

# Phyto-Oestrogens and Chaste Tree Berry: A New Option in the Treatment of Menopausal Disorders

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## Abstract

For a woman, menopause represents a transitional phase from a fertile to a non-fertile age, in which there is a gradual reduction in ovarian function accompanied by a gradual cessation of oestrogen production.

The clinical presentation can involve a series of disorders, including hot flushes with episodes of sweating, particularly at night, palpitations, changes in sleep-wake rhythm, irritability, anxiety and mood changes, vaginal dryness due to a process of progressive atrophy with thinning of the outer and inner labia, reduction of vascularisation and elastic fibres, and decreased sexual desire; subsequently, Many women use alternative therapies to treat hot flushes and other menopausal symptoms. The purpose of this review is to summarize current information on the efficacy and safety of phytoestrogens and the herbal medicine. Given the importance that these symptoms assume for the woman, not only for the perceived quality of life, but also for the increased risk of developing all the diseases, all the treatments adopted for menopausal women are directed primarily to resolving vasomotor disorder

**Keywords:** Menopause; Vasomotor symptoms; Hot flushes; Phyto-oestrogens; Magnolia; Chaste tree berry

## Introduction

For a woman, menopause represents a transitional phase from a fertile to a non-fertile age, in which there is a gradual reduction in ovarian function accompanied by a gradual cessation of oestrogen production [1]. During this period, women are faced with irregular ovulatory or anovulatory cycles without a systematic progression from one to the other.

The mean age of onset of this phase is 40 to 50 years and it is certainly the most vulnerable period in a woman's life in that hormone deficiency causes neuroendocrine changes that constitute the pathophysiological basis of neurovegetative disorders (Figure 1).

The clinical presentation can involve a series of disorders, including hot flushes with episodes of sweating, particularly at night, palpitations, changes in sleep-wake rhythm, irritability, anxiety and mood changes, vaginal dryness due to a process of progressive atrophy with thinning of the outer and inner labia, reduction of vascularisation and elastic

fibres, and decreased sexual desire; subsequently, the process of atrophy also affects the epidermis with thin, pale skin that is easily susceptible to bacterial and viral infections. A similar condition is observed in the vagina with a reduction in thickness of the mucosa, which becomes atrophic with reduced vascularisation and results in dyspareunia (Table 1) [2].

Among the most important long-term complications, attention should be drawn to the loss of minerals and consequent reduction in bone mass, which is associated with osteopenia and osteoporosis of varying degrees and dysfunction and atrophy of the genitourinary tract. With the passage of time, oestrogen deficiency in fact accelerates the process of bone demineralisation, as oestrogens promote the absorption of calcium in the intestine and the mineralisation process in bone [3].

The most common symptoms of menopause, even when taking into account all the different populations studied, are hot flushes, which affect between 65% and 86.8% of the menopausal female population, whereas night sweats affect between 65% and 82.1%, insomnia between 61% and 67.8% and mood changes between 57% and 47.5% [4,5].

The symptom for which postmenopausal women most frequently visit their doctor for relief is the occurrence of hot flushes [6]. This symptom is present in more than 80% of women entering into physiological menopause, while it affects more than 90% of women who have undergone surgical removal of the ovaries. Menopausal symptoms must not be regarded simply as disorders associated with deterioration in the quality of the life, but also as a risk factor for the development of osteoporosis, as well as cardiovascular diseases and brain deterioration [7,8].

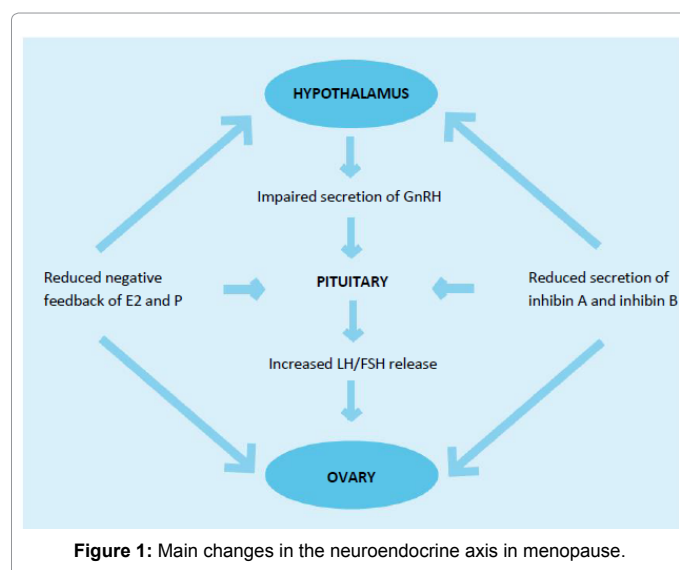


Figure 1: Main changes in the neuroendocrine axis in menopause.

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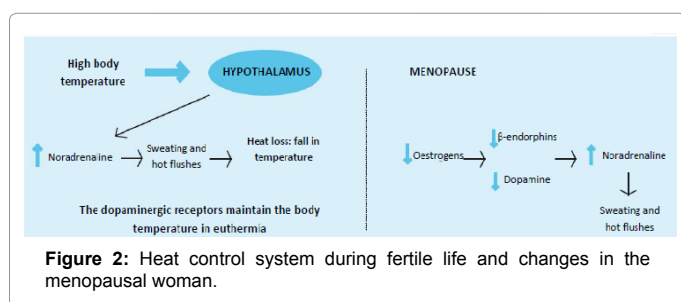
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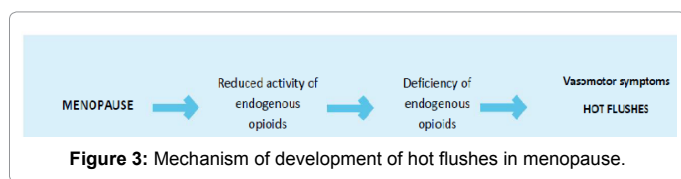
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Short-term symptoms	Medium-term symptoms	Long-term symptoms
<ul style="list-style-type: none"> <li>- Menstrual irregularity</li> <li>- Hot flushes</li> <li>- Sweating (including at night)</li> <li>- Insomnia</li> <li>- Anxiety</li> <li>- Depression</li> <li>- Asthenia</li> <li>- Irritability</li> </ul>	<ul style="list-style-type: none"> <li>- Urogenital disorders                             <ul style="list-style-type: none"> <li>o Vaginal dryness</li> <li>o Dyspareunia</li> <li>o Urinary incontinence</li> </ul> </li> <li>- Cutaneous and mucosal atrophy</li> <li>- Cutaneous hypoelasticity (increased wrinkles)</li> <li>- Atrophy of the oral mucosa</li> <li>- Eye symptoms</li> <li>- Obesity</li> </ul>	<ul style="list-style-type: none"> <li>- Osteoporosis</li> <li>- Cardiovascular disorders</li> <li>- Atherosclerosis</li> <li>- Alzheimer's disease</li> </ul>

**Table 1:** Schematic representation of the main short-term, medium-term and long-term symptoms of menopausal women.



**Figure 2:** Heat control system during fertile life and changes in the menopausal woman.



**Figure 3:** Mechanism of development of hot flushes in menopause.

A review from 2009 on this subject shows that more severe hot flushes can be correlated with rapid bone loss and the subsequent development of osteoporosis within a short period of time [9]; they are also related to a weaker verbal memory [10] and reduced levels of plasma antioxidants, but also to an increased cardiovascular stress response and to changes in blood pressure.

The vasomotor symptoms are also correlated with a significant increase in the risk of coronary heart disease, which does not appear to be entirely explicable by other risk factors for coronary heart disease [11].

Given the importance that these symptoms assume for the woman, not only for the perceived quality of life, but also for the increased risk of developing all the diseases listed above, all the treatments adopted for menopausal women are directed primarily to resolving vasomotor disorders.

### Changes in Thermoregulation During Menopause

The hypothalamus is the CNS structure that, as well as various other functions, is specifically devoted to maintaining body temperature and the sleep-wake rhythm, as well as to maintaining water and salt balance and regulating food intake.

In the hypothalamus, the anterior and preoptic nuclei are responsible for cooling, whereas the posterior nucleus is devoted to heating; these centres possess cells that are able to respond to variations in body temperature, which is recorded from the temperature of the blood that reaches the encephalon. When the temperature is higher than physiological levels, the posterior nucleus releases *noradrenaline*, which in turn stimulates the nuclei in the anterior hypothalamus, culminating in a response that causes an increase in sweating and

peripheral vasodilatation and thus returning the system to a state of equilibrium. It is specifically the increase in noradrenaline which results in sweating and hot flushes in menopausal women with the aim of reducing raised body temperature [12].

*Dopamine* also plays an important role in thermoregulation in that it too is devoted to maintaining a state of eutheria via the  $D_2$  receptors. As has long been known, bromocriptine, a dopamine agonist, is able to increase the activity of the hypothalamic endogenous opioid system ( $\beta$ -endorphins) on the mechanisms regulating body temperature in menopause [13]. In fact,  $\beta$ -endorphins are also involved in thermoregulatory homeostasis and inhibit the noradrenergic neurons below the threshold at which heat loss is activated.

During fertile life, oestrogens play an important role in modifying the synthesis, release and metabolism of many neurotransmitters, including dopamine and melatonin, which are responsible for modulating the hypothalamic and limbic systems.

It is therefore clear that the decrease in oestrogen levels from the perimenopausal period until overt menopause is accompanied by changes in function of these systems, which is of particular relevance to thermoregulation and vasomotor stability.

The resultant outcome is connected with menopausal symptoms. The menopausal changes therefore induce a temporary imbalance of thermoregulation in the hypothalamus, modulating the homeostasis of the body temperature to values below physiological levels, which are then achieved by the dispersal of heat by means of vasodilatation and profuse sweating.

Postmenopausally, the decrease in oestrogens reduces the inhibitory activity of  $\beta$ -endorphins on noradrenaline and causes an increase in activity of the noradrenergic system but also a reduction of the dopaminergic system, which is significantly less active than in premenopausal women (Figures 2 and 3) [7,8].

All these mechanisms explain the positive effect of hormone therapy, resulting in stimulation of the  $D_2$  dopaminergic receptors and the subsequent attenuation of the menopausal symptoms associated with hot flushes and sweating, with a consequent improvement also in the psychological correlations and a decrease in the risk factors for osteoporotic and cardiovascular diseases.

*Melatonin* levels and the time during which these levels remain high during the night also differ during the various phases of life, with a significant decrease with advancing age; this explains why sleep is often disturbed and is of poorer quality in the elderly [14].

Perimenopausally, it has been shown that the reduction in melatonin secretion precedes the increase in FSH in menopause.

Moreover, the instability of the ovarian hormones and their fluctuation during the perimenopausal period destabilises the physiological circadian rhythm and the decrease in oestrogens can also contribute significantly to changes in mood and physiological well-being.

A genuine problem that frequently occurs when a woman asks for relief of the vasomotor disorders that afflict her is represented by the fact that, as is now well known, the traditional Hormone Replacement Therapy (HRT) is accepted and used by only a small percentage of women (about 8%), as the literature reports that there is a state of fear of an increased risk of breast cancer that in fact causes doctors not to prescribe such drugs, although very often it is the women themselves who refuse to use them.

HORMONE REPLACEMENT THERAPY	
Positive effects	Risks
Reduction of menopausal symptoms	Venous thromboembolism
Prevention of osteoporosis	Cardiovascular risk
Increased trophism of the urogenital tract	Risk of breast Ca

**Table 2:** Schematic representation of the main positive effects and possible risk factors of the use of hormone replacement therapy (HRT).

ISOFLAVONES	COUMESTANS	LIGNANS
Genistein – Soya and derivatives	Coumestrol – Beans, soya sprouts 4-Methoxycoumestrol – Cloves, soya sprouts, red clover, sunflower seeds	Enterodiol – Linseed and sesame seeds Enterolactone – Soya, hops, fruit and vegetables, cereals
Daidzein – Legumes		
Glycitein – Clover		
Biochanin A – Whole grains Formononetin		

**Table 3:** Subdivision of classes and subclasses of phyto-oestrogens and principal dietary sources.

## Hormone Replacement Therapy (HRT)

A reasoned choice of the therapeutic protocol in terms of preparation type, dosage, therapeutic regimen and route of administration is essential for the rational use of HRT. As confirmed by the results of the WHI study, different therapeutic strategies must be chosen with an individualised risk-benefit assessment. In recent years, following a few clinical studies that had aroused considerable fear, the therapeutic approaches to postmenopausal women have been reviewed [15]. Additionally, new treatment protocols have been identified with low oestrogen doses that are effective in controlling postmenopausal symptoms and reducing the incidence of side effects and potential risks associated with the duration of treatment (Table 2).

The reduction in the dose of oestrogens to be administered does not preclude the fact that all women must undergo tests before starting treatment. Women who take hormone therapy should undergo a clinical follow-up at least once a year, including a gynaecological visit, updating of the medical history, laboratory and instrumental tests and a lifestyle assessment. Mammography must be performed, preferably within 12 months of the start of treatment [16]; increased breast density can be attributed predominantly to the effects of the progestin component of HRT [17,18].

The woman must be examined from an endocrine and metabolic standpoint, the type of oestrogen and possibly the most suitable type of progestin must be chosen, as well as the best route of administration and the combination modality best suited to the individual [15].

The main aim of hormone replacement therapy is to improve the quality of life of patients in spontaneous or surgical postmenopause who are experiencing menopausal symptoms [2]: hot flushes [6], nocturnal sweating, vaginal atrophy, dyspareunia, neurovegetative problems, osteoporosis [3] or a familial history of osteoporosis, with high levels of total cholesterol and low levels of HDL-cholesterol, and with a family history of cardiovascular diseases [19-21]. HRT should be considered in the absence of contraindications and after discussing the potential risks and benefits with the woman [22]. HRT is contraindicated in women with a positive history of breast cancer [23,24] or endometrial cancer [25], in women with thromboembolic episodes [26] during pregnancy or in those taking oral contraceptives, with any current liver diseases or, at all events, with impaired liver function.

## Phyto-oestrogens

In recent times, the pharmaceutical market has been enriched by numerous products known as food supplements based predominantly on phyto-oestrogens, or plant oestrogens, derived from soya and combined with vitamins and other plant substances, which have made them greatly appreciated by women, both for the relief of disorders of the perimenopausal and overt menopausal period, and during the fertile life. It is the gynaecologist's task to identify the right products to recommend to women based on the quantities and quality of substances present.

Phyto-oestrogens are compounds that are present in many plants with a very similar action to mammalian oestrogens.

However, some clarifications are needed about phyto-oestrogens, since they do not all have the same therapeutic efficacy.

These products exert a gentle and balanced oestrogenic action due to the active ingredients they contain; more precisely, by virtue of their particular chemical structure, they are able to bind to oestrogen receptors and thus exert biological activity of an oestrogenic or antioestrogenic nature. The diversification of this effect depends on their concentration, that of the oestrogens produced by the body and on certain individual characteristics (tissue concentration of receptors and enzymes involved in the metabolism of these hormones).

Phyto-oestrogens are commonly divided into three main classes: isoflavones, coumestans and lignans (a fourth category that of lactones is of little therapeutic value) (Table 3). They are ubiquitous in the plant world (present in at least 300 varieties of plants, few of which are edible). In terms of food sources, mention may be made of soya, legumes and, albeit in small quantities, many types of fruits, vegetables and wholegrain.

Soya, its derivatives (flour, soya milk and tofu) and red clover represent the main commercial sources of phyto-oestrogens.

Soya isoflavones in particular have a higher oestrogenic activity than other phyto-oestrogens. They bind to the oestrogen receptor, albeit with lesser affinity, forming a receptor complex that functions in a similar way. Many of the health-giving properties of isoflavones are attributable to the weak oestrogenic action of genistein and daidzein, the two most important isoflavones, and their interaction with the oestrogen receptors that are distributed throughout the body. Genistein has a seven-fold greater oestrogenic activity than daidzein.

As well as the biological significance, the indications for phyto-oestrogens are also now well known; these substances have a known antioxidant and oestrogenic activity (they reduce disorders due to both a deficiency and an excess of oestrogens).

Recent studies have shown the progressive reduction in hot flushes and sweating following treatment with phyto-oestrogens. Doses of 45-90 mg of soya isoflavones, equal to about 2-3 soya-based meals a day, should be used to provide protection against hot flushes.

It has emerged from these studies that soya isoflavones do not stimulate endometrial growth and therefore they do not increase the risk of endometrial or uterine tumours [27]. Other studies have shown that the continuous administration of phyto-oestrogens derived from soya isoflavones exerts a protective action against cardiovascular diseases and postmenopausal osteoporosis.

It has been shown that phyto-oestrogens exert a protective action on blood vessels and against heart diseases. Following constant and

sustained intake, they can in fact reduce levels of triglycerides and low-density lipoproteins (LDL or bad cholesterol) and increase levels of high density cholesterol (HDL or good cholesterol) [28].

Isoflavone supplements allow a better knowledge of the dosage than the consumption of soya-rich foods, which is reflected in greater efficacy. The results can be appreciated more clearly after the second week of intake. In addition, these products do not cause any side effects.

The commercially available soya isoflavone-based supplements are not all equal. As well as high-quality products, unregulated products and/or those of a low technological level can be found. Many commercialised products refer to generic extracts of soya or isoflavones without specifying the type of isoflavones they contain and exhibit a different genistein/daidzein ratio from that found in nature; in addition, some contain less active isoflavones, such as glycitein.

Following the example of oral therapy, some soya isoflavone-based topical formulations have been marketed with the aim of treating and preventing postmenopausal vulvovaginal symptoms. The availability of products containing an adequate dose of soya isoflavones has shown to be effective, not only in curing vulvovaginal symptoms by more continuous administration, but also in preventing their development by periodic administration, in alternate 3-month cycles, which is met with greater approval by the women.

Among other effects, oestrogens also possess an antioxidant activity, thus inhibiting the formation of free radicals. Phytoestrogens have also been shown to exert marked antioxidant, anti-inflammatory and antihypertensive activity. Therefore, food supplements, in particular multivitamins, represent a valid alternative to hormone replacement therapy in menopausal woman.

Supplements that contain vitamin D and calcium as well as phyto-oestrogens are indicated in the prevention of osteoporosis as a result of their joint action of increasing intestinal absorption of calcium and increasing its availability in bone, thus making the latter less fragile.

Combinations of phyto-oestrogens and other substances produce an improvement in menopausal symptoms.

Over the years, there have been numerous combinations of phyto-oestrogens and various other vitamin or beneficial substances, but recently pharmaceutical companies have particularly focussed on some substances that can help relieve the disorders suffered by women in the peri- and postmenopausal period as much as possible. Various substances have been studied and, of these, some deserve particular mention, such as magnolia, lactobacilli, vitamin D and calcium, which act specifically on the disorders that women complain of most often [4]. Vitamin D and calcium are very well known for their activity on bone and therefore in the prevention of osteopenia and, in time, osteoporosis, and their beneficial properties are now confirmed.

In terms of the beneficial activity of the combination of phyto-oestrogens and probiotic lactic ferments, mention may be made of *Lactobacillus sporogenes* (*Bacillus coagulans*), which reaches the distal part of the small and large intestine in live form, where it germinates and produces enzymes, vitamins and lactic acid, thus creating favourable conditions for the absorption of calcium, magnesium, phosphorus, iron and copper, but also trace elements and vitamins. In combination with phyto-oestrogens, it is useful by virtue of its capacity for producing glycosidase, an enzyme that releases the main active ingredients of soya isoflavones by cleaving their glycoside bond; lactobacilli therefore

improve the activity of phyto-oestrogens by stabilising the intestinal bacterial flora and allowing the constant absorption of the active ingredients.

A 2011 study shows that bioavailability varies with single doses of two oral formulations of isoflavones (genistein) with and without lactobacilli, with a significant increase in the peak plasma concentration compared with the same dose of isoflavones without lactobacilli.

A symptom that is often associated with hot flushes in a large number of women is a poorly tolerated state of anxiety that often causes a profound state of psychological prostration; this condition is also often correlated with a sense of constant tiredness and asthenia, with a deterioration in the quality of rest and with a decrease in actual hours of sleep.

In terms of this important symptom, the marked anti-anxiogenic properties of *magnolia* extract are well known [29]. Magnolia extract exerts a calming and comforting effect, without however causing daytime drowsiness, and does not have the side effects that characterised prescription anxiolytics. The main active ingredients are magnolol and honokiol, which have modulating capacities on the GABAA receptors of the cerebral limbic system, which is the centre devoted to emotions and feelings. This explains how this substance can have beneficial effects on changes in the sleep-wake rhythm through a calming, muscle-relaxing and balance-restoring action.

Magnolia extract also reduces blood cortisol levels, which are increased in stress states; therefore, this substance also exhibits adaptive activity in situations of severe psychological and physical stress [30].

Recent studies comparing magnolia extract with diazepam in women who have stress-related anxiety and are overweight have shown its equivalent efficacy to that of the drug [31,32].

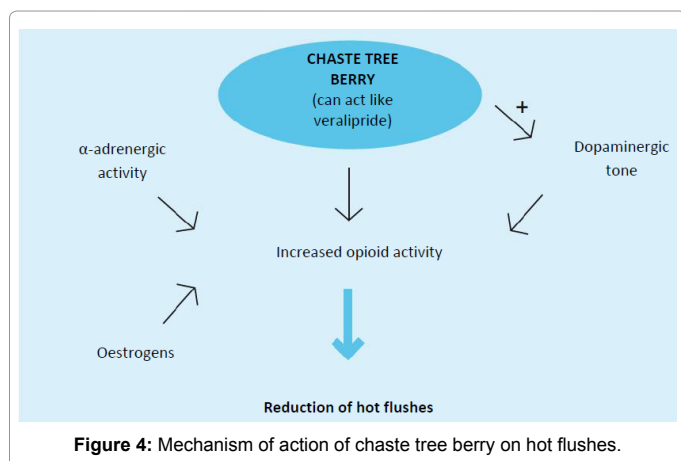
Because postmenopause is a condition in which weight gain represents a clinical condition that affects many women and in most cases is associated with anxiety, this mechanism is converted into a greater sensation of hunger with a preference for carbohydrates and simple sugars, causing a sort of vicious cycle.

There have been no reports of relevant side effects for any of these ingredients and there is optimal compliance on the part of the women mainly because they know they are taking natural products that do not negatively interfere with their own genital tract and with the risk of developing breast cancer.

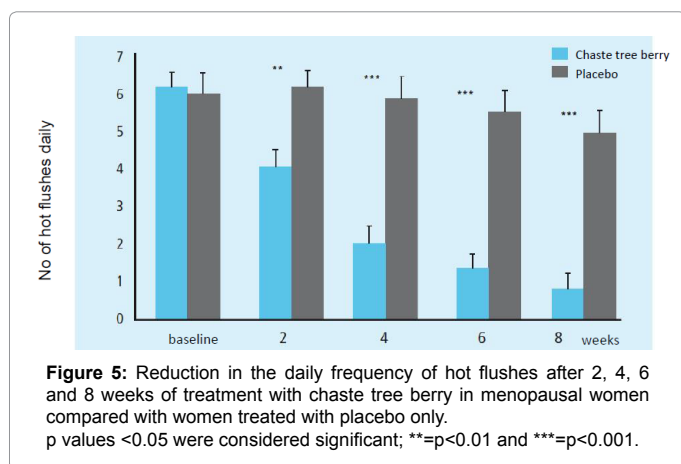
## Chaste tree berry

Particular mention should be made of chaste tree berry, which is characterised by a few specific beneficial properties for postmenopausal women.

Chaste tree berry (*Vitex Agnus-castus*) is a phytocomplex containing glycosides, flavonoids, terpenes and alkaloids, and its main active ingredient is agnuside; it has always been known as a product that can resolve premenstrual syndrome problems in women of fertile age and recently its usefulness has also been observed in menopause, particularly in respect of vasomotor symptoms [5]. These data have suggested that there may be an analogy between this syndrome and menopausal symptoms. The mechanism of action of chaste tree berry involves an increase in hypothalamic dopaminergic tone; it expresses a binding affinity with oestrogen  $\alpha$  (ER $\alpha$ ) and  $\beta$  (ER $\beta$ ) receptors and stimulates m-RNA expression by the progesterone receptor (PR expression) and that of pS2 (presenelin-2), another oestrogen-inducible gene (Figure 4) [5,33]. Dopamine is the main neurotransmitter that



**Figure 4:** Mechanism of action of chaste tree berry on hot flashes.



**Figure 5:** Reduction in the daily frequency of hot flashes after 2, 4, 6 and 8 weeks of treatment with chaste tree berry in menopausal women compared with women treated with placebo only. p values <0.05 were considered significant; \*\*=p<0.01 and \*\*\*=p<0.001.

controls the secretion of prolactin (Prl) by way of inhibition. There are clear data to show how it corrects the deficiency of progesterone in the corpus luteum during fertile life, by its action as a dopamine agonist, and how it causes an improvement in menopausal symptoms by reducing Prl levels.

in recent years, it has also emerged that, through its dopaminergic action, chaste tree berry is also capable of engendering beneficial effects by improving the emotional symptoms typical of the menopause, because a decrease in dopaminergic tone is correlated with psychological symptoms [34].

A 2011 study has shown how the daily incidence of hot flashes after 8 weeks of treatment is significantly decreased in women taking chaste tree berry compared with a group taking placebo (Figure 5) [35]; in addition, Kupperman's index in the group treated with chaste tree berry showed a statistically significant difference in terms of the severity of hot flashes, night-time sweating, insomnia, anxiety, depression, asthenia and headache compared with the control group. However, there are few studies to date that focus on the possible activity of chaste tree berry on sexual desire in menopausal women, although data available to us regarding the dopaminergic and opioid action also suggest the possibility of a topical formulation for treating dyspareunia in these women [36].

This evidence suggests that the combination of phyto-oestrogens and chaste tree berry can convincingly resolve the vasomotor and psychological symptoms typical of peri- and postmenopausal women.

On the basis of these considerations, the potential availability of a complete product consisting of phyto-oestrogens, chaste tree berry and magnolia extract can be particularly useful, not only in resolving vasomotor symptoms, but also in acting on the neuroendocrine component that is the main cause of anxiety and certain neurovegetative symptoms, such as sweating and night-time awakenings

### Correlations Between Premenstrual Syndrome and Vasomotor Symptoms in Menopause

There is a correlation between premenstrual syndrome and vasomotor symptoms, i.e. women who have suffered from premenstrual syndrome during their fertile life show more severe vasomotor symptoms in the postmenopausal period.

One of the factors predominantly involved in the aetiopathogenesis of both conditions is certainly the change in the dopaminergic and serotonergic systems, so that the administration of dopaminergic drugs, such as bromocriptine and/or cabergoline, can improve both sets of symptoms by normalising the dopaminergic and serotonergic systems.

The success of administration of chaste tree berry in women with premenstrual syndrome is due to the restoration of a normal dopaminergic tone. Postmenopausally, the combination of phyto-oestrogens and chaste tree berry produces a more beneficial effect on dopaminergic tone with a more significant reduction in the incidence of vasomotor symptoms and, particularly, hot flashes.

The simultaneous presence of magnolia also encourages more physiological sleep with fewer night-time awakenings.

### Conclusions

For all of the above reasons, soya isoflavones, which, in the light of numerous clinical studies and according to reports from women, appear to act by improving vasomotor symptoms, represent a valid alternative to HRT. The properties of isoflavones are not limited to vasomotor symptoms alone, but they also have positive effects on bone mass in that oestrogen  $\beta$  receptors, with which soya phyto-oestrogens have a greater affinity, are strongly expressed in bone.

In addition, isoflavones exert an antioxidant action, reducing free radicals, and have an inhibitory effect on the enzyme aromatase that converts androgens to oestrogens in adipose tissue and increases the risk of endometrial and breast cancer. Products used postmenopausally not only contain phyto-oestrogens, but are often combined with calcium, vitamin D and other components, as is the case with the latest preparation in which magnolia and in particular chaste tree berry contribute significantly to improving vasomotor and neurovegetative symptoms.

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