Phytotherapeutic Interventions in Polycystic Ovarian Disease: Evaluating Efficacy, Safety, and Future Perspectives of Soybean

Ramandeep Kaur[1], Dr. Rohit Mittal[*2]
[1]Research Scholar, University College of Pharmacy, Guru Kashi University, Talwandi Sabo, Bathinda &
Assistant Professor, Pharmacy Department, Guru Kashi University, Talwandi Sabo, Bathinda
[*2]Associate Professor, Pharmacy Department, Guru Kashi University, Talwandi Sabo, Bathinda
*Corresponding Author: Dr. Rohit Mittal, rohitmittal04@gmail.com

Abstract
Polycystic ovary syndrome (PCOS) is a prevalent and multifactorial endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, oxidative stress, inflammation, and associated metabolic abnormalities. Although conventional pharmacological therapies remain central to PCOS management, their limitations and variable tolerability have stimulated interest in complementary phytotherapeutic approaches. Soybean (*Glycine max*) has emerged as a promising candidate because of its diverse bioactive constituents, particularly the isoflavones genistein, daidzein, and glycitein, as well as soy proteins, bioactive peptides, saponins, phytosterols, polyphenols, and unsaturated fatty acids. This review critically examines the phytochemical profile, therapeutic mechanisms, clinical efficacy, and safety of soybean-based interventions in PCOS. Available evidence indicates that soybean-derived constituents may potentially improve insulin sensitivity, modulate hyperandrogenism, support reproductive endocrine function, improve lipid metabolism, and attenuate oxidative stress and inflammation. Isoflavones may exert these effects through estrogen receptor modulation and regulation of metabolic and cellular signaling pathways, including PI3K/AKT, AMPK, NF-κB, and antioxidant defense mechanisms. Preliminary clinical studies suggest beneficial effects on insulin resistance, testosterone-related parameters, triglycerides, and selected oxidative stress biomarkers; however, evidence regarding menstrual regularity, ovulation, fertility, and long-term clinical outcomes remains limited. Variability in soybean composition, isoflavone bioavailability, individual metabolism, gut microbiota, and equol-producing capacity further complicates therapeutic translation. Overall, soybean appears to have potential as an adjunctive phytotherapeutic intervention within an integrated PCOS management strategy, but it should not currently replace established medical treatments. Future research should focus on standardized formulations, optimal dosing, large-scale randomized controlled trials, long-term safety assessment, advanced delivery systems, and personalized approaches integrating nutrigenomics and microbiome-based profiling.

Keywords: Polycystic ovary syndrome; PCOS; *Glycine max*; Soybean; Soy isoflavones; Genistein; Daidzein; Phytotherapy; Insulin resistance; Hyperandrogenism; Oxidative stress; Nutraceuticals.
How to cite this article: Kaur R, Mittal R. Phytotherapeutic Interventions in Polycystic Ovarian Disease: Evaluating Efficacy, Safety, and Future Perspectives of Soybean. Int J Drug Deliv Technol. 2026;16(71s): 774-799. DOI: 10.25258/ijddt.16.71s.93

1. Introduction

Polycystic ovary syndrome (PCOS), also frequently referred to as polycystic ovarian disease (PCOD), is a complex and heterogeneous endocrine–metabolic disorder affecting women predominantly during the reproductive years. It is characterized by a combination of reproductive, hormonal, and metabolic abnormalities, including ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology. The clinical presentation is highly variable, and affected women may experience irregular or absent menstruation, hirsutism, acne, infertility, obesity, insulin resistance, and dyslipidemia. The 2023 International Evidence-Based Guideline emphasizes that PCOS should be considered a lifelong condition requiring comprehensive management of reproductive, metabolic, cardiovascular, psychological, and other associated health risks (Teede et al., 2023). The diagnosis is generally based on the presence of characteristic clinical or biochemical hyperandrogenism, ovulatory dysfunction, and/or polycystic ovarian morphology after exclusion of other relevant disorders. This multifaceted nature makes PCOS considerably more than an isolated ovarian disorder and highlights the need for therapeutic strategies capable of addressing its interconnected endocrine and metabolic manifestations.

PCOS represents one of the most common endocrine disorders among women of reproductive age and constitutes a major global public health concern because of its effects on fertility, metabolic health, and quality of life. Estimates of prevalence vary considerably according to the diagnostic criteria, geographical region, and characteristics of the population studied, but the condition is widely recognized as affecting a substantial proportion of reproductive-aged women worldwide. The increasing occurrence of obesity, sedentary lifestyles, and metabolic dysfunction has further intensified interest in PCOS as a significant chronic health problem. In addition to reproductive complications, women with PCOS may have an increased risk of impaired glucose tolerance, type 2

diabetes mellitus, cardiovascular risk factors, obstructive sleep apnea, and psychological complications. Consequently, the burden of PCOS extends beyond menstrual irregularity and infertility, affecting long-term health and requiring continuous monitoring and individualized management (Teede et al., 2023).

The pathophysiology of PCOS is complex and multifactorial, involving interactions between genetic predisposition, endocrine abnormalities, metabolic disturbances, environmental factors, and lifestyle-related influences. Hyperandrogenism is considered a central feature of the disorder and may originate from excessive androgen production by the ovaries and, in some cases, the adrenal glands. Elevated androgen concentrations contribute to clinical manifestations such as hirsutism, acne, androgenic alopecia, and reproductive dysfunction (Cassidy et al., 1994). At the same time, impaired follicular development and abnormal ovarian steroidogenesis can interfere with normal ovulation, resulting in menstrual irregularity and reduced fertility. The metabolic component of PCOS is strongly associated with insulin resistance, which may occur independently of body mass index and can further stimulate ovarian androgen production. Compensatory hyperinsulinemia may enhance theca-cell androgen synthesis and contribute to reduced sex hormone-binding globulin concentrations, thereby increasing the bioavailability of circulating androgens (Teede et al., 2023).

Insulin resistance, hyperandrogenism, oxidative stress, and chronic low-grade inflammation are closely interconnected mechanisms in the development and progression of PCOS. Insulin resistance can promote hyperinsulinemia, which may exacerbate ovarian androgen production and impair normal follicular maturation. In parallel, increased oxidative stress and inflammatory signaling may contribute to disturbances in ovarian function, metabolic homeostasis, and insulin sensitivity (Ahsan et al., 2019). These mechanisms can create a self-perpetuating cycle in which metabolic abnormalities worsen endocrine dysfunction and vice versa. The presence of obesity, particularly central adiposity, may further intensify these pathological processes. Therefore, therapeutic approaches that simultaneously target metabolic dysfunction, androgen excess, inflammation, and oxidative imbalance may provide broader benefits than interventions directed toward a single symptom or pathway (Teede et al., 2023).

The current management of PCOS generally involves lifestyle modification and pharmacological interventions tailored to individual reproductive and metabolic goals. Depending on the clinical presentation, conventional treatment may include combined oral contraceptives for menstrual irregularity and hyperandrogenic symptoms, insulin-sensitizing agents such as metformin for selected metabolic indications, antiandrogenic therapies, and ovulation-induction agents for women seeking pregnancy. Although these interventions can be effective, their use may be associated with adverse effects, contraindications, drug interactions, or inadequate control of all manifestations of the syndrome. Moreover, PCOS is a chronic and heterogeneous condition, and no single pharmacological intervention is universally effective for every patient. These limitations have stimulated increasing interest in complementary approaches, including dietary interventions, nutraceuticals, medicinal plants, and phytotherapeutic agents that may act through multiple biological pathways (Teede et al., 2023; Koshy et al., 2024).

Phytotherapeutics have consequently emerged as an area of growing interest in the complementary management of PCOS. Plant-derived bioactive compounds may possess antioxidant, anti-inflammatory, insulin-sensitizing, lipid-modulating, and endocrine-regulatory properties, potentially allowing them to influence several pathological mechanisms simultaneously. Among the various botanical sources investigated, soybean (*Glycine max*) has attracted particular attention because of its rich content of biologically active compounds, especially isoflavones such as genistein and daidzein. Soybean isoflavones are classified as phytoestrogens because of their structural similarity to endogenous estrogens and their ability to interact with estrogen receptors. In addition to estrogen receptor-mediated actions, these compounds have been investigated for their potential antioxidant, metabolic, and anti-inflammatory effects, suggesting a possible role in addressing several components of PCOS pathophysiology (Koshy et al., 2024; Hooper et al., 2009).

The rationale for investigating soybean-derived phytoconstituents in PCOS management is supported by emerging experimental and clinical evidence suggesting that soy isoflavones may influence both metabolic and reproductive abnormalities associated with the syndrome. In a randomized, double-blind, placebo-controlled clinical trial involving women with PCOS, 12 weeks of soy isoflavone supplementation was associated with improvements in insulin-related parameters, free androgen index, triglyceride concentrations, and selected oxidative stress biomarkers (Jamilian et al., 2016). Similarly, a systematic review and meta-analysis of randomized controlled trials reported that soy isoflavone supplementation significantly reduced total testosterone concentrations in women with PCOS, although no significant effect on follicle-stimulating hormone was observed and the authors

emphasized the need for better-designed studies (Khani et al., 2020). These findings indicate that soybean-derived compounds may have potential as adjunctive interventions, although the available evidence remains insufficient to establish them as replacements for standard PCOS therapy (Anderson et al., 1995).

Despite the promising findings, the therapeutic application of soybean in PCOS requires careful evaluation of efficacy, safety, dose, formulation, bioavailability, and long-term effects. Existing studies differ in the type and dose of soy intervention, duration of supplementation, participant characteristics, and outcome measures, making direct comparison difficult. Furthermore, the biological response to soy isoflavones may vary according to individual metabolism, gut microbiota composition, dietary patterns, and baseline hormonal and metabolic status. Therefore, a comprehensive assessment of current evidence is necessary to distinguish established therapeutic benefits from preliminary or inconsistent findings. The present review aims to critically examine the potential role of soybean and its bioactive phytoconstituents in the management of PCOS, with particular emphasis on their effects on insulin resistance, hyperandrogenism, reproductive dysfunction, oxidative stress, inflammation, and metabolic abnormalities. It further evaluates the available evidence regarding efficacy and safety and discusses current limitations, research gaps, and future opportunities for the development of soybean-based phytotherapeutic and nutraceutical strategies for PCOS management.

2. Phytochemical Profile and Bioactive Constituents of Soybean

2.1 Botanical Overview and Nutritional Significance of *Glycine max*

Soybean, botanically identified as *Glycine max* (L.) Merr., belongs to the family Fabaceae and is one of the most nutritionally and economically important leguminous crops cultivated worldwide. It is an annual herbaceous plant whose seeds are consumed directly or processed into a wide range of food products, including soy milk, tofu, tempeh, miso, natto, soy flour, soy protein concentrates, and isolated soy protein. Historically, soybean has been an important component of traditional diets in East and Southeast Asia, while its use has subsequently expanded globally because of its high-quality protein content, favorable lipid profile, and abundance of biologically active phytochemicals (Hymowitz, 2004; Rizzo & Baroni, 2018).

From a nutritional perspective, soybean is particularly distinctive among plant foods because it combines a relatively high protein content with substantial quantities of unsaturated fatty acids, dietary fiber, minerals, vitamins, and a broad spectrum of secondary metabolites. Mature soybean seeds generally contain approximately 35–40% protein, 18–22% lipid, around 9% dietary fiber, and variable quantities of carbohydrates and moisture, although the exact composition is strongly influenced by cultivar, geographical origin, climate, soil conditions, and agricultural practices (Rizzo & Baroni, 2018; Singh et al., 2008). Soybean proteins contain all essential amino acids and are therefore considered a valuable plant-based protein source. The lipid fraction is predominantly unsaturated and includes linoleic acid and α-linolenic acid, while the minor lipid fraction contains phytosterols and other lipid-soluble compounds with potential metabolic relevance (Rizzo & Baroni, 2018).

The biological significance of soybean extends beyond its macronutrient composition. Soybean seeds contain several classes of bioactive compounds, including isoflavones, saponins, phytosterols, phenolic acids, flavonoids, bioactive peptides, phospholipids, and other minor constituents. These compounds may exert antioxidant, anti-inflammatory, hypolipidemic, insulin-sensitizing, immunomodulatory, and endocrine-modulating effects. Consequently, soybean has increasingly been considered a functional food with potential relevance to chronic metabolic and hormone-related disorders (Messina, 2016; Rizzo & Baroni, 2018).

The nutritional and phytochemical composition of soybean is particularly relevant to polycystic ovary syndrome (PCOS) because the disorder involves a complex interaction among insulin resistance, hyperandrogenism, oxidative stress, inflammation, dyslipidemia, and reproductive dysfunction. Thus, a food-derived phytotherapeutic approach containing multiple bioactive components may theoretically influence several pathological pathways simultaneously. However, the effects observed with whole soy foods cannot necessarily be attributed to a single constituent, and the contribution of individual compounds may vary according to their concentration, bioavailability, metabolism, and interactions with other components of the diet (Rizzo & Baroni, 2018; Messina, 2016).

Table 2.1. Approximate nutritional composition and major bioactive components of soybean

Component	Approximate characteristics	Potential biological relevance
Protein	~35–40% of dry seed weight	Provides essential amino acids; source of bioactive peptides
Lipids	~18–22%	Predominantly unsaturated fatty acids; contributes to cardiometabolic health

Dietary fiber	~9%	Supports gastrointestinal health and may influence glucose and lipid metabolism
Isoflavones	Variable according to cultivar and processing	Phytoestrogenic, antioxidant, and potential metabolic effects
Saponins	Variable minor constituents	Potential antioxidant, anti-inflammatory, hypolipidemic, and immunomodulatory activities
Phytosterols	Minor lipid fraction	May reduce intestinal cholesterol absorption
Phenolic compounds	Variable	Antioxidant and anti-inflammatory potential
Bioactive peptides	Released during digestion, fermentation, or enzymatic hydrolysis	Potential antioxidant, antihypertensive, and metabolic effects
α-Linolenic acid	Plant-derived omega-3 fatty acid	Potential relevance to inflammatory and cardiometabolic pathways
Phospholipids	Minor lipid fraction	Structural and functional roles in cellular membranes
Minerals and vitamins	Variable	Contribute to overall nutritional value

Note: Values are approximate and may vary considerably according to soybean genotype, cultivation conditions, processing, and analytical method.

2.2 Major Phytoconstituents of Soybean

The phytochemical profile of soybean is complex and includes both primary nutritional components and secondary metabolites. Among these, isoflavones are the most extensively investigated because of their phytoestrogenic properties (Badger et al., 2002). However, soybean also contains saponins, phytosterols, phenolic acids, flavonoids, bioactive peptides, protease inhibitors, phospholipids, and polyunsaturated fatty acids. The biological activities of these constituents may be complementary, and the overall physiological effects of soy consumption may result from interactions among multiple components rather than from one isolated compound (Messina, 2016; Rizzo & Baroni, 2018).

Table 2.2. Major bioactive constituents of soybean and their potential relevance to PCOS

Bioactive class	Representative compounds	Major biological activities	Potential relevance to PCOS
Isoflavones	Genistein, daidzein, glycitein	Phytoestrogenic, antioxidant, signaling modulation	May influence hyperandrogenism, insulin resistance, oxidative stress, and ovarian function
Saponins	Soyasaponins A, B, E and DDMP-conjugated saponins	Antioxidant, anti-inflammatory, lipid-modulating	Potential influence on metabolic dysfunction and inflammation
Phytosterols	β-Sitosterol, campesterol, stigmasterol	Cholesterol absorption modulation	Potential improvement in dyslipidemia
Phenolic acids	Caffeic acid, ferulic acid, p-coumaric acid	Antioxidant and anti-inflammatory	Potential reduction of oxidative stress and inflammation
Flavonoids	Various flavonoid derivatives	Antioxidant and cellular signaling effects	Potential metabolic and anti-inflammatory relevance
Proteins	Glycinin, β-conglycinin	Nutritional and metabolic effects	May influence lipid and glucose metabolism
Bioactive peptides	Digestion- or fermentation-derived peptides	Antioxidant, ACE-inhibitory, metabolic activities	Potential cardiometabolic benefits
Lipids	Linoleic acid, α-linolenic acid, phospholipi	Membrane and metabolic functions	Potential relevance to lipid metabolism and

	ds		inflammation
Phospholipids	Phosphatidylcholine and related compounds	Membrane and signaling functions	Possible metabolic and cellular effects

The concentration of these compounds is not constant. Soybean genotype, environmental conditions, maturation stage, storage, thermal processing, fermentation, and food preparation can substantially modify the phytochemical profile. In particular, processing can alter the chemical form and bioavailability of isoflavones, while fermentation may increase the relative abundance of aglycone forms. Therefore, the physiological effects of whole soybean, soy milk, tofu, fermented soy products, soy protein isolates, and concentrated isoflavone preparations may not be identical (Setchell & Cassidy, 1999; Barnes, 2010).

2.3 Soybean Isoflavones: Genistein, Daidzein, and Glycitein

Isoflavones represent the most extensively studied class of soybean phytochemicals and are often considered the principal compounds responsible for many of the endocrine and biological effects associated with soy consumption. The three principal soybean isoflavones are **genistein, daidzein, and glycitein**. In soybean seeds, these compounds occur in several chemical forms, including free aglycones, β-glycosides, acetylated glycosides, and malonylated glycosides. The major glycosides include genistin, daidzin, and glycitin, which correspond to genistein, daidzein, and glycitein, respectively (Barnes, 2010; Otieno et al., 2006).

Genistein is a major soybean isoflavone and has received extensive scientific attention because of its structural similarity to 17β-estradiol and its ability to interact with estrogen receptors (Cassidy et al., 1994). It has been reported to possess antioxidant, anti-inflammatory, kinase-modulating, and metabolic effects. Genistein can interact with multiple intracellular signaling pathways, including pathways involved in glucose homeostasis, cellular proliferation, oxidative stress, and inflammatory responses. Its estrogen receptor activity is not equivalent to that of endogenous estrogen and depends on the tissue, receptor subtype, concentration, and hormonal environment (Setchell & Cassidy, 1999; Barnes, 2010).

Daidzein is another major soybean isoflavone. A particularly important characteristic of daidzein is its metabolism by intestinal microorganisms to compounds such as **equol** and O-desmethylangolensin (O-DMA). Equol has a relatively high affinity for estrogen receptor β compared with estrogen receptor α and may contribute to some biological effects attributed to soy consumption. However, only a proportion of individuals possess the intestinal microbial capacity to produce equol, creating substantial interindividual variation in the response to soy isoflavones (Setchell & Clerici, 2010).

Glycitein generally occurs in smaller quantities than genistein and daidzein but contributes to the overall isoflavone profile of soybean. It is a methoxylated isoflavone and may undergo metabolic conversion after ingestion. Although it has received less attention than genistein and daidzein, glycitein may contribute to the biological activity of soy isoflavone mixtures and should therefore not be completely overlooked when evaluating the pharmacological effects of soybean-derived preparations (Setchell & Cassidy, 1999; Barnes, 2010).

Table 2.3. Principal soybean isoflavones and their characteristics

Isoflavone	Major dietary form	Key characteristics	Potential relevance
Genistein	Genistin and related conjugates	Major isoflavone; interacts with estrogen receptors; antioxidant and signaling effects	Potential influence on insulin sensitivity, inflammation, oxidative stress, and hormone-related pathways
Daidzein	Daidzin and related conjugates	Phytoestrogen; metabolized by gut microbiota	Potential endocrine and metabolic effects
Glycitein	Glycitin and related conjugates	Methoxylated isoflavone; generally present at lower concentrations	May contribute to overall biological activity of soy isoflavone mixtures
Equol	Microbial metabolite of daidzein	Produced only by equol-producing individuals	May contribute to interindividual differences in response to soy

The distribution of isoflavones in soybean is influenced by cultivar and growing conditions. Genistein, daidzein, and glycitein collectively represent the principal isoflavone aglycones, while their glycosylated and acylated derivatives constitute important storage forms. Processing, especially fermentation, can modify these chemical forms and consequently influence their absorption

and biological availability (Barnes, 2010; Otieno et al., 2006).

2.4 Saponins

Soybean saponins are triterpenoid glycosides consisting of a hydrophobic aglycone linked to one or more sugar moieties. They are structurally diverse and are commonly classified into groups such as soyasaponins A, B, E, and DDMP-conjugated saponins. Their concentration and composition vary according to soybean genotype, maturity, tissue distribution, and processing conditions (Guajardo-Flores et al., 2012).

Saponins have attracted attention because of their potential antioxidant, anti-inflammatory, immunomodulatory, hypolipidemic, and metabolic activities. Some studies suggest that soybean saponins may influence cholesterol metabolism and oxidative processes. Their amphiphilic structure may also influence lipid digestion and intestinal interactions. However, compared with soybean isoflavones, evidence regarding their specific role in endocrine disorders such as PCOS remains considerably less developed.

From the perspective of PCOS, the potential relevance of soy saponins may arise from their ability to influence metabolic and inflammatory pathways. Since insulin resistance, dyslipidemia, and low-grade inflammation frequently coexist in PCOS, compounds with lipid-modulating and anti-inflammatory properties may have indirect therapeutic relevance. Nevertheless, these effects should currently be regarded as mechanistically plausible rather than clinically established specifically for PCOS (Guajardo-Flores et al., 2012).

2.5 Phytosterols

Soybean contains several phytosterols, including **β-sitosterol, campesterol, and stigmasterol**. These plant sterols structurally resemble cholesterol and can interfere with intestinal cholesterol absorption by competing with cholesterol for incorporation into mixed micelles. Consequently, dietary phytosterols may contribute to improvements in circulating lipid profiles, particularly reductions in LDL cholesterol (Rizzo & Baroni, 2018).

The potential importance of phytosterols in PCOS is primarily related to the metabolic phenotype of the disorder. Dyslipidemia, elevated triglycerides, and unfavorable lipoprotein patterns are frequently observed in women with PCOS, particularly in association with obesity and insulin resistance. Although phytosterols cannot be considered direct treatments for the endocrine abnormalities of PCOS, their potential lipid-modulating effects may contribute to the broader cardiometabolic benefits of soybean-containing diets.

The effects of soybean phytosterols may also interact with other components of the soybean matrix. Therefore, the cardiovascular and metabolic effects of whole soy foods may reflect the combined action of proteins, unsaturated fatty acids, fiber, phytosterols, and polyphenolic compounds rather than the activity of phytosterols alone.

2.6 Polyphenols and Flavonoids

Soybean contains a variety of phenolic compounds, including phenolic acids and flavonoid-related constituents. Representative phenolic acids reported in soybean include caffeic acid, ferulic acid, p-coumaric acid, and related derivatives. These compounds are capable of participating in antioxidant mechanisms through free-radical scavenging and modulation of cellular antioxidant defense systems.

Oxidative stress is increasingly recognized as an important component of PCOS pathophysiology. Excessive production of reactive oxygen species may contribute to ovarian dysfunction, impaired insulin signaling, inflammation, and metabolic abnormalities. Therefore, the antioxidant capacity of soybean phenolics could theoretically provide supportive effects in PCOS. However, the concentration and bioavailability of individual phenolic compounds in commonly consumed soy foods can vary considerably.

Polyphenols may also influence inflammatory signaling and cellular pathways associated with metabolic homeostasis. Their combined effects with isoflavones may be particularly relevant because soybean is consumed as a complex food matrix rather than as a single purified compound. Nevertheless, further studies are required to determine whether the concentrations achievable through dietary soybean consumption are sufficient to produce clinically meaningful effects in women with PCOS.

2.7 Soy Proteins and Bioactive Peptides

Soybean is recognized as a high-quality plant protein source, with protein representing approximately 35–40% of the dry weight of mature seeds. The principal storage proteins are **glycinin (11S globulin)** and **β-conglycinin (7S globulin)**, which together constitute the majority of soybean storage proteins (Rizzo & Baroni, 2018).

The biological importance of soy protein extends beyond its amino acid composition. During gastrointestinal digestion, fermentation, or enzymatic hydrolysis, soybean proteins can release short bioactive peptides with physiological activities. These peptides have been investigated for potential antioxidant, antihypertensive, anti-inflammatory, hypocholesterolemic, and metabolic effects (Singh et al., 2008).

Some soybean-derived peptides may influence glucose and lipid metabolism, although the evidence is predominantly experimental and the specific mechanisms remain under investigation. Since insulin resistance and dyslipidemia are important metabolic characteristics of PCOS, soy protein and its derived peptides may theoretically

contribute to metabolic improvement. However, it is important to distinguish the effects of **soy protein as a nutritional intervention** from the pharmacological effects of isolated soy peptides.

Table 2.4. Potential biological activities of soybean proteins and peptides

Component/activity	Proposed effect	Possible relevance to PCOS
High-quality protein	Supports nutritional adequacy and muscle protein synthesis	May support healthy body composition and metabolic health
Soy protein	Potential lipid-modulating activity	May benefit PCOS-associated dyslipidemia
Bioactive peptides	Antioxidant activity	Potential reduction in oxidative stress
ACE-inhibitory peptides	Potential blood-pressure regulation	May contribute to cardiometabolic risk reduction
Metabolic peptides	Possible effects on glucose and lipid pathways	Potential relevance to insulin resistance
Anti-inflammatory peptides	Modulation of inflammatory signaling	Potential relevance to chronic low-grade inflammation

The overall metabolic effects of soy protein may also be influenced by its replacement of animal proteins or other dietary components. Therefore, dietary context is an important consideration when interpreting clinical studies involving soybean-based interventions.

2.8 Omega-3 and Other Bioactive Lipids

The lipid fraction of soybean is characterized by a high proportion of unsaturated fatty acids. **Linoleic acid (omega-6)** is generally the predominant polyunsaturated fatty acid, while **α-linolenic acid (ALA; omega-3)** represents an important fraction of soybean lipids. Soybean also contains monounsaturated fatty acids, phospholipids, and minor lipid-soluble compounds (Rizzo & Baroni, 2018).

Although soybean is not a major dietary source of the long-chain marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), its ALA content provides a plant-derived omega-3 fatty acid. ALA can undergo limited endogenous conversion to EPA and DHA, although conversion efficiency is relatively low. Nevertheless, the presence of ALA contributes to the favorable unsaturated lipid profile of soybean (Cassidy et al., 2006).

In the context of PCOS, bioactive lipids may be relevant to metabolic health and inflammatory pathways. Altered lipid metabolism is frequently observed in PCOS, and dietary patterns rich in unsaturated fats may be associated with more favorable cardiometabolic profiles. However, the specific contribution of soybean-derived ALA to PCOS outcomes has not been established independently of the overall dietary pattern.

2.9 Estrogenic and Phytoestrogenic Properties of Soybean Isoflavones

The term **phytoestrogen** refers to plant-derived compounds capable of interacting with estrogen receptors or influencing estrogen-sensitive pathways. Soybean isoflavones are among the most extensively studied dietary phytoestrogens. Their structural resemblance to endogenous estrogens allows them to interact with estrogen receptor subtypes, particularly estrogen receptor α (ERα) and estrogen receptor β (ERβ). However, their estrogenic activity is substantially weaker than that of endogenous 17β-estradiol and can vary according to tissue, receptor expression, circulating hormone levels, and concentration (Setchell & Cassidy, 1999).

Genistein and daidzein show preferential interactions with ERβ relative to ERα. This receptor selectivity is important because ERα and ERβ may produce different physiological effects in reproductive tissues and metabolic organs. Consequently, soybean isoflavones may act as **selective estrogen receptor modulators-like compounds**, exhibiting estrogenic effects in some tissues and weak or anti-estrogenic effects in others.

In PCOS, the estrogenic properties of soy isoflavones are of particular interest because ovarian steroidogenesis and reproductive hormone balance are disrupted. However, the relationship between phytoestrogen activity and PCOS is complex. Isoflavones should not be considered equivalent to conventional estrogen therapy. Their effects are dependent on dose, timing, hormonal environment, receptor expression, and individual metabolism.

The potential benefits of isoflavones in PCOS may extend beyond direct estrogen receptor activation. Genistein, daidzein, and their metabolites have been investigated for their effects on oxidative stress, inflammatory pathways, glucose metabolism, and cellular signaling. Therefore, their potential contribution to PCOS management may involve a combination of endocrine and non-endocrine mechanisms (Barnes, 2010; Messina, 2016).

2.10 Bioavailability, Metabolism, and Pharmacokinetic Characteristics

The biological effects of soybean isoflavones depend not only on their chemical composition but also on their absorption, metabolism, tissue distribution, and elimination. This is particularly important because the major isoflavones in unfermented soybean foods occur predominantly as glycosides and conjugated derivatives rather than as free aglycones.

After ingestion, isoflavone glycosides such as genistin, daidzin, and glycitin undergo hydrolysis of their sugar moieties. This process can occur through intestinal enzymes and microbial β-glucosidases, producing the aglycones genistein, daidzein, and glycitein. The resulting aglycones are more readily absorbed than the intact glycosides. Processing and fermentation can alter the proportion of glycoside and aglycone forms, thereby influencing the pharmacokinetic profile (Barnes, 2010; Nielsen & Williamson, 2007).

Following intestinal absorption, isoflavones undergo extensive **phase II metabolism**, primarily glucuronidation and sulfation in the intestinal wall and liver. Consequently, circulating isoflavones are found predominantly as conjugated metabolites rather than as free aglycones. These metabolites may undergo enterohepatic circulation, and the compounds or their metabolites are eventually eliminated mainly through urine and bile (Barnes, 2010).

Daidzein undergoes additional metabolism by intestinal microorganisms. In individuals harboring specific bacterial populations, daidzein can be converted into **equol**, a metabolite with distinct biological properties and relatively high affinity for ERβ. However, equol production is highly variable between individuals and is influenced by gut microbiota composition, dietary habits, age, and other factors. This variability may partly explain differences in the physiological response to soybean isoflavones among individuals (Setchell & Clerici, 2010).

The pharmacokinetic behavior of soybean isoflavones is also influenced by the food matrix and chemical form. Aglycones may be absorbed more rapidly than glycosides, whereas glycoside-containing preparations require hydrolysis before efficient absorption. In addition, processing methods such as heating, fermentation, and microbial transformation can modify the relative concentrations of individual isoflavone forms (Barnes, 2010; Nielsen & Williamson, 2007).

Table 2.5. Absorption, metabolism, and pharmacokinetics of major soybean isoflavones

Stage	Major process	Principal outcome
Dietary intake	Consumption of soybean or soy products	Intake of isoflavones mainly as glycosides and conjugates
Deglycosylation	Enzymatic and microbial hydrolysis	Release of genistein, daidzein, and glycitein aglycones
Intestinal absorption	Uptake of aglycones	Entry into enterocytes and portal circulation
Phase II metabolism	Glucuronidation and sulfation	Formation of circulating conjugated metabolites
Hepatic metabolism	Further conjugation and biotransformation	Modification of systemic exposure
Gut microbial metabolism	Daidzein → equol/O-DMA in some individuals	Generation of biologically active metabolites
Enterohepatic circulation	Biliary excretion and intestinal reabsorption	Prolonged systemic exposure
Elimination	Primarily urinary and biliary pathways	Removal of metabolites from the body

The bioavailability of soybean isoflavones therefore represents a major consideration when interpreting experimental and clinical research. A standardized extract containing a specified amount of genistein may not produce the same pharmacokinetic profile as a whole-soy food containing genistin, daidzin, glycitin, and other constituents. Similarly, individuals who produce equol may respond differently from non-producers. These differences have important implications for future PCOS research because variations in exposure may contribute to inconsistent clinical findings.

2.11 Potential Relevance of Soybean Constituents to PCOS Pathophysiology

The phytochemical complexity of soybean provides a mechanistic rationale for investigating its potential role in PCOS. PCOS is characterized by interconnected pathological processes, including insulin resistance, hyperinsulinemia, hyperandrogenism, oxidative stress, chronic low-grade inflammation, and metabolic abnormalities. Soybean constituents may potentially influence several of these pathways simultaneously.

Isoflavones are particularly relevant because of their potential effects on estrogen receptor

signaling, glucose metabolism, oxidative stress, and inflammation. Genistein and daidzein may influence pathways associated with insulin signaling and cellular metabolism, while their antioxidant properties may help counter excessive reactive oxygen species (Choi & Kim, 2008). Their phytoestrogenic activity may also have implications for ovarian and reproductive endocrine function, although the precise clinical consequences in PCOS remain to be fully established.

Soy protein and bioactive peptides may contribute primarily to metabolic effects, including potential improvements in lipid metabolism and cardiometabolic health. Phytosterols may reduce intestinal cholesterol absorption, while unsaturated fatty acids may contribute to a favorable dietary lipid profile. Saponins and phenolic compounds may provide additional antioxidant and anti-inflammatory effects. Collectively, these activities suggest that soybean may exert a **multi-target phytotherapeutic effect**, potentially addressing several pathological components of PCOS simultaneously.

Table 2.6. Hypothesized relationship between soybean constituents and major pathological features of PCOS

PCOS pathological feature	Relevant soybean constituents	Proposed biological action	Potential therapeutic implication
Insulin resistance	Isoflavones, soy protein, peptides	Possible modulation of insulin signaling and glucose metabolism	Improved metabolic control
Hyperandrogenism	Isoflavones	Potential influence on endocrine signaling and steroidogenesis	Possible reduction in androgen-related abnormalities
Oxidative stress	Genistein, daidzein, phenolics, saponins, peptides	Antioxidant activity and modulation of endogenous defense systems	Reduction of oxidative damage
Chronic inflammation	Isoflavones, phenolics, saponins	Potential modulation of inflammatory pathways	Reduced low-grade inflammation
Dyslipidemia	Phytosterols, soy protein, unsaturated fatty acids	Reduced cholesterol absorption and favorable lipid metabolism	Improved cardiometabolic profile
Ovarian dysfunction	Isoflavones	Estrogen receptor-mediated and non-estrogenic signaling	Potential support of reproductive endocrine function
Obesity-associated metabolic dysfunction	Protein, fiber, phytochemicals	Nutritional and metabolic effects	Potential support for weight-management strategies
Gut microbiota alterations	Isoflavones and dietary matrix	Microbial metabolism and production of metabolites such as equol	Possible modulation of host metabolic and endocrine responses

The potential relevance of soybean to PCOS can therefore be conceptualized as a **multi-component and multi-target mechanism**. Rather than acting through one specific molecular target, soybean-derived compounds may collectively influence metabolic, endocrine, oxidative, inflammatory, and lipid pathways. This concept is particularly attractive for PCOS because the disorder itself is heterogeneous and involves multiple interacting mechanisms.

Nevertheless, a distinction should be made between **biological plausibility** and **clinical efficacy**. Evidence demonstrating that a soybean constituent can modulate a signaling pathway in vitro or improve a biomarker in an animal model does not automatically establish a clinically meaningful therapeutic effect in women with PCOS. Differences in dosage, bioavailability, metabolism, formulation, and study population must be carefully considered.

2.12 Integrated Perspective

The phytochemical profile of *Glycine max* provides a strong scientific basis for its investigation as a potential phytotherapeutic and nutraceutical intervention in PCOS. Soybean is not merely a

source of phytoestrogenic isoflavones; it represents a complex matrix containing proteins, peptides, unsaturated fatty acids, saponins, phytosterols, phenolic compounds, and other bioactive constituents. These compounds may interact with pathways associated with insulin resistance, hyperandrogenism, oxidative stress, inflammation, dyslipidemia, and reproductive dysfunction.

Among these constituents, genistein, daidzein, and glycitein remain the most extensively studied because of their estrogen receptor activity and broad biological effects. However, the overall therapeutic potential of soybean may arise from synergistic or additive interactions between isoflavones and other nutritional and phytochemical components. The bioavailability and metabolism of these compounds are highly variable, with intestinal microbiota playing an important role in determining the formation of metabolites such as equol.

From the perspective of PCOS research, these characteristics emphasize the importance of studying soybean not only as an isolated isoflavone preparation but also as a whole food, standardized extract, functional food ingredient, or combination formulation (Clarkson, 2002). Future investigations should establish standardized doses, characterize the specific bioactive composition of interventions, account for interindividual differences in isoflavone metabolism, and determine whether improvements in biochemical markers translate into meaningful reproductive and metabolic outcomes. Such research may help clarify whether soybean-based interventions can serve as effective adjuncts to lifestyle modification and conventional PCOS management.

3. Therapeutic Potential and Mechanisms of Soybean in Polycystic Ovary Syndrome

Soybean (*Glycine max*) and its bioactive constituents, particularly genistein, daidzein, and glycitein, have attracted increasing attention as potential phytotherapeutic agents for the management of polycystic ovary syndrome (PCOS). The therapeutic rationale for soybean is based on the multifactorial pathophysiology of PCOS, in which insulin resistance, hyperinsulinemia, hyperandrogenism, abnormal gonadotropin signaling, oxidative stress, inflammation, mitochondrial dysfunction, dyslipidemia, and alterations in the gut microbiome interact with one another. Unlike conventional therapies that often target individual manifestations of PCOS, soybean-derived compounds may influence several of these pathways simultaneously through antioxidant, anti-inflammatory, metabolic, endocrine, and signaling mechanisms.

Among the soybean constituents, isoflavones have been investigated most extensively. Genistein and daidzein possess phytoestrogenic properties and can interact with estrogen receptors, while also influencing intracellular signaling pathways involved in glucose metabolism, oxidative stress, inflammation, and cellular proliferation. Soy protein, peptides, saponins, phytosterols, phenolic compounds, and unsaturated fatty acids may further contribute to the overall biological effects of soybean. However, the strength of evidence differs considerably between individual mechanisms. Some effects have been demonstrated in cell and animal models, whereas human clinical evidence remains relatively limited. Therefore, the therapeutic potential of soybean in PCOS should currently be considered promising but not yet definitive.

3.1 Effects on Insulin Resistance and Glucose Metabolism

Insulin resistance is one of the most important metabolic abnormalities associated with PCOS and may occur in both lean and overweight women. It is characterized by impaired cellular responsiveness to insulin, resulting in compensatory hyperinsulinemia. Increased insulin concentrations can stimulate ovarian theca cells to produce androgens and may also reduce hepatic production of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen levels. Thus, insulin resistance can contribute directly to the endocrine abnormalities characteristic of PCOS.

Soybean isoflavones have been investigated for their potential insulin-sensitizing effects. Genistein may influence glucose metabolism through multiple mechanisms, including modulation of insulin receptor signaling, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathways, AMP-activated protein kinase (AMPK), and glucose transporter activity. These mechanisms may improve cellular glucose uptake and metabolic flexibility. In addition, the antioxidant effects of isoflavones may indirectly improve insulin signaling because oxidative stress can impair insulin receptor pathways.

Evidence from human studies provides preliminary support for these effects. In a randomized, double-blind, placebo-controlled trial involving 70 women with PCOS, supplementation with 50 mg/day of soy isoflavones for 12 weeks significantly reduced serum insulin and HOMA-estimated insulin resistance while improving the quantitative insulin sensitivity check index compared with placebo. The same study also reported improvements in free androgen index and triglyceride concentrations, suggesting that metabolic and endocrine effects may be interconnected (Jamilian et al., 2016). (PubMed)

The potential insulin-sensitizing action of soybean may therefore occur through both direct and indirect mechanisms. Isoflavones may influence intracellular insulin signaling, while soy proteins and peptides may contribute to improved metabolic

profiles. Furthermore, replacement of high-saturated-fat animal proteins with soy-based foods may improve overall dietary quality and cardiometabolic health.

Table 3.1. Potential mechanisms by which soybean constituents may influence insulin resistance in PCOS

Soybean constituent	Proposed mechanism	Potential metabolic outcome
Genistein	Modulation of PI3K/AKT and AMPK signaling	Improved insulin sensitivity
Daidzein	Effects on glucose and metabolic signaling	Potential improvement in glucose utilization
Soy protein	Modification of postprandial metabolic responses	Improved glucose and lipid homeostasis
Bioactive peptides	Possible effects on glucose-regulating pathways	Potential improvement in insulin sensitivity
Phenolic compounds	Reduction of oxidative stress	Protection of insulin signaling
Saponins	Potential metabolic and lipid-modulating effects	Improved metabolic profile
Dietary fiber	Slower glucose absorption and microbiota modulation	Improved glycemic control

It is important to emphasize that evidence from clinical trials remains limited and that the magnitude of benefit may depend on the dose, duration, baseline metabolic status, and chemical composition of the soybean intervention.

3.2 Modulation of Hyperandrogenism and Androgen Production

Hyperandrogenism is a defining feature of PCOS and contributes to hirsutism, acne, androgenic alopecia, and reproductive dysfunction. Excess androgen production may result from increased ovarian theca-cell activity, altered adrenal androgen production, insulin-mediated stimulation of steroidogenesis, and disturbances in hypothalamic-pituitary-ovarian regulation.

Soy isoflavones may potentially influence androgen excess through several mechanisms. Their phytoestrogenic activity may alter estrogen receptor signaling and modify endocrine feedback mechanisms. In addition, improvement in insulin sensitivity may indirectly reduce ovarian androgen production because hyperinsulinemia can stimulate theca-cell steroidogenesis. Therefore, the metabolic effects of soybean may have secondary endocrine consequences.

Clinical evidence is emerging. The randomized trial by Jamilian et al. (2016) reported a significant reduction in free androgen index following 12 weeks of soy isoflavone supplementation. A systematic review and meta-analysis of randomized controlled trials also found that soy isoflavone supplementation significantly decreased total testosterone in women with PCOS, although no significant effect was observed on follicle-stimulating hormone (FSH). The authors emphasized that the number of available studies was small and that additional high-quality trials are necessary (Zilaee et al., 2020).

The potential antiandrogenic effect of soybean should therefore be interpreted as a combination of direct endocrine modulation and indirect metabolic improvement. Reduction in insulin resistance may decrease the insulin-mediated stimulation of ovarian androgen synthesis, whereas phytoestrogenic signaling may influence reproductive endocrine pathways.

3.3 Regulation of Reproductive Hormones and Ovarian Function

The reproductive endocrine system in PCOS is characterized by disturbances involving hypothalamic gonadotropin-releasing hormone (GnRH) pulsatility, luteinizing hormone (LH) secretion, ovarian steroidogenesis, and follicular development. Elevated LH activity and increased ovarian androgen production can interfere with normal follicular maturation and contribute to anovulation.

Soy isoflavones may potentially influence reproductive function through estrogen receptor-mediated mechanisms. Genistein and daidzein have greater relative affinity for estrogen receptor β (ERβ), which is expressed in reproductive tissues and may participate in ovarian regulation. Through selective receptor interactions, isoflavones may influence gene transcription and cellular signaling related to ovarian function.

The phytoestrogenic action of soybean is complex because isoflavones are considerably weaker than endogenous estradiol and their effects depend on tissue type, receptor expression, endogenous estrogen levels, and circulating concentration. Therefore, soybean should not be considered a direct estrogen replacement therapy. Rather, its isoflavones may act as selective estrogen receptor modulators with context-dependent effects (Setchell & Cassidy, 1999; Barnes, 2010).

The improvement in insulin resistance and androgen status observed in some clinical studies may further contribute to restoration of reproductive endocrine balance. However, direct evidence demonstrating that soybean supplementation consistently normalizes LH/FSH ratios or restores menstrual cyclicity remains

insufficient. The available evidence suggests potential rather than established efficacy.

3.4 Effects on Follicular Development and Ovulation

Follicular arrest is a characteristic feature of PCOS and results from impaired follicular maturation and abnormal ovarian steroidogenesis. Excess androgen exposure, insulin resistance, oxidative stress, inflammation, and disrupted gonadotropin signaling can interfere with the transition of follicles from early developmental stages toward dominant follicle selection and ovulation.

Soybean-derived compounds may theoretically influence follicular development through several interconnected pathways. First, improvement in insulin sensitivity may reduce hyperinsulinemia-associated androgen excess. Second, antioxidant compounds may protect granulosa and theca cells from oxidative damage. Third, phytoestrogenic signaling may influence ovarian estrogen-responsive pathways. Fourth, anti-inflammatory effects may help reduce the local inflammatory environment associated with ovarian dysfunction.

Genistein has been investigated experimentally for its effects on ovarian cells and steroidogenic pathways, while soy isoflavone mixtures have been examined for their ability to modulate reproductive hormone profiles. Nevertheless, direct evidence that soybean consistently promotes ovulation specifically in women with PCOS remains limited (Davis et al., 1999).

A potentially important hypothesis is that soybean may improve ovulatory function indirectly by modifying the metabolic environment rather than by directly stimulating ovulation. This distinction is important because the restoration of insulin sensitivity and reduction of androgen excess may create a more favorable physiological environment for normal follicular maturation.

Table 3.2. Potential reproductive effects of soybean in PCOS

Reproductive abnormality	**Possible soybean-related mechanism**	**Expected potential effect**
Hyperandrogenism	Improved insulin sensitivity and endocrine modulation	Reduction in androgen excess
Follicular arrest	Antioxidant and metabolic effects	Improved follicular environment
Abnormal ovarian steroidogenesis	Isoflavone-mediated signaling	Potential normalization of steroidogenic activity
Menstrual irregularity	Improvement of metabolic and endocrine abnormalities	Possible improvement in cycle regularity
Anovulation	Indirect improvement through insulin and androgen pathways	Potential enhancement of ovulatory function
Reduced reproductive potential	Combined metabolic and endocrine effects	Possible supportive role in fertility management

3.5 Improvement of Lipid Profile and Metabolic Abnormalities

Dyslipidemia is frequently associated with PCOS, particularly among women with obesity and insulin resistance. Elevated triglycerides, LDL cholesterol, and altered HDL cholesterol may contribute to long-term cardiovascular risk.

Soybean may influence lipid metabolism through several complementary mechanisms. Soy protein has been associated with favorable effects on cholesterol metabolism, while phytosterols may reduce intestinal cholesterol absorption. Unsaturated fatty acids in soybean may also contribute to a more favorable dietary lipid profile. In addition, isoflavones may influence hepatic lipid metabolism and oxidative processes (Cornwell et al., 2004).

In the PCOS-specific randomized controlled trial conducted by Jamilian et al. (2016), soy isoflavone supplementation significantly reduced serum triglycerides compared with placebo. However, significant changes were not observed in all lipid parameters, indicating that the metabolic response may be selective and dependent on baseline lipid status and intervention characteristics.

The metabolic relevance of soybean is therefore likely to extend beyond a single biochemical parameter. The combined effects of protein, unsaturated fatty acids, phytosterols, fiber, and polyphenols may contribute to an overall improvement in cardiometabolic health.

3.6 Antioxidant and Anti-Inflammatory Activities

Oxidative stress and chronic low-grade inflammation are increasingly recognized as important contributors to PCOS pathogenesis. Increased production of reactive oxygen species (ROS) may cause lipid peroxidation, protein oxidation, mitochondrial dysfunction, and impaired cellular signaling. Oxidative stress can also interact with inflammation, creating a self-amplifying cycle that may worsen metabolic and reproductive abnormalities.

Soy isoflavones possess antioxidant properties that may be mediated through direct radical-scavenging effects as well as modulation of endogenous antioxidant defense mechanisms. Genistein and daidzein may influence antioxidant enzymes and intracellular redox signaling. Other soybean constituents, including phenolic compounds and saponins, may further contribute to antioxidant capacity.

Clinical findings provide preliminary support for this mechanism. In the study by Jamilian et al. (2016), 12 weeks of soy isoflavone supplementation significantly increased plasma total glutathione and decreased malondialdehyde compared with placebo. These findings suggest improved redox status and reduced lipid peroxidation. However, not all inflammatory and oxidative stress biomarkers were significantly altered, indicating that the effects may be selective rather than universal.

The anti-inflammatory activity of soybean may involve modulation of pathways such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and other inflammatory signaling networks. By reducing inflammatory signaling, soybean constituents may potentially improve insulin sensitivity and ovarian function.

3.7 Modulation of Oxidative Stress and Mitochondrial Dysfunction

Mitochondria are central to cellular energy production, steroidogenesis, and ROS regulation. In PCOS, mitochondrial dysfunction has been proposed as a contributing mechanism to metabolic abnormalities and ovarian dysfunction. Excessive ROS production can impair mitochondrial membrane potential, ATP generation, and cellular redox balance (D'Anna et al., 2007).

Soy isoflavones may potentially protect mitochondrial function through antioxidant and signaling mechanisms. Genistein, in particular, has been investigated in experimental systems for its effects on mitochondrial oxidative stress, cellular antioxidant defenses, and metabolic signaling. By reducing ROS accumulation, isoflavones may theoretically preserve mitochondrial integrity and improve cellular energy metabolism.

A proposed mechanism involves the interaction between **AMPK, mitochondrial biogenesis, oxidative stress, and antioxidant defense pathways**. AMPK acts as an important metabolic sensor and can regulate glucose uptake, fatty-acid oxidation, and mitochondrial function. Activation of AMPK-related pathways could theoretically improve metabolic flexibility and reduce metabolic stress.

However, the majority of evidence directly linking soybean isoflavones with mitochondrial improvement in PCOS remains preclinical. Therefore, this mechanism should be viewed as a promising research hypothesis rather than a clinically established therapeutic effect.

3.8 Potential Effects on Gut Microbiota and Metabolic Health

The gut microbiome has emerged as an important component of PCOS pathophysiology. Alterations in gut microbial composition may influence insulin resistance, inflammation, intestinal permeability, bile-acid metabolism, and hormonal regulation. These mechanisms may create a bidirectional relationship between intestinal dysbiosis and PCOS-associated metabolic abnormalities.

Soybean isoflavones have a particularly interesting relationship with the gut microbiota because their metabolism depends partly on intestinal bacteria. Daidzein can be converted by specific microorganisms into equol, while microbial metabolism can also influence the absorption and biological activity of soybean isoflavones. Consequently, the microbiome may determine an individual's response to soy-derived compounds.

At the same time, soybean consumption may itself influence the intestinal microbial environment. Dietary fiber, oligosaccharides, proteins, and polyphenolic compounds can act as substrates or modulators of microbial communities. This creates a potentially bidirectional interaction:

soybean intake → microbiota modulation → altered isoflavone metabolism → production of metabolites such as equol → systemic endocrine and metabolic effects.

Recent reviews have proposed that the interaction between soy isoflavones and gut microbiota may influence both the bioavailability of isoflavones and metabolic and hormonal pathways relevant to PCOS. However, direct evidence from well-controlled human PCOS studies remains limited, and this field requires further investigation.

3.9 Molecular Mechanisms and Signaling Pathways Involved

The therapeutic potential of soybean in PCOS is likely to arise from simultaneous modulation of several molecular pathways rather than a single pharmacological target.

3.9.1 PI3K/AKT Signaling

The PI3K/AKT pathway is central to insulin signaling and glucose metabolism. Impairment of this pathway contributes to insulin resistance. Soybean isoflavones, particularly genistein, have been investigated for their potential to influence this signaling cascade. Improved PI3K/AKT activity may enhance glucose utilization and improve insulin sensitivity.

3.9.2 AMPK Signaling

AMPK acts as a cellular energy sensor and regulates glucose uptake, fatty-acid oxidation, and mitochondrial metabolism. Potential modulation of AMPK by soybean constituents may contribute to improved metabolic function and reduced oxidative stress.

3.9.3 Estrogen Receptor Signaling

Genistein and daidzein interact with estrogen receptors, with relative preference for ERβ. This mechanism may influence reproductive tissues, endocrine feedback, and metabolic processes. However, the physiological consequences depend strongly on tissue-specific receptor expression and endogenous estrogen concentrations.

3.9.4 NF-κB and Inflammatory Signaling

Chronic inflammation may contribute to insulin resistance and ovarian dysfunction. Soybean polyphenols and isoflavones have been investigated for their potential to modulate NF-κB and related inflammatory pathways. Reduced inflammatory signaling could potentially improve metabolic and ovarian function.

3.9.5 Oxidative Stress and Nrf2-Related Defense

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway regulates endogenous antioxidant defense. Soy-derived polyphenolic compounds may influence cellular antioxidant responses, potentially increasing resistance to oxidative stress.

3.9.6 MAPK Signaling

MAPK pathways participate in cell proliferation, differentiation, inflammation, and stress responses. Genistein and related compounds can influence MAPK signaling, although the effects may be concentration- and cell-type-dependent.

3.9.7 Gut Microbiota–Metabolite Axis

The gut microbiota contributes to the biotransformation of isoflavones and determines the formation of metabolites such as equol. In turn, these metabolites may affect estrogen receptor signaling, inflammation, and metabolic pathways, creating a potential microbiota–endocrine–metabolic axis.

Table 3.3. Major molecular pathways potentially modulated by soybean constituents in PCOS

Molecular pathway	Potential soybean-related action	Possible relevance to PCOS
PI3K/AKT	Modulation of insulin signaling	Improved glucose uptake and insulin sensitivity
AMPK	Potential metabolic activation	Improved energy metabolism and fatty-acid oxidation
ERα/ERβ	Phytoestrogenic interaction	Endocrine and ovarian modulation
NF-κB	Potential suppression of inflammatory signaling	Reduced chronic inflammation
Nrf2	Enhancement of antioxidant defense	Reduced oxidative stress
MAPK	Modulation of stress and inflammatory signaling	Potential cellular protection
Mitochondrial pathways	Reduction of ROS and metabolic stress	Improved mitochondrial function
Gut microbiota axis	Microbial metabolism of isoflavones	Altered bioavailability and systemic effects
Steroidogenic pathways	Possible modulation of ovarian androgen synthesis	Potential reduction in hyperandrogenism

3.10 Evidence from In Vitro, Animal, and Preclinical Studies

The preclinical evidence supporting soybean-derived compounds in PCOS is broader than the current clinical evidence. In vitro studies provide valuable information regarding cellular mechanisms, while animal models allow investigation of whole-organism metabolic and reproductive outcomes.

In vitro evidence

Cellular studies have examined the effects of genistein and other isoflavones on insulin signaling, oxidative stress, steroidogenesis, inflammatory pathways, and ovarian cell function. Such experiments suggest that soybean-derived compounds can influence molecular pathways relevant to PCOS. However, concentrations used in cell culture may exceed physiological plasma concentrations achievable through ordinary dietary intake.

Animal evidence

Rodent models of PCOS induced by androgens, letrozole, or metabolic interventions have been used to investigate the effects of soybean-derived compounds. Preclinical studies suggest possible improvements in insulin resistance, oxidative stress, ovarian morphology, and reproductive hormone disturbances. These models provide mechanistic evidence but may not fully reproduce the heterogeneity of human PCOS (de Lima et al., 2017).

Clinical evidence

Human evidence remains comparatively limited. The strongest PCOS-specific clinical evidence currently includes small randomized controlled trials examining soy isoflavone supplementation and systematic reviews of these trials. The 2016 randomized trial reported improvements in insulin resistance, free androgen index, triglycerides, glutathione, and malondialdehyde after 12 weeks of 50 mg/day soy isoflavones (Jamilian et al., 2016). The subsequent meta-analysis reported a significant reduction in total testosterone but no significant

change in FSH, while emphasizing the limited number and quality of available trials (Zilaee et al., 2020).

Thus, the current evidence can be summarized as follows: **mechanistic plausibility is relatively strong, preclinical evidence is encouraging, and clinical evidence is promising but insufficient for definitive therapeutic recommendations**. A recent review similarly concluded that although preclinical and selected clinical findings are encouraging, the small number of studies and methodological limitations prevent firm clinical recommendations at present.

Table 3.4. Evidence hierarchy for soybean-based interventions in PCOS

Evidence level	Main findings	Interpretation
In vitro	Effects on insulin signaling, oxidative stress, inflammation, and cellular pathways	Supports biological plausibility
Animal models	Potential improvements in metabolic abnormalities, oxidative stress, and ovarian dysfunction	Supports preclinical efficacy
Small clinical trials	Improvements in insulin resistance, free androgen index, triglycerides, and oxidative stress biomarkers	Preliminary evidence of clinical benefit
Meta-analysis	Reduction in total testosterone but no significant FSH effect	Potential endocrine benefit, but evidence remains limited
Large long-term RCTs	Currently insufficient	Major research gap
Standardized clinical guidelines	Soy isoflavones are not established as primary PCOS therapy	Should not replace evidence-based conventional treatment

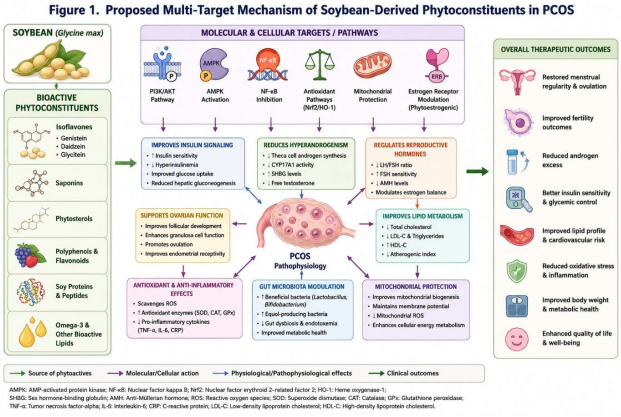

Figure 1. Proposed Multi-Target Mechanism of Soybean-Derived Phytoconstituents in PCOS

Figure legend: The proposed model illustrates the multi-target activity of soybean-derived constituents in PCOS. Isoflavones may influence estrogen receptor signaling, insulin-related pathways, oxidative stress, inflammation, and gut microbial metabolism, while soy proteins, peptides, saponins, phytosterols, and other constituents may contribute to metabolic effects. These mechanisms may converge to improve insulin sensitivity, hyperandrogenism, ovarian function, and the metabolic environment. The model represents a proposed mechanistic framework based on preclinical and emerging clinical evidence rather than a definitively established pathway.

Table 3.5. Integrated therapeutic potential of soybean in major PCOS pathological domains

PCOS domain	Major pathological process	Potential soybean action	Evidence strength
Insulin resistance	Impaired insulin signaling	Potential PI3K/AKT and AMPK modulation	Moderate/preliminary clinical
Hyperandrogenism	Excess ovarian androgen production	Reduced free androgen index and possible testosterone reduction	Preliminary clinical
Reproductive dysfunction	Follicular arrest and anovulation	Potential indirect improvement through metabolic and endocrine	Mainly preclinical/theoretical

		pathways	
Dyslipidemia	Increased triglycerides and altered lipoproteins	Lipid-modulating effects of soy protein, phytosterols, and isoflavones	Moderate general evidence; limited PCOS-specific evidence
Oxidative stress	Increased ROS and lipid peroxidation	Antioxidant effects and increased glutathione	Preliminary clinical
Inflammation	Chronic low-grade inflammatory signaling	Potential NF-κB/MAPK modulation	Mainly preclinical
Mitochondrial dysfunction	ROS accumulation and impaired energy metabolism	Potential mitochondrial protection	Mainly preclinical
Gut dysbiosis	Altered microbial composition and metabolism	Microbiota–isoflavone interaction and equol production	Emerging
Ovarian dysfunction	Abnormal steroidogenesis and follicular development	Potential endocrine and antioxidant effects	Mainly preclinical
Overall PCOS management	Multifactorial endocrine-metabolic disorder	Multi-target phytotherapeutic potential	Promising but not established

3.11 Critical Evaluation of the Therapeutic Mechanism

The available evidence indicates that soybean may have therapeutic relevance to PCOS through a **multi-dimensional mechanism** involving metabolic, endocrine, antioxidant, anti-inflammatory, mitochondrial, and microbiome-related pathways. This multi-target profile is particularly attractive because PCOS is itself a heterogeneous syndrome that cannot be adequately explained by a single molecular abnormality.

The most clinically encouraging evidence relates to improvements in insulin resistance, free androgen index, triglycerides, oxidative stress biomarkers, and total testosterone. However, these findings should be interpreted cautiously because clinical studies have generally involved relatively small sample sizes and short intervention durations. Moreover, differences in soybean preparation, isoflavone dosage, participant characteristics, and outcome measures complicate comparisons among studies.

Another important consideration is that **soybean food consumption and concentrated isoflavone supplementation should not automatically be considered equivalent interventions**. Whole soybean foods contain proteins, fibers, lipids, phytosterols, and multiple phytochemicals, whereas isolated isoflavone supplements provide a much narrower chemical profile. The clinical effects may therefore differ.

The gut microbiome represents another major source of interindividual variability. Since only some individuals efficiently produce equol from daidzein, the endocrine and metabolic effects of soybean may differ substantially among individuals. Future PCOS research should therefore consider microbiome composition and equol-producing status as potential determinants of therapeutic response (Goodman-Gruen & Kritz-Silverstein, 2001).

Overall, soybean-derived phytoconstituents appear to possess a scientifically plausible and potentially beneficial role in PCOS, particularly as an **adjunctive nutritional or phytotherapeutic strategy**. Nevertheless, current evidence does not justify replacing established medical treatment with soybean supplementation alone. Further standardized, adequately powered randomized controlled trials are required to establish optimal dose, duration, formulation, patient selection, and long-term efficacy.

4. Clinical Evidence: Efficacy and Safety of Soybean-Based Interventions in Polycystic Ovary Syndrome

Clinical interest in soybean-based interventions for polycystic ovary syndrome (PCOS) has increased because of the potential multi-target actions of soybean proteins, isoflavones, peptides, phytosterols, and other bioactive constituents. PCOS is a heterogeneous endocrine-metabolic disorder characterized by varying combinations of hyperandrogenism, ovulatory dysfunction, insulin resistance, obesity, dyslipidemia, and chronic low-grade inflammation. Consequently, an intervention capable of simultaneously influencing metabolic,

endocrine, and oxidative pathways may have potential value as an adjunct to conventional management. Soybean-derived interventions are particularly interesting because their principal isoflavones—genistein, daidzein, and glycitein—possess phytoestrogenic activity and may also influence insulin signaling, oxidative stress, inflammation, and lipid metabolism (Setchell & Cassidy, 1999; Barnes, 2010).

However, it is essential to distinguish between the extensive literature concerning soy consumption and general cardiometabolic health and the considerably smaller body of evidence specifically involving women with PCOS. Clinical trials directly investigating soybean or soy isoflavones in PCOS remain relatively limited in number, sample size, and duration. Therefore, although preliminary findings are encouraging, soybean-based interventions should currently be viewed as potential adjunctive strategies rather than established replacements for evidence-based PCOS treatment **(Teede et al., 2023).**

4.1 Overview of Clinical Studies Involving Soybean, Soy Protein, and Soy Isoflavones in PCOS

Clinical studies of soybean-based interventions in PCOS can broadly be divided into three categories: **whole-soy foods**, **soy protein preparations**, and **isolated or concentrated soy isoflavone supplements**. These interventions are not pharmacologically equivalent because their composition, bioavailability, and biological activity differ considerably.

Whole-soy foods such as tofu, tempeh, soy milk, and minimally processed soybean products provide a complex matrix of protein, fiber, unsaturated fatty acids, phytosterols, isoflavones, and other phytochemicals. Soy protein preparations provide a concentrated source of protein and may contain variable amounts of isoflavones depending on the processing method. Isolated isoflavone preparations, in contrast, provide standardized quantities of compounds such as genistein and daidzein but may not reproduce the physiological effects of whole soybean foods (Jenkins et al., 2002).

Among the PCOS-specific clinical studies, a randomized, double-blind, placebo-controlled trial reported that 12 weeks of soy isoflavone supplementation improved several metabolic and hormonal parameters in women with PCOS. The intervention was associated with reductions in serum insulin, HOMA-estimated insulin resistance, free androgen index, and triglycerides, together with improvements in selected oxidative stress biomarkers (Jamilian et al., 2016). These findings provided an important clinical basis for further investigation of soybean-derived isoflavones in PCOS.

A subsequent systematic review and meta-analysis of randomized controlled trials evaluating soy isoflavones in women with PCOS reported a significant reduction in total testosterone, although no significant effect was observed on FSH levels. The authors emphasized that the evidence base was limited and that further well-designed clinical trials were required to confirm the findings (Khani et al., 2020).

Table 4.1. Major categories of soybean-based interventions relevant to PCOS

Intervention	Major active components	Potential therapeutic targets	Main evidence base
Whole soybean foods	Protein, isoflavones, fiber, phytosterols, unsaturated fatty acids	Metabolic and cardiovascular health	General clinical nutrition; limited PCOS-specific evidence
Soy protein	Glycinin, β-conglycinin, peptides	Insulin and lipid metabolism	Metabolic studies; limited direct PCOS trials
Soy isoflavones	Genistein, daidzein, glycitein	Hyperandrogenism, insulin resistance, oxidative stress	Emerging PCOS-specific clinical evidence
Soy isoflavone extracts	Standardized isoflavone mixtures	Hormonal and metabolic pathways	Small clinical trials
Fermented soy products	Aglycones, peptides, microbial metabolites	Bioavailability and metabolic pathways	Limited PCOS-specific evidence
Soy-derived peptides	Bioactive protein hydrolysates	Antioxidant and metabolic pathways	Predominantly preclinical

4.2 Effects on Menstrual Regularity

Menstrual irregularity is one of the most common clinical manifestations of PCOS and generally reflects chronic anovulation resulting from disrupted follicular development, hyperandrogenism, insulin resistance, and altered hypothalamic-pituitary-ovarian signaling.

The potential effect of soybean on menstrual regularity is biologically plausible but remains insufficiently characterized in clinical studies. Soy

isoflavones may influence reproductive endocrine pathways through estrogen receptor interactions, particularly ERβ, while metabolic improvement may indirectly promote more favorable ovarian function. Reduction in hyperinsulinemia may decrease insulin-mediated ovarian androgen production, potentially improving follicular maturation and menstrual cyclicity.

However, most clinical studies involving soy isoflavones have focused primarily on biochemical endpoints such as testosterone, insulin, HOMA-IR, and oxidative stress rather than menstrual-cycle outcomes. Consequently, there is currently insufficient high-quality evidence to conclude that soybean supplementation consistently restores regular menstrual cycles in women with PCOS (Harland & Haffner, 2008).

This represents an important research gap because menstrual regularity is a clinically meaningful outcome that may provide a better indication of reproductive benefit than isolated biochemical changes.

4.3 Ovulation and Fertility Outcomes

Anovulation is a major cause of infertility in women with PCOS. The therapeutic objective in women attempting conception is to restore ovulation and achieve pregnancy while addressing underlying metabolic abnormalities.

Theoretically, soybean may contribute to improved ovulatory function through several mechanisms:

1. Improvement of insulin sensitivity.
2. Reduction of compensatory hyperinsulinemia.
3. Potential reduction in androgen excess.
4. Antioxidant protection of ovarian cells.
5. Modulation of estrogen receptor signaling.
6. Possible improvement of the ovarian metabolic environment.

However, direct evidence regarding pregnancy rates, ovulation rates, oocyte quality, and live birth outcomes following soybean supplementation remains very limited. Existing clinical studies have generally been too small or too short to determine whether biochemical improvements translate into meaningful fertility outcomes (Hooper et al., 2010).

Therefore, soybean-based interventions should not currently be considered substitutes for established ovulation-induction treatments in women with PCOS-related infertility. Evidence-based pharmacological approaches remain the primary treatment strategy for achieving pregnancy, while nutritional interventions may potentially be considered as complementary measures within an individualized treatment plan (Teede et al., 2023).

4.4 Effects on Testosterone and Other Androgen Levels

Hyperandrogenism is a central feature of PCOS and may manifest as elevated circulating testosterone, increased free androgen index, hirsutism, acne, and androgenic alopecia.

Soy isoflavones may potentially influence androgen status through both direct and indirect mechanisms. The phytoestrogenic properties of genistein and daidzein may alter estrogen receptor signaling, while improved insulin sensitivity may indirectly reduce ovarian androgen production. Furthermore, reductions in insulin concentrations may increase hepatic synthesis of SHBG, potentially decreasing free testosterone availability.

The randomized controlled trial by Jamilian et al. (2016) demonstrated a significant improvement in free androgen index following 12 weeks of soy isoflavone supplementation. A systematic review and meta-analysis subsequently reported a significant reduction in total testosterone among women with PCOS receiving soy isoflavones, although the overall evidence was based on a limited number of trials (Khani et al., 2020).

These findings suggest a potential antiandrogenic effect, but important questions remain regarding whether reductions in biochemical androgen levels translate into improvements in clinical symptoms such as hirsutism and acne.

Table 4.2. Potential effects of soybean-based interventions on androgen-related outcomes

Outcome	Potential effect of soybean	Current evidence
Total testosterone	Possible reduction	Preliminary clinical evidence
Free androgen index	Possible reduction	Supported by a small RCT
SHBG	Potential increase through improved insulin sensitivity	Inconsistent/limited evidence
Free testosterone	Theoretically reduced	Insufficient direct evidence
Hirsutism	Possible indirect benefit	Insufficient clinical evidence
Acne	Possible indirect benefit	Insufficient evidence
Androgenic alopecia	Unclear	No convincing evidence
LH/FSH ratio	Potential modulation	Inconsistent evidence

4.5 Effects on Insulin Sensitivity and Glycemic Control

Insulin resistance is among the most clinically important metabolic abnormalities associated with PCOS. It contributes to hyperinsulinemia and may exacerbate androgen excess by stimulating ovarian steroidogenesis.

Soybean-based interventions may improve insulin sensitivity through multiple mechanisms. Soy

isoflavones may influence insulin signaling pathways, while soy protein may affect postprandial glucose metabolism and appetite regulation. Antioxidant activity may also indirectly preserve insulin signaling because oxidative stress can impair insulin receptor pathways (Lissin & Cooke, 2000).

The randomized trial conducted by Jamilian et al. (2016) reported significant improvements in insulin-related parameters following soy isoflavone supplementation. These findings are particularly relevant because improvement in insulin resistance may have downstream effects on androgen production and reproductive function.

Nevertheless, evidence concerning fasting glucose, HbA1c, and long-term diabetes prevention in women with PCOS remains insufficient. Soy-based interventions should therefore not be considered replacements for established interventions such as weight management, physical activity, and clinically indicated pharmacotherapy.

Table 4.3. Metabolic effects potentially associated with soybean interventions in PCOS

Metabolic parameter	Expected potential effect	Evidence status
Fasting insulin	Reduction	Preliminary positive evidence
HOMA-IR	Improvement	Preliminary positive evidence
Insulin sensitivity	Improvement	Emerging evidence
Fasting glucose	Possible improvement	Limited evidence
HbA1c	Uncertain	Insufficient PCOS-specific evidence
Triglycerides	Possible reduction	Supported by selected clinical evidence
LDL cholesterol	Possible improvement	Inconsistent PCOS-specific evidence
HDL cholesterol	Potential improvement	Limited evidence
Cardiometabolic risk	Potential long-term benefit	Requires long-term studies

4.6 Effects on Lipid Metabolism

Women with PCOS may exhibit increased triglycerides, elevated LDL cholesterol, reduced HDL cholesterol, and other adverse lipid changes. These abnormalities are particularly prominent in women with obesity and insulin resistance.

Soybean may influence lipid metabolism through several mechanisms. Soy protein may affect hepatic cholesterol metabolism, phytosterols may reduce intestinal cholesterol absorption, and unsaturated fatty acids may improve dietary lipid quality. Isoflavones may provide additional antioxidant and metabolic effects.

In the PCOS-specific clinical study by Jamilian et al. (2016), soy isoflavone supplementation significantly reduced triglyceride concentrations. However, the effects on other lipid parameters were less consistent. This suggests that soybean interventions may have selective rather than universal effects on lipid metabolism.

Importantly, the lipid effects of whole soy foods may differ from those of isolated isoflavone supplements. Therefore, future clinical trials should clearly distinguish between dietary soy protein interventions and pharmacologically standardized isoflavone preparations.

4.7 Effects on Body Weight and Obesity-Related Parameters

Obesity is not a diagnostic requirement for PCOS, but it is highly prevalent and can exacerbate insulin resistance, hyperandrogenism, and reproductive dysfunction. Weight reduction of even modest magnitude may improve metabolic and reproductive outcomes in women with PCOS.

Soy-based foods may potentially contribute to weight management because of their high protein content and relatively favorable nutritional composition. Soy protein may promote satiety and may support preservation of lean body mass during energy restriction (Messina & Redmond, 2006). However, soy isoflavone supplementation alone should not be expected to produce substantial weight loss in the absence of appropriate dietary and lifestyle changes.

Evidence from general populations suggests that soy consumption does not consistently produce major reductions in body weight. PCOS-specific studies are similarly insufficient to establish soybean as a weight-loss intervention.

Therefore, soybean may be better viewed as a component of a **balanced dietary strategy** rather than as an independent anti-obesity therapy.

4.8 Effects on Inflammatory and Oxidative Stress Biomarkers

Chronic low-grade inflammation and oxidative stress are increasingly recognized as important features of PCOS. Elevated oxidative stress may contribute to insulin resistance, mitochondrial dysfunction, and abnormal ovarian function.

Soy isoflavones possess antioxidant properties and may modulate inflammatory pathways. In the randomized clinical study by Jamilian et al. (2016), soy isoflavone supplementation increased plasma total glutathione and reduced malondialdehyde, suggesting improvement in antioxidant capacity and lipid peroxidation (Pabich & Materska, 2019).

These findings are mechanistically relevant because oxidative stress may worsen both metabolic and reproductive abnormalities. However, clinical evidence concerning

inflammatory biomarkers such as C-reactive protein, TNF-α, IL-6, and other cytokines remains inconsistent and limited.

4.9 Comparative Efficacy with Conventional PCOS Therapies

Soybean-based interventions should be considered complementary rather than direct alternatives to established PCOS therapies. Conventional management is individualized according to the primary clinical objective, including menstrual regulation, treatment of hyperandrogenism, metabolic management, or fertility.

Combined oral contraceptive pills are commonly used for menstrual irregularity and hyperandrogenic symptoms in women who do not seek pregnancy. Metformin is primarily used for selected metabolic indications and may be considered in women with insulin resistance or impaired glucose metabolism. For infertility due to anovulation, ovulation-induction therapy is generally required.

Compared with these interventions, soybean has a potentially favorable advantage in that it may influence multiple metabolic pathways simultaneously and may be incorporated into dietary strategies. However, the evidence for soybean is much weaker, and there are currently no robust clinical trials demonstrating that soy isoflavones are equivalent to metformin, combined oral contraceptives, or established ovulation-induction therapies (Sirtori et al., 2002).

Table 4.4. Conceptual comparison of soybean-based interventions with conventional PCOS therapies

Intervention	**Primary target**	**Evidence in PCOS**	**Major advantage**	**Major limitation**
Soy isoflavones	Metabolic, endocrine, oxidative pathways	Preliminary	Multi-target potential	Limited clinical evidence
Whole soy foods	Nutritional/metabolic health	Limited PCOS-specific evidence	Food-based and generally accessible	Dose not standardized
Metformin	Insulin resistance/metabolic abnormalities	Established	Strong clinical evidence	Gastrointestinal adverse effects in some patients
Combined oral contraceptives	Menstrual regulation/hyperandrogenism	Established	Effective symptom control	Not suitable for all women
Antiandrogens	Clinical hyperandrogenism	Established	Useful for selected symptoms	Pregnancy-related safety concerns
Ovulation-induction therapy	Anovulatory infertility	Established	Direct fertility benefit	Requires medical supervision
Lifestyle intervention	Weight/metabolic health	Strong evidence	Broad health benefits	Requires sustained adherence

Current international PCOS guidelines emphasize lifestyle management as a core component of care and recommend pharmacological treatment according to individual symptoms and reproductive goals. Soy-based interventions may potentially complement these approaches but should not replace established treatments (Teede et al., 2023).

4.10 Dose, Duration, and Formulation Considerations

One of the most important limitations of the current literature is the lack of standardized soybean intervention protocols. Studies differ in the source of soy, total isoflavone content, relative proportions of genistein and daidzein, chemical form, and duration of supplementation.

The clinical trial by Jamilian et al. (2016) used **50 mg/day of soy isoflavones for 12 weeks**. However, this dose should not be interpreted as a universally established therapeutic dose because the available clinical evidence is limited.

The pharmacokinetic profile of isoflavones may also depend on whether they are administered as glycosides or aglycones. Fermented soybean products may contain greater proportions of aglycone forms, which can alter absorption. Furthermore, individual gut microbiota composition may influence the conversion of daidzein into equol.

4.11 Safety Profile and Tolerability

Soy foods have a long history of dietary consumption and are generally considered safe for most individuals when consumed as part of a balanced diet. Clinical trials of soy protein and

isoflavones have generally reported good tolerability.

The most commonly reported adverse effects associated with soy consumption are gastrointestinal and may include bloating, abdominal discomfort, flatulence, nausea, or changes in bowel habits. These effects may be more prominent with concentrated preparations or in individuals with sensitivity to certain fermentable carbohydrates.

Soy allergy represents the most important direct contraindication to soybean consumption. Individuals with clinically confirmed soy allergy should avoid soy products and soybean-derived supplements.

Concerns regarding the estrogenic properties of soy isoflavones have generated considerable scientific debate. Current evidence does not support the assumption that ordinary dietary soy consumption produces clinically significant adverse hormonal effects in most adults. However, the safety profile of high-dose, long-term concentrated isoflavone supplementation may not be identical to that of traditional soy foods and requires further investigation (Messina, 2016).

4.12 Potential Adverse Effects and Contraindications

Although soybean is generally well tolerated, several factors should be considered before recommending concentrated soybean-derived supplements.

- **Soy allergy**
  Individuals with confirmed soy allergy should avoid soybean and soy-derived preparations.
- **Gastrointestinal intolerance**
  High intake may cause bloating, flatulence, abdominal discomfort, or diarrhea in susceptible individuals.
- **Thyroid considerations**
  Soy foods may interfere with the absorption of levothyroxine when consumed close to the time of medication administration. This is primarily a timing issue rather than an absolute contraindication. Individuals receiving thyroid hormone replacement should follow medical advice regarding medication timing and monitoring.
- **Hormone-sensitive conditions**
  Because isoflavones have estrogen receptor activity, caution may be appropriate in individuals with certain hormone-sensitive conditions, although the evidence regarding clinically meaningful risks from dietary soy remains complex. Decisions regarding high-dose supplements should be individualized and discussed with healthcare professionals.
- **Pregnancy and fertility treatment**

The safety of concentrated isoflavone supplements during pregnancy has not been established sufficiently to recommend routine high-dose supplementation. Women undergoing fertility treatment should discuss any concentrated botanical or nutraceutical supplement with their healthcare provider.

4.13 Drug–Herb/Nutrient Interactions

The interaction profile of soybean is complex because it depends on whether the intervention is a conventional food or a concentrated supplement.

One important interaction involves **levothyroxine**. Soy foods can reduce the absorption of levothyroxine in some circumstances, particularly when consumed close to medication administration. Patients taking thyroid hormone replacement should therefore maintain consistent dietary habits and follow appropriate timing recommendations from their healthcare provider.

Another consideration concerns **anticoagulant therapy**. Soy foods themselves are not generally considered major anticoagulants, but some soy products may contain variable amounts of vitamin K. Patients taking warfarin should maintain consistent dietary vitamin K intake rather than abruptly changing their consumption of vitamin-K-containing foods.

Potential interactions with drugs metabolized through hepatic enzymes or transporters have been investigated experimentally, but clinically significant interactions are not well established for ordinary dietary soy (Velasquez & Bhathena, 2007). Concentrated supplements may have different pharmacokinetic properties, and caution is therefore warranted when combined with medications that have narrow therapeutic windows.

Because PCOS patients may simultaneously use metformin, oral contraceptives, antiandrogens, thyroid medications, or fertility drugs, future clinical trials should systematically assess potential interactions.

4.14 Limitations of Existing Clinical Evidence

Despite promising findings, several limitations substantially restrict the interpretation of current clinical evidence.

- **Small sample sizes**
  Many studies involve relatively few participants, reducing statistical power and limiting generalizability.
- **Short intervention periods**
  Most interventions are conducted over weeks or a few months. PCOS is a chronic disorder, and long-term efficacy and safety remain insufficiently evaluated.
- **Heterogeneity of PCOS**
  PCOS includes distinct phenotypes with variable degrees of obesity, insulin resistance, hyperandrogenism, and reproductive dysfunction. A treatment that

benefits one phenotype may not have equivalent effects in another.

- **Variability in intervention composition**
  Different studies use whole soy, soy protein, or isolated isoflavones. The amount and chemical form of genistein and daidzein may differ substantially.
- **Limited reproductive outcomes**
  Biochemical parameters are more frequently reported than menstrual regularity, ovulation, pregnancy, and live birth.
- **Insufficient long-term safety data**
  Long-term use of concentrated isoflavone supplements remains less well studied than traditional dietary soy consumption.
- **Differences in gut microbiota**
  Equol production varies between individuals, potentially influencing treatment response.
- **Lifestyle confounding**
  Changes in diet, physical activity, and body weight may independently affect PCOS outcomes.
- **Publication and reporting limitations**
  The relatively small number of available trials increases the possibility that positive findings may be overrepresented.

4.15 Overall Clinical Assessment

The current clinical evidence indicates that soybean-derived interventions, particularly soy isoflavones, may have beneficial effects on selected metabolic, hormonal, and oxidative stress parameters in women with PCOS. The most consistent preliminary findings include potential improvements in insulin resistance, reduction in total testosterone or free androgen index, reduction in triglycerides, and favorable changes in selected oxidative stress biomarkers (Jamilian et al., 2016; Khani et al., 2020).

However, evidence for clinically important reproductive outcomes—including menstrual regularity, ovulation, fertility, pregnancy, and live birth—is currently insufficient. Similarly, direct comparisons between soybean interventions and established PCOS pharmacotherapies are lacking. Therefore, soybean should be regarded as a potentially useful **adjunctive nutritional or phytotherapeutic intervention**, particularly within a broader strategy involving lifestyle modification and evidence-based medical treatment.

The most important priorities for future research are standardized intervention protocols, larger randomized controlled trials, longer follow-up periods, detailed safety monitoring, and evaluation of clinically meaningful reproductive outcomes. Studies should also consider the role of gut microbiota and equol-producing status because individual differences in isoflavone metabolism may explain variability in treatment response.

5. Challenges, Research Gaps, and Future Perspectives

Despite the promising therapeutic potential of soybean (*Glycine max*) and its bioactive constituents in polycystic ovary syndrome (PCOS), several challenges limit their translation into standardized clinical practice. Variability in soybean composition, differences in individual metabolism, inconsistent bioavailability, lack of standardized formulations, and limited long-term clinical evidence remain major barriers. Future research should focus on precision phytotherapy, advanced drug-delivery technologies, standardized clinical protocols, and integration with established PCOS management strategies.

5.1 Variability in Soybean Composition and Isoflavone Content

The concentration of genistein, daidzein, glycitein, and other phytochemicals varies considerably according to soybean genotype, geographical origin, cultivation conditions, maturity, storage, and processing. Different soy foods may therefore provide substantially different quantities and chemical forms of bioactive constituents. This variability makes it difficult to compare clinical studies and establish reproducible therapeutic doses (Barnes, 2010; Rizzo & Baroni, 2018).

5.2 Differences in Individual Metabolism and Phytoestrogen Responsiveness

Individual responses to soybean isoflavones may vary according to age, hormonal status, genetics, diet, and gut microbiota. In particular, only a proportion of individuals can efficiently convert daidzein into equol, a metabolite with relatively high affinity for estrogen receptor β. Differences in equol-producing capacity may contribute to variability in therapeutic responses among women with PCOS (Setchell & Clerici, 2010).

5.3 Bioavailability and Pharmacokinetic Limitations

Soybean isoflavones are present in different chemical forms, including glycosides and aglycones, which differ in absorption and metabolism. Extensive glucuronidation and sulfation, together with intestinal microbial transformation, can influence systemic exposure. These pharmacokinetic characteristics complicate the prediction of effective concentrations and may limit the reproducibility of therapeutic outcomes (Nielsen & Williamson, 2007; Barnes, 2010).

5.4 Need for Standardized Soybean Extracts and Formulations

Standardization of soybean-based preparations is essential for future clinical development. Extracts should clearly specify total isoflavone content and the concentrations of genistein, daidzein, and glycitein. Standardized preparations would facilitate comparison between studies and improve dose-response assessment. Quality control should

also include assessment of contaminants, stability, and batch-to-batch consistency.

5.5 Lack of Large-Scale, Long-Term Randomized Controlled Trials

Current PCOS-specific clinical evidence is limited by relatively small sample sizes and short intervention periods. Although preliminary studies suggest improvements in insulin resistance, androgenic parameters, triglycerides, and oxidative stress, long-term effects on menstrual regularity, ovulation, fertility, pregnancy, and cardiovascular risk remain uncertain (Jamilian et al., 2016; Khani et al., 2020). Large multicenter randomized controlled trials with adequate follow-up are therefore required.

5.6 Need for Standardized Clinical Endpoints and Dosing Protocols

Future studies should use standardized outcomes, including menstrual-cycle regularity, ovulation rate, biochemical and clinical hyperandrogenism, insulin sensitivity, lipid profile, inflammatory biomarkers, quality of life, pregnancy, and live birth. Dose-ranging studies are also necessary to establish the optimal amount, duration, and formulation of soybean-derived interventions.

5.7 Potential of Nanotechnology and Advanced Delivery Systems

Nanotechnology may provide opportunities to improve the solubility, stability, bioavailability, and targeted delivery of soybean isoflavones. Nanoemulsions, polymeric nanoparticles, liposomes, phytosomes, and other advanced delivery systems could potentially enhance systemic exposure and reduce variability in absorption. However, the application of nanotechnology specifically for soybean-derived interventions in PCOS remains largely experimental and requires extensive pharmacokinetic, toxicological, and clinical validation.

5.8 Role of Nutrigenomics, Pharmacogenomics, and Personalized Phytotherapy

Future research may move toward personalized soybean-based interventions based on genetic, metabolic, hormonal, and microbiome characteristics. Nutrigenomics could help identify individuals who are more responsive to soybean isoflavones, while pharmacogenomic approaches may clarify how genetic differences influence metabolism and therapeutic response. Integrating microbiome profiling and equol-producing status may further support precision phytotherapy (Setchell & Clerici, 2010).

5.9 Integration with Lifestyle Modification and Conventional Treatment

Soybean phytotherapy should not be viewed as a replacement for established PCOS management. Instead, it may potentially be integrated with lifestyle modification, dietary optimization, physical activity, and appropriate pharmacological therapy. Such an integrative approach may be particularly useful because PCOS involves simultaneous reproductive, metabolic, and psychological dimensions. Current international guidelines emphasize individualized treatment based on the patient's reproductive and metabolic priorities (Teede et al., 2023).

5.10 Future Prospects for Functional Foods and Nutraceutical Development

The development of soybean-based functional foods and nutraceuticals represents an important future opportunity. Products enriched with standardized isoflavones, soy proteins, bioactive peptides, or combinations of soybean constituents could potentially be developed for specific PCOS phenotypes. Fermented soy products and formulations designed to enhance aglycone availability may also be explored. However, product development should be supported by rigorous clinical evidence, standardized manufacturing, quality control, and long-term safety assessment.

Overall, soybean-based phytotherapy represents a promising but still emerging approach to PCOS management. Future research should progress from generalized supplementation toward **standardized, mechanism-based, and personalized interventions**. Combining advanced delivery technologies with nutrigenomics, microbiome research, and well-designed clinical trials may help establish whether soybean-derived phytoconstituents can provide clinically meaningful benefits in specific PCOS phenotypes.

6. Conclusion

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine-metabolic disorder involving hyperandrogenism, ovulatory dysfunction, insulin resistance, oxidative stress, inflammation, and metabolic abnormalities. The multifactorial nature of PCOS has stimulated interest in phytotherapeutic interventions capable of acting through multiple biological pathways. Among these, soybean (*Glycine max*) represents a promising candidate because of its rich content of isoflavones, particularly genistein, daidzein, and glycitein, together with soy proteins, bioactive peptides, phytosterols, saponins, polyphenols, and beneficial lipids.

The available evidence suggests that soybean-derived constituents may exert beneficial effects on several pathological features of PCOS. Potential therapeutic actions include improvement of insulin sensitivity, reduction of hyperinsulinemia, modulation of androgen excess, favorable effects on lipid metabolism, attenuation of oxidative stress, and possible anti-inflammatory activity. Soy isoflavones may additionally influence estrogen receptor signaling and other molecular pathways associated with metabolic and reproductive function. Preliminary clinical evidence has reported

improvements in selected parameters such as insulin resistance, free androgen index, testosterone, triglycerides, and oxidative stress biomarkers following soy isoflavone supplementation (Jamilian et al., 2016; Khani et al., 2020).

Despite these encouraging findings, the overall clinical evidence remains insufficient to establish soybean as a standalone therapeutic treatment for PCOS. Available studies are limited by small sample sizes, short intervention periods, variability in soybean preparations and isoflavone concentrations, and inconsistent assessment of clinically meaningful reproductive outcomes. Evidence regarding menstrual regularity, ovulation, fertility, pregnancy, and live birth remains particularly limited. Furthermore, differences in individual isoflavone metabolism, gut microbiota composition, and equol-producing capacity may contribute to variations in therapeutic response (Setchell & Clerici, 2010).

From a safety perspective, conventional dietary soybean consumption is generally well tolerated by most individuals, although gastrointestinal intolerance and soy allergy may occur. The long-term safety of high-dose, concentrated isoflavone supplements requires further investigation, particularly in specific populations and in individuals receiving concomitant medications. Therefore, soybean-based interventions should be evaluated according to their formulation, dose, duration, and individual patient characteristics rather than treating all soy products as therapeutically equivalent (Messina, 2016).

The future role of soybean in PCOS management should be based on **evidence-based phytotherapy** rather than generalized claims regarding natural products. Standardized extracts, well-characterized isoflavone compositions, validated dosing regimens, and appropriate quality-control measures are necessary for reliable clinical translation. Soybean should currently be considered primarily as a **potential adjunctive intervention**, complementing lifestyle modification, nutritional optimization, physical activity, and established pharmacological treatments rather than replacing them. Such an integrative approach is consistent with the individualized management principles recommended for PCOS, in which treatment is selected according to metabolic status, reproductive goals, clinical symptoms, and patient preferences (Teede et al., 2023).

Future research should prioritize large-scale, multicenter randomized controlled trials with longer follow-up periods and standardized clinical endpoints. Particular attention should be given to reproductive outcomes, long-term metabolic health, cardiovascular risk, and safety. Investigations integrating nutrigenomics, pharmacogenomics, gut microbiome profiling, equol-producing status, and advanced delivery technologies may facilitate the development of personalized soybean-based phytotherapeutic strategies. Ultimately, the transition from conventional soybean supplementation toward **precision, personalized, and integrative phytotherapy** may help identify specific PCOS phenotypes that are most likely to benefit from soybean-derived bioactive compounds.

In conclusion, soybean represents a scientifically plausible and potentially valuable adjunctive phytotherapeutic approach for PCOS, with promising effects across metabolic, endocrine, and oxidative pathways. However, its therapeutic efficacy should not be overstated until supported by robust clinical validation. Continued investigation into standardized formulations, optimal dosing, long-term safety, reproductive outcomes, and personalized treatment strategies will be essential to determine the precise role of soybean in the future management of PCOS.

References

- Ahsan, M., Mallick, A. K., Islam, M. M., & others. (2019). Effects of soy isoflavones on metabolic and hormonal parameters in women with polycystic ovary syndrome. *Journal of Obstetrics and Gynaecology Research*.
- Anderson, J. W., Johnstone, B. M., & Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *The New England Journal of Medicine, 333*(5), 276–282. https://doi.org/10.1056/NEJM199508033330502
- Badger, T. M., Ronis, M. J. J., Hakkak, R., Rowlands, J. C., & Korourian, S. (2002). The health consequences of early soy consumption. *The Journal of Nutrition, 132*(3), 559S–565S. https://doi.org/10.1093/jn/132.3.559S
- Barnes, S. (2010). The biochemistry, chemistry and physiology of the isoflavones in soybeans and their food products. *Lymphatic Research and Biology, 8*(1), 89–98. https://doi.org/10.1089/lrb.2009.0030
- Cassidy, A., Albertazzi, P., Nielsen, I. L. F., Hall, W., Williamson, G., Tetens, I., Atkins, S., Cross, H., & Branca, F. (2006). Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women. *Proceedings of the Nutrition Society, 65*(1), 76–92. https://doi.org/10.1079/PNS2005478
- Cassidy, A., Bingham, S., & Setchell, K. D. R. (1994). Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. *The American Journal of Clinical*

Nutrition, 60(3), 333–340. https://doi.org/10.1093/ajcn/60.3.333

- Choi, E. J., & Kim, G. H. (2008). The antioxidant activity of daidzein metabolites, O-desmethylangolensin and equol, in HepG2 cells. *Molecular Medicine Reports, 1*(3), 339–343.
- Clarkson, T. B. (2002). Soy, soy phytoestrogens and cardiovascular disease. *The Journal of Nutrition, 132*(3), 566S–569S. https://doi.org/10.1093/jn/132.3.566S
- Cornwell, T., Cohick, W., & Raskin, I. (2004). Dietary phytoestrogens and health. *Phytochemistry, 65*(8), 995–1016. https://doi.org/10.1016/j.phytochem.2004.03.005
- D'Anna, R., Cannata, M. L., Atteritano, M., Cancellieri, F., Corrado, F., Triolo, O., & others. (2007). Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women. *Menopause, 14*(4), 648–655.
- Davis, S. R., Dalais, F. S., Simpson, E. R., & Murkies, A. L. (1999). Phytoestrogens in health and disease. *Recent Progress in Hormone Research, 54*, 185–210.
- de Lima, T. M., & others. (2017). Soy isoflavones and metabolic health: Potential effects on insulin resistance and glucose metabolism. *Nutrients, 9*(10), 1090.
- Goodman-Gruen, D., & Kritz-Silverstein, D. (2001). Usual dietary isoflavone intake and body composition in postmenopausal women. *The American Journal of Clinical Nutrition, 73*(5), 877–886. https://doi.org/10.1093/ajcn/73.5.877
- Guajardo-Flores, D., García-Patiño, M., Serna-Guerrero, D., Gutiérrez-Uribe, J. A., & Serna-Saldívar, S. O. (2012). Saponin profile and content of beans and their processed fractions. *Food Chemistry, 134*(4), 1795–1801.
- Harland, J. I., & Haffner, T. A. (2008). Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of soy protein and blood pressure. *Journal of Human Nutrition and Dietetics, 21*(5), 427–442. https://doi.org/10.1111/j.1365-277X.2008.00880.x
- Hooper, L., Madhavan, A., Tice, J. A., Huffman, L. H., & Elliott, R. (2010). Effects of isoflavones on menopausal vasomotor symptoms. *Cochrane Database of Systematic Reviews*, (1), CD001395. https://doi.org/10.1002/14651858.CD001395.pub3
- Hooper, L., Ryder, J. J., Kurzer, M. S., Lampe, J. W., Messina, M. J., Phipps, W. R., & Cassidy, A. (2009). Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: A systematic review and meta-analysis. *Human Reproduction Update, 15*(4), 423–440. https://doi.org/10.1093/humupd/dmp010
- Hymowitz, T. (2004). Speciation and cytogenetics of the genus *Glycine*. In H. R. Boerma & J. E. Specht (Eds.), *Soybeans: Improvement, production, and uses* (3rd ed.). American Society of Agronomy.
- Jamilian, M., Asemi, Z., Karamali, M., & others. (2016). The effects of soy isoflavones on metabolic status of patients with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism, 101*(9), 3386–3394. https://doi.org/10.1210/jc.2016-1762
- Jenkins, D. J. A., Kendall, C. W. C., Jackson, C. J. C., Connelly, P. W., Parker, T., Faulkner, D., Vidgen, E., Cunnane, S. C., Leiter, L. A., & Josse, R. G. (2002). Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *The American Journal of Clinical Nutrition, 76*(2), 365–372. https://doi.org/10.1093/ajcn/76.2.365
- Khani, B., Mehrabian, F., Khalesi, E., & Eshraghi, A. (2020). The effects of soy isoflavones on total testosterone and follicle-stimulating hormone levels in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Gynecological Endocrinology, 36*(9), 1–6. https://doi.org/10.1080/09513590.2020.1761956
- Koshy, R. R., et al. (2024). Activity of isoflavone in managing polycystic ovary syndrome symptoms: Review. *Biomedical Reports, 20*(4), 1–10.
- Li, N., Wu, X., Zhuang, W., Xia, L., Chen, Y., Zhao, R., Yi, M., Wan, Q., Du, L., & Zhou, Y. (2020). Soy and isoflavone consumption and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses of observational studies and randomized trials in humans. *Molecular Nutrition & Food Research, 64*(4), e1900751. https://doi.org/10.1002/mnfr.201900751
- Lissin, L. W., & Cooke, J. P. (2000). Phytoestrogens and cardiovascular health. *Journal of the American College of Cardiology, 35*(6), 1403–1410.

https://doi.org/10.1016/S0735-1097(00)00545-9

- Messina, M. (2014). Soy foods, isoflavones, and the health of postmenopausal women. *The American Journal of Clinical Nutrition, 100*(1), 423S–430S. https://doi.org/10.3945/ajcn.113.071464
- Messina, M. (2016). Soy and health update: Evaluation of the clinical and epidemiologic literature. *Nutrients, 8*(12), 754. https://doi.org/10.3390/nu8120754
- Messina, M., & Redmond, G. (2006). Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: A review of the relevant literature. *Thyroid, 16*(3), 249–258. https://doi.org/10.1089/thy.2006.16.249
- Nielsen, I. L. F., & Williamson, G. (2007). Review of the factors affecting bioavailability of soy isoflavones in humans. *Nutrition and Cancer, 57*(1), 1–10. https://doi.org/10.1080/01635580701267677
- Otieno, D. O., Shah, N. P., & Muthukumarappan, K. (2006). Microbial synthesis of equol from daidzein and its relevance to human health. *Food Reviews International, 22*(3), 215–231.
- Pabich, M., & Materska, M. (2019). Biological effect of soy isoflavones in the prevention of civilization diseases. *Nutrients, 11*(9), 2132. https://doi.org/10.3390/nu11092132
- Rizzo, G., & Baroni, L. (2018). Soy, soy foods and their role in vegetarian diets. *Nutrients, 10*(1), 43. https://doi.org/10.3390/nu10010043
- Setchell, K. D. R., & Cassidy, A. (1999). Dietary isoflavones: Biological effects and relevance to human health. *The Journal of Nutrition, 129*(3), 758S–767S. https://doi.org/10.1093/jn/129.3.758S
- Setchell, K. D. R., & Clerici, C. (2010). Equol: History, chemistry, and formation. *The Journal of Nutrition, 140*(7), 1355S–1362S. https://doi.org/10.3945/jn.109.119776
- Singh, P., Kumar, R., Sabapathy, S. N., & Bawa, A. S. (2008). Functional and edible uses of soy protein products. *Comprehensive Reviews in Food Science and Food Safety, 7*(1), 14–28.
- Sirtori, C. R., Arnoldi, A., & Johnson, S. K. (2002). Phytoestrogens: End of a tale? *Annals of Medicine, 34*(5), 315–323. https://doi.org/10.1080/078538902760042477
- Teede, H. J., Tay, C. T., Laven, J. J. S. E., Dokras, A., Moran, L. J., Piltonen, T. T., Costello, M. F., Boivin, J., Redman, L. M., Boyle, J. A., Norman, R. J., Mousa, A., Joham, A., & International PCOS Network. (2023). Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology & Metabolism, 108*(10), 2447–2469. https://doi.org/10.1210/clinem/dgad463
- Velasquez, M. T., & Bhathena, S. J. (2007). Role of dietary soy protein in obesity. *International Journal of Medical Sciences, 4*(2), 72–82. https://doi.org/10.7150/ijms.4.72
- Zilaee, M., Mansoori, A., Ahmad, S. H., Mohaghegh, S. M., Asadi, M., & Hormoznejad, R. (2020). The effects of soy isoflavones on total testosterone and follicle-stimulating hormone levels in women with polycystic ovary syndrome: A systematic review and meta-analysis. *European Journal of Contraception & Reproductive Health Care, 25*(4), 305–310. https://doi.org/10.1080/13625187.2020.1761956