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SHORT REVIEW

Flavonoids and Their Potential in Alleviating PCOS Symptoms: A Thorough Review

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Abstract

Polycystic Ovary Syndrome (PCOS) is marked by morphological changes, ovulatory dysfunction and elevated androgen levels. One of the main factors that can lead to PCOS is hyperandrogenism. PCOS impairs follicle growth, which results in ovulatory dysfunction, PCOM, and follicular arrest. Follicle growth is a process that requires Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) coordination. In PCOS, alterations in FSH and LH levels hinder follicular development and result in anovulation. The Rotterdam criterion is used to determine the condition when two of the three features are present and other etiologies are eliminated. When diagnosing PCOS, several parameters should be considered, such as the ovarian USG, FAI level, and the LH/FSH ratio. Flavonoid intake has been demonstrated to have positive impacts on the daily diet and help in lowering the risk of chronic metabolic disorders. The study examines the mechanisms by which particular flavonoids have therapeutic effects in the management of PCOS and reviews recent scientific literature to assess the potential of flavonoids in reducing symptoms of PCOS, such as insulin resistance, oxidative stress, inflammation, and hormonal imbalance. The study contributes to the assessment of flavonoids' capacity to mitigate the symptoms of Polycystic Ovary Syndrome (PCOS). These symptoms include Oxidative Stress (OS), Insulin Resistance (IR), and hormonal imbalance. A few flavonoids that may be useful in the treatment of PCOS are the focus of this review paper.

Major Findings: Flavonoids can significantly reduce PCOS symptoms through multiple mechanisms. They help to manage hormonal imbalances by lowering androgen levels and improving the LH/FSH ratio. Flavonoids also improve insulin sensitivity, lower oxidative stress, and reduce inflammation. Animal studies indicate improved ovarian morphology and ovulation. Additionally, flavonoids help to improve lipid profiles. There is growing evidence that their multi-targeted activities may promote integrative therapy approaches and enhance current PCOS therapies.

Keywords: Dysfunction, Flavonoids, Hyperandrogenism, Management, Metabolic Syndrome

1. Introduction

PCOS is a gynaecological condition that impacts reproductive-aged women between 15-49 years[1]. PCOS occurrence in India varies from 9.13 to 36%. PCOS serves as the main cause of emotional issues and female infertility. Problems with fertility affect up to one-third of women with PCOS, and they experience more anxiety and depression compared to other women[2]. As a "syndrome," PCOS is a collection of four conditions known as "phenotypes", which have been combined due to several common clinical traits. There are four distinct phenotypes: (i) Oligo-anovulation PCOM (polycystic ovarian morphology); (ii) Androgen excess PCOM; (iii) Androgen excess Oligo-anovulation; and (iv) Androgen excess Oligo-anovulation PCOM[3,4]. By Rotterdam criteria, the condition is identified when two of three features are met: clinical indicators of polycystic ovaries and hyperandrogenism, oligo- or anovulation and exclusion of other etiologies[5]. One of the main factors that can lead to PCOS is hyperandrogenism (HA). Its overproduction by the ovaries or adrenal cortex causes skin-related issues (acne, hirsutism, androgenic alopecia), hypothalamic-pituitary-gonadal axis alterations, and problems with

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the regulation of ovarian folliculogenesis, which results in menstrual and fertility problems[6].

PCOS hinders follicle growth, which can result in ovulatory dysfunction, follicular arrest and PCOM. The complex process of follicle growth necessitates the appropriate synchronisation of FSH and LH, along with testosterone, estrogen and other possible factors[7]. Among women with PCOS, the extent of anxiety and depression ranges from 11 to 25% and 28 to 39%, respectively[2]. Indeed, based on the PCOS criteria employed and demographics of the studied populations, as much as 75% of PCOS women are obese, with increased central adiposity regardless of the underlying body mass index[8]. Oral contraceptive pills and lifestyle changes are first-line therapy for PCOS. The most successful first-line treatment approach is still lifestyle management, which includes reducing body weight or maintaining a normal weight[9].

Most PCOS women have high serum insulin and Insulin Resistance (IR) levels while having a high level of androgen and obesity[10]. According to the studies, this syndrome is characterised by low-grade chronic inflammation that exists simultaneously with obesity, IR, and compensatory hyperinsulinemia. Therefore, improving reproductive function and reducing IR are the two most crucial objectives of medical nutritional therapy for PCOS women[11]. Antiandrogens and insulin sensitisers are given to treat IR and hyperandrogenic problems. When it comes to treating irregular menstruation and hyperandrogenic signs in PCOS, oral contraceptives are believed to be the best option[12].

The polyphenolic structure of flavonoids, an essential family of natural compounds, is represented by a structure composed of two benzene rings (heterocyclic ring and two phenyl rings)[13]. Their chemical nature is determined by their class and structure, degree of polymerisation and hydroxylation, conjugations, and other substitutions. Different classes of flavonoids have different levels of oxidation and different substitution patterns in ring C. Individual compounds within flavonoid classes have different substitution patterns on rings A and B[14]. Flavonoids are found in fruits, seeds and plants and give them their colour, flavour and fragrance[15]. By limiting the enzymes' metabolic activity in pathways involved in the production of Reactive Oxygen Species (ROS), flavonoids promote the antioxidant system. It is important to note that

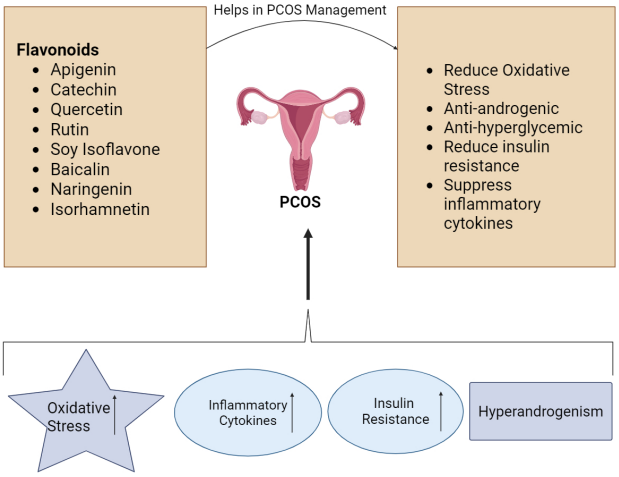


Figure 1. Role of flavonoids in reducing PCOS symptoms.

flavonoids' diverse structures allow them to interact with a vast array of biomolecules[16]. Over 8000 distinct flavonoids have been documented to date and mostly found in the surfaces or cells of different plant tissue organs[17]. The main key flavonoids that are used for the management of polycystic ovary syndrome have been mentioned in Table 1 (Figure 1).

2. Methodology

The search strategy employed for this study encompassed several databases, including PubMed, Scopus, Science Direct, Web of Science and Google Scholar. Key search items such as PCOS, Apigenin, Catechins, Quercetin, Rutin, Soy Isoflavone, Naringenin, Isorhamnetin, Baicalin and pharmacological approaches and variations of these terms were utilised to identify pertinent literature. This review paper highlights various flavonoids which help to reduce PCOS symptoms. Studies that were not directly related to these topics were filtered out using exclusion criteria. To ensure thorough coverage of the topic, expert opinions were sought, and the reference list of relevant articles was manually reviewed to supplement the database search.

3. Flavonoids

3.1 Apigenin

Formally a member of the flavone subclass, in plants, apigenin is the most prevalent flavonoid. The Asteraceae

family in plants, including those in the genera Achillea, Tanacetum, Artemisia and Matricaria, are its main source[18]. By mono-substituting apigenin at positions 4′, 5′, and 7′, distinct compounds can be formed, including (a) 4′-hydroxyflavone, (b) 5-hydroxyflavone, and 7-hydroxyflavone[19]. The biological effects of apigenin include antiviral, anti-inflammatory, anti-cancer, purgative, and antioxidant properties. Apigenin is an essential contributor to the considerable alteration in pituitary ovarian axial hormone levels that occur in PCOS because of its higher antioxidant capacity[20]. Apigenin is largely metabolised by glucuronidation and sulfation processes and is primarily absorbed in the small intestine. It is present in plants as a polymer or as O- and C-glucosides[21]. Apigenin reduced IR, hyperglycemia, and hyperinsulinemia while decreasing plasma levels of cytokines and chemokines. Apigenin also enhanced glucose metabolism by inhibiting the activities of hepatic gluconeogenic enzymes[22].

Although apigenin lacks a hydroxyl group at the third position and a catechol structure in the B-ring, the double bond at the 2, 3 carbon enhances the reactivity of its structure, making apigenin a suitable antioxidant[23]. Apigenin may suppress Oxidative Stress (OS) by lowering the total oxidative state and boosting the total antioxidant capacity along with the activity of Superoxide Dismutase (SOD), nicotinamide adenine dinucleotide phosphate and Glutathione Reductase (GR). So, apigenin helped to restore the pleura of follicles, increase healthy follicles, and regenerate ovarian tissue[24]. Antidiabetic, anti-inflammatory, and anti-obesity characteristics of apigenin were investigated in various studies; still, the long-lasting additional impacts of flavonoids on obesity at low amounts remain unknown[25]. By blocking cluster of differentiation 38 (CD38) and lowering protein acetylation, apigenin increased the amount of nicotinamide adenine dinucleotide (NAD+) in the liver of obese mice in a study. Accordingly, apigenin seems to be a CD38 inhibitor that could be employed as a potentially effective treatment approach for metabolic syndrome by activating Sirtuin-1(SIRT1) and NAD+[26].

In another study, rats given dehydroepiandrosterone (DHEA) experienced an increase in ovarian diameter and cysts along with alterations in their lipid levels. Progesterone level increased, and estradiol and testosterone levels decreased in PCOS rats following apigenin administration[27]. Furthermore, apigenin, a flavonoid, has a selective effect on the estrogen receptor-β (ERβ), which will aid in increasing the ovulatory cycles[28]. Apigenin consumption is mostly determined by lifestyle choices, with estimates ranging from 3.4 to 26 mg/day across various countries. Apigenin must be consumed in its pure form with ideal release kinetics in order to produce therapeutic benefits[29].

3.2 Catechins

Many herbs and foods contain catechins, including apples, tea, cacao, grapes, persimmons, and berries[30]. Tea leaves contain significant amounts of catechins, which have potent antioxidants and physiologically significant properties. Among many different types of plants, they belong to the class of polyphenol compounds. *Camellia assumica* and *Camellia sinensis* (*C. sinensis*) are the main sources of catechins[31]. Native to Eastern Asia, *Camilla sinensis* leaves are used to make green tea. There are lower levels of epicatechin, gallocatechin, gallocatechin gallate, and epicatechin gallate, but (−)-epigallocatechin gallate (EGCG) is the main green tea catechin. The antioxidant potential of these compounds accounts for most of the health advantages of green tea[32]. Through direct methods, such as scavenging ROS and indirect processes, such as inhibiting pro-oxidant enzymes, activating antioxidant enzymes, catechins employ their antioxidant activity. The cycle of producing new radicals can be broken by phenolic hydroxyl groups of catechins reacting with ROS and reactive nitrogen species in a termination reaction[33]. Free radicals struggle for active oxygen as the activity of hydrogen on the phenolic hydroxyl group intensifies, thus halting the free radicals' auto-oxidation process[34].

Green tea contains catechins that are believed to have beneficial impacts against PCOS[35]. Because green tea inhibits the 5α-reductase enzyme with EGCG and suppresses the conversion of testosterone into dihydrotestosterone, it has a favourable effect on androgenism[27]. With an antioxidant potential of 25 times greater than vitamin E, EGCG is the most potent antioxidant[36]. Insulin-resistant hyperinsulinism affects about half of women with PCOS. Hyperinsulinism in PCOS is normalised by green tea or its derivatives. After taking green tea tablets, a clinical study found

that PCOS women who were overweight or obese had significantly lower fasting insulin levels[35].

Excess fat and sugar consumption is a major contributor to metabolic syndrome, and as levels of these substances rise in the blood, lipid storage in adipose tissue and liver accelerates due to dyslipidemia. By increasing glucose level in the blood, lipid deposits in hepatic tissue trigger the activation of immune cells that release inflammatory cytokines like interleukin 1 beta and tumour necrosis factor-alpha (TNF-alpha), which promote gluconeogenesis and glycogenolysis. It also starts IR and early diabetic symptoms[37]. Following nuclear factor-κB (NF-κB) activation, chemokine and cytokine formation contribute to the onset of diabetes. Catechins, gallic acid, epicatechin and proanthocyanidins found in grape seed extract can increase insulin sensitivity and macrophage infiltration in liver tissue as well as considerably reduce high-fat diet-induced plasma levels of TNF-α and interleukin-6 (IL-6) in obese mice[38]. In mice with insulin- and hCG-induced PCOS, oolong tea catechins reduced uterine inflammation, reversed abnormalities in ovarian morphology, and improved insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3-kinase (PI3K) signals[24].

3.3 Quercetin

Fruits and vegetables include quercetin, a flavonoid with special biological characteristics that could benefit mental and physical performance and lower the risk of health issues[39]. A three-carbon bridge connects two phenyl groups to form the basic flavonoid structure. The two primary classes of flavonoids are those with an "open" three-carbon bridge and those with a three-carbon bridge that is a part of a heterocyclic ring, or ring C[40]. When the quercetin chemical structure was examined, it was discovered that the polyphenol benzo-dihydropyran ring contains four hydroxyl groups. This indicates that quercetin has a potent antioxidant, helps to get rid of free radicals that the body generates and can help to maintain a stable state[41].

To reduce cellular OS, quercetin has also shown the capacity to trigger the antioxidative signalling pathway involving nuclear erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE)[42]. Intracellular oxidative or electrophilic stress activates the transcription factor Nrf2 that controls the expression of several genes encoding detoxification and antioxidant enzymes[43]. OS can separate Nrf2 from Nrf2-Keap1 complex and move it to the nucleus, where it connects with ARE to trigger the transcription of antioxidation-related genes[42].

By controlling the enzyme-mediated and non-enzyme-dependent antioxidant defence systems, as well as 5'-Adenosine Monophosphate-Activated Protein Kinase (AMPK), NRFB, Mitogen-Activated Protein Kinases (MAPK) and other signalling pathways triggered by ROS, quercetin may strengthen the antioxidant system and preserve oxidative equilibrium[44]. By controlling GSH levels, quercetin improves the antioxidant capability of the body. This is because SOD rapidly takes O2 and converts it into H2O2 when oxygen free radicals are formed in body. H2O2 is further broken down by this enzyme into the non-toxic H2O[45].

According to studies, IR affects between 50 and 70 per cent of PCOS patients. IR-induced hyperinsulinemia can impact follicle growth and development by reducing glycolysis, glucose consumption, and follicle energy supply[46]. In the PCOS model rats, quercetin could successfully lower blood lipid, serum insulin and HOMA-IR levels[47]. The hypoglycemic impact of quercetin is linked to insulin signal transduction, including increased tyrosine phosphorylation of the insulin receptor, protein expression, a number of glucose transporters (GLUTs) and IRS. Additionally, quercetin increases insulin secretion and glucose metabolism while also boosting the growth of pancreatic β-cells, resulting in the insulin-sensitising action[48]. Because quercetin mimics estrogen and acts as a phytoestrogen, it may reduce the signs of obesity and infertility associated with PCOS[47].

Quercetin is an anti-inflammatory agent. Both directly and indirectly, quercetin reduces inflammation. Preventing the gene expression and protein release of inflammatory factors, like TNF-α, NF-κB, and Extracellular Signal-Regulated Kinase (ERK), is the direct method. By inhibiting the cyclooxygenase (COX) and lipooxygenase, quercetin reduces mediators of inflammation like prostaglandins and leukotrienes[49]. By supporting the structural physiology and appropriate functioning of the reproductive system, quercetin is a well-known phytoestrogen and potent gonadotropin secretion stimulant. Following quercetin treatment,

ovarian morphology, folliculogenesis, and luteinisation all showed notable improvements, according to several histological findings[50].

3.4 Rutin

Rutin is mainly present in plants like apples, buckwheat, tea and passion flowers[51]. Because of its strong antioxidant characteristics, rutin appears to have a broad range of therapeutic uses. Traditionally, rutin has been utilised as an antiallergic, antifungal, and antimicrobial agent[52]. According to research, rutin treatment lowers blood glucose levels in PCOS patients because it has anti-hyperglycemic properties and lowers glycemic levels by boosting insulin secretion in the beta cells of Langerhans, which helps the cells absorb glucose. Rutin is a potent compound that can regulate blood sugar levels by boosting the function of the insulin-dependent receptor kinase. Consequently, activating the insulin signalling pathway improves migration of GLUT 4 onto the membrane and promotes glucose absorption[20].

Rutin may trigger the thermogenesis of adipose tissue because it lowers food intake, which in turn causes weight loss, which in turn triggers the thermogenesis of adipose tissue[53]. By likely lowering HMGCoA reductase activity, rutin decreased the lipid contents in the serum of hypercholesterolemic rats[54]. High Density Lipoprotein- Cholesterol (HDL-C) is a key player in transporting total cholesterol from various tissues within the body to the liver in regular physiological conditions, where it is metabolised to bile juice as a free sterol. These cellular processes raise HDL-C in the blood, which often results in lower cholesterol levels in the blood and peripheral tissues[55]. A high-cholesterol diet promotes hyperlipidemia and dyslipidemic syndrome, which is marked by a rise in total cholesterol and a fall in HDL-C[56].

Increased inflammatory cytokines may result from an insufficient or excessive inflammatory response[57]. Because of its antioxidant properties and/or activation of the ERK and PI3K/Akt pathways, rutin has been extensively utilised in studying its role in cardiovascular diseases, including diabetic cardiomyopathy, myocardial ischemia, and isoproterenol-induced myocardial infarction[58]. Anti-inflammatory and anti-carcinogenic effects are possessed by rutin. It helps with high cholesterol, atherosclerosis, osteoarthritis, haemorrhoids, infections, hypertension, chronic venous insufficiency, and stroke prevention[59].

3.5 Soy Isoflavone

Around the world, especially in Asia, soybeans and products are widely utilised as safe food items. Among the active substances found in soy products are isoflavones. Isoflavones, often known as phytoestrogens, have a similar physiological role to estrogen[60]. Plants mostly contain isoflavones as biologically inactive glycosides. When they are consumed, intestinal bacterial β-glucosidases hydrolyse them in the gut, producing the proper bioactive aglycones (for example, genistein, daidzein)[61]. Being lipophilic, isoflavones use the same metabolism and absorption mechanisms as other lipophilic substances. As a result, isoflavones absorbed in the intestine interact with chylomicrons to be distributed to every cell in the body via blood flow and lymph nodes[62]. It is widely recognised that isoflavones have antioxidant and anti-inflammatory actions. Studies on humans, along with *in vivo* and *in vitro* systems, have documented the antioxidant effects of isoflavones[63].

Soy isoflavones use in metabolic syndrome-related diseases is gaining interest. Studies on nutritional interventions in animal models and humans indicate that dietary isoflavones have beneficial impacts on symptoms of menopause, hyperlipidemia, coronary heart disease, various chronic renal diseases and osteoporosis. This interest is primarily based on the findings of epidemiological surveys [64]. Type-2 diabetes mellitus is significantly more probable to develop in PCOS females who have both insulin resistance and inadequate insulin[65]. According to preliminary findings from animal and human dietary intervention studies and epidemiological surveys, phytoestrogens may lower insulinemic and glycemic levels[66]. It appears that soy isoflavones also activate particular cellular signalling pathways through non-genomic control[67].

Numerous health benefits are associated with genistein, including osteoporosis prevention, decreased chances of cardiovascular disease, relief of postmenopausal symptoms and anticancer potential[68]. Soy-based foods and beverages are the most widely recognised sources of genistein. Mature soybeans have been found to contain genistein at levels varying from 5.6 to 276 mg/100 g; for comparison, an average of 81 mg/100 g has been observed[69]. By triggering serine

phosphorylation of IRS1, proinflammatory cytokines like TNF-α could disrupt insulin signalling. Reducing IR is a primary objective in PCOS, as it can exacerbate hyperandrogenism and cause other metabolic problems[70]. Due to its structural resemblance to estrogen, genistein is an important phytoestrogen and has been previously studied for its antioxidant, hypolipidemic, and estrogenic effects (genistein binds to estrogen receptors in different tissues, resulting in a mild estrogenic-like effect)[71].

By increasing the migration of GLUT4 to the cell membrane, genistein may enhance the absorption of glucose. The effects of genistein on IR have been attributed to PI3K, protein kinase C and AMPK pathways[70]. Studies conducted on rats and C2C12 myotube cells have shown that genistein can increase fatty acid oxidation in skeletal muscle, which activates the enzyme AMPK and improves insulin sensitivity. Remarkably, genistein additionally triggers pathways involved in the excretion of cholesterol and stimulates AMPK in mouse hepatocytes[72].

The imbalanced levels of FSH and LH hinder follicular development and result in anovulation. Furthermore, high LH levels cause increased release of estrogen and testosterone by inhibiting aromatase activity, leading to disruption of the sexual cycle and ovulation in PCOS[73]. The affinity of genistein for estrogen receptors, which are mostly found in ovarian and uterine tissue, is attributed to its anti-estrogenic properties. The lowering of testosterone in PCOS rats after treatment with genistein was presumably mediated by the suppression of aromatase activity mediated by estradiol components [74]. Phytoestrogens, particularly genistein found in soy food, are found in plant diets and traditional remedies. They have positive effects on female reproduction and lower testosterone levels in PCOS women. They affected the sex hormones and their receptors both directly and indirectly[75]. Genistein therapies have enormous potential; they use genistein's various actions, which are hormone receptor content-mediated, cell- and organ-specific and concentration-dependent, to enhance medical outlook for a wide array of women's health issues[76].

3.6 Baicalin

In the past few years, Baicalin has been utilised extensively for the preparation of pharmaceutical products for the treatment of specific disorders[77]. Baicalin quantity in S. baicalensis roots varied from 8.1% to 15.6%[78]. Baicalin has the potential to scavenge ROS and free radicals, suppress oxidase activity, and enhance the expression of detoxifying and antioxidant enzymes[79].

It is commonly recognised that AMPK acts as a cell's "energy sensor." IR and PCOS endocrine and reproductive function are both associated with AMPK dysfunction. For instance, by suppressing inflammation and enhancing insulin signalling transduction, AMPK may control insulin sensitivity and glucose homeostasis[80]. It is well known that the energy sensor AMPK regulates the metabolism of lipids and glucose. Several metabolic functions that undergo disruption due to diabetes are influenced by AMPK, according to evidence[81]. Baicalin reduced the symptoms of PCOS, such as inflammation, IR, histopathological alterations, and improper hormone release. Among these mechanisms, AMPK upregulation is linked to the favourable effect of baicalin[80].

Ageing and the external environment have an impact on the development of granulosa cells in ovarian follicles. This results in OS and high concentration of ROS in the granulosa cells, which causes inappropriate follicular growth and development[82]. Baicalin has antioxidant activity by neutralising ROS and anti-inflammatory properties by inhibiting the NF-κB pathway. This inhibits the expression of inflammatory mediators and reduces expression of lipoxygenases, COX-2, interleukins, TNF-α and cell adhesion molecules[83].

In PCOS women, IR specifically and simultaneously impacts the metabolism or mitotic pathways in both classical (like pituitary gland and ovary) and nonclassical (like liver, adipose tissue and skeletal muscle) insulin target tissues[84]. Early study on skeletal muscle (*in vivo*) and cultured myotubes and fibroblasts (*in vitro*) revealed a serine residue on the IRS 1/2 that was elevated in phosphorylate. This phosphorylation restricts the progression of signalling beyond this proximal protein, resulting in a decrease in glucose transporter 4 translocation and glucose uptake[85]. *In vitro* studies demonstrated that baicalin enhances the uptake of glucose by influencing GLUTs, promotes glycogen synthesis and increases sugar consumption, hence decreasing liver IR[86]. IL-6 and TNF-α are

proinflammatory cytokines produced by circulating mononuclear cells (MNC) and MNC-derived macrophages in tissue. Although IL-6 has a varying effect on IR, TNFα is a mediator of IR[87]. By lowering serum TNF-α level, baicalin treatment reduced systemic inflammatory stress and reduced IR[88].

3.7 Naringenin

Naringenin is a flavonoid, mostly present in various edible fruits, such as species, figs, citrus and tomatoes that belong to the smyrna-type *Ficus carica*[89]. With a MW of 272.25 g/mol, it is a hydrophobic molecule that dissolves in organic solvents[90]. From a pharmacological perspective, narigenin has a number of significant characteristics, including insulin-like effects, antioxidant, anti-inflammatory potential and a number of other characteristics like cardioprotective, anti-atherogenic, immunomodulatory, neuroprotective and hepatoprotective[91].

A balance between antioxidants and oxidants within the body is known as OS. To become stable, oxidants, which are extremely reactive and unstable, take electrons from other molecules that are antioxidants[92]. Significantly, OS is involved in the pathophysiology of several gynaecological issues such as endometriosis, PCOS, preeclampsia, and infertility[93]. Both by its structure and by activating the cell antioxidant system, naringenin can influence the balance of antioxidants within cells. According to reports, naringenin upregulates key antioxidant enzymes, including GST, GPx, catalase, and SOD[94]. In terms of its antioxidant properties, studies have suggested that narigenin could enhance mitochondrial membrane potential, decrease DNA damage and caspase-3/7 activity, and decrease lactate dehydrogenase leakage and production of ROS[95].

Obesity is one pathophysiological condition that dysregulates the adipose function and leads to the development of IR, dyslipidemia, and overt diabetes. Inflammatory cytokines, like IL-6 and TNF-α, are secreted by dysregulated adipocytes, which hinder the insulin action in peripheral tissues[96]. 65–78% of essential hypertension is caused by obesity, making it one of the main causes of hypertension. Weight loss is the main objective of treatment for obesity-associated hypertension[97]. Hypertension prevalence varies in the studied individuals and clinical manifestations of PCOS. It is yet unknown how obesity and ethnicity affect the occurrence of hypertension in PCOS[98]. By lowering blood pressure and body weight, naringenin helped treat obesity-related hypertension. Furthermore, naringenin controlled biomarkers linked to OS and serum lipid parameters triggered by a High-Fat Diet (HFD)[97].

Additionally, because polyphenols and steroids share structural similarities, naringenin might affect the steroidogenic enzymes that are altered in PCOS. Naringenin is a bioactive natural insulin sensitiser, which indicates that it may be useful in the treatment of PCOS[99]. PCOM results from ovarian dysfunction, which includes the overproduction of androgens and is related to abnormal growth of follicles and ovulatory dysfunction[100]. In addition to significantly reducing ovarian dysfunction, naringenin also has protective effects by managing serum sex hormones, enhancing intestinal barrier function, reducing intestinal problems and boosting the predominant flora in PCOS-like rats[101].

3.8 Isorhamnetin

Isorhamnetin is a secondary metabolite within the flavonoid family, specifically the flavonols[102.] The naturally occurring O-methylated flavonol isorhamnetin is a flavonoid that is the metabolite of quercetin[103]. IR seems to be unrelated to obesity and particularly linked with PCOS, with disturbances in the insulin action and receptor function having been recorded. As a co-gonadotropin, this intensifies the effects of the elevated LH stimulus observed in most women with PCOS, as well as a direct inducer of excess androgen synthesis by theca cells, hyperinsulinemia seems to play a significant role in maintaining hyperandrogenemia. Being linked to the central effects of androgen in compromising progesterone suppression of the GnRH pulse generator, the increased insulin may function in different ways[104]. IR is associated with insulin signalling defects, IRS-1/2, PI3K/AKT serine/threonine kinase, downstream of the insulin receptor and GLUT4[105]. Insulin resistance is triggered by inefficient glucose transportation, which is mediated by decreased skeletal muscle GLUT-4 protein expression and inhibition of GLUT4 translocation[106]. Ovarian IR prevents the ovaries of obese females from responding effectively to the

metabolic requirements required for maintaining the oocyte during the periovulatory duration, potentially leading to a decreased estrus phase[107]. Isorhamnetin can increase the expression of p-AMPK and GLUT4 in skeletal muscle, indicating that it can promote the uptake of glucose[106]. Pharmacological actions of isorhamnetin are associated with regulating the activity of downstream factors and signalling pathways, including NF-κB, MAPK and PI3K/AKT[108].

Inflammation is recognised as a key risk factor for PCOS, due to the interaction of inflammatory indicators in the PCOS ovary. TNF-α levels in PCOS women were higher than those in healthy controls, according to a meta-analysis[109]. TNF α overexpression in adipose tissue leads to IR by acute and chronic effects on insulin-sensitive tissues. Adipose tissue in obese people is probably the reason for high circulating TNF α in PCOS, but it is unknown in lean women with the disorder. However, in lean women with PCOS, excess TNF α may be triggered by increased visceral obesity[110]. In the rat model of PCOS, isorhamnetin inhibits the inflammatory response. By inhibiting the TNF signalling system, isorhamnetin minimises the ovarian damage that results from PCOS[109].

4. Drawbacks associated with the current treatment options available for PCOS

Insulin-sensitising medications can help reduce PCOS symptoms. Pioglitazone is a thiazolidinedione that activates PPAR-γ. Pioglitazone works primarily by boosting peripheral glucose absorption, modulating adipogenesis, and insulin action. It has been shown to improve insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with PCOS.

Table 1. Key Flavonoids used in Polycystic Ovary Syndrome with their pharmacological effect

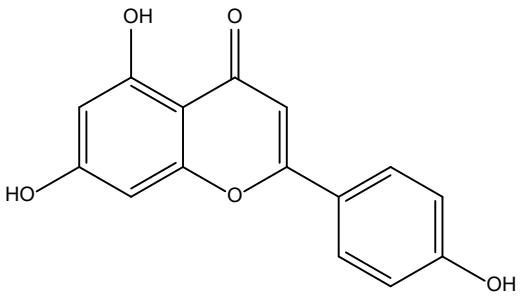
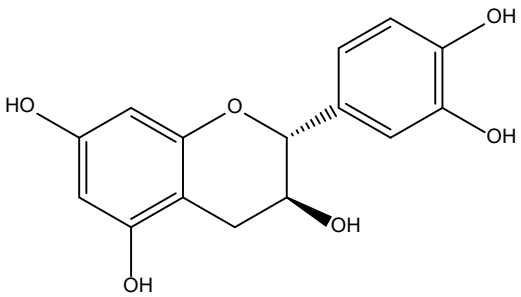
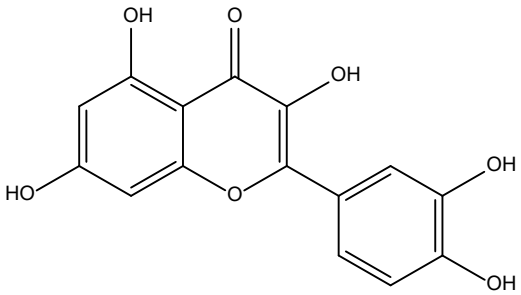
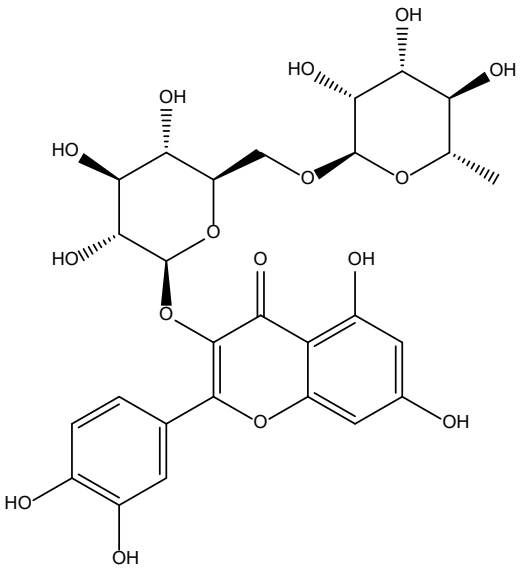
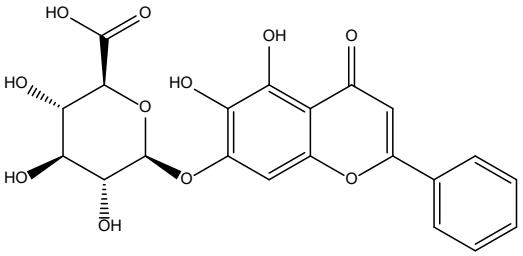
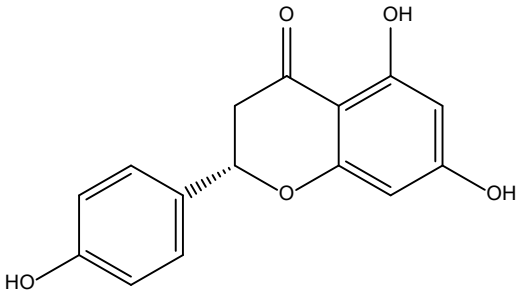
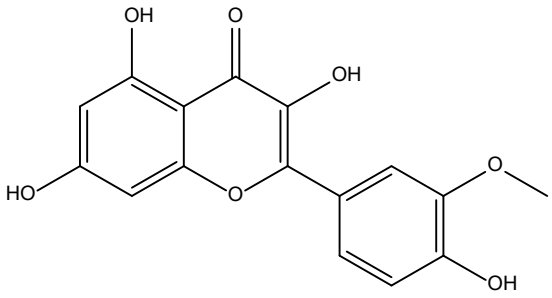
Flavonoids	Structure	Activity	References
Apigenin		Minimise oxidative stress, increase the healthy follicles, and restore the pleura of follicles.	115
Catechins		Catechins improve uterine function in PCOS mice, suppress MMP9 and MMP2-mediated endometrial damage, and upregulate IRS1/PI3K expression.	124
Quercetin		Favourable impacts on glucose uptake, hormone indices, and lipid levels, as well as significant antioxidant properties.	125

Table 1. (*Continued*)

Flavonoids	Structure	Activity	References
Rutin		Anti-androgenic, anti-hyperglycemic actions, ovarian cyst recovery, and hormonal profile and ovarian function restoration. Lowering lipid peroxidation and ROS while increasing antioxidant status.	126
Baicalin		Reduced the symptoms of PCOS, such as inflammation, IR, histopathological alterations, and abnormal hormone release.	80
Naringenin		Eliminated ovarian follicular cysts, restores normal androgen levels, and maintains primordial and primary follicles as well as the corpus luteum.	99
Isorhamnetin		Inhibit the apoptosis of ovarian tissues, reduce the TNF signalling pathway	109

Despite pioglitazone's beneficial effect on metabolic parameters in PCOS, there is significant concern regarding the possibility of congestive heart failure and pulmonary oedema due to fluid retention. While the absolute risk is low in young women with PCOS, thiazolidinediones may cause weight gain in obese women with PCOS. Metformin, a biguanide, is both safe and effective. Metformin has long been used to treat

type 2 diabetes, and it is one of the insulin-sensitising medications most widely used in the treatment of PCOS. Common adverse effects of metformin include nausea, vomiting, diarrhoea, and abdominal bloating. There has also been evidence that long-term metformin use can lead to vitamin B12 deficiency. As a result of metformin intolerance and its related side effects, it is crucial to examine other therapeutic options for the treatment of metformin-intolerant women with PCOS[111]. Hormonal contraceptives, whether oral, patch, or vaginal, typically include an estrogen (ethinyl estradiol or estradiol valerate) and a progestin. Their activity is mediated by decreasing gonadotropin secretion, and hence ovarian androgen secretion, boosting SHBG synthesis, and lowering total and free circulating androgen levels. Combined Oral Contraceptives (COCs) may improve the clinical and biochemical picture of hyperandrogenism, as well as some metabolic aspects such as cholesterol and fat distribution alterations, but they can also have side effects that must be considered, particularly in PCOS women with metabolic and cardiovascular risk factors. COCs also aggravate the inflammatory condition in these patients, which is most likely due to elevated aldosterone-renin ratio and C-reactive protein. Aldosterone is known to be the primary proinflammatory hormone, and unfortunately, the use of COCs boosts angiotensinogen production and activates the Renin-Angiotensin-Aldosterone System (RAAS). As a result, these patients typically complain of fluid retention, hypertension (which is more common in PCOS women), increased insulin resistance, weight gain, and depression. Another common side effect of long-term contraceptive use is amenorrhea after withdrawal of the contraceptive. It is widely recognised that the beneficial effect of COCs on hyperandrogenism necessitates a sufficient duration of therapy, and in many cases, post-contraceptive hypothalamic amenorrhea develops. The most often used antiandrogens are cyproterone acetate, spironolactone, finasteride, and flutamide. As a result, all of the suggested medications contain antiandrogenic properties; however, the potential adverse effects of each treatment are usually overlooked. Finasteride and dutasteride inhibit the 5 alpha reductase, reducing the action of androgens by preventing their conversion to DHT. Recently, this medication has been linked to severe disorders, with some authors emphasising post-finasteride syndrome since the medicine would also affect brain neurosteroids, which are required for the functioning of specific regions in the cerebral cortex. Flutamide has excellent androgen receptor blocking efficiency, but in some situations, it can have significant consequences, including fulminant hepatitis [112].

5. Discussion

PCOS is considered to be a complex condition where people with genetic predispositions are influenced by surrounding conditions. But surroundings are far more important than genetic ones. These environmental influences could include the follicular microenvironment, lifestyle after birth, and the intrauterine environment during pregnancy[100]. The metabolic complications associated with PCOS, such as adipocyte hypertrophy, adipocyte dysfunction, and global adiposity, are triggered by an excess of androgens and ultimately result in central obesity and IR[113]. Furthermore, an imbalance in the HPO axis is thought to be a significant aetiology behind PCOS. Because PCOS women have abnormally elevated LH pulse frequency and amplitude, GnRH pulse, hypothalamic GnRH neurons function as a central regulator of LH synthesis. This boosts androgen synthesis in ovarian theca cells and increases hyperandrogenemia, metabolic disorders and ovarian dysfunction in PCOS women[7].

Flavonoids have been widely employed as antiangiogenic, anticancer, neuroprotective, antitumor, antimalarial, antioxidant and anti-proliferative agents[114]. Furthermore, high dosages of flavonoids were used in various clinical trials for disease prevention, and no significant side effects were found[115]. The study on flavonoids has progressed over time from extremely basic chemistry to human clinical studies. Thus, fairly basic chemistry was used to synthesise flavonoid derivatives, including actual products of flavonoid metabolism, and to separate and characterise flavonoids found in plants[116]. Because of their low toxicity, multi-targeted efficacy, and polyphenolic compounds, herbal plants are widely utilised to avoid chronic diseases[48].

A higher level of OS than normal has been seen in PCOS patients, indicating that OS contributes to the pathophysiology of PCOS[117]. Flavonoids are thought to have beneficial effects in biological systems because

of their ability to suppress oxidases, transfer electrons from free radicals, activate antioxidant enzymes and decrease alpha tocopherol radicals[118]. It is necessary to produce antioxidants to protect the human body from free radicals. To extract flavonoids from plants, many innovative extraction technologies have been developed[119].

Quercetin prevents the progression of disease by modulating the enzymes or antioxidant compounds that boost antioxidant power through its effects on signal transduction pathways. Studies have demonstrated that quercetin's protective mechanism against acute spinal cord injury is caused by its downregulation of MDA level, upregulation of SOD activity to improve antioxidant activity, and inhibitory effect on the p38MAPK/iNOS signaling pathway[45]. Apigenin prevents oxidative and electrophilic stress in cells by increasing the expression of antioxidant enzymes. Additionally, it increases the expression of nuclear translocation of Nrf-2[18]. PCOS patients are susceptible to several problems, such as OS, inflammation, and metabolic issues[64]. Daizein and genistein, two soy isoflavones, are utilised more frequently in premenopausal and menopausal women because they are believed to suppress the expression of androgen receptors. However, studies have shown that PCOS women who consume soy isoflavones experience varying hormonal effects[120].

A naturally occurring flavanone found in grapefruit and other plant species is naringenin. Its cytoprotective and anti-inflammatory properties were demonstrated in recent studies on PCOS mouse models. In women with PCOS, naringenin can lower testosterone and estrogen levels while increasing the concentration of enzymes that scavenge ROS[121]. Flavonoids have been shown to suppress the expression of isoforms of inducible nitric oxide synthase, lipooxygenase, and cyclooxygenase, which contribute to generating significant levels of prostanoids, leukotrienes and other inflammatory mediators like adhesion molecules, cytokines, and chemokines[122]. Modifying one's lifestyle is the primary approach for treating PCOS patients with moderate symptoms. It is well known that dietary modification is a promising therapy approach for PCOS. Flavonoids, a type of phytonutrient found in dietary macronutrients, are gaining a lot of interest for their possible free radical scavenging and antioxidant activity on metabolism and endocrine-related diseases[123].

6. Conclusion

A complex endocrine and metabolic condition, Polycystic Ovarian Syndrome (PCOS) can be identified by anovulation, hyperandrogenism, and polycystic ovarian shape. Insulin resistance, oxidative stress, and low-grade inflammation are frequently present as well. While oral contraceptives and insulin sensitisers are examples of conventional treatments that target certain symptoms, they may have side effects or be ineffective in treating the whole range of PCOS indications. The multi-targeted therapeutic potential of flavonoids, which are naturally occurring polyphenolic chemicals that are commonly found in fruits, vegetables, and medicinal plants, has made them promising applicants for the treatment of PCOS. Certain flavonoids, including apigenin, quercetin, catechins, rutin, and genistein, are highlighted in this review as having anti-inflammatory, antioxidant, insulin-sensitising, and hormone-regulating qualities. Infertility and irregular menstruation are among the symptoms that these bioactivities help to alleviate, as well as ovarian function, hyperandrogenism, and metabolic balance. Flavonoids are a strong alternative or supplementary strategy in the treatment of PCOS because of their minimal toxicity and wide range of positive benefits. To confirm their effectiveness, establish the ideal dosages, and successfully incorporate them into evidence-based treatment plans for PCOS management, more clinical research and standardised formulations are required.

7. Author Contribution

Saloni Upadhyay: Writing-review and editing; Avijit Mazumder: Conceptualization; Saumya Das: Literature review. All authors have read and agreed to the published version of the manuscript.

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