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Alternatives of Non-hormonal therapy in the climacteric: A narrative review and promising new treatment

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ABSTRACT
Climacteric is the physiological period characterized by endocrine, somatic, and psychic changes related to the termination of ovarian function in women. This process causes women to experience some of the symptom's characteristic of climacteric syndrome, such as hot flashes or hot flashes, which are the most common. Insomnia, nervousness, depression, high blood pressure, urinary incontinence, dyspareunia, and vaginal dryness are also reported. In this context, we have prepared a review of the literature on non-hormonal treatment methods used in the relief of climacteric symptoms. In addition, we evaluate the specific benefits of each treatment. We selected 4,701 articles through a narrative literature review, which were published in the last 5 years. With this, we filtered the work done on humans, women, middle-aged women, resulting in 276 studies. From the reading of the texts, we selected 16 studies that dealt with studies on alternative therapy to hormone replacement for menopausal women. In these articles, the authors cite several drug and non-drug forms for the treatment of climacteric, but many are still inconclusive or still in the experimental phase. A new therapy under study is achieving good results and shows long-term promise for the treatment of hot flashes.

Keywords: Climacteric, Treatment, Symptoms.

1 INTRODUCTION

It is known that the climacteric is a period of transition, with variable duration and, undoubtedly, special for the biological cycle of the woman, which brings with it several hormonal influences influencing daily life and family and social relationships. According to the World Health Organization (WHO), the climacteric corresponds to the period of life of the woman between the end of the reproductive phase until senescence that, in general, varies from 40 to 65 years. In this period occurs menopause which is defined as amenorrhea for 12 months due to the end of hormone secretion from the ovaries. In climacteric there is a decrease in fertility and, progressively, a decline in the production of estradiol by the ovary, although a certain hormonal balance is maintained by the greater

production of androgens and their peripheral conversion into estrogen. Menopause is considered early when it sets in before the age of 40, and late after the age of 55. (ALVES, 2015; AMORIM, 2020; FEBRASGO, 2012).

The fall in female hormone production is a physiological process that occurs with age, occurring due to an increasing reduction in ovarian activity, which is responsible for the secretion of "female" hormones, especially estradiol, estrone and estriol. (POLONINI; et al, 2011) This process causes women in the climacteric to present some of the characteristic symptoms of climacteric syndrome, such as hot flashes or hot flashes, which are the most common symptoms, and are the main reason for seeking medical treatment, occurring in more than 50% of women in the period of menopause transition and may persist for a few years after menopause, in addition to these symptoms, there is insomnia, nervousness, depression, hypertension, urinary incontinence, dyspareunia (pain during sex) as a consequence of vaginal dryness, due to hypoestrogenism and many others (ALVES, 2015; Felix, 2009).

It is also important to be put that the clinical picture presented in the climacteric is not due only to hormonal reduction, because, associated with it, there are very important psychosocial factors, among them, there is the perception of aging that occurs in this phase, because in this period the woman begins to be seen as someone who is losing her youth and vitality, In this way, the woman seeks medical and aesthetic alternatives to promote her health and well-being, both physical and psychological. (POLONINI; et al, 2011)

It is known that women with low self-esteem have more symptoms and usually have a negative attitude in this period of life. Thus, these factors, together, can contribute to the reduction of quality of life, as well as lead to decreased productivity at work and difficulties in personal and social relationships. (VALADARES, et al., 2008) Most women, in this period, experience a crisis experienced by their female part, either in the maternal sphere or in their ability to seduce, helping in the development of the symptoms already mentioned. (VALADARES, et al., 2008). Thus, a broader knowledge about the climacteric and its treatment, make them safer and reduces negative beliefs regarding menopause (VALADARES, et al., 2008)

Hormone therapy with estrogen alone or in combination with progesterone is the most effective treatment available to reduce climacteric symptoms, including hot flashes, vaginal dryness, urinary symptoms, and emotional lability. (Alves, 2015; Felix, 2009). However, not all women can use this therapy. Some conditions such as breast and endometrial cancer, severe liver disease, unclear genital bleeding, history of acute and recurrent thromboembolism, and porphyria are part of absolute contraindications to this type of treatment, in addition to conditions in which it should the benefit of its use, such as the presence of uncontrolled hypertension or diabetes mellitus, endometriosis and uterine myomatosis, should be carefully evaluated. In addition to contraindications, the use of hormone

therapy has side effects, and when estrogen is used, nausea, gastrointestinal disorders, breast tenderness, headache, fluid retention, edema and probable stimulation of leiomyomas and endometriosis can be caused in some patients. (MINISTRY OF HEALTH, 2008)

Thus, in view of the risks established to this therapy, the interest and demand for alternative therapies to hormone therapy has currently increased to improve the quality of life of women who experience climacteric symptoms. (BARRA; et al, 2014)

Among the non-hormonal drugs, already documented we have raloxifene, which is a selective modulator of estrogen receptors, which promotes the prevention of osteoporosis, reduction in the risk of cardiovascular diseases, and prevention against breast cancer and endometrial cancer; In addition to it, it has tibolone, which is highly specific, improving libido and sexual performance. There are also phytoestrogens, which are able to inhibit the proliferation of cells responsible for breast cancer, act in the prevention of heart disease and increase the mineral content of the bones preventing osteoporosis. (FREITAS, et al., 2016)

In addition to drug therapy, we also have treatment not based on drugs in which the practice of physical exercises that help strengthen the bones and muscles, in addition to helping in the proper functioning of the heart. It is also recommended the cessation of tobacco, and the reduction of intake of coffee, alcohol and fried foods, as well as increasing the consumption of foods rich in isoflavones that are substances present in soy and its derivatives mainly, called phytoestrogens because they have a structure similar to estrogen (FREITAS, et al., 2016)

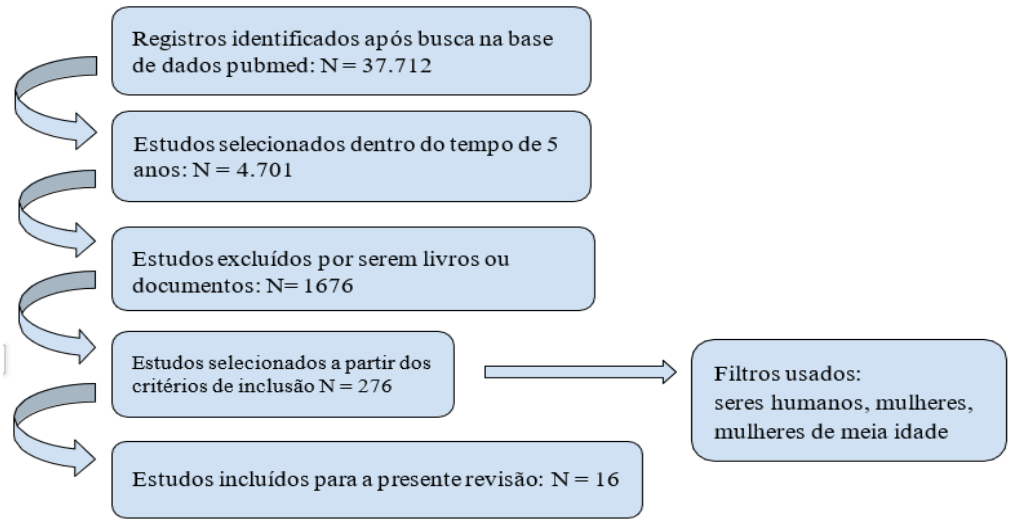
It is known that the use of therapies is related to high educational and socioeconomic levels. The fact is that there seems to be a lack of information about the benefits and risks of hormone therapy or other forms of treatment of climacteric syndrome, which generates doubts and insecurities to women. (VALADARES, et al., 2008). Thus, this study is important to enable a broader view of the non-hormonal treatments available.

2 METHODOLOGIES

This is a literature review study which consists of presenting new information by providing current knowledge on the topic explored or emphasizing gaps in the body of research and thus instigating researchers to improve the scientific database. For the construction of this study, the following steps were considered: selection of the theme and definition of the guiding question, search for a sample in the literature, establishment of inclusion and exclusion criteria, classification of data, analysis of selected contents, interpretation of collected data and synthesis and presentation of results. The precepts of Law No. 13 9.610/1998 were obeyed, topreserve and respect the ideas, concepts and definitions of the authors of the analyzed productions, which will be presented reliably, described and cited. The data were presented through the descriptive approach, which allows the analysis, annotation

and characterization of the data of a sample being divided into thematic categories, for the presentation of the results obtained.

For our work we used pubmed as a database. To select the texts, we used as keywords: climacteric, menopause, perimenopause, postmenopause, premenopause, hot flashes, therapy, drug therapy, complementary therapies, alternative therapy, alternative medicine, and excluded from the search the keywords estrogen replacement therapy and hormone replacement therapy, thus resulting in 37,712 articles found. Of these, we selected 4,701, which were published in the last 5 years. From this number, we exclude the books and documents, leaving 1676. With this, we filtered the work done in humans, women, middle-aged women (from 45 years old), resulting in 276 studies. From the reading of the texts, we selected 16 studies that dealt with studies on alternative therapy to hormone replacement for menopausal women. Exclusion criteria were: duplicate studies, not available, theses, dissertations, monographs, literature review, editorials and abstracts published in annals of events, presented outside the selected period, published in other languages and studies conducted outside Brazil. The articles that will be included are those that are available in full free of charge in Portuguese, English or Spanish.



3 FINDINGS

To facilitate the evaluation and analysis of the data, an instrument was developed that could provide the detailed information of the studies (Chart 1).

Article	Title	Authors	Goal	Method	Conclusion	Year
1	**Fezolinetant in the treatment of vasomotor symptoms associated with menopause.**	DEPYPERE, Herman; LADEMACHER, Christopher; SIDDIQUI, Emad; *et al*.	To identify the results of Fezolinetant in the treatment of vasomotor symptoms associated with menopause.	Descriptive review through dataset	Results to date have demonstrated a rapid and substantial reduction in the frequency and severity of VMS and associated improvements in health-related quality of life. NK3R antagonists offer a non-hormonal alternative to TH for the treatment of menopause-related VMS.	2021
2	**Neurokinin 3 Receptor Antagonists Compared with Serotonin Norepinephrine Reuptake Inhibitors for Non-Hormonal Treatment of Menopausal Hot Flushes:** A Systematic Qualitative Review.	MENOWN, Sara J.; TELLO, Javier A.	To evaluate whether NK3R antagonists (NK3Ras) are more effective than serotonin and noradrenaline reuptake inhibitors (SNRIs).	Systematic literature review	Administration of the NK3R antagonist resulted in a greater reduction from baseline in the frequency and severity of hot flashes in addition to night sweats compared with SNRIs.	2021
3	**Hormone Therapy for Postmenopausal Women**.	PINKERTON, JoAnn V.	Analyze the benefits and risks of menopausal hormone therapy, as well as revising the shapes Alternatives for the treatment of symptoms of menopause.	Review of Guidelines Formal followed by the Recommendations author's clinics.	After 3 to 5 years of hormone therapy, it must be an attempt to diminish and, occasionally stop treatment. If the symptoms persist, decrease doses or transdermal therapy may be offered, with periodic risk reassessment and Benefits.	2020
4	**Menopausal Hormone Therapy:** Comprehensive Review.	LUNGBERG, G.; WU, P.; WENGE, N.	Evaluate the relationship between the use of MHT and hypertension in ELSA-Brasil participants.	A study transverse using the baseline data of the ELSA-Brazil	The current use of MHT was not related to hypertension, especially in healthy women and in those under 60 years of age age	2020

5	**A phase 2b, Randomized placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause.**	FRASER Graeme L.; LEDERMAN, Samuel; SILVICULTURE M, Arthur; *and al.*	This phase 2b study had the following OBJECTIVE: To evaluate seven regimens of dosageof fefelinetant, a selective receptor antagonist of neurokinin 3, as a non-hormonal approach to VMS treatment	Mulheres at menopause with age >40-65 years with VMS moderate/severe (50 episodes/week) were randomizadas (double-blind) for fezolinetant 15, 30, 60, 90 mg BID ou 30, 60, 120 mg QD or placebo per 12 Weeks.	Fezolinetant is a non-therapy effective and well-tolerated hormonal that reduces quickly VMS menopausal grave.	2020
6	**European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis**	REES, Margaret; ANGIOLI, Roberto; COLEMAN Robert L.; *Et al.*	The goal is to establish a individualized approach to management, with or without therapy menopausal hormone, symptoms of menopause and prevention and treatment of osteoporosis in women with gynecological cancer.	Review of literature and consensus of opinion of Experts.	Caution is required with therapy systemic menopausal hormone and topical in women with tumors serous and granulosa cells due to their hormonal dependence, and The non-hormonal options are recommended as initial therapy. There is no evidence to contraindicate the use of menopausal hormone therapy systemic or topical by women with cervical, vaginal or vulvar cancer, for these tumors are not considered hormone-dependent.	2020
7	**Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms**:	SANTORO N. et al.	Identify Antagonist Effect neurokinin receptor 3 fezolinetant in the results reported by the patient in postmenopausal women with vasomotor symptoms	In this study double-blind of 12 Weeks women in the post-menopause with VMS moderate/severe Were randomizadas for fezolinetant	Oral fezolinetant has been associated with response rates higher than placebo and greater improvements in quality of life and other measures of PRO, including a reduction in VMS-related interference at daily life.	2020

	Results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA			15, 30, 60 or 90 mg BID ou 30, 60 or 120 mg QD or placebo.		

8	**Treatment of Menopausal Vasomotor Symptoms with Fezolinetant, a Neurokinin 3 Receptor Antagonist**: A Phase 2a Trial	DEPYPERE, H. et al.	To evaluate the safety and efficacy of NK3R antagonist fecalolinetant in menopause VMS	Twelve-week, double-blind, randomized, placebo-controlled study.	Fezolinetant rapidly and significantly reduced moderate/severe VMSs, supporting its potential as an effective non-hormonal treatment option for menopausal women.	2019
9	**Acupuncture or phy(F)itoestrogens vs. (E)strogen plus progestin on menopausal symptoms.**	PALMA, F; FONTANESI, F.; FACCHINETT T, F.; CAGNACCI, A	Identify The effect of acupuncture and phytoestrogens on climacteric symptoms was compared to the effect of hormone therapy (HT) with estrogen plus progesterone	Randomized Study	Three months after the end of treatment, the benefits in MenQoL were conserved more after acupuncture than in TH ($p < .006$). Current data indicate that acupuncture, and to a lesser extent phytoestrogens, may be effective therapies for climacteric symptoms.	2019
10	**Menopause:** Hormones, Lifestyle, and Optimizing Aging	MINKIN, Mary Jane	Identify updates on the care of menopausal women, focusing on the symptoms and health problems that arise related to the decline of all reproductive hormones.	Study of descriptive approach	This article offers updates on the care of menopausal women, focusing on the symptoms and health problems that arise related to the decline of all reproductive hormones. Lifestyle adaptations and non-medical approaches and non-hormonal and hormonal medications are discussed.	2019
11	**Efficacy of a Homeopathic Medicine of Capsicum frutescens L. (Solanaceae) in the Treatment of Hot**	ANDRADE Deborah; CARMONA, Fabio; ANGELUCCI Matthew; *Et al.*	Test the hypothesis that in menopausal women, the homeopathic medicinal product of chili pepper pepper, compared to placebo, will reduce the intensity of heat waves,	Study Randomized double-blind, controlled by placebo clinical trial of phase 2 in	The homeopathic medicine of C. frutescens (Malagueta) was significantly higher than placebo in reducing the intensity of hot flashes in women in menopause after 4 weeks of treatment.	2019

	Flashes in Menopausal		after 4 weeks of treatment.	homeopathy clinic		
	Women: A Phase-2					
	Randomized Controlled Trial. Homeopathy					

12	. **Postmenopausal health interventions**: Time to move on from the Women's Health Initiative?	ZAW, J. J. T.; HOWE, P. R. C.; WONG R. H. X.	Identify Postmenopausal Health Interventions	Study of descriptive analysis, through referential.	Alternative therapies, such as phytoestrogens and non-hormonal prescriptions, may be beneficial for elderly women or unsuitable for HT. Direct long-term comparisons of HT with alternative interventions are warranted to confirm its effectiveness in preventing chronic disease	2018
13	**A Multi-center, Randomized, Controlled and Open Clinical Trial of HeyanKuntai Capsule) and Hormone Therapy in Perimenopausal Women**	SUN, A.; et al	To evaluate the efficacy and safety of HeyanKuntai Capsule (, HYKT) and hormone therapy (HT) in perimenopausal syndromes (PMS).	From 2005 to 2008, 390 women with PMS were recruited from 4 clinical centers.	HYKT can effectively relieve PMS and improve patients' quality of life without serious adverse reactions. Although HYKT exerted healing effects more slowly than the hormone, it has a better safety profile than the hormone	2018
14	**Menopause.** Primary Care:Clinics in Office Practice	POTTER, Beth; SCHRAGER, *et al.*	Identify, Signs and Symptoms in Menopause	Descriptive study, with referential analysis.	For women without a uterus, menopause should be based on the symptoms alone. For women under the age of 45 who are going through the menstrual cycle	2018
15	**Managing menopausal symptoms after cancer:** An evidence-based approach for primary care	MARINO, J. L.; MCNAMARA, H. C.; HICKEY, Mr.	Identify a Overview of current evidence for hormonal and non-hormonal treatments for vasomotor symptoms and vaginal dryness after cancer	Review, an approach to the management of Symptoms of menopause after cancer in all settings.	Primary care physicians should be aware of the problematic and ongoing nature of menopausal symptoms after cancer, should discuss them with all patients after cancer treatment, and should consider treatment or referral to a specialist for appropriate treatment.	2018

16	**Factors associated with complementary and alternative medicine use among women at midlife**	COSTANIAN, C.; CHRISTENSEN, R. A. G.; EDGELL, H.; *et al.*	Identify Factors Associated with the Use of Complementary and Alternative Medicine Among Midlife Women	A comprehensive bibliographic search conducted electronically, using Web	More studies are needed to confirm the characteristics of women who employ CAM to control their night sweats and hot flashes.	2017

4 DISCUSSIONS

After reading in full all the works that are included in this literature review, it was possible to evidence several established therapies that have been used for some time and also new therapies that are in studies evaluating efficacy and safety of the treatment.

One class of drugs already used in clinical practice are selective serotonin reuptake inhibitors (SSRIs). The North American Menopause Society recommends the use of escitalopram and paroxetine for the treatment of vasomotor symptoms of menopause. Paroxetine is currently the only non-hormonal treatment and the only SSRI at a dose of 7.5 mg/day that is FDA-approved for moderate to severe vasomotor symptoms; The use of all others is off-label. (LUNDBERG; WU; WENGER, 2020). It has been shown to decrease menopausal hot flashes by approximately 1 to 2 per day. Its side effects include dry mouth, headache, decreased appetite, nausea, constipation and insomnia. (POTTER; et al., 2018). Paroxetine (as well as fluoxetine) should not be used in patients using tamoxifen, as it may impair the conversion of tamoxifen to its active metabolite, and thus its action. (MARINO; et al., 2018).

Citalopram (10 and 20 mg per day) has been evaluated in patients with breast cancer and has shown benefit in reducing the frequency of flushing in these patients. (MARINO; et al, 2018). Effective doses of antidepressants for the relief of hot flashes are lower than those commonly used for treating depression, with onset of relief usually occurring within 2 to 3 weeks. (PINKERTON, 2020).

There is evidence of the efficacy of serotonin and norepinephrine reuptake inhibitors (SNRIs) for vasomotor symptoms of menopause. The mechanism is not clearly understood; However, serotonin and norepinephrine are known to be involved in the regulation of body temperature. (POTTER; et al, 2018). The North American Menopause Society recommends the use of desvenlafaxine and venlafaxine for the treatment of vasomotor symptoms of menopause. (POTTER; et al, 2018). Venlafaxine at a dose of 75 mg daily, which has been shown to reduce the frequency of hot flashes in breast cancer patients by up to 40%, and when compared with clonidine, requires less time for symptom reduction onset. (75 mg extended-release daily). (MARINO; et al., 2018).

Another non-hormonal (and off-label) option is gabapentin. Several well-designed randomized controlled trials (RCTs) have demonstrated the efficacy of gabapentin in reducing the frequency of hot flashes by approximately 2 per day. (POTTER; et al, 2018). Used lower doses than for neurological indications, it may be effective for relieving hot flashes. Given potential side effect of sedation, it is

usually prescribed before bedtime, starting in a small dose; A level of 300 mg is generally tolerated. (MINKIN, 2021). Doses of 900 mg/immediate-release dose (divided 3 times daily) and 1800 mg/dose of a long-acting formulation showed a greater benefit when compared to the former. (POTTER; et al, 2018). The mechanism of action of gabapentin in the treatment of vasomotor symptoms is not yet well understood. (POTTER; et al, 2018). Side effects include drowsiness, dizziness and headache, which may improve after the first few weeks of use. (POTTER; et al, 2018). Thus, this anticonvulsant has been shown to reduce menopausal symptoms, but has significant side effects. (ZAW; et. al, 2018)

Clonidine, an antihypertensive, has been shown to be effective in treating mild menopausal symptoms. (ZAW; et. al, 2018) It is an alpha-2-adrenergic agonist of central action, which has been shown to be more effective than placebo in decreasing vasomotor symptoms, although it is less effective when compared to estrogen, SSRIs/SNRIs, and gabapentin. (POTTER, et al., 2018). A 2006 meta-analysis showed a decrease in one heat wave per day with the use of clonidine compared to placebo. (POTTER, et al., 2018). Adverse effects include hypotension, headache, nausea, dizziness, sedation, and constipation. With abrupt cessation, rebound hypertension may occur. (POTTER, et al., 2018). Such a drug is little used in clinical practice due to the adverse effects that patients may present. (LUNDBERG; WU; WENGER, 2020)

As already mentioned, during climacteric urogenital complaints and/or urogenital atrophy are frequent, in this context, Ospemifene which is a selective modulator of the estrogen receptor (derived from toremifene) and intravaginal dehydroepiandrosterone (DHEA) are forms of non-hormonal treatment used to improve genitourinary symptoms. (ZAW; et. al, 2018) For problems related to vulvovaginal atrophy, a variety of bioadhesive lubricants and moisturizers are affordable.

Regarding moisturizers, the American Menopause Society recommends their use to relieve symptoms of vaginal dryness, but there is little evidence to support their effectiveness. (MARINO; et al, 2018).

Vaginal lubricants are substances applied to contact surfaces to reduce friction during sexual activity and thus pain, and common lubricating bases include water, mineral oils, vegetable oils, and polymerized siloxanes (i.e., silicone-based lubricants). (MARINO; et al, 2018). Laser therapy for vulvovaginal atrophy is a new approach, but larger, long-term studies are needed to explore its efficacy and safety before definitive conclusions can be drawn. (REES; et al, 2017).

Another approach studied is the Mona Lisa Touch (MLT), which is a non-hormonal therapy (fractionated carbon dioxide), in which laser is applied to the genital regial in order to restore tissues before menopause and provide relief from vulvovaginal symptoms. (ZAW; et. al, 2018)

Stellate ganglion block is a recent and minimally invasive approach, performing an injection of a local anesthetic into sympathetic nerve fibers in the neck in order to control temperature regulation. This treatment has been shown to reduce 45-90% of the symptoms of hot flashes and cold sweat,

having this effect a duration of 6 weeks to several months after the blockage. (ZAW; et. al, 2018). However, the use of this treatment is still controversial because stellate ganglion blockade is an invasive and costly approach, and there is not yet sufficient evidence to prove its efficacy in the treatment of vasomotor symptoms. (MARINO; et al., 2018)

Studies are being conducted with the use of Resveratrol for Healthy Aging in Postmenopausal Women. RESHAW is a 2-year, double-blind, randomized, placebo-controlled crossover study conducted with 140 postmenopausal women aged 45 to 85 years, at least 12 months postmenopausal, nonsmokers, and non-users of HT. (ZAW; et. al, 2018). Research evaluates the effects of 75 mg of the drug twice daily on cognition (main outcome), cerebrovascular function, mood and other aspects of well-being, cardiometabolic and bone health, and function

In addition to these, it also seems to influence cardiovascular function and cognition. The study had not yet been finalized, but the expected benefits of long-term resveratrol supplementation include counteracting accelerated cognitive, cerebrovascular and physical decline and improving overall well-being, cardiometabolic health and bone mineral density in postmenopausal women. (ZAW; et. al, 2018)

When it comes to non-pharmacological therapies, studies have proved controversial. While Costanian and Pinkerton say acupuncture, exercise, naturopathy, yoga, tai chi and self-help approaches that include relaxation and stress management are not recommended for relief of vasomotor symptoms as they have shown inconsistent or negative results. However, they are shown to be effective in reducing stress. (COSTANIAN; et al, 2017), (PINKERTON, 2020). Lundberg and Wenger say some lifestyle changes have been shown to decrease menopausal symptoms, such as weight loss and control, exercise, dietary changes such as avoiding spicy foods, and avoiding alcohol intake and nicotine. (LUNDBERG; WU; WENGER, 2020).

Other therapies aimed at reducing stress such as hypnosis, mindfulness and cognitive therapies are being studied to treat menopausal symptoms, but data are still limited (LUNDBERG; WU; WENGER, 2020). Hypnosis techniques appear to be promising, so a study of breast cancer patients showed good results regarding relief of vasomotor symptoms, mood and sleep. (MARINO, et al., 2018).

The HeyanKuntai capsule is a non-hormonal treatment alternative for women who have contraindications or who do not feel safe to make use of hormonal therapies to control climacteric symptoms. (SUN, et. al., 2018) Its effect is to regulate the level of estrogen slowly, modulating the ovary in order to induce follicular development. (SUN, et. al., 2018) In addition, this treatment can stimulate luteinization, increase the wet weight of the uterus, increase serum estrogen and promote the maturation of vaginal cells. (SUN, et. al., 2018). Its effect is compared to estradiol valerate, so its effect

may be related to the ovarian condition, and may help in the transition period of menopause. (SUN, et. al., 2018).

A randomized controlled trial was conducted in four clinical centers in Beijing and Shanghai over a period of 1 year, conducted with 318 women (who continued in the study until its completion) in menopause, in which it was seen that the HeyanKuntai capsule showed good results as an alternative therapy to hormone replacement therapy, to treat climacteric symptoms. (SUN, et. al., 2018) It has been seen to be helpful in relieving symptoms such as sleep disturbances, anxiety and depression, and in sexual quality of life, as well as less common symptoms such as paresthesia, dizziness, fatigue, muscle and joint pain and headaches in perimenopausal women. (SUN, et. al., 2018). When it was compared to Hormone Therapy (HT), it was seen that the capsule is as effective as, in the long term, presenting even fewer adverse symptoms, but requires higher doses than in HT, for its effects to be achieved. (SUN, et. al., 2018).

A study was conducted using chili pepper to treat climacteric symptoms. A phase 2, randomized, placebo-controlled, double-blind clinical trial was designed to test the hypothesis that in menopausal women, the homeopathic drug Malaguette (30 CH), compared to placebo, will significantly reduce the intensity of hot flashes. (ANDRADE, et. al., 2019). The primary outcome was the intensity of hot flashes, measured by the Measure Yourself Medical Outcome Profile (MYMOP) instrument. (ANDRADE, et. al., 2019). A total of 40 women were included in the study, 20 in each group. It was shown in this study that in menopausal women, the homeopathic medicine of chili pepper, compared to placebo, significantly reduced the intensity of hot flashes after 4 weeks of treatment. (ANDRADE, et. al., 2019). Malagueta was also shown to improve secondary symptoms, activity level and well-being. (ANDRADE, et. al., 2019). The authors say the results are important because Malagueta is the first homeopathic medicine to be effective for hot flashes in a clinical trial. In addition, it is an inexpensive source and available worldwide, making it an excellent alternative for women seeking relief from hot flashes. (ANDRADE, et. al., 2019).

Non-prescribed therapies that were no more effective than placebo in high-quality randomized trials of vasomotor symptoms include the use of: black cohosh (which is associated with liver toxicity), dongquai, evening primrose oil, flaxseed, apple, n-3 fatty acids, ginseng, red clover, vitamin E, and medicinal herbs. (COSTANIAN; et al, 2017), (PINKERTON, 2020).

A new non-hormonal oral therapy called fezolinetant is in clinical development for the treatment of the vasomotor symptoms of moderate to severe menopause. (SANTORO, et al., 2020).

A subset of hypothalamic neurons that co-expresses the neuropeptides kisspeptin, neurokinin B (NKB), and dynorphin (KNDy neurons) project from the nucleus arc to the preoptic area of the hypothalamus and are believed to play a key role in thermoregulation. (GRAEME; et al, 2020). These

KNDy neurons are inhibited by estrogen and stimulated by NKB. (SANTORO, et al., 2020). During menopause, estrogen levels decrease, leading to increased NKB signaling. (SANTORO, et al., 2020).

The altered activity of this neural circuit results in the thermoregulatory center becoming hypersensitive to external signals from peripheral receptors, activating the dissipation of heat effects (e.g., sweating, vasodilation), and is believed to be the physiological basis of why many menopausal women experience vasomotor symptoms. (GRAEME; et al, 2020).

Fezalinether is a neurokinin 3 receptor antagonist (NK3R) that blocks neurokinin B signaling (SANTORO, et al., 2020). The drug selectively and reversibly blocks NKB signaling, decreasing the pulse rate of GnRH consistent with a decrease in KNDy neuron activity, leading to a decrease in vasomotor symptoms. (DEPYPERE, et al., 2019).

This therapy has been shown to be beneficial in reducing vasomotor symptoms. (SANTORO, et al., 2020). In a study of 287 menopausal women, it was found that it was superior to placebo to decrease vasomotor symptoms and also showed the mean time to reduction of 50% of the frequency of vasomotor symptoms of moderate/severe ranged from 8.4 days for fezolinetant 15 mg BID to 2.2 days for fezolinetant 90 mg BID. At higher doses, better results were seen in symptom control. (SANTORO, et al., 2020)

In the first pilot/phase 2a clinical trial of an NK3 Antagonist conducted in accordance with the US Food and Drug Administration Guidelines (FDA) for the clinical evaluation of treatments for VMSs demonstrated that fezolinetant significantly reduced the frequency of moderate/severe VMSs and moderate/severe VMS score, with its beneficial effects achieved as early as the first day of treatment and sustained throughout the study. (DEPYPERE, et al., 2019). Fezolinetant also improved sleep quality and other patient-reported outcomes, which measure the impact of VMSs on quality of life. (DEPYPERE, et al., 2019). In comparison, paroxetine reduced VMS frequency by 6.2 to 9.2 episodes per week at week 12 compared to placebo. (DEPYPERE, et al., 2019) In another randomized, double-blind, placebo-controlled study also in phase 2b, conducted at 51 sites in the United States in the period from July 19, 2017 to September 19, 2018, with a total of 356 participants who received either the medication or placebo showed that such a drug reduced vasomotor symptoms of moderate/severe intensity by about 62% to 81% at week 4 of the study, depending on the dose, compared to about 39% reduction with placebo; at week 12, moderate/severe MVR was reduced by about 74% to 87% with ferolitant versus 55% with placebo, and it was well tolerated by participants. (GRAEME; et al, 2020).

Again, in a new study conducted in 2021, fezolinetant significantly reduced the frequency of hot flashes (OC) when compared to placebo. The frequency of reduction in the fezolinetant group was from an average of 80.7 weekly episodes at baseline to 5.7 at week 12. (DEPYPERE; et. al, 2021). In the placebo group, the reduction in frequency was 46%, from an average of 72.0 weekly episodes at

baseline to 39.0 at week 12. Severity and frequency of moderate/severe VMS were reduced from the first day of treatment. Treatment with ferolinetant resulted in improvement from baseline in sleep quality, overall daily interference, symptoms, and function at weeks 4, 8, and 12. (DEPYPERE; et al, 2021).

Fraser also reports the results of a randomized, double-blind, placebo-controlled, dose-varied, parallel group study conducted at 51 U.S. sites of a different compound in the same class of NK3R—fezolinetant antagonists (Astellas Pharma Inc, Northbrook, IL; formerly ESN364, Ogeda SA) for the treatment of VMS in postmenopausal women. Fraser's study in this issue adds to the growing evidence that pharmacological blockade of NKB signaling with an NK3R antagonist can markedly improve symptoms of "vasomotor instability" regardless of any effect, suggesting great promise for such agents as a novel therapy. This new direction in hot flash research may represent just the tip of the iceberg that foreshadows the development of a number of non-hormonal compounds with potential broad clinical implications for women's health in middle age.

Finally, when the use of ferolinetant was compared with SNRI, administration of the NK3R antagonist resulted in a greater reduction from baseline in the frequency and severity of hot flashes, as well as night sweats compared with SNRIs. (MENOWN, Sara J.; TELLO, Javier A., 2021). The authors showed a reduction in the frequency of vasomotor symptoms that was statistically significant (from 48 to 67% at weeks 8 or 12), while all NK3R antagonist trials showed a statistically significant reduction in HF frequency (from 62 to 93% from baseline at weeks 2, 4, or 12). (MENOWN, Sara J.; TELLO, Javier A., 2021). While the SNRI studies reported low tolerability, particularly nausea, the fezolinetant studies reported good overall tolerability, although they reported elevation in transaminases. (MENOWN, Sara J.; TELLO, Javier A., 2021).

5 FINAL CONSIDERATIONS

Based on the study, it was possible to identify several forms of alternative therapies for the relief of climacteric-related symptoms, although some of them still need more studies to prove their efficacy and safety.

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