Review

**Use of soy isoflavones on hormone replacement therapy during climacteric**

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Menopause is the physiological stage of women's lives, which occurs in the transition from reproductive to non-reproductive phase. During this period, physiological and clinical changes may occur due to the decline of estrogen production by the ovaries. In expectation of a better quality of life during this period, women seeking hormone replacement therapies that can minimize the unpleasant symptoms of menopause. The large number of women with contraindications to hormone replacement with synthetic estrogens boosted research on the constituents of plants with phenolic structure, especially phytoestrogens. Soy isoflavones have the ability to bind to estrogen receptors in several human cells and can act as estrogen, antiestrogen and antioxidant. The aim of this study is to determine the use of soy isoflavones on hormone replacement therapy in the climacteric period, thus presenting its activities in relieving symptoms.

**Key words:** Soy isoflavones, hormone replacement therapy, climacteric.

INTRODUCTION

Climacteric is understood as the phase of a woman's life, which occurs in the transition from the reproductive to non-reproductive period. The period, in which the irregular menstruation is present is identified as perimenopause and at the time menses cease, is denoted as the onset of menopause. The decline of estrogen production by the ovaries is a slow and gradual process, extending for a few years after the menses disappear. This gradual process of reducing hormone is also called menopause and lasts approximately twelve months (Moya and Calleja, 2005; Pedro et al., 2003).

According to the Ministry of Health of Brazil, the average age of onset of menopause is between 48 and 50 years old, but in some cases, it can happen prematurely due to several other factors such as hysterectomy, ovarian failure, hyperprolactinemia, hypothyroidism, hypothalamic tumors, autoimmune diseases, among others (Aldrighi et al., 2005; Giacomini and Mella, 2006). Currently, the treatment of climacteric symptoms involves the change in lifestyle, such as smoking cessation, physical exercise, healthy diet, to the use of drugs. The hormone replacement therapy (HRT) held by ingesting synthetic hormones, constitutes the main treatment. However, synthetic HRT also have negative aspects, such as the increased relative risk of some hormone-dependent cancers as well as the increased risk of cardiovascular disease and thromboembolism. In addition, some patients may experience other side effects such as breast tenderness, increased body weight and lipid profile (Mosquette et al., 2006).
Soybean, *Glycine max*, is consumed as food for millennia, and in recent decades stand as a functional food with a view proof of some pharmacological actions. Much of the responsibility of these activities is related to compounds belonging to the group of isoflavones, such as genistein, daidzein and glycitein (Da Silva et al., 2009). The concentrations of isoflavones in soy vary depending on the quality of grain, growing conditions, soil and processing (Goés-Favoni et al., 2004). Their effects vary according to the type of fabric, depending on the affinity for specific receptors (Anderson and Garnier, 1997; Ye et al., 2009).

Isoflavones are phenolic compounds that may be present or not bound to sugar molecules (Grings et al., 2009). However, the most active types are forms of aglycones, without the sugar molecule. They have a similar chemical structure to human estrogen such as 17β-estradiol, and therefore, exhibit estrogenic activity (Queiroz et al., 2006). They can act in three different ways in the body, such as estrogens and antiestrogens being justified by the fact that they bind to estrogen receptors in the body and they can act as antioxidants, since they inhibit the production of reactive oxygen, which is involved in the formation of free radicals (Pimentel et al., 2005). The use of this phytoestrogen derived from soy can act as a natural hormone replacement therapy alternative, minimizing the unpleasant symptoms of menopause.

This work intends to conduct a literature review on the use of soy isoflavones on hormone replacement therapy in the climacteric period, presenting its activities in the alleviation of climacteric symptoms by acting as a natural hormone replenishes.

**THE CLIMACTERIC**

The main features of menopause are the depletion of functional ovarian follicles and ovarian failure with permanent cessation of menses. It is important in the decrease of female hormone production which occurs, and this change may affect other organs in the system simultaneously (Freitas et al., 2001; Zahar et al., 2005).

Estrogen is an important female hormone that exerts effects on multiple organs. The consequences of their disability can provide unpleasant symptoms that imply changes in the quality of life. Due to physiological and clinical changes, they manifest early and vasomotor symptoms (hot flashes), sweating, nervousness, irritability, insomnia, headache, dizziness, depression, emotional lability, decreased storage capacity, paresthesia, numbness, palpitations, myalgia, arthralgia and decreased libido, which accordingly, occur probably due to changes hypothalamic α2, caused by falling estrogen. Later, there is atrophy of the skin, urogenital disorders, joints and cardiovascular changes (Mosquete et al., 2006).

Santos et al. (2007) reported that hot flashes could be accompanied by flushing, sweating, chills, palpitations or tachycardia episodes, which consist of warmth feeling that radiates from the upper chest to the neck and head, accompanied by profound sweating. They are more unpleasant at evening, causing restlessness, insomnia and fatigue, and during the episodes, skin temperature is elevated. They suffer deterioration by a number of factors, such as, bed linen, hot weather and/or stress. They are associated with physiological changes that occur even during sleep, although they are influenced by psychological dynamics.

Kos (2004) reports that "hormonal fluctuations complicate the regular hypothalamus functions of the body temperature, the sleep rhythm, blood composition, and also affects the attitudes and behavior with symptoms such as hot flashes, mood swings, and depression. Moreover, without estrogen, bones may become porous, the protection against the evils of the heart decreases, the vagina develops less moisture, and the skin becomes dry and thin.

The uncertainty determined by the physical problem leads to psychological problems and can interfere with family relationships, sexual adaptation and social integration. The woman turns away from the environment and retracts when it is time to expand the field of relations. The rejection and insecurity can stimulate environmental and occupational changes.

**MECHANISM OF ACTION FOR SOY ISOFLAVONES**

Isoflavones are considered a subclass of flavonoids and polyphenols belonging to the family. The isoflavones are non-steroidal compounds structurally similar to the natural 17β-estradiol, and have a phenolic ring with an hydroxyl radical at the 3 carbon structure which gives them the capability of selectively binding high affinity to estrogen receptors (Figure 1) (Sena et al., 2007).

The chemical structures of 17β-estradiol and equol, a metabolite of isoflavones can be overlapped. It is possible to observe that the distance between the hydroxyl groups at the ends of the molecules is virtually identical (Matos et al., 2005), as shown in Figure 2. Such structural similarity provides the ability of these compounds to bind to estrogen receptors in various human cells.

According Graef et al. (2012), phytoestrogens are natural substances that exhibit similarities to endogenous estrogens, with greater ability to interact directly with betaestrogens receptors, providing better risk/benefit ratio in its therapeutic use, compared with hormone replacement therapy (HRT) synthetic.

Isoflavones are found in various plants as *Cimicifuga racemosa*, licorice, red clover, but the abundant source is soy (Guidoni et al., 2007). In consumption of soybeans and their products, isoflavones are hydrolyzed by intestinal glucosidases in the intestine (Figure 3), releasing the aglycones, daidzein, genistein and glycitein.
Figure 1. Structure of isoflavone.
Source: Aguiar (2002).

Figure 2. Similarity between the chemical structure of estrogen and isoflavones
Source: Aguiar (2002).

Figure 3. Obtaining daidzein through hydrolysis catalyzed by an esterase and/or glycosidase.
Source: De Oliveira and Oliveira (2012).

(Figure 4), which are the biologically active forms (Queiroz et al., 2006).

The daidzein is formed from formononetin (biochanin B) and their metabolic products are equal and O-
desmetilangolensina. Genistein is formed from biochanin A and its metabolite in humans is the p-ethylphenol,
which has no estrogenic activity (Reinli and Block, 1996).

Isoflavones when glycosylated receive a β-glucose
molecule at position 7 (Figure 5) (Izumi et al., 2000).

**METABOLISM, ABSORPTION AND BIOAVAILABILITY OF ISOFLAVONES**

Isoflavones are found in foods and sugars linked to beta-glucosides. These forms are not absorbed by humans. After ingestion, the conjugated forms of isoflavones are hydrolyzed by beta-glicosidases of intestinal bacteria, releasing the main aglycones, genistein and daidzein (Setchell, 1997). These compounds may be absorbed and/or metabolized by intestinal bacteria with formation of specific metabolites (Setchell, 1987).

Only the free sugar molecules without isoflavone aglycones are able to cross the plasma membrane. Hydrolytic enzymes of intestinal bacteria are responsible for these reactions. In the lumen, bacteria convert most of these aglycones to other molecules. There is considerable variability in the digestive efficiency of isoflavones. Only the aglycone forms or their metabolic products are absorbed by the intestinal epithelial barrier, which occurs passively via micelles. After absorption, these molecules are incorporated into chylomicrons that are carried to the circulatory system. Chylomicrons isoflavones distribute in all extra tissues-liver, where they will exert their metabolic effects, before returning them to the liver as chylomicron remnants (Anderson and Garner, 1997).

The recovery of circulating blood occurs passively in isoflavones, and all cells that contain estrogen receptors can potentially be influenced by these molecules. When these molecules are secreted into bile by the liver, some part is reabsorbed by enterohepatic circulation and is excreted by stool, and mostly 10 to 30% of the dietary intake in the urine (Setchell, 1997).

Studies in humans have demonstrated that plasma and urine concentrations of isoflavones increases with the amount consumed, indicating that absorption occurs in a dose-dependent manner (Kahn et al., 1998).

The bioavailability of soy isoflavones, and other factors, is positively influenced by a healthy gut microflora that is important because the translation of these substances to their active forms, and surveys conclude that administration of antibiotics blocks your metabolism (Setchell, 1997).

**MAJOR STUDIES USING SOY ISOFLAVONES**

The isoflavones may reduce menopausal symptoms, both in intensity and in frequency (Glaizer and Bowman, 2001). These observations are verified through epidemiological studies in regions of high soy consumption, as in the East, since Japanese women have 20% fewer hot flashes when compared to European, since 80% of these women have symptoms (Murkies et al., 1998). The intake of isoflavones for menopausal women does not eliminate the number of heat waves, but reduces its intensity depending on the amount ingested (Han et al., 2002).

It was found in a study that the isoflavones in postmenopausal reduces by 40 to 50% complaints of hot flushes, whose consumption was 50 to 80 mg/day for one year (Albertazzi and Purdie, 2002). Another study also
showed significant improvement of hot flashes in women who used isoflavone capsules for 50 mg/day for six weeks (Scambia et al., 2000). In a third study with 190 women investigated, the efficacy of isoflavones in relieving symptoms of estrogen deficiency derived mainly hot flashes, but also other symptoms such as sleep disturbances, anxiety, depression, vaginal dryness, loss of libido and bone pain. Each patient received 35 mg/day in two doses of isoflavones. During the four months of treatment, there was a significant decrease in the number of hot flashes as well as an improvement in symptomatology that accompanies the lack of estrogen during menopause (Albert et al., 2002).

Although studies show that the estrogenic effects of isoflavones are small (1/1,000-1/100,000; the least activity of estradiol), they can both exert an agonistic effect on estrogen. In the presence of estrogens, they act as antiestrogens by competing with it for binding sites on the estrogen receptors present in the cell. The prevention of this hormone exerts its negative effects, such as increasing the risk of breast cancer in women. In the absence of estrogen (menopause), these substances have estrogenic effect and replace the hormone that exhibits a low level, alleviating the undesirable symptoms.
of menopause and reduce the risk of cardiovascular disease and osteoporosis arising from the absence of the human estrogen (Queiroz et al., 2006). According to Sena et al. (2007), estrogen and antiestrogen property depends on the concentration of isoflavones. The concentration of endogenous sex steroids and specific target organ involves interaction with estrogen receptors. Estrogens exert their effect through two types of receptors: ERα and ERβ, which have different tissue distributions. ERβ are found in non-reproductive tissues such as brain, pituitary, urinary tract, circulatory system, prostate, and reproductive tissues such as testis and ovary. The ERα are found in breast, uterus, liver and kidney. However, both are expressed in the ovary, brain, bone, cardiovascular system and breast. Estradiol has affinity for both receptors, while the isoflavones are more selective for β-receptor in the proportion of 1/20 for α and 1/3 for β (Clapauch et al., 2002). They are potent agonists ER and weak ERβ, which classify them as blocking or modulating the natural selective estrogen receptor (selective estrogen receptor modulators, SERMs).

The role of genistein and daidzein on the β-estrogen receptors present in the liver results in improving the lipid profile, which is justified by an increase in the number of hepatic low density lipoprotein (LDL) receptors, favoring catabolism of cholesterol. This stimulation of estrogen-β receptors gives rise to an inhibition of hepatic lipase involved in the metabolism of high density lipoprotein (HDL) cholesterol, leading to its increase (Anderson et al., 1995). Marques et al. (2002) observed that studies claim that soy consumption allows the reduction of total cholesterol, LDL cholesterol and triglyceride levels, but the mechanisms responsible for these events have not yet been elucidated, thus there are several hypotheses.

Ferrari and Mottin (2001) reported that epidemiological data suggest that phytoestrogens have the function of lowering LDL cholesterol levels, as the oxidation occurs within the arteries when these particles become isolated from the circulating water soluble antioxidant; thus, the isoflavones could be inserted in lipoproteins, possibly protecting against oxidation, which is considered atherogenic.

With regard to dermatological symptoms such as dry and thin skin, the antioxidant effect of isoflavones was beneficial, reducing the action of free radicals and inhibiting the damage caused by ultraviolet (Han et al., 2002; Clarkson et al., 1995).

Angelis (2001) reported that in postmenopausal women treated with 80 mg of isolated soy isoflavones/day, there was a significant decrease in lumbar bone loss. In a study on the effects of isoflavones in 58 Japanese menopausal women, who used 40 mg/day of isoflavones for eight weeks, the rate of urinary deoxypyridinoline (Dpyr), a marker of bone loss, decreased significantly with isoflavones. This trend was mainly observed when using the equol, metabolite secondary compounds. However, the plasma levels of osteocalcin and bone mineral density did not change by four weeks of treatment.

In a meta-analysis of randomized controlled trials to clarify the various effects of soy isoflavones on bone loss in the spine, 10 studies with a total of 608 individuals were selected. Bone mineral density of the spine in subjects who consumed isoflavones increased compared to individuals who do not consume. These substances attenuated the intervention of the spine bone loss in postmenopausal women. These favorable effects became more significant when more than 90 mg/day of isoflavones have been consumed for six months. Beneficial effects on bone, with stimulation of bone formation and decreased urinary concentration of deoxypyridinoline (Dpyr), which decreased significantly compared with individuals who did not consume these compounds were observed (Ma et al., 2008).

Studies have shown effectiveness in increasing bone mineral density in women who take isoflavones derived from soy postmenopausal suggesting a reduction in the risk of developing postmenopausal osteoporosis, because osteoblasts and osteoclasts target cells for the action of daidzein and genistein (Bhajmandi et al, 2005; Esteves and Monteiro, 2001). Studies in cell culture emphasize that genistein binds with estrogen receptors and perform their actions in the same way as the hormone (Grings et al., 2009).

Genistein is a major component of isoflavones; it produces vasodilation by direct comparable to 17β-estradiol effect. Also, it acts as an inhibitor of oncogenesis (inhibiting tyrosine kinase - PTK), the epidermal growth factor (EGF-R), topoisomerases I and II, the ribosomal S6 kinase (DNA), inhibitor of angiogenesis and cell differentiation in vivo (Han et al., 2002a; b).

CONCLUSION

Climacteric is a physiological stage of life of women who brings many changes, causing discomfort and even disease derived from decreased estrogen. In the pursuit of alleviating these unpleasant symptoms, many women are using soy isoflavones as an alternative to replace therapy hormone. The soy isoflavones has been shown to be beneficial in reducing climacteric symptoms, since its structure is similar to endogenous estrogen. These compounds may alleviate the undesirable symptoms of menopause and reduce the risk of osteoporosis and cardiovascular disease. In addition, acting as the physiological antiestrogen hormone, avoiding the risk of breast cancer, and inhibit the production of reactive oxygen, helping to decrease LDL cholesterol levels and reducing the formation of free radicals. Despite various beneficial activities of soy isoflavone, these results are insufficient to complete the quantity or dosage of isoflavones needed.
for the purpose of prevention or treatment, because it varies from woman to woman and depend on the clinical condition and dietary habits. Like this, isoflavones do not eliminate heat waves, but decreases its frequency and intensity. A rich diet in phytoestrogens associated with healthy lifestyle habits can improve the clinical responses in the replacement therapy hormone.

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