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REVIEW ARTICLE

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Herbal medicine and climacteric: a systematic review of the main clinical outcomes

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Abstract

Introduction: The climacteric is the stage of life in which the transition from the productive or fertile period to the non-reproductive period occurs. Climacteric and menopause are intrinsically linked and may bring about various psychological and physiological changes. The use of medicinal plants (Herbal Medicine) is an important tool in an attempt to relieve symptoms. **Objective:** It was to develop a systematic review to present the main considerations and scientific evidence of the use of herbal medicines in climacteric and menopause to the reduction of symptoms and improvement of quality of life. **Methods:** The systematic review rules (PRISMA) were followed. The research was carried out from September to October 2022 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, covering scientific articles from various eras to the present day. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 121 articles were found. A total of 32 articles were fully evaluated and 23 were included in this systematic review. Most studies showed homogeneity in their results, with I^2 =96.7% >50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 30 studies with a high risk of bias and 37 studies that did not meet GRADE. An asymmetrical funnel plot does not suggest a risk of bias among small sample-size studies. In search of symptom relief and based on knowledge of the side effects of hormone replacement therapy, many women resort to alternative therapy with herbal medicines. The main results support that supplementation with soy isoflavones as a natural source of phytohormones is associated with a reduction in the frequency and intensity of hot flashes, a recurrent symptom in the climacteric. The formulated blend of four herbal extracts (*Glycine max, Cimicifuga racemosa, Vitex agnus-castus,* and *Oenothera biennis*) supports skin health and antioxidant status in women of menopausal age. Furthermore, purified pollen cytoplasm can be considered an effective non-hormonal treatment alternative for the treatment of vasomotor symptoms, as well as mood and sleep disturbances in peri and post-menopause. Three clinical trials using the Danggui Buxue Tang herbal formula have been shown to alleviate menopausal syndrome, providing solid scientific evidence of its effectiveness.

Keywords: Climacteric. Menopause. Treatments. Herbal medicine.

Introduction

In the context of women's physiology, the climacteric is the stage of life in which the transition from the productive or fertile period to the non-reproductive period occurs, due to the decrease in sex hormones, and sexuality gains priority over reproduction **[1-3]**. Menopause is an event within the climacteric and represents the last menstruation of a woman's life. Climacteric and menopause are intrinsically linked and may bring about various psychological and physiological changes **[1,2]**.

In this regard, knowing that the life expectancy of Brazilian women is currently estimated at 72 years, denotes that women have started to live longer, experiencing changes in their bodies that other generations have not been able to **[3,4]**. Climacteric is

considered a natural event, occurring as a result of ovarian failure and may or may not present symptoms called climacteric syndrome **[5,6]**.

In this sense, with the increase in longevity and the maintenance of the age at menopause, the woman will be able to spend more than a third of her life after the climacteric, which implies the concern with the treatment of the symptoms that accompany the period of comorbidities, associated to aging, aiming at a better quality of life **[7]**.

Although menopause, like aging itself, is a physiological event, the resulting decrease in estrogen and progesterone is associated with numerous negative repercussions on the female body **[2,8]**. The main problems that are presented by women in the climacteric are menstrual irregularities, vasomotor symptoms, insomnia, mood instability, urogenital atrophy, osteoporosis, cardiovascular diseases, cancer, and cognitive problems **[9]**.

As a corollary of this, the use of medicinal plants (herbal medicine) is an important tool for health professionals, users, researchers, and managers, which led the Ministry of Health to create the National Policy for Integrative and Complementary Practices in the SUS. Later, the National Policy on Medicinal Plants and Herbal Medicines and the National Program of Medicinal Plants and Herbal Medicines were also created **[10]**. In this context, therapy using phytohormones (phytoestrogens) can have estrogenic and antiestrogenic effects by occupying the receptors, thus proposing a symptomatic therapy for cases in which conventional hormone replacement therapy is contraindicated or not desired.

There are several alternatives to symptomatic phytohormone therapy to alleviate menopausal symptoms. The literature describes that *Cimicifuga racemosa* (L.), a new combination for *Actaea reacemosa* (L.), had beneficial effects on hot flashes in climacteric women, being one of the most studied and applied plants in these cases, as it presents a safer alternative **[11,12]**. Symptoms related to attitudes and behavior are subjective symptoms such as mood swings or depression. The literature states that hot flashes and other acute symptoms associated with the perimenopause period may become more intense close to menopause when circulating estrogen levels rapidly decrease **[1]**.

Thus, for relief or elimination of these symptoms, symptomatic therapy is indicated with the use of phytoestrogen concentrates against the effects of menopause, highlighting the use of symptomatic therapy by alternative and natural means **[13]**. The use of phytotherapy is a practice of great popular acceptance that involves several health professionals and the implementation of the National Policy on Medicinal Plants and Phytotherapeutics.

Therefore, the present study aimed to develop a systematic review to present the main considerations and scientific evidence of the use of herbal medicines in climacteric and menopause concerning the reduction of symptoms and improvement of quality of life.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and metaanalysis: //www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: *Climacteric. Menopause. Treatments. Phytoterapics. Herbal medicine*, and using the Boolean "and" between MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 121 articles were found that were submitted to the eligibility analysis and, then, 23 of the 32 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed

homogeneity in their results, with I2 = 96.7% > 50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 30 studies with a high risk of bias and 37 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

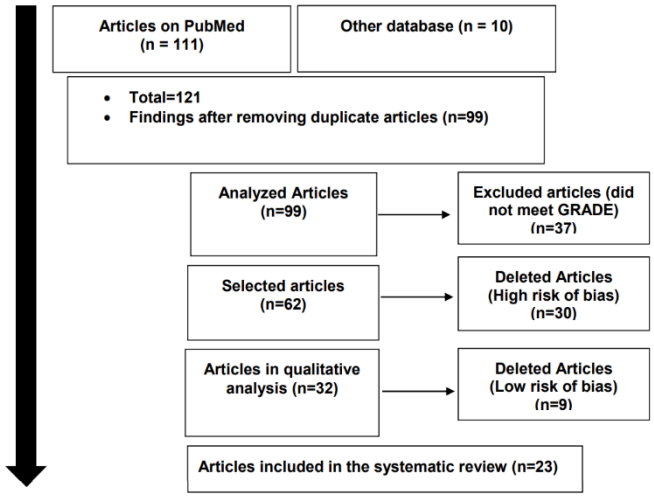
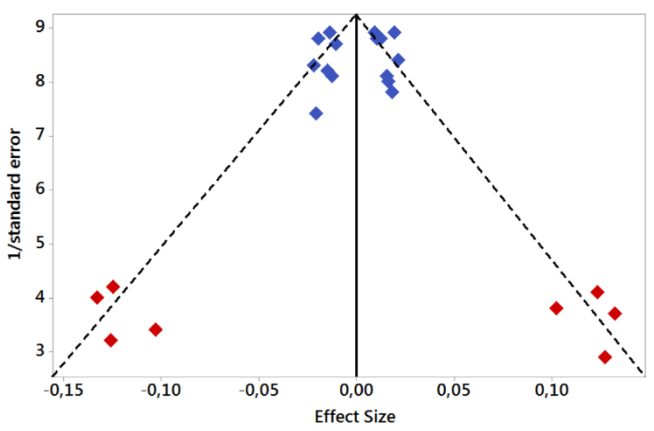


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph (studies shown in red color) and in studies with large sample sizes that are presented at the top (studies shown in blue color).

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot (studies shown in red color). High confidence and high recommendation studies are shown above the graph (studies shown in blue color) (n=23 studies).



Climacteric - Main Literary Findings

The World Health Organization (WHO) considers that the climacteric (perimenopause) comes to an end one year after menopause. Pre-menopause is the period that begins with the appearance of climacteric symptoms, that is, hot flashes or menstrual irregularities, almost always from the age of 45 **[14,15]**. The decrease in hormone levels is a fact that occurs in all women and starts around the age of 40. Some women may have a more pronounced picture of signs and symptoms, but all will reach menopause. The decrease or lack of female sex hormones can affect various parts of the body and determine signs and symptoms known as a climacteric syndrome **[16]**.

In the climacteric, the ovaries do not respond to pituitary stimulation, causing hormonal changes and an increase in pituitary gonadotropins, luteinizing hormones, and follicular stimulating hormones. Thus, there is a decrease in estrogen production by the ovary and a loss of regeneration and inhibition at the hypothalamic-pituitary level. As a result, the decrease in estrogen leads to metabolic changes, clinical signs, and climacteric symptoms at various levels such as morphological, hormonal, metabolic, functional, psychological, and cognitive **[17]**.

In this context, the most noticeable change is the spontaneous cessation of the menstrual cycle (menopause) and to consider a menopausal woman, menstruation must have ceased for one year. Once menopause is established, the woman reaches the end of her reproductive period, during the years that precede menopause **[18]**. The climacteric woman, who has a balanced emotional state, seeks a better quality of life **[15]**. The symptomatology of the climacteric is directly linked to estrogen deficiency and its intensity is generally proportional to the level of this deficiency. If there is a drop in circulating estrogens, as in cases of surgical removal or irradiation of the ovaries, the symptoms are usually intense and manifest almost immediately.

When the fall in ovarian function occurs more slowly and progressively, the symptoms are milder, sometimes even imperceptible. Between these extremes, there is a wide spectrum of symptoms, variable from one woman to another and subject to sociocultural and psychological conditions **[2,3,7]**. Sometimes, the climacteric goes unnoticed. The symptoms are those that characterize the climacteric syndrome, highlighting the fear of aging, concern with self-image, marital instability, empty nest syndrome, and competition with the husband **[19]**. Still, many women report psychological symptoms during the climacteric. Some experience anxiety and depression

but, generally, a woman's personality and premenopausal structure predisposes her to premenopausal syndrome **[20]**.

Furthermore, the skin is affected by estrogen deprivation, as well as general agerelated changes, easy bruising, dryness, hair loss and broken nails, elastic fibers and collagen degeneration, sebaceous and sweat glands become less active and blood vessels show signs of sclerosis. The distribution of hair also changes, there is an increase in the face and a reduction in pubic, axillary, and scalp hair purification, caused by the increase in the androgen-estrogen ratio. This condition is important for women's self-esteem and self-confidence, it is observed that postmenopausal changes in skin and hair affect the quality of life **[16]**.

Main Clinical Studies – Herbal Medicines in Climacteric and Menopause

The purpose of symptomatic therapy is to occupy hormone receptors, to supply the lack of hormones that can be used in the conventional way in which synthetic drugs are used, and the alternative through phytoestrogens. Studies have reported that women who used synthetic hormones had a higher incidence of cancer cell formation. Therefore, numerous studies are being carried out as complementary therapy, through food, in particular those that use soy isoflavones as a natural source of phytohormones **[1-3,13]**.

In this context, taking into account the search for naturally maintaining health, a promising area in the development of herbal therapies, regarding the treatment of climacteric symptoms, given that the current protocol for symptomatic therapy, through phytohormones (phytoestrogens), which can have estrogenic and antiestrogenic effects by occupying the receptors, has been considered an alternative means of treating the symptoms presented by women in this phase of life **[21]**. Soy, for example, is an important source of these compounds and has been associated with a reduction in the frequency and intensity of hot flashes, a recurrent symptom in the climacteric **[22]**.

Thus, in recent years, phytohormones, with hormone-like characteristics, have emerged to replace hormone replacement therapy **[23,24]**. Currently, Brazilian legislation has started to encourage the search for new therapeutic alternatives and even determines a list of essential medicines, such as soy, aimed at treating climacteric symptoms. In this sense, studies have shown that *Trifolium pratense* and *Cimicifuga racemosa* are already indicated by the Manual for Attention to Women in Climacteric **[25]**. According to Brasil (2008b) **[26]**, the main herbal medicines used are commonly a source of phytoestrogens due to their estrogen-like action, the most used being *Glycine max*, *Trifolium pratense*, and *Cimicifuga racemosa*, although there are many other herbal medicines for this purpose.

There are also specific herbal medications for the relief of mild and moderate depression and anxiety, also used in cardiology, neurology, and psychiatry, among others. For psycho-emotional symptoms, which may accompany this phase of a woman's life, it is worth mentioning the use of *Hypericum perforatum, Valeriana officinalis*, and *Melissa officinalis* **[27]**.

Also, menopausal symptoms and gynecological disorders (such as premenstrual syndrome and dysmenorrhea) are indications where pharmacological therapy can have serious adverse effects, so many women prefer to use herbal products to help with these symptoms. Thus, a study by Kenda et al. 2021 reviewed plants and derived products as alternative treatments. Results showed that black cohosh (*Cimicifuga racemose*) and red clover (*Trifolium pretense*) have been shown to significantly reduce menopausal symptoms in clinical studies, and to a lesser extent the use of fenugreek (*Trigonella foenum-graecum*), hops (*Humulus lupulus*), valerian (*Valeriana officinalis*) and soya (*Glycine max* and *Glycine soya*) for this indication. For premenstrual syndrome and premenstrual dysphoric disorder, chaste tree (*Vitex agnus-castus*) shows efficacy, but more clinical studies are needed to confirm such effect with the use of evening primrose (*Oenothera biennis*) **[28]**.

Added to this, skin aging is one of the most worrying issues during the postmenopausal period. Nutraceuticals containing estrogenic and antioxidant effects have gained much attention as an alternative therapy for delaying age-related skin changes in women after menopause. Based on this, a randomized, double-blind, placebo-controlled clinical study was developed by the authors Tumsutti et al. 2022 to evaluate the effects of a combination of nutraceuticals on skin health and antioxidant status in postmenopausal women. Postmenopausal women aged 45 to 60 years were enrolled and randomly allocated (n=110) equally to the treatment or placebo group (n=55 per group). The test product, a nutraceutical containing a mixture of *Glycine max, Cimicifuga racemosa, Vitex agnus-castus*, and *Oenothera biennis* extracts, was administered over 12 weeks, with dermatological parameters evaluated at baseline, week 6, and week 12. In addition, glutathione (GSH) and malondialdehyde (MDA) levels were detected at baseline and week 12 to assess antioxidant status. At week 6, skin roughness significantly improved in the treatment group, while at week 12, significant improvement and large effect sizes were seen in skin elasticity, roughness, smoothness, scaling, and wrinkles

compared to the placebo. Furthermore, GSH significantly increased while MDA significantly decreased in the test group compared to the placebo. These data indicate that supplementation with the formulated blend of four herbal extracts supports skin health and antioxidant status in menopausal women [29].

Furthermore, purified pollen cytoplasm (PPC) is a herbal medicine used to control vasomotor symptoms (VMS), sleep, and mood disorders in menopausal women who do not depend on hormone replacement therapy (HRT). Many studies have demonstrated its efficacy and safety in postmenopause, but little data is available on perimenopause. Therefore, a multicenter prospective observational study in symptomatic peri- and postmenopausal Italian women evaluating the effects of PPC therapy on hot flashes and other parameters included in the Greene Climacteric Scale (GCS). A total of 108 peri- and postmenopausal women (mean age 53.8±4 years) were recruited, with a 3-month follow-up of PPC treatment. A significant improvement in hot flashes and night sweats was found. Furthermore, all GCS items, except the loss of limb sensation, improved significantly after PPC therapy [30].

A randomized, double-blind, placebo-controlled clinical trial conducted by the authors Hyun et al. 2022 evaluated the safety of herbal extract and red ginseng (HRG) complex, which are used to relieve menopausal symptoms. This study recruited and divided 120 women with menopausal symptoms into HRG and placebo groups (60 women per group). Subjects received 2 g of HRG or placebo daily for 12 weeks. Adverse reactions, female hormone changes, and uterine thickness were observed and recorded at weeks 0, 6, and 12. The reactions of subjects who received HRG or placebo at least once were analyzed. A total of six adverse reactions occurred in the HRG group, while nine occurred in the placebo group; common reactions observed in both groups were genital, subcutaneous tissue, and vascular disturbances. However, there was no statistically significant difference between the administration groups and no serious adverse reactions occurred in either group, confirming the safety of daily intake of 2 g of HRG for 12 weeks by menopausal women [31].

Finally, the author's Wong et al. 2022 explored the efficacy and safety of Danggui Buxue Tang (DBT), a simple herbal formula, to improve the quality of life for women suffering from menopausal symptoms. A third clinical trial was conducted to determine the clinical efficacy of high-dose DBT over 12 weeks. The menopause-specific quality of life assessment (MENQOL) was used. Safety was defined as the absence of direct estrogenic effects, serum inflammatory cytokines such as interleukin IL-6, IL-8, and tumor necrosis factor TNF-α, known to be directly related to estrogenic reactions in menopausal studies. The third clinical trial indicated an overall improvement in all four MENQOL domains, providing further evidence of the efficacy of DBT demonstrated in the previous two trials. Random behavioral reactions of the three cytokines provided indirect indications that DBT improved MENQOL independently of estrogen activities. The three clinical trials using DBT to alleviate menopausal syndrome provided solid scientific evidence of its effectiveness [32].

Conclusion

It was concluded that in the search for relief of symptoms and based on knowledge of the side effects of hormone replacement therapy, many women resort to complementary symptomatic therapy with herbal medicines. The main results support that supplementation with soy isoflavones as a natural source of phytohormones is associated with a reduction in the frequency and intensity of hot flashes, a recurrent symptom in the climacteric. The formulated blend of four herbal extracts (*Glycine max, Cimicifuga racemosa, Vitex agnus-castus*, and *Oenothera biennis*) supports skin health and antioxidant status in women of menopausal age. Furthermore, purified pollen cytoplasm can be considered an effective symptomatic complementary therapy for vasomotor symptoms, as well as mood and sleep disturbances in peri- and postmenopause. Three clinical trials using the Danggui Buxue Tang herbal formula have been shown to alleviate menopausal syndrome, providing solid scientific evidence of its effectiveness.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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