

Hop Extracts and Hop Substances in Treatment of Menopausal Complaints

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- *Humulus lupulus* L.
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- safety

Abstract

Hop extract is a long used medicinal product and, regarding hormonal activities, in 1999 a number of prenylflavanones have been identified as its major constituents with 8-prenylnaringenin (8-PN) being the main active estrogenic compound. There have been several *in vivo* studies performed that demonstrate the potential of hop extract and the single compound 8-PN to alleviate climacteric symptoms like osteoporosis, vasomotoric complaints, and sexual motivation. On the other hand,

only a few clinical studies have been performed so far, and these mainly focused on menopausal discomforts, especially hot flushes, yielding rather inconclusive results. Despite preferentially activating estrogen receptor α , 8-PN is only slightly uterotrophic, but it also elucidates estrogenic effects on the mammary gland. In conclusion, although hop extract and especially 8-PN are promising candidates as a relief for climacteric symptoms, data on the safety and efficacy is still scarce.

Hop Secondary Metabolites

Humulus lupulus L. (hop) (Cannabaceae) is well-known for the usage of female inflorescences such as bitterness, preservative, and a flavoring agent in beer brewing, but at the same time it has a long history as a medicinal herb. Hop baths have been recommended to alleviate gynecological disorders with reference to the frequently observed menstrual disorders in female hop-pickers suggesting an estrogenic mode of action [1]. Its importance as a traditional medicinal herb has also been recognized by the European Medicines Agency EMA that has published a monograph about its use and safety [2]. Among terpenes and bitter acids, a number of prenylflavanoids secreted by lupulin glands have been identified in the strobiles. In 1999, the investigation of an estrogenically active fraction containing as the main compound xanthohumol (XH; 0.1–1% in dry hops) but also isoxanthohumol (IX), 6-prenylnaringenin (6-PN), and 8-prenylnaringenin (8-PN; 100 mg/kg dry hops) (• Fig. 1) led to the discovery of 8-PN as the major active constituent, turning out to be the most potent phytoestrogen known to date [1,3–8]. Prior to this, 8-PN or 8-isopentenylnaringenin, as it was originally called by its discoverers [9], had already been isolated

from the Thai tree *Anaxagorea luzonensis* A. Gray (Annonaceae) [9]. In addition, 8-PN is a constituent in *Sophora tomentosa* L. (Fabaceae) and in *Marshallia grandiflora* Beadle & F.E. Boynt (Asteraceae) [10,11]. In contrast to most other known phytoestrogens, 8-PN exhibits a twofold higher preference for estrogen receptor α (ER α) than for ER β [6].

The majority of the chalcones found in *H. lupulus* easily isomerize to their corresponding flavanones as they possess free 2'-OH groups. The conversion of xanthohumol leads solely to isoxanthohumol, whereas desmethylxanthohumol (DMX) isomerizes to 8-prenylnaringenin or 6-prenylnaringenin, thus DMX is the major source of most known hop flavonoids [12,13]. The conversion of XH can be induced by thermal treatment or by an increased pH value, hence IX is the most abundant prenylflavanone found in beer [14,15]. The metabolic activation of the weakly estrogenic IX to the strong ER agonist 8-PN by the gut flora increases estrogenic potency of hops preparations [16–19]. The achieved levels of 8-PN and other metabolites show high interindividual variability justifying the separation into poor, moderate, and high producers [17,19].

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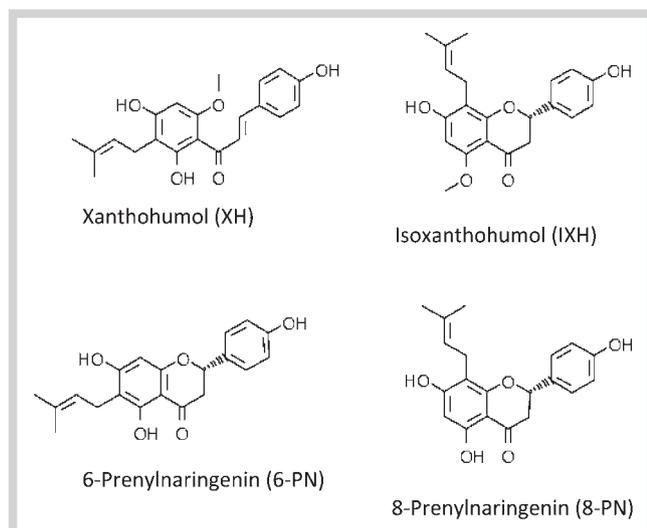


Fig. 1 Prenylflavanones contained in hops and hop extracts.

Experimental Data

Effectiveness of hop flavanones in preventing osteoporosis

One of the most prominent physiological effects of the hormonal decline associated with menopause is the loss of bone mass ultimately leading to osteoporosis. It has been shown that in addition to hop-derived rho iso-alpha acids [20,21], all major hop flavanones 8-PN, 6-PN, XH, and IXH possess E2-like effects on osteogenic differentiation *in vitro* [22].

Concerning the *in vivo* situation, one of the first publications on 8-PN elucidated its effect on bone mineral density (BMD) of ovariectomized (ovx) rats following 14 days of treatment. It showed that a dose of 30 mg/kg body weight/day starting at the second day after ovx resulted in an even higher BMD than that observed in sham-operated untreated animals, while untreated ovx animals had reduced BMD. Hümpel et al. demonstrated a dose-dependent inhibition of ovx-induced bone loss in rats following s.c. treatment with 18 mg/kg 8-PN over a period of 28 days [23]. Since hop contains about equal amounts of both 2S(-) and 2R(+) 8-PN enantiomers, the second part of this study compared effects of the racemic mixture to those of 2S(-)-8-PN alone. No significant difference was observed indicating that both enantiomers are nearly equally potent at preventing menopause-induced bone loss. More recent work also suggests improved biomechanical properties due to increased bmp when 8-PN is taken up orally as a food content [24]. Interestingly, in this study the effect of 8-PN on these parameters was much larger than that of genistein or resveratrol.

Alleviation of hot flashes by 8-PN

Vasomotor climacteric complaints like hot flashes and sweating are thought to be caused by a small increase in core body temperature in conjunction with a narrowing of the thermoneutral zone that describes the range of the body temperature in which no shivering or sweating occurs [25]. These processes are regulated by the thermoregulatory nucleus in the anterior hypothalamus. The only common experimental model to investigate the potency of a drug to alleviate hot flashes is the measurement of differences in tail skin temperature (TST) of ovx rats. While intact rats

display a marked decrease of TST during the active phase, this response is lost in ovx animals. This can be reverted by treatment with either estrogens or the α -adrenoceptor agonist clonidine which is widely used for the treatment of hot flashes in patients for whom hormone replacement therapy is contraindicated, suggesting that both irregularities in thermoregulation are triggered by a similar mechanism [26]. Using this *in vivo* model, 8-PN has been shown to restore normal TST after 5 days of treatment with the relatively low dose of 400 μ g/kg per day s.c. as well as after oral treatment with 7.5 mg/animal/day, indicating that 8-PN may indeed be able to alleviate climacteric hot flashes [27].

Influence on sexual motivation

Although difficult to differentiate from general age-related effects, sexual motivation seems to decrease due to menopause [28]. One possibility to test sexual motivation in animals is the so-called partner preference test [29]. According to Di Viesta et al., oral treatment of female rats with hop extract dose-dependently decreases the number and cumulative time of visits to a female stimulus animal although the number and time of visits to a male stimulus animal is increased slightly. In addition, perceptive behavior was increased dose-dependently in general, but lordosis was unaffected [30]. This hints at the potency of this extract to improve at least some aspects of sexual motivation. On the other hand pure hop secondary metabolites have not been tested so far.

Clinical Data

Clinical data are essential to assess the effectiveness as well as the safety of hop extracts and 8-PN for the treatment of menopausal discomforts.

One small clinical trial assessed pharmacokinetics, endocrine effects, and tolerability of a single dose of 50, 250, or 750 mg 8-PN in healthy postmenopausal women. It demonstrated that 8-PN is quickly and completely resorbed in the human intestine and that relevant plasma levels are achieved. This was inferred from a decrease of LH levels, an effect assumed to be necessary for the successful treatment of menopausal symptoms [31].

For the first prospective clinical study assessing the effectiveness of a hop extract against climacteric complaints, 67 women between 45 and 60 years of age were treated for 12 weeks with capsules containing either placebo or hop extract standardized to a dose of 100 μ g/day or 250 μ g/day 8-PN, identical to that contained in the food supplement MenoHop. Results show that hop extract may be somewhat effective in treating menopausal discomforts especially against hot flushes, but no clear dose-response correlation could be demonstrated [32].

In a subsequent crossover pilot study by the same group, the effectiveness of hop extract as a drug to relieve menopausal complaints was tested in more detail. And although the number of participants was very low, the outcome also showed a slight improvement of menopause-related symptoms [33]. Interestingly, both hop extract and placebo treatment led to an improvement after eight weeks of treatment, but the subsequent treatment swap led to a further improvement only in the active-treatment-after-placebo group, while the women in the placebo-after-active-treatment group experienced a slight regression of all outcome measures.

Another study assessed the efficacy and safety of vaginal application of a gel containing hop extract among others in postmeno-

pausal women with urogenital atrophy. Unfortunately, this study was noncontrolled, making it hard to draw solid conclusions [34]. Taken together, evidence for the effectiveness of hop extracts from clinical studies is still very weak. The number of participants in these studies was very low. In addition, the outcome was inevitably based on questionnaire data. These are subjective, and in the case of the Kupperman index, outdated, incomplete and include an arbitrary weighting of the queried symptoms [35]. No clinical information is available on the effects of hop extracts on factors associated with osteoporosis even though the effects of 8-PN on bone are among the more pronounced in cell culture as well as in animal experiments, and there have been no trials conducted so far using pure 8-PN instead of hop extract.

In contrast to classical hormone therapy, for which there is a plethora of prospective and retrospective studies with very large patient numbers [36–41], there is very little information on the safety of hop extracts or 8-PN treatment. It is known that 8-PN is an ER α agonist [42], and proliferative, cancer-promoting effects of estrogens are predominantly mediated by this ER subtype. Uterotrophic assays demonstrate only a mild effect of 8-PN on the uterus wet weight [7, 8], but evidence for long-term safety of hop extracts and 8-PN in particular is very weak except for a 90-day feeding experiment with ovariectomized rats where 8-PN affected uterine wet weight as well as uterine and mammary histology similar to E2, albeit much weaker [43]. In addition, *in silico* analysis of hop extract constituents identified a number of substances that are potentially hepatotoxic [44].

Conclusion

It has been shown that the soy constituent genistein, which is by far the most thoroughly investigated phytoestrogen, is not a good substitute for classical HT, since its effectiveness is dependent on lifelong exposure, but the studies reviewed here indicate that hop extracts may be more promising. While the estrogenicity of the main constituent 8-PN is well established [1, 3–5, 8, 45], the *in vitro* and *in vivo* experimental data on the effectiveness of hop extracts on climacteric symptoms is so far limited to osteoporosis, hot flashes, and to some degree sexual motivation. There is no high quality clinical data on the effectiveness and safety of hop extracts or 8-PN. An even less characterized alternative to 8-PN may be the structurally very similar flavanone 6-(1,1-dimethylallyl)naringenin which has been isolated from the African tree *Monotes engleri*. While this compound is also a potent ER agonist, it does not possess selectivity for ER α (unpublished data) and appears not to be uterotrophic [8]. This has to be seen as an advantage with regard to safety as tumor promotion should be a smaller concern with this substance.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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