

Efficacy of Soybean in Menopausal Syndrome (Literature Review)

Review Article

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Abstract

Menopause is the critical time period in the life of a woman when menstruation ceases. It is also known as the climacteric. There is a decrease in hormone estrogen production by the ovaries and is commonly associated with symptoms such as fatigue, hot flashes, joint pain, mood fluctuations, sweating and vaginal dryness. Approximately one third of the Indian women experience menopausal symptoms. Alternative methods to deal with these menopausal symptoms are lifestyle changes, use of Yoga and meditation, use of hormone replacement therapy, and phytoestrogen-rich foods such as soybeans. Some studies reveal that phytoestrogen supplementation offers a possible alternative to conventional hormonal replacement therapy (HRT). Among available food soybean exhibits the highest concentration of isoflavones. Regular consumption of soybeans had been evidenced to have diminished menopausal symptoms. Due to safety profile and benefit to overall female health soybean is preferred food.

Keywords: Menopause; Phytoestrogen; Soybeans

Introduction

India has a large population, with 71 million people over 60 years of age and about 43 million menopausal women already above one billion marks. The expected population in India is projected to be 1.4 billion in 2026. Out of which 173 million people will be over 60 years and 103 million menopausal women. In Indian women, the median age of menopause is 47.5 years with an average life expectancy of 71 years [1]. Also India, with a population of 1.2 billion people, is the second largest emerging economy and second most populated country in the world. According to the latest World Health Organization (WHO) data published in 2018, the life expectancy in India for a female is 70.3 years, expected to increase to 77 years by 2050. Non-communicable diseases account for 60% of the total deaths in India. Currently, approximately 10% of India's population, i.e., more than 100 million, is aged over 50 years [2].

The estimated mean age of menopause is 46 years in India. This early age of menopause predisposes a woman to chronic health disorders. Breast cancer is the most common cancer in Indian women, and the incidence peaks before the age of 50 years [3].

Although menopause is a physiological process it leads to various symptoms due to estrogen deficiency. This affects quality of life. Soybean commonly available in India is one of the most nutritious pulses feasible under cultivation. It has all macronutrients for better nutrition, protein, fat, carbohydrates, calcium, iron, vitamin B1, and phytoestrogens which are helpful to alleviate the menopausal problems [4]. Also soybean is available in many forms. Soy products of wide varieties have been prepared such as roasted soybean, boiled soybean, soymilk, soy mayonnaise, miso, soy cheese, soy yogurt, tempeh, soy sauce, tamari, Textured Vegetable Protein (TVP), or Textured Soy Protein (TSP) and tofu [5]. This article is a review article that has assessed the efficacy of soy beans in menopausal symptoms.

An overview of menopause

Menopause is a natural biological and physiological process that leads to the permanent cessation of menstrual cycle of a woman's reproductive life. It usually occurs around 40 to 50 years of age. It is characterized by the cessation of menstrual periods for twelve continuous months, hormonal disturbances, and menopausal symptoms, which include hot flashes and night sweats along with

vasomotor symptoms⁵. During menopause various organs undergo changes, e.g., the cortex of the ovaries becomes thinner and contains fewer follicles and the vaginal layers become dry and thinner and lose elasticity. Furthermore, evidence suggests that estrogen deficiency leads to an increase in osteoclastic activity, which results in an imbalance between osteoclastic and osteoblastic activities. Moreover, estrogen deficiency leads to vasoconstriction in the wall of arteries and an accelerated increase of low-density lipoproteins, thereby increasing the risk of cardiovascular diseases, disturbed sleep patterns, mood swings, vasomotor symptoms, and generally a lower quality of life[6].

The symptom complex can be divided into VMS, somatic symptom, genitourinary syndrome of menopause (GSM), and neuropsychiatric symptom. Vasomotor symptoms (VMS) such as hot flushes and sweating, are very common in menopausal populations and can cause physical and mental discomfort⁷. There is deficiency in the production of estrogen. This deficiency leads to various symptoms such as hot flashes, night sweats, mood swings, lack of concentration, loss of confidence, fatigue, dryness of vagina, sleep disturbances, irritability etc. Throughout the menopause transition, estrogen deficiency results in an increase in weight and fat accumulation. Also, various organs undergo changes, e.g. the cortex of the ovaries becomes thinner and contains fewer follicles and the vaginal layers become dry and thinner and lose elasticity[8]. Furthermore, evidence suggests that estrogen deficiency leads to an increase in osteoclastic activity, which results in an imbalance between osteoclastic and osteoblastic activities⁶. Moreover, estrogen deficiency leads to vasoconstriction in the wall of arteries and an accelerated increase of low-density lipoproteins, thereby increasing the risk of cardiovascular diseases, disturbed sleep patterns, mood swings, vasomotor symptoms, and generally a lower quality of life[9]. In short, estrogen deficiency is responsible for range of physiological and psychological changes during menopause.

Management of Menopausal Symptoms

Traditionally estrogen remains the most effective treatment for all menopausal symptoms. Administration of estrogen is called as Hormone Replacement Therapy (HRT). It is also called as menopausal hormone therapy (MHT). MHT covers therapies including estrogens, progestogen, combined therapies, androgens, and tibolone. Various terminology used in MHT: ET-estrogen therapy: EPT-estrogen progesterone therapy: AT-androgen therapy: SERMs-selective estrogen receptor modulators (raloxifene and bazedoxifene): Gonadomimetics- tibolone, which contains estrogen, progestogen, and androgen activity[10]. But it causes breast pain or tenderness, vomiting, loss of appetite, leg cramps and joint pain, weight gain or loss, nervousness, depression and irritability. Non-hormonal drugs or agents may relieve VMS but have their own side effects.

Adverse effects of MHT

In the WHI trial, prior randomized use of CEE plus MPA, compared with placebo, among women who had an intact uterus, was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality [10]. MHT affects glucose metabolism, both in women with and without type 2 diabetes

mellitus. MHT is relatively contraindicated – in leiomyosarcoma, EC type II, advanced metastatic malignant melanoma, lung cancer, gastric cancer, and bladder cancer, breast cancer, endometrial stromal sarcoma, uterine carcinosarcoma, ovarian cancer (estrogen dependent granulosa cell, low grade serous, and Sertoli-Leydig, endometrioid types of ovarian tumors), adenocarcinoma of the cervix meningioma, glioma, and hormone receptor positive gastric and bladder cancer. If bleeding starts after commencement of progesterone therapy in cyclical regimens or there is a change in the duration or intensity of blood flow which is not normal for that woman extensive investigations are required. The dose and duration of use of MHT should be individualized after extensive follow up. Risk-benefit assessment is carried out annually. Follow-up every month may also be required.

MHT is generally preferred to women below the age of 50 years or within 10 years of menopause. The risk of VTE (Venous thromboembolism) is increased by oral MHT. There is an increased risk of stroke with oral MHT. There is a dose dependent relationship among the dose and duration of MHT with VTE. Risk of gallstones, cholecystitis, and cholecystectomy is increased with oral estrogen alone and combination MHT. If economy is considered menopause management has significant direct and indirect costs. Direct costs include gynecologist's visits, specialist's visit, traditional pharmacotherapy or alternative, complementary medicine therapy. Indirect costs include laboratory testing, management of adverse events, loss of productivity at home and at workplace, treatment of associated medical disorders.

Menopause is a critical window of opportunity for use of other non-hormonal, traditional dietary regimen and adopting healthy life style.

Soybean: A boon for menopause

Due to the potential undesirable health consequences and many adverse effects caused by hormonal therapies, numbers of women are searching for herbal therapies or secondary metabolites from plants as alternatives to treat typical menopausal symptoms. This trend has been increasing since last decade.

In recent years, nutraceuticals such as phytoestrogens and herbal derivatives have gained popularity due to their claimed ability to relieve menopausal symptoms. Nutraceuticals are defined as foods, parts of foods, or botanicals that provide medical and health benefits, such as the prevention and treatment of disease[11].

The word "phytoestrogen" comes from the Greek term for plant ("phyto") and from the term

"Estrogen", that is a hormone that influences the female fertility in vertebrates. Phytoestrogens are compounds found in plants.

Among the phytoestrogens, isoflavones and lignans are commonly used to relieve menopausal symptoms, as they are abundant in fruits, vegetables, legumes, and soy[12]. A study on soy intake in various countries revealed that the average daily soy intake is nine times higher in Asian countries compared to North American and European countries, resulting in a higher life expectancy on average[13]. Among the isoflavones used to treat menopause symptoms, genistein has

been widely used because of its important properties and the fact that it accounts for about 60% of the total isoflavones found in soy[14]. A search for the terms “genistein” and “cancer” using PubMed revealed that the main molecular targets of genistein are estrogen receptors, protein tyrosine kinases, and topoisomerase II. So genistein can be used in the treatment of typical postmenopausal symptoms, cancer, obesity, osteoporosis, hormonal changes, gene activity alterations, cardiovascular disease, atherosclerosis, and diabetes, and provide a comprehensive overview of the underlying mechanisms and therapeutic actions of genistein[15].

Isoflavone Classification

Phytoestrogens are naturally occurring nonsteroidal phenolic plant compounds and can be divided into two main groups: flavonoids and non-flavonoids[16]. Flavonoids include isoflavones, coumestans and prenylfavonoids, and non-flavonoids include lignans.

Genistein, daidzein, glycitein, biochanin A, and formononetin belong to isoflavone phytoestrogens. Equol, as a daidzein metabolite, is sometimes also ranked among this group[16]. It is solely a metabolic product of intestinal bacteria. Isoflavones are ranked among the compounds having substantial amount of estrogen. The main source of isoflavones is legumes from the family Fabaceae, namely soybean (*Glycine max*) as a source of daidzein, genistein, and glycitein and red clover (*Trifolium pratense*) as a source of formononetin and biochanin A.

Absorption

Soy isoflavones (genistein, daidzein and glycitein) are present in significant quantities (up to 4-5 mg g⁻¹ on a dry basis) in legumes, mainly soy, green beans, mung beans[17]. In cereals (raw materials) they are generally present as glycosides, and are poorly absorbed. The main metabolite of soy isoflavones is equol, produced through digestion by the bacterial flora, and is thought to be the most responsible for the isoflavone activity[18]. After soy intake, a biphasic model is found in the absorption of soy isoflavones in plasma and urine, which appears to be due to the absorption in the small intestine (about 10%) during the first 2 hours after the intake and to that in the large intestine (about 90%) 4-6 hours after taking. The bioavailability of isoflavones is also influenced by intestinal bacteria and treatment with oral antibiotics. While daidzein and genistein begin to be absorbed a few minutes after intake, the equol appears in plasma only at least 8 hours after taking soy, due to the required transit time of daidzein to colon, where the conversion of daidzein to equol occurs thanks to the intestinal microbiota[18].

Phytoestrogens, found in the diet as glucoconjugates (daidzin, genistin), are hydrolysed in the intestine in the active aglycon forms (daidzein and genistein) by the action of UDP-glucuronosyltransferase, which is secreted by intestinal bacteria. Genistein and daidzein are also produced by the demethylation of their precursors, respectively biochanin A and formononetin. The aglycones are absorbed from the intestinal tract towards the liver, where they are mainly conjugated with glucuronic acid and sulfates. Some of the conjugated aglycones are excreted in the bile, where they are hydrolysed, and some of the unconjugated aglycones are excreted in the faeces, whereas some of them are reabsorbed in the liver through the enterohepatic

circulation. In the blood, isoflavones are metabolised mainly in equol and O-desmethylangolensin, which are excreted in the urine[18]. In short the major factor that presence of specific bacteria equipped with the right β -glucosidase in the intestinal microbial flora regulates the production of equol.

Estrogenic Activity of Isoflavones

Vasomotor symptoms of menopause, including hot flashes, night sweats, and insomnia (as a consequence), are the essential symptoms of postmenopausal estrogen deficiency[19]. Various study showed that soy intake reduced the incidence of hot flashes as compared to the beginning of the study. During clinical research, a randomized double-blind study in menopausal women found that the administration of 30 mg of genistein for 12 weeks reduced hot flashes by 51% (9.4–4.7/day), whereas, the placebo group experienced only a 27% reduction (9.9–7.1/day)[20].

Studies have also pointed out that the ability of women to produce equol may be the major determinant of whether or not isoflavones can effectively reduce VMS. A systematic review and meta-analysis of RCTs assessed the efficacy of soy isoflavones and equol for alleviating menopausal symptoms (especially vasomotor symptoms) in postmenopausal women who were either equol producers or nonproducers[20]. The result of this meta-analysis revealed a significant benefit of equol for decreasing hot flash scores. This study concluded that supplementing equol to equol nonproducers significantly lowered the incidence and/or severity of hot flashes in menopausal women[21].

The mechanistic mode of action of Isoflavones is not yet completely understood. The limitations of definitive conclusions is due to the reason that studies have mostly been done through in vitro assays using concentrations higher than those found under physiological conditions. These isoflavones particularly equol is found in plasma mainly as a 7-O-glucuronide derivative[22], which makes it difficult to discern the biologically-active form(s) at tissue and cellular levels. In spite of these deficits, evidence from experimental studies suggests that equol may act in multiple ways[23]. Based on its structural similarity to 17- β -estradiol, equol binds to both estrogen receptors (ERs) alpha (ER alpha) and beta (ER beta which is the preferred target) with greater affinity. It is well-known fact ERs are not equally distributed among the different tissues. So equol might have different effects depending on the ratio of ER alpha and ER beta isoforms present. Whether it acts as an agonist or an antagonist may further depend on the level of endogenous estrogens present, as they bind to both receptors more tightly[24]. The antioxidant activity of equol seems to be mostly mediated by its interaction with the ER beta, which induces the extracellular signal-regulated protein kinases (ERK1/2) and the NF- κ B peptide, factors that control transcription, cytokine production, and cell survival[24]. Isoflavones and equol may not act as antioxidants themselves but rather by triggering cell signaling pathways leading to changes in the expression of cellular enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (all involved in counteracting oxidative stress)[25]. These activities may provide the basis for therapeutic strategies, for instance by restoring endothelial function in cardiovascular diseases. An improvement in atherosclerosis has also been reported via equol

attenuating ER stress, mediated by the activation of the NF-E2 p45-related factor 2 (Nrf2) signaling pathway[26].

It can be hypothesized that genistein may act in cells via the classical genomic mechanism, entering the cells by diffusing through the lipid bilayer due to genistein being an effective ER modulator. This complex moment stimulates the nucleus, mRNA synthesis, and production of tissue-specific proteins[27]. These findings suggest that genistein has the potential to ameliorate some emotional and vasomotor symptoms. Further studies using genistein could help to find a promising agent to treat typical symptoms associated with menopause[27].

Combination of soybean and exercise

Fontvieille et al.[28]verified the efficacy of phytoestrogen supplementation (PHY: each capsule contained 325 mg of soy extract with 17.5 mg of isoflavones for a 70-mg daily dose of 44 mg of daidzein, 16 mg of glycitein and 10 mg of genistein) combined with exercise (EXT) on improving climacteric symptoms in postmenopausal women, compared with EX plus placebo (PL). The 12-month exercise program consisted of three non-consecutive sessions (1 h each) per week of combined exercise, which means combination of aerobic (30 min) and resistance (30 min) exercises. Climacteric symptoms were assessed using the Kupperman Index questionnaire, including 11 symptoms: hot flushes, night sweats, insomnia, nervousness, melancholy, dizziness, asthenia, arthralgia, headache, palpitation and vaginal dryness. After 1 year of intervention, while the EX + PL group showed improvements in the total score of menopausal symptoms and hot flushes, the combination with phytoestrogens prevented positive effects in the long term in overweight postmenopausal women. The results of this study did not support the usefulness of phytoestrogen supplementation in the long term when exercise is performed on a regular basis and suggested that adding phytoestrogens may interfere with exercise training adaptations as beneficial impacts were observed in the EX + PL group only. Authors[28]suggested that exercise (activating ERα) and phytoestrogens (activating ER β) may induce opposite effects in the long term(Table 1).

Abbreviations

5-HIAA: 5-Hydroxyindoleacetic acid; 5-HT: serotonin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MAO:

Table 1: Other effects of Isoflavones.

Symptoms/ Disease	Effects of isoflavens
Vasomotor	Reduction of hot flashes, night sweats, and sleep disturbances frequency; as well as depression symptoms and memory loss [29]
Cardiovascular	Reduction of myocardial necrosis, macrophage and serum levels of TNF-α, severity of atherosclerosis, and myocardial infarctions incidence [30]
Obesity	Reduction of serum concentration of total cholesterol, LDL, triglycerides, and HDL[31]
Diabetes	Reduction of fasting glucose concentration, insulin resistance, and improves glycemic metabolism [32]
Cancer	Reduces the incidence of breast, hepatocellular, lung, gastric, and ovarian cancer [33]
Stress responses	Improves 5-HT metabolism, stabilizes MAO activity, and improves turnover ratio of 5-HIAA/5-HT [34]

monoamine oxidase; TNF-α tumor necrosis factor alpha. Information is supported by references [29-34].

Adverse effects of Isoflavones

Isoflavones are generally well-tolerated by women. Some gastrointestinal disturbances are found such as nausea, bloating, diarrhea, and constipation. They are generally mild.

Conclusions

Isoflavones are polyphenolic compounds usually represent most common categories of phytoestrogens.They are structurally similar to 17 beta estradiol and are found in the Fabaceae family. Before metabolism, they are hydrolysed into aglycones by the micro flora present in the human digestive tract by the enzymes present in the gastrointestinal tract.

Isoflavones reduce hot flashes, has good effect on attenuate lumbar spine BMD loss, may show beneficial effects on systolic blood pressure during earlymenopause, and may improve glycemic control in vitro. Also benefits ofisoflavones on urogenital symptoms were observed.

A survey found that 70% of women would be “satisfied with a nonhormonal intervention that provided at least a 50% reduction in hot flashes”[35]. As far as the safety profile of isoflavones combined with exercise their makes them a compelling treatment option for postmenopausal women unwilling or unable to use hormone replacement therapy.

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