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## Isoflavones in gynecology, non-conventional therapy

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### Abstract

Soy and its components, isoflavones such as genistein, daidzein, and ipriflavone are currently marketed by those who practice alternative medicine for the promotion and prevention of neoplastic, osteoporosis, climacteric and cardiovascular diseases. Different medical publications present studies carried out in order to confirm its pharmacological benefits in light of the scientific method. Although there is clear evidence of its effects when interacting with steroid receptors in the human body, recognized by entities such as the Food and Drugs Administration of the United States, controlled studies are still lacking to determine its real therapeutic impact; Biases in the populations analyzed must be improved and more studies dedicated to each of the isoflavone components separately in order to assess their own therapeutic spectrum.

**Keywords:** polyphenols, phytoestrogens, isoflavones, genistein, daidzein, ipriflavone, SERM.

### Introduction

The concept that as specialists we have of alternative medicine products, of their reactions in health and especially in our field, regarding the therapeutic effects in climacteric is a common question in recent times by patients. Given the rise and dissemination by the mass media of this type of substances, it is necessary to have concrete knowledge based on the results of experience under the light of the scientific method, which appear more and more frequently in recognized medical publications.

The use of alternative and complementary therapies for the promotion and prevention of neoplastic diseases, osteoporosis, climacteric and cardiovascular diseases, was calculated that in the United States in 2000 it reached between 40% and 55% of the adult population, with an expenditure of approximately 20 billion dollars <sup>[2, 3]</sup>. For therapeutic purposes of problems associated only with menopause, 600 million dollars in alternative medicine products were sold <sup>[4]</sup>. 24% of these products included herbal components and phytoestrogens <sup>[2]</sup>.

The classification into which the different types of complementary and alternative medicine practice are grouped <sup>[5]</sup>.

The Food and Drugs Administration (FDA), the regulatory body for the production and distribution of substances with pharmacological effect in North America, does not require control of the products generated for this type of practice prior to marketing, regardless of their origin. The pronouncement of this entity is reduced to the verification of the authenticity of the products at its point of sale. No tests are required from the production houses on the pharmacological capacity of their components or their possible side effects, as to date there is an absence of evidence against safety in those who consume them <sup>[1, 2, 6]</sup>.

### Phytoestrogens, isoflavones

In nature there are substances other than endogenous human steroids with the ability to bind to their steroidal receptors, including estrogens. Its origin can be natural such as equine estrogens or phytoestrogens, or synthetic such as Selective Estrogen Receptor Modulator (SERM), equinyl estrogens and xanthoestrogens (industrial products such as DDT) <sup>[6]</sup>.

The observation by modern medicine of natural products with pharmacological properties of folklore dates back to the beginning of the 20th century with the publication of Allen Doisy, in 1923, in which he describes products derived from plants with estrogenic activity <sup>[6]</sup>.

Phytoestrogens are non-steroidal compounds derived from plants, with weak estrogenic activity, 100 to 1,000 times less than estradiol. Chemically they belong to the group of polyphenols and are structurally divided into three groups according to their molecular structure: isoflavones, lignans and coumestans. Phytoestrogens have been isolated from many types of plants, among which soy is the food with the highest concentration. Among the polyphenol constituents of soy are saponins, lignans, phytoosterols, protease inhibitors, phytates and isoflavones, all under investigation for their pharmacological properties. Isoflavones (among 600 types of isoflavonoids) are the most widely known group, to which genistein, daidzein and ipriflavone belong [4, 6, 7].

The research on soy originated from the observation by some authors of the difference in risk for the population of the West and the regions of Asia where there is a high consumption of soy for breast, prostate and colon cancer [6-8]. In turn, they observed a difference in the incidence of vasomotor symptoms due to climacteric of 75% in the West against 25% in the female population of Japan, a region where there is no word to describe them [7]. A difference in consumption was demonstrated. amount of isoflavones in the diet between the two cultures: in the West 5 mg / day is ingested, while in Asian countries 40-50 mg / day and in Japan 200 mg / day [7]. However, the concentration of isoflavones The amounts in each gram of soy may differ between different regions of the world due to genetic differences in the seeds, according to their variety or subtype, due to the diversity of the soils, due to the use of pesticides or the way they are grown, among other variables [6].

### Metabolism and absorption

Isoflavones are found in plant foods as precursors, biochanin A for genistein and formononetin for daidzein. The bacteria of the small intestine transform them by means of enzymes to their active forms: equol, o-demethylangolensis, dihydrogenysteine, and p-ethylphenol. A diet rich in fiber alters its absorption by up to 55%, as well as the use of antibiotics. After their absorption, via the portal route, they are transported and conjugated in the liver, then they are excreted in the bile and in the urine [7, 9]. Lignans and isoflavones have been isolated and measured in humans in urine, plasma, feces, semen, bile, saliva and breast milk in all cultures of the world [6].

### Mechanism of estrogenic action

The molecular basis on which its steroid action is based initially lies in its structural similarity with estrogens [2, 7, 9]. The binding capacity of phytoestrogens to estrogen receptors was assessed in a human cell culture study with respect to 17 beta-estradiol, which was given an arbitrary number of 1:00; the following results were observed [6, 10]:

- Coumestrol 0.202
- Genistein 0.084
- Equol 0.061
- Daidzein 0.013
- Biochanine 0.0006
- Formononetin 0.0006

After binding to steroid receptors, isoflavones behave like SERMs for estrogen receptors alpha, beta, or delta [2, 4, 6, 11]. Selectivity of genistein for receptors was demonstrated in

human cell cultures estrogens with a 7 to 30 times more affinity for the beta type (Er $\beta$ ), triggering a 10 to 300 times more inhibitory activity of transcription, compared to activation, unlike 17 $\beta$ -estradiol, which presents the same affinity to ER $\alpha$  and Er $\beta$  without selective activity [2, 9]. This study demonstrated poor regulation of genistein mediated by alpha receptors (Er $\alpha$ ), which theoretically translates into a low incidence of side effects on the breast and endometrium ; its ability to bind to progesterone, androgen and oxytocin receptors, with a clinical significance as yet unknown.9 Another study demonstrated the activity of some isoflavonoids like SERMs, ruling out some type of estrogen agonist action in MCF-7 breast cancer cell culture equol, enterolactone, nordihydroguaiaretic acid and kaempferol [9, 12].

A non-steroidal cellular mechanism of action has also been identified, which is mediated by enzymes. Its capacity to inhibit the cell cycle has been demonstrated in some cell types by inhibition of DNA topoisomerase I and II, inhibition of protein tyrosine kinase (PTK) and inhibition of gastric H + / K + ATPase [2, 7].

Likewise, the possibility of antiestrogenic action by isoflavones has been identified. There are studies that have shown evidence of how genistein and coumestrol inhibit the conversion of estrone to 17 -beta estradiol, 7 as well as for the increase in the hepatic synthesis of sex hormone-binding globulin (SHBG), with which they are modulated serum steroid concentrations [6, 7, 9].

### Pharmacology

The polyphenol constituents of soy have been exposed in the world medical literature with pharmacological capacity of the following types: estrogenic, antiestrogenic, antiviral, anticarcinogenic, bactericidal and antifungal (Table 2) [7].

### Evidence-based medicine

The evidence-based review is summarized according to the main objectives of the medical literature for isoflavones: their epidemiological effect on populations and their pharmacological potential on specific problems.

Effects of soy in the population Experimental models in animals, in which high concentrations of isoflavones have been administered, demonstrate a possible interference, similar to that produced by estrogens in the development of the reproductive system of fetuses during gestation [13]. However, after hundreds of years, millions of Asians have consumed soy in pregnancy with no obvious teratogenic effects. When carrying out measurements in human milk in different populations worldwide, isoflavones concentrations directly proportional to their consumption by the mother have been isolated and are ingested by infants; Similarly, today many of the milk formulas for newborns and infants are made based on soy, with no epidemiological evidence of adverse effects [6, 7].

There are studies in which the administration of high doses of isoflavones in premenopausal women decreased serum estradiol levels by 31% on days 5 to 7 of the cycle, and progesterone by 81% on days 12-14, 49% on days 20 - 22 and 35% in the luteal phase 14. A decrease in adrenal androgens DHEA sulfate of 14 - 30% was achieved. [7, 9, 15] In another study suppression of the peaks of half of FSH and LH cycle [7, 9, 14, 16]. In a third study, a stimulatory effect was obtained in breast tissue, with increased breast secretion, development of epithelial cell hyperplasia and elevated

serum estradiol [6, 17].

However, the physiological characteristics of the menstrual cycle in Asian women does not differ from other cultures. On the other hand, in a study in which low doses of isoflavones were administered, a reduction in the concentration of circulating ovarian steroids, mainly 17 beta-estradiol, was demonstrated without alteration of gonadotropins or their preovulatory peaks, which determines its protective role in steroid-dependent pathologies by modulating the hepatic production of SHBG, among other mechanisms [18, 19].

### Problems associated with menopause

#### Genital atrophy

Administration of soy products or isoflavones valued in case studies and controls, did not register changes in the vaginal maturation index, as well as estrogen-dependent vaginal cytology effects [14, 20, 21, 22].

#### Vasomotor symptoms

Vasomotor symptoms are one of the major research focuses to determine the usefulness of soy, its derivatives and isoflavones, as well as the different types of alternative therapy. The studies include cases and controls in the general population, in patients with a history of breast cancer or oophorectomized patients, among others. Although some studies support its benefit in improvement, evidence-based studies do not support the therapeutic utility of any of these products in the treatment of these types of symptoms [3, 6, 9, 22-30].

#### Cardiovascular protection

There is epidemiological evidence of a lower incidence of coronary heart disease in cultures that consume soy. 4, 8, 29 A protective role of isoflavones for cardiovascular diseases has been demonstrated based on the following summary of processes: [3, 6, 7, 31]

- Inhibition of platelet activating factor.
- Inhibition of thrombin formation.
- Increased hepatic secretion of lipoproteins: increased clearance of cholesterol.
- Antioxidant: they inhibit the formation of free radicals, hydrogen peroxide and superoxide anions.

The possibility of modifying the lipid profile with the input of isoflavones such as genistein was clearly documented in a meta-analysis of 38 controlled studies, with the following effects: [7]

- Decrease in cholesterol.
- Increased activity of the LDL receptor.
- Increase in bile synthesis.
- Increased activity of apolipoprotein B and E receptors.

The FDA recognizes the clinically significant effect of genistein in lowering serum LDL-cholesterol levels [29, 30].

#### Osteoporosis

In vitro and animal studies show how the administration of isoflavones prevents osteoporosis by findings such as: [2, 4, 6, 29, 30, 32]

- Increased DNA synthesis, modulation of alkaline phosphatase activity and prevention of apoptosis in MC3T3-E1 osteoblast-like cells.
- Increased calcium content in the femoral shaft and

metaphyseal tissues.

- Increased RNA activity in femur metaphysis, increased expression of the TNF gene and the expression of osteocalcin in oophorectomy rats.
- Increased density in bone mass by densitometry.

A recent study demonstrated a lower urinary excretion of deoxyypyridinoline, a specific marker of bone absorption, in postmenopausal patients without hormone replacement therapy and the administration of isoflavones [33].

Ipriflavone for therapeutic purposes on osteoporosis is the only isoflavone marketed by a medical laboratory in our environment.

#### Cancer

Numerous epidemiological studies in humans, animals and in vitro have demonstrated the inhibitory action of isoflavones during the initiation and development phases of cancer [6, 8, 29, 30, 34].

Messina and his group conducted a meta-analysis of 21 studies aimed at assessing the antineoplastic role of soy in regions of Asia where its consumption is common, on 26 different sites of the organism. Ten studies demonstrated protective evidence for rectal, stomach, breast, prostate, colon, and lung cancer. 7

The molecular bases on which the antineoplastic activity of isoflavones is based are summarized in: [7, 34-38]

- Inhibitory binding to steroid-type receptors.
- Inhibition of angiogenesis.
- Inhibition of thrombin formation and platelet aggregation.
- Increase in LDL receptor activity.
- Modulation of SHBG, with regulation of the concentrations of steroid hormones. Enzyme-mediated action:
  - Inhibition of PTK, for the protein phosphorylation necessary for cell regulation including replication.
  - Inhibition of free radical production.
  - Inhibition of 5- $\alpha$ -reductase.
  - Inhibition of sulphation by phenolsulfotransferase.
- Action on enzymes:
  - Repairing DNA topoisomerases, necessary for transcription.
  - S6 ribosomal kinase.
  - Phospholipase C-Gamma.
  - Phosphatidyl inositol kinases.
  - Mitogen-Activated Protein-kinase.

#### Breast cancer

Epidemiological studies show an inverse relationship between soy intake and the incidence of breast cancer. The North American population has two to three times more risk than the Asian population for the disease [6, 7].

A study in Asian-American women documented how soy intake is related to a decrease in the incidence of breast cancer, isolating nutritional variables, factors menstrual and reproductive, both in pre and postmenopausal women [39].

#### Endometrial cancer

A meta-analysis assessed the protective effect of isoflavones for endometrial cancer in patients with perimenopause, in whom progesterone production is decreased due to the presence of anovulatory menstrual cycles, in light of their potential selective theoretical effect on this tissue like



SERM, in which it has no alpha agonist activity and behaves as anti-estrogen. Retrospective studies show ten times lower incidence of endometrial cancer in Asian women than in Eastern Caucasians. The evidence to date determines that the role of isoflavones is still a theory to be established in directed case-control studies; however, it recognizes that there are measurable physiological effects on the endometrium after administration or consumption [40-42].

### Analysis

Since its heyday at the beginning of the nineties, several studies have been carried out both in the laboratory and in the population, in which it has been tried to measure under the rigor of the scientific method the pharmacological benefits exposed by alternative medicine of soy derivatives and isoflavones. Most of these studies have not achieved a significant impact due to biases that limit their value.

The population studies on which the epidemiological theories are based are retrospective in nature, so they cannot assess the volume of consumption of these elements by the population. The results may show differences by not considering possible variables dependent on the racial condition between people from the West and the East. There are biases due to not defining the social and economic condition of the study groups, their previous nutritional status, the division of the groups by age, and the definition of other clinical variables such as previous cardiovascular status, bone metabolism, and previous estrogenic status of patients.

Studies carried out in cohorts and some review of the topic on isoflavones fall into errors such as not differentiating the administration of food based on the totality of soy and its polyphenol components separately. Pharmacological impact studies do not differentiate isoflavones from each other, ignoring that they may have a different potency and pharmacological spectrum.

The lack of a standard dose for each substance does not allow an adequate interpretation of the studies by the meta-analyses.

Today, the NIH pronouncement recognizes and highlights the importance of findings from a history of research on isoflavones, and invites studies targeting each of the isoflavonoid components of soy [1, 2, 6].

Regarding the different types of alternative medicine aimed at the management of vasomotor symptoms and climacteric in general, it is an opportunity to present the results of cohort studies that document that there is no evidence of clinical improvement with products such as black cohosh, dong quai, prepared from St. John's, cousin-rose oil, red clover, among others, which are available in health food stores in our area [4, 29, 30, 44]. Those who have access to this type of product are patients with adequate economic conditions, if the figures consumed by the Americans mentioned at the beginning of this presentation are taken into account.

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