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**NARRATIVE REVIEW**

# Non-hormonal options for managing menopause symptoms: a narrative review

*Short title: Alternative menopause management*

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## ABSTRACT

**Objective.** An increasing number of menopausal womenexperience significant symptoms but are either contraindicated or choose electively to avoid Hormone Replacement Therapy (HRT). Therefore, there is an increasing and urgent need for rigorous research and validate alternative therapeutic options to mitigate menopausal symptoms and prevent potential long-term disturbances in this population. The aim of this review was to summarize the most recent non-hormonal options for the management of early symptoms and the prevention of potential long-term complaints of menopause.

**Materials and Methods.** Relevant publications were identified through systematic searches of PubMed, Scopus, Medline, Cochrane Library, ClinicalTrials.gov, and Embase. The search was complemented by cross-referencing the bibliographies of the retrieved articles.

**Results.** In menopause, lifestyle and nutritional improvements are crucial for maintaining and promoting overall well-being alongside any treatments. While botanicals, supplements, vitamins, acupuncture, hypnosis, and behavioral therapies may alleviate early symptoms, their effectiveness remains insufficiently proven. Particular caution is needed with phytoestrogens due to their significant estrogenic and anti-estrogenic properties. Additionally, antidepressants like SSRIs and SNRIs show promise for managing symptoms.

**Conclusions.** It is important to recognize that non-hormonal therapies should be recommended based on their primary mechanisms of action. For instance, gabapentin may be the preferred option for patients experiencing hot flashes and restless legs syndrome. However, due to the uncertainties surrounding the neuroendocrine causes of menopausal symptoms, the development of targeted therapies is still in progress.

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**Key words**

Non hormonal treatments; menopause; Selective Serotonin Reuptake Inhibitors; Serotonin-Norepinephrine Reuptake Inhibitors.

## INTRODUCTION

The treatment of menopausal disorders in the short, medium, or long term, either through Hormone Replacement Therapy (HRT) or other alternative therapies, has become a clinical reality that requires increasingly qualified and responsible attention. Hot flashes, sweating, insomnia, fatigue, irritability, joint pain, paresthesia, palpitations, depression, dizziness, headache, dyslipidemia, and bone rarefaction represent the main symptoms of the "Climacteric Syndrome" that initially affects a large number of women during the menopausal transition. These disorders are predominantly related to estrogen deficiency associated with a complex variation in the production and secretion of various endocrine substances: increased gonadotropins, increased androgens, fluctuations in dopamine, serotonin, acetylcholine, and GABA.

However, from a clinical perspective, it is not possible to implement a true etiological classification of climacteric disorders because it has been widely demonstrated that, along with hormonal influences, several other elements interact in determining the syndrome, including socio-cultural and environmental influences combined with psychological factors. Menopausal symptoms arise in different ways and at different times in women. Generally, vasomotor alterations, sleep disturbances, and uro-genital symptoms appear early, immediately after the cessation of ovarian function. Changes in carbohydrate and lipid metabolism, cardiovascular pathologies, osteoporosis, and hormone-sensitive neoplasms represent potential long-term complications of menopause. HRT has been shown to act favorably on the resolution of early symptoms and the prevention of late pathologies. If used within a context of rigorous and organized medical intervention, it manages to have a certainly positive value, albeit with different effectiveness and peculiarities depending on the individual molecules used.

However, an increasing number of women, despite experiencing significant climacteric disturbances, are averse to or have contraindications for hormone therapy. For these reasons, there is an increasingly urgent need to research and validate therapies alternative to HRT, capable of resolving or reducing menopausal symptoms and their long-term consequences, thereby improving the quality of life of women during this particular period of their existence. Improving lifestyle and certain behaviors (avoiding smoking, engaging in regular physical activity, reducing or avoiding alcohol and spicy foods, reducing stress and overweight) are important choices to associate with any treatment to maintain and promote psychophysical well-being during menopause. We will now examine the latest non-hormonal options used for managing menopausal symptoms.

### Materials and Methods

A comprehensive literature search was conducted on the following databases: PubMed, Scopus, Medline, Cochrane Library, ClinicalTrials.gov, and Embase. All the relevant studies published until February 2024 were screened. The search terms used were “menopause”, “treatment”, “non hormonal”, “clonidin”, “pregabalin”, “serotonin reuptake inhibitors”, “serotonin-norepinephrine reuptake inhibitors”, “gabapentin”, “pregabalin”. The Boolean operators “AND” and “OR” were used to combine search terms as appropriate. Additional articles that met the inclusion criteria were identified by searching through the reference lists of the included articles. Articles that were not

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written in English or did not focus on non-hormonal treatment for menopausal symptoms were excluded. The search was conducted independently by two reviewers, and further supervised by a third, reliable member of the research group. Any discrepancies were resolved by discussion. The data were extracted and summarized using a narrative synthesis approach.

**Results**

EARLY MENOPAUSAL SYMPTOMS

Vasomotor symptoms (VMS) such as "hot flashes" and "sweating" affect 75-85% of menopausal women and often also impact premenopausal women with wide ethnic and racial variations in prevalence, frequency, and severity [1]. They frequently constitute the pathognomonic sign of the incipient depletion of gonadal function. They start suddenly with flushing of the skin on the face and chest and a sense of widespread warmth followed by profuse sweating. The duration and frequency are not constant, and in most cases, the symptoms last for a few minutes, more frequently during the night or in moments of stress [2]. VMS also occur after some time of acute estrogen deficiency and are determined by dysfunctional alterations in hypothalamic thermoregulatory centers. The pathogenetic mechanism is complex and seems to be determined by fluctuations in catecholamines, especially norepinephrine, at the level of the preoptic nucleus of the hypothalamus. Most experimental investigations concur that the initiation of hot flashes and sweating is due to a central instability of adrenergic tone caused by the reduction in the activity of endogenous opioids [3, 4]. Based on this mechanism, many drugs acting on central neurotransmitters also have beneficial effects on these disorders [5]. Longitudinal studies have observed an average persistence of VMS between 5 and 10 years before their spontaneous resolution. However, a small but significant percentage of women report bothersome hot flashes with sweating even 10 years after their last menstrual cycle [6, 7]. Data highlighted by the Study of Women's Health Across the Nation (SWAN: Heart Study) suggested a possible link between VMS and adverse outcomes for women's health. More intense and persistent vasomotor symptoms have been associated with an increased risk of cardiovascular diseases, especially when associated with insulin resistance and obesity [8, 9]. VMS have also been linked to lower mineral density and increased bone turnover [10, 11]. The psycho-emotional picture of the climacteric and menopause is difficult to assess due to the subjectivity of the symptoms. Studies conducted have reported contradictory results, and it's undeniable that environmental and family changes have an effect on a woman's psyche. Therefore, the psychological effects of estrogen deficiency, primarily present in the pre- and perimenopausal period rather than the postmenopausal one, are not easily identifiable and sometimes appear debatable. It's challenging to establish whether phenomena commonly reported and generally attributed to hormonal deprivation, such as emotional instability, depression, anxiety, irritability, and sleep disturbances, are instead a consequence of factors external to the hormonal context, such as the changing social role of the individual woman within the family group and its modifications. Nevertheless, the psychological state can be indirectly influenced by estrogen deficiency: various estrogen-deprivation symptoms such as hot flashes and poorer sleep quality may be sufficient to alter a woman's psychological balance [12]. Hormones, physical exercise, and placebos have a beneficial effect on both hot flashes and the psycho-emotional aspects of the climacteric through a change in endogenous opioid levels [13].

VULVOVAGINAL ATROPHY (VVA) and GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

Vulvovaginal atrophy (VVA) with symptoms of vaginal dryness, vulvar irritation, and dyspareunia is strongly associated with the tissue sensitivity of the genitalia to reduced estrogen levels and is

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prevalent in peri- and post-menopause. An epidemiological study with a large sample of women over 45 years observed a prevalence rate of 45%; starting from 4% in early peri-menopause to 21% in late peri-menopause, increasing to 47% within 3 years after the last menstrual cycle [14]. Alongside vulvovaginal atrophy, painful urination and recurrent urinary tract infections are often present. Hence, in 2014, a Consensus Conference among experts from the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) proposed a new nomenclature, replacing the terms vulvovaginal atrophy and atrophic vaginitis with the term Genitourinary Syndrome of Menopause (GSM), deemed more precise and comprehensive [15]. Unlike vasomotor symptoms (VMS), GSM is a progressive chronic condition that doesn't tend to improve over time but requires prolonged treatments, after cessation of which the symptoms tend to reappear. For the correct therapy of vulvovaginal disturbances in menopause, other non-estrogen-related etiologies should be excluded, as various inflammatory conditions of the vulva such as contact dermatitis, squamous hyperplasia, lichen sclerosus, lichen planus, or neoplasia can cause similar disorders. Patient history should include an inquiry into the use of exogenous agents like soaps, perfumes, powders, or sanitary products that can mimic or exacerbate vulvovaginal irritation due to atrophy. The objective examination should involve microscopic examination of vaginal smears to assess the vaginal maturation index (VMI), which is the ratio between parabasal, intermediate, and superficial squamous cells. Vaginal pH can also be useful in determining hormonal influence [16]. All these investigations aid in the diagnostic process of VVA, but there isn't a singular diagnostic method. Treatment can be gradually approached based on the severity of symptoms.

MANAGEMENT OF MENOPAUSAL SYMPTOMS:

1. LIFESTYLE MODIFICATIONS

Physical Exercise: Consensus on the benefit of proper physical exercise for the most common menopausal symptoms has not been reached, as data from various studies aren't always consistent, and many are purely observational. A Cochrane Review analyzed 5 RCTs (733 women) comparing physical exercise with inactivity, yoga, and hormone replacement therapy (HRT). It concluded that there isn't sufficient evidence to demonstrate that physical exercise is an effective treatment for menopausal vasomotor symptoms, whether compared to controls, HRT, or yoga [17]. While physical exercise alone may not effectively control the most frequent menopausal symptoms, it cannot be denied that a proper lifestyle brings slight improvements in sleep quality, depression, and insomnia, which often affect women in this delicate transition between life phases [18].

Diet: At any age, not just during menopause, maintaining a proper diet helps improve quality of life. It's recommended to follow the classic Mediterranean diet, rich in fruits, vegetables, legumes, calcium, and Vitamin D, and low in fats and sugars. In women over 50, calcium and Vitamin D supplementation has proven highly effective in the preventive treatment of osteoporosis. The best results are obtained with calcium dosages of 1200mg/day alone or combined with 800UI of Vit. D [19].

2. BEHAVIORAL THERAPIES

Cognitive Behavioral Therapy, Behavioral Techniques, and Meditation: Some RCTs have shown that cognitive-behavioral treatments combining relaxation techniques, sleep hygiene, and a positive psychological approach to menopausal symptoms are very effective in reducing the negative perception of hot flashes, even though they don't reduce their frequency. Studies were conducted in both healthy women and those with a history of breast cancer, reporting similar results, namely a benefit in terms of reducing hot flashes [20, 21].

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3. ALTERNATIVE MEDICINE REMEDIES

Acupuncture is an alternative medicine technique that involves inserting needles at specific points on the human body to promote health and well-being. Acupuncture treatment is almost devoid of side effects, as confirmed and recognized by the WHO in 1997. Within menopause, this ancient "alternative medicine" has proven effective in treating some symptoms induced by hormonal changes in this phase of a woman's life, such as reduced estrogen levels and increased gonadotropins (LH and FSH). Studies suggest that acupuncture increases estrogen levels and reduces LH levels. Moreover, it increases endorphin production, leading to a reduction in the intensity of hot flashes, stabilizing body temperature control. The most credible hypotheses suggest that acupuncture is a form of neurophysiological (sensory) stimulation that acts through a mechanism of peripheral (needle insertion points) and central (brain and spinal cord) control, releasing neurotransmitters that reduce vulnerability to hot flashes, including serotonin and endorphins. However, much of the mechanism of action remains to be explained. In addition to this specific effect, the "placebo" effect, which is neurobiological in reality, of positive expectations towards this method should be considered. The more positive the expectation, the more the beneficial effects of acupuncture may be amplified by the person's trusting attitude. A Cochrane review demonstrated that acupuncture, while less effective than hormone therapy, yielded better results in reducing vasomotor symptoms compared to the placebo [22]. A recent meta-analysis of 12 studies also confirmed that acupuncture improves vasomotor symptoms, their frequency, and severity, enhancing the quality of life [23].

Breathing Techniques: These techniques involve slow, deep breathing using the diaphragm, reducing the brain's stress mediators and facilitating relaxation. In an intriguing randomized study involving 218 menopausal women, the effectiveness of breathing techniques in controlling hot flashes and mood disturbances during menopause was assessed. Enrolled women were instructed on applying breathing techniques when experiencing hot flashes through explanatory DVDs and/or brochures. The conclusions, however, were unsatisfactory in proving that stimulated breathing provides clinical benefits for vasomotor symptoms or other menopausal symptoms in women with a history of breast cancer or healthy menopausal women [24].

Hypnosis: Hypnosis is a natural state of consciousness that, using the therapist-patient relationship, creates a series of "plastic mono-ideisms" that privilege right hemisphere activity over the left, resulting in a range of positive responses, both emotionally (such as increased confidence and self-esteem) and organically, resolving pathologies with a pronounced psychosomatic component. The endocrine system is an important tool for communication between the mind and the body. Hypnosis acts by expanding the effectiveness of positive emotions, either new or already present in the hippocampus memory. Plastic mono-ideism stimulates and guides brain plasticity, expressing itself through biochemical and emotional changes. During menopause, this results in improving a woman's adaptability to the new situation, increasing opportunities for psycho-dynamic reprocessing and growth in self-esteem, finding new existential stimuli that make her feel once again at the center of her existence, the unique and irreplaceable manager of her complete and harmonious well-being. A controlled, single-blind clinical study involving 187 post-menopausal women reporting a minimum of seven hot flashes per day or at least 50 hot flashes per week highlighted greater effectiveness of hypnosis compared to structured active attention, reducing the number and intensity of hot flashes by 74.2% and 17.1%, respectively [25]. Another study compared hypnosis efficacy in reducing hot flashes to Gabapentin, finding similar efficacy [26].

Chiropractic (or Chirotherapy): From the Greek "cheir" (hand) and "praxis" (action), chiropractic is an alternative medicine that aims to maintain and restore human health, ranging from diagnosis to treatment and prevention of its functional deficiencies. It focuses on the integrity of the nervous system, assuming that it controls all other systems of the human body and paying particular attention

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to the bony spinal column containing it, presupposing that spinal cord dysfunctions may interfere with what chiropractors define as the "innate ability of the body to self-heal" ("innate intelligence"). Unfortunately, evidence supporting this technique in improving vasomotor symptoms and menopause-related sleep disturbances has not been established, as highlighted by a recent review compiling all available literature data [27].

4. NON-HORMONAL PHARMACOLOGICAL THERAPIES

Clonidine: Belongs to the category of α2 agonists and in many countries is the only non-hormonal drug used for managing hot flashes in menopause. Stimulation of central α2-adrenergic receptors decreases the release of catecholamines, especially norepinephrine, which play a significant role in the genesis of hot flashes by raising blood pressure and triggering vasomotor disturbances. Several studies demonstrate the effectiveness of these drugs in controlling the number, intensity, and duration of hot flashes. One, in particular, tested this drug in women with a history of breast carcinoma, showing a significant reduction in hot flashes and an improvement in the quality of life [28]. Unfortunately, these drugs manage vasomotor symptoms well at dosages often associated with the appearance of unacceptable side effects. Patients already suffering from initial hypertension are the best candidates for this type of therapy.

Dosage: 0.15mg/day orally, up to a maximum of 0.10mg twice a day.

Side effects: orthostatic hypotension, sedation, depression, weakness, fatigue, nervousness, agitation, decreased libido, and gastrointestinal disturbances.

Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI): Despite these drugs' primary use for anxiety and depression disorders, they can be used as a second line of treatment for menopause disorders if HRT is not recommended. Among SSRIs, Paroxetine gained FDA approval in 2015 for controlling hot flashes in menopause, as it has shown the best scientific evidence [29]. Alongside Paroxetine, other drugs in this class, such as escitalopram, citalopram, and sertraline, have been studied for their effects on reducing the frequency and severity of hot flashes [30]. SNRIs like venlafaxine and desvenlafaxine have been used in treating menopausal symptoms, especially in women for whom HRT was not advised [31]. Since some SSRIs inhibit the activity of cytochrome P450 [32], an enzyme involved in Tamoxifen metabolism, women taking Tamoxifen are better off with an SNRI.

Dosage: Paroxetine 10mg/day. Venlafaxine 75mg/day.

Side effects: dry mouth, nausea, constipation, decreased libido.

Antiepileptics (Gabapentin and Pregabalin): Analogous to gamma-aminobutyric acid, they bind to voltage-dependent calcium channels, decreasing the activity of numerous neurotransmitters like glutamate, norepinephrine, and substance P. Their primary use is in diabetic neuropathy and post-herpetic neuralgia. Several studies have tested their efficacy in reducing the number of hot flashes during menopause. A meta-analysis confirmed that Gabapentin is effective in reducing hot flashes, both those induced by natural menopause and those caused by Tamoxifen use [33]. Conflicting results among studies arise from the search for the right drug dosage to achieve the desired effect and minimize side effects. An example of this is Pinkerton et al.'s study [34], which observed a reduction in the number and severity of hot flashes but had to suspend 5% of the patients treated with Gabapentin compared to the placebo due to the severity of the drug's side effects. Gabapentin can be an excellent treatment choice for women with sleep disturbances caused by hot flashes because it induces drowsiness [35]. Regarding Pregabalin, it has also shown effectiveness in reducing hot flashes but is still underexplored, especially in comparison to Clonidine [36] and Gabapentin [37].

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Dosage: Gabapentin 300mg/day, up to a maximum of 300mg three times a day. Pregabalin 75-150mg twice a day.

Side effects: dry mouth, nausea, constipation, decreased libido.

Beta Blockers: They have been proposed as they reduce palpitations and anxiety, although their impact on managing hot flashes or insomnia is limited [38].

Stellate Ganglion Block (SGB): It's a technique widely used in anesthesia for pain treatment and might be a significant promise for controlling menopause symptoms, but further studies are needed. The stellate ganglion is a bilateral nervous structure located in the C6-T2 region of the spinal cord, which can be safely inhibited through ultrasound-guided injection of local anesthetic at the C6 level. The mechanism of action in controlling hot flashes is still unknown, and severe complications, such as transient seizures or hemorrhages, rarely occur [39]. Four uncontrolled open-label randomized studies have shown that SGB reduces hot flashes, with results ranging from 45% to 90% for a minimum of 6 weeks up to several months after the block [40–43]. A controlled randomized study involving 40 menopausal women, either natural or surgical, compared the effects of SGB with bupivacaine against subcutaneous saline injection on the total frequency of VMS and moderate to severe symptoms. During a 6-month follow-up, the frequency and intensity of hot flashes were monitored daily in the clinic using skin conductance monitors. There were no significant differences between the two groups in the overall frequency of VMS, but the frequency of moderate to very severe VMS was significantly reduced in the active group compared to the sham group. The objective frequency of VMS was also reduced to a greater extent in the active treatment group without related adverse events [44]. Therefore, SGB could represent an effective non-hormonal treatment for VMS, but further studies with larger samples are required.

Neurokinin 3 Receptor Antagonists: It has been highlighted that a Neurokinin 3 receptor antagonist (NK3Ra) improved vasomotor symptoms in menopausal women without the need for estrogen exposure, both in the short and long term. This is a Phase II study, randomized, double-blind, placebo-controlled, and crossover, conducted on 37 women aged between 40 and 62 years who reported at least seven hot flashes within 24 hours. The women received the drug at a dose of 40 mg twice a day for 4 weeks, followed by a 2-week washout period. At the end, the women received either the placebo or the drug for 4 weeks, depending on which they had not received during the first intervention period. The oral NK3Ra antagonist MLE4901 reduced the frequency of hot flashes by 72% on the third day of treatment compared to baseline and by 51% compared to the placebo. The effect was sustained for all 4 weeks of the study without attenuation. Besides improving the frequency of hot flashes, the severity of vasomotor symptoms also significantly improved, with a reduction of 38% compared to baseline on the third day, increasing to 44% on day 28. According to the authors, signals mediated by Neurokinin 3/NK3R are a key factor in menopausal hot flashes that can be attenuated by administering an oral NK3R antagonist without the need for estrogen intake [45]. More recently, a qualitative systematic review compared the results of various controlled randomized clinical trials using Neurokinin 3 receptor antagonists (NK3Ras) with those using serotonin-norepinephrine reuptake inhibitors (SNRIs) for the non-hormonal treatment of hot flashes and night sweats in menopause. Examined studies using NK3Ras reported superior efficacy and better safety/tolerability compared to those using SNRIs [46]. Phase 3 trials will be necessary to confirm the efficacy, safety, and tolerability data of these new NK3Ras drugs. However, phase 2 results suggest they are more effective than SNRIs for non-hormonal treatment of VMS in menopause. Therefore, NK3Ras could radically change VMS treatment and particularly represent the preferred non-hormonal therapy in menopausal women with a history of breast or uterine cancer. Impaired neurological pathways, alongside molecular mechanisms, could be responsible for the process of uterine aging in patient transitioning to menopause [47].

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## 5. HERBAL PRODUCTS AND PLANT EXTRACTS

Cimicifuga Racemosa (Black Cohosh): It is an extraordinarily decorative garden plant distinguished by its spectacular flowering. Green bugs strictly avoid it, a characteristic that was fundamental in creating the plant's name (from the Latin cimex = bug and fuga = repel). It was used in traditional medicine practiced by Native American shamans in North America, who used the rhizome cut into slices to treat various diseases, also depending on the time of day it was collected. The active ingredients of Cimicifuga Racemosa are TRITERPENIC GLYCOSIDES (Xiloside actein, Cimicifugoside, 27-deoxyactein, other aglycones) characterized by the structural presence of a cyclopropane ring (Fig.1). Other active constituents include: the isoflavone formononetin, isoferulic acid, salicylic acid, tannins, resins, fatty acids, starches, and sucrose. The mechanism of action of Cimicifuga is not yet well understood. Selective modulation of estrogen receptors (SERMs), a partial serotonin agonist mechanism, antioxidant, and anti-inflammatory effects have been suggested [48]. Several studies have shown that therapy with Cimicifuga has no effect on serum concentrations of FSH, LH, E1, E2, P, SHBG, vaginal maturation index, and endometrial thickness, demonstrating that the compound can act without estrogenic effects [49, 50]. It has long been used for treating neurovegetative disorders during menopause. A Cochrane systematic review of 16 RCTs, involving 2,027 symptomatic menopausal women [51], found no consistent significant difference between cimicifuga and placebo in the frequency of VMS, concluding that there is no firm evidence to support the use of Black Cohosh in controlling menopausal symptoms. Inconsistency in the results might be due to the use of different parts of the plant or different extraction methods of the products used in various studies [52]. Due to its SERM-like mechanism of action, Cimicifuga has been proposed for controlling VMS in patients with a history of breast cancer, but this use is still controversial. Only a few RCTs have been conducted to prove the effectiveness and safety of Cimicifuga in this type of patient. In the RCT by Jacobson et al., 85 breast cancer survivors, mostly on tamoxifen treatment, were assigned to Cimicifuga or placebo. No significant difference was observed in the frequency and intensity of VMS with both treatments; however, in the cimicifuga group, a significant improvement in sweating was noted [53]. The initial effects appear after 4 weeks of treatment; it should be taken for at least 12 weeks. Regarding the side effects of cimicifuga, earlier, suspected hepatotoxicity had been reported, but a subsequent meta-analysis of five double-blind, randomized, controlled clinical studies involving 1,020 women found no evidence that cimicifuga has adverse effects on liver function [54].

Dosage: Cimicifuga 20mg 1cp × 2 times/day.

Side effects: Constipation, weight gain, abdominal cramps.

Phytoestrogens: these are plant-derived substances that exhibit estrogenic hormone-like properties. Ubiquitous in the plant world, high concentrations are found in soy, and though in lesser amounts, in many types of fruits, vegetables, and whole grains. Despite not being steroid in nature (they are heterocyclic phenols), functionally and in part structurally, they resemble 17 beta-estradiol (Fig.2). Due to this structural analogy, they compete for the same estrogen receptor sites (ERα and ERβ), sharing the same affinity but possessing an activation capacity 100 to 1,000 times lower. Over 300 plants with estrogenic activity have been identified, of which only a few are edible. Chemically, phytoestrogens can be grouped into three main categories: Lignans, Coumestans, and Isoflavones.

Lignans are represented by matairesinol and secoisolariciresinol, which are activated by intestinal bacterial flora into enterodiol and enterolactone. Present in almost all cereals and in a large number of plant substances, they have higher concentrations in sesame and flax seeds.

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Coumestans form during germination, and the main representative of this group is coumestrol, found in significant quantities in bean sprouts, Brussels sprouts, clover, and sunflower seeds.

Isoflavones are represented by daidzein, genistein, biochanin A, and formononetin. They are the most active and widespread, hence considered the archetypal phytoestrogens. They are present in soy and all its derivatives: flours, oil, milk, cheese, soy sauces. They are also found in other legumes: lentils, beans, peas, broad beans, chickpeas, and in whole grains like wheat, rice, barley, rye, and oats.

Widely present in the diet of Eastern populations (soy and derivatives), they represent the most used and studied phytoestrogens. Lesser scientific evidence exists for lignans and coumestans, which constitute the main dietary source of phytoestrogens in Western populations (whole grains, legumes, fruits, vegetables). The therapeutic effects of phytoestrogens are controversial since potential benefits often appear insignificant and variable among different individuals. The variability in the efficacy of these products may be due to individual variations in metabolism, the multiplicity and variability in the concentration of active principles present in each product (depending on the location and characteristics of the cultivation soil, climate, storage, and extraction methods), as well as the lack of selectivity and specificity of these active principles.

Phytoestrogens exhibit two main activities: antioxidant and estrogenic. The antioxidant activity is primarily expressed by blocking free radicals in the biological environment. The estrogenic activity is due to their molecular structure, very similar to that of ovarian estrogens, and is exerted through both hormone-like and non-hormonal mechanisms. Through a hormonal mechanism, phytoestrogens bind to estrogen receptors α and β, predominantly to the beta receptor, which could form the basis for potential tissue specificity. In vivo, phytoestrogens can also have anti-estrogenic actions because they reduce FSH secretion and stimulate the synthesis and release of sex hormone-binding globulin (SHBG) in the liver, reducing the free quota of endogenous estrogens in the blood. Through a non-hormonal mechanism, they inhibit numerous enzymes (aldehyde-alcohol dehydrogenase, steroid dehydrogenases) important in the metabolism of alcohol, serotonin, norepinephrine, and dopamine [55]. Due to these action characteristics, phytoestrogens can modulate any deficiencies or excesses of endogenous estrogens in vivo. In fact, if the level of endogenous estrogens is low, phytoestrogens substitute their functions by occupying and stimulating, albeit much more weakly, specific receptors. However, when the level of endogenous estrogens is high, phytoestrogens compete with them for receptor occupancy, thus counteracting a much stronger estrogenic stimulation (100 - 1,000 times more potent).

Given these properties, the fields of application for phytoestrogens appear to be diverse. Experimental and epidemiological evidence dating back to the early 1950s reported favorable effects on menopausal symptoms. However, a meta-analysis by Eden, encompassing more significant randomized controlled trials (RCTs) in terms of sample size and duration of observation, did not reveal consistent results on the efficacy of phytoestrogens in controlling menopausal disorders [56]. Theoretically, phytoestrogens could increase the risk of adverse effects associated with their estrogenic activity, such as breast and endometrial neoplasms and thromboembolic pathologies. However, epidemiological evidence in Eastern populations suggests that long-term intake of soy-based products may reduce the risk of breast cancer. These findings do not apply to Western women who consume soy supplements or undergo phytoestrogen treatments for only a few months or years after menopause.

Palacios et al. conducted a randomized controlled study involving a total of 395 menopausal women treated with 70 mg of soy isoflavone extracts compared to a placebo with a 3-year follow-up. No cases of endometrial hyperplasia or neoplasia or breast carcinoma were detected in the study. There were also no increases in endometrial thickness or breast tissue density during or at the end of the 3-year

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study [57]. Similar results were reported by Steinberg et al. [58]. Ollberding et al. conducted a prospective cohort study on 46,027 women with intact uteri followed for an average of 13.6 years. With meticulous dietary history collection, the precise dietary intake of isoflavones for each participant was calculated. Data analysis revealed a significant inverse relationship between dietary intake of isoflavones and the risk of developing endometrial cancer [59].

Regarding thromboembolic pathologies, no specific RCT data are available in the literature. Recent literature reviews and meta-analyses have highlighted that in menopausal women, isoflavones improve blood flow through vasodilation but do not affect the vascular wall [60]. In conclusion, after over four decades of research on phytoestrogens, their therapeutic effects have not been satisfactorily elucidated. Their efficacy in climacteric symptomatology, particularly in relation to vasomotor disorders and bone demineralization, is modest compared to HRT but superior to that of placebo. It's worth noting that the quantity of purified isoflavones to be taken remains the same, regardless of the symptoms being treated. Frequent adverse reactions or severe side effects among users have not been reported.

Dosages: vary from 50 to 90 mg/day for an initial therapy, reduced to 25-45 mg/day for maintenance.

Side effects are rare and limited to abdominal pain, muscle aches, and drowsiness.

Ginseng: It is considered an aphrodisiac with estrogenic actions that improve menopausal symptoms. A placebo-controlled study was conducted in the United States by a Swiss multinational, a major producer and marketer of ginseng-based products, lasting 16 weeks on a sample of 400 postmenopausal women. Although vasomotor disturbances were not reduced, improvements were reported on depression assessment scales, overall health, and well-being. Evaluation of estrogenic effects, including cellular maturation index and plasma levels of FSH and E2 after 16 weeks, showed no difference between the effects of ginseng and those of the placebo [61, 62]. Further independent studies are desirable to more thoroughly verify whether ginseng can offer any real benefit for menopausal women.

Vitamin E: It is indicated as a substance capable of improving vasomotor disturbances, based on pilot studies and citations reported in medical and generic literature. The first randomized, placebo-controlled, crossover study on the effects of vitamin E in postmenopausal women demonstrated only marginal clinical benefits in treated women. Among 105 women who completed treatment with 400 IU of vitamin E or placebo twice daily, the reduction in hot flash frequency was similar (25% and 22% respectively). Cross-analysis of data from patients who completed the 4 weeks of treatment showed a small but statistically significant clinical improvement for vitamin E: one less hot flash per day compared to the placebo group [63].

Purified Pollen Extract (PPE): It is a supplement composed of a combination of purified dry pollen extract (GC Fem) and pistil (PI 82) from plants of the Poaceae family, with the addition of vitamin E. Each tablet contains 40 mg of GC Fem, 120 mg of PI 82, and 5 mg of vitamin E. The beneficial effects of PPE on vasomotor symptoms may stem from the inhibition of serotonin reuptake at the synaptosomal junction, with a mechanism of action similar to SSRIs. PPE contains none of the common phytoestrogens and does not exhibit estrogenic effects. A clinical study by Winther et al. using 2 tablets/day of PPE for 3 months demonstrated the efficacy of PPE in treating menopausal symptoms such as sweats, hot flashes, and insomnia in healthy women. PPE also showed positive effects on other symptoms related to quality of life, such as dizziness, mood swings, and fatigue, often associated with vasomotor symptoms [64]. Data for PPE in women with breast cancer are not available, but the lack of estrogenic effect demonstrated in a preclinical study by Hellstrom suggests that PPE may be a suitable option. In this study, high-performance liquid chromatography found low and sub-effective concentrations of daidzein and genistein in PPE, while genistein, formononetin, and

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biochanin were not detected [65]. Additionally, in the aforementioned study by Winther, serum measurements of FSH (follicle-stimulating hormone), E2 (estradiol), T (testosterone), and SHBG (sex hormone-binding globulin) before and after treatment did not show any hormonal effect of PPE.

## 6. TOPICAL THERAPIES

Vaginal Lubricants and Moisturizing Creams: They are used as the first line of defense to alleviate milder symptoms of GSM. Vaginal gels made of water, silicone, oil, or hyaluronic acid offer increased tissue hydration and, when applied to the vagina and external genitals, provide relief from symptoms and sexual discomfort. However, these products do not reverse the aging of urogenital tissues, and symptomatic improvement is often temporary, requiring frequent reapplications. According to a randomized controlled clinical study, hyaluronic acid-based gel more effectively improves clinical disturbances than others and can be considered a valid alternative to estrogen-based treatments to alleviate vaginal dryness symptoms [66]. However, a significant disadvantage of these products is poor compliance. A 2013 survey of over 3000 postmenopausal women reported patient experiences and perceptions of available treatments. Concerning all vaginal therapies used, women reported high dissatisfaction due to bothersome application procedures and vaginal discharge inconvenience [67].

Vaginal Laser: It represents a non-pharmacological second-line option, particularly useful for treating GSM in symptomatic women unresponsive to previous treatments who refuse or cannot take hormones. This procedure, using the thermal effect of the laser, causes microlesions of the vaginal mucosa necessary to trigger a process of tissue reorganization and rebalancing with collagen neogenesis. The laser's action reactivates the functionality of the structures involved at the urogenital level, improving associated symptoms in a completely safe and painless manner. It initiates a tissue regeneration process that lasts several weeks, but the stimulation is immediate, and significant improvements are observed after the first treatment. The two main types of lasers used for GSM treatment are the fractional microablative CO2 laser and the non-ablative photothermal Erbium: YAG laser. The CO2 microablative vaginal laser was introduced in 2014, and several histological studies have confirmed its effectiveness in modifying and rejuvenating vulvovaginal tissue with improvements in vaginal atrophy symptoms [68, 69]. It utilizes the heat generated by water vaporization in the deeper lamina propria cells. Energy and microablative impact are precisely delivered to limit damage to surrounding tissues. The final effect of this hyper-regulated lesion includes neocollagenogenesis and neovascularization, improving vaginal pH, moisture, blood flow, and the turgor of the fundamental substance, which also demonstrates at the ultrastructural level [70]. The effectiveness of the Erbium: YAG laser for vaginal atrophy was first described in 2015. Vizintin and colleagues reported this non-surgical and non-ablative technique, producing vaginal collagen hyperthermia followed by remodeling and synthesis of new collagen fibers. This results in increased tightness and elasticity of the vaginal tissue, consequently improving vaginal atrophy symptoms [71]. The mechanism of action of these two laser technologies with subsequent tissue modifications produced by both have led to the utilization of their potential to treat vulvovaginal symptoms caused by hypoestrogenism. These benefits observed immediately after treatment tend to remain valid even in long-term follow-ups. A recent review demonstrates that almost all studies show statistically significant improvements in vulvovaginal symptoms and sexual function without severe adverse events related to the procedure, even in breast cancer survivors [72] [71]. These women report the same genital symptoms as menopause, with the aggravating factor that their oncological condition worsens these disturbances or manifests them at a younger age, with huge consequences for their quality of life, considering that the various restrictions in treatment options make their management more challenging. Therefore, vaginal laser treatment can be considered an effective and safe innovative therapy, minimally invasive for treating symptoms of Genitourinary Syndrome of Menopause (GSM) in women who do not want or cannot undergo hormonal therapy. It is particularly important to maintain a healthy vaginal

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environment in postmenopausal patients, as chronic oxidative stress might be a risk factor for the development of cervical intraepithelial neoplasia, as recently hypothesized [73].

**Discussion**

Several pharmaceutical preparations, botanical products, supplements, over-the-counter products, and behavioral practices are used, even as self-prescriptions, to treat menopausal disorders. Scientific evidence for many of these substances and procedures is certainly limited, and information regarding their beneficial effects is sometimes anecdotal. Certainly, none of these treatments can effectively improve the entire symptomatic range of the climacteric syndrome as effectively as estrogen, nor have any of these treatments demonstrated the ability to reduce long-term risks to women's health associated with estrogen deficiency and advancing biological age.

For those women experiencing menopausal symptoms but unwilling or unable to use hormone therapy (HT), many other therapeutic options are available, although there is still insufficient evidence regarding their actual effectiveness. All postmenopausal women should actively take appropriate measures to improve their lifestyle, such as avoiding smoking and engaging in regular physical activity. Most importantly, reducing or avoiding alcohol and spicy foods, lowering stress, and managing overweight, are considered risk factors for the onset of more severe menopausal symptoms. Non-hormonal therapies should be tailored based on their primary mode of action. For example, gabapentin would be the first choice for a woman reporting main symptoms of hot flashes, sweating, and restless leg syndrome; or hypertensive women experiencing vasomotor symptoms might benefit from clonidine. Of particular interest is the use of phytoestrogens during menopause, which are steroid compounds with estrogenic and anti-estrogenic properties and if used as supplements, can primarily exert estrogenic effects. Among the experimental therapies is Ovarian tissue cryopreservation and transplantation, potentially capable of inducing a resumption of endogenous estrogen production, and therefore avoiding HRT [74]. Aromatase inhibitors could also play a role among the adjuvant treatments for conditions rarely associated with menopause, such as symptoms related to endometriosis [75]. The presence of endometriotic lesions in postmenopausal women is rare but documented in literature, and these lesions can sometimes reach considerable sizes [76]. The possibility of using antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), has shown efficacy in reducing hot flashes significantly in frequency and severity. For the treatment of Genitourinary Syndrome of Menopause (GSM), first-line treatments include local therapies with moisturizing creams, silicone, lubricating gels, oil, or hyaluronic acid. Vaginal laser treatment represents a non-pharmacological second-line option, innovative, effective, safe, and minimally invasive for treating GSM symptoms, particularly in women who are highly symptomatic and unresponsive to previous treatments. However, it is worth noting that the proper management of the menopausal transition remains an area yet to be fully explored. Studies such as SWAN (Study of Women's Health Across the Nation) and the Melbourne Women’s Midlife Health Project have provided numerous epidemiological, physiological, and descriptive data on the organic changes that occur during the menopausal transition. However, this data primarily concerns younger post-reproductive age women. There are still numerous gaps in knowledge about the causes of hot flashes or the correlation in the post-menopausal phase between vasomotor symptoms and cardiovascular diseases in older women compared to younger ones. Furthermore, gaps still exist in the relationships between menopause and sleep-related or mood-related disorders, which can have significant social and economic repercussions in women in this age group. Premature menopause can raise the chances of experiencing menopausal symptoms and noncommunicable diseases. Therefore, it's crucial to grasp how reproductive factors are linked to the age at which menopause occurs [77].

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IMPLICATIONS

This narrative review underscores the need for more robust scientific evidence to support the use of non-hormonal therapies for menopausal symptoms, given the current limitations and empirical nature of many existing treatments. While these alternative therapies offer potential benefits, none match the comprehensive efficacy of estrogen in alleviating the full spectrum of climacteric symptoms or in mitigating long-term health risks associated with estrogen deficiency. Therefore, it is crucial to continue rigorous research to validate these options and tailor them based on their primary mechanisms of action. Moreover, lifestyle improvements, such as avoiding smoking, managing weight, reducing alcohol and spicy food consumption, and lowering stress, should be emphasized as foundational strategies for all postmenopausal women. There is a need for targeted, individualized treatment plans and for studies to bridge the knowledge gaps regarding menopause and its broader health implications.

STRENGTHS AND LIMITATIONS

This review offers a comprehensive summary of non-hormonal therapeutic options for managing menopausal symptoms and preventing long-term issues. The systematic search of multiple reputable databases ensures a thorough identification of relevant studies, providing a robust evidence base. Additionally, with this review we highlight the importance of individualized treatment based on the primary mechanisms of action, ranging from medical treatments to herbal products, plant extracts, supplements and topic therapies, promoting tailored therapeutic approaches. However, despite the comprehensive search strategy, the effectiveness of many non-hormonal therapies remains insufficiently proven, indicating a need for further rigorous studies. We also underscore the cautious use of phytoestrogens due to their potential estrogenic effects, yet the variability in response among individuals is not fully addressed. Finally, the ongoing uncertainties regarding the neuroendocrine causes of menopausal symptoms suggest that the development of more targeted therapies is still required, limiting the current applicability of some treatment recommendations.

**Conclusions**

Due to uncertainties regarding the neuroendocrine causes underlying menopausal symptoms, the development of targeted therapies is still ongoing. Further studies involving women in more advanced menopausal ages are needed, and future research should aim to discover the definite causes underlying menopausal symptoms, in order to gather more useful information to identify increasingly effective and safe therapies.

**Authors contribution**

Conceptualization, R.A. and G.R.D.; methodology, D.D.G.; data curation, I.R.; validation, A.D.; writing—original draft preparation, G.T. and A.V.; writing—review and editing, E.C. and A.D.; supervision, G.M. All authors have read and agreed to the published version of the manuscript.

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