Health Effects of 8-Prenylnaringenin

Subjects: Others

Contributor: Catherine Bennetau-Pelissero

8-Prenylnaringenin is a natural compound biosynthesised in the lupulin glands of the hop inflorescences. It is the substance with the highest estrogenic activity known so far in the plant kingdom. As estrogens have many targets in animals and humans, the health effects of 8-prenylnaringenin can be either beneficial or adverse depending on the physiological status of the consumers.

Keywords: 8-Prenylnaringenin

1. Introduction

- Human exposure

8-Prenylnaringenin, the most potent phytoestrogen known so far, is exclusively present for human consumers in hoppy beers. 8-prenylnaringenin and its precursor in human: isoxanthohumol are also present in hop extracts used in dietary supplements for menopausal symptoms [1]. Currently, the Belgium food safety Agency authorized hop extracts in food supplement only if their content in 8-prenylnaringenin and isoxanthohumol does not lead to an exposure to 8-prenylnaringenin greater than 400 µg/day for an adult [2]. According to Stevens *et al.* [3], 8-prenylnaringenin can be present in beer from 0.001 up to 0.069 mg/L in lager and stout, respectively, besides, isoxanthohumol can be converted into 8-prenylnaringenin and can be present from 0.3 up to 2.1 mg/L in Am. Hefeweizen and Strong ale, respectively. 8-Prenylnaringenin bioavailability has been reported in humans in [4] and in [5]. T*max* for 8-prenylnaringenin ranges between 1 and 2 hours in [4] based on an ingestion of 500 mg of 8-prenylnaringenin. Moreover, the urine recovery showed that the absorption rate ranges between 1.2 and 1.6%. In addition, in [5], where more dietary doses were used (0.25 mg 8-prenylnaringenin, 1.30 mg 6-prenylnaringenin, 0.80 mg isoxanthohumol, and 21.3 mg xanthohumol) T*max* occurred at 5.3 ± 4.5 hours for 8-prenylnaringenin and the percentage recovered in urine during the first 24 hours was found to be 0.693 ± 0.597%. Therefore, although 8-prenylnaringenin is the most active phytoestrogen known so far *in vitro*, its bioavailability and dietary levels of exposure are low. In addition, the low T*max* prevents from reaching a steady-state level in normal conditions of beer or food supplement consumption. However, isoxanthohumol can be converted into 8-prenyl-naringenin in people harboring the competent microflora. According to [6], the conversion rate of isoxanthohumol into 8-prenylnaringenin can vary from 0% to 46%. Currently, the proportion of 8-prenylnaringenin producers is insufficiently documented. Finally, according to [7], 8-prenylnaringenin and isoxanthohumol can act synergistically at a nanomolar range with estrogenic endocrine disruptors like pesticides. These synergistic effects were obtained using physiological plausible concentrations.

- Blood concentrations in humans

Considering 8-prenylnaringenin, serum concentrations were cited in [5] while volunteers were on a classical food supplementation. The data were obtained after a single administration of 250 µg of 8-prenylnaringenin in a hop extract. Therefore, the situation represented neither a chronic exposure nor a steady-state level. Nevertheless, the 8-prenylnaringenin serum concentration reached 1.4 ± 0.3 ng/mL which represent 4.12 nM. Therefore, when *in vitro* effects are screened, the relevant dose should be less than 0.01µM. This would concern circulating forms *i.e.* glucurono- or sulfo-conjugates of 8-prenylnaringenin.

2. Beneficial Effects

2.1. Hormonal Effects

2.1.1. Menopausal symptoms

Among all phytoestrogens health effects that were studied so far in humans, menopausal symptoms are those most documented. Currently, the market of food supplements offers preparations based on soy, clover, alfalfa, kudzu, linseed and hop. Other plants are used for menopausal symptoms including black cohosh, chasteberry or yam but their action modes are not strictly estrogenic. Although effects are reported and confirmed by meta-analyses, the effects of phytoestrogens on menopausal symptoms are still debated. The reasons are: a great interindividual variability, different effects according to the peri- or post-menopausal status, strong placebo effects and studies based on self-declarations.

Hop extracts have been shown to be active on vasomotor symptoms, for instance in [1]. This Randomised Control Trial (RCT) involved 120 menopausal women and assessed the Greene score and the number of hot flashes in treated women compared to placebo. The differences between the groups were significant after 4, 8 and 12 weeks of treatment. The hop tablets used contained 500 mg of hop extract with 100 µg of the active ingredient *i.e*. 8-prenylnaringenin. Although hop extracts are currently offered as food supplements for menopausal symptoms, few RCT were published so far.

2.1.2. Bone health

In rat, it was shown that hop extracts standardized in 8-prenylnaringenin and administered orally could prevent bone losses without action on rat uterus [8]. The efficient dose of hop extract was 60 mg/kg/bodyweight, and the serum levels of potential estrogens or precursors were: 8-prenylnaringenin: 0.25mg/kg bodyweight/day; 6-prenylnaringenin: 1.31 mg/kg bodyweight/day; isoxanthohumol: 0.81 mg/kg bodyweight/day. The serum levels in treated rats were: 26.7 ± 16.9 nM, 2.9 ± 1.4 nM and 5.8 ± 5.6 nM of 8-prenylnaringenin, 6-prenylnaringenin and isoxanthohumol, respectively. There is no data in humans.

2.1.3. Estrogen responsive tissues

There is hardly any data on hop phytoestrogens and breast cancer. As far as we know, the only existing data were given by Boucher and co-workers [9] who stated that the use of dietary supplements based on hop did not significantly induce breast cancer (AOR = 1.14; 95% CI = 0.36–3.56). However, the origin of these data was not clearly mentioned. In addition to that, although hop extracts are used in food supplements with the claim: “breast enhancing” no serious clinical study has ever been published on such an effect.

2.2. Metabolic Beneficial Effects

2.2.1. Effect on cholesterol

No data were found on the potential effect of 8-prenylnaringenin on cholesterol.

2.2.2. Effect on metabolic syndrome

Few data exist on regulation of glucose tolerance by prenyl-flavonoids. The only study found [10] was performed in obese mice and included xanthohumol, one precursor of 8-prenylnaringenin. This research showed that the prenylflavanones tested, which were not estrogenic, improved peripheral glucose metabolism in High Fat Diet-fed mice. However, there are no data so far on the effect of 8-prenylnaringenin itself on metabolic syndrome neither in animals nor humans.

2.2.3. Effects on diabetes

Several data exist on the reduction of diabetes features in mice by xanthohumol and 8-prenylnaringenin [11] and previous works [12]. However, in these studies, the dosage used *i.e.* 10 mg/L in drinking water of young C57 Black-6 mice probably exposed animals to 10 µg of 8- prenylnaringenin which is enough to induce an uterotrophy. However, none of the study investigated this aspect since all studies were performed on male mice. However, although the anti-diabetes effect is possible, the estrogenic effect on male reproductive features should have been investigated.

3. Adverse Effects

Based on the discovery of phytoestrogens, here the reproductive issues will be carefully scrutinized. However, because isoflavones are also known to interact with the thyroid function, this issue will be addressed also for 8-prenylnaringenin which is included in the phytoestrogen familly. In addition, in 1977, Farnsworth and co-workers, reported a large list of plants that were long used in Western countries as anti-fertility agents [6][7]. Hop is included in this list and sustain the estrogenic activity of 8-prenylnaringenin and its precursors.

3.1 Hormonal Based Effects

3.1.1. Pituitary interactions

Estrogens are known to regulate pituitary reproductive hormones, namely Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH). Such an effect is due to the regulation of the hypothalamic Gonadotrophin Releasing Hormone (GnRH) [13]. Depending on the cycle period, estradiol can either stimulate or repress pituitary hormone release. Using this property, contraceptive drugs have been developed essentially based on the synthetic ethynyl-estradiol which pharmacokinetic is longer than that of estradiol conferring it a higher potency. Therefore, expecting an effect of phytoestrogens on pituitary hormones release seems sensible. If such an effect is recorded it should induce menstrual cycle impairment and steroid synthesis modifications. Doing that phytoestrogens can act as endocrine disruptors and affect male and female fertility. As will be seen below, such effects are sometimes recorded but other studies failed to identify any endocrine disruption. This may be due to low dosages of phytoestrogenic substances, to short treatments or too few tested subjects.

As far as 8-prenylnaringenin is concerned, it is known that the estrogenic effect of hop inflorescences was first discovered in hop-working-women who used to lick their fingers while picking up the hop buds [14]. As a consequence of this high 8-prenylnaringenin exposure, their menstrual cycles were disturbed. In rat, 8-prenylnaringenin was shown to modulate both FSH and LH release [15]. More precisely, 8-prenylnaringenin was tested at 2 doses (6.8 and 68.4 mg/kg bodyweight) in rat parallelly to 17b-estradiol-3-benzoate (0.17 and 0.7 mg/kg bodyweight). Both doses of estradiol and the highest dose of 8-prenylnaringenin decreased serum LH and FSH, and increased serum prolactin levels, uterine weight, and progesterone receptor mRNA transcripts. In the anterior pituitary, ERb and GnRH receptor transcripts were reduced under both estradiol doses and the highest 8-prenylnaringenin dose. The mRNA concentrations of the LHa and -b subunits in the pituitary were suppressed by both estrogen treatments. These results showed that 8-prenylnaringenin had very similar though milder effects than estradiol, on the parameters tested. However, the effective dose were high and can only correspond to the use of dietary supplements for breast enhancement. Finally, in [16] it was shown that 750 mg of 8-prenylnaringenin was able to decrease LH serum concentration by 16.7% (95% confidence interval 0.5, 30.2) in postmenopausal women. This dose was high considering that a 50% decrease is obtained in postmenopausal women using 0.3 mg/day of ethynyl-estradiol [17]. The poor bioavailability of 8-prenylnaringenin explains this poor *in vivo* efficacy.

3.2.2. Estrogen based toxic effects

In humans, there are no rigorous studies showing an effect of 8-prenylnaringenin on reproduction. 8-prenylnaringenin is claimed by dietary supplement manufacturers to have breast enlargement properties. However, no scientific report exists so far documenting such an effect in women. In addition, the lactogenic compounds in beer are most probably water soluble beta-glucans that stimulate the pituitary secretion of prolactin [18]. In [8] where a hop extract was orally administered to rats, no effect was recorded on the uterus for a dose of 2.37 mg/kg bodyweight/day of 8-prenylnaringenin and precursors isoxanthohumol and 6-prenylnaringenin.

3.2.3. Thyroid based toxic effects

No published data were retrieved on 8-prenylnaringenin and thyroid.

4. Conclusions

8-Prenylnaringenin is considered as an active compound potentially usable in drugs for menopausal women. Nevertheless its estrogenic activity leads to the application of the caution principle in women at risk or with estrogen-dependent diseases. This includes estrogen dependent breast cancer.

References

1. Aghamiri, V.; Mirghafourvand, M.; Charandabi, M.A.S; Nazemiyeh H. The effect of Hop (Humulus lupulus L.) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial. Complement Ther Clin Pract. 2016; 23, 130-135. doi: 10.1016/j.ctcp.2015.05.001.
2. ARRETE ROYAL du 29 AOUT 1997. relatif à la fabrication et au commerce de denrées alimentaires composées ou contenant des plantes ou préparations de plantes (M.B. 21.XI.1997)
3. Stevens, J.F.; Taylor, A.W.; Deinzer, M.L. Quantitative analysis of xanthohumol and related prenylflavonoids in hops and beer by liquid chromatography-tandem mass spectrometry. J Chromatogr A. 1999, 32(1-2), 97-107. doi: 10.1016/s0021-9673(98)01001-2.
4. Calvo-Castro, L.A.; Burkard, M.; Sus, N.; et al. The Oral Bioavailability of 8-Prenylnaringenin from Hops (Humulus Lupulus L.) in Healthy Women and Men is Significantly Higher than that of its Positional Isomer 6-Prenylnaringenin in a Randomized Crossover Trial. Mol Nutr Food Res. 2018, 62(7), e1700838. doi: 10.1002/mnfr.201700838.

5. van Breemen, R.B.; Yuan, Y.; Banuvar, S.; et al. Pharmacokinetics of prenylated hop phenols in women following oral a dministration of a standardized extract of hops. Mol Nutr Food Res. 2014, 58(10), 1962-1969. doi: 10.1002/mnfr.20140 0245.
6. Possemiers, S.; Heyerick, A.; Robbens, V.; De Keukeleire, D.; Verstraete, W. Activation of proestrogens from hops (Hu mulus lupulus L.) by intestinal microbiota; conversion of isoxanthohumol into 8-prenylnaringenin. J Agric Food Chem. 2 005, 53(16), 6281-6288. doi: 10.1021/jf0509714.
7. Aichinger, G.; Bliem, G.; Marko, D. Systemically Achievable Doses of Beer Flavonoids Induce Estrogenicity in Human E ndometrial Cells and Cause Synergistic Effects With Selected Pesticides. Front Nutr. 2021, 8, 691872. doi: 10.3389/fnu t.2021.691872.
8. Keiler, A.M.; Helle, J.; Bader, M.I.; et al. A standardized Humulus lupulus (L.) ethanol extract partially prevents ovariecto my-induced bone loss in the rat without induction of adverse effects in the uterus. . Phytomedicine. 2017, 34, 50-58. do i: 10.1016/j.phymed.2017.08.001.
9. Boucher, B.A.; Cotterchio, M.; Anderson, L.N.; Nancy Kreiger, N.; Kirsh, V.A.; Thompson, L.U. Use of Isoflavone supple ments is associated with reduced postmenopausal breast cancer risk. Int. J. Cancer 2013, 132, 1439-1450. doi: 10.100 2/ijc.27769
10. Miranda, C. L.; Johnson, L.A.; de Montgolfier, O.; et al.; Non-estrogenic Xanthohumol Derivatives Mitigate Insulin Resis tance and Cognitive Impairment in High-Fat Diet-induced Obese Mice. Sci Rep. 2018, 8(1), 613. doi: 10.1038/s41598-0 17-18992-6.
11. Luís, C.; Costa, R.; Rodrigues, I.; et al. Xanthohumol and 8-prenylnaringenin reduce type 2 diabetes-associated oxidati ve stress by downregulating galectin-3. Porto Biomed J. 2018,4(1), e23. doi: 10.1016/j.pbj.0000000000000023.
12. Park, S.; Sim, K.S.; Hwangbo, Y.; Park, S.J.; Kim, Y.J.; Kim, J.H. Naringenin and Phytoestrogen 8-Prenylnaringenin Pro tect against Islet Dysfunction and Inhibit Apoptotic Signaling in Insulin-Deficient Diabetic Mice. Molecules. 2022, 27(13), 4227. doi: 10.3390/molecules27134227.
13. Nedresky, D.; Singh, G. Physiology, Luteinizing Hormone. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2 022.
14. Milligan, S.R. Chapter 72 - Reproductive and Estrogenic Effects of 8-Prenylnaringenin in Hops. In Beer in Health and D isease Prevention 2009, Pages 711-723. doi: 10.1016/B978-0-12-373891-2.00072-9
15. Christoffel, J.; Rimoldi, G.; Wuttke, W. Effects of 8-prenylnaringenin on the hypothalamo-pituitary-uterine axis in rats aft er 3-month treatment. J Endocrinol. 2006, 188(3), 397-405. doi: 10.1677/joe.1.06384.
16. Rad, M.; Hümpel, M.; Schaefer, O.; Schoemaker, R.C.; Schleuning, W.D.; Cohen, A.F.; Burggraaf, J. Pharmacokinetics and systemic endocrine effects of the phyto-oestrogen 8-prenylnaringenin after single oral doses to postmenopausal w omen. Br J Clin Pharmacol. 2006, 62(3), 288-296. doi: 10.1111/j.1365-2125.2006.02656.x.
17. Odell, W.D.; Ross, G.T.; Rayford, P.L. Radioimmunoassay for Luteinizing Hormone in Human plasma or Serum: Physiol ogical Studies J Clin Invest. 1967, 46(2), 248-255. doi: 10.1172/JCI105527.
18. Sawagado, L.; Houdebine, L.M. Identification of the lactogenic compound present in beer. Ann Biol Clin (Paris). 1988, 4 6(2), 129-134.