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Role of Plant-Based Phytoestrogens in PCOS Management: Focus on Isoflavones

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Abstract

Poly cystic ovary syndrome (PCOS) is a widespread endocrine disease with particular features of hyperandrogenism, ovulation defect, and polycystic ovarian morphology in girls of reproduction age. The latest potential non-hormonal treatment in the management of PCOS-related symptoms is isoflavones, which are a type of phytoestrogens; soy-based products contain these phytoestrogens. These phytoestrogens have estrogenic properties and affect metabolic and reproduction processes. Recent clinical and preclinical exercise findings which have been portrayed in the literature have indicated that isoflavones have the capacity to improve insulin sensitivity, decrease serum and androgen levels, normalize menstrual periods and also ovulation. Also, they have antioxidant and anti-inflammatory effects that can be therapeutically useful. The isoflavone is also in evidence as discussed in this review where there is the prospect of isoflavone in PCOS treatment in both aspects of mechanistic knowledge as well as clinical results and safety. Their efficacy should be proven and clinical guidelines should be established through further well-designed large-scale randomized controlled trials.

Keywords: ***Polycystic ovary syndrome, PCOS, isoflavones, phytoestrogens, soy extract, hormonal imbalance, insulin resistance, ovulation, reproductive health, natural therapy.***

1.Introduction

The polycystic ovary syndrome (PCOS) is one of the most widespread endocrine disease in women due to childbearing years. PCOS is defined by a cluster of symptoms including irregular periods, hyperandrogenism (excess male hormones), and a specific ovarian appearance, but it is much more than a gynaecological issue because it represent the manifestation of a global maladjustment with metabolic, reproductive, and psychological consequences. Although the diagnosis has been developed on a basis of clinical criteria, such as those proposed by the Rotterdam consensus, the symptom heterogeneity has remained an obstacle to clinicians. The most important part of PCOS pathology is the disruption of androgen secretion, which is usually characterized by an increase in testosterone and a decrease in sex hormone-binding globulin (SHBG), which not only changes the physical features of reproduction but also promotes the development of significant metabolic disorders such as insulin resistance and dyslipidemia(1).

PCOS etiology is multifactorial whereby it is a combination of genetic, endocrine, metabolic, and environmental factors. The studies have been able to determine that excess androgen production is produced not only in the ovaries theca cells but also in the adrenal glands. This excess of androgens may be as a result of impaired aromatase activity which is a hormone that transforms testosterone into estradiol. Therefore, inhibition of aromatase represses the estrogen synthesis, which worsens the situation with testosterone overflow. Also, as seen in most PCOS patients, increased levels of insulin inhibits the formation of SHBG by the liver thereby increasing the free androgen immediately available in the blood. These alterations help to feature the typical phenotypes of PCOS like hirsutism, acne, and ovulatory dysfunction and are usually accompanied by morphological disorders in the ovaries including formation of multiple tiny antral follicles that instead of maturing and spawning ova, remain immature in the follicles.

Management of PCOS has traditionally been based on mitigating symptoms, mostly by means of synthetic pharmacological agents. Estrogen and progestin containing combined oral contraceptives (COCs) can be used as the first-line therapy against menstrual irregularities. The mechanism of action of these drugs has been by inhibiting the hypothalamus pituitary ovarian axis and blocking ovulation. Agents that combat its manifestations which include hirsutism, infertility, and insulin resistance such as anti has been frequently seen to prescribe anti-androgenic agents like spironolactone, clomiphene, metformin, and insulin sensitizers. Nevertheless, such drugs are usually accompanied with side effects that include a stomach upset and, worse, birth defects and risk of

cardiovascular problems. In its turn, this has encouraged the subsequent interest in alternative and complementary methods.

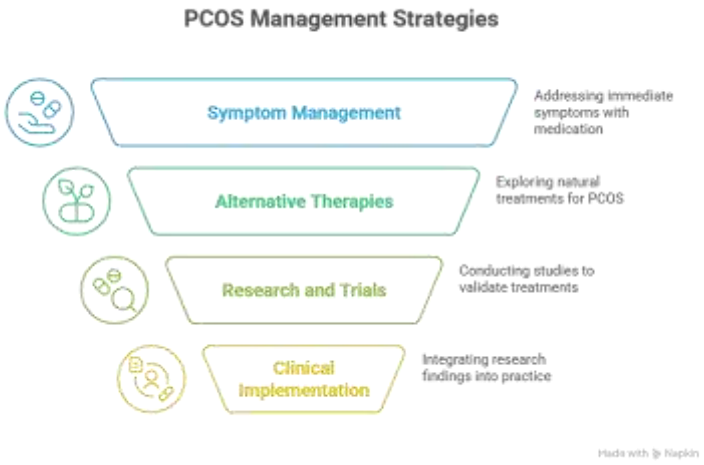

FIGURE 1 PCOS Management Strategies

Recent researches into the world of phytotherapy have highlighted the use of plant-based products as possible agent to treat PCOS. Of these, isoflavones, which are mainly derived out of soy and other legumes, have received special interest because they have estrogen-like capabilities. The isoflavones have been placed in the category of phytoestrogens as they have a comparable substance structure to 17β-estradiol which is the main kind of estrogen in premenopausal women(2). They have the capacity to bind with estrogen receptors (ERalpha and ERbeta), and thus, exert anti-estrogenic or estrogenic activity, which is dependent on the physiology of the situation. This two-fold action makes them a good prospect in treating hormonal imbalance in estrogen sensitive disorders such as PCOS.

The isoflavones, genistein, daidzein, and glycitein are some of the isoflavones which have been proposed to have multiple advantages to PCOS women. These advantages can be expanded not only in reproductive hormones balancing but also in enhancement of metabolic indicators, such as insulin sensitivity, lipid profiles, oxidative stress, and inflammation. The possibility of altering the concentration of testosterone with isoflavones also deserves particular attention; this is because they have the ability to inhibit some steroidogenic enzymes, in this case, 3 levels-hydroxysteroid dehydrogenase and 17-HSD, thereby successfully lowering androgen formation at an ovarian scale. This would relieve hyperandrogenic symptoms besides helping to normalize menstrual cycles and ovulatory fault.

However, the evidence of preclinical studies and other clinical trials indicate the potential of therapeutics but it is not consistent in terms of efficacy of isoflavones. Other studies have shown great changes in the improved hormonal and metabolic parameters in PCOS patients treated with isoflavone supplements whereas others have shown non-significant or no effects. The discrepancy between the studies highlights the need to perform an in-depth study of the following variables: dosage, the source of isoflavones (e.g., soy, red clover, chickpeas), treatment duration, bioavailability, and individual factors like BMI, age, and the severity of PCOS.

Simultaneously, animal models have been used as an inexhaustible resource to analyze the mechanisms by which isoflavones posit the biological impacts. One of the most accepted models is the induced PCOS in rats (treated with Letrozole), as the condition in rats depicts most of the human condition such as hyperandrogenism, ovarian cysts and disregular estrous cycles(3). These models have enabled scientists to examine isoflavones parameters in a controlled condition through which the study clarified their effects on ovarian morphology, hormone axes, oxidative stress parameters, and cytokine profiles. The findings of these studies point towards the possibility of isoflavones inducing restoration of the ovarian functionality, decreasing the inflammatory cytokines (TNF-q and IL-q), and mitigating the oxidative damage.

This being the case, the current review will establish evidence based on both in vivo and in clinical trial studies to critically report on how isoflavones can be used in the management of PCOS symptoms. The review will offer a critical interpretation of how isoflavones could be used as natural supplement or adjunct to pharmacotherapy based on the review of their bio-chemical pathways, molecular target as well as their therapeutic effects. By this

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synthesis, it will be possible to come up with a way to close the gap between the experimental research and clinical implementation to open a new hope to the millions of women who have to struggle with the issue of PCOS.

2.PCOS Symptom Model for In Vivo and Clinical Research

To know how isoflavone can be used therapeutically in polycystic ovary syndrome (PCOS) it is vital to have a well-developed experiment scheme, and it is important to start with biologically valid models and well-conducted clinical trials. Since PCOS presents itself with a variety of metabolic and reproductive deficiencies, both animal in vivo experiments and human clinical trials are significant in assessing possible therapies. These models enable investigators to recreate conditions of PCOS as well as intervene in the hormonal processes and assess the outcomes of therapeutic intervention like isoflavone supplementation. The development of standard animal models, especially those of rats, has allowed major pathological mechanisms to be discovered and randomised controlled trials (RCTs) in human populations are of a translational nature; they relate findings in the experimental setting to practice in the clinical setting(4).

The most widely used in vivo model of PCOS is the use of nonsteroidal aromatase inhibitor letrozole as it is powerful in causing PCOS. An aromatase is a crucial enzyme that catalyzes the conversion of such androgens as testosterone and androstenedione to the production of estrogens (estradiol and estrone). Suppression of this enzyme activity by Letrozole destabilizes the hormonal balance, which causes an increased level of androgens, which is the primary characteristic of PCOS. Letrozole causes a series of signs and symptoms, similar to those manifested in human PCOS, when applied over the course of 21 days at a dose of about 1 mg/kg daily to young female Sprague-Dawley rats. These factors are estrous cycle disruption, hyper testosterone, polycystic ovarian morphology, infertility indications. The resulting phenotype which somewhat resembles clinical PCOS and allows examination of action of therapeutic drugs like phytoestrogens in a reproducible model.

The other model that is employed extensively is the use of estradiol valerate which is a synthetic ester of estrogens. At higher doses (24 and 48 mg/kg; sc, routine 60 days) estradiol valerate first maintains and then hyperstimulates estrogen, then desensitizes the hypothalamic-pituitary-ovarian axis. The result is absence of ovulation, development of cysts, and morphological changes in the ovaries. The model is specially useful in replicating the chronic anovulatory condition evident during PCOS. Besides, rats exposed to estradiol valerate create an endocrine and metabolic profile that generates the human condition, such as luteinizing hormone (LH) hypersecretion, decreased follicle-stimulating hormone (FSH), and the appearance of many atretic follicles.

The benefit of the usage of these animal models is that they serve to give a controlled scenario by which to decipher the processes of disease development and response to treatment. Apart from the example of the ovary, ovarian tissue can be used to examine histopathological changes, quantitate enzyme activities (such as 3l-HSD, 17l-HSD), measure inflammatory cytokines (such as TNF- o and IL-6), oxidative stress measures (such as malondialdehyde or MDA), and antioxidant enzyme activity (such as glutathione peroxidase or GPx, superoxide dismutase or SOD). In human studies such comprehensive evaluations are impractical or invasive, however such an appraisal is essential in defining the bioactivity of isoflavones.

Parallel to this, the clinical trials are the litmus test of efficacy and safety of isoflavones in human beings. Such trials favorably utilize the design of randomized, placebo-controlled, and double-blind studies, which are statistically rigorous, and the bias is minimized(5). Participants of these trials are identified by meeting pre-determined criteria used to diagnose the disorder-most frequently Rotterdam Criteria that specify that a woman must meet at least two of the following criteria: irregular menstrual cycles, clinical or biochemical hyperandrogenism and polycystic ovarian morphology as seen in ultrasounds. Other exclusions are the recent exposure to oral contraceptives, antioxidant supplements, drugs interfering with reproduction hormones or glucose metabolism and co-existing endocrine or systemic diseases.

The screening of the participants will be important so as to see that the study group is actually representatives of people with idiopathic PCOS and not other similitude disorders such as congenital adrenal hyperplasia, Cushing syndrome, or hypothyroidism. The subjects are randomized to get an isoflavone supplement mostly genistein or soy-based preparations or a placebo in a duration that generally varies between 8 and 12 weeks. The results of testosterone, lipid profile, LH, FSH and SHBG by means of a biochemical test, anthropometric measures, including weight, waist circumference, and body mass index (BMI) along subjective measures, including menstrual regularity and quality of life will be used as outcome measures.

The characteristics of some of the distinguished trials that were conducted using such a methodology include the soy isoflavones of 50 mg/day within three months. Serum testosterone, which was significantly lowered as well as improved insulin sensitivity (reflected by HOMA-IR and QUICKI indices) and reduced oxidative stress f markers (MDA) were observed in the participants. In another study, where they used genistein as supplement (36 mg/day), it was found that not only the testosterone level dropped, but also there was an increase in the level of SHBG- which is a very vital change since it tends to sequestrate the free androgens and make them less bioavailable. Imperatively, these clinical trials verified the fact that isoflavones are well tolerated and the number of adverse effects was also minimal, which validates their safety aspect.

The combination of these two routes- animal and human model- makes a very strong story of predictive potential of isoflavones about its therapeutic potential. Although in vivo models provide us with the mechanistic knowledge and tissue confirmation, the findings have to be translated in clinical research and determine their effectiveness in the real-life context(6). An example is that rat studies have shown that isoflavones may inhibit nuclear factor-kappa B (NF-kB) activation which is a master regulator in inflammatory cytokines and human studies have shown decreases in TNF-alpha and IL-6 after isoflavone consumption. In addition, considering the antioxidant effect in the rats, with increased levels of GPx and SOD, the same effect was reflected in the human studies, where serum levels of GSH and TAC were better after intervention.

Nevertheless, there are limits. The presence of the complexity of the psychological, dietary and environmental condition of human PCOS cannot be reproduced in animal models and hormonal regulation in the animal model (rodents) and that in human women are different. On the clinical side trial sample sizes tend to be small and follow ups short. Standardization on the types and dosages and administration of isoflave is also lacking. These differences create difficulties in cross-study comparisons and create an obstacle in providing definite clinical guidelines.

Finally, not only in vivo rat experimentations but also human clinical randomized studies will give invaluable information about the therapeutic effectiveness of isoflavones in the curative regimes of PCOS. Their complementary application has enlightened the role of phytoestrogens on hormonal pathways, metabolic, and inflammatory pathways. Despite the need of conducting more large-scale, long-term research, the existent evidence points to the idea that isoflavones are a potentially beneficial natural alternative or supplement to classical pharmacologic treatments. It is necessary to aim at harmonization of methods, and consider the potential importance of patient-specific modifiers, such as genetic predisposition to PCOS, the content of intestinal microbiology, and lifestyle, in order to reveal the potential of isoflavones in the treatment of PCOS.

3.Isoflavone’s Role in Testosterone Regulation and Body Composition

PCOS does not only reduce reproductive health but also has tremendous implications on metabolic health specifically leading to increased abdominal obesity and an increased level of androgen levels. The two outcomes are not independent but in a pathogenic loop. Hypersupplies of androgens enhance the growth of fat including visceral adiposity, whereas the increment in adipose tissue, in turn, enhances androgen production by raising inflammatory and endocrine pathways. Thus, of great interest are therapeutic agents that can complete this cycle by lowering testosterone levels and improving the composition of the body. Isoflavones are plant products of phytoestrogens, which are mainly present in soybeans and have proven to be potential candidates in this. This characteristic of their modulation of steroidogenesis and body weight makes them an attractive natural replacement with conventional pharmacological treatments(7).

Hyperandrogenism is a characteristic feature of PCOS, which is commonly seen in the menstrual cycle i.e. hirsutism, acne and alopecia and biochemically high concentration of serum testosterone and androstenedione. Along with its reproduction related effects, an excess of testosterone also causes abdominal obesity by modifying the differentiation and the metabolism of adipocytes. The answer to this question is now well established because testosterone has been shown to inhibit lipolysis in subcutaneous adipose tissues by inhibiting the expression of hormone sensitive lipase and beta 2 adrenergic receptors. Such an anti-lipolytic activity results in the storage of lipids in the adipose tissue, especially, at the abdominal level, which gives rise to the so-called phenotype termed, android obesity. Therefore, the treatment modalities that can inhibit and melt fat indirectly through low level of circulating testosterone do exist.

Isoflavones have demonstrated potential of being anti-androgens in in vivo and clinical studies. As structurally analogous to 17-B-estradiol, isoflavones perform the doping of estrogen receptors hence institute estrogenic or

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anti-estrogenic effects in a tissue-specific manner. More to the point isoflavones, like genistein and daidzein, seem to disrupt the action of important enzymes implicated in the androgen biosynthesis such as 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-HSD. These catalyse the process of transformation of pregnenolone and androstenedione into testosterone. These enzymes are inhibited leading to a major decline in the serum testosterone and finally, this restores the hyperandrogenic symptoms, and consequently results in enhancing downstream metabolic effects.

A number of studies with animals respond to them. Examples have been shown in which in letrozole induced models of PCOS in rats, two weeks of usage of 100mg/kg soy isoflavones exposed to lower weight, reduced testosterone levels, and 3 beta / 17 beta-HSD activity. There were also a reduction of cystic follicles and well-developed granulosa and theca layer on ovarian histology. In the same way, other experiments involving feeding of red clover or chickpea derived isoflavones to rats led to some significant decline in abdominal fat mass, testosterone level of serum, and adipocytes lipid content. Notably, these effects were associated with augmentation of the rate of estradiol and sex hormone-binding globulin (SHBG) that aid in immobilizing free androgens.

Similar results are also recorded in the clinical trials. A three-month randomized controlled trial of 35 women with PCOS administered a daily 50 mg dose of soy isoflavone reduced serum testosterone and body mass index (BMI) significantly. Besides, the trial documented the benefits of the Free Androgen Index (FAI), insulin resistance, and lipid profile. Such increase in metabolical responses is especially pertinent considering that insulin resistance is a local and resultant cause of hyperandrogenism(8). Isoflavones have a two-modality strategy that can perturb the vicious cycle of PCOS pathology by targeting both.

The mechanism through which isoflavones bring about weight loss is various. In addition to enzyme inhibition, isoflavones seem to regulate adipokine- leptin and adiponectin, are key determinants of satiety, lipid oxidation, and energy expenditure. In addition, certain isoflavones boost thermogenic processes through the action of peroxisome proliferator-activated receptor gamma (PPAR-g) and help to boost basal metabolic rate and fat oxidation. Some of these effects matched those attained by the commonly used insulin sensitizer, metformin, though with a superior safety profile and a reduced gastrointestinal peri-effect.

Nevertheless, it is crucial to review the fact that the results of the studies are not always constant. Other trials provide significant and considerable decreases of testosterone and body weight; however, other trials exhibit insignificant and slight decreases. Such variations can be explained by isoflavone type (e.g. genistein vs. daidzein), dose, duration of treatment, and baseline characteristics of patients (BMI, insulin sensitivity, SHBG levels), as well as bioavailability. It is important to note that the composition of the population of gut microbiota also plays an important role in the metabolism of isoflavones; only with the help of a specific set of microflora, daidzein can be converted into the form of equol, which binds to estrogen receptors more strongly. Therefore, the issue of individual response variability is a weighty behest of standardization of isoflavone-based treatment.

In a bid to provide a better comparison among the core studies, the information below gives a summary of the effects of isoflavone administration on testosterone levels and body weight of PCOS models:

TABLE 1 Summary of Isoflavone Impact on Testosterone and Body Weight in PCOS

Study	Isoflavone Type	Model	Dosage & Duration	Key Outcomes
Rajan et al. (2017)	Soy isoflavones	Letrozole-induced rats	50/100 mg/kg for 2 weeks	↓ Testosterone, ↓ Body weight, ↓ HSD activity, ↑ Estradiol
Jamilian & Asemi (2016)	Soy isoflavones (50 mg/day)	Human (RCT, n=35)	3 months	↓ Testosterone, ↓ BMI, ↓ FAI, ↑ SHBG
Abbasian et al. (2020)	Red clover isoflavones	Letrozole-induced rats	100–150 mg/200 g for 4 wks	↓ Testosterone, ↓ LDL, ↓ MDA, ↑ SOD, ↑ GSH
Ali et al. (2021)	Chickpea isoflavones	Letrozole-induced rats	50/100 mg/200 g for 4 wks	↓ Testosterone, ↓ Body fat, ↑ Granulosa cell thickness
Karamali et al. (2018)	Soy-based diet	Human (RCT, n=30)	2 months	↓ Body weight, ↓ VLDL, ↓ MDA, ↑ GSH, ↑ NO

To sum up, the ability of isoflavones to influence hormonal and metabolic markers makes them one of the effective natural treatment options of PCOS. Thereby affecting major players in steroidogenesis, enhancing SHBG binding,

and decreasing the fat accumulation, isoflavones go to the root of the pathophysiology of the disorder. They are particularly appealing in the treatment of hyperandrogenic and metabolic phenotypes of PCOS because they have the effect of reducing testosterone levels whilst causing weight loss simultaneously. Although larger scale, more uniform trials are necessary, there is as yet evidence to indicate that isoflavones may be an especially potent adjuvant or substitute therapy, with fewer adverse effects and more widespread systemic effects than conventional therapies.

4.Antioxidant Potential of Isoflavones in PCOS: Neutralizing Oxidative Stress for Endocrine Restoration

Polycyclic ovary syndrome (PCOS) is not only a hormone-related pathology it is also closely connected with oxidative stress an ability of the body to produce reactive oxygen species (ROS) in excess, which cannot be neutralized or otherwise detoxified, a biochemical imbalance. Oxidative stress linked to increased levels of reactive oxygen species causes ovarian malfunction, persistent inflammation, insulin resistance, and reproductive hormone disorders, which are the main processes of PCOS. Anti-oxidative use Plants In the past few years, naturally occurring compounds like isoflavones, plant-derived polyphenolic compounds, have been studied with an eye to their anti-oxidant activity. Isoflavones could provide protection against oxidative damage, since most of them are derived in part by soy, red clover, and legumes and therefore, could be an agent of promoting the mitigation of PCOS symptoms when acting on the molecular level(9).

Oxidative stress and its relationship to PCOS is established. In women with PCOS, malondialdehyde (MDA) as well as advanced glycation end-products (AGEs), xanthine oxidase (XO) and nitric oxide (NO) are highly elevated in comparison with PCOS controls. These oxidative products give an implication of the level of peroxidation of the lipids, proteins and oxidation of DNAs in the cells. Conversely, glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as antioxidant lines of defense, are usually deficient in PCOS, particularly the ovarian microenvironment. The resultant effect is the high oxidative burden which hindering folliculogenesis, deepened the insulin resistance, and maintained low chronic inflammation.

Isoflavones have the property of free radical scavenging because they have a polyphenolic framework that enables them to transfer hydrogen atoms to stabilize ROS. Good antioxidant effect is attributed to phenolic ring (particularly the B-ring and the hydroxyl groups of isoflavones. In addition they also increase the expression of several key antioxidant enzymes via NOC modulation of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor regulating the expression of detoxification and antioxidant genes. The mechanism is more applicable in PCOS where the granulosa cell does not work properly due to oxidative stress that alters the quality of oocyte.

Soy or red clover isoflavones showed a significant antioxidant recovery in animal studies in animals with PCOS that were induced by letrozole or estradiol. Such an example is the case of the rats that were provided with 100 mg/kg of soy isoflavones, which showed reduced concentration of MDA, higher GSH and GPx activities, and better histology of ovary with a lower population of cystic follicles. The biochemical findings were directly related to the reduction of androgen and the increased steroidogenic production of estradiol which signified that the decreased oxidative stress could partially repair steroidogenic balance. In another animal experiment, it was noted that isoflavones lowered the level of NO as well as lipid peroxidation but increased the levels of total antioxidant capacity (TAC) in the ovarian tissues. This suggests that the biochemical correction is systemic in effect because of the twofold effect on oxidative and endocrine parameters by isoflavones.

These results are also confirmed by clinical trials. In a duration of 8 weeks, Karamali et al. examined that the women with PCOS on the pro-inflammatory diet with high amounts of isoflavones in soy had substantially reduced Key findings that have been reported in studies assessing the antioxidants properties of isoflavone in PCOS have been captured in the table below, with both animal and human outcomes being identified.

MDAs and improved levels of GSH and SOD. Also, the levels of NO went up after treatment which is probably a compliance of soy-derived L-arginine which stimulates the production of NO. Whereas, NO is a free radical, at small physiological doses, it enhances endothelial activity and ovarian blood supply. Consequently, regulated production of NO through isoflavones could be potentially useful in other ways than just regulating oxidation(10). Surprisingly, the effect of isoflavone therapy is entitled to be dose-related. Higher doses (150 mg/200 g) of isoflavones derived in red clover were highly antioxidant in rat-based models than lower doses. Furthermore, research presented that the structural state of isoflavone; aglycone or glycoside, could influence the bioavailability

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and the bioefficacy (antioxidant). The presence of aglycone forms (such as that of genistein) promotes absorption and responds better to the action of intracellular enzymes and receptors implying that the formulation might be a game-changer in clinical results.

Although there is a lot of evidence, the outcomes on total antioxidant capacity (TAC) are not consistent in investigations. There were researches that described high levels of TAC after the intervention with isoflavone but also there were no significant changes in this level. Such discrepancy may be ascribed to methodological divergence, the mixed nature of both metabolism type within PCOS group and the difference in the baseline antioxidant status of individuals. However, a decrease in MDA, which is a direct indicator of lipid peroxidation, is always enhanced by isoflavone in both rat and human experiments, a factor that reaffirms a belief that isoflavones can ameliorate oxidative damage.

TABLE 2 Summary of Antioxidant Effects of Isoflavones in PCOS Models

Study	Model Type	Isoflavone Source	Dosage/Duration	Key Antioxidant Outcomes
Karamali et al. (2018)	Human (RCT)	Soy	0.28 g/kg for 2 months	↑ GSH, ↑ SOD, ↑ NO, ↓ MDA
Jamilian & Sahebkashaf (2017)	Human (RCT)	Soy Isoflavone (50 mg)	3 months	↑ GSH, ↓ MDA
Abbasian et al. (2020)	Letrozole-induced rats	Red Clover	150 mg/200 g for 4 weeks	↑ GSH, ↑ SOD, ↓ NO, ↓ MDA, ↑ CAT
Ma et al. (2021)	Letrozole-induced rats	Soy	20 mg/200 g for 4 weeks	↑ GPx, ↑ SOD, ↓ TNF-α, ↓ MDA
Rajaei et al. (2019)	Estradiol-induced rats	Soy (genistein)	1 mg/kg for 2 weeks	↑ TAC, ↑ SOD, ↑ GPx, ↓ MDA
Rajan et al. (2017)	Letrozole-induced rats	Soy	100 mg/kg for 2 weeks	↑ SOD, ↑ GSH, ↓ Lipid Peroxidation, ↓ NO

Overall, antioxidant effects of isoflavones in PCOS manifest themselves in the twofold manner: by decreasing reactive oxidative species, as well as by increasing the intrinsic antioxidant defense of the body. This redox adjustment also leads to the recovery of the ovarian physiology and high oocyte quality and relieves the metabolism aberrations. Although the data are mostly supportive, additional studies are indicated into the investigation of dose optimization, the ways to improve bioavailability, and long-term safety. The inclusion of isoflavones in the treatment approach to PCOS presents the potential not only in the field of reproductive health but also in the reduction of oxidative-stress-associated-complications, which can inflict cardiovascular and metabolic disease.

5.Conclusion and Future work

PCOS is among the most difficult and common endocrinopathies women of reproductive age encounter, with an incidence of up to 5--10 percent of the available population of women all over the world. PCOS is a set of symptoms that includes hyperandrogenism, oligo/anovulation, and polycystic morphology of the ovaries and can be characterized by a great variety of metabolic, reproductive, and psychological manifestations. Although traditional pharmacological therapies like metformin, clomiphene citrate, and oral contraceptives have some effect, their application is usually embroiled with adverse effects or lack adequate long-term safety or is contraindicated in some groups of people. Against these inabilities, alternative and adjunct therapies based on phytomedicine practices have come under greater scrutiny, especially those which include the use of certain naturally occurring polyphenols, called isoflavones, that are found most commonly in legumes and soy as well as in red clover. The similarity of isoflavones with 17β-estradiol allows them to affect the activity of the estrogen receptor and interact with numerous pathways linked with PCOS pathogenesis. The themes in this review illustrate the multidimensionality of how isoflavones exert their effects in PCOS symptoms, i.e., anti-androgenic, antioxidant, anti-inflammatory, and metabolism regulatory properties, which implies that they can be readily used as an effective and low-risk complementary treatment in the PCOS management therapeutic ecology.

The anti-androgenic property of isoflavones has been found in one of the most profound conclusions of clinical trials as well as preclinical trials. Hyperandrogenism, one of the characteristics of PCOS, has the adverse effect of

unbalancing the hormonal axis and crashing follicular maturation leading to menstrual irregularities, infertility, hirsutism, and acne. Genistein and daidzein isoflavones have been shown to inhibit enzymes essential to androgen biosynthesis: 3b- hydroxysteroid dehydrogenase, and 17 beta- HSD. Isoflavones reduce testosterone levels and regulate luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio through the suppression of these enzymatic pathways and normalize the hormonal situation. Isoflavone supplement in both letrozole and estradiol induced PCOS rat models and randomized human trials dramatically reduced blood testosterone and raised blood estradiol and FSH. These hormonal changes were frequently allied with a regularization of the estrous or menstrual cycle and a better ovulatory outcome the most crucial clinical outcomes in PCOS patients wishing to have a child.
The antioxidant ability of isoflavones is also extremely interesting. Oxidative stress is a critical factor in the advancement of PCOS and aggravates insulin resistance, destroys ovarian follicles, and induces systemic inflammation. Isoflavones scavenge reactive oxygen species (ROS) directly and even increase antioxidant enzymes that include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and glutathione (GSH) in the human body. In animals, there was a significant reduction of malondialdehyde (MDA), as well as nitric oxide (NO) levels (an indicator of oxidative stress), but the total antioxidant capacity (TAC) increased with the administration of isoflavones. Such molecular responses are not just any improvement in biochemical terms, but rather, a sign of an improved cellular survival in the face of damaging apoptosis of ovarian cells. In human beings, corresponding results have been recorded in numerous clinical studies where consumption of isoflavones not only positively influenced oxidative indicators but also increased insulin sensitivity the two-pronged effects that have a direct applicability to metabolic-PCOS phenotype.
Anti-inflammatory activity of isoflavones complements their therapeutic interest. A longstanding low-grade inflammation belonging to PCOS is a pathogenic factor of hyperandrogenism and metabolic dysfunction. Genistein and other isoflavones inhibit the expression of proinflammatory cytokines (TNF-a, IL-6, IL-1 b), which is probably due to an inactivation of the nuclear factor-kappa B (NF-x B) signaling pathway. Phosphorylated NF-kB and I k b alpha were downregulated greatly in the presence of soy and red clover isoflavones in PCOS-induced rats therefore contributing to reduced inflammatory signaling and recovery of the ovarian tissues. At the clinical level, such anti-inflammatory actions mean lower levels of insulin resistance and enhanced endothelial functioning, which play a significant role in reducing the risks of long-term CV adverse events frequently related to PCOS.
The other important aspect of isoflavone therapy is that it has an effect on the PCOS metabolic profile of patients. The presence of insulin resistance, dyslipidemia and abdominal obesity is not just a symptom of PCOS but a causative factor of the development of PCOS. Sustainable effects of isoflavones to reduce serum insulin levels, to improve the insulin resistance and to improve the quantitative index insulin-sensitivity check (QUICKI) have also been evidenced. They also assist in rectifying dyslipidemia as it decreases triglycerides, LDL cholesterol, and very-low-density lipoprotein (VLDL). It also elevates high-density lipoprotein (HDL). These are the consequences of isoflavone-mediated regulation of the pathways of the peroxisome proliferator-activated receptors (PPAR) and the transcription related to estrogen receptors. The metabolic effects of of isoflavones as soy protein, pure genistein, and red clover extract are identical in their various formulations and doses with little or no adverse effects.

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Conflicts of interest

The authors have no conflicts of interest to declare

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