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PHARMACEUTICAL CARE AND ASSISTANCE IN THE USE OF SOY PROTEIN ISOLATE FOR MENOPAUSAL AND POSTMENOPAUSAL WOMEN: A SYSTEMATIC LITERATURE REVIEW

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Abstract: Currently, the use and consumption of soybeans is one of the topics that is arousing interest among researchers, health agencies and departments and populations around the world. Belonging to the legume family, soya is the only source of protein of plant origin that has all the essential amino acids and is considered to be of high biological value. Its beans are rich in fats, with a predominance of polyunsaturated fatty acids such as linolenic acid (omega 3) and linoleic acid (omega 6). Soya also contains around 1 to 3 milligrams (mg) of isoflavones per gram (g) of protein, which has aroused interest among researchers because it is rich in this phytoestrogen, considered to be a non-hormonal chemical compound with a structure similar to that of human estrogen hormones, which, in addition to antioxidant properties, play a role as selective modulators of estrogen receptor SERMs. In recent decades, interest in the management of menopausal patients has increased, largely due to improved life expectancy, which means that the female population is expected to live around a third of their lives after the menopause. The aim of this study is to carry out a systematic review of the literature on the effects of selective estrogen receptor modulators (SERMs) in pre- and post-menopausal women. The methodology used is a strategic research study with descriptive objectives, a qualitative approach using a systematic literature review procedure and an exploratory research technique to acquire new knowledge about selective modulators in menopausal and post-menopausal women, including a simultaneous analysis of the articles used as inclusion criteria, which were discussed in order to update the scientific and general community on the subject of the research using the descriptors. Considering the studies carried out and some controversial results regarding the effects of soy isoflavones as an alternative treatment for menopausal symptoms, further research is essential in order to confirm the

effectiveness of this therapy, as well as to disseminate knowledge about the benefits of soy for the population. Therefore, the aim of this research is to evaluate the effectiveness of soy protein supplementation on menopausal and post-menopausal symptoms and the appearance of side effects.
Keywords: ***Glycine max;*** Fogachos; Alternative therapy.

INTRODUCTION

The female cycle in the climacteric is divided into periods, perimenopause is the period that precedes menopause and lasts about four years, in this period ovarian function declines, eggs slowly decrease and menstrual cycles can be anovulatory, resulting in irregular bleeding (CIVANTOS *et al.*, 2019).

The typical symptoms of perimenopause, in addition to menstrual irregularity, include vasomotor changes, such as night-time hot flushes and sweating, sleep changes, vaginal dryness, dyspareunia, decreased libido, urinary symptoms, muscle pain and mood swings. For many women, vasomotor symptoms are short-lived and specific treatment is unnecessary, but for others, they interfere with their ability to work, social life and routine activities, resulting in a decreased quality of life. (JOHNSON; ROBERTS; ELKINS, 2019).

Soy isoflavones are considered phytoestrogens, due to their chemical structure being very similar to human estrogen, where they behave like true estrogens, binding to estrogen receptors, but not being able to cause the same side effects as them and although the estrogenic effect of isoflavones is considered weak, they can exert both an agonistic and antagonistic effect on endogenous estrogens, because they compete for the same receptors. (KIM, I. S., 2022).

Hormone replacement therapy is currently considered the treatment of choice for relieving symptoms related to menopause, such as hot flushes, vaginal dryness, loss of libido and mood swings, as well as combating osteoporosis, however, studies have attributed estrogenic or estroprogestative therapy to the emergence of side effects such as increased risk of breast cancer, endometrial cancer and thromboembolism and, therefore, its use has been limited. (DELI; OROSZ; JAKAB, 2020). To this end, isoflavones act as "hormones" with the advantage of not causing side effects such as those observed in patients taking synthetic hormone treatment, despite their similar structure.

In view of the above, this literature review is justified by the relevance of the topic and the limited evidence of the benefits of soy consumption for women's health, with the aim of analyzing the benefits of consuming soy isoflavones during the menopause and post-menopause.

OBJECTIVES

GENERAL OBJECTIVE

To review the literature on the use of soy isoflavones as selective estrogen receptor modulators (SERMs) in menopause and post-menopause.

SPECIFIC OBJECTIVES

- Analyze the use of soy isoflavone as a phytoestrogen;
- To investigate the use of soy phytoestrogen as a selective modulator of estrogen receptors;
- Understand the action of this phytoestrogen in the menopause and post-menopause periods.

THEORETICAL FRAMEWORK

SOY

History

Soybeans are the main crop produced in Brazil, ranking first in grain production, with Brazilian soybean production in the 2022/2023 harvest estimated at 81.5 million tons, in a cultivated area of just over 27.5 million hectares, making the country the world's second largest producer of this oilseed (Figure 01). (BU *et al.*, 2021).

Figure 1- Soybean Cultivar

Source 1 - *https://br.depositphotos.com/stock-photos/glycine-max.html*

Historical data shows great advances in crop productivity since the first commercial--scale farms began in Rio Grande do Sul, from an average of around 1,500 kg h^{a-1} in the late 1970s to around 3. 000 kg h in the 2022/2023 harvest, where a large part of the gains can be attributed to genetic improvement through obtaining cultivars adapted to different soil and climate conditions.000 kg h^{a-1} in the 2022/2023 harvest, where a large part of the gains can be attributed to genetic improvement, by obtaining cultivars adapted to the soil and climatic conditions of the different Brazilian regions, as well as the development of new technologies for managing the crop. In addition, there is no disconnecting this leap in productivity from scientific and technological advances in soil management and conservation (Figure 02).

Figure 2-Soybean seeds

Source 2 - https://br.depositphotos.com/stock-photos/glycine-max-gr%C3%A3os.html

In this sense, due to its genetic diversity, wild soybean is a fruitful source for the study of defense attributes and can provide valuable information to improve the agronomic and defensive characteristics of cultivated soybean, where a recent study revealed through transcriptomic comparisons that the alteration of gene expression is extensive between wild and cultivated soybean, and that Glycine soja has undergone an accelerated evolution throughout its genome, which allows it to adapt and face different conditions and environments compared to *Glycine max* (LIU, J. Z. *et al.*, 2015).

Similarly, Bian *et al.* (2020) showed through molecular and genetic analysis of wild soybeans that a protein is responsible for improving salt stress tolerance in Glycine soja by increasing flavonoid biosynthesis in the plant's roots, showing how flavonoids are involved in abiotic stress responses in soybeans (RIZZO *et al.*, 2022).

On the other hand, chemical profiles and antioxidant activity between wild and cultivated black soybeans were investigated, revealing differences in the metabolic profile of the plants and a higher antioxidant activity in wild black soybeans compared to cultivated black soybeans (BHUIYAN *et al.*, 2012).

Similarly, Hyeon *et al*. (2017) examined the metabolic variations induced by the domestication of black soybeans, where the results of this study showed notable differences in the metabolic profile of the cultivars, wild black soybeans showed higher amounts of flavonoids and phenylpropanoids, while cultivated black soybeans showed high levels of amino acids, polysaccharides and fatty acids.

In addition, wild soybeans have been used to find resistance traits to the soybean aphid (*Aphis glycines Matsumura*) and the caterpillar *Spodoptera litura Fabricius*, which are considered to be soybean pests with resistance to some insecticides. Thus, it has been shown that the use of Glycine soja strains shows promise in the development of pest-resistant varieties and as a source of new genetic variation for modern crop improvement (SCOTT *et al.*, 2022).

Flavonoids

Flavonoids are a class of low molecular mass polyphenolic compounds, with a C6-C3-C6 carbon structure consisting of two aromatic rings, A and B, joined by a 3-carbon bridge, usually in the form of a heterocyclic ring, C (HA, J. *et al.*, 2018).

The aromatic A ring is derived from the acetate/malonate pathway, while the B ring is derived from phenylalanine via the shikimate pathway. These metabolites can be classified as flavonols, flavones, flavanones, isoflavones, flavanonols, flavanols (or catechins) and anthocyanidins, which will depend on the position in which the B ring is attached to the C ring and on the oxidation state and degree of saturation of the heterocyclic ring (FIGURE 1.5). (BI, W. *et al.*, 2022).

For example, isoflavones have the B ring attached at position 3 of the C ring, while the other groups have the B ring attached at position 2 of the C ring. Thus, changes in the skeleton of each flavonoid class give rise to different basic structures known as aglycones (FIGURE 1.5(a-f)). These structures can undergo enzymatic modifications through processes such as glycosylation (usually at position 3 or 7) with sugars such as: D-glucose, L-rhamnose, D-galactose, D-xylose and L-arabinose, methylation, prenylation, acetylation and sulfation, forming conjugates with unique biochemical characteristics (HA, J. *et al.*, 2018).

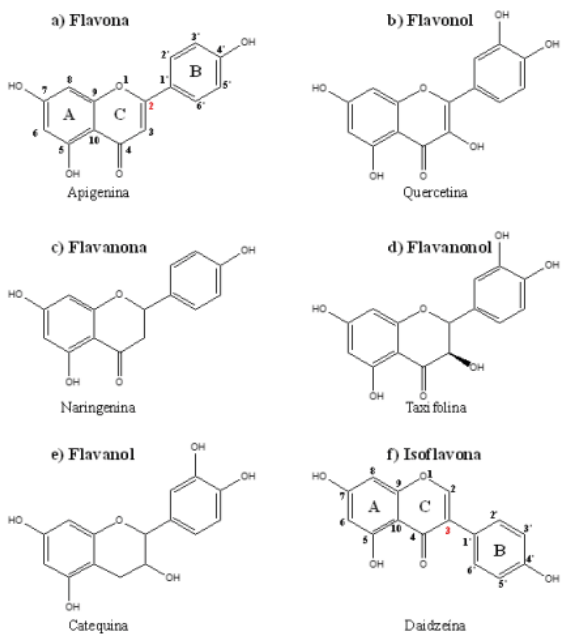

Figure 3- Chemical structures of the main classes of flavonoids in aglycone form a) flavone (apigenin), b) flavonol (quercetin), c) flavanone (naringenin), d) flavanonol (taxifolin), e) flavanol (catechin) and f) isoflavone (daidzein).

Source 3-*Internet*

Flavonoids are present in different parts of the soybean in varying concentrations, performing functions such as regulating oxidative stress, participating in hormonal signaling, protecting against UV radiation and metal ions, and defending against pathogens and insects (KILMER, 2010).

Among the great structural diversity of known flavonoids, the flavonols kampferol, quercetin and isorhamnetin and the isoflavones daidzein, genistein and glycitein predo-

minate in soybeans, along with their glycoside derivatives, where these metabolites are generally more prominent in the vegetative stages compared to the reproductive stage of soybeans (STEC; KORDAN; GABRYŚ, 2021).

Several studies have reported that soybean resistance against some herbivores is associated with the concentration of flavonoids in the seeds and leaves, where six isoflavonoids were identified in the seeds of two soybean varieties (resistant Dowling and susceptible Silvânia), including three aglycones (genistein, daizein and glycitein) and three glycosides (daidzin, genistein and glycitein), as well as the glycosylated flavonol rutin, detecting a higher total amount of flavonoids in the Silvânia cultivar when compared to Dowling, indicating that these compounds are not directly related to the constitutive resistance observed in the seeds of the Dowling variety against *Euschistus heros* (SOUZA *et al.*, 2013).

Piubelli *et al*. (2005) found that extracts from the leaves of some soybean genotypes contain high concentrations of rutin and genistein, and it was observed that these substances cause detrimental effects on the physiology of *Anticarsia gemmatalis*, similarly, Bentivenha *et al*, (2018) showed that rutin and genistein play a role in the resistance of various soybean cultivars against the bed bug *Piezodorus guildinii*, where the production of flavonoids varies depending on the type of herbivory.

O'NEILL et al, (2010), showed that leaf damage by the Japanese beetle *P. japonica* induced significantly higher concentrations of naringenin methyl hexose, kaempferol diglycoside, kaempferol triglycoside and quercetin triglycoside, verifying that damage caused by the caterpillar *V. cardui* increased levels of a genistein glycoside, while an aphid that feeds on the phloem, *A. glycines*, did not affect the production of any compound in soybean leaves.

Similarly, Romero *et al*. (1979) used two commercial soybean cultivars with different levels of susceptibility to insect attack and two species of insects with different forms of feeding, in which the results showed that the larvae of *Spodoptera frugiperda* performed similarly in the two soybean cultivars, however, the *thrips Caliothrips phaseoli* had a preference and developed faster in one of the cultivars.

Thus, the differentiated resistance of soybean varieties to insects can be explained not only by induced defenses (for example, malonyl genistein and genistein were induced by thrips), but also by differences in constitutive defenses (for example, quercetin triglycosides and quercetin diglycosides were present only in the foliage of variety DM 4210, while kaempferol triglycosides, kaempferol diglycosides and isorhamnetin triglycoside were present at higher levels in variety DM 5.8 variety than in DM 4210, and daizin was detected in both plants) between the cultivars.

Additionally, Cheng *et al*. (2011) carried out an integrated metabolomic study by LC--MS and NMR in order to investigate metabolites induced by a herbicide, where the results showed the presence of six prenylated compounds described for the first time in soybeans, including 7,8- dihydroxy-4′ -methoxy-3′ -prenylisoflavone and 7-hydroxy--4′ ,8-dimethoxy-3′ -prenylisoflavone not previously reported.

This highlights the versatility of soybean metabolic pathways and indicates that prenylation may be associated with defense responses. In addition, the use of individual flavonoids in artificial diets has been found to impair the development of herbivores due to their pro-oxidant characteristics (WATANABE *et al.*, 2022).

Taking into account all this information, we hypothesize that the differences in resistance levels between wild soybeans and the various existing conventional cultivars are

related to the variability of secondary metabolite profiles accumulated in their tissues, where it is also assumed that wild soybeans have different secondary metabolite profiles compared to cultivated soybean varieties, in this context, identifying these substances and their distribution among different genotypes and understanding the role they play in insect-plant interaction mechanisms is important for a more comprehensive and reliable characterization of soybean resistance (STEC; KORDAN; GABRYŚ, 2021).

THERAPEUTIC PROPERTIES OF ISOFLAVONES

Phytoestrogens are natural non-steroidal compounds, usually constituents of plants or their metabolites, which induce biological responses in mammals by mimicking or modulating the action of endogenous estrogens (17β-estradiol, estriol, estrone), these compounds have relatively weak estrogenic properties, so very high concentrations are required in relation to those of estradiol to produce an equivalent biological response (KŁADNA *et al.*, 2016).

Through the results of in vitro and in vivo studies, a ranking was established to assess the potency of these compounds and it was found that among the isoflavones, the most potent was genistein, followed by glycitein, daidzein and, finally, formononetin and bioquanine A, which have very similar levels of potency (KŘÍŽOVÁ *et al.*, 2019).

Despite being less potent than estradiol, simple isoflavones, such as daidzein, have sufficient estrogenic activity to affect the reproduction of domestic or grazing animals. These molecules are planar and mimic the shape and polarity of the steroid hormone oestradiol and have the ability to bind to an oestrogen receptor, although their activity is much lower than that of oestradiol (TOPRAK *et al.*, 2023).

Some structural elements are crucial for binding to estrogen receptors (ERs) and, consequently, the estrogenic action of isoflavones, such as the indispensable presence of a phenolic ring and a molecular weight similar to that of estradiol, components that isoflavones have and which give them the ability to mimic this hormone, as well as the distance between the two hydroxyl groups attached to the aromatic rings in the isoflavone nucleus, which is almost identical to the distance between the two hydroxyl groups of estradiol and these structural similarities between these phytoestrogens and estradiol are found among the isoflavone classes. (DEECHER; DORRIES, 2007).

CHARACTERIZATION OF MENOPAUSE

Menopause is a biological stage marked by the end of menstruation due to a reduction in the function of the ovaries. When a woman reaches the age of between 40 and 50, the menstrual cycle becomes irregular and ovulation stops occurring, finally, the menstrual cycles cease completely, this definitive absence of menstruation is called menopause and the time that elapses between the beginning of the changes in the menstrual cycle and the amenorrhea of menopause, which often reaches 3 to 5 years, is called climacteric or peri-menopause. (HILL, A.; CRIDER; HILL, S., 2016).

Iatrogenic menopause is the result of the destruction of ovarian follicular heritage by various methods (chemo or radiotherapy), including surgical removal (surgical menopause), where early menopause is considered to occur before and between the ages of 40 and 45, and late menopause is considered to occur after the age of 50. (GRACIA; FREEMAN, 2018).

Menopause is associated with changes that occur in the ovary, where the number of ovarian follicles that remain in the woman at menopause is small, in addition, the remaining

follicles become less sensitive to stimulation by luteinizing hormone (LH) and follicle stimulating hormone (FSH), even if the latter's values remain high, so as the response of the ovaries to stimulation by FSH and LH becomes lower, the number of follicles that mature and the number of yellow bodies that give rise is lower (DELIGDISCH-SCHOR; MICELI, 2020).

In women, gradual morphological changes occur in response to the decrease in the amount of estrogen and progesterone produced by the ovaries and various changes are caused by the decrease in ovarian hormone secretion in postmenopausal women (the period beginning with the last menstrual period), such as a menstrual cycle between five and seven years before menopause. (SILVA, J. S. DA *et al.*, 2022).

Then the cycles begin to be more irregular and finally, the number of cycles in which ovulation does not occur and the yellow body does not develop increases, the uterus with irregular menstruation is gradually followed by the absence of menorrhea and finally there is atrophy of the endometrium and a decrease in uterine volume, the vagina and external genitalia, skin and subcutaneous cellular tissue become thinner, the vulva becomes thinner and less elastic and there is a decrease in vaginal secretions determining vaginal dryness, with more inflammation and infection. (RIVARD *et al.*, 2019).

The skin becomes thinner and melanin synthesis increases, hypertension and atherosclerosis are more frequent, sudden increases in heat and sweating are related to vasodilation of the cutaneous blood vessels; "hot flushes" are related to a decrease in estrogen levels, temporary changes such as an increase or decrease in sexual desire are evident and fertility begins to decline ten years before menopause (MORGAN; DERBY; GLEASON, 2018).

Some women experience a variety of symptoms during the climacteric period, including hot flushes, irritability, tiredness, anxiety and sometimes serious emotional disturbances. It is also common to see changes in sleep and urinary problems in which women become more susceptible to urinary tract infections such as cystitis or a need to urinate more frequently (MORGAN; DERBY; GLEASON, 2018).

SYNTHETIC HORMONE REPLACEMENT A

Many women do not seek medical advice during this phase of their life, but many also do not need treatment, however, a doctor's appointment should be made if menopausal symptoms are affecting a woman's quality of life (VERDONK; BENDIEN; APPELMAN, 2022).

The realization that the main signs and symptoms of the climacteric are the result of a decline in estrogenproduction has led to its use as a therapeutic agent, where many of these symptoms can be successfully treated if small amounts of estrogen are administered and then treatment is gradually decreased (GEMMELL *et al.*, 2017).

Its mode of action is essentially genomic, mediated by alpha and beta nuclear estrogen receptors, where free estrogens passively enter the cells, where they bind to specific nuclear receptors, exerting their function in each organ and the liver is the main organ for conjugating estrogens, with a view to their subsequent excretion by the kidney (SETCHELL, 2001).

The effects of the lack of estrogen are varied, manifesting themselves through the cardiovascular system with an improvement in the lipid profile and a small increase in blood pressure, osteoarticular, cognitive function and others, it is verified that the administration of estrogen after menopause helps to prevent osteoporosis and although estrogen therapy is considered effective, in many cases it prolongs the symptoms associated with menopause (GOLDEN, 1998).

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There are some side effects of estrogen therapy that should be considered, such as a small increase in the likelihood of developing uterine and breast cancers, and some data indicate an increased risk of heart disease in the first years after menopause. (DELI; OROSZ; JAKAB, 2020).

The types of oestrogen hormone treatments used to combat the symptoms of the menopause are: 17β-estradiol administered orally, can also be used transdermally, percutaneously, intranasally (not marketed in Portugal) and vaginally; estradiol valerate (prodrug administered orally); echinoconjugated estrogens (EEC) (administered orally and vaginally); estriol (only used topically) and ethinylestradiol, which is a synthetic derivative of 17β-estradiol and is part of most combined contraceptive formulations. (DANDO; CURRAN, 2005).

But most of the drugs used for hormonal treatments with estrogen have several adverse effects such as: increased risk of hyperplasia and endometrial cancer with estrogens alone, depending on the duration and dose used; increased triglycerides; increased risk of choledocholithiasis and gallstones; increased risk of venous thromboembolism and risk of bronchospasm (MORGAN; DERBY; GLEASON, 2018).

Many other hormonal treatments can be adopted to relieve menopausal symptoms, such as progestative treatments, sympathomimetic hormones, selective estrogen receptor modulators (SERMs), tissue-selective estrogen complex (conjugated estrogens and bazedoxifene acetate), androgens and others (HODIS; MACK, 2022).

The symptoms associated with hot flushes occur as a result of dysfunction in the body's thermoregulation mechanism, which is made up of three main players: the central nervous system, body temperature and the peripheral vascular system (GRACIA; FREEMAN, 2018).

Knowing that the reason for this dysfunction is the reduction in serum estrogens, it is easy to see that hormonal therapy is the most effective, however, any therapy that acts in these areas can have a beneficial effect on the vasomotor symptoms of menopause and the other symptoms derived from the reduction of this female hormone in women. (SILVESTRIS *et al.*, 2018)obese women undergo perturbations of the 'hypothalamic pituitary ovarian axis', and frequently suffer of menstrual dysfunction leading to anovulation and infertility. Besides the hormone disorders and subfertility that are common in the polycystic ovary syndrome (PCOS.

HORMONE REPLACEMENT BASED ON SOY ISOFLAVONE ALONE

In several situations, non-hormonal therapy is indicated, especially in some groups of women whose non-hormonal treatment is preferable, such as:

- Women with breast cancer: most studies contraindicate the use of hormone therapy because of the increase in recurrence (ANGELIS, 2001).
- Women with an increased cardiovascular and thromboembolic risk: smokers, morbidly obese women, women with a history of thromboembolism, women with uncontrolled diabetes and hypertension, women with thrombophilia or autoimmune pathologies (ANGELIS, 2001).
- Women with meningioma: estrogen therapy is contraindicated in this group; however, in the absence of an endometrium/uterus, these women can take hormone therapy with estrogens alone. (ANGELIS, 2001).
- Women who don't want to take "hormones" (ANGELIS, 2001).

In addition to hormone therapy, there is a group of drugs, supplements and other measures for treating menopause symptoms,

including antidepressants, gabapentin, pregabalin and clonidine, pollen extract, phytoestrogens and others. (PARDINI, 2014).

It should be noted that adopting a healthier lifestyle, such as practicing physical exercise, getting enough sleep, eating a healthy diet and not smoking, are essential for improving quality of life, taking into account the biological phase women are going through (SILVESTRIS *et al.*, 2018).

The use of phytoestrogens is due to the fact that they are plant-derived compounds that have estrogenic and antiestrogenic effects (FORTES *et al.*, 2007).

These effects of isoflavones were demonstrated in rodents almost 50 years ago, but only in the last 30 years has research focused on the possibility that foods rich in isoflavones may be especially useful for women in perimenopause and menopause (TORREZAN *et al.*, 2008).

One of the facts that helped reach the conclusion about the effect of isoflavones was when it was detected that Japanese women have a quarter of the breast cancer mortality rate and only a third of the menopausal symptoms of Western women, as well as the lowest rates of osteoporosis and cardiovascular disease in the world, researchers studied their lifestyle and eating habits, and the association with this data and the conclusion they reached was that the consumption of soy products is 30 to 50 times higher than that of Westerners, this food being extremely rich in isoflavones (TANABE; DREHMER; NEUTZLING, 2013).

Supplementing with genistein alone has been found to reduce menopausal symptoms more than supplementing with all isoflavones or low amounts of this particular isoflavone, and 15 mg of genistein is the minimum required (CARBONEL *et al.*, 2011).

Due to the number of studies and clinical trials carried out to investigate the potential influence of isoflavones on menopausal symptoms, it is difficult to draw firm conclusions. The heterogeneity between the results of clinical trials based on the frequency of symptoms varies individually in the metabolism of isoflavones and the amount of genistein used, however, it has been found that the daily consumption of at least 30 mg of isoflavones (containing at least 15 mg of genistein), in foods such as soy or derivatives and supplements, can reduce symptoms such as "hot flashes" by up to 50%. (GARCÍA-RODRÍGUEZ; VALLE-CASTILLO; HERNÁNDEZ-CORTÉS, 2023).

The 50% reduction in symptoms is due to a 30% contribution from the placebo effect, which results in clinically relevant improvements in quality of life, where this efficacy increases with increasing doses of up to 100 mg of isoflavones per day. (KŁADNA *et al.*, 2016).

Some health professionals recommend taking 50 to 100 mg of isoflavones (minimum 15 mg of genistein) to menopausal women to relieve their symptoms, more particularly with symptomatology, and the effectiveness of the treatment depends on each individual and the benefits should be evident within four weeks. (ESTEVES; MONTEIRO, 2001).

METHODOLOGY

SAMPLE

The sample comprised 406 articles according to the theme and a search of the databases, from which a total of 10 articles were selected for discussion. The main aim of this systematic literature review is to integrate existing information on a specific topic by studying the population, the intervention process, the control group and the intervention process using the PICOT method.

The grouping and analysis of articles and monographs carried out in different places and at different times by independent research groups, allowing the generation of up-to-date scientific evidence from 2018 to 2023.

ELIGIBILITY CRITERIA

Inclusion criteria

The inclusion criteria were full-text articles, freely accessible and indexed in journals from 2018 to 2023, written in English, Portuguese and Spanish.

Exclusion criteria

Exclusion criteria were articles that were older than the years used as the inclusion limit, that dealt with plants other than soy in the treatment of menopausal and post-menopausal women, theses, dissertations, articles that were off-topic and articles that were cited.

DESIGN

Carrying out this research follows a series of steps which are standard for methodological rigor: 1) elaborating the subject of the study; 2) carrying out the literature search; 3) organizing the data collected; 4) interpreting and evaluating the results of the study; 5) presenting and disseminating the review of the results presented in a clear and concise manner, identifying the characteristics of the studies used to set up the discussion of them (SOBRAL *et al.*, 2014).

The study topic was developed using a qualitative and quantitative approach. The data used in this integrative review to construct the research question came from the acronym PICOT, which stands for Patient, Intervention, Comparison, Outcomes, which was based on the answers to the following question from the hypothesis with the purpose of intervention: Is the treatment of hormone replacement in women with menopausal and post-menopausal symptoms in the literature with the use of soy ***isoflavone*** viable?

The relevant studies were identified through an electronic search of the following databases: PubMed, Scielo (Scientific Electronic Library Online) and Google Schoolar for data extraction using the health terminology DeCS (Health Science Descriptors) and MeSH (Medical Subject Headings of the U.S. National Library of Medicine) using the boolean "AND".

The descriptors applied in the research were: "Menopause"; "Fogachos"; "estradiol; "medicinal plant" and "Hormone Therapy" and the bibliometric indicators analyzed were: year of publication, place of study, area of knowledge, type of publication, type of study, population and sample.

The systematization of the selection of publications, the number of publications included and excluded, as well as the reasons for exclusion, is shown in the flowchart (**Figure**) (GALVÃO *et al.,* 2015). This type of research focuses on well-defined questions, which aim to identify, select, evaluate and synthesize the relevant evidence available.

RESULTS AND DISCUSSION

We analyzed 10 studies published in the databases consulted and which met the eligibility criteria. They were all quantitative, population-based, cross-sectional, cohort, case, trial, experimental, observational and exploratory studies, which were categorized according to their general objective, title, year of publication and design. Reviewing the texts in search of answers to the guiding question resulted in the construction of a synoptic table presented below.

In X1 and X2, the authors relate the classic symptoms of the menopause, showing the beneficial effects of using isoflavones in relation to hot flushes, minimizing hot flushes. The authors also illustrate the beneficial effect of the use of isoflavones on vasomotor symptoms, collaborating with the current study, and it can also be noted that the use of isoflavone proved to be effective in reducing the number and intensity of hot flushes in postmenopausal women with insomnia.

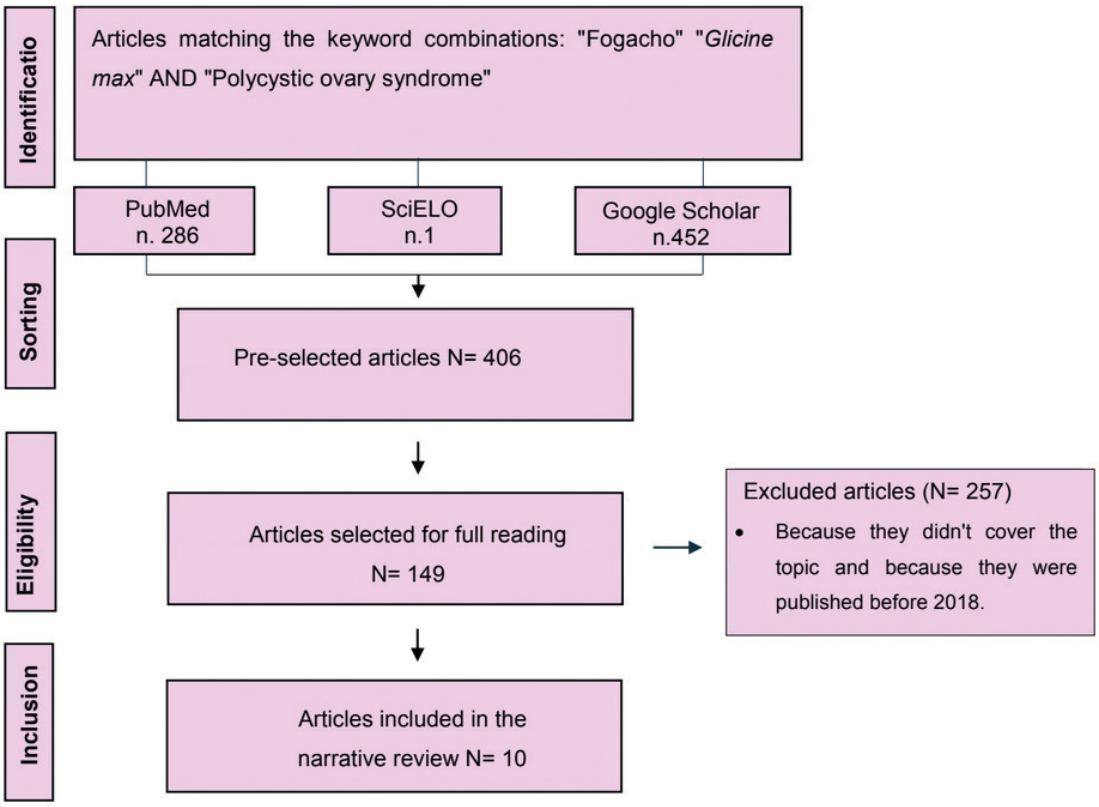

Figure 4 - Flowchart of the selection of the sample of articles included in the final review.

Source - Own authorship

AUTHOR(S) YEAR	ARTICLE TITLE	TYPE OF STUDY	OBJECTIVE	MAIN RESULTS
X1 KUCUCK, Omer.2017	Soy-based foods, isoflavones and breast cancer	Bibliographical research	To study soy-based foods and their possible impact on breast cancer risk.	Soy has nutritional value, but in populations where consumption is low, the risk of breast cancer is increased
X2 MIGOWSKI, ARN *et al.*,2018	Guidelines for early detection of breast cancer in Brazil. II - New national recommendations, main evidence and controversies	Clinical trials.	Present the recommendations and update the evidence synthesis, discussing the main existing controversies	The recommended screening strategy is biennial mammography between the ages of 50 and 69
X3 SILVA, Dagmar.2016	The Influence of Soy-Based Foods on Sexuality	Theoretical research based on bibliographic discussion	Analyze the damage to sexuality that soy-based foods cause in children's physiological and sexual development	Physical changes brought about by the consumption of soy-based foods alter human sexuality intensely
X4 ALDRIGHI *et al.*,2018	Caution in prescribing soy derivatives (ipriflavone) after the menopause.	Bibliography	Find benefits for bone mineral density	Herbal medicine can be an alternative for those who don't want to use hormones
X5 OLIVEIRA, Liliane *et al*, 2018	Benefits of soy in breast cancer prevention: a literature review	Exploratory literature review	Analyze the effect of soy extract Describe the benefits of soy in preventing breast cancer based on an analysis of scientific publications.	Consumption of soy isoflavones has been shown to have beneficial effects on women's health and disease prevention, and no adverse effects have been reported with the use of soy.

X6 BELO,Mariana.2012	Use of pesticides in soybean production in the state of Mato Grosso: a preliminary study of occupational and environmental risks	Descriptive exploratory study.	Analyze biological indicators of exposure to pesticides.	It was detected by analyzing biological indicators of exposure to pesticides among workers and residents of areas close to the plantation zones.
X7 BRITO,Paula. 2009	Pesticides and health: reality and challenges for changing agricultural practices	The methodological approach was qualitative and the main source of data was a semi-structured questionnaire.	Characterize the context and practices related to pesticide use among farmers.	Research findings point to the indiscriminate use of pesticides in family farming.
X8 FORTES, Érika M, 2019	Excessive Intake of Phytoestrogens and Early Telarche: Case Report with Possible Correlation	Case studies	Report of early telarche with breast development associated with high phytoestrogen intake.	Daily consumption of phytoestrogens deregulated the endocrine system, triggering early puberty
X9 CASTRO-CORREIA, C.; FONTOURA, M 2015	The influence of environmental exposure to endocrine disruptors on the growth and development of children and adolescents.	The authors carried out a literature search.	the authors aim to briefly review the current state of knowledge regarding this type of substance and its impact on children's and young people's health.	Early exposure has alerted pediatric endocrinologists to exposure to certain substances.
X10 DAL,Forno. 2022	Susceptibility of the hypothalamic axis - pituitary - thyroid to soy isoflavones.	Literature review	Evidence of the possible changes caused by the consumption of isoflavones and their impact on thyroid hormone production.	The increase in its consumption and the creation of new products using soy as a raw material has heightened concerns about the impact of isoflavones on people's health. Compromising thyroid functions, causing hypothyroidism

Chart 1: Distribution of the references included in the literature review, according to author and year of publication, title of article, type of study, country of origin, main results according to the inclusion and exclusion criteria.

Source: author

In X3, there was a significant decrease in subjective insomnia (fewer women reported moderate/severe insomnia) and a significant increase in sleep efficiency, and none of the articles analyzed in this study found benefits in relation to cognitive health, which may be explained by the small number of articles.

X4 in a double-blind randomized study carried out over a period of 1 year with 202 women aged 60 to 75 also found no benefits in relation to cognitive function, corroborating the present study, in which there were findings only related to visual function. This could be explained by the fact that genistein and daidzein bind better to the estrogen body receptor than to the brain receptor and also by the greater number of receptors in the hippocampus, suggesting a greater benefit in relation to visual episodic memory.

In X5, the authors raise an important point, justifying the findings and the greater efficiency of isoflavone in women capable of producing "equol", a metabolite of daidzein produced by the intestinal flora in 1/3 of the population. Equol has a selective affinity for estrogen receptors and a greater action than unconverted daidzein, which may or may not intensify its action.

In X6, on the prevention of osteoporosis and maintenance of bone mass, the results provided were positive. And in X7, the results show a contradiction in one of the studies that

did not point to benefits, and limitations can be observed such as a higher than expected drop-out rate and significantly higher in the placebo group, another explanation may be related to the reduced ability to produce "equol" in some women, however in the study there was no benefit in women who were equol producers.

In X7, a double-blind randomized study of 389 women selected to receive the isoflavone genistein (54 mg/day), it was observed that after 2 years there was a 5.8% increase in the BMD of the lumbar spine and a 5.2% increase in the BMD of the femoral neck, while participants taking placebo experienced a loss of 6.3% and 5.3% in both skeletal sites, suggesting that genistein is the most active isoflavone for treating bone loss.

In X8, in a meta-analysis, 10 clinical trials concluded that nutritional intervention with isoflavones can attenuate bone loss in the spine, corroborating the findings observed in this study. Of the studies on the effects related to the vaginal epithelium, all showed beneficial effects, indicating that isoflavone vaginal gel is effective for treating the symptoms of vaginal atrophy caused by oestrogen deficiency. In addition, it may influence the proliferative effect and increased expression of estrogen receptors in the vaginal epithelium.

In X9 another study showed a significant increase in vaginal vascularization compared to the placebo group, which may explain the benefits observed in this study. In addition, the use of isoflavones, in gel form, topically on the vaginal epithelium proved to be effective in relieving moderate to intense symptoms of vulvovaginal atrophy and dyspareunia.

In X10, the authors discuss the action of isoflavones on lipid profiles and atherosclerosis, only 1 in 4 of which showed beneficial effects on triglyceride levels. The results of the current study indicate that a beneficial treatment effect may be restricted to women who start isoflavone supplementation close to the menopause (within 5 years). This suggests a potential benefit in a more restricted age range where one explanation could be lower conversion to equol, however, there was no difference in atherosclerosis progression comparing placebo groups with treatment groups defined by equol production.

FINAL CONSIDERATIONS

Hormone Replacement Therapy (HRT) has been the subject of extensive study due to its potential risks and benefits in the management of menopausal symptoms and women's general health. In general, HRT has shown significant benefits in relieving menopausal symptoms by promoting the preservation of vaginal trophismus, preservation of bone health, improvement of lipid profile, reduction of vasomotor symptoms and improvement of sex life. There is no data in the literature to exclude the cardiovascular benefits of HRT in women at the start of the climacteric period. However, there is a need to better define HRT as a protective factor against cardiovascular disease. Despite the numerous benefits, the contraindications associated with HRT cannot be ignored. Attention should be paid to the presence of estrogen-dependent tumors, such as breast and endometrial tumors, whether active or recent, previous thromboembolic events and the presence of liver disease.

Special attention is also needed for HRT in older women, as there have been significant concerns about the increased risk of breast cancer, pulmonary embolism and deep vein thrombosis with certain formulations of HRT, especially when used by women in older age groups. The decision to prescribe HRT must be individualized, and the patient's expectations of the treatment must be very well aligned before it begins. Regular pharmacotherapeutic follow-up is essential to make possible dose adjustments and to monitor side effects.

It is also important that, before starting treatment, patients are advised to lead a healthier lifestyle, with proper nutrition, regular physical activity and no smoking. In short, HRT is a valuable treatment for managing menopausal symptoms, but it must be prescribed individually, taking into account the risks, benefits and contraindications of each patient.

The use of plants has always been essential for human survival, in various circumstances and needs, from food to their use as medicines.

Phytotherapy consists of the use of medicines derived from plants for the treatment or prevention of a disease. It is therefore a science based on medical practice controlled by clinical trials, rigorous pharmacological and phytotherapeutic studies.

According to Decree-Law no. 176/2006, of August 30, "herbal medicinal product means any medicinal product whose active ingredients are exclusively one or more herbal substances, one or more herbal preparations or one or more herbal substances in combination with one or more herbal preparations".

As with all medicines, there are various procedures that are required to approve the use of a given substance for market entry or to justify its use and recommendation by a health professional.

There are a number of plants that contain isoflavones and which are therefore used to treat or prevent various diseases such as osteoporosis or to reduce the symptoms of the menopause due to their estrogenic action.

These plants are extremely important both in food and in dietary supplements.

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