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Phytotherapy for menopausal symptoms: recommendations of the Italian Menopause Society (SIM) and the Italian Society of Gynaecology for the Third Age (SIGiTE)

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ABSTRACT

Evidence on the efficacy of phythotherapic remedies for the treatment of menopausal symptoms were reviewed. Evidence of the literature were graded and level of reccomandation defined. A strenght A recommendation was given for isaproponol extract of *Cimicifuga recemosa* (systematic review and metanalysis). Strength B recommendation, due to some inconsistent findings or lower quality studies, was given to the use of soy isoflavones, genistein above 30 mg/day, equol containing product and pollen extract. Strength C reccomendation for very weak evidence of efficacy was given to resveratrol, hops, dioscorea, enotera. No evidence of efficacy on vasomotor symptoms was found for *Hyperycum perforatum*, matcha, ginseng, that find no place in the treatment of vasomotor symptoms.

SOMMARIO

Sono stati valutati gli studi sull'efficacia di rimedi fitotetrapici nel trattamento dei sintomi vasomotori. I livelli di evidenza sono stati definiti in base al tipo e numero di studi presenti e sulla base delle evidenze è stata formulate la forza delle raccomandazioni. Una raccomandazioe di tipo A è stata definita per l'estratto isopropilico della *Cimicifuga recemosa* (sulla base di review e meta-analisi). Una raccomandazione di tipo B, basata su alcuni dati inconsistenti o studi di più bassa qualità, è stata definita per l'uso degli isoflavoni della soia, genisteina a livelli superiori ai 30 mg/die, prodotti contenenti equolo, ed estratto di polline. Una raccomandazione di tipo C, dovuta ad evidenze molto deboli, è stata definita per l'uso del resveratrolo, del luppolo, della dioscorea o dell'olio di enotera. Nessuna evidenza di efficacia è stata trovata per l'*Hyperycum perforatum*, il matcha ed il ginseng che quindi non hanno nessun ruolo nella cura dei sintomi vasomotori della menopausa.

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Phytoestrogens; genistein; daidzein; equol; pollen extract; Cimicifuga racemosa; hot flush.

INTRODUCTION

The use of non-hormonal therapies and treatments for menopausal symptoms is becoming increasingly widespread in conventional healthcare settings, and there are numerous scientific publications dealing with complementary and alternative medicine (CAM). In particular, some CAM therapies are based on substances present in nature and derived from plants of various types in different concentrations and obtained via different extraction methods. Among these, nutraceuticals are chemicals of natural origin that are exploited for their therapeutic and pharmacological potential. For example, nutraceutical supplements and phytopharmaceuticals are often used for the treatment of menopausal vasomotor syndrome (MVS). MVS presents in more than 75% of women; typically, its symptoms last for 5-7 years, but many women present its symptoms for up to 10-15 years. Hormone replacement therapy (HRT) is the most effective treatment available for MVS symptoms, and is therefore the first-line choice. However, other therapeutic options are needed to treat those who are not candidates for HRT due to either contraindications, personal choice or individual preference. In fact, the majority of women would prefer non-hormonal treatments.
Due to the wide range of non-hormonal products available for the treatment of MVS, the Italian Menopause Society (SIM) and the Italian Society of Gynaecology for the Third Age (SIGiTE) think it is timely to emphasize several key aspects of these therapies further to ensuring medical integrity and patient safety. As physicians, we know that the medications we prescribe are substances with well-defined chemical structures whose pharmacokinetics are largely understood, and for which solid and reproducible data is available on their efficacy and safety. However, the purported benefits of phytopharmaceutical products, which are classified as non-hormonal treatments in alternative, complementary or supplementary medicine, are often only supported by small and less than rigorously conducted trials. Although extensive literature has been produced, it is difficult to give a clear and comprehensive assessment of the effectiveness of these products from a scientific perspective. This is mainly due to great differences and flaws in the design of the clinical trials conducted to date, which have often not been either randomized or controlled. Furthermore, efficacy testing in MVS must take into account the placebo effect and non-oestrogenic central nervous system (CNS) effects, as well as oestrogen-like mechanisms of action (selective oestrogen receptor modulator, or SERM, effects).
Neverthless, it is reassuring to know that to be marketed as such in Europe, nutraceutical substances have to undergo controls similar to those typical of drugs. It is good practice to check that such substances are EFSA (European Food Safety Authorities) certified, as they only grant marketing authorization after scientific assessment to demonstrate their efficacy and safety, as well as to verify the quality of raw materials and compliance with good manufacturing practice regulations.

PHYTOTHERAPIES AND NUTRACEUTICALS IN MENOPAUSE: CHARACTERISTICS AND EFFECTIVENESS

Phytoestrogens (isoflavones, lignans and coumestans)

Phytoestrogens are a large group of plant-derived non-steroidal phenol compounds with different chemical structures.

Mechanism of action
The oestrogen-like activities of phytoestrogens are linked to their ability to modulate estrogen receptors (ER). They have both agonistic and antagonistic effects, binding to both ERα and ERβ receptors, and activating ER-dependent gene transcription. Their binding affinity varies greatly from substance to substance, but is generally greater for ERα than ERβ. Functionally, their activity depends not only on their concentration, intestinal absorption and tissue selectivity, but also on individual concentrations of endogenous hormones and intestinal flora profile. Some of these molecules may also have antioxidant and/or antiproliferative activities, linked to their interactions with non-ER-dependent cellular mechanisms (1).
Phytoestrogens can be divided into three main groups:

1. Isoflavones: derived from soy, red clover and other roots, this group includes genistein and daidzein (which are the two compounds of greatest clinical interest), as well as glycitein, biochanin A, and formononetin.
2. Lignans: derived from flaxseeds and other seeds and foods, the lignans include enterodiol and enterolactone.

3. Coumestans: less relevant for the treatment of climacteric symptoms, include coumestrol and 4-methoxycoumestrol.

Genistein and daizein, the most promising active ingredients, are found in high concentrations in soybean and other soy products, but they are also contained in red clover and peanuts. Daizein, which is generally the most abundant substance in various isoflavones, has less intense oestrogen-like activity than genistein; its concentration differs depending on its source, *i.e.*, whether from soy seeds, whole bean or soy-derived proteins, which, in turn, can be extracted in various ways (2). The respective quantities also vary depending on the method of extraction and production of the individual pharmaceutical composition.

Isoflavones from Soybeans

The therapeutic efficacy of the different compounds containing soy extracts on the market changes in relation to several factors. First it depends on the concentrations of the active ingredients, which are essentially genistein and daidzein. These two active ingredients have different affinities for the oestrogen receptor – genistein is much more active than daidzein, and, in turn, the potency of genistein and daizein is 500 to 1000 times lower than that of oestradiol (3). The therapeutic efficacy of these active ingredients also depends very much on the ability of the individual to metabolize them at the intestinal level. They are absorbed in the form of glycosides (binding to a sugar molecule), and the resulting sugar is hydrolysed (and therefore eliminated) by beta-galactosidase intestinal bacteria. Daizein can be transformed into its active metabolite, equol, which, once absorbed, has oestrogenic action similar to that of genistein, being able to bind to both ERα and, with greater affinity, ERβ. However, only 25-30% of the adult female population of Western countries have the ability to metabolize daidzein by transforming it into equol (4). Indeed, equol is produced from daizein by intestinal microorganisms that naturally occur much more frequently in Oriental populations, and inoculation of the Western subjects with S-equol-producing bacteria or through the administration of pre- or probiotics, has thus far been unsuccessful (5).

Finally, it is important to bear in mind that isoflavones may take longer to take effect than the observation periods considered in most trials. In fact, according to studies by Lujin Li *et al*. (6, 7), it takes about 12 weeks of intake for soy isoflavones to achieve half of their maximum effect on vasomotor symptoms, while half the maximum effect of estradiol is reached after three weeks of intake.

Other effects

The positive effects of soy proteins on cardiovascular risk are still the subject of research and debate (8). An initial report by the American society of Cardiology, based on a 1995 meta-analysis, stated that a diet containing at least 25 grams of soy protein per day could reduce total and LDL cholesterol. However, subsequent trials have not confirmed this claim, reporting only modest effects on lipid metabolism (9). Later studies on different soy isoflavones have however, reported different levels of beneficial effects on cardiovascular risk factors, including changes in lipid and carbohydrate metabolism. These findings lend support to the theory that such compounds can reduce cardiovascular risk in the menopausal period (10). Moreover, recent studies have shown that some isoflavones, especially genistein, also exert a protective effect on the endothelium. Evidence from short-term RCTs and observational studies suggest that soy isoflavones, in particular S-equol, are anti-atherogenic, and improve arterial compliance, and may therefore potentially prevent cardiovascular disease and the associated cognitive decline (11, 12). However, many of the possible metabolic benefits of isoflavones may require even longer administration time frames than those needed for MVS therapy.

Isoflavones from Red Clover

Isoflavones found in red clover are biochanine A and formononetin. Both bind to ERα and ERβ, with greater affinity for the latter, but considerably lower than that of oestrogen. In regards to their effectiveness on vasomotor symptoms, the literature reports a fair number of trials, and a specific meta-analysis on red clover extracts (13, 14). However, many meta-analyses and literature reviews consider findings on red clover extract together with those of soybeans, drawing conclusions on the effectiveness of isoflavones as a whole. Hence, their effect on vasomotor symptoms is not entirely clear or definitive. They do not appear to reduce the number of hot flashes in 24 hours significantly (- 3), but a significant improvement in the Kuppermann Index has been reported (**table I**). Some studies have shown that red clover extracts are also effective when administered during the menopausal transition (15). As regards the dura-

tion of therapy and long-term efficacy, the literature only contains a few studies, none of which have reported significant adverse events or side effects.

Lignans from Flaxseed

Flaxseed is considered a rich source of lignans, such as enterodiol and enterolactone, which possess a weak oestrogenic action, capable of modulating oestrogen receptors with an action similar to that of SERMs (16). To date, however, reported effects are not always significant, and there is little evidence to support the use of flaxseeds for MVS therapy (17). That being said, there are other indications for their use in menopause, *i.e.*, for their anti-inflammatory and antioxidant effects, as well as improvements in lipid profile, reducing LDL cholesterol and increasing HDL cholesterol, associated with an improvement in glucose tolerance and a reduction in the risk of metabolic syndrome and atherosclerosis progression. In addition, some experimental evidence

Table I. *Major reviews and meta-analyses on the efficacy of soy isoflavones on vasomotor symptoms.*

Literature	Products	Conclusions	Trial quality	Duration
Nelson *et al*. (2006) (41) Review and meta-analysis of 17 RCTs in Cochrane database on non-hormonal therapies (isoflavones)	a) Red clover (40, 80 or 120 mg) b) Soybean extract (50, 70, or 150 mg)	Red clover does not reduce frequency of hot flashes Results on soy isoflavones are variable*	a) 6 trials (1 good quality, 2 moderate quality) b) 11 trials (8 moderate quality)	12–52 weeks 12–52 weeks
2012 Taku *et al*. (20) Review and meta-analysis of 13 RCTs on soy isoflavones *vs* placebo	54 mg soybean isoflavones (median)	Soy isoflavones reduce the frequency and intensity of hot flashes as compared to placebo	13 good quality studies	6–52 weeks
2013 Lethaby *et al*., Cochrane Review (42) Review of 43 RCTs on phytoestrogens, 39 on isoflavones	a) Genistein b) Soy extract c) Soy-rich diet d) Red clover extract e) Other phytoestrogens	Some trials show significant results for genistein concentrates. Generally non-conclusive evidence on effectiveness in reducing the frequency and severity of hot flashes	a) 4 moderate quality trials b) 11 trials (all sufficient quality) c) 13 trials (6 moderate quality, 1 sufficient) d) 5 trials (2 moderate quality) e) 6 sufficient/poor quality trials	12–104** Weeks
2015 NAMS (43) Position statement based on studies included in the main previous meta-analyses and original studies, predominantly RCTs	Takes into account trials published in previous meta-analyses	Only low-level recommendations for the effectiveness of S-equol (soybean derivative)	Studies with level II evidence (RCTs, systematic reviews with Level II studies or Level I studies with inconsistent results)	12–52 weeks
Chen *et al*. (2015) (44) Meta-analysis and review of 15 RCTs on phytoestrogens	Isoflavones S-equol Red clover	In some study groups meta-analysis has shown that soy isoflavones are effective in reducing the frequency of hot flashes	Differences in outcome measures: - 6/15 trials measured efficacy via KI# - 10/15 trials measured efficacy via hot flash frequency	Parameter not evaluated
Grant *et al*. (2015) (45) Review of comparative efficacy trials on different menopausal symptoms	Generic isoflavones as non-hormonal therapies	Low strength of evidence of efficacy of isoflavone treatment for vasomotor symptoms compared with placebo	5 good quality, 2 moderate, and 28 poor	Parameter not evaluated
2016 Franco *et al*. (46) Review and meta-analysis of 65 RCTs on nutraceutical products, 17 on isoflavones	Soy-rich diet Soy supplements and extracts Red clover extract	Supplementation with different compounds and specific isoflavones significantly associated with modest reductions in the frequency of daytime hot flashes	Does not specify quality assessment of the evidence considered	Parameter not evaluated
2017 Myers and Vigar (14) Meta-analysis of 3 RCTs *vs* placebo	Red clover 80 mg	Red clover significantly reduces hot flashes and KI	Good quality	Parameter not evaluated
2017 Moore *et al*. (47) General review of CAM RCTs and previous reviews (5 years)	Soy beans and soy isoflavones Red clover Phytoestrogens (isoflavones, lignans, coumestans, black cohosh)	Soybeans and soy isoflavones (especially supplements with S-equol) may be recommended for vasomotor symptoms	Does not specify quality assessment of the evidence considered	Parameter not evaluated
2019 DAILY *et al*. (48) Review and meta-analysis of 5 RCTs	S-equol Equol-containing soy isoflavone products	Both products improve hot flash score***	Does not specify quality assessment of the evidence considered	Parameter not evaluated

*Symptomatology improved significantly in 3 of the 7 trials; #Kupperman Index; **1 trial only; ***symptomatology improved in 3 of the 5 trials.

shows that lignans may have anticancer effects, reducing the growth of colon, breast and endometrial tumours; both *in vitro* and *in vivo* studies in mice injected with breast cancer cells show that flaxseeds increase or maintain the effectiveness of tamoxifen in reducing tumor growth and increase the apoptosis of neoplastic cells, while no effect on the activity of aromatase inhibitors has been observed (18).

Evidence on the effectiveness of Isoflavones in Vasomotor Syndrome

The literature on the use of treatments based on soy foods or extracts and the various active metabolites of isoflavones in vasomotor syndrome is very extensive. However, most studies have significant methodological limitations, many not being controlled or being carried out with very different and difficult-to-compare formulations. In addition, trials often have different objectives and evaluate efficacy in different ways, using different scales to assess menopausal symptoms (Kuppermann scale or Greene scale), and/or different criteria for the frequency or intensity of hot flashes and/or night sweats.

Quality of scientific studies

The quality of scientific literature is graded according to the following Levels of Evidence:

- Level 1: high quality randomized controlled trials (RCTs) (Ia) and systematic reviews and meta-analyses (Ib);
- Level II: lower quality RCTs, second-level systematic reviews or level I studies with inconsistent results;
- Level III: non-RCTs, case-control studies, systematic reviews including low-level studies;
- Level IV: case series, small case-control studies.

Strength of recommendations

The strength of recommendations based on the above are classified as follows:

a. Based on level Ia or Ib scientific information
b. Based on level II scientific information
c. Based on level III-IV information

Overall, soy isoflavones have an efficacy comparable to placebo (which in itself has an estimated efficacy of 30-50%), as in many studies their efficacy is not significantly higher. However, the oestrogen-like effect of soy isoflavones does result in a reduction in the frequency and intensity of hot flashes, which in some meta-analyses, mostly from Oriental authors, is statistically significant. Nevertheless, this effect seems to take a long time to reach maximal levels (at least 12 weeks to reach half the maximum effect) and is not always clinically significant (Evidence quality level II). This has led to a type B recommendation regarding the lower effectiveness of treatment of vasomotor symptomatology.

The numerous good quality meta-analyses have often arrived at inconclusive considerations on specific issues, because they take into account different products, dosages, evaluation methods and objectives. However, a number of good individual studies of specific products and dosages have yielded more meaningful conclusions about the effectiveness of these non-hormonal treatments on vasomotor symptoms. In order to clarify these concepts, **table I** provides a detailed overview of the most important and recent literature reviews and meta-analyses, illustrating the relative characteristics of the studies under consideration (**table I** and references).

An important aspect to be assessed with respect to the efficacy of such products is the evaluation of the dose, *i.e.*, the total amount of titrated isoflavones or dose of the specific active ingredient. In general, the dose required for isoflavones to achieve a biological effect is 50-90 mg per day, while the dose of isoflavones considered safe is 100 mg/day. Genistein at a dose of more than 30 mg/d was found to be more effective than placebo (evidence level II), leading to a recommendation strength B on genistein efficacy at a dose of more than 30 mg/day (19).

A meta-analysis by Japanese authors (20) found that, beyond the placebo effect, there is a 20.6% reduction in the frequency of hot flashes in 24 hours, and a 26.2% reduction in their intensity, in studies lasting at least 12 weeks, when at least 18.8 mg/day of genistein was administered. However, it is always necessary to consider the individual intestinal absorption capacity. As mentioned, the majority of the Western population is unable to convert daidzein to equol and therefore provide a satisfactory clinical response. Hence, some manufacturers directly include equol in their formulations, making them more effective even in populations such as Italians unable to activate intestinal conversion (evidence level II, recommendation strength B on the effectiveness of the equol).

Side effects

Based on the numerous studies in the literature, isoflavones are not associated with any major ad-

verse events (evidence level I; recommendation strength A). The most frequent side-effects are gastrointestinal irritation, with flatulence, diarrhoea and a sense of abdominal bloating.

Cancer risk

Due to the oestrogen-like effects of these substances, the risks related to breast cancer and endometrial hyperplasia (21, 22) have also been examined, although there have been few reliable studies in this respect. From the poor-quality and scarse literature that exists, however, it does not appear that phytoestrogens increase the risk of endometrial cancer, and, in fact, in combination with lignans seem to reduce the risk (evidence level III, recommendation strength C).
Few observational studies have been carried out on breast cancer risk, but in those involving a fairly large population overall (23), no increased risk of breast cancer was detected. An RCT on breast biopsies in pre-menopausal and post-menopausal women with early-stage breast cancer given doses of isoflavones of 100 mg/day for 7-30 days found no difference in KI-67 marker expression either pre- *vs* post-treatment or treatment *vs* placebo. However, two genes (FANCC and UGT2A1) were found to be upregulated in the treatment group, and overexpression of 126 genes involved in cell cycle and proliferation was observed in women with high plasma levels of genistein (> 16 ng/ml) *vs* women with low levels (< 6.8 ng/ml) (24). Other isolated studies have shown no histological or mammographic changes following the administration of isoflavones in humans either *in vitro* or *in vivo*. Nonetheless, some *in vitro* studies in animals have shown an increase in the proliferation of breast cancer cells with high doses of the most effective active ingredients, such as genistein (evidence level III, recommendation C on the cancer risk of high-dose genistein). In view of this, and the fact that no specific safety data in populations with breast cancer is available, soy isoflavone supplements are not recommended in such patients.

OTHER PHYTOESTROGENS

Hops

Hop flowers contain a potent flavonoid, 8-prenylnaringenin (8-PN), which is believed to exert more powerful oestrogenic activity than soy-derived isoflavones. In the few individual placebo-controlled and randomized studies we have to date, 8-PN has been shown to reduce the number of hot flashes and improve Greene's score (25) (evidence level III, recommendation strength C).

Resveratrol

Resveratrol is a non-flavonoid diphenol present in different varieties of plants (raspberries, blueberries, peanuts, *Polygonum cuspidatum* roots) and has been extracted in modest concentrations from fermented red grapes with particular fungal contaminations. It has weak phytoestrogenic activity, good bioavailability and good absorption, and exists in free and conjugated forms, but is metabolized very rapidly and consequently has a short half-life. Only a few studies have supported its effectiveness in MVS (evidence level III; recommendation strength C), while its antioxidant properties are much better known and extensively studied (26). Resveratrol is frequently administered in combination with other polyphenols, and in this role also exerts important synergistic activity on hot flashes.

OTHER PLANT-DERIVED NUTRACEUTICALS WITH NON-PHYTOESTROGENIC ACTIVITIES

Black Cohosh (Cimicifuga racemosa or Actaea racemosa)

This has long been used as a medicinal plant by Native Americans, and is currently the most widely used product for menopausal disorders. *Cimicifuga racemosa* (CR) rhizome has several chemical constituents that are extracted in various ways, including nitrogenous alkaloids, phenolic isoflavone compounds such as formononetin, organic acids such as isoferulic acid, and triterpenoids such as cimiracemoside A, 25-O-methyl-cimigenoside, actein, and 23-26-deoxy-actein. Formononetin and triterpenoids are some of its best known bioactive components.
Some initial research reported oestrogen-like effects, but isopropyl alcohol extract, which is the most widely used in current phytotherapy, is devoid of the phytoestrogenic component and therefore cannot exert oestrogen-like effects. Triterpene glucosides are the main bioactive component present in the alcoholic extract, and are responsible for therapeutic effects via central modulation of the se-

rotonin system (27). However, CR does not change circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) or oestradiol, and does not result in an increase in endometrial thickness; therefore, it has a mechanism of action unrelated to ER activation (28). Although its mechanism of action has not been fully clarified, several recent studies show that the anolic isoproponol extract of *Cimicifuga racemosa* (iCR) has some antioxidant and anti-inflammatory properties, and a mainly central neuromodulatory action (29).
According to the scientific literature, including a major meta-analysis (30), the effectiveness of CR on hot flashes is not higher than that of a placebo, but in this case too the important lack of homogeneity among scientific studies must be taken into account, as pointed out by a subsequent review. In particular, it is necessary to bear in mind the different species of black cohosh used and the different preparations thereof. Numerous individual studies conducted on the isoproponol preparation (iCR) provide significant evidence of its effectiveness in the treatment of MVS, despite a total lack of oestrogenic effects on the levels of circulating hormones. In particular (31), with regard to iCR, one meta-analysis on 28 clinical efficacy studies identified 9 placebo-controlled clinical trials on 9,391 patients which confirmed the efficacy (evidence level Ib, recommendation strength A) and safety (evidence level Ia) of iCR-based medicines.
Several trials have also demonstrated their safety in breast cancer patients, although the duration of observation in these trials was invariably limited (32). Furthermore, iCR can be used without pharmacological interference in patients treated with tamoxifen and aromatase inhibitors, oestrogen and/or progestin, platelet antiaggregants and/or anticoagulants. In general, adverse effects are rare, but hepatotoxicity, pain, abdominal cramps and jaundice have been reported. However, a review of reported cases of hepatotoxicity has made it clear that these effects are not associated with preparations of isopropanol extracts of CR (33).

Pollen extract

Cytoplasmic pollen extract (GC Fem), pistil extract (PI 82), and vitamin E products are also commercially available (34). These extracts are extremely purified, and seem to be safe even for patients prone to allergies. Both *in vitro* and *in vivo* studies demonstrate that these substances neither bind to oestrogen receptors nor exert any oestrogenic effects. Instead, their proposed mechanism of action, in addition to their antioxidant and anti-inflammatory properties, involves modulation of the serotonin system, in particular by inhibiting serotonin re-uptake. This may account for their effectiveness in the treatment of hot flashes, which has been demonstrated by a number of cohort studies and randomized trials reporting a significant reduction in climacteric symptoms (34) (evidence level II, recommendation strength B for vasomotor symptoms). In fact, in a randomized comparative trial (35) pollen extract was not only more effective than placebo, but also it attenuated climacteric symptoms to an extent only slightly lower than oestrogen–progestin therapy. Furthermore, the efficacy and safety of these products have been recently confirmed by other studies, overall showing improvements of women's quality of life (36, 37).

OTHER PLANT DERIVATIVES

Ginseng

Ginseng has no oestrogenic effects on FSH levels, endometrial thickness, vaginal maturation index or vaginal pH. Accordingly, ginseng has no effect on MVS, although some data in the literature show an improvement in depressive syndrome, Kupperman index and Menopause Rating Scale, but not on hot flashes.

Matcha

Matcha, grown mainly in South America, and for its edible root, is recommended as a tonic/adaptogen, against stress and tiredness, Anti-anaemic and aphrodisiac actions have been also reported. The mechanism of action is unknown, but it is has been hypothesized that it may modulate steroid receptors. Matcha contains a weak phytosterol, but the evidence does not support its use for the therapy of vasomotor symptoms.

St. John's Wort

This is a herb derivative (of *Hypericum perforatum*) which has shown effectiveness mainly on depressive symptoms of menopause, and partly on vasomotor symptoms. It may interfere with antidepressant drugs.

Wild Yam* (*Dioscorea*), *Dong Quai* (*Chinese Angelica*), *Evening Primrose* (*Enotera*) *Oil

Only a few low-evidence-level studies are currently available on this group of derivatives. In fact, as yet there is no reliable data on efficacy, minimum effective dose and long-term safety. Due to the limited evidence on efficacy and safety, there is no strong recommendation for their use in the therapy of vasomotor symptoms (38, 39) (evidence level III–IV, recommendation strength C). The few available studies refer to combinations of different substances with non-uniform doses, as often occurs in the Chinese phytotherapy tradition. Bacause of both the paucity of data and the low quality of the published articles (38, 39), it is not possible to give scientifically accurate recommendations regarding these preparations.

CONCLUSIONS

These recommendations have taken into account only some of the many products on the market, considering only those that underwent scientific assessment according to the current criteria for evidence-based medicine. Many of the studies conducted to date have a very limited sample size and period of treatment and do not provide long-term safety and efficacy data. Furthermore, only few studies compared the efficacy of different formulations. As it is the case of drugs, also for these products it is of particular importance to carefully assess contraindications. These may include previous adverse reactions to products of plant origin, or the intake of other medications that may pose a risk of pharmacological interaction. Thus, the choice of therapy will depend on the characteristics and clinical history of the patient, her previous and current use of any other therapeutic agent. The prescription of plant-derived supplements must also take into account the dietary habits of the subject; specifically, Western women tend to have very low dietary intake of soy isoflavones (0.27-1.43 mg/day) but, the diet of vegetarians or women who consume a lot of soy-based products (beverages, yoghurt and tofu, *etc*.) may contain similar amounts to those present in dietary supplements (30-80 mg/day) (40).

MVS generally improves over time, but if patients get some benefits from phytotherapy, there is no need to progressively reduce or stop it abruptly. Conversely, if a patient does not respond to treatment, it would be advisable to reassess her options, bearing in mind that 12 weeks of treatment with soy isoflavones are necessary to reach 50% of their maximum efficacy. In any case, therapy should be regularly re-evaluated, at least every 6-12 months, since the long-term safety and efficacy of these phytopharmaceuticals has not yet been determined.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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