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Impact of microbiota on the use and effects of isoflavones in the relief of climacteric symptoms in menopausal women – A review

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ABSTRACT

Menopause is a natural event that occurs in women around the age of 50 years, causing irregularities in the menstrual cycle until its complete end, due to the hormonal deficit, especially estrogen, that causes several unpleasant urogenital and vasomotor symptoms. Hormone replacement therapy has many benefits, but should be prescribed with caution in women with a history of stroke, thromboembolic events, certain types of cancer, or increased risk (genetic predisposition) for these events, so many women seek alternatives to hormonal therapy. Phytoestrogens, especially isoflavones, have many benefits in the climacteric phase, due to the similarity of their chemical structure with the hormone estradiol (E2), reducing the rate of menopause side effects and resulting in symptom relief. Furthermore, the isoflavones may still have their effects potentiated by an intestinal microbiota modulated with probiotic strains, which act on metabolism and increase the bioavailability of these phytoestrogens, and can benefit menopausal women's health.

1. Introduction

Menopause, a spontaneous physiological transition event, is characterized by permanent cessation of menstrual cycles and loss of ovarian function; it may be natural or iatrogenic (secondary menopause), which can be the result of surgery, illness, or use of medications. Characterized by progressive hypoestrogenism and clinically confirmed after 12 full months of amenorrhea, menopause can begin between 35 and 40 years and extend until around the age of 65 years. This event brings a reduced production of estradiol, the more active form of estrogen, as well as increased levels of follicle stimulating hormone (FSH) and decreased levels of inhibin, a hormone that inhibits the release of FSH, and progesterone (Davis, 2015; Sapre & Thakur, 2014; WHO, 1996).

Considered a marker of biological aging, the worldwide median age of input at natural menopause (approximately 46–52 years) may be variable according to socioeconomic position and lifestyle factors, with an important association between a lower socioeconomic position (education and income) and later menopause, as well as smoking with earlier menopause. In general, women from developed countries enter menopause later in life than those living in developing countries (Schoenaker, Jackson, Rowlands, & Mishra, 2014). This later age in natural menopause has been associated with reduced risk of cardiovascular disease (CVD) and CVD death, maintenance of bone density with reduced risk of osteoporosis and fracture, increase in life expectancy, and improvement in overall survival. On the other hand, later menopause is associated with increased risk of cancer, mainly breast, endometrial, and ovarian (Gold, 2011).

The decline in the secretion of sex hormones leads to the onset of menopause symptoms, being the vasomotor symptoms most commonly reported, followed by urogenital complaints. Hot flushes are the most common menopausal symptom, being reported by up to 85% of women. According to the Melbourne Women's Health Project, the most intense and important vasomotor symptom, hot flushes, can last for an average duration of 5.2 years, beginning about 1 year before the final menstrual period (Santoro, Epperson, & Mathews, 2015).

The decline in the secretion of sex hormones converges with the appearance of vasomotor symptoms, including heat waves and nocturnal sweating, in addition to other signs like insomnia, vaginal dryness, irregular menstrual bleeding, depressed mood, irritability, headache, forgetfulness, dizziness, irregular heartbeat, difficulty concentrating, memory loss, deterioration in postural balance, dry eyes,

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dry mouth, reduced skin elasticity, restless legs, muscle, joint pain, and general malaise (Davis, 2015; Moilanen et al., 2010; Santoro et al., 2015; Trimarco et al., 2016).

These symptoms occur in 3 out of 4 menopausal women, which corresponds to approximately 72 million women in the world, with 2 million among the Brazilian population. The duration and severity are not uniform, as it may develop in the final menstrual period and persist for a few to many postmenopausal years (Kim, Kang, Chung, Kim, & Kim, 2015; Rapkin, 2007; Rozenfeld, 2007; Sarri, Pedder, Dias, Guo, & Lumsden, 2017).

Besides the climacteric symptomatology, the hormonal fall predisposes women to accelerated bone loss, accumulation of central abdominal fat, and metabolic changes, such as increased blood pressure, which can cause cardiovascular disease and type 2 diabetes mellitus (Davis, 2015).

Hormone replacement therapy is the first-line therapy for symptom relief and prevention of comorbidities, such as osteoporosis and coronary heart disease (NAMS, 2017). It is important to evaluate the route of administration of estrogen, the dosage, and type of progestin associated with estrogen to increase effectiveness of the therapy, and reduce adverse effects. Although the contraindications of hormonal therapy are few, oral estrogen therapy may not benefit women with a genetic predisposition to increased thromboembolic events; transdermal estrogen therapy in standard doses is better indicated for these postmenopausal women (Level of evidence: 1A) (Mohammed et al., 2015). Moreover, women with no indication of hormone therapy may seek alternative therapies when there are potential health risks and uncertainty about the actual benefits they can provide (NAMS, 2012; Roussouw et al., 2002; Taylor, 2015; Utian, Jones, & Setchell, 2015).

Menopausal hormone replacement therapy was the mainstay of treatment for postmenopausal women until the publication of the Women's Health Initiative (WHI) in 2002. This publication rekindled the discussion on the safety of menopausal hormone replacement due to a randomized clinical trial where researchers found more risks associated with continued administration of estrogen, and progesterone outweighed the benefits, leading to increased risk of breast cancer and cardiovascular events (Roussouw & et al., 2002).

Fifteen years later, the confusion prevails, with studies that support and others that refute the relationship of hormone replacement use with increased incidence of cancer (Beral, 2003; Rozenberg, Vandromme, & Antoine, 2013). According to the (National Collaborating Centre for Women's and Children's Health, 2015) (Level of evidence: 1A), very few conditions are now considered as absolute contraindications: women with breast cancer or history of breast cancer should not make use of hormone replacement therapy (HRT), including tibolone and progestogens, which are being indicated as treatment options, as well as antidepressants or complementary therapies, such as isoflavones, which should be evaluated for drug interaction and safety. Evidence from this study shows that oral HRT increases the risk of venous thromboembolism, but transdermal HRT does not, where the therapy should be individualized based on clinical factors, patient preference, mode of delivery of estrogen, with the safety of hormone therapy depending on age and time since menopause (Baber, Panay, & Fenton, 2016; Marko & Simon, 2017; Sood, Faubion, Kuhle, Thielen, & Shuster, 2014; Stuenkel et al., 2015). Corroborating these findings, an observational follow-up of 27,347 postmenopausal women, conducted by (Manson et al., 2017) (Level of evidence: 2C), with conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8506) vs placebo (n = 8102) for 5.6 years (median) or CEE alone (n = 5310) vs placebo (n = 5429) for 7.2 years (median) noted that long-term hormone replacement therapy was not associated with a risk of all-cause (27.1% in the hormone therapy group vs 27.6% in the placebo group, p = .60), cardiovascular (8.9% with hormone therapy vs 9.0% with placebo, p = .98), or total cancer mortality (8.2% with hormone therapy vs 8.0% with placebo, p = .50). The trials were not heterogeneously significant during a cumulative follow-up of 18 years, evidencing safety outcomes from this intervention.

The drop-in prescription of hormone therapy was especially prevalent among women with a family history of cancer, cardiovascular disease, or bleeding disorders, and among those who, even having an indication, choose not to use hormone therapy. A family history of breast cancer (Colditz, Kaphingst, Hankinson, & Rosner, 2012) (Level of evidence: 2A) is not a contraindication; individual history is more important, prepondering the view that HRT is a low-risk intervention that provides effective relief of menopausal symptoms and providing long-term protection against the major chronic diseases affecting women in their lifetime. Thus, for prescription, the risk/benefit assessment is the most important consideration for health care professionals (Baber et al., 2016; Chlebowski & Anderson, 2015; Currie, Abernethy, & Gray, 2017; Ko, 2014; Langer, 2017; Moreira, Silva, Santos, & Sardão, 2014; Nachtigall, 2001; Stuenkel et al., 2015). However, (NAMS, 2017) (Level of evidence: 1A) highlights that women aged younger than 60 years or who are within 10 years of menopause and have no contraindications for hormone replacement therapy have more benefits than risks when adhering to this treatment, as HT is probably the most appropriate bone-active therapy and most favorable for treatment of vasomotor symptoms.

Many treatment options are available, both pharmacological and non-pharmacological, to relieve menopausal symptoms, especially vasomotor symptoms. The pharmacological possibilities are: (1) hormone replacement therapy, which commonly combines a progestogen with estrogen being used for most women; estrogen isolated is indicated for women with hysterectomies, or vaginal hormone creams, as local estrogen therapy, is suitable for treatment of genitourinary syndromes of menopause, chronic conditions that include genital symptoms (burning, itching, dryness or irritation), sexual symptoms (dyspareunia, lack of lubrication, pelvic discomfort and pain or impaired function), and also urinary symptoms (urgency, dysuria or recurrent urinary tract infections) (Kim, Kang, et al., 2015; NAMS, 2012); (2) tibolone, a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions (Sarri et al., 2017); (3) alternatives non-hormones for hot flushes including the selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI); these antidepressants are used off-label to treat menopausal hot flushes and sleep quality, improving only vasomotor symptoms by acting specifically in a thermoregulatory-neutral zone (Ensrud et al., 2012), and finally (4) phytoestrogens, which are phenolic compounds with estrogenic activity, due to their chemical structure similar to the endogenous estradiol (E2), and these compounds are found in vegetables, usually in the most common forms of lignans, coumestans, stilbenes, and isoflavones. The phytoestrogens are capable of binding to estrogen receptors (ER), with greater affinity for the β receptor than for α, promoting agonist and antagonist functions about them (Chlebowski & Anderson, 2015; Ko, 2014; Moreira et al., 2014; Nachtigall, 2001).

Phytoestrogens are phenolic compounds found in plants, such as flavonoids, isoflavones, and lignans, which possess estrogenic or antiestrogenic activities due to its similarity to mammalian estrogens (Cassidy, 2003; Frankenfeld, 2017). They belong to a huge family of secondary plant metabolites that are present in the diet, promoting several potentially health-benefits, like antioxidant, apoptotic, anti-inflammatory, anti-proliferative activities, cholesterol-lowering, and many other biological functions reported in the literature, in addition to presumably inhibiting cancer cell proliferation and stimulating immune function (Burkard et al., 2017; Landete et al., 2016).

Flavonoids, which are subdivided based on their chemical structure, into the subgroups flavonols, flavanols (or catechins), isoflavones, flavones, flavanones, and anthocyanidins, are found in plants often conjugated to sugar residues, known as flavonoid glycosides, creating a complex mixture with their respective aglycones (structure without the sugar residue) (Hollman, 2004). Some flavonoid glycosides are actively carried through the small intestinal epithelium by glucose transporters (Cermak, Landgraf, & Wolffram, 2003; Wolffram, Blöck, & Ader, 2002),