

A Critical Review of Graminex Flower pollen extract for Symptomatic Relief Of Lower Urinary Tract Symptoms (LUTS) in Men

Walter G. Chambliss, Ph.D.

National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, University of Mississippi, University, Ms. 38677

January 12, 2003

Objective

To review published data concerning the ability of a Graminex's Flower Pollen Extract to provide symptomatic relief in men suffering from lower urinary tract symptoms (LUTS).

Introduction

The National Institutes of Health (NIH) estimates 9 million men suffer from symptoms related to an enlarged prostate and 400,000 surgeries are conducted each year in the U.S.¹ The term lower urinary tract symptoms (LUTS) is used to describe symptomatology in men who are experiencing one or more symptoms on the International Prostate Symptom Score (IPSS) questionnaire that includes urgency, daytime and nighttime urinary frequency, hesitancy, intermittency, sensation of incomplete voiding, and force of urine stream.² LUTS is used to describe urinary tract disorders in men with benign prostatic hyperplasia (BPH), prostatodynia, acute and chronic prostatitis caused by a bacterial infection and acute and chronic abacterial prostatitis.

Bruskewitz stated the primary aim of pharmacological treatment is to improve quality of life by relieving bothersome symptoms since serious complications from BPH are rare³. However, he reported the results of a study conducted in the U.S. that showed Urologists gave no treatment 77% of the time to men with mild symptoms. Prescription drugs were given 89% of the time and surgery was conducted on 1% of the time for men with moderate symptoms. The primary therapeutic treatment was alpha(1)-adrenoceptor antagonists such as terazosin hydrochloride (Hytrin®) that provides symptomatic relief but has not been shown to provide long-term effects on the incidence of surgery, acute urinary obstruction or other complications of BPH.⁴ The need exists for safe, effective products that can be used by men to treat mild to moderate LUTS in lieu of or in addition to prescription drugs. This review focuses on

the potential for flower pollen extract, a dietary supplement, to fill this therapeutic void.

Graminex Flower Pollen Extract is a standardized extract of rye pollen (*Secale cereale*), corn pollen (*Zea mays*) and timothy pollen (*Phleum pratense*). The extract contains a blend of water-soluble and lipid-soluble fractions and is available around the world under other brand names such as Cernitin, and in capsule and tablet forms as Cernilton. In vitro⁵ and animal model studies⁶ have shown that both fractions have anti-inflammatory properties through inhibition of the prostaglandin and leukotrien synthesis. The water-soluble fraction has been shown to reduce the size of the ventral and dorsal prostate in the rat⁷ and to inhibit testosterone-induced BPH in castrated animals⁸. Both fractions have been shown to relax the smooth muscle of the mouse and pig urethra, increase bladder muscle contractions⁸ and reduce prostate size in mature Wistar rats⁹.

Methods

Literature searches were conducted on Medline and the Cochrane Library. Secondary sources such as review articles and monographs in botanical reference books were included in the analysis. Open label and comparative trials were included in the assessment, although more weight was placed on placebo-controlled, double-blind studies. Emphasis was placed on subject ratings of symptoms in light of the potential for self-medication of this extract.

Results

Secondary Literature

Four reviews of the clinical efficacy and safety of flower pollen extract have been published in the past 8 years. Although each used their own criteria in selecting valid studies they all concluded that flower pollen extract was very safe with few or no side effects so summaries below are limited to efficacy.

Commission E, an expert committee established by the German government to evaluate the safety and efficacy of over 300 botanical and botanical combinations sold in Germany, concluded in 1994 that the combination extract of rye, corn and timothy pollen was useful in the treatment of "micturition difficulties associated with Alken stage I-II benign prostatic enlargement (BPH)".¹⁰

The Natural Medicines Comprehensive Database concluded that rye grass pollen extract (Cernilton®) was "possibly effective" for the management of BPH symptoms, for shrinking prostate size and when used for prostatitis and prostatodynia.¹¹

McDonald et al concluded in reviews published in 1999¹² and 2000¹³ that results from 4 double-blind studies (444 men in total, 2 studies with placebo; 2 with active controls) consistently showed a "modest" improvement in subjective symptoms and nocturia in the flower pollen extract groups compared to placebo, and 2 control products, Paraprost and Tadernan, although the authors called for additional studies to evaluate long-term effects.

Shoskes concluded that there was credible clinical and scientific evidence that treatment with flower pollen extract was efficacious for the majority of patients with nonbacterial prostatitis and prostatodynia.¹⁴

Primary Literature

Flower pollen extract was well tolerated in all of the published studies with minimal reported side effects therefore the discussion will be limited to efficacy considerations.

Double-Blind, Placebo-Control Studies

Two double-blind, placebo-controlled studies have been published with a total of 149 subjects. Becker et al¹⁵ reported data for 96 subjects with BPH in stages II or III according to the Vahlensieck. Subjects received 2 Cernilton® capsules or placebo three times daily for 12 weeks. The results showed significant improvement in nocturia (68.8% on Cernilton® versus 37.2% on placebo), daytime frequency (65.8% on Cernilton® versus 43.9% on placebo), freedom from daytime frequency (48.8% on Cernilton® versus 19.5% on placebo) and freedom from sensation of residual urine (37.1% on Cernilton®

versus 7.7% on placebo). In addition there was significant improvement in global assessment scores of both the physicians and patients. Physicians rated the overall response as very good or good for 68.1% on Cernilton® versus 13.7% on placebo. Patients rated the overall response as very good or good for 72.1% on Cernilton® versus 27.3% on placebo. There was no significant change in the size of the prostate as determined by palpitation.

Buck et al¹⁶ reported data for 53 subjects awaiting operative treatment for outflow obstruction due to prostate enlargement. Patients were instructed to take 2 capsules of Cernilton® or placebo twice a day over a 6-month period. The results showed 60% of the subjects on Cernilton® had improve nocturia compared to 30% on placebo ($p < 0.063$), 57% showed improvement in bladder emptying compared to only 10% on placebo. There was a significant difference in overall improvement in subjective symptoms in the Cernilton® group (69%) versus placebo (29%). There was no significant change in peak urine flow rate or voided volume. Residual urine volume decreased significantly in the Cernilton® group compared to placebo.

Double-Blind, Active-Control Studies

Maekawa M., et al¹⁷ conducted a double-blind study comparing Cernilton®, 2 capsules twice daily for 12 weeks to Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) in 159 patients with BPH. The two supplements were comparable in improving symptoms from baseline (55% for Cernilton® and 62% for Paraprost). There was a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the Cernilton® group versus Paraprost. Greater than moderate effectiveness rating was 49.1% for Cernilton® and 41.2% for Paraprost.

Open Label Studies

Eleven published open label studies with a total of 2291 subjects were reviewed. The results indicate significant beneficial effects in subjective LUTS when Cernilton® is used on average for 13.6 weeks.

Becker et al¹⁸ continued the placebo-controlled study¹⁵ described above with an open label study in which 92 subjects previously treated in the first phase of the study with Cernilton® (n=45) or placebo (n=47) were treated with Cernilton® for 12 weeks. Physicians were blinded as to whether the subjects received Cernilton® or placebo in the first phase. The results showed that the differences observed between the two groups in the first phase were eliminated in the 2nd phase. Subjects previously treated with placebo improved significantly when treated with Cernilton®. Significant improvements were observed in nocturia, frequency, feeling of incomplete emptying,

palpable enlargement of the prostate and prostatic congestion.

Hayashi et al¹⁹ treated 20 BPH patients with Cernilton®, 6 tablets a day for an average of 13.2 weeks. They reported improvements in sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%), and forceless urinary stream (53%). Overall subjective effectiveness was 80% and overall objective effectiveness was 54%. Overall effectiveness was rated 80%.

Yasumoto and colleagues²⁰ conducted an open label trial with 79 BPH patients. Patients were given 2 Cernilton® tablets 3 times a day for at least 12 weeks. The results showed that symptom scores improved significantly from baseline. Overall clinical efficacy was rated 85%. Clinical efficacy at 12 weeks was rated satisfactory or better in 85% of the patients.

Bach and Ebeling²¹ reported the results from a large open label trial in Germany involving 208 physicians and 1798 evaluable patients with BPH. The patients were treated for 24 weeks with Cernilton®; 2 tablets 3 times daily. The patients were divided into 3 groups (stage 1, 2 and 3) for data analysis based on the severity of the BPH symptoms. Patients in stage 1 had the most improvement of the three groups in irritative symptoms whereas patients in stage 2 had significant improvement in both irritative and obstructive symptoms. Peak urine flow rate increased significantly in all 3 groups. A continuing improvement in symptoms was noted when comparing the results after 12 and 24 weeks of treatment. Efficacy in stage 1 and 2 patients was judged to be satisfactory or better in 90% of the patients. Efficacy in stage 3 patients was judged to be satisfactory or better in 65% of the patients. The authors concluded that treatment with Cernilton® is justified even for stage 3 patients until surgery is performed.

Dutkiewicz²² reported on a study in 51 patients with BPH were given Cernilton®, 2 capsules three times daily for 2 weeks then 1 capsule 3 times daily for an additional 14 weeks. Thirty-eight subjects were given Tadenan (Pygeum africanum extract) for 4 months. Significant improvement in subjective symptoms was reported for the Cernilton® group (78%) versus the Tadenan group (55%).

Horii et al²³ reported the results of 30 subjects with BPH who were given Cernilton®; 2 tablets, 3 times daily for at least 12 weeks. The overall clinical efficacy for subjective symptoms was rated at 80% and objective symptoms at 43%.

Ueda et al²⁴ treated 22 patients with stage I and II BPH with Cernilton® for over 4 weeks. Eighty-two percent of the patients were rated as moderately improved or better.

In a recently published study 24 patients with chronic prostatitis (NIH-category III) were treated with Cernilton® for at least 6 weeks. The results showed a significant decrease in the symptom scores at 4 and 6 weeks.²⁵

In another open study, Buck et al²⁶ studied the effect Cernilton®, 2 tablets twice daily for up to 18 months on 15 patients with chronic, relapsing abacterial prostatitis and prostodynia. Seven patients became symptom-free, 6 patients were significantly improved and 2 patients failed to show improvement in symptoms. Improvement in symptomatology occurred for most patients after 3 months of treatment.

Jodai et al²⁷ reported the results of a study on 32 patients with chronic prostatitis given 6 tablets of Cernilton® daily for an average of 12 weeks. Subjective symptoms improved in 74.2% of the subjects and objective symptoms improved in 65.6%. The overall efficacy rate was 75%.

Rugendorff et al²⁸ reported the results of a study on 90 patients with abacterial prostatic pain and chronic prostatitis. Subjects were given Cernilton®, 1 tablet 3 times daily for 6 months. Seven-two patients were identified as without complicating factors (such as bladder neck sclerosis, prostatic calculi or urethral stricture) and the remaining 18 with complicating factors. Seventy-eight percent of the patients without complications responded to the treatment with 36% of these becoming asymptomatic whereas only 6% of patients with complicating factors improved. Peak urine flow rate in the uncomplicated group increased significantly from 15.9 to 23.5 ml/s.

Discussion

A review of 2 placebo controlled trials and 11 open label studies indicate that flower pollen extract is a safe and effective therapy for the management of mild to moderate LUTS. The studies showed a consistent reduction in subjective symptoms and overall effectiveness ratings of 75% and greater. The extract reduces bothersome symptoms thereby improving quality of life. The two placebo-controlled, double-blind studies provide evidence that the extract is effective in reducing nocturia, daytime frequency and sensation of residual urine.

Potential Role of Combination Therapy

Although published clinical trials support the safety and efficacy of flower pollen extract in the relief of mild to moderate LUTS, a precedent exists to examine beneficial effects of combining flower pollen extract with other dietary supplement or pharmaceutical products. A recently completed clinical study sponsored by the National Institutes of Health concluded that the combination of 2 prescription drugs, finasteride and doxazosin were

more effective than either treatment alone in preventing progression of BPH.¹ This study demonstrates the therapeutic advantages of combining pharmacologically active constituents with different mechanisms of action.

Although the mechanism of action of flower pollen extract is not fully understood, it appears to work via an anti-inflammatory effect, therefore a combination with a botanical or prescription drug that works via a different mechanism may provide additional symptomatic relief. Two recently published trials on combinations with flower pollen extract are very encouraging. Preuss et al²⁹ reported on a double-blind, placebo controlled trial comparing a combination of flower pollen extract (378 mg), saw palmetto fruit standardized to 43% B-sitosterol (286mg) and vitamin E (100 IU). Seventy subjects completed the combination therapy and 57 subjects completed the placebo over a 90-day period. There was a significant reduction in nocturia, daytime frequency and overall symptomatology as measured by the American Urological Association Symptom Score. This combination therapy is logical since saw palmetto may have a different mechanism of action than flower pollen extract. It is generally believed that Saw Palmetto prevents the conversion of testosterone to dihydroxytestosterone, a potent androgen that stimulates enlargement of the prostate³⁰.

Aoki et al³¹ conducted an open label trial to study tamsulosin hydrochloride (Flomax®), an alpha1A adrenoceptor antagonist, flower pollen extract and their combination in 243 patients with symptomatic BPH over a 12 week period. The results showed that whereas symptoms improved in each group, supporting the efficacy of flower pollen extract, the best results were obtained in the group that used the combination product.

Conclusions

Sufficient evidence exists in the primary and secondary literature to indicate that Graminex's Flower Pollen Extract is safe and effective for the treatment of mild to moderate LUTS. This dietary supplement ingredient has the potential to be used in combination with other dietary supplements or pharmaceuticals to provide relief of bothersome symptoms and improve quality of life for millions of men with this common condition.

References

1. National Institutes of Health, "Two-Drug Therapy is Best for Symptomatic Prostate Enlargement, Combination Should Change Clinical Practice", NIH News Release, May 28, 2002 (www.nih.gov/news/pr/may2002/niddk-28.htm).
2. Denis L.J., Editorial review of "Comparison of phytotherapy (Permixon®) with finasteride in the treatment of benign prostates hyperplasia: A

- randomized international study of 1098 patients," Prostate 29:241-242, 1996.
3. Bruskewitz, R., "Management of symptomatic BPH in the US: who is treated and how?", Eur Urol 1999, 36, Suppl 3:7-13, 1999.
4. Hytrin® (terazosin hydrochloride) Capsules, 01G-501-0118-1 Master, February 2001, <http://www.rxabbott.com/hy/hypi.htm>; accessed on 11/22/02.
5. Loschen, G. and Ebeling, L., "Hemmung der Arachidons-ureKaskade durch emen Extrakt aus Roggenpollen. Arzneim-Forsch./Drug Rse.41:162-167, 1991.
6. Ito, R., Ishi, M., Yamashita, S., et al., "Cernitin™ pollen-extract (Cernilton®): Anti-prostatic hypertrophic action of Cernitin™ pollen extract", Pharmacometrics 31:214, 1986.
7. Hanamoto, M., Liao, M., Suzuki, H., et al., "Effect of Cernitin pollen-extract on the Sex-hormone-induced Nonbacterial Prostatitis in Rats", Jpn Pharmacol Ther., 11:65, 1998.
8. Kamijo, T., Sato, S. and Kitamura, T., "Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats", Prostate 49:122-131, 2001.
9. Bales G.T., Christiano A.P., Kirsh E.J., Gerber G.S., "Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Illinois", Urology, 54: 86-89, 1999.
10. Schulz, V., Hansel, R., Tyler, V.E., Rational Phytotherapy, A Physicians' Guide to Herbal Medicine, 3rd Edition, Springer, Berlin, 230-231, 1998.
11. Rye Grass Monograph, Natural Medicines Comprehensive Database, Therapeutic Research Faculty, Stockton, Ca., 919, 2000.
12. MacDonald, R., Ishani, A., Rutks, I., and Wilt, T.J., "A systematic review of Cernilton for the treatment of benign prostatic hyperplasia", BJU Int. 85:836-841, 1999.
13. Wilt, T., MacDonald, R., Ishani, A., Rutks, I., and Stark, G., "Cernilton for benign prostatic hyperplasia", Cochrane Database Syst Rev., (2), CD001042, 2000.
14. Shoskes, D.A., "Phytotherapy and other alternative forms of care for the patient with prostatitis", Curr Urol Rep 3(4):330-334, 2002.
15. Becker, H., and Ebeling, L., "Conservative treatment of benign prostatic hyperplasia (BPH) with Cernilton®. Results of a placebo-controlled double-blind study", Urologe(b) 28:301-306, 1988.
16. Buck, A.C., Cox, R., Rees, W.M., Ebeling, L., and John, A., "Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernilton®. A double-blind, placebo-controlled study", Br. J. Urol. 66:398-404, 1990.
17. Maekawa, M., Kishimoto, T., Yasumoto, R., et al, "Clinical evaluation of Cernilton on benign prostatic hypertrophy – a multiple center double-blind study with Paraprost", Hinyo Kiyu, 36:495-516, 1990.
18. Becker, H., and Ebeling, L., "Phytotherapy of BPH with Cernilton®. Results of a controlled prospective study", Urologe (B) 31:113-116, 1991.
19. Hayashi J., Mitsui, H., Yamakawa, G., et al., "Clinical evaluation of Cernilton® in benign prostatic hypertrophy", Hinyo Kiyu, 32:135-141, 1986.

20. Yasumoto, R., Kawanishi H., Tsujino, T., et al, "Clinical evaluation of long-term treatment using Cernilton® pollen extract in patients with benign prostatic hyperplasia", *Clin Ther* 17:82-87, 1995.
21. Bach, D., and Ebeling, L., "Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH): Results of Treatment with Cernilton®N for Stages 1-3 according to Alken (or II-IV according to Vahlensieck)", www.graminex.com/clinical_studies/study12_sum.php, unpublished report.
22. Dutkiewicz, S., "Usefulness of Cernilton in the treatment of benign prostatic hyperplasia", *Int Urol Nephrol* 28:49-53, 1996.
23. Horii, A., Iwai, S., Maekawa, M. and Tsujita, M., "Clinical evaluation of Cernilton in the treatment of the benign prostatic hypertrophy", *Hinyo Kiyo* 31:739-746, 1985.
24. Ueda, K., Kinno, H. and Tsujimura, S., "Clinical evaluation of Cernilton on benign prostatic hyperplasia", *Hinyo Kiyo*, 31:187-191, 1985.
25. Monden, K., Tsugawa, M., Ninomiya, Y., Ando, E., and Kumon, H., "A Japanese version of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI: Okayama version) and the clinical evaluation of cernitin pollen extract for chronic non-bacterial prostatitis", *Nippon Hinyo Gakkai Zasshi*, 93:539-547, 2002.
26. Buck, A.C., Rees, R.W.M., and Ebeling, L., "Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract", *Br J Urol* 64:496-499, 1989.
27. Jodai, A., Maruta, N., Shimomae, E., et al, "A long-term therapeutic experience with Cernilton in chronic prostatitis", *Hinyo Kiyo* 34:561-568, 1988.
28. Rugendorff, E. W., Weidner, W., Ebeling, L., and Buck, A.C., "Results of Treatment with Pollen Extract (Cernilton®) in Prostatodynia and Chronic Prostatitis", *Br J Urol*, 71:433-438, 1993.
29. Preuss, H.G., Marcusen, C., Regan, J., et al, "Randomized trial of a combination of natural products (cernitin, saw palmetto, B-sitosteriol, vitamin E) on symptoms of benign prostatic hyperplasia (BPH)", *Int. U. and Neph.*, 33:217-225, 2001.
30. Sultan, C., "Inhibition of androgen metabolism and binding by a liposterolic extract of *Serenoa repens* B" in human foreskin fibroblasts". *J. Steroid Biochem* 20:515-519, 1984.
31. Aoki, A., Naito, K., Hashimoto, O., et al., "Clinical evaluation of the effect of tamsulosin hydrochloride and cernitin pollen extract on urinary disturbance associated with benign prostatic hyperplasia in a multicentered study", *Hinyo Kiyo*, 48:259-267, 2002.

