

Go-Less™

Natural Bladder Support for Aging Men and Women

Overactive bladder is a widespread condition, affecting about one in six adults over the age of 40. Overactive bladder is defined as having an urgent need to empty the bladder, more frequent urination during the day and night, and incontinence.^{1,2} Urinary incontinence, or the accidental leakage of urine affects 13 million Americans and occurs twice as often in women than men.³ Although incontinence occurs more often in older individuals, it is not considered a normal part of the aging process.

Overactive bladder and incontinence are often embarrassing for those affected by the condition. Having to go to the bathroom frequently or leaking urine can interfere greatly with daily activities and researchers have found that about one-third of individuals with the condition report feeling depressed or stressed.¹ In addition, frequent trips to the bathroom at night can decrease sleep quality for both the individual and their partner or caretakers. Drugs that treat overactive bladder and incontinence are available; however, less than half of people affected would consider seeing a doctor about their problem.¹ Therefore, natural supplements that can improve symptoms of overactive bladder and incontinence have the potential to significantly improve quality of life for individuals affected.

Frutarom has developed *Go-Less™*, a proprietary blend of EFLA® 940 special pumpkin seed extract and SoyLife® soy germ isoflavones to support bladder health in aging men and women. Such a blend of pumpkin seed extract and soy isoflavones has been clinically studied and proven to be effective in addressing the cause of overactive bladder as well as improving its symptoms. This document reviews recent information on urinary incontinence and overactive bladder and summarizes the most up-to-date research on *Go-Less* and how it can provide natural bladder support for aging men and women.

What is overactive bladder?

Overactive bladder is actually a form of urinary incontinence. Symptoms of overactive bladder include an urgent feeling to urinate, increased frequency of urinating during the day and night and incontinence. Urinary incontinence is the accidental leakage of urine. This often occurs when individuals cough, laugh, sneeze, or have sudden urges to go to the bathroom and can't get there in time. Typically, urinary incontinence does not cause major health problems, but it can be embarrassing and affect self-esteem and quality of life. There are different kinds of incontinence³:

- **Stress incontinence** is urine loss during physical activity that increases abdominal pressure, such as sneezing, coughing, laughing, etc.
- **Urge incontinence or overactive bladder** is an urgent need to urinate that is so strong that individuals often cannot make it to the toilet in time. Also called overactive bladder, urge incontinence occurs when your bladder contracts when it shouldn't. This can happen even when there is only a small amount of urine in the bladder.

- **Overflow incontinence** is leakage that occurs when the bladder fails to empty properly, due to a blockage or weak bladder muscle contractions. Obstruction is usually related to either enlargement of the prostate or narrowing of the urethra from scar tissue.
- Stress and urge incontinence often occur together in women. This combination is sometimes referred to as "**mixed incontinence.**"

In **men**, urinary incontinence is often related to a problem involving the prostate gland, such as enlargement of the prostate (benign prostatic hyperplasia, or BPH). Hormonal imbalances are a well-known cause of BPH in aging men. Hormone imbalances are also associated with a weakening of the pelvic floor in postmenopausal **women**. Stress incontinence in women can also result from childbirth, weight gain, or other conditions that stretch the pelvic floor muscles.

GoLess™ background

Go-Less™ is a proprietary blend of EFLA® 940 special pumpkin seed extract and SoyLife® 40% soy germ isoflavones. The seeds of the medicinal pumpkin (*Cucurbita pepo L.*) have been used for centuries as a natural remedy for urination problems. EFLA® 940 is a water-soluble pumpkin seed special extract that contains the complete spectrum of polar and semi-polar constituents of the seed. Frutarom uses a proprietary EFLA® HyperPure process that ensures highly selective removal of the fat-soluble components from the extract. Being virtually fat free, EFLA® 940 allows for increased stability and solubility and absence of rancidity.

Soy isoflavones are a class of phytoestrogens, or plant estrogens, which are suggested to help balance hormone levels in the body. SoyLife® is a soy germ isoflavone extract containing a standardized amount of isoflavones, as well as other phytonutrients in soy that are associated with improved health. SoyLife is also the only patent protected soy germ isoflavone ingredient on the market for use in dietary supplements.

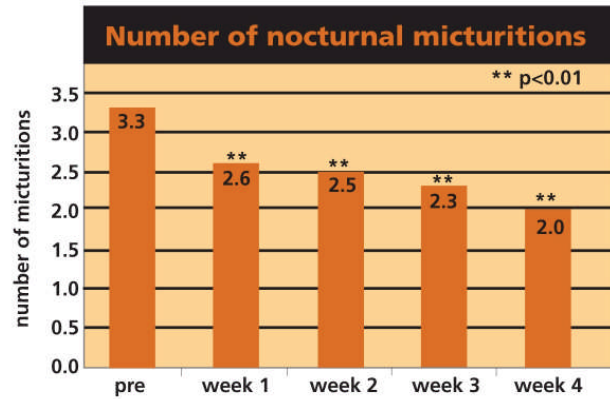
Summary of studies

The combination of EFLA® 940 special pumpkin seed extract and soy germ isoflavones has been shown to be effective in the treatment of urinary disorders associated with hormonal imbalances as demonstrated by pre-clinical in vivo research.

Effects on urination at night

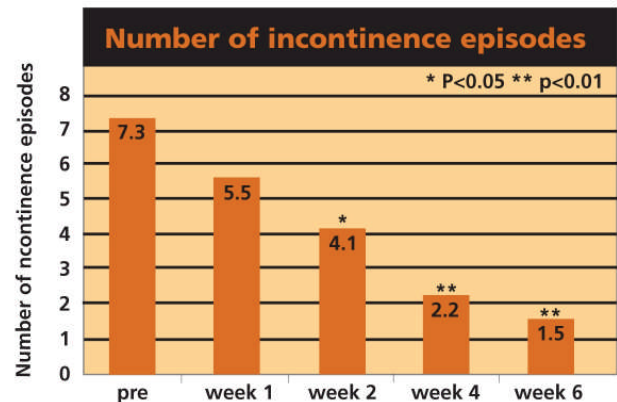
In a study of 39 women aged 52 to 86 years, it was found that a supplement containing EFLA® 940 and soy germ isoflavones decreased the frequency of urination during the day as well as at night (nocturia). Subjects also reported improved sleep satisfaction. The study consisted of a one-week pre-trial observation period followed by six weeks of supplement intake. Subjects recorded the frequency of urination during the day and night and their degree of sleep satisfaction. Researchers found that the frequency of urination was significantly improved at week 1, followed by continued improvement (Figure 1). The degree of sleep satisfaction was also improved at week 1 with additional improvement at week 2. Urinary incontinence was decreased significantly by week 2 and further at week 4 (Figure 2).⁴

Figure 1: frequency of urination at night



Sogabe H, et al. (2001) J Med Pharm Sci. 46 (5) 727-37

Figure 2: frequency of incontinence

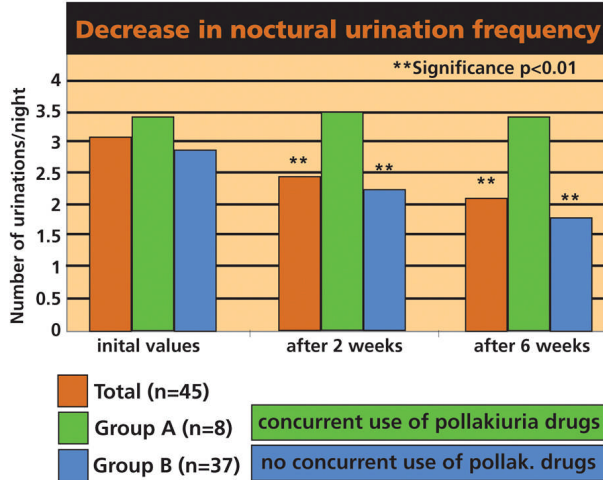


Sogabe H, et al. (2001) J Med Pharm Sci. 46 (5) 727-37

Pollakuria is defined as the condition in which one is awakened to urinate at night. In a study of 45 males over the age of 65 suffering from pollakuria, it was shown that a supplement containing EFLA® 940 and soy germ isoflavones reduced pollakuria and improved sleep satisfaction. The subjects were divided into two groups; one with concurrent use of therapeutic drugs for pollakuria at night (group A) and those without use of drugs of pollakuria (group B). The study consisted of a one-week pre trial observation period, followed by 6 weeks of supplement intake. Subjects recorded the number of times they urinated during the day, night, any adverse symptoms as well as their sleep satisfaction. The frequency of urination at night started to decrease within the first week of taking the supplement and had decreased by approximately 40% after 6 weeks. Researchers concluded that the

frequency of urination at night was significantly reduced compared to before taking the supplement (Figure 3).

Figure 3: frequency of nocturnal urination



Terado T. et al. (2004) Jap. Med. Pharm. Sci. 46(5): 727-737

The supplement was also found to increase sleep satisfaction. More than 86% of subjects also reported that their symptoms improved or significantly improved.⁵

Effects on stress incontinence

A supplement containing EFLA® 940 and soy germ isoflavones was found to reduce urinary incontinence in women suffering from overactive bladder and stress incontinence. Researchers studied 50 women aged 35 to 84 with overactive bladder and stress urinary at two different clinics in Japan. The study involved a one-week observation period (pre-trial), followed by six weeks of supplement administration. During the test period, patients recorded the frequency of urination during the day and at night. They also recorded the number of incontinence episodes and rated their satisfaction with the treatment. At the end of the study it was shown that the episodes of incontinence improved significantly (Figure 4). In particular, patients with the largest number of incontinence episodes showed the greatest improvement.⁶

Mechanism of Action

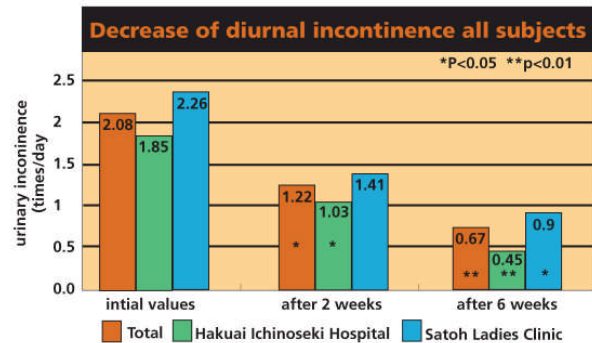
Frutarom has performed several *in vitro* and *in vivo* experiments to determine the mechanism of action for how Go-Less contributes to bladder health. Results of the experiments suggest that EFLA® 940 special

pumpkin seed extract and soy germ isoflavones exert beneficial activity in two ways: one on the hormonal level, resulting in anabolic, muscle strengthening effects; the other on a direct muscle relaxing effect resulting in a decreased urination frequency of the bladder.

In vitro experiments have shown that the ingredients in Go-Less inhibit enzymes involved in hormone metabolism. Human **5-alpha reductase** is an enzyme involved in the conversion of testosterone to dihydrotestosterone, DHT. An overproduction of this enzyme is thought to play a role in the development of BPH. Inhibition of 5-alpha reductase may therefore lead to balanced levels of testosterone and DHT. EFLA® 940 pumpkin seed extract was found to inhibit 5-alpha reductase in a dose dependent fashion.

During menopause, women experience estrogen deficiency, which leads to symptoms of menopause such as hot flashes and night sweats and increases a woman's risk of developing osteoporosis and heart disease. In addition, estrogen deficiency has been linked to the reduction of vaginal and periurethral collagen content. Therefore, menopause is associated with urogenital complaints, including stress urinary incontinence and urgency.¹⁰ Isoflavones are classified as phytoestrogens. They have a chemical structure similar to human estrogen, which allows isoflavones to attach to estrogen receptors and exert weak estrogenic and anti-estrogenic effects. *In vitro* studies by Frutarom have shown that isoflavones and EFLA®940 pumpkin seed extract inhibit **aromatase**, an enzyme involved in the conversion of testosterone to estradiol. In women, a decrease in this conversion can help maintain healthy testosterone levels, supporting the strengthening of pelvic muscles.

Figure 4: frequency of incontinence

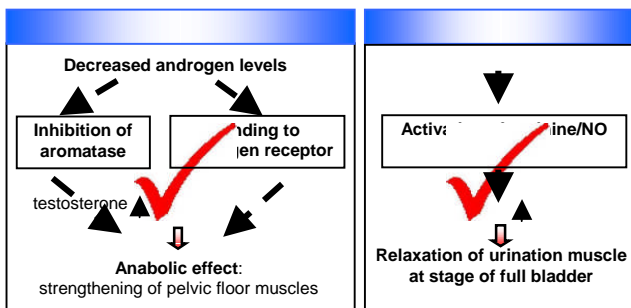


Yonagisawa E. et al. (2003) Japanese Journal of Medicine and Pharmaceutical Science 14: 3:313-322

Another *in vitro* study found that EFLA® 940 pumpkin seed extract binds to androgen receptors. The androgen receptor is a ligand-activated nuclear transcription factor that mediates responses to androgens (testosterone and its metabolite DHT) in a variety of tissues. In addition to being strongly present in male sexual organs, androgen receptors are also present in muscle tissues and female reproductive organs.⁷ Androgens produce direct anabolic effects on skeletal muscle. Recently it has been observed that androgens may potentially play an important role in the pelvic-floor and lower urinary track disorders because certain muscles in the urinary tract are sensitive to androgens and contain large number of androgen receptors.^{8,9}

Findings of an *in vivo* experiment in rats also suggest that the clinical effects of EFLA 940 might also be mediated by an activation of the arginine/ nitric oxide pathway, resulting in an increased production of the muscle relaxing nitric oxide.¹¹

Figure 5: mechanisms by which Go-Less supports bladder health



In Summary

In summary, clinical studies in men and women have found a reduction in the frequency of urination at night as well as during the day. Incontinence episodes in women were also shown to decrease and subjective improvement in symptoms of overactive bladder were reported. Greater than 60% of subjects reported improvements within two weeks of taking the supplement and more than 80% had improved after 6 weeks. The studies show high compliance and confirm the safety and tolerance of preparations with EFLA®940 pumpkin seed extract and soy germ isoflavones.

Dosage Recommendations

A daily dose of 600 mg of Go-Less, providing 525 mg of EFLA 940 and 75 mg SoyLife 40% is recommended to provide the amount of pumpkin seed extract and soy germ isoflavones used in the human studies. Point of consideration: the studies used a higher dose for the first two weeks, followed by a reduced dose for the last four weeks. To mirror the studies, you may suggest 1000 mg of Go-Less for the first two weeks, followed by 600 mg of Go-Less in future weeks.^{4,5,6}

References:

1. Irwin DE, et al. (2006). Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. *BJU Int.* 97(1):96-100.
2. WebMD. Incontinence/Overactive Bladder Guide. <http://www.webmd.com/urinary-incontinence-oab/default.htm>. Accessed April 15, 2007.
3. Nazarihvili G, Gabunia N, Gagua G. (2007). Prevalence of urinary incontinence in women population. *Georgian Med News.* 143:39-42.
4. Sogabe H and Terado T. (2001). Open Clinical Study of Effects of Pumpkin Seed Extract/ Soybean Germ Extract Mixture-containing Processed Food on Nocturia. *Jpn J Med Pharm Sci.* Nov;46(5):727-37.
5. Terado T, et al. (2004). Clinical Study of mixed processed foods containing pumpkin seed extract and soybean germ extract on pollikiuria in night in elderly men. *Jap J Med Pharmaceut Sci.* 52(4): 551-561.
6. Yanagisawa, EI et al. (2003). Study of effectiveness of mixed processed food containing cucurbita pepo seed extract and soybean seed extract on stress urinary incontinence in women. *Japanese Journal of Medicine and Pharmaceutical Science* 14;3:313-322.
7. Keller ET, et al. (1996) The androgen receptor: a mediator of diverse responses. *Front Biosci.* 1;1:d59-71.
8. Ho MH, et al. (2004). Anabolic effects of androgens on muscles of female pelvic floor and lower urinary tract. *Current Opin Obstet Gynecol.* 16(5): 405-9.
9. Copas P, et al. (2001). Estrogen, progesterone, and androgen receptor expression in levator ani muscle and fascia. *J Womens Health Gen Based Med.* 10(8): 785-95.
10. Tomaszewski J, et al. (2003) Effect of 17 beta-estradiol and phytoestrogen daidzein on the proliferation of pubocervical fascia and skin fibroblasts derived from women suffering from stress urinary incontinence. *Ginekol Pol.* 74(10):1410-4.
11. Hata K et al. (2005) Effects of pumpkin seed extract on urinary bladder function in anesthetized rats. *Medical Science and Pharmaceutical Science.* 54(3): 339-345.

GoLess Science US 050907