

Hops for Menopausal Vasomotor Symptoms: Mechanisms of Action

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Menopause is a critical stage of women's life associated with various complaints and distresses. Vasomotor symptoms (VMS), such as hot flashes, night sweats, sleep disturbances, and fatigue, are the most common menopause symptoms affecting about 50% to 80% of middle-aged women. Obviously, these symptoms, resulting from estrogen deficiency during menopause, can exert negative effects on women's health and quality of life and thus require to be managed through approaches such as hormone replacement therapy (HRT). Many herbal treatments for menopause symptoms contain and its components such as 8-prenylnaringenin, 6-PN, isoxanthohumol and xanthohumol. Recent in-vivo studies have highlighted the ability of 8-prenylnaringenin to reduce serum-luteinizing hormone (LH) and follicle-stimulating hormone (FSH), to increase serum prolactin levels and uterine weight, and to induce vaginal hyperplastic epithelium. Previous research has shown that hops extract can strongly bind to both estrogen receptors, stimulate alkaline phosphatase activity in Ishikawa cells, and upregulate presenelin-2 and progesterone receptor mRNA in Ishikawa cells. Numerous clinical trials have documented significant reductions in the frequency of hot flashes following the administration of hop-containing preparations. Nevertheless, further clinical trials with larger sample size and longer follow-up are warranted to confirm such benefits. (**J Menopausal Med 2016;22:62-64**)

Key Words: Hormone replacement therapy · Hot flashes · Humulus · Menopause

Menopause, also known as the second puberty, is a critical stage of women's life associated with various complaints and distresses.¹ Vasomotor symptoms (VMS), such as hot flashes, night sweats, sleep disturbances, and fatigue, are the most common menopause symptoms affecting about 50% to 80% of middle-aged women. Although VMS generally subside after five–seven years, some women have to deal with these symptoms for as long as 10 to 15 years.^{2,3} Along with psychological and physical effects, Menopause can also cause VMS and these symptoms can affect the quality of life. Obviously, these symptoms, resulting from estrogen deficiency during menopause, can exert negative effects on

women's health and quality of life⁴ and thus require to be managed through approaches such as hormone replacement therapy (HRT). However, according to the Women's Health Initiative and other clinical trials, HRT can increase the risk of various health issues in postmenopausal women. Estrogen deficiency is associated with complaints that may increase the risks for both morbidity and mortality including increased cognitive changes and osteoporosis. For this reason, there is an interest in utilizing HRT in menopausal women.⁵ However, according to the Women's Health Initiative and other clinical trials, HRT can increase the risk of various health issues such as breast cancer, endometrial

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cancer, thromboembolism disorders, stroke and coronary heart disease in this population.⁶ Therefore, during the past decade, growing attention has been paid to the use of herbal medicines for the treatment of menopausal symptoms. Many herbal treatments for menopausal symptoms contain hops (*Humulus lupulus* L.) and its components such as 8-prenylnaringenin (8-PN; a potent phytoestrogen), 6-PN and isoxanthohumol (two well-known flavanones), and xanthohumol (a prenylated chalcone).⁷ The high estrogenic potency of 8-PN was confirmed by its ability to interact with estrogen receptors (ERs) in a radioligand binding assay on rat uterine cytosol. On the other hand 6-PN showed a very weak estrogenic activity as isoxanthohumol did, while xanthohumol was inactive.⁸ Eight-PN displayed two fold higher affinity for ER- α ($ER\alpha$) than ER- β (β) measured by in vitro competitive binding assay.⁹ Phytoestrogens are secondary metabolites of herbs and characterized by a polyphenolic structure with phenol rings. Phytoestrogens have similar structures with 17β -estradiol generated by the ovaries, and bind to ERs. Hops containing terpenoid, flavonoid glycoside and catechin are widely used to treat tension, headache, edema¹⁰ sleep disorders (through impact on the central nervous system), activating the stomach and appetite. Other beneficial effects of this plant is joint pain reducing, sedation, anxiety and nervousness reducing and effect on kidney. In recent years has been working on anticancer and estrogenic properties its.¹¹ Despite its confirmed benefits, the mechanisms through which hops relieves menopausal symptoms are not clearly understood. Nevertheless, preparations based on hops have been found to decrease the severity and frequency of hot flushes.¹² The frequent menstrual disturbances observed in female hop-pickers, during the early days of hop cones harvesting, suggested a potential hormonal activity of *Humulus lupulus*.¹³ In two randomized placebo-controlled clinical trials performed by Erkkola et al.¹⁴ and Heyerick et al.¹⁵ on the efficacy of *Humulus lupulus*, hot flushes, sweating, insomnia, palpitation and other VMS were identified to be declined. Recent in-vivo studies have highlighted the ability of 8-PN to reduce serum-luteinizing hormone (LH) and follicle-stimulating hormone (FSH), to increase serum prolactin levels and uterine weight, and to induce vaginal hyperplastic epithelium.¹⁶ Bowe et al.¹² reported the efficacy

of daily subcutaneous administration of 8-PN in decreasing elevated skin temperatures in a rat model of menopausal hot flushes. Since the peripheral ER antagonist, ICI 182,780, could completely block the effects of 8-PN, the researchers concluded that peripheral mechanisms were involved in the regulation of the vasomotor response by phytoestrogens. Previous research has shown that hops extract can strongly bind to both ERs ($ER\alpha$ and $ER\beta$), stimulate alkaline phosphatase activity in Ishikawa cells, and upregulate presenilin-2 (an estrogen-inducible gene in S30 cells) and progesterone receptor mRNA in Ishikawa cells.¹³ All these findings suggest the estrogenic activity of hops extract. Numerous clinical trials have documented significant reductions in the frequency of hot flushes following the administration of hop-containing preparations (compared to the control group).^{14,15,17,18} Nevertheless, further clinical trials with larger sample size and longer follow-up are warranted to confirm such benefits. In conclusion, considering the negative effects of HRT, prenylated flavonoids extracted from hops can serve as a useful alternative treatment for the alleviation of menopausal symptoms.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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