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The most abundant isoflavone contained in soy beans and its effects on menopausal symptoms and related pathophysiologies: A review

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Abstract

Active compounds from plants have been and continue to be of interest in the field of developing new therapeutic agents and many studies have demonstrated the biological effects of a variety of these compounds. Among these natural compounds are polyphenols, such as isoflavones derived from soy, also called phytoestrogens, which have been widely studied for their anti-cancer, antitumor, hypoglycemic, antioxidant properties, among others. Phytoestrogens are natural substances obtained from plants and have a chemical structure similar to 17β-estradiol and thus mimic the binding and estrogenic effects in different target tissues. Genistein is a phytoestrogen that represents approximately 60% of the total isoflavones found in soybeans and clinical and epidemiological studies demonstrate the beneficial effects of genistein against cardiovascular disease, diabetes, osteoporosis and against the symptoms of anxiety and depression related to menopause. Although the biological effects of genistein are beneficial and promising, certain implications, such as a mechanism of action not yet fully elucidated, effective therapeutic doses not established for humans, lack of specific scientific work with humans, among other conditions, have limited the clinical applications of genistein in a certain way. This study aimed to describe the potential benefits of genistein against symptoms observed in post-menopause and its biological effects on pathophysiology related to that period. The ability of genistein to exert different beneficial effects against changes induced by the absence of female gonadal hormones and without determining the adverse effects related to hormone replacement therapy with female gonadal hormones makes this phytoestrogen a likely candidate or therapeutic alternative in the treatment of signs and symptoms.

Keywords: Genistein, Isoflavone, Phytoestrogens, Therapeutic potential

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1. Introduction

The condition called menopause is characterized by the cessation of spontaneous monthly menstruation for at least 12 months and this usually happens in women over forty. After this period, post-menopause occurs, characterized by high levels of follicle-stimulating hormone (FSH) and low levels of circulating estradiol and this change in hormone levels leads to the occurrence of signs and symptoms such as menstrual irregularity, frequent hot flashes, intense night sweats, sleep disturbances, dryness of the vaginal mucosa, atrophy of the vulva and vagina and dyspareunia, among others [1-2]. During the transition from the woman's reproductive period to the non-reproductive period (climacteric period), the decrease in plasma levels of estrogen also implies the accumulation of adipose tissue and consequent increase in body weight, in morpho-functional changes in the organs of the lower urinary tract, where the cortex of the ovaries becomes thinner and with a reduced number of follicles, the layers of the vaginal mucosa become dry, thinner and with drastically reduced elasticity [3]. The literature also reports that estrogen deficiency during menopause leads to increased arterial vascular tone, increased plasma concentrations of low-density lipoproteins, and these pathophysiological conditions may imply an increased incidence of cardiovascular diseases that result in a low quality of life of postmenopausal women [2-5]. Current therapeutic strategies for the treatment of menopausal symptoms basically focus on hormone replacement therapy (HRT) in order to minimize and prevent the complications that these pathophysiological conditions can cause in the long term. However, although HRT is a treatment used by many postmenopausal women, the complications caused by this therapy can outweigh its beneficial effects. These complications are characterized by thromboembolism, uterine hyperplasia, and cancer,

endometrial hyperplasia, increased risk of breast and ovarian cancer, coronary heart disease, stroke, among others [6].

Due to these possible complications caused by HRT, the number of menopausal women undergoing treatment with natural plant-derived substances as a therapeutic alternative in the treatment of typical menopausal symptoms has increased over the years [7]. According to the literature, this treatment is performed through the ingestion or administration of phytoestrogens that are biologically active compounds, plant-derived and chemically similar to endogenous estrogens and mimic the properties of 17-beta estradiol [8]. In this way, isoflavones and lignans are widely used to alleviate menopause symptoms and these phytoestrogens are abundantly found in fruits, vegetables, and especially soy [9-10]. In Asian countries, the population consumes food with soy in a much higher proportion when compared to the population in Europe and America, and this eating habit results in a higher life expectancy of the population of these Asian countries [11]. Genistein is the most abundant iso-flavone present in soybean (*Glycine max* L.) representing about 60% of all isoflavones contained in this leguminous and many biological effects are attributed to this iso-flavone [12-13].

This article is a literature review, which aims to present the main findings of the therapeutic potential of genistein in the treatment of signs and symptoms of menopause, as well as the mechanisms of action of this iso-flavone that have already been elucidated.

2. Methodology

The present work is a literature review where the identification of articles of interest was performed using the PubMed databases of the US National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/), database Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), and the search tool attached to the Virtual Health Library (VHL). The Institutional Repository of different Brazilian Universities for researching articles along with theses, dissertations, and monographs was also consulted. The predefined keywords “Genistein”, “Isoflavone”, “Phytoestrogens”, “Therapeutic potential” were used in the searches. The search expression was the Boolean operator "AND", limiting the searches to the words of the title or abstract of articles, in English, Portuguese and Spanish, studies with human beings and/or experimental animals, as well as *in vivo* studies and/or *ex-vivo*. To ensure the quality of articles, only indexed publications were included in this database and articles that presented title and abstract according to the theme were included and those that did not fit were excluded.

3. Results and discussion

3.1. Genistein: chemical characteristics and general biological effects

Genistein is an iso-flavone structurally similar to endogenous estrogen, but it has much greater specificity for the estrogen receptor beta isoform (ER-β) than for the estrogen receptor alpha isoform (ER-α) when compared to the specificity of estrogen, which may be a beneficial property of phytoestrogens, considering the scientific consensus of that most unwanted effects associated with the use of estrogens during hormone replacement treatment (HRT) are related to the interaction and stimulation of ER-α by these hormones, while the beneficial effects of estrogens are related to the interaction of these hormones with ER-β [12]. Many studies, both in vitro and in vivo, suggest that the therapeutic properties of genistein are related to its ability to act in different biochemical pathways, and thus it is expected that this iso-flavone does not have only one mechanism of action [14]. Overall, the literature reports that genistein induces its actions by targeting several enzymes such as topoisomerase I and II [13], by inhibiting ATP binding cassette transporters [15], and by the stimulation of estrogen receptors [16]. Moreover, genistein decreases the activity of protein tyrosine kinases [17], modulates the stimulation of the peroxisome proliferator-activated receptor-PPAR gamma [18-19], decrease the activity of mitogen-activated protein kinase-MAPKA [20]. decrease the activity of 5-reductase and histidine protein kinase [21-22] among others. Genistein also alters the plasma quantity and functions of different hormones, such as thyroid hormones, as it decreases the activity of thyroid peroxidase [23], suppresses glucose oxidation, and insulin-induced anti-lipolytic effects [24]. In addition, genistein inhibits adrenocortical 3-hydroxysteroid dehydrogenase and decreases cortisol production in adrenal cortical cells. This decrease in plasma cortisol contributes to the maintenance of ideal blood pressure values and alters lipid metabolism, reducing the development of obesity [25-27]. The effects of genistein have an even greater impact on menopausal women, and some of these effects are summarized in Table 1.

3.2. Vasomotor symptoms related to genistein and menopause

Hot flashes, intense night sweats are vasomotor symptoms that can occur both in the early menopause and postmenopausal period, and these symptoms are inherent to the low levels of circulating estrogens during these periods of a woman's life [32-33]. These vasomotor symptoms can trigger emotional and affective problems such as insomnia, depression, anxiety disorders, mood alterations, decreased mood, and intellectual deficits, and these problems significantly affect the quality of life [34]. In this way, treatment with genistein or consumption of genistein-rich foods improves these symptoms, especially hot flashes, sleep disturbances, insomnia, and depressive symptoms [35-

36] and that this effect of genistein may be related to the ability of genistein to modify gene expression and the production of specific proteins in vascular tissue and in the central nervous system [28]. The literature also reports that the increase in vascular reactivity to catecholamines is related to the decrease in circulating estrogens during menopause and during ovariectomy, as nitric oxide (NO), the most potent endothelial-derived relaxing factor has its endothelial production stimulated by estrogen, regardless of gender [37].

Genistein is able to reverse the vascular changes related to the decrease in basal levels of NO observed during menopause and this reversal is directly related to the increase in endothelium-dependent NO production similar to that induced by estrogen, as well as related to the decrease in the production of endothelin-1 (potent endothelium-derived contraction factor) which implies the improvement of vasomotor symptoms observed during menopause [38-42]. The results obtained in these studies point to the consideration that genistein has the potential to effectively improve the vasomotor and emotional symptoms related to the postmenopausal period. However, future specific studies of the effects of genistein on these symptoms may strengthen the idea of its use in the therapy of these pathophysiological conditions.

3.3. Genistein and cardio-protection

Postmenopausal women are more likely to develop cardiovascular disease than women during the reproductive period and the occurrence of these diseases is directly related to the abrupt reduction in circulating estrogen levels observed during the menopause event [43]. Replacing the gonadal hormones lost during menopause can prevent cardiovascular disease, but according to the World Women's Health Initiative, the risks of this therapy may outweigh its benefits. Among these risks are the increased probabilities of developing breast, ovarian and endometrial cancer, uterine bleeding, venous thromboembolism, and stroke [44].

The consumption of natural substances that contain a large amount of genistein improves bone mineral density, reduces some menopausal symptoms, and improves cardiac functions [45-46]. Thus, different studies reinforce the idea that alternative therapeutic approaches, such as the consumption of soy isoflavones, fruits, and vegetables rich in phytoestrogens, determine significant health benefits in postmenopausal women safely and without causing undesirable effects [47]. In this way, genistein exerts beneficial effects on the cardiovascular system through its hypocholesterolemic effect observed both in humans and experimental animals. Genistein inhibits the early stages of atherogenesis and prevents the rupture of the atherosclerotic plaque by inhibiting the activity of tyrosine kinases, and in this way, inhibits the cascade of events that lead to thrombus development. Furthermore, genistein prevents LDLc oxidation, endothelial cell proliferation, and angiogenesis, in addition to enhancing the vasodilator response dependent on endothelium-derived relaxing factors in atherosclerotic arteries [48].

Inhibition of tyrosine kinase activity by genistein also prevents cardiac hypertrophy resulting from increased activity of cardiac fibroblasts and increased cardiac work evoked by hyper-stimulation of cardiac β-adrenergic receptors with isoprenaline, decreases cardiomyocyte apoptosis observed after intoxication by arsenic trioxide, and decreases the proliferation of vascular smooth muscle cells of rats [49-50] Genistein also positively modulates basal insulin secretion in postmenopausal and diabetic women by modifying tyrosine kinase activity in pancreatic beta cells which implies reduced fasting serum glucose levels and subsequent reduction of fat deposition in blood vessels and cardiac tissue and these events are associated with a cardioprotective effect [51-52]. In experimental models of coronary artery occlusion in rodents, intravenous administration of genistein is able to reduce myocardial necrosis, serum TNF levels, and intercellular adhesion molecule-1 levels, as well as reduce serum creatinine phosphokinase activity and the ability to prevent the occurrence of heart disease, rhythm disturbances and the increase in cardiac inotropism [48]. Also in studies with experimental animals, it was observed that genistein prevents myocardial damage in rats with type I diabetes induced by streptozotocin, reducing the inflammatory process, oxidative stress, and platelet aggregation and that, through these mechanisms, genistein prevents diabetes-induced thrombotic occlusion in mouse femoral arteries [53]. All these findings described support the idea that genistein may be an agent with great potential for maintaining heart health in postmenopausal women.

3.4. Genistein and obesity

During the postmenopausal period, many changes in carbohydrate and lipid metabolism due to the estrogen-depleted state are observed. These changes lead to the accumulation and increase in the human body's fat content, which may represent the trigger for the development of obesity [54]. Different studies show that genistein accelerates the utilization rate of carbohydrates and lipids, reduces plasma levels of low-density lipoproteins (LDLc) and cholesterol, restricts lipogenesis, and positively modulates lipolysis in adipocytes. Thus, these effects of genistein decrease obesity-related morbidity and mortality and metabolic syndrome in postmenopausal women [55-58]. The literature also reports that chronic treatment with low concentrations of genistein for six or twelve months is able to increase the levels of high-density lipoprotein (HDLc) in the blood of healthy postmenopausal women with metabolic syndrome and this increase lead to a decreased risk of developing obesity, metabolic syndrome, and other related pathophysiological conditions [58-59].

Adiponectin and visfatin are hormones related to fat and adipose tissue metabolism, and the production of these hormones may be altered in postmenopausal women with metabolic syndrome. In this way, it is known that low plasma concentrations of adiponectin are associated with an increased risk of obesity and that high plasma concentrations of visfatin are associated with increased fat metabolism [60-63]. The treatment of menopausal and obese women with genistein for six or twelve months increases plasma levels of adiponectin and considerably reduces plasma levels of visfatin [51, 64-66]. Thus, this treatment is related to the reduction in plasma levels of triglycerides, LDLc, and fat metabolism in postmenopausal women suggesting that genistein may be a promising isoflavone in the treatment of some metabolic syndrome events, as well as in the treatment of obesity [51, 59, 64]. In rodents, ovariectomy mimics the post-menopausal condition in women [67] and, although by mechanisms not fully understood, genistein modulates the hypothalamic activity and the expression of peripheral orexigenic genes in ovariectomized rats, o which results in decreased food intake with subsequent reduction in body weight in these animals [68]. Studies also suggest that genistein can reduce body weight in experimental animals by increasing the activity of hepatic fatty acid synthase and carnitine palmitoyltransferase (CPT), as well as increasing the activity of liver enzymes [56, 69-72]. All these results suggest that genistein can be a therapeutic and preventive agent for obesity in women in the natural or surgical postmenopausal period.

3.5. Genistein and diabetes

Millions of people in adulthood suffer from Diabetes mellitus (DM), and there are more diabetic women than men worldwide [73]. Women are more vulnerable to developing DM after natural or surgical menopause due to the reduction or absence of ovarian hormones in these conditions. The absence of ovarian hormones impairs glucose metabolism, leading to fluctuations in blood sugar levels, which contributes to the high incidence of morbidity and mortality [27]. However, information that these fluctuations in blood sugar levels depend exclusively on hormonal changes is scarce in the literature, since not all women present alterations in glucose metabolism and a higher risk of developing postmenopausal DM. Thus, hormone replacement therapy (HRT) can determine possible benefits in glucose metabolism [27]. On the other hand, HRT is directly related to an increased risk of cardiovascular disease (CVD) and, therefore, its use to control DM in postmenopausal women is, to say the least, questionable. Genistein restores basal glucose metabolism in postmenopausal women without causing undesirable effects similar to those seen with HRT [74]. In addition, the literature also reports that treatment with phytoestrogens in postmenopausal women with type 2 diabetes is able to reduce plasma levels of fasting insulin, and this reduction negatively modulates the insulin resistance observed in these women [75]. Furthermore, in studies with experimental animals, prolonged administration of genistein reduces fasting plasma glucose concentration, plasma glucagon levels, and plasma glycated hemoglobin concentrations. In addition, the nine-week treatment with genistein added to the feed accelerates plasma glucose metabolism and increases the activity of enzymes related to both glycolysis and lipid degradation. Thus, the increased activity of these enzymes reduces blood sugar levels, which implies a reduction in the risk of developing postprandial hyperglycemia and worsening of DM [76]. All these findings observed both in humans and in experimental animal's point to the benefits of genistein in the regulation of glucose metabolism, and show the great therapeutic potential of this phytoestrogen against the development of DM.

3.6. Genistein and anticancer activity

The literature reports that genistein can be considered a compound with high biological potential in the field of oncology, as its effects are related to the reduction in the risk of mortality caused by different types of cancer [77] and that the anticancer activity of this isoflavone is related to its ability to induce apoptosis, suppression of cell proliferation, histone modification, DNA promoter methylation [78], among other activities that are described in Table 2. The most common type of cancer among women in developed countries is breast cancer [79-81]. The literature reports that the risk of developing breast cancer is related to several factors, including age, the woman's fertile period [82] and circulating levels of plasma estrogen, as this hormone has the characteristic of induce initiation, progression, and promotion of metastatic cells in the breast [83]. In this way, the increase in circulating estrogen levels induced, by the use of oral contraceptives during the fertile period and by hormone replacement therapy during the postmenopausal period are conditions that can greatly increase the incidence of different types of cancer, including breast cancer [84, 85]. There is a consensus that many natural substances contained in fruits and vegetables have many benefits for human health [86-88]. In particular, phytoestrogens may represent an option for hormone replacement therapy with ovarian hormones, since these substances have a great structural similarity to 17β-estradiol, which is one of the main human estrogens [89-91]. In this way, there is a positive correlation between a diet rich in soy and a reduction in cancer prevalence. Studies show that in Asian countries, where diets are rich in soy, women have a lower prevalence of breast cancer when compared to postmenopausal women in Western countries and that soy intake decreases the risk of breast cancer in postmenopausal Asian women [92-94]. However, the habit of consuming isoflavones contained in soy is directly related to the local oriental culture, as the literature reports that Asian women

who migrated to Western countries started to present an increased risk of breast cancer, justified by the abrupt change in eating habits [29]. According to epidemiological studies, diets rich in soy contain large amounts of isoflavones that have anticancer properties. These epidemiological studies provided reasons for researchers to investigate the particularities of isoflavones both in molecular aspects and their effects in animal models [95]. The predominant isoflavone present in soy is genistein. This natural substance has promising anticancer biological effects demonstrated in preclinical studies [96]. Furthermore, in vitro studies on the anticancer effects of genistein on cancer cell lines have also demonstrated the ability of genistein to induce apoptosis of these cells, which points to the possibility that genistein is considered a promising chemotherapeutic agent against different types of cancer (Table 2). These results obtained in all these studies reinforce the idea that genistein may represent a safe option in terms of mimicking the effects of estrogens during the treatment of menopausal symptoms and that this isoflavone, unlike estrogens, is free of carcinogenic effects.

3.7. Effects of genistein on psychiatric illnesses during menopause

Lowering plasma estrogen levels in menopausal women may increase the rates of development of depression and anxiety symptoms [97]. On the one hand, hormone replacement therapy with gonadal hormones (HRT) is able to reverse these behavioral changes, but it causes many undesirable effects [98-100]. On the other hand, isoflavone-based diets are able to reduce symptoms related to pathological depression and anxiety caused by menopause, without determining the undesirable effects observed with HRT [9]. Although the mechanism of action of the antidepressant isoflavone genistein has not been fully elucidated, studies reveal its ability to abolish the behavioral changes induced by the loss of female gonadal hormones and, thus, restore the quality of life of postmenopausal women [101]. The literature reports that the antidepressant and anxiolytic effects of genistein observed in both humans and experimental animals may be related to the ability of genistein to decrease levels of microRNAs (miRNAs) related to the etiology and/or development of various CNS diseases in humans [9, 102-103]. Another effect of genistein that helps to elucidate its mechanism of action is related to the modulation of plasma levels of cortisol, brain-derived neurotrophic factor, serotonin (5-HT), and other monoamines. Thus, the behavioral changes observed during depression are associated with an elevated serum cortisol level, as well as a decrease in the levels of 5-HT and other monoamines in the CNS. In this way, the literature reports that genistein is able to reduce cortisol secretion by the adrenal gland, able to increase the expression of brain-derived neurotrophic factor in experimental animals as well as to increase the bioavailability of monoamines in the CNS, through the reversible reduction of the enzymatic activity of monoamine oxidase (MAO) [104-105].

It has also been hypothesized that due to the structural similarity of genistein to estrogen, genistein is able to cross the blood-brain barrier and specifically interact with ER-β in the hippocampus in the same way as estrogen, thus mimicking the antidepressant effects of this gonadal hormone [106]. Another finding that reinforces the hypothesis of the antidepressant action of genistein in the hippocampus is the fact that genistein can also modulate the serotonergic pathway in stressful conditions, through a decrease in the serotonin turnover, which results in an increase in the concentration of 5-HT in the hippocampus similarly to that seen with treatment with some anti-depressants [31]. Different studies with experimental animals also show the anxiolytic effects of genistein. Thus, the literature reports that genistein is able to decrease the number of neurons immuno-reactive to the nitric oxide synthase enzyme and to modify the NO-producing neuronal circuits in the baso-lateral amygdala, which is a neural region directly related to the pathophysiology of anxiety [107]. Other behavioral studies also show that genistein has an anxiolytic effect in ovariectomized rats similarly to diazepam and that in these experimental animals, genistein is also able to increase serotoninergic neurotransmission in the amygdala, resulting in an anxiolytic effect [10, 108]. Low doses of genistein are able to antagonize CNS glucocorticoid receptors in ovariectomized rats [109] and that the anxiolytic effects of genistein observed in ovariectomized rats are similar to the effects induced by 17-beta estradiol at low doses suggesting that genistein may mimic the estrogen-dependent effects at basal concentrations in the CNS [110].

Furthermore, the plasma amount of malondialdehyde (a marker of oxidative stress) is increased while the plasma amount of superoxide dismutase (an antioxidant enzyme system) is decreased after the ovariectomy procedure in experimental animals and these conditions result in hippocampal neurodegeneration and behavioral changes. The treatment of these animals with genistein for eight weeks reverses the harmful effects induced by ovariectomy on the antioxidant mechanisms, as well as reducing the plasma levels of malondialdehyde, thus determining an improvement in the behavioral changes observed in ovariectomized rats [111]. The literature also reports that the long-term treatment of ovariectomized rats with genistein decreases oxidative stress in the frontal cortex and hippocampus, which determines the reduction of neurodegenerative processes and anxiety symptoms [111-112]. Although all these studies point to the anti-depressant and anxiolytic potential of genistein, most of these studies were conducted in experimental animals and, therefore, specific pharmacological studies from a molecular point of view and performed in humans can be useful in providing

subsidies for the possible establishment of the benefits of using genistein as an anxiolytic and/or antidepressant agent.

Table 1: Genistein effects on pathophysiological conditions induced by ovarian hormone deficit

Symptoms/Diseases	Dose, route of administration and duration of treatment with genistein	Observed effects	References
Cardiovascular	54 mg/v.o./1 year	Reduction of myocardial necrosis, macrophage activation and serum levels of TNF-α, severity of atherosclerosis and incidence of myocardial infarctions in humans	[28-29]
Vasomotor	54 mg/v.o./1 year	Reduction of hot flashes, night sweats, and frequency of sleep disturbances; as well as symptoms of depression and memory loss in humans	[29-30]
Obesity	108 mg/v.o./12 weeks	Reduction in the serum concentration of total cholesterol, LDLc, triglycerides, and HDLc in humans	[27]
Stress responses	10 mg/kg/v.o./14 days	Improves 5-HT metabolism, stabilizes MAO activity, and improves 5-HIAA/5-HT positive neuronal feedback in rodents	[31]
Diabetes	108 mg/v.o./12 weeks	Reduced fasting plasma glucose concentration, reduced insulin resistance, and improved glycemic metabolism in humans	[27]

Abbreviations: v.o.: oral administration; 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: serotonin; HDLC: high density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; MAO: monoamine oxidase; TNF-α: tumor necrosis factor alpha

Table 2: *In vitro* anticancer activity of genistein

Type of cancer	Cell lineage	Genistein concentration	Mechanisms of action	References
Breast cancer	MDA-MB-231, MCF-7	30-50μM	Reduced or decreased PK-induced phosphorylation decreased expression of human epidermal growth factor receptor 2, increased activity of tumor suppressor proteins, and apoptosis	[113-116]
Lung cancer	H446, A549	25-50 μM	Inhibition of cyclin B effects, decrease in survivin effects, inhibition of cell division and increase in apoptosis induction	[117-120]
Colon cancer	SW480, DLD-1, SW1116, HT29, HCT116	10–120 μM	Decreased cell proliferation, induction of histone acetylation, inhibition of cell division, decreased activity of PKs and topoisomerase II	[121-123]
Stomach cancer	SGC-7901, BGC-823	10-25 μM	Positive modulation in caspases, decreased tyrosine kinase and MAPK activity, inhibition of cell division and decreased cell proliferation and induction of apoptosis	[124-126]
Liver cancer	Bel-7402,HepG2, Hep3B, HuH-7, SMMC-7721	10-25 μM	Decreased MAPK activity, inhibition of cell division, decreased NF-kB activity, decreased IP3 formation with consequent ER dysfunction, mitochondrial aggression, decreased TNF and IL-6, DNA fragmentation and apoptosis	[127-131]

Abbreviations: PKs = protein kinases; MAPK = mitogen-activated protein kinase; NF-kB = nuclear factor kappa B; IP3 = inositol triphosphate; ER = endoplasmic reticulum; TNF = tumor necrosis factor; IL-6 = interleukin six; DNA = deoxyribonucleic acid.

4. Considerations

Genistein has a high biological potential and may represent a hormone replacement therapy option in the sense of abolishing most symptoms observed in post-menopause and related diseases. The use of this iso-flavone for this purpose is safe and free from the serious undesirable effects that hormone replacement therapy determines and is based on the ability of genistein to simulate the effects of estrogen in different systems. In addition to mimicking the effects of estrogen, genistein acts through other different mechanisms of action, many of which are not yet fully understood. The advancement of studies in this regard, the determination of the ideal routes of administration, and the characterization or standardization of effective dosages of genistein aimed at the specific treatment of the various symptoms of menopause and related diseases can collaborate to establish a scientific consensus on the benefits and the advantages of using this iso-flavone as an alternative to hormone replacement treatment during menopause.

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