

## REPORT

### Relieving Menopausal Symptoms Naturally

By Lane Lenard, PHD

As women approach menopause, they become susceptible to a host of complaints, ranging from night sweats and low libido to mood disorders and insomnia. One of the main culprits in menopausal discomforts is declining levels of estrogen.

Ever since the *Women's Health Initiative* revealed potentially dangerous side effects of estrogen drugs like Premarin®, women have been seeking comparative but safer methods to relieve menopausal concerns. Plant-based phytoestrogens are among the most promising of these natural menopause solutions that capture the benefits of estrogen without its side effects.

Now, scientists have discovered that the hops plant contains the most powerful phytoestrogen ever identified. Human studies show that this potent compound—known as *8-prenylnaringenin* or 8-PN—effectively combats menopausal complaints and shows promise in protecting against bone loss and heart disease. For added protection, the estrogenic properties of 8-PN may also be complemented by the Norway spruce-derived phytoestrogen *hydroxymatairesinol* (HMR).

Together, this combination of phytonutrients promises to naturally and safely restore well-being to women during their menopausal years and beyond.

#### THE CHALLENGES OF MENOPAUSE

As women approach menopause (usually around age 50), they commonly experience symptoms, such as hot flashes (also called “hot flushes”), mood disorders, irritability, loss of libido, insomnia, depression, and other discomforts.

Hot flashes typically begin a year or two before women reach menopause (defined officially as 12 consecutive months with no menstruation) and may last from just a few months up to five years or longer. For some fortunate women, the sudden and intense warmth and sweating of hot flashes and its associated discomforts may occur just a few times a week, but for others, they can strike several times a day, making it hard for them to work, to spend time with friends and family, and even to go out in public. Hot flashes that occur overnight, known as “night sweats,” can make it difficult to get a good night's sleep.<sup>1</sup>

The physiologic mechanisms that trigger and control menopausal symptoms are not completely understood, but one thing is eminently clear: they result from the pre-programmed shutdown of a woman's ovaries and the resulting deficiency of the ovaries' primary hormonal product, estrogen.

#### THE SEARCH FOR SOLUTIONS

Since ancient times, women have tried to ease their way through the menopausal passage by using various plant-based remedies, such as soy, red clover, flaxseed, black cohosh, and chaste tree berry. Thanks to modern science, we now know that many of the effects of these herbal medicines are due to their constituents known as *phytoestrogens*, plant-based estrogen-like substances.<sup>2</sup> Since phytoestrogens resemble estradiol in their chemical structure and function, they can help substitute for a woman's declining ovarian estrogen, and thus prevent, or at least modulate, many menopausal symptoms.

For several decades, the pharmaceutical industry's answer to menopause has been estrogens derived from horse urine (Premarin®) and 100% estradiol products, which they have marketed—with enormous success—as menopausal “hormone replacement therapy” (HRT). Although the highly potent estrogens in these products are quite capable of inhibiting hot flashes and some other symptoms, they carry the risk of potentially serious adverse health consequences—including increased risks of



breast cancer and cardiovascular disease—as confirmed in recent years by the results of the Women’s Health Initiative (WHI)<sup>3</sup> and other important clinical trials.

In light of this rising tide of negative data, many women have been turning back to traditional herbal remedies. While these phytoestrogens may meet the needs of some menopausal women, others find that they do not offer sufficient relief from menopausal discomforts.<sup>2</sup> They long for one that is safe enough not to cause them health concerns, yet still strong enough to reliably suppress their hot flashes and other common discomforts and complaints.



Now, that phytoestrogen may finally be at hand. It’s been identified as an extract of the female flower of the hops plant (*Humulus lupulus L.*). Yes, that’s right, hops, the very same plant used since the Middle Ages to help process and flavor beer, has been found to contain a constituent that is, without question, the most potent phytoestrogen ever tested.<sup>4</sup> So effective is this hops extract—now known as *8-prenylnaringenin* (8-PN)—that controlled clinical research has shown that most menopausal women who take it experience a rapid and significant reduction in hot flashes and other discomforts.<sup>5</sup> And this may just be the beginning of its health benefits. It may also be helpful against osteoporosis and heart disease—with no sign of HRT-like risks.<sup>6-8</sup>

Moreover, a compelling theory suggests that 8-PN’s anti-hot flash action, as well as its other health benefits, may be magnified when it is combined with another type of common phytoestrogen from a lignan, that is, *7-hydroxymatairesinol* (HMR), extracted from Norway spruce trees.<sup>9,10</sup> For women approaching menopause or for those already distressed by its symptoms, the combined actions of 8-PN and HMR may be the best news in centuries.

### THE ESTROGENIC EFFECTS OF HOPS

Although the main use of hops has always been in brewing beer, it has been believed since ancient times to have certain medicinal properties, particularly as a sedative and hypnotic (sleep-inducing agent).<sup>4,11</sup>



Research by German investigators beginning in the 1950s found that crude hops extracts possessed estrogenic activity. In fact, this activity, as tested in animal studies, was many times stronger than that found in any other phytoestrogenic plants.<sup>4</sup> In common phytoestrogenic plants, like soy beans, clover, and legumes, the estrogenic activity has long been linked to the presence of high concentrations of chemicals known as *isoflavones*, especially *daidzein* and *genistein*. In nuts and oilseeds (e.g., flaxseed), as well as some cereals, fruits, and vegetables known to have estrogenic properties, a different class of chemicals, known as *lignans*, was deemed responsible.

Modern scientists from Japan,<sup>12,13</sup> Belgium,<sup>4</sup> and the UK<sup>14</sup> found that the most estrogenically potent compound in the hops cone—and consequently, the most potent phytoestrogen ever isolated—was *8-prenylnaringenin* (8-PN), a member of a previously unknown class of nonsteroidal phytoestrogens known as *prenylflavonoids*. Lab studies indicated that the estrogenic actions of 8-PN are several times more potent than daidzein and genistein, but still significantly less estrogenic than estradiol<sup>14</sup>—in other words, the near ideal blend of power and safety that menopausal women have been craving.

### ANIMAL STUDIES CONFIRM ESTROGENIC EFFECT

Declining levels of estrogen with menopause can result in atrophy of the vaginal epithelium, which is associated with symptoms such as dryness, itching, and burning. Research in ovariectomized rats (ovaries surgically removed) indicates that 8-PN produces mild estrogen-like functions in vaginal and uterine epithelial tissues.<sup>15</sup> After three months of treatment with either estradiol or 8-PN, both in low and high doses, examination of the animals’ uteri and vaginas showed that high and low doses of estradiol, and the high dose of 8-PN, caused typical estrogen-related growth in the epithelial tissue of these organs. These results suggest that 8-PN shares many of the typical estrogenic functions of estradiol, but in general, 8-PN is less potent, and may thus be safer.

The first clear indication that 8-PN might be useful for helping suppress hot flashes came from a British study of ovariectomized rats. Just as removing ovarian estrogen is a sure-fire way to trigger hot flashes in women, ovariectomy in rats causes their tail skin temperature to rise. Using a telemetric device to measure the animals’ tail skin temperature, the researchers fed one group of rats a diet that included estradiol and a second group a diet containing 8-PN. A third control group consumed a normal estrogen-free diet. The results showed that, compared with their pretreatment baselines, both estradiol and 8-PN significantly lowered the rats’ mean tail skin temperature.<sup>16</sup> Dietary phytoestrogens, such as soy isoflavones, have also been shown to suppress elevated tail skin temperature levels in ovariectomized rats, although those effects were less intense than those produced by 8-PN.<sup>17</sup>

## WHAT YOU NEED TO KNOW: RELIEVING MENOPAUSAL SYMPTOMS NATURALLY

- Hot flashes and other menopausal symptoms are a consequence of the pre-programmed shutdown of the ovaries and the subsequent decline in their primary hormone, estrogen.
- Hormone replacement therapies such as pharmaceutical HRT products made from horse estrogens or 100% estradiol, as well as natural remedies made from phytoestrogens (e.g., isoflavones) are designed to provide the body with estrogen substitutes that ideally prevent menopausal symptoms. Unfortunately, pharmaceutical HRT products can be potentially dangerous, whereas natural remedies may be too mild to produce desired effects in some women.
- Recently, an extract of the hops cone has been found to contain a previously unknown class of nonsteroidal phytoestrogens (*prenylflavonoids*), of which 8-PN is the most potent. Lab studies show 8-PN to be significantly more potent than the isoflavones daidzein and genistein, but significantly less estrogenic than estradiol, thus making for a near ideal balance of potency and safety.
- Clinical studies in postmenopausal women show that daily doses of 8-PN significantly suppress hot flashes, while also reducing associated insomnia, irritability, and heart palpitations. Lab studies suggest that 8-PN may one day provide valuable protection for menopausal women against osteoporosis, heart disease, and breast cancer.
- Research suggests that the lignan phytoestrogen HMR significantly reduces hot flashes by about 50%. Since 8-PN and HMR appear to work via different mechanisms of action, the combination of both phytoestrogens in a single product promises menopausal women the possibility of the most potent and complete natural relief available.

### 8-PN SUPPRESSES MENOPAUSAL DISCOMFORTS IN WOMEN

In the first randomized, double-blind, placebo-controlled study of its kind, Belgian researchers evaluated the effects of a hops extract *enriched in 8-PN* for the relief of hot flashes and other menopausal discomforts in 67 naturally menopausal (ovaries not surgically removed) women, aged 45 to 60 years.<sup>5</sup> Before treatment, the 67 participating women all reported experiencing mild-to-severe menopausal discomforts, including two to five hot flashes per day. They were randomly divided into three groups: 1) 8-PN 100 mcg/day; 2) 8-PN 250 mcg/day; and 3) placebo. At intervals of six and 12 weeks, the researchers assessed the women's frequency of hot flashes along with their other menopausal discomforts and complaints.



The results (In Figure 1 below) show that both doses of 8-PN were about equally effective in significantly reducing the average frequency of hot flashes after six and 12 weeks of treatment, compared with placebo. Beyond hot flashes, 8-PN was also superior to placebo in improving *total menopausal discomfort score*, which included not only hot flashes, but also insomnia, irritability, and heart palpitations as assessed by the women themselves.<sup>5</sup>

### OSTEOPOROSIS PROTECTION FROM 8-PN

8-PN might also help women keep their bones strong after menopause. Since ovarian estrogen helps maintain bone strength, it is common for women to develop the bone-thinning disease *osteoporosis* as their estrogen levels decline after menopause. Using an established animal model of human hormone-dependent osteoporosis, a team of European researchers assessed bone strength by measuring bone mineral density in ovariectomized rats.<sup>8</sup> They found that daily injections of 8-PN inhibited subsequent bone loss compared with control injections without 8-PN; the higher the dose of 8-PN, the better the bone was protected. In fact, the highest dose of 8-PN (18 mg/kg/day) completely prevented bone loss. Another study showed that 8-PN's bone-health benefits can be achieved through oral supplementation.

When ovariectomized rats received chow containing 8-PN, they demonstrated increased bone mineral density as well as improvements in bone bio-mechanical properties. Genistein-supplemented chow produced smaller benefits for the animals' bone biomechanical strength.<sup>18</sup>

These results are very exciting on several fronts. First, this phytoestrogen has been shown to provide a significant anti-osteoporotic benefit. Second, if a dose of estradiol were extrapolated to provide a comparable amount of bone protection in women as 8-PN provided in these rats, it would almost certainly also stimulate excess growth in the endometrium (the lining of the uterus), thus raising the risk of endometrial cancer. Yet, the 8-PN dose that completely prevented osteoporosis in rats

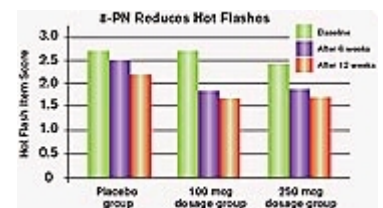


Figure 1. 8-PN at doses of 100 mcg/day and 250 mcg/day significantly reduced hot flash frequency scores after six weeks of treatment, compared with placebo.<sup>5</sup>

stimulated uterine growth at a rate at least 10 times lower than the comparable dose of estradiol, a reassuring sign of 8-PN's safety. The researchers believe such an extrapolation of 8-PN's tissue selectivity from rats to humans is valid, because the most important pharmacokinetic parameters (absorption, distribution, metabolism, and excretion) for 8-PN are largely the same for both species.<sup>19</sup> Clearly, though, long-term trials in postmenopausal women are needed to confirm such bone-protective benefits of 8-PN.

## CANCER PROTECTION BENEFITS OF 8-PN

Numerous studies have shown that some isoflavones and lignans may have significant cancer-fighting capabilities, especially in the colon, endometrium (uterus), and breast, all important sites of estrogen activity.<sup>20-25</sup> Now *in vitro* research suggests that 8-PN can also be added to this list of possible natural breast cancer inhibitors. Using human MCF-7 cells, an extensively studied model for breast cancer, Italian investigators found that high concentrations of 8-PN slowed the growth of estrogen-sensitive MCF-7 cells by inhibiting their proliferation and inducing their programmed death (apoptosis).<sup>7</sup> This promising preliminary finding suggests that 8-PN could one day find applications in breast cancer management strategies. Until human studies are done, women with pre-existing breast cancer may want to avoid using even this natural phytoestrogen (8-PN).

## 8-PN AND CARDIOVASCULAR HEALTH

Data from the world-famous Framingham Heart Study have shown that higher dietary consumption of phytoestrogens—primarily isoflavones and lignans—may favorably modulate cardiovascular risk factors, which may lower women's risk of suffering a heart attack or stroke.<sup>26</sup>

A recent study in ovariectomized rats suggests that 8-PN may also have cardiovascular benefits and, in fact, may be superior to natural estradiol in normalizing cardiovascular risk factors. While both estradiol and 8-PN lowered cholesterol and low-density lipoprotein (LDL), estradiol produced the unwanted effects of increasing triglycerides and lowering high-density lipoprotein (HDL). In contrast, 8-PN did not alter triglycerides, and low-dose 8-PN increased levels of beneficial HDL.<sup>6</sup> Noted the authors, "*taken together, 8-PN displays an anti-atherosclerotic profile that appears to be even more beneficial than the one displayed by [estradiol], and thus might demonstrate a remarkable potential for the prevention of [cardiovascular disease] associated with estrogen deficiency.*"

## HMR BOOSTS POSTMENOPAUSAL BENEFITS

*Hydroxymatairesinol* (HMR) is a phytoestrogen of the plant lignan class that is extracted from knots of Norway spruce trees (*Picea abies*).<sup>27</sup>

Plant lignans (e.g., those from flax seed, sesame seeds, rye, wheat, oat, barley, pumpkin seeds, soybeans, broccoli, beans, and some berries) have been studied most for their anticancer potential, including cancers of the breast, endometrium, colon, and prostate.<sup>21-25,28</sup> Evidence indicates that plant lignans acquire their anticancer properties only after being ingested and converted by intestinal bacteria to *mammalian lignans, particularly enterolactone and enterodiol*.<sup>29</sup>



In a study from Finland, HMR was fed to rats pretreated with a chemical that induces mammary tumors. After 51 days of HMR treatment, the researchers found decreased numbers of growing tumors and an increased proportion of regressing and stabilized tumors.<sup>9</sup> A Finnish clinical study found a significant association between higher serum human enterolactone levels—attributed to dietary intake of plant lignans—and lower risk of breast cancer among both pre- and postmenopausal women.<sup>30</sup>

A new study of HMR in postmenopausal women found that eight weeks of treatment with daily doses of 50 mg was very effective, reducing the frequency of hot flashes by 53% compared with baseline. From a mean of about four hot flashes per day before treatment, HMR reduced the rate to about two per day.<sup>10</sup>

Together, these findings suggest that HMR may offer relief from the discomforts of menopause while providing a rich source of cancer-preventive lignans.

## SUMMARY

The hops extract 8-PN has recently been identified as a potent phytoestrogen for alleviating the misery of hot flashes and other symptoms related to the menopausal decline in estrogen levels. 8-PN is significantly more potent than soy isoflavones, the most common phytoestrogens used for alleviating menopausal symptoms naturally, yet it is significantly less estrogenic than estradiol, thus making for a near ideal balance of potency and safety for a natural phytoestrogen. Both animal and clinical studies

confirm that 8-PN relieves common menopausal symptoms, and preliminary lab studies suggest that 8-PN may provide protection for postmenopausal women against osteoporosis, breast cancer, and cardiovascular disease. Combining 8-PN with the lignan HMR may magnify these benefits even more. Since HMR and 8-PN appear to relieve menopausal symptoms via different mechanisms, the combination of these two phytoestrogens offers menopausal women the possibility of natural relief available today.

Note: Postmenopausal women seeking to optimize hormone balance should also consider using a *natural progesterone cream* (not a synthetic progestin) to maintain youthful progesterone levels.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

---

## References

---

1. Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. *Mayo Clin Proc.* 2002 Nov;77(11):1207-18.
2. Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev.* 2007 Oct 17;(4):CD001395.
3. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002 Jul 17;288(3):321-33.
4. De Keukeleire D, De Cooman L, Rong H, Heyerick A, Kalita J, Milligan SR. Functional properties of hop polyphenols. *Basic Life Sci.* 1999;66:739-60.
5. Heyerick A, Vervarcke S, Depypere H, Bracke M, De KD. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas.* 2006 May 20;54(2):164-75.
6. Bottner M, Christoffel J, Wuttke W. Effects of long-term treatment with 8-prenylnaringenin and oral estradiol on the GH-IGF-1 axis and lipid metabolism in rats. *J Endocrinol.* 2008 Aug;198(2):395-401.
7. Brunelli E, Minassi A, Appendino G, Moro L. 8-Prenylnaringenin, inhibits estrogen receptor-alpha mediated cell growth and induces apoptosis in MCF-7 breast cancer cells. *J Steroid Biochem Mol Biol.* 2007 Nov;107(3-5):140-8.
8. Humpel M, Isaksson P, Schaefer O, et al. Tissue specificity of 8-prenylnaringenin: protection from ovariectomy induced bone loss with minimal trophic effects on the uterus. *J Steroid Biochem Mol Biol.* 2005 Nov;97(3):299-305.
9. Saarinen NM, Warri A, Makela SI, et al. Hydroxymatairesinol, a novel enterolactone precursor with antitumor properties from coniferous tree (*Picea abies*). *Nutr Cancer.* 2000;36(2):207-16.
10. Available at: <http://www.hmrlignan.com/images/HotFlash.pdf>. Accessed November 18, 2008.
11. No authors listed. *Humulus lupulus*. Monograph. *Altern Med Rev.* 2003 May;8(2):190-2.
12. De KD, De CL, Rong H, et al. Functional properties of hop polyphenols. *Basic Life Sci.* 1999;66:739-60.
13. Kitaoka M, Kadokawa H, Sugano M, et al. Prenylflavonoids: a new class of non-steroidal phytoestrogen (Part 1). Isolation of 8-isopentenylnaringenin and an initial study on its structure-activity relationship. *Planta Med.* 1998 Aug;64(6):511-8.
14. Miyamoto M, Matsushita Y, Kiyokawa A, et al. Prenylflavonoids: a new class of non-steroidal phytoestrogen (Part 2). Estrogenic effects of 8-isopentenylnaringenin on bone metabolism. *Planta Med.* 1998 Aug;64(6):516-9.
15. Rimoldi G, Christoffel J, Wuttke W. Morphologic changes induced by oral long-term treatment with 8-prenylnaringenin in the uterus, vagina, and mammary gland of castrated rats. *Menopause.* 2006 Jul;13(4):669-77.
16. Bowe J, Li XF, Kinsey-Jones J, et al. The hop phytoestrogen, 8-prenylnaringenin, reverses the ovariectomy-induced rise in skin temperature in an animal model of menopausal hot flashes. *J Endocrinol.* 2006 Nov;191(2):399-405.
17. Pan Y, Anthony MS, Binns M, Clarkson TB. A comparison of oral micronized estradiol with soy phytoestrogen effects on tail skin temperatures of ovariectomized rats. *Menopause.* 2001 May-Jun;8(3):171-4.

18. Sehmisch S, Hammer F, Christoffel J, et al. Comparison of the phytohormones genistein, resveratrol and 8-prenylnaringenin as agents for preventing osteoporosis. *Planta Med.* 2008 Jun;74(8):794-801.
19. Rad M, Humpel M, Schaefer O, et al. Pharmacokinetics and systemic endocrine effects of the phyto-oestrogen 8-prenylnaringenin after single oral doses to postmenopausal women. *Br J Clin Pharmacol.* 2006 Sep;62(3):288-96.
20. Branca F, Lorenzetti S. Health effects of phytoestrogens. *Forum Nutr.* 2005;(57):100-11.
21. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst.* 2003 Aug 6;95(15):1158-64.
22. Jenab M, Thompson LU. The influence of flaxseed and lignans on colon carcinogenesis and beta-glucuronidase activity. *Carcinogenesis.* 1996 Jun;17(6):1343-8.
23. McCann SE, Muti P, Vito D, et al. Dietary lignan intakes and risk of pre- and postmenopausal breast cancer. *Int J Cancer.* 2004 Sep 1;111(3):440-3.
24. Serraino M, Thompson LU. Flaxseed supplementation and early markers of colon carcinogenesis. *Cancer Lett.* 1992 Apr 15;63(2):159-65.
25. Sung MK, Lautens M, Thompson LU. Mammalian lignans inhibit the growth of estrogen-independent human colon tumor cells. *Anticancer Res.* 1998 May;18(3A):1405-8.
26. de Kleijn MJ, van der Schouw YT, Wilson PW, Grobbee DE, Jacques PF. Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal U.S.women: the Framingham study. *J Nutr.* 2002 Feb;132(2):276-82.
27. Cosentino M, Marino F, Ferrari M, et al. Estrogenic activity of 7-hydroxymatairesinol potassium acetate (HMR/lignan) from Norway spruce (*Picea abies*) knots and of its active metabolite enterolactone in MCF-7 cells. *Pharmacol Res.* 2007 Aug;56(2):140-7.
28. Bylund A, Saarinen N, Zhang JX, et al. Anticancer effects of a plant lignan 7-hydroxymatairesinol on a prostate cancer model in vivo. *Exp Biol Med (Maywood).* 2005 Mar;230(3):217-23.
29. Borriello SP, Setchell KD, Axelson M, Lawson AM. Production and metabolism of lignans by the human faecal flora. *J Appl Bacteriol.* 1985 Jan;58(1):37-43.
30. Pietinen P, Stumpf K, Mannisto S, et al. Serum enterolactone and risk of breast cancer: a case-control study in eastern Finland. *Cancer Epidemiol Biomarkers Prev.* 2001 Apr;10(4):339-44.

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.