

Role of Hop Extract in Menopause

THE BURDEN OF MENOPAUSE

Hot flashes and vasomotor symptoms occur in approximately 75% of women during perimenopause and in most women these last for one to two years after menopause, however they can continue up to 10 years or more.¹ Additionally, long-term consequences of the lack of estrogenic stimulation are increased risk of atherosclerosis, decrease in bone density, and progressive development of osteoporosis.²

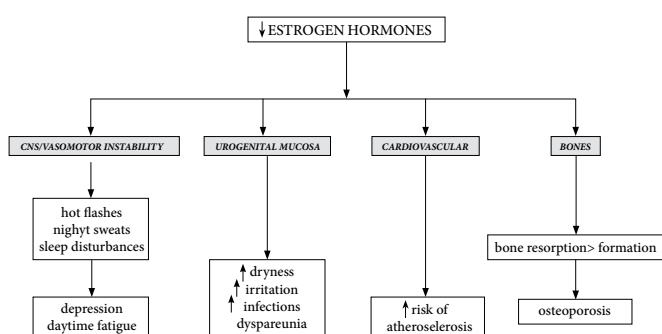


Figure 1: Scheme summarizing the immediate and long-term effect of estrogen decline during menopause.²

Clearly, the symptoms resulting from estrogen deficiency during menopause can exert a detrimental effect on women's health and their quality of life and thus require appropriate management. It is generally recognized that postmenopausal hormone therapy (HT - previously and commonly known as hormone replacement therapy or HRT) is the most efficient way for the relief of climacteric discomforts and symptoms.³

However, downsides to this form of hormonal therapy include serious adverse events. Indeed, the heart and estrogen/progestin replacement study (HERS) demonstrated an increase of cardiovascular (CVD) events in postmenopausal women in the first year.⁴ Similarly, results from the highly publicized women's health initiative study (WHI) showed that HRT can increase the risk of various health issues such as breast cancer, endometrial and ovarian cancer, thromboembolism disorders, stroke and coronary heart disease in this population of women. Despite the many sub-analysis of data from this large study showing a positive benefit-risk ratio from HRT in the majority of patients, the widespread publicity of the WHI study led many women to discontinue the use of HRT and look for other alternatives to overcome their menopausal condition.⁵

PHYTOESTROGENS AS ALTERNATIVE TO HRT

Indeed, during the past 15 years, growing attention has been paid to the use of herbal medicines and food supplements for the management of menopausal symptoms.⁶ Plant extracts with potential estrogenic activities include soy, red clover, kudzu, licorice, rhubarb, yam, chasteberry and hops.⁷ The extracts with estrogenic properties found in these plants are called phytoestrogens.

Hop (*Humulus lupulus* L.) is a key ingredient for beer brewing.⁸ It is also a source of many biologically active molecules including 8-prenylnaringenin (8-PN), 6-prenylnaringenin (6-PN), 6,8-diprenylnaringenin (6,8-DPN) and 8-geranylnaringenin (8-GN). These biologically active compounds are fundamental for the potent estrogen activity of hops. However, the remarkable compound 8-PN, which structurally belongs to the group of prenylated flavonoids, is the strongest known phytoestrogen.²

8-PN has a higher affinity for estrogen receptors alpha, ER α , where it is 70 times weaker than estradiol. However, it was reported that 8-PN is 20,000 times weaker than estradiol for the binding affinity to estrogen receptor beta, ER β .⁸ The majority of known phytoestrogens have a higher affinity for the ER β receptor while 8-PN binds mainly to ER α , the receptor responsible for decreasing vasomotor symptoms when activated. 8-PN has approximately 20 to 300 times higher affinity to ER β compared to the isoflavones genistein and daidzein,^{8,9} two commonly used phytoestrogens in the management of menopause and found in red clover.

CLINICAL EFFICACY OF HOP IN RELIEVING VASOMOTOR SYMPTOMS

How does this in vitro potency translate into clinical efficacy? The first prospective clinical study assessing the effectiveness of a hop extract against climacteric complaints included 67 women between 45 and 60 years of age who were treated for 12 weeks with capsules containing either placebo or the hop extract (100 μ g of 8-PN).¹⁰ The responses were determined by means of a modified Kupperman index (KI) and a patients' questionnaire. The KI is a scale indicating the severity of the most common menopausal symptoms. The decrease in hot flushes score (isolated from the KI) was found significant for the hop treatment group after 6 weeks ($P < 0.01$) compared to placebo.

The same group of investigators repeated the efficacy study of hop extracts on another number of menopausal women four years later, using a crossover prospective randomized placebo-controlled study model.¹¹ Capsules containing standardized hop extract (100µg 8-PN) was administered to a group of 36 menopausal women for a period of 8 weeks. For a further 8 weeks, the treatment method was switched from active treatment to placebo, and vice versa. Efficacy and severity of symptoms were assessed using the KI, the Menopause Rating Scale (MRS) and a multifactorial Visual Analogue Scale (VAS). After 16 weeks, only the hop active treatment, after placebo, reduced all outcome measures, whereas placebo after active treatment did not result in a reduction in symptoms. Time-specific estimates of treatment efficacy indicate significant reductions for KI ($p = 0.02$) and VAS ($p = 0.03$), however the symptoms assessed by MRS showed a marginally significant reduction ($p=0.06$)

In 2016, another randomized placebo-controlled trial was carried on 120 peri- and post-menopausal women aged 40-60 years where the assessment of symptoms improvement was carried out using the changes in total Greene Climacteric Scale score over a period of 12 months.¹² The patients were randomly allocated into two groups, receiving the hop or placebo tablets for 12 weeks. Some of the women experienced premenopausal hot flashes with less than 12 menstrual bleedings within the past 12 months, and the selection parameter for post-menopausal women was a minimum of one year and maximum of 5 years after the last menstruation. At the end of the study the mean Greene score was significantly lower in the hop group than the placebo group at the end of weeks 4 and 12 and the number of hot flashes was significantly lower in the hop group than the control group during the weeks 4 and 12. Hop also decreased significantly all the variables at weeks 4, 8 and 12 such as the psychiatric symptoms for anxiety, the psychiatric symptoms for depression, physical and vasomotor symptoms as well as the loss of interest in sex ($p<0.001$). No adverse effects related to the treatment were identified during the study period.

In many women who suffer from menopause, somatic signs like fatigue, myalgia, arthralgia, paresthesia, palpitations and vaginal dryness are part of climacteric symptoms. These were assessed in a clinical trial using a combination of soy and hop extracts in 78 menopausal women over a duration of 12 weeks.¹³ At the end of the study these somatic symptoms decreased significantly compared to the group who did not receive the combination ($p<0.05$). Moreover, measurements of urine N-telopeptide – a biomarker that measures the rate of bone turnover – in participants over 50 years in the treatment group showed a reduced increase of the biomarker possibly indicating an early antiresorptive efficacy on postmenopausal women's bones.

HOP EXTRACTS AND OSTEOPOROSIS

Osteoporosis is another unfavorable condition associated with menopause and is also the target of women seeking phytotherapy or food supplements to prevent its occurrence. In contrast to most other phytoestrogens that

have been investigated for the treatment of menopause-related osteoporosis with disappointing results, 8-PN from hop showed more favorable outcomes due to its preferential binding to ER β , which is predominant in bone tissue.⁸ Although the potential of 8-PN to prevent osteoporosis has been assessed using in vitro and in vivo models, unfortunately, no clinical trials in humans have yet been conducted.

In vivo studies have evaluated the ability of 8-PN to promote differentiation of osteoblasts.

8-PN showed a stronger capability to induce the expression of osteoprotegerin (OPG) – an osteoclastogenesis inhibitor – and to increase levels of osteoblast differentiation markers in cultured rat osteoblasts when compared to naringenin, which is another flavanone.¹⁴ Moreover, in rabbit bone marrow cells, 8-PN inhibited the formation and induced apoptosis of osteoclasts to a greater extent than naringenin, confirming the essential role of the prenyl group of 8-PN in bone protective activities. As with vasomotor symptoms, the effects of 8-PN on bone metabolism were shown to be mediated by the ER β signaling pathway, but the intensities of responses in osteoblast and osteoclast cell lines were weaker in comparison with the effect of 17 β -estradiol, but stronger than in the case of genistein and daidzein.¹⁵

Moreover, in an animal in vivo study using mice osteoblastic cell line MC3T3-E1, 8-PN inhibited the expression of receptor activator of nuclear factor- κ B ligand (RANKL), and led to increased expression of OPG. This effect was also facilitated by ER α and was stronger than genistein and daidzein but again weaker than estradiol.¹⁶

The experimental in vitro and in vivo studies results indicate that hop and 8-PN could play a positive role in the prevention or treatment of osteoporosis and improve mineral bone density, provided more trials are performed in humans.

CONCLUSION

In conclusion, the use of alternative and complementary therapies during menopause has somewhat expanded despite the many re-appraisals of the benefit-risk ratio of large outcome HRT studies, like the WHI or HERS, showing better safety than originally thought and even positive effect of HRT use in younger women or in early postmenopause on the cardiovascular system and all-cause mortality. Nonetheless, the public opinion on HRT has not changed yet, leading to important negative consequences for women's health and quality of life and a shift towards alternative medicine to overcome this issue.¹⁷ The available clinical data on hop extract use for the alleviation of menopausal symptoms show that these products help improve the many climacteric symptoms of early menopause and indicate an absence of side-effects in women using those extracts during the assessment period of time. Yet, more clinical trials are needed to evaluate the long-term impact of phytoestrogens and hop extracts on women's health despite the long safety history of beer consumption.

References can be accessed on
www.thesynapse.net