

Hormones, herbal preparations and nutraceuticals for a better life after the menopause: part II

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ABSTRACT

Long-term estrogen replacement therapy with estrogen has benefits for many postmenopausal women. However, some women prefer non-steroidal substitution with herbal preparations. The effectivity against vasomotor symptoms has been evidenced for the extracts of pine bark, of linseed and of *Lepidium meyenii* (Maca), whereas there is controversy about the effectiveness of genistein-rich soy extract. The extracts of cruciferous vegetables such as Broccoli and of linseed induce changes in the metabolism of estrogens, and antioxidants may reverse altered epigenetic DNA methylation, possibly reducing the risk of breast cancer or its recurrence. Indirect evidence from the literature and from clinical trials supports that a nutraceutical composed of plant extracts, low-dose vitamins and minerals may improve the quality of life by delaying certain age-related diseases. On the basis of epidemiologic studies, physiopathological considerations and controlled prospective trials, it is suggested that transdermal substitution therapy with estradiol together with nutraceutical food supplementation may increase the number of quality-adjusted life years of postmenopausal women, but complementary, large-scale, prospective trials are still needed.

INTRODUCTION

There is no doubt that hormone replacement therapy (HRT) with estrogen is successful in alleviating menopausal symptoms and preventing menopause-associated health problems. A decade ago, the Women's Health Initiative (WHI) published an alarming report regarding possible health risks of HRT¹. Although this conclusion has repeatedly been questioned from the methodological point of view^{2–4} and overturned by the outcome of follow-up studies^{5,6}, many women request 'natural products' to alleviate their symptoms. Several herbal preparations and over-the-counter nutraceuticals have been recommended because of their phytoestrogenic and alleged health-promoting properties⁷.

The present article aims to quantify and critically review the benefits and undesired side-effects, the capacity to prevent cancer and to delay age-related diseases, and the potential health risks of commonly used phytoestrogens and of nutraceutical food supplementation.

MATERIALS AND METHODS

An extensive literature search was performed using the Pubmed system, Google scientific and derived articles. The papers were critically reviewed by analyzing the evidence of possible effectiveness regarding menopausal symptoms and women's health. Whenever possible, the number needed to treat (NNT) was calculated based on the result of controlled trials (see Part I⁸). This review examines present knowledge on the use of herbal preparations and of a specific nutraceutical.

RESULTS

Phytotherapy

Soy isoflavones

Soy extracts are the most commonly used plant extracts and contain the isoflavones genistein and daidzein. These bind to

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the human estrogen receptors, but their estrogenic effect is weak.

In meta-analyses^{9,10}, it was concluded that extracted soy isoflavones, particularly genistein, were effective in treating vasomotor complaints, although the results of some placebo-controlled trials are contradictory^{11,12}. However, no significant correlation was found between the intake of food rich in fibers and phytoestrogens, on the one hand, and the prevention of menopausal complaints, on the other hand¹³.

In a study of 150 postmenopausal women, we have evidenced important inter-individual variations regarding the intestinal uptake and metabolism of the soy isoflavones. The gut bacterial flora and dietary factors¹⁴ play an important role in the metabolism of the soy isoflavones into S-equol¹⁵. Women with an adequate intestinal bacterial flora, and who were able sufficiently to produce S-equol, were found to experience significant benefit from soy isoflavone intake with reduced vasomotor symptoms. Among women who were poor equol-producers, a favorable effect was detected when taking a fermented daidzein derivative rich in natural S-equol¹⁶. It remains to be proven whether the addition of certain probiotics to soy extract does enhance the intestinal metabolism to S-equol *in vivo*, similar to what was observed in the SHIME model (Simulator of the Gastrointestinal Microbial Ecosystem)¹⁷.

During the reproductive period of life, the isoflavones may reduce the risk of breast cancer, since they inhibit the binding of the more potent estrogen 17 α -estradiol to the estrogen receptor, thus exerting an effect that has been compared with that of pharmacological selective estrogen receptor modulators (SERMs)¹⁸. Protection against breast cancer has indeed been observed in Asian women¹⁹, and the protective effect of long-term soy isoflavone supplementation in the western population is claimed in some publications^{20,21} but rejected by others²². After menopause, the concentration of endogenously produced estrogens is extremely low, and the soy isoflavones exert an intrinsic estrogenic action. However, the long-term intake of extracted soy isoflavones did not increase the mammographic density²³.

Whether it is safe to give soy isoflavones to women who have been treated for estrogen-sensitive breast cancer remains a topic of debate^{21,24}. Contradictory results have been published regarding the concentration of genistein, daidzein and equol in breast tissue of women who had taken soy supplementation during 5 days. *In vitro* studies suggest that genistein may counteract the antiestrogenic effect of tamoxifen²⁵, but no such effect was observed *in vivo*²⁶.

Estradiol is converted by the enzymes cytochrome-oxidase in the liver, primarily into 2-hydroxy, 4-hydroxy-en and 16 α -hydroxy-estrogens (Figure 1). The 2-OH-estrogens exert virtually no hormonal effect. In contrast, the 16 α -OH-estrogens are highly estrogenic and are considered oncogenic, since they may increase the risk of estrogen-dependent breast cancer. Also, one of the oxidized metabolites of 4-OH-estrogens, namely the 3,4-O-quinone, can interact with DNA, inducing depurination and mutagenesis^{27,28}.

Endocrine-disrupting compounds, particularly man-made xeno-estrogens present in the environment, such as phthalates, alkylphenols, methylparabene, bisphenol-A, polychlorinated biphenyls, and certain pesticides influence the metabolic pathway of endogenous estrogens favoring the production of the oncogenic 16 α -OH estrogens²⁹. Several prospective controlled trials have shown soy isoflavones to correct this process by redirecting the pathway to the hormonally inactive 2-OH-estrogens. Also, in mice, genistein was shown to counteract the hypomethylating effect of bisphenol-A on metastable epialleles during development³⁰. Both the findings on estrogen metabolism and on epigenetic effects may explain the alleged protective effects of soy isoflavones against breast cancer.

There are data to sustain that soy intake may temporarily reduce or delay the occurrence of osteoporosis³¹, but controlled studies on the prevalence of bone fractures are lacking. The dosage and duration of consumption probably determine the alleged effect of soy consumption on cognition³². Though genistein induces epigenetic modifications that stabilize genes involved with colon carcinogenesis³³ and estrogen intake was shown to reduce age-related DNA-methylation in colon mucosa³⁴, the possible role of soy isoflavones in the prevention of colon cancer and its metastasis awaits confirmation³⁵.

Cimicifuga racemosa

Extracts of *Cimicifuga racemosa* ('black cohosh') are commonly recommended for the phyto-therapy of menopausal symptoms. Randomized, placebo-controlled trials have not revealed any statistically significant effect on vasomotor complaints compared to placebo³⁶. Recently, contradictory reports have been published regarding possible hepatotoxic damage in relation to the use of black cohosh^{37,38}. After having received a large number of case reports, the Medicines and Healthcare Products Regulatory Agency has obliged the distributors of black cohosh to include a warning that liver damage may occur, such as abnormal liver enzymes in blood, jaundice and hepatitis³⁹. In addition, black cohosh has been suspected to increase the risk of cardiovascular disease⁴⁰.

Vitex agnus-castus

The fruit-oil of the *Vitex agnus-castus* has been used in natural medicine for the treatment of the premenstrual syndrome. Its binding to the estrogen receptor is attributed to the presence of linoleic acid which induces certain estrogen-dependent genes. This substance seems to exert some dopaminergic action, but a favorable effect on menopausal symptoms could not be evidenced in a randomized, controlled trial, also when combined with the extract of *Hypericum perforatum* (St John's Wort)⁴¹.

Hopflavonoides

The most important flavonoid extracted from hop (*Humulus lupulus*) is 8-pregnylnaringenin (8-PN). *In vitro* this molecule

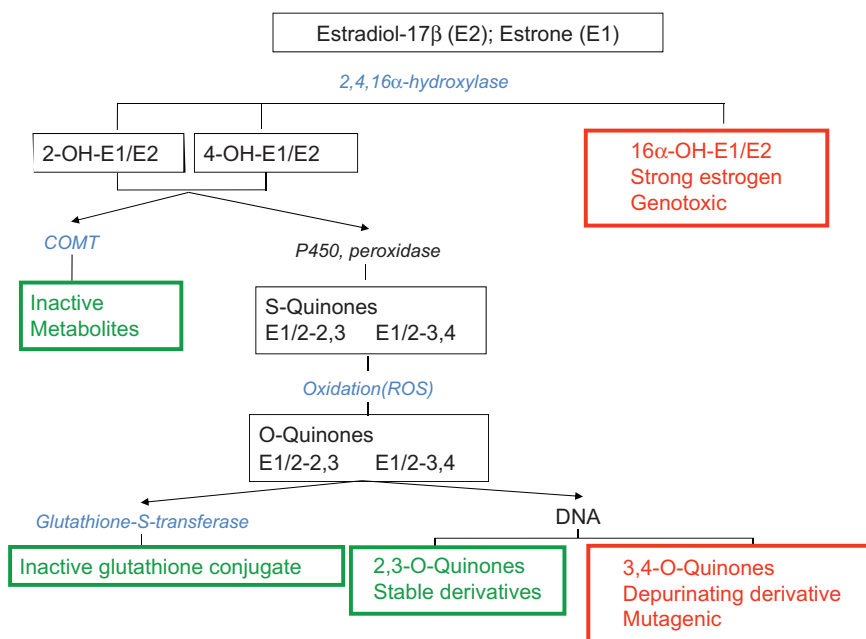


Figure 1 The hydroxylase iso-enzymes metabolize estradiol (E2) and estrone (E1) into water-soluble hydroxy-estradiol and hydroxy-estrone. There are three different *hydroxylases* that interact at either the position 2, or 4, or 16 α of the estradiol/estrone. The 16 α -hydroxy-estradiol/estrone (16 α -OH-E1/E2) exert a strong estrogenic action. They induce cell division and are genotoxic, hence are considered cancerogenic. The 2- and 4-hydroxy-estrogens (2-OH-E1/E2, 4-OH-E1/E2) can either be metabolized by the enzyme *Catechol-O-methyltransferase* (COMT) into inactive metabolites, or by *Cytochrome P450* or *peroxidase* being converted 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. The S-quinones are non-enzymatically oxidized by *reactive oxygen species* (ROS) into their respective O-quinones. Both these O-quinones can be inactivated by the enzyme *Glutathione-S-transferase* into inactive glutathione conjugates which are devoid of estrogenic effect. However, both O-quinones can also bind to DNA. The binding of the 2,3-O-quinone to DNA generates stable adducts that do not induce genetic risks. The binding of the 3,4-O-quinones of estradiol and estrone to DNA induces depurination of particular DNA-nucleotides. These derivatives can cause strand breaks of the DNA and mutations in the daughter cells after replication, which may be cancerogenic

has an up to 100-fold stronger estrogenic action than the soy isoflavones⁴². There is some evidence that 8-PN may be efficacious against vasomotor complaints. However, two randomized, controlled trials come to contradictory results. Indeed, Heyerick and colleagues⁴³ recorded a significant benefit of 8-PN during the first 12 weeks of intake. Though this benefit remained present after 12 weeks, it was not significantly better than that of placebo. In contrast, Erkkola and colleagues⁴⁴ 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.

In vitro 8-NP reduced the malignant transformation of MCF-10A cells and the production of the oncogenic estrogen-O-quinone⁴⁵. However, it is questionable whether the concentration of 8-PN in breast tissue, after the daily intake of 100 μg ⁴⁶, is sufficient to exert any local chemoprotective effect against breast cancer⁴⁷.

Dioscorea villosa

Diosgenin is the saponine extracted from the *Dioscorea villosa* (wild yam). We have shown that diosgenin does not

bind to the human estrogen receptor *in vitro*⁴⁸, and it cannot be converted into progesterone. Dioscorea may be given to women who have been treated for breast cancer. A significant favorable effect of Dioscorea extract on menopausal symptoms has been observed, but it seems to be rather weak⁴⁹. Dioscorea extract decreases the estrogen metabolism into the genotoxic metabolite 16 α -OH-estrone.

In animal experiments, diosgenin was found to exert an anti-osteoporotic effect by appositional growth to the long bones⁵⁰, possibly through the inhibition of osteoclast formation. However, studies on a possible bone-protecting effect in humans are lacking.

Linum usitatissimum

Linseed or flaxseed (*Linum usitatissimum*) extract is a rich source of lignans, which are converted into enterodiol and enterolacton by the gut bacteria. These lignans exert a weak estrogenic effect. Linseed extract was moderately effective on menopausal vasomotor symptoms⁵¹, and its effectiveness compared to placebo was confirmed in one randomized trial, but not in another trial⁵².

In a controlled, parallel-design trial in 46 postmenopausal women, linseed extract increased the 2-OH/16-OH-estrogen ratio significantly more effectively than the soy isoflavones⁵³. In addition, enterolacton inhibits the aromatase enzyme, so that less estradiol is produced intracellularly from the precursors testosterone and dehydroepiandrosterone⁵⁴. Several publications suggest that the intake of linseed extracts may protect against hormone-dependent breast cancer⁵⁵, but this could not be confirmed in a recent population study⁵⁶. Lignans were reported to increase the time of survival of a cohort of breast cancer patients⁵⁷. Also, dietary lignans may have the potential to protect against cardiovascular risk⁵⁸.

Pine bark extract

The extract of the bark of the (Mediterranean) pine tree is rich in polyphenols, namely anthocyanidins with antioxidant effect, and it reduces inflammatory reaction through the inhibition of the cyclo-oxygenase enzymes 1 and 2⁵⁹ and of the nuclear factor kappa B⁶⁰. In several randomized, double-blind trials, pine bark extract was found to significantly reduce vasomotor symptoms and to improve the quality of life of menopausal women⁶¹. Pine bark extract is a rich source of polyphenols⁶², the higher intake of which was found to be associated with a 46% decreased risk of atherosclerotic vascular disease⁶³ and to reduced overall mortality (odds ratio 0.63, 95% confidence interval 0.41–0.97) after an average of 4.8 years follow-up in 7447 participants of a parallel-group, randomized, multicenter, controlled trial⁶⁴. On the basis of the life-table survival curve published in this paper, it can be derived that the persons belonging to the highest quartile of polyphenol intake survived 1.5 years longer than those belonging to the group with the lowest intake⁶⁴.

Cruciferous vegetable

The extract of several plants of the *Brassica* species, including Broccoli, Brussels sprouts, cabbage and savoy, contains glycosylates which are hydrolyzed in the body into indol-3-carbinol and di-indolmethane. These constituents are under investigation in clinical trials for their chemoprotective effects against gynecological cancers⁶⁵. They activate the P450 enzyme and promote estrogen metabolism toward the 2-OH-estrogens⁶⁶. Also, Broccoli extract is an important source of sulforafane that has a demethylating effect, favorably influencing the epigenoma⁶⁷. Meta-analysis of epidemiologic studies concluded that the consumption of cruciferous vegetables was inversely associated with the risk of (breast) cancer⁶⁸. The extract contains phyloquinone, also called vitamin K1, which has been reported to reduce the risk of bone fractures in aging women and to slow the progression of coronary artery calcium deposits⁶⁹. Although Brassica extract does not reduce menopausal symptoms, the benefit of its moderate consumption is considered to outweigh the potential risks.

Lepidium meyenii

Lepidium meyenii, also called Maca, is another plant belonging to the cruciferous (*Brassica*) family and grows in the Peruvian Andes mountains. It is considered to be a phytoadaptogen which increases the production of the heat shock protein P 72, thus reducing the negative impact of stress⁷⁰ on protein conformation and cell death. *Lepidium meyenii* has been tested against menopausal symptoms and was found to reduce the Kupperman menopausal index and the Greene Climacteric Score in a controlled trial⁴⁹. Tolerability is excellent and no serious adverse effects have been noted.

Food supplementation and nutraceuticals

Nutraceuticals are over-the-counter food supplements composed of natural substances such as minerals, vitamins and herbal extracts. The amount of multivitamins may not significantly exceed the recommended daily intake, and the combination of substances with complementary antioxidant effects is expected to act in synergism because some are lipophilic (such as the tocopherols), others are hydrophilic (such as vitamin C), some act as reducing agents and others as oxygen-radical scavengers⁷¹. Neither vitamins nor nutritional food supplementation had immediate or long-term risk of adverse effects^{72,73}. Their role and importance have been acknowledged by the World Health Organization⁷⁴. Nutraceuticals may delay the effects of aging and this will cause substantial economic returns and improve public health⁷⁵.

The nutraceutical discussed below has been formulated specifically for menopausal women and aims at attenuating the signs and symptoms of the menopause and at preventing or delaying aging and the occurrence of age-related diseases as well as of certain cancers.

The nutraceutical food supplement is composed of the following constituents (Nutriphyt Ltd, Oostkamp, Belgium): Vitamin B6 0.5 mg; vitamin B9 100 µg; vitamin B12 1.5 µg; vitamin C 15 mg; vitamin E 15 mg; lipoic acid 25 mg; glutathione 7.5 mg; selenium methionine 10 mg (= 50 µg Se); co-enzyme Q10 7.5 mg; zinc glycinate 50 mg (= 10 mg Zn); phosphatidyl choline/serine 50 mg; Pycnogenol® 10 mg; *Lepidium meyenii* extract (root) 75 mg; Linum extract (seeds) 20 mg.

Low doses of several antioxidants are presumed to act in synergism, e.g. natural vitamin E is composed of the eight isomers of tocopherol and tocotrienol. It is a lipophilic scavenger and is regenerated by vitamin C, which is a hydrophilic reducing agent. Both vitamin E⁷⁶ and alpha lipoic acid, which is both lipo- and hydrophilic, may mitigate bone loss in osteopenic postmenopausal women⁷⁷, and the latter also exerts a neuroprotective effect⁷⁸. The anti-oxidant ubiquinone Q10 is active at the level of the mitochondria, improving energy production, and it may be beneficial in preventing coronary heart disease⁷⁹. Glutathione is known for its complementary detoxifying effect via glutathione-S-transferase and glutathione peroxidase. Thus, glutathione may facilitate the elimination of xeno-estrogens, and it favorably influences estrogen

metabolism (Figure 1). Selenium methionine acts as a protein antioxidant, and higher selenium levels have been associated with higher bone mineral density in population studies⁸⁰. Zinc is part of many enzymes playing a pivotal role in cell function. In association with multivitamin supplementation, long-term supplementation with zinc was found to protect women from developing breast cancer⁸¹.

The herbal preparations from *Lepidium meyenii* (Maca), pine bark, linseed, Broccoli, and *Dioscorea villosa* have been described above.

The nebulized extract of *Vinca minor* has been reported to increase blood circulation, glucose uptake, and metabolism of the brain. This extract, together with phosphatidyl serine/choline, which is incorporated in the outer cell membrane of Schwann cells, improves brain function⁸² by optimizing the composition of the axonemal myelin sheath⁸³.

The association of vitamins B6 (pyridoxin), B9 (folic acid), and B12 (cyanocobalamin) reduces the production of homocysteine⁸⁴ and DNA methylation, but there are contradictory reports regarding the protection against cognitive decline^{85,86} or vascular disease^{87,88}. Recently, it has been documented that the regular intake of these vitamins B prevents brain shrinkage and the resulting dementia among women with a high homocysteine concentration in blood⁸⁹. The association of vitamins B may also reduce the incidence of bone fractures.

It is generally recommended to complement nutrition with long-chain polyunsaturated fatty acids of the ω -3 group (docosahexaenoic acid or cervonic acid, DHA, and eicosapentaenoic acid, EPA) present in fish oil and krill oil. These fatty acids improve cell membrane fluidity and function, may possibly protect against cardiovascular diseases^{90,91}, reduce the risk of thromboembolism⁹², improve cognitive performance and the metabolic syndrome⁹³ and general health⁹⁴, and reduce total mortality⁹⁵, though perhaps not in patients suffering from diabetes.

Nutraceuticals and multivitamins may exert a chemoprotective effect against cancer through epigenetic mechanisms⁹⁶ as well as against certain age-related diseases⁹⁷, whilst being devoid of any toxic side-effects. In fact, a significant decrease by up to 12% of cancers, other than prostate cancer, was observed in a double-blind, prospective trial in general practitioners, after an average of 11.2 years' use of a low-dose multivitamin supplement⁹⁸ (NNT: 8.3). From published life-table curves^{64,98}, it can be calculated that between 1 and 1.5

quality-adjusted life years can be gained after 5–10 years' intake of polyvitamins or polyphenols.

It should be emphasized that the impeccable quality of food supplements must be carefully monitored. Also, certain food supplements containing high doses of artificial vitamins and analogs, such as alfa-tocopherol succinate⁹⁹, or ascorbic acid¹⁰⁰, or retinol^{101,102}, or pro-oxidant metals such as iron¹⁰³ have been documented not to cause any beneficial effects, and may even exert a negative influence on general health and increase mortality¹⁰⁴.

CONCLUSION

The best treatment of menopausal complaints, and to prevent osteoporosis, is with estradiol given via the transdermal route. Food supplements containing phytoestrogens from plant extracts improve vasomotor symptoms in between one- and two-thirds of women, but some controlled trials suggest that a similar effect is obtained with placebo. Women with equol-producing gut bacterial flora seem to benefit from soy isoflavones. Also, the extracts of *Lepidium meyenii*, of (Mediterranean) pine bark or linseed were proven effective. Whereas *Cimicifuga racemosa* (black cohosh) extract may be toxic for the liver, the extracts of hop, wild yam, *Dioscorea villosa*, pine bark, and soy are safe. Whether some of these extracts and lignanes from linseed can protect against breast cancer and osteoporosis remains to be firmly established.

The long-term intake of a judiciously composed nutraceutical containing low-dose vitamins, antioxidants, minerals and particular herbal preparations seems justified for older persons who take medication¹⁰⁵, or who consume an unbalanced diet¹⁰⁶, or who are exposed to environmental toxins. Recent reports suggest these nutraceuticals may delay age-related diseases¹⁰⁷, reduce mortality, and lower the risk of cancer. It is suggested for postmenopausal women to combine transdermal estrogen substitution with the regular intake of the nutraceutical, which should result in an increase of at least one quality-adjusted life-year.

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