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Review

Herbal preparations for the menopause: Beyond isoflavones and black cohosh

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ABSTRACT

Complementary and alternative medicines (CAM) such as isoflavones and black cohosh are commonly used to deal with menopausal symptoms, but benefit a limited proportion of women. The aim of this minireview is to summarize the evidence of the efficacy and safety of other herbal preparations. Randomized controlled trials (RCTs) find that the extracts of Mediterranean pine bark (Pycnogenol®), linseed, and *Lepididium meyenii* (Maca) reduce vasomotor symptoms. The results of RCTs of the hop flavonoid 8-*prenylnaringenin* are conflicting. Animal and human studies suggest that *Dioscorea villosa* (Wild yam),and Broccoli may protect against osteoporosis and breast and gynecological cancers but further evidence is required. Linseed may protect against breast cancer but the results are conflicting.

Contents

1. Introduction

The abrupt decrease of ovarian estrogen production at the menopause leads to vasomotor hot flashes, cognitive and emotional instability, sleep disturbance, urogenital atrophy and osteoporosis. Menopausal hormone therapy (MHT) with estradiol is the most effective treatment for menopausal complaints. However, many women prefer complementary or alternative remedies such as herbal preparations or nutraceuticals, which are perceived to be more natural than hormones and believed to be safer. This trend has increased after publications regarding increased breast cancer risk with combined estrogen/progestogen MHT. Soy extracts, containing the isoflavones diadzeïn and genisteïn [1] are effective against vasomotor complaints in some women [2]. Black cohosh (*Cimicifuga racemosa*) is commonly used, but concerns have been raised about possible liver toxicity [3,4].

This review aims at analyzing the evidence of possible effectiveness regarding menopausal symptoms and women's health of

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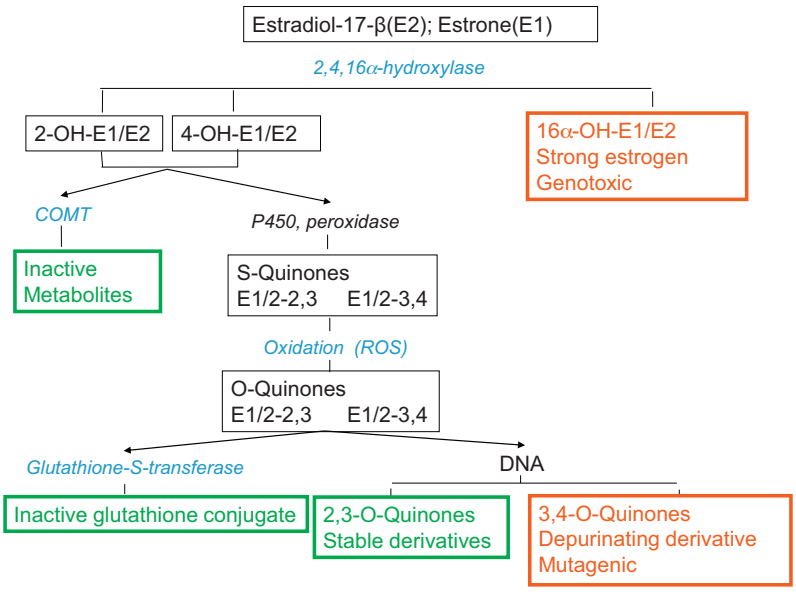

Fig. 1. Estradiol (E2) and estrone (E1) are converted by the hydroxylase-enzymes into watersoluble hydroxy-estradiol/estrone. There are 3 different hydroxylases that act in the positions 2 or 4, or 16α of the estradiol/estrone molecules. The 16-α-hydroxy-estradiol/estrone (16α-OH-E1/E2) displays a strong estrogenic action, inducing cell division. These hydroxy-estrogens are considered genotoxic and cancerogenic. The 2- and 4-hydroxy-estrogens (2-OH-E1/E2, 4-OH-E1/E2) can be converted by the enzyme cathechol-O-methyltransferase (COMT) into inactive metabolites. Or they may be converted by cytochrome P450 or peroxidase into their respective S-quinones (the 2,3 S-quinone for the 2-hydroxy E1/E2, and the 3,4 S-quinone for the 4-hydroxy E1/E2). These S-quinones are both oxidized by a non-enzymatic reaction under the influence of reactive oxygen species (ROS) into their corresponding O-quinones. Both O-quinones can either be inactivated by the enzyme glutathione-S-transferase into glutathione conjugates, which are devoid of estrogenic activity. Both these O-quinones can also bind to DNA. The binding of 2,3-O-quinone to DNA generates stable adducts which carry no risk. The binding of the 3,4-O-quinone of estradiol or estrone to DNA cause depurination of particular DNA-nucleotides. The resulting derivatives can induce strand breaks and mutations in the daughter cells that may be cancerogenic.

herbal preparations beyond soy isoflavones and black cohosh. It is based on publications from the last decade that were selected through PubMed.

1.1. Hop (*Humulus lupulus*)

Hop is a climbing plant of which the flower cones are an ingredient of many beers. The hop-flavonoid *8-prenylnaringenin* (8-PN) is a stronger estrogen than soy isoflavones. There is some evidence that 8-PN may be efficacious against vasomotor complaints, but two RCT's regarding menopausal symptoms come to conflicting conclusions. Heyerick et al. [5] recorded a statistically significant benefit of 8-PN during the first 12 weeks of intake, remaining present after 12 weeks, though not significantly better than that of placebo. In contrast, Erkkola et al. [6] did not find a significant advantage of 8-PN over placebo in the first 16 weeks of treatment, while after this time period the difference became significant, as a result of the decreasing effect of placebo.

Prenylnaringenin reduces the malignant transformation of breast cancer cells *in vitro*, and the production of the oncogenic estrogen-O-quinone (Fig. 1). However, the *in vivo* concentrations in breast tissue after daily oral intake of 100 μg per day may be insufficient to exert chemoprotection [7].

1.2. Vitex agnus-castus

The fruit-oil of *Vitex agnus-castus* binds to the estrogen receptor, inducing expression of estrogen-dependent genes, and it is commonly recommended for the treatment of premenstrual syndrome. This substance may exert dopaminergic action, but a favorable effect on menopausal symptoms has not been shown, even when combined with *Hypericum perforatum* (St John's wort) [8].

1.3. Dioscorea villosa

Diosgenin, the saponin extracted from the *Dioscorea villosa* (wild yam), does not bind to the human estrogen or progesterone receptor *in vitro* and cannot be converted in the human body to progesterone. Dioscorea could theoretically be given to women who have been treated for breast cancer, but safety data are required. When given as a cream, the effect on menopausal symptoms was not statistically significant compared to placebo [9]. Dioscorea was found to increase bone mineral density in ovariectomised rats [10], but studies in humans are lacking. A study where 22 women were given 390 g of yam per day for 30 days found that urinary concentrations of the genotoxic metabolite of estrogen, 16alpha-hydroxyestrone decreased significantly by 37% suggesting the potential to reduce breast cancer risk, but again clinical trial data are required [11] (Fig. 1).

1.4. Linseed or flaxseed (*Linum usitatissimum*)

Linseed extract is a major source of lignans that are metabolized by the intestinal flora into the weakly active estrogens enterodiol and enterolactone. In a RCT flaxseed meal and flaxseed extract were found to be significantly, albeit moderately, effective against menopausal symptoms [12]. Linseed extract increases the 2OH/16OH-estrogen ratio in urine to a greater extent than soy isoflavones [13]. It also inhibits intracellular aromatase activity, with less estradiol being produced from the precursors testosterone and dehydroepiandrosterone. Because of these effects, several publications have suggested that the intake of linseed extracts may protect against hormone-dependent breast cancer [14]. However, this could not be confirmed in a recent population study [15] and a prospective cohort study reported