 1994. Intake of $\geq$2 servings of tomato sauce per week was associated with a reduced risk of prostate cancer [relative risk (RR) = 0.77 relative to <1 serving of tomato sauce per month, $P_{trend} < 0.001$]. Lycopene intake was also associated with a reduced risk of prostate cancer, but the association was weaker (Giovannucci et al. 2002). A study by Lu et al. (2001) quantified lycopene in blood plasma of 65 prostate cancer patients and 132 cancer-free controls. A significant inverse association between prostate cancer and plasma lycopene concentration [odds ratio (OR) = 0.17, $P_{trend} = 0.005$] was observed between the highest and lowest quintiles of intake (Lu et al. 2001). Another group of researchers observed men (n = 4770) from the placebo arm of the Prostate Cancer Prevention Trial from 1994–2003 who were free of BPH at baseline (Kristal et al. 2008). Over the course of the study, 876 men developed BPH (Kristal et al. 2008). FFQ data revealed that there was an 18% reduction in risk of BPH in men who consumed the greatest amount of lycopene as a food or a supplement ($P_{trend} = 0.056$). A recent meta-analysis demonstrated a modest inverse relationship between intake of raw tomatoes (RR = 0.89 for highest versus lowest quartile of intake) and tomato products (RR = 0.81 for highest versus lowest quartile of intake) and prostate cancer (Etminan et al. 2004). Collectively, these studies suggest that the consumption of lycopene or lycopene-containing foods reduces the risk for developing prostate cancer.

In contrast, other observational studies have found weak (Chang et al. 2005) or inconclusive (Peters et al. 2007) evidence supporting a link between prostate cancer or BPH and lycopene intake.

Since 1999, at least 12 clinical trials have examined the relationship between tomato products or lycopene containing supplements and prostate cancer. Most of these studies measured prostate specific antigen (PSA). PSA levels are routinely measured to determine prostate cancer risk and to monitor prostate cancer treatment (Chen et al. 2001). In one study by Chen et al. (2001), 32 prostate cancer patients consumed tomato sauce daily for three weeks

(30 mg lycopene/day) before a radical prostatectomy. Serum PSA levels decreased after the dietary intervention by 20% ($p < 0.001$). In addition, analysis of the prostate tissue revealed a decrease in the ratio of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a DNA adduct indicative of oxidative stress and associated with cancer, to 2′-deoxyguanosine (a marker of oxidative DNA damage) in the treated patients as compared with random controls (ratio = 0.76 versus 1.06, respectively; $p = 0.03$) (Chen et al. 2001). A separate clinical study examined the effects of tomato and tomato product consumption with and without soy protein isolate in men ($n = 41$) with recurrent, asymptomatic prostate cancer (Grainger et al. 2008). Consumption of tomatoes and tomato products daily (target intake level 25 mg/day lycopene) for eight weeks reduced serum PSA levels in 34% of the subjects (Grainger et al. 2008). A phase II clinical trial was performed in men ($n = 71$) diagnosed with prostate cancer investigating the effects on PSA levels of a tomato extract capsule (Lyc-o-Mato®, 15mg/day lycopene) consumed twice daily for up to 6 months with or without soy isoflavones (Vaishampayan et al. 2007). Lyc-o-Mato® is a tomato extract oleoresin containing 15 mg lycopene along with other tomato phytochemicals including phytoene (1.5 mg), phytofluene (1.4 mg), β-carotene (0.4 mg), and tocopherols (5 mg) (Voskuil et al. 2008). These researchers observed that subjects in both treatment groups had a decline in the rate of rise of PSA levels (Vaishampayan et al. 2007). A placebo-controlled clinical study, in 37 men with confirmed BPH, had men consume either a LycoVit® synthetic lycopene supplement (15 mg/day) or a placebo pill daily for six months (Schwarz et al. 2008). The consumption of the LycoVit® tablet reduced serum PSA levels by 10% ($p < 0.05$) over the course of six months, whereas there was no change in serum PSA in the placebo group (Schwarz et al. 2008). In contrast to the clinical trials showing a reduction in PSA levels as a surrogate marker for prostate cancer status, some studies observed a weak effect (Barber et al. 2006) or no effect (Clark et al. 2006, Bunker et al. 2007, Jatoi et al. 2007) of tomato consumption or lycopene supplementation on prostate cancer risk.

Epidemiological evidence has suggested that consumption of lycopene containing foods may decrease risk for breast cancer. A prospective cohort study by Cui et al. (2008) found that lycopene consumption, as estimated by an FFQ, was inversely associated with estrogen and progesterone receptor positive breast cancer risk in postmenopausal women ($n = 84{,}805$) followed for an average of 7.6 years (RR = 0.85 for highest quartile of intake as compared with lowest quartile of intake, $P_{trend} = 0.064$). Two case-control studies comparing the dietary habits of women with and without breast cancer also observed a significant decrease in the odds ratio of those who consumed the highest amount versus the lowest amount of dietary lycopene (Ronco et al. 1999, Levi et al. 2001).

Effects on biomarkers of breast cancer risk have also been investigated. A cross-sectional study of 207 breast cancer survivors by Thomson et al. (2007) demonstrated that increased plasma lycopene concentrations were modestly correlated with reduced levels of 8-OHdG. A recent randomized, placebo-controlled, double-blind, crossover trial conducted by Voskuil et al. (2008) determined that tomato-extract supplementation (Lyc-o-Mato®, 30 mg/day lycopene) for two months in premenopausal women with a high breast cancer risk ($n = 36$) reduced free insulin-like growth factor-I (IGF-I) by 7.0% ($p < 0.05$). IGF-I is a biomarker associated with increased breast cancer risk in premenopausal women (Hankinson et al. 1998).

Lung cancer is the leading cause of cancer death in the U.S. for both men and women. Most lung cancers are related to tobacco use. Lung cancer is of particular interest with regards to carotenoid research given the increased risk of lung cancer development observed in smokers consuming a β-carotene supplement (Omenn et al. 1996, Albanes et al. 1996). Most recently, the VITamins And Lifestyle (VITAL) cohort study observed how previous β-carotene supplement usage was correlated with incidence of lung cancer development in 77,126 free-living Washington State

8-hydroxy-2′-deoxyguanosine (8-OHdG): a DNA adduct indicative of oxidative stress, which could lead to cancer or other diseases

Randomized, placebo-controlled, double-blind, crossover trial: clinical trial in which treatments are randomly assigned, neither researchers nor participants are aware of treatment groupings, and each participant receives each participant received each treatment over the course of the study

Insulin-like growth factor-1 (IGF-I): a biomarker of growth that is sometimes used to monitor the development and progression of several cancers, including prostate, lung, and colon

residents. This study reported that β-carotene supplementation was associated with a threefold increase in lung cancer incidence (Satia et al. 2009). Epidemiological studies suggest that higher intake of lycopene is associated with either a reduced risk of lung cancer (Yuan et al. 2001, Holick et al. 2002, Michaud et al. 2000, Ito et al. 2005b), or no change in lung cancer risk, as compared with lower intake levels (Yuan et al. 2003, Rohan et al. 2002, Voorrips et al. 2000, Knekt et al. 1999, Steinmetz et al. 1993, Satia et al. 2009). A recent meta-analysis by Gallicchio et al. (2008) summarizes the available data on lycopene and lung cancer.

There have also been mixed results in the epidemiological studies examining the association between lycopene and colorectal cancer risk. In a prospective cohort study of 3182 free-living subjects in rural Japan, higher serum levels of lycopene were significantly associated with a reduced risk of colorectal cancer mortality (Ito et al. 2005a). However, a case-control study by Kune & Watson (2006), a meta-analysis of 11 cohort studies by Männisto et al. (2007), and a study by Leung et al. (2008) found that lycopene intake and plasma lycopene levels were not associated with colorectal cancer risk or survival in patients already diagnosed with cancer.

Several clinical trials have reported beneficial effects of lycopene-containing supplements on colorectal cancer biomarkers. A randomized, placebo-controlled, double-blind crossover study conducted by Vrieling et al. (2007) demonstrated that tomato derived lycopene supplementation (Lyc-o-Mato®, 30 mg/day lycopene) for eight weeks in 40 men and 31 postmenopausal women at high risk for colorectal cancer increased serum insulin-like growth factor binding protein-1 (IGFBP-1) concentrations in women by 22%. Serum IGFPB-2 concentrations in men and women were also increased by 8.2% and 7.8%, respectively (Vrieling et al. 2007). IGFBPs have been shown to bind and inactivate IGF (higher concentrations of IGF are associated with a higher risk of developing cancer) (Vrieling et al. 2007). Another double-blind, randomized, placebo-controlled study by Walfisch et al. (2007) observed the effects of lycopene supplementation on IGF levels in colon cancer patients. This study found that supplementation with tomato extract (Lyc-o-Mato®, 30 mg/day lycopene) in 30 patients waiting for colectomy surgery led to a 25% decrease in plasma IGF-I concentration ($p = 0.02$). A 24% decrease in the ratio of IGF-I/IGFBP-3 was also observed ($p = 0.03$) (Walfisch et al. 2007). This was considered to be a positive result as a study by Ma et al. (1999) reported that men in the highest quintile of plasma IGF-I concentrations had an increased risk of colorectal cancer compared with men in the lowest quintile ($p = 0.02$). In another study, 20 healthy subjects participated in a double-blind crossover dietary intervention and consumed a tomato juice beverage (250 ml of Lyc-o-Mato® drink, 5.7 mg lycopene, 3.7 mg phytoene, 2.7 mg phytofluene, 1 mg β-carotene, and 1.8 mg α-tocopherol), and a placebo beverage for 26 days each, with a 26-day washout in between (Riso et al. 2006). Blood plasma levels of IGF-I were inversely correlated with lycopene consumption (Riso et al. 2006). In contrast, a study by Graydon et al. (2007) did not find evidence to suggest that synthetic lycopene reduces IGF-I and IGFBP-3 in healthy men.

Gastric cancer is not common in the United States, but is a common disease in Korea, Japan, and other Asian countries. The majority of human studies examining the effects of lycopene on gastric cancer have been observational rather than clinical. A 12-year case-control study of 191 cases and 570 controls within a cohort of 18,244 middle-aged men in Shanghai, China observed higher serum levels of lycopene in individuals who developed gastric cancer as compared with controls (Yuan et al. 2004). Similarly, a 2 year case-control study in Uruguay observed a strong inverse relationship between dietary lycopene intake (as determined by FFQ) and gastric cancer when comparing 120 cases of stomach cancer with 360 controls (De Stefani et al. 2000). A prospective cohort study observed a subset of 243 subjects from the α-tocopherol, β-carotene (ATBC) Cancer Prevention trial who were diagnosed with gastric adenocarcinomas and compared them with the ~29,000 male smokers in the original trial (Nouraie et al. 2005). Data from this study demonstrated

that higher lycopene intake, as determined by an FFQ, was correlated with a reduced risk of gastric noncardia cancer (hazard ratio = 0.67). Gastric noncardia cancer is a type of gastric cancer strongly associated with *Helicobacter pylori* (Nouraie et al. 2005). In contrast, a number of observational studies from the Netherlands, Spain, Sweden, and Japan found no association between lycopene intake or plasma lycopene levels and gastric cancer risk (Botterweck et al. 2000, Garcia-Closas et al. 1999, Larsson et al. 2007, Persson et al. 2008).

Few studies have investigated the effect of lycopene on pancreatic cancer. Early evidence has suggested that increased levels of serum lycopene were associated with a reduced risk of pancreatic cancer (Burney et al. 1989, Comstock et al. 1991). More recently, a case-control study of Kuwaitis (11 cases with matched controls) by Abiaka et al. (2001) found that low plasma lycopene levels (0.12 μM for cases versus 0.72 μM for controls) were associated with pancreatic cancer ($p < 0.0001$). Another case-control study (462 cases and 4721 population-based controls) in Canada by Nkondjock et al. (2005) reported that increased dietary lycopene intake (assessed by FFQ) was associated with a reduction in pancreatic cancer risk in men when comparing the highest versus lowest quintiles of intake (OR = 0.69, $P_{trend} = 0.026$).

There are a limited number of epidemiological studies that have been done regarding lycopene and ovarian cancer. A case-control study (549 cases, 516 controls) by Cramer et al. (2001) in pre- and postmenopausal women found that dietary lycopene intake (determined by FFQ) was significantly and inversely associated with ovarian cancer risk (OR = 0.53 for the highest quintile as compared with the lowest quintile of intake, $P_{trend} = 0.003$). A recent case-control study (45 cases, 135 controls) by Jeong et al. (2009) of Korean women also found that increased plasma lycopene was associated with reduced risk of ovarian cancer (OR = 0.09 between highest and lowest tertiles of intake, $P_{trend} = <0.0001$). In contrast to these studies, others have found no relationship between serum lycopene and ovarian cancer risk (Helzlsouer et al. 1996, Zhang et al. 2007).

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in the United States and was responsible for more than 652,000 deaths in 2005 (U.S. Mortality Data 2008). Increased plasma lycopene levels have been associated with reductions in CVD risk and have also been reported to improve biomarkers associated with CVD. For example, a study by Sesso et al. (2003) of 38,445 women found that higher levels of tomato-based product intake were associated with a reduced risk of cardiovascular disease (RR = 0.71, $P_{trend} = 0.029$) and myocardial infarction (RR = 0.43, $P_{trend} = 0.033$) between the highest and lowest quintiles of intake. A separate study in Finnish men (n = 1028) found an inverse association between serum lycopene concentrations and common carotid artery intima-media thickness, a measure of early atherosclerosis (Rissanen et al. 2003). In addition, a study using a subset of data (n = 4557) from the third National Health and Nutrition Survey (NHANES III) observed decreased serum levels of carotenoids (including lycopene) in individuals with higher levels of C-reactive protein, a marker of inflammation (Kritchevsky et al. 2000).

Some clinical trials have also supported a relationship between cardiovascular disease and lycopene intake. Some studies have shown that lycopene may reduce cholesterol synthesis and increase low-density lipoprotein (LDL) degradation (Arab & Steck 2000). A randomized crossover study by Agarwal & Rao (1998) used four different treatments: placebo (0 mg lycopene), tomato juice (50.4 mg lycopene), spaghetti sauce (39.2 mg lycopene), and tomato oleoresin (75 mg lycopene). Nineteen healthy subjects consumed each treatment daily for one week and went through a one-week washout period between each treatment week. Serum lycopene concentration doubled in subjects on the lycopene-containing treatments. In addition, a significant decrease in serum

lipid peroxidation and LDL oxidation was observed after subjects consumed any one of the three lycopene-containing treatments (Agarwal & Rao 1998). In a study by Hadley et al. (2003), healthy individuals received one of three tomato treatments for 15 days (condensed tomato soup, ready-to-serve tomato soup, or V8® vegetable juice). Blood samples were taken at baseline and after treatment, and the LDL + VLDL (very-low-density lipoprotein) fraction was exposed ex vivo to oxidative stress (Hadley et al. 2003). The lipoprotein oxidation lag period, a measure of protection against oxidative stress, was significantly increased in all three treatment groups (Hadley et al. 2003). A separate clinical trial by Shen et al. (2007) treated 24 subjects with either fresh tomato, tomato juice, or a lycopene drink (all delivering 40 mg lycopene/day) for six weeks. This study found that triglyceride levels and LDL cholesterol were decreased, and high-density lipoprotein (HDL) cholesterol increased in subjects who consumed fresh tomato and tomato juice. In a more recent study, 18 healthy men and women consumed a soy-tomato beverage daily (21 mg lycopene/day) for eight weeks (Bohn et al. 2009). Again, consumption of the beverage significantly reduced the susceptibility of the LDL + VLDL blood plasma fraction to oxidative damage. In addition, HDL cholesterol levels significantly increased, and the ratio of total cholesterol/HDL cholesterol significantly decreased over the course of the study (Bohn et al. 2009).

In contrast, a four-week dietary intervention study by Paterson et al. (2006) observed that consumption of a carotenoid-rich diet did not have an effect on plasma antioxidant status or markers of oxidative stress.

Other Diseases

Although studies on the ability of lycopene to modify cancer and CVD risk are most prevalent, there have been numerous other diseases that have also been investigated in relation to lycopene consumption. These conditions include ultra violet (UV)-induced sunburn, gingivitis, osteoporosis, mental disorders, and asthma.

The ability of lycopene to affect UV-induced sunburn was investigated in nine healthy individuals consuming 40 g tomato paste (~16 mg lycopene) with olive oil daily for 10 weeks. The control group (n = 10) consumed olive oil alone. At week = 0 and week = 10, subjects were irradiated with a solar simulator, and the a-value (i.e., redness) of skin tone was measured by chromatometry. Individuals in the treatment group had a 32% reduction in a-values between week = 0 and week = 10, and 40% lower a-values as compared with controls. This study indicates that the tomato paste treatment was protective against UV-induced sunburn (Stahl et al. 2001). A separate clinical study was performed in 36 healthy adults, whereby subjects consumed synthetic lycopene alone, a soft-gel encapsulated tomato extract, or a tomato drink for 12 weeks. Dorsal skin was irradiated at weeks 0, 4, and 12 with artificial UV light at levels high enough to cause mild sunburn. The subjects consuming the tomato extract and tomato drink had a 38% and 48% decrease, respectively, in solar simulator–induced sunburn at week 12, compared with only a 25% decrease in the group treated with synthetic lycopene (Aust et al. 2005).

A randomized, placebo-controlled, split-mouth study of gingivitis was performed by Chandra et al. (2007) in 20 healthy subjects with clinical signs of gingivitis. The treatment group (n = 10) was supplemented with 8 mg/day lycopene (LycoRed®), whereas the control group (n = 10) received a placebo daily for two weeks. In this study, patients receiving the lycopene treatment showed statistically significant reductions in gingivitis and bleeding index (Chandra et al. 2007).

Low serum levels of lycopene have also been associated with increased risk of psychiatric disorders (Li & Zhang 2007). A cross-sectional study using NHANES III data (n = 6680) observed an inverse association between serum levels of certain vitamins and carotenoids and whether subjects had attempted suicide (Li & Zhang 2007). Suicide attempters had lower levels of antioxidant

vitamins and carotenoids in their serum than did nonattempters. The difference between mean serum lycopene levels in suicide attempters versus nonattempters = 0.142 μmol/L (Li & Zhang 2007).

Research has also suggested that lycopene may have a therapeutic effect on asthma. A randomized, crossover study of 17 asthmatic adults treated with placebo, tomato extract (Lyc-o-Mato®, 45 mg/day lycopene), and tomato juice (45 mg/day of lycopene) for seven days showed a reduced airway neutrophil influx and a reduced sputum neutrophil elastase activity after the tomato extract and tomato juice treatment (Wood et al. 2008). During placebo treatment, plasma lycopene concentration decreased, percent neutrophils increased, and neutrophil elastase levels increased (Wood et al. 2008). This study suggests that intake of lycopene may improve lung function in asthmatics.

Finally, a recent report also indicated that dietary lycopene intake, as measured by FFQ, was inversely related to risk of fracture in a 17-year follow-up study of elderly adults (Sahni et al. 2009). Although all of these studies are preliminary, they have presented positive results and indicate potential directions for future lycopene research and dietary interventions with tomato products.

LYCOPENOIDS: POTENTIAL OXIDATIVE METABOLITES OF LYCOPENE

Researchers have recently used the term lycopenoids to refer to oxidative products of lycopene that contain at least one oxygen atom (Lindshield et al. 2007). Historically, lycopenoids have been reported in tomatoes and tomato products, but only recently have they garnered attention from individuals interested in the potential health benefits of lycopene or its metabolites. This newfound interest is largely stimulated by the recent discovery of a second carotenoid cleavage enzyme in mammals (β-carotene oxygenase 2, or BCO2) and the possibility that it may cleave lycopene to produce metabolites (Kiefer et al. 2001). Previous to this report, only one carotenoid cleavage enzyme, the enzyme responsible for converting provitamin A carotenoids into vitamin A, was known to exist in mammals.

A handful of lycopenoids have been identified in food products. Apo-6′-lycopenal and apo-8′-lycopenal were reported in tomato paste (Winterstein et al. 1960). Later in 1973, Ben-Aziz et al. confirmed the presence of apo-6′-lycopenal and apo-8′-lycopenal in raw tomatoes, indicating that these products are present in the unprocessed fruit as well. Recently, we observed apo-10′-, -12′-, and -14′-lycopenal (in addition to the previously reported apo-6′- and apo-8′-lycopenals) in raw tomatoes, watermelon, grapefruit, and tomato products (Kopec et al. 2008, 2009). Epoxide derivatives have also been reported in tomatoes. Lycopene-1,2-epoxide and lycopene-5,6-epoxide were identified in tomatoes and tomato products by multiple groups (Britton & Goodwin 1969, 1975; Ben-Aziz et al. 1973; Kamber & Pfander 1984; Khachik et al. 1992). Later, nuclear magnetic resonance (NMR) research revealed that lycopene-5,6-epoxide had been misidentified and was actually 2,6-cyclolycopene-1,5-epoxide (Khachik et al. 1998b). An alcohol derivative, 2,6-cyclolycopene-1,5-diol, was also identified in tomato products and later found to be present in human blood plasma and breast milk (Khachik et al. 1992, 1997, 1998a). These researchers hypothesized that 2,6-cyclolycopene-1,5-epoxide was converted to 2,6-cyclolycopene-1,5-diol in humans, presumably during digestion, given that none of the epoxide was identified in human samples, and the alcohol is present in small quantities in the food (Khachik et al. 1998b).

The presence of apo-lycopenoids in tomato tissues is not surprising. Analysis of the *Arabidopsis* genome has revealed nine potential carotenoid cleavage enzymes (Schwartz et al. 2001). Carotenoid cleavage dioxygenase 1 (CCD1) in the annatto plant has been shown to cleave lycopene to produce bixin aldehyde, a precursor of the carotenoids bixin and norbixin (Bouvier et al. 2003).

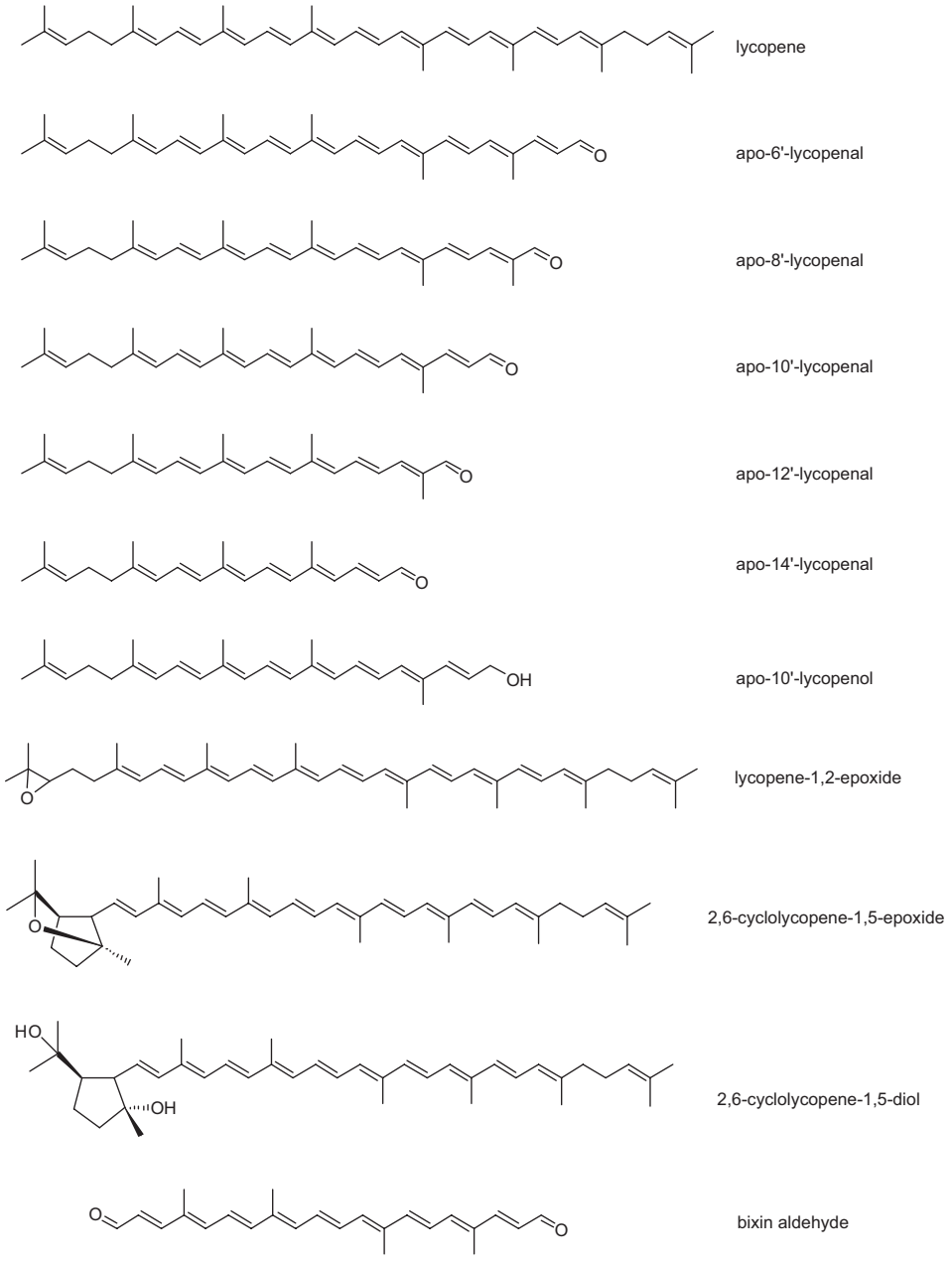

Figure 3

Structure of various lycopenoids.

CCD1 from tomato has also been shown to cleave lycopene at the 5′-6′ and 9′-10′ double bonds when transfected into an *Escherichia coli* model that accumulates lycopene (Vogel et al. 2008). The nonvolatile fragments of these reactions would be apo-6′-lycopenal and apo-10′-lycopenal, respectively (see **Figure 3**), although they were not investigated in this study (Vogel et al. 2008).

Carotenoid cleavage dioxygenase 7 (CCD7) has been shown to cleave the 9′-10′ bond of lycopene (Schwartz et al. 2004). However, it is not known if the other identified CCDs cleave lycopene. Alternatively, lycopene could be broken down nonspecifically by reaction with reactive oxygen species or co-oxidation with other lipids in the plant tissue.

More recently, lycopenoids have been identified in the tissues of animals consuming lycopene. In one study, ferrets consumed a lycopene supplement (LycoVit® powder, 10% lycopene) daily for nine weeks (Hu et al. 2006). Following sacrifice, apo-10′-lycopenol was found in the lung tissue of these animals (Hu et al. 2006). In a separate study by Gajic et al. (2006), rats were fed lycopene as part of their daily diet for 50 days, followed by a radioactive dose of lycopene on day 51. Rat livers were then extracted and apo-8′-lycopenal and putative apo-12′-lycopenal were identified (Gajic et al. 2006). In addition, we identified apo-6′, -8′-, -10′-, -12′-, and -14′-lycopenal in the blood plasma of humans who had consumed 300 mL of a tomato juice based beverage daily for eight weeks (Kopec et al. 2008, 2009).

The presence of lycopenoids in animals has been hypothesized to be the result of enzymatic cleavage. In fact, lycopene has been shown to be cleaved enzymatically by BCO2 in vitro (Keifer et al. 2001, Hu et al. 2006). Other researchers have incubated lycopene with various tissue homogenates ex vivo and produced oxidative products, but it is unclear whether these are products of a BCO reaction or whether they could be produced in vivo (dos Anjos Ferreira et al. 2004).

There are very limited data on the biological effects of lycopenoids. Apo-10′-lycopenoic acid has been shown to inhibit the growth of BEAS-2B human bronchial epithelial cells in vitro (Lian & Wang 2008). The feeding of apo-10′-lycopenoic acid has also been shown to reduce lung tumor multiplicity in an A/J mouse model, an effect that was dose dependent (Lian et al. 2007).

CONCLUSIONS

In this paper, we summarized lycopene chemistry, sources, intake, bioavailability, and recent data regarding the potential health effects of lycopene. Many questions remain, however. First, and most importantly, does lycopene produce health effects in humans? A review of the epidemiological literature by Giovannucci (2005) suggests that it is still too early to determine whether tomatoes or lycopene have health benefits.

Further, it is unclear whether apparent reductions in disease risk observed in epidemiological and short-term prospective studies result from the whole tomato or from lycopene alone (Giovannucci 2005, Clinton 2005). Lycopene studies have been performed with tomato products, tomato-based supplements, and synthetic lycopene. These treatments are not interchangeable and should not be considered equivalent. In fact, the distinction between lycopene and tomatoes was made by the Food and Drug Administration (FDA) in their 2005 review of the literature to evaluate a proposed health claim on tomatoes, lycopene, and cancer (Kavanaugh et al. 2007). The FDA concluded that there is "no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial or pancreatic cancer," but the FDA found "very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers" (Kavanaugh et al. 2007). This conclusion was based on the limited high-quality human clinical trial data necessary to meet FDA standards and could change if more rigorously designed studies with positive results are reported.

As with other natural products with potential health benefits, lycopene continues to be researched because of promising epidemiological data as well as encouraging results in cell culture and animal studies. Discrepancies between animal data, which are generally positive, and human data, which are less clear, may be due to differences in carotenoid absorption and metabolism in

humans relative to other species as well as inter-individual differences in humans. Animal studies are typically conducted using inbred animals, reducing genetic variability and producing clearer results. Lycopene's effects may vary from person to person based on dietary lycopene and fat intake, probiotics, genetic differences in metabolism, and other factors. One further limitation of human studies is the lack of easily accessible, specific disease biomarkers to estimate the effects of a treatment on a disease process. Although PSA is frequently used to monitor prostate-cancer risk, and LDL is widely accepted as a marker for cardiovascular disease, many other diseases lack specific biomarkers. For this reason, more general markers, such as IGF-I or 8-OHdG, are often used to assess the effects of lycopene or tomato products on biochemical disease processes.

When considering the effects of a dietary component on health, it is difficult to separate the effect of a single compound from that of multiple compounds found in whole foods and whole diets. If lycopene in tomatoes does affect health, is it the major active component, or does it act synergistically with other bioactive compounds in tomatoes (provitamin A, flavonoids, vitamin C, fiber, etc.)? In fact, tomato flavonoids, including rutin, quercetin, naringenin, have been reported to have potential health effects. Quercetin and rutin have been shown to reduce IGF-1-induced prostate cell proliferation in vitro (Wang et al. 2003). Quercetin has been shown to reduce neutrophil-induced LDL oxidation (Loke et al. 2008). Naringenin chalcone from tomato skin has also been shown to produce anti-inflammatory effects in mice (Yamamoto et al. 2004). These studies provide evidence that flavonoids may play a role in the health effects of tomatoes and tomato products. Other studies have demonstrated that glycoalkaloids present in tomato also produce multiple biological effects (see review by Friedman 2002). In addition, recent research has suggested that water soluble components of tomatoes may reduce platelet aggregation, a risk factor for cardiovascular disease (O'Kennedy et al. 2006), although the components present in this fraction have not been clearly identified. Likewise, some authors have suggested that blood levels of lycopene and other carotenoids are simply indicative of a diet that includes fruits and vegetables. A growing body of evidence indicates that whole foods may be more effective than individual compounds for lowering disease risk (Clinton 2005, Gómez-Romero et al. 2007).

If lycopene does produce positive health effects, what are the mechanisms involved? Does lycopene act by itself, or is it metabolized into a biologically active compound in humans? Are the oxidative products of lycopene found in foods (lycopenoids) absorbed? Lycopene can be a potent antioxidant under the appropriate chemical conditions, but it is present at such low levels in the human body some researchers have speculated that any health effects observed may be due to the effects of lycopene or its metabolites on gene regulation (Erdman et al. 2009). However, the accumulation of lycopene in some organs may allow for multiple mechanisms of action, including antioxidant activity. Evidence from animal studies suggests that lycopene could be metabolized in the human body (Hu et al. 2006, Gajic et al. 2006), whereas data from human studies suggest that oxidative products of lycopene can be absorbed and further metabolized in humans (Khachik et al. 1992, 1997, 1998a, 1998b). It is possible that there are other bioactive lycopene metabolites that are yet to be identified. Further work must be done to understand how lycopene is metabolized in fruits and vegetables and whether these products are absorbed into the bloodstream and distributed and stored in tissues. In addition, more research is needed to understand how lycopene is metabolized in humans and whether these metabolites have biological effects.

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RELATED RESOURCES

http://www.foodsafety.gov/~dms/qhclyco2.html
http://www.cancer.org/docroot/ETO/content/ETO_5_3X_Lycopene.asp
http://www.dietandcancerreport.org/
http://whqlibdoc.who.int/publications/2004/9241546123_chap8.pdf

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Contents

Errata

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Puff Ball

Lycoperdon species

DESCRIPTION

Medicinal Parts: The medicinal parts are the aerial parts and the mature spores of the fungus.

Flower and Fruit: The giant form of this fungus attains a diameter of 20 to 50 cm and a weight of 9 kg. The outer covering is at first whitish, smooth and downy. It later turns gray-yellow or ochre, develops grooves and patches, and starts to break off from above. The now-visible inner section bursts at the vertex and disintegrates. The content is composed of a whitish mass, which turns yellow and mushy and finally breaks down into greenish-brown spore dust. A cup-shaped receptacle with torn edges remains.

Habitat: Lycoperdon species are indigenous to Europe.

Production: Puff Ball is the aerial part and the mature spores of Lycoperdon species.

Other Names: Bovista, Hart's Truffle, Deer Balls

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Calvacin (mucoprotein)

Steroids: mycosterols

Urea

EFFECTS

The main active agents are various amino acids, glucosamine, sterol, enzymes and approximately 3% urea.

INDICATIONS AND USAGE

Unproven Uses: The drug is used for dysmenorrhea, nose bleeds and skin disorders.

Homeopathic Uses: Lycoperdon is used for anemia, skin complaints and chronic catarrh.

PRECAUTIONS AND ADVERSE REACTIONS

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. The young mushroom is edible.

DOSAGE

Mode of Administration: Puff Ball is available ground or in alcoholic extracts.

LITERATURE

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Pulmonaria officinalis

See Lungwort

Pulsatilla pratensis

See Pasque Flower

Pumpkin

Cucurbita pepo

DESCRIPTION

Medicinal Parts: The medicinal parts are the fresh and dried seeds.

Flower and Fruit: The flower is yellow, monoecious, very large and solitary in the leaf axils. The male flower has a longer pedicle. The calyx is fused to the corolla except for the 5 awl-shaped tips. The corolla is 5-tipped and funnel-shaped. The interior is pubescent. There are 3 stamens fused to the anther. The ovary is inferior and 3-locular. The fruit is very large with many seeds. The flesh is fibrous, yellow-orange to white, and has a viscous placenta. The seeds are 7 to 15 mm long, narrow, broad or narrow-ovate with a shallow groove and flat ridge around the margin.

Leaves, Stem and Root: Annual plant 3 to 8 m long. The stem is sharply-angular with longitudinal grooves and hairy spines. The leaves are alternate, very large and bristly, petiolate with 5 to 7 lobes from a cordate base.

Characteristics: The seeds taste somewhat like almonds.

Habitat: Pumpkin is indigenous to America and widely cultivated, especially in temperate climates.

Production: Pumpkin seed consists of the ripe, dried seed of Cucurbita pepo and cultivated varieties of Cucurbita pepo.

Other Names: Field Pumpkin

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Steroids: Delta5-, Delta7- and Delta8-phytosterols (24- alkyl sterols), including clerosterol, isofucosterol, sitosterol, stigmasterol, cholesterol, isoavenasterol, spinasterol

Fatty oil: chief fatty acids are oleic acid and linoleic acid

Proteic substances (25 to 42%)

Unusual amino acids: including cucurbitin (vermifuge)

I *Gamma-tocopherol*

EFFECTS

As well as amaroids (cucurbitacin), the drug contains delta-7-sterols, which are similar in conformation to the dihydrostesterone. Cucurbitacin has anthelmintic properties.

There are no pharmacological studies that substantiate the empirically documented clinical efficacy; the empirical evidence indicates efficacy for prostate hyperplasia. Pumpkin is also antiphlogistic and antioxidative.

INDICATIONS AND USAGE

Approved by Commission E:

- Irritable bladder
- Prostate complaints

Unproven Uses: Pumpkin is used for irritable bladder, micturition problems accompanying prostate adenoma stages I to II. This medication relieves only the difficulties associated with an enlarged prostate without reducing the enlargement. Medical supervision is essential.

In folk medicine, it is also used for kidney inflammation, intestinal parasites, particularly tape worm, and vulnary.

PRECAUTIONS AND ADVERSE REACTIONS

Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded.

DOSAGE

Mode of Administration: Whole and coarsely ground seed and other galenic preparations are for internal use.

Daily Dosage: The average daily dose is 10 gm of ground seeds; I to 2 heaping dessert spoons with liquid in the mornings and evenings.

Storage: It should be protected from light and moisture.

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Punica granatum

See Pomegranate

Purple Gromwell (Ying Zicao)

Lithospermum erytrorhizon

DESCRIPTION

Medicinal Parts: The medicinal part of the plant is the root, which is dried.

Flower and Fruit: The radial flowers are in axillary or apical racemes. The calyx has up to 5 tips, and the sepals are fused. The petals are white and also fused. The corolla tube is approximately 4 mm long. The diameter of the corolla is approximately 4 mm. There are 5 stamens and one superior, 2-carpeled, 4-chambered ovary. The fruit is a glossy nutlet, approximately 3 mm long, ovoid and gray-white.

Saw Palmetto

View 3011 Products Containing: Saw Palmetto

View 272 Canadian Licensed Products Containing: Saw Palmetto

Scientific Name

Serenoa repens, synonyms Serenoa serrulata, Sabal serrulata.

Family: Arecaceae/Palmae.

Background

Saw palmetto, also known as the American dwarf palm tree, is a tree native to the West Indies and the southeast coast of North America. It grows to a height of 6 to 10 feet and is characterized by thorn-shaped leaves that are arranged like a fan (89449). The berries, which are maroon colored and oblong shaped, are used for medicinal applications (6751,89449).

Also known as: American Dwarf Palm Tree, Baies du Chou Palmiste, Baies du Palmier Scie, Cabbage Palm, Chou Palmiste, Ju-Zhong, Palma Enana Americana, Palmier de Floride, Palmier Nain, Palmier Nain Américain, Palmier Scie, Sabal, Sabal Fructus, Saw Palmetto Berry.

History

People Use This For

Orally, saw palmetto is used for symptoms of benign prostatic hyperplasia (BPH), to prevent complications during transurethral resection of the prostate (TURP), and to treat prostatitis and chronic pelvic pain syndrome. It is also used as a mild diuretic and a sedative. Saw palmetto is used to increase breast size, to improve sexual vigor, and as an aphrodisiac. It is also used to treat the common cold, coughs, irritated mucous membranes, sore throat, asthma, chronic bronchitis, migraines, cancer, hypotonic bladder, androgenic alopecia, and hirsutism.

In combination with other herbs, saw palmetto is used to treat prostate cancer.

Topically, saw palmetto is used for androgenic alopecia and hirsutism.

Vaginally, the powdered fruit is used as a uterine and vaginal tonic.

Safety

LIKELY SAFE ...when used orally and appropriately. Saw palmetto has been safely used in clinical studies lasting up to three years (2732,2735,6750,6751,6752,6762,6764,6772,6773,6777,6778) (8330,11354,14274,14275,15550,17202,17304,17306,17684) (73309,73315,73416,73417,73363,73380,73383,73384,73385,73389,73420,73421,73422,73423,96410,96412).

POSSIBLY SAFE ...when used rectally and appropriately. Saw palmetto has been used safely in clinical research at doses of 640 mg once daily for 30 days (73387). However, the long-term safety of saw palmetto administered rectally is not known.

PREGNANCY AND LACTATION: **LIKELY UNSAFE** ...when used orally. Saw palmetto has hormonal activity (6766); avoid using.

Effectiveness

See detailed evidence summary

POSSIBLY EFFECTIVE

Transurethral resection of the prostate (TURP). Clinical research shows that taking saw palmetto (Permixon, Pierre Fabre Medicament) 320 mg daily for 2 months prior to surgery reduces the duration of surgery, the development of intraoperative complications, blood loss, the duration of catheterization, and the length of hospitalization compared to placebo (73323,73353). Although these studies have found benefit, a smaller study using a lower dose of saw palmetto (Prostagood Mono, Abdi Ibrahim) 160 mg orally once daily 5 weeks prior to transurethral resection of the prostate (TURP) found no benefit for lowering the risk of perioperative hemorrhage or decreasing the density of prostatic tissue (17202).

POSSIBLY INEFFECTIVE

Benign prostatic hyperplasia (BPH). Research on saw palmetto for treating symptoms of BPH is inconsistent and contradictory. Several clinical studies lasting up to three years have shown that orally administered saw palmetto provides mild to moderate improvement in urinary symptoms such as frequent urination, painful urination, hesitancy, urgency, and perineal heaviness. Some studies also show that saw palmetto decreases nocturia, improves urinary flow, and lowers residual urine volume in patients with BPH (2732,5094,6750,6751,6752,6762,6764,6772,6777,6778)(8330,14275,73309,73315,73416,73417,73363,73380,73383,73385)(73411,73412,73420,73421,96570). Rectally administered saw palmetto has also shown similar efficacy when compared to orally administered treatment (73387).

Several clinical trials have compared saw palmetto to conventional drugs. Some of these studies suggest that saw palmetto is comparable in overall symptom relief to the 5-alpha reductase inhibitors finasteride (Proscar) and dutasteride (Avodart) and might be better tolerated (96570). Some data also suggest that saw palmetto might have a positive effect on sexual dysfunction associated with BPH (6424,6763,14275,18215). However, saw palmetto does not seem to reduce prostate size or prostate-specific antigen (PSA) levels to the same degree as finasteride (6424). Alpha-adrenergic blockers such as prazosin (Minipress) seem to be more effective than saw palmetto for relieving some symptoms of BPH (6775,6776), although some preliminary research suggests that saw palmetto is similar in efficacy to tamsulosin (Flomax) after 12 months of treatment (11243,96570). However, adding saw palmetto to an alpha-blocker such as tamsulosin does not seem to relieve symptoms any better than the alpha-blocker alone (8901,89443,89448). Additionally, while alpha-blockers tend to provide significant and rapid improvement, studies evaluating saw palmetto suggest that it may take 1-2 months before significant symptomatic

improvement occurs (2732,6750,6778).

Treatment with saw palmetto has improved obstructive symptoms and prostate size similar to the effects of gestonorone caproate (Depostat) (73413), but was reported to be less effective than subcutaneously injected mepartricin (Ipertrofan) (73425).

Some clinical research also shows that a specific commercial product containing saw palmetto and stinging nettle root (PRO 160/120, Dr. Willmar Schwabe Pharmaceuticals) modestly improves some BPH symptoms compared to placebo and might be comparable to finasteride (Proscar) and tamsulosin (Flomax) for relieving symptoms of BPH (6763,17304,17307,73330). Clinical research also suggests that a combination of saw palmetto, cernitin, beta-sitosterol, and vitamin E significantly improves overall symptoms of BPH, nocturia, and daytime frequency of urination but does not improve urinary flow rates, residual urine volume, or PSA levels compared to placebo after 90 days of treatment (11241). Additional research shows that taking a specific combination product containing saw palmetto, selenium, and lycopene (Profluss, Konpharma) may improve symptoms of BPH compared to baseline and is non-inferior to tadalafil (Cialis) for improving symptoms and urinary flow (90354,97255). However, improvements are approximately 27% greater when this combination product is used along with tamsulosin (90354). Also, preliminary clinical research shows that taking a specific product containing saw palmetto, Alga Ecklonia bicyclis, tribulus, D-glucosamine, and N-acetyl-D-glucosamine daily for two months improves some BPH symptoms but not nocturia frequency compared to baseline (89446). In addition, taking a specific combination product containing saw palmetto, pygeum, lycopene, smallflower willowherb (Epilobium parviflorum), and pumpkin seed oil (ProstateEZE Max, Caruso's Natural Health) daily for three months seems to improve symptoms by about four-fold, frequency of urination during the day by about 15%, and frequency of urination at night by about five-fold compared to placebo in men with moderate to severe BPH (92164). Preliminary clinical research also shows that taking a specific combination of saw palmetto 400 mg, quercetin 200 mg, and beta-sitosterol 60 mg (Difaprost, Difass International) daily for 3 months decreases residual urine volume and increases average urine flow rate slightly compared to baseline but does not improve symptoms overall (96784).

Although several clinical trials suggest that saw palmetto is modestly effective for improving BPH symptoms, several clinical trials show no benefit. In one high-quality National Institutes of Health (NIH)-sponsored study, saw palmetto 160 mg twice daily was ineffective for reducing symptoms in men with moderate to severe symptoms of BPH after a year of treatment (14274). In another high-quality NIH-sponsored study, taking saw palmetto in doses of 320-960 mg daily for 72 weeks did not significantly improve symptoms compared to placebo (17684). Additional studies also show no clinically meaningful effect of saw palmetto, alone or in combination with other ingredients, on BPH symptoms or BPH related clinical measures including prostate volume (5093,11314,73343,96409).

One meta-analysis of saw palmetto studies shows that saw palmetto does not reduce nocturia to a clinically meaningful extent or improve measures of BPH symptoms or peak urine flow compared to placebo, despite a few measures of improvement (17304). Saw palmetto is not superior to tamsulosin or finasteride in reducing nocturnal voiding. Other meta-analyses show that moderate to long-term saw palmetto treatment does not significantly improve lower urinary tract symptoms associated with BPH, maximal flow rate, nocturia scores, or prostate volume compared to placebo (73357,89441). One meta-analysis that assessed the effects of a specific saw palmetto product (Permixon, Pierre Fabre Medicament) shows that taking this product does not significantly reduce nocturnal voiding or improve flow rate compared to placebo (96410). Although this saw palmetto product seems to have similar effects on measures of BPH symptoms and flow rate as tamsulosin when taken for 12-52 weeks, this was only evaluated in two, low-quality studies. Adding Permixon to tamsulosin does not improve BPH symptoms or flow rate compared

to tamsulosin alone (96410). Interestingly, relatively short-term treatment with this saw palmetto product for 12 weeks to 6 months seems to improve overall BPH symptom scores compared to placebo; however, high study heterogeneity limit the applicability of these findings (73357).

The reason for these confusing and inconsistent research findings is not clear. Differences may be due to different study methodologies, patient populations, symptom measurement methods, and saw palmetto products used in studies. Research shows significant variation in the chemical composition of commercially available saw palmetto extracts which might explain the conflicting study findings (17304,17305). Most clinical studies, including studies with both positive and negative findings, have used liposterolic extracts of saw palmetto berry containing approximately 80% and 90% free fatty acids. One of the most commonly studied products is Permixon (Pierre Fabre Medicament). This formulation is also similar to Super Saw Palmetto (Enzymatic Therapy), Saw Palmetto (Centrum), Standardized Saw Palmetto Extract (Nature's Way), and others.

Many of the saw palmetto studies are small, short-term, and of poor quality. Larger, higher-quality and more reliable studies appear more likely to show no beneficial effect of saw palmetto (17304,17305).

Overall it appears that saw palmetto does not offer significant benefit for symptoms of BPH. Any benefits are modest at best.

INSUFFICIENT RELIABLE EVIDENCE to RATE

Androgenic alopecia. The effects of saw palmetto when taken orally by patients with androgenic alopecia are inconsistent and unclear. Preliminary clinical research shows that a combination of saw palmetto extract 200 mg plus beta-sitosterol 50 mg taken twice daily improves subjective scores of hair quantity and quality in men with androgenic alopecia (15550). However, other clinical research shows that taking saw palmetto extract 320 mg daily for 24 months is less effective at improving hair growth in men with androgenic alopecia compared to taking finasteride 1 mg daily (89444).

Some early clinical research shows that saw palmetto lotion applied topically twice daily for 50 weeks improves hair density by 27% in men and women with androgenic alopecia. However, an improvement of 13% was observed in the placebo group, and no between-group comparisons were made. Therefore, it is unclear if saw palmetto provided a statistically significant improvement compared to placebo (73435).

Hypotonic bladder. Preliminary clinical research suggests that taking 90-120 drops of a combination product containing echinacea 84-112 mg and saw palmetto 78-104 mg (Urgenin, Meda Pharma) daily for 77 days improves mean bladder capacity and post-void residual volume compared to pre-treatment measurements in women with idiopathic hypotonic urinary bladder (73352).

Prostate cancer. Population research has found that people who take saw palmetto supplements do not have a lower risk of developing prostate cancer (15217). Preliminary clinical research shows that taking saw palmetto 960 mg daily before, during, and after radiation treatment for early prostate cancer does not significantly improve lower urinary tract symptoms compared to placebo. Lower urinary tract symptoms tend to affect about 75% to 80% of men with prostate cancer who are undergoing radiation treatment (96412).

Prostatitis and chronic pelvic pain syndrome. The effects of saw palmetto on prostatitis and chronic pelvic pain syndrome are inconsistent and unclear. Some initial preliminary research found that saw palmetto improved symptoms of prostatitis compared to no treatment in patients with nonbacterial prostatitis (73329). Other preliminary clinical evidence suggests that taking saw

palmetto extract daily for eight weeks in addition to prulifloxacin 600 mg daily for 15 days reduces pain and urinary symptoms more significantly than prulifloxacin alone in patients with bacterial prostatitis. However, the combination does not appear to improve bacterial eradication or sexual dysfunction compared to treatment with prulifloxacin alone (89442). Other preliminary clinical research suggests that saw palmetto 325 mg taken orally for one year does not significantly improve nonbacterial prostatitis and chronic pelvic pain syndrome compared to treatment with finasteride 5 mg (11354).

Other preliminary clinical research shows that taking a combination of saw palmetto, selenium, and lycopene for 8 weeks significantly improves symptoms and peak flow in patients with chronic prostatitis and/or chronic pelvic pain syndrome compared to pre-treatment. However, these effects were not observed or were less significant in patients treated with saw palmetto alone, indicating that saw palmetto may not be the active component in this combination treatment (60442). Other clinical research suggests that adding a combination of saw palmetto, indol-3-carbinol, and epigallocatexin-3-gallate to standard treatment with sparfloxacin 200 mg improves the rate of bacterial eradication and symptom regression in patients with chronic infectious prostatitis compared to treatment with sparfloxacin alone (73355). Also, clinical research suggests that adding a combination of saw palmetto, stinging nettle, curcumin, and quercetin extracts to standard treatment with prulifloxacin 600 mg daily improves symptoms in patients with chronic bacterial prostatitis compared to treatment with prulifloxacin alone (73346). Additional preliminary research shows that adding a specific combination of saw palmetto, Bacillus coagulans, and arbutin (Lactorepens) daily for 30 days to standard treatment with prulifoxacin 600 mg daily for 21 days reduces recurrence and measures of urinary symptoms and quality of life by 50% to 75% in patients with chronic bacterial prostatitis (96411).

More evidence is needed to rate saw palmetto for these uses.

Dosing & Administration

- Adult

  Oral:

  Androgenic alopecia: Saw palmetto extract 200 mg plus beta-sitosterol 50 mg, taken twice daily for 18 to 24.7 months, has been used (15550).

  Hypotonic bladder: Taking 90-120 drops of a combination product containing echinacea 84-112 mg and saw palmetto 78-104 mg (Urgenin, Meda Pharma) daily for 77 days has been used (73352).

  Transurethral resection of the prostate (TURP): Saw palmetto extract (Permixon, Pierre Fabre Medicament) 320 mg daily for two months before TURP procedure has been used (73323,73353).

  Prostatitis and chronic pelvic pain syndrome: Saw palmetto extract (Prostamol Uno, Profluss) 320 mg daily has been used (60442,73329). Also, a combination of lycopene oil extract 5 mg, saw palmetto oil extract 320 mg, and seleniated sodium 50 mcg daily for eight weeks has been used (60442). A specific combination product containing saw palmetto 160 mg plus stinging nettle 120 mg (ProstaMEV), along with another product containing curcumin 200 mg plus quercetin 100 mg (FlogMEV), has been used in combination with prulifloxacin 600 mg daily for two weeks (73346). A combination of saw

palmetto 320 mg, Bacillus coagulans 200 mg, and arbutin 100 mg (Lactorepens) has been used with prulifloxacin 600 mg daily for 30 days (96411).

Topical:

Androgenic alopecia: Saw palmetto lotion applied twice daily for 50 weeks has been used (73435).

- Standardization & Formulation

  An analysis of saw palmetto products that are commercially available in Europe shows substantial variation in chemical profile. The free fatty acid content in these products ranges from about 41% to 81% (17305). The majority of clinical studies evaluating saw palmetto for clinical applications have used saw palmetto extracts containing 80% to 95% free fatty acids (17684,60442).

Adverse Effects

Report an Adverse Reaction to Saw Palmetto

General: Orally, the adverse effects of saw palmetto are generally mild and comparable to placebo (73336,73348,96410). Dizziness, headache, and gastrointestinal complaints such as nausea, vomiting, constipation, and diarrhea are the most frequently reported adverse effects. Other side effects reported in clinical trials include asthenia, headaches, loss of libido, ejaculation disorders, and postural hypotension (6751,6752,6762,11354,17304,17306,73383). More serious adverse events, such as death and cerebral hemorrhage, have been reported in isolated case reports (73348). There have been two case reports of clinically significant bleeding associated with saw palmetto products (6772,8659). One case of complete heart block has also been reported (96413).

- ⊞ Cardiovascular
- ⊞ Dermatologic
- ⊞ Endocrine
- ⊞ Gastrointestinal
- ⊞ Genitourinary
- ⊞ Hematologic
- ⊞ Musculoskeletal
- ⊞ Neurologic/CNS
- ⊞ Ocular/Otic
- ⊞ Psychiatric
- ⊞ Pulmonary/Respiratory
- ⊞ Hepatic

Toxicology

There is insufficient reliable information available about the toxicology of Saw palmetto.

Interactions with Drugs

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **D**

Saw palmetto is reported to prolong bleeding time (8659). Theoretically, saw palmetto might increase the risk of bleeding when used concomitantly with anticoagulant or antiplatelet drugs. Some of these drugs include aspirin; clopidogrel (Plavix); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others); dalteparin (Fragmin); enoxaparin (Lovenox); heparin; warfarin (Coumadin); and others.

CONTRACEPTIVE DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **B**

Saw palmetto might have antiestrogenic effects (6766). Theoretically, concomitant use with saw palmetto might interfere with contraceptive drugs.

ESTROGENS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Saw palmetto might have antiestrogenic effects (6766). Theoretically, concomitant use with saw palmetto might interfere with hormone therapy.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Saw palmetto is reported to prolong bleeding time (8659). Theoretically, concomitant use of saw palmetto with other herbs and supplements that affect platelet aggregation may increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, and others.

Interactions with Foods

None known.

Interactions with Lab Tests

BLEEDING TIME: Saw palmetto may prolong bleeding time and increase the results of bleeding time tests (8659).

LIVER FUNCTION TESTS: Saw palmetto has been associated with isolated reports of liver toxicity (14457,73351). Whether saw palmetto is the actual cause of these adverse effects is unclear. In these reports, patients had increased liver function tests including alkaline phosphatase, aspartic acid transaminase (AST, SGOT), alanine aminotransferase (ALT, SGPT), and bilirubin.

PROSTATE-SPECIFIC ANTIGEN: Contrary to earlier concerns, saw palmetto extract appears to have no significant effect on serum prostate-specific antigen (PSA) levels (764).

Interactions with Diseases

SURGERY: There is concern that saw palmetto might have antiplatelet effects and could potentially cause excessive bleeding during surgery. Excessive intraoperative bleeding has been reported in one case in a patient who took saw palmetto before surgery (8659). Advise patients to discontinue saw palmetto at least 2 weeks prior to elective surgery.

Mechanism of Action

General: The applicable part of saw palmetto is the ripe fruit. The lipid fraction contains volatile oils and fatty oils, which are thought to be the active components in treating benign prostatic hyperplasia (BPH). Many saw palmetto products are standardized based on the fatty acid content (73313). Most saw palmetto extracts used in clinical studies for benign prostatic hyperplasia (BPH) are berry extracts prepared with lipophilic non-polar solvents containing 80% to 90% free fatty acids. However, an analysis of saw palmetto products that are commercially available in Europe shows that the free fatty acid content in these products ranges from about 41% to 81% (17305).

Water extraction, including brewed tea, probably does not adequately extract fat-soluble active constituents.

Adrenergic effects: In vitro evidence suggests that saw palmetto extract has alpha-adrenergic inhibitory properties (5095). However, other evidence suggests that saw palmetto does not act as an alpha1-adrenoceptor antagonist in vivo (73310).

Antiandrogenic effects: Saw palmetto has antiandrogenic, antiproliferative, and anti-inflammatory properties that are purportedly responsible for improving symptoms of benign prostatic hyperplasia (BPH). Saw palmetto appears to noncompetitively inhibit 5-alpha-reductase types 1 and 2 and to prevent the conversion of testosterone to dihydrotestosterone (DHT) in

vitro, which might reduce prostate growth (6765,6769,6770,6773,17308,70232,73359,73369,73371). However, 5-alpha-reductase levels in prostatic tissue and serum testosterone, DHT, and PSA are not significantly reduced by saw palmetto in vivo (2735,5093,6771,17308,73364,73373,73398,73399). Saw palmetto does not seem to affect overall prostate size, but shrinks the inner prostatic epithelium (2736,5093,73400). Saw palmetto might slow prostate cell proliferation by inhibiting fibroblast growth factor and epidermal growth factor and stimulating apoptosis (6765,6769,6770,11224,73325,73359,73376,73378,73390,73391,73392,73399).

Inhibition of 5-alpha-reductase and prevention of conversion of testosterone to DHT may contribute to activity of saw palmetto in androgenic alopecia. It is suggested that this condition involves increased sensitivity of hair follicles to DHT, reducing their growth phase and size (15550).

Anticarcinogenic effect: In vitro evidence suggests that, in human urological cancer cell lines, saw palmetto extract can inhibit urokinase-type plasminogen activator, an enzyme implicated in tumor cell invasion (73312). Other in vitro evidence suggests that saw palmetto extract induces dose-dependent antiproliferative and/or apoptotic effects on various malignant cell lines, including hormone-sensitive prostate cancer (LNCaP), hormone-insensitive prostate cancer (DU-145), breast cancer (MCF-7), highly metastatic breast cancer (MDA MB231), renal cell carcinoma (Caki-1), urinary bladder cancer (J82), colon cancer (HCT 116), and lung cancer cell lines (A549) (73339).

Anti-inflammatory effects: Inflammatory mediators appear to contribute to the etiology of BPH. In men with BPH, a liposterolic extract of saw palmetto berry seems to lower tumor necrosis factor (TNF)-alpha and interleukin (IL)-1beta, which are markers of inflammation in prostate tissue (11224). Laboratory evidence suggests that saw palmetto inhibits lipoxygenase and cyclooxygenase (COX), which are involved in inflammation (6769,6779,73328). In addition, evidence from animal research suggests that saw palmetto inhibits mast cell accumulation portions of the prostate (73396).

Increased COX-2 expression is also associated with an increased incidence of prostate cancer. Preliminary research indicates that saw palmetto reduces the proliferation of experimental prostate cells, possibly by inhibiting COX-2 expression (8902).

Drug metabolism effects: There is conflicting evidence about the effects of saw palmetto on cytochrome P450 (CYP450) enzymes 2D6 (CYP2D6) and 3A4 (CYP3A4). In vitro evidence suggests that saw palmetto might inhibit CYP2D6 and CYP3A4 (11026). But when used in healthy volunteers, saw palmetto 320 mg/day does not seem to affect CYP2D6 or CYP3A4 (11225,13712). Saw palmetto also does not seem to affect CYP1A2 or CYP2E1 in healthy volunteers (13712).

Fertility effects: Laboratory fertility studies indicate that saw palmetto has no effect on oocytes or sperm motility, but it might induce metabolic changes in sperm (4239,4240).

Hormonal effects: Some evidence from animal research suggests that saw palmetto fruit extract has estrogenic activity due to its relatively high concentration of beta-sitosterol (73366), However, evidence from human research suggest that saw palmetto extract displays antiestrogenic activity in prostatic tissue of men with BPH (6766).

Immunomodulatory effects: In vitro evidence suggests that saw palmetto extract stimulates the immune system by increasing macrophage phagocytosis up to 2.3-fold and increasing natural killer cell synthesis of interferon-gamma up to 6.3-fold (73341).

Pharmacokinetics

Absorption: In one pharmacokinetic study, a peak plasma concentration of 2.6 mg/L (Cmax) at 1.5 hours following intake (Tmax) was reported after a single dose of saw palmetto extract 320 mg (73374).

Elimination: In one pharmacokinetic study, a half-life of 19 hours was reported for saw palmetto (73374).

Classifications

5-Alpha Reductase Inhibitors, Anticoagulant Agents, Immunomodulators, Immunostimulants

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References

See Monograph References

This monograph was last reviewed on 10/15/2019 and last updated on 3/14/2019. Monographs are reviewed at least once per year. If you have comments or suggestions on something that should be reviewed or included, please tell the editors. For details about our evidence-based approach, see our Editorial Principles and Process.

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Pygeum

Latin name: Pygeum africanum

A Remedy For

- Prostate enlargement

What It Is; Why It Works
Pygeum is an evergreen tree found in the mountains of central and southern Africa. Its bark, once used as a tea for relief of urinary disorders, has been found to contain not one, but three types of compounds that relieve the symptoms of prostate enlargement (benign prostatic hyperplasia):

Beta-sitosterol, the most important of the three, interferes with the formation of prostaglandins that cause inflammation and swelling in the prostate. *Pentacyclic terpenes* also reduce swelling. And *ferulic esters* combat enlargement by reducing levels of prolactin, a hormone which promotes uptake of growth-promoting testosterone in the prostate.

Avoid If...
No known medical conditions preclude the use of Pygeum.

Special Cautions
Side effects from Pygeum extract are rare, but a few men experience mild stomach irritation.

Improvement is gradual; allow 6 to 9 months for the herb to work. Remember, too, that the symptoms of enlargement can also be a sign of cancer. Check with your doctor to make sure that the problem is benign.

Possible Drug Interactions
No interactions have been reported.

Special Information If You Are Pregnant or Breastfeeding
Not for use by women.

How To Prepare
Look for a standardized extract containing 13 percent beta-sitosterol.

Typical Dosage
Extract: 50 to 100 milligrams 2 times per day

Overdosage
No information on overdosage is available.