



Anti-infertility roles of flavonoids: insights into the female reproductive system

Morteza Abdi^{1,2} · Hadi Karimzadeh³ · Amirreza Jourabchi² · Amin Khameneh¹ · Ali Abedelahi²

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Abstract

Female infertility is a complex and multifactorial disease affecting millions of women worldwide, wherein oxidative stress and inflammation play major roles in its pathophysiology. Flavonoids, a class of polyphenolic compounds derived from plants, show promise in alleviating infertility-related disorders such as polycystic ovary syndrome (PCOS), endometriosis, and uterine implantation abnormalities. The antioxidant and anti-inflammatory properties of flavonoids can be useful in overcoming oxidative damage and disturbances of inflammatory conditions within the reproductive system. Key flavonoids, including quercetin and apigenin, have demonstrated the ability to regulate hormonal imbalances, enhance follicular development, and improve oocyte quality. Flavonoids may also act by interacting with essential inflammatory and hormonal pathways to suppress the synthesis of pro-inflammatory cytokines while increasing antioxidant defenses. The integration of flavonoid-based strategies with conventional treatments opens up promising avenues in improving reproductive outcomes and advancing fertility therapies. This review will highlight the molecular mechanisms underlying the efficacy of flavonoids and point out their potential as nutraceutical interventions in the management of female infertility.

Keywords Antioxidant · Infertility mechanisms · Oxidative stress · Polyphenolic compound

Introduction

Infertility, a complex and multifaceted medical condition, has become an increasingly prevalent issue worldwide, affecting individuals and couples alike. According to the World Health Organization, infertility is defined as the inability to achieve pregnancy after a year of regular, unprotected sexual intercourse, and it is estimated to impact approximately 15% of couples[1]. The prevalence of infertility varies across different regions and demographics, with some studies suggesting that as many as 1 in 6 people

globally are affected by this condition[2]. It is estimated to affect between 8 and 12% of reproductive-aged couples worldwide, with both male and female factors contributing to the overall burden. Secondary infertility, often due to reproductive tract infections, is the most common form of female infertility globally [3].

The factors contributing to infertility are varied, encompassing both male and female influences that play a significant role in the overall issue. On the male side, lifestyle, environmental, and additional health factors have been associated with an increased prevalence of sperm DNA fragmentation, which can significantly impact fertility. Factors such as obesity, smoking, exposure to environmental toxins, and certain medical conditions like varicocele and infections can all negatively affect sperm quality and quantity [1]. There is a diverse array of risk factors for female infertility, including maternal health and lifestyle, as well as reproductive history. Other non-modifiable risk factors that affect infertility include age and genetic conditions [4].

The prevalence of female infertility varies across different regions and populations. A meta-analysis reported a pooled prevalence of infertility among females to be 45.85%, with primary infertility at 51.5% [5]. Female infertility can result

✉ Morteza Abdi
m.abdi@tbzmed.ac.ir

✉ Ali Abedelahi
abedelahia@gmail.com

¹ Student Research committee, Tabriz University of Medical Sciences, Tabriz, Iran

² Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

³ Department of Immunology, Faculty of Medicine, Tabriz University of Medical Science, Tabriz, Iran

from a variety of factors, often categorized into ovulatory dysfunction, tubal factors, uterine factors, and other systemic conditions. Disorders affecting ovulation are among the most common causes of female infertility. Conditions such as polycystic ovary syndrome (PCOS) lead to irregular or absent ovulation, significantly impacting fertility [6]. Anovulation, the absence of ovulation, is a direct cause of infertility, as no oocyte is available for fertilization [7].

Flavonoids, a diverse group of plant-based compounds, have emerged as a potential therapeutic target in addressing various aspects of female infertility. Compounds such as quercetin and apigenin have shown potential to modulate oxidative balance, suppress inflammatory cytokines, and influence hormonal pathways, including estrogen and progesterone receptors. These naturally occurring molecules have been investigated for their ability to modulate reproductive processes and mitigate factors associated with female infertility. The antioxidant and anti-inflammatory properties of flavonoids may play a role in protecting reproductive tissues from oxidative stress and reducing the impact of inflammatory conditions, which can contribute to infertility [8]. Additionally, flavonoids have been studied for their potential to regulate hormonal imbalances, a common factor in polycystic ovary syndrome and other reproductive disorders [9]. However, despite their potential, key challenges remain—such as poor bioavailability, variability in metabolic responses, and limited data on long-term safety and efficacy in human populations. So, this review aims to explore the potential therapeutic role of flavonoids in managing female infertility by examining their antioxidant, anti-inflammatory, and hormonal regulatory properties.

ROS and female reproductive system

At the beginning of embryonic development, primordial germ cells move to the developing gonads. This occurs during the early stages of development. In this stage, they continue to divide through the mitotic process before transitioning into the meiotic phase and colonizing the gonads. The transformation of these cells into oogonia takes place during this period, during which they organize into formations known as germ-cell nests. At the beginning of the meiotic process, individual oocytes are surrounded by one layer of pre-granulosa squamous cells, which results in the formation of primordial follicles [10]. Approximately thirty percent of the initial oogonia are able to survive and establish a pool of primordial follicles after the germ-cell nests have been programmed to be destroyed. In the initial meiotic division, these oocytes remain dormant until they are activated at a later stage [11]. The development of atresia, which is the transformation of follicles into scar tissue, is a consequence of early activation, which starts in childhood and continues

until puberty. At the time of puberty, there are approximately 300,000 primordial follicles that are still present. Out of these, approximately 400 will complete their growth cycle and ovulate, while the remaining follicles face atresia [12].

ROS are chemically reactive molecules containing oxygen, including free radicals like superoxide anion (O_2^-) and non-radical species like hydrogen peroxide (H_2O_2). Within the ovarian environment, ROS perform dual roles: at physiological levels, they act as essential signaling molecules; in excess, they induce oxidative stress (OS), leading to cellular damage and reproductive dysfunctions [11] (Fig. 1).

Pre-ovulation

During the pre-ovulatory phase, follicles develop under the influence of gonadotropins, and ROS are generated as byproducts of cellular metabolism within ovarian cells. Physiological levels of ROS contribute to follicular development by modulating steroidogenesis and oocyte maturation. Regulation of follicular atresia and choosing of the dominant follicle is also controlled by ROS, which have an effect on the sensitivity of granulosa cells to gonadotropins and steroidogenic acts [12]. Steroid production during the pre-ovulatory stages raises levels of ROS and cytochrome P450 activity, both of which are essential for ovulation. However, decreased levels of ROS can make ovulation more difficult [13]. Significant quantities of ROS are generated during electron transfer, suggesting that functioning granulosa cells are associated with the pro-oxidant condition in the follicles [14].

Excessive ROS production—unbalanced by antioxidant defenses—can impair folliculogenesis. When oocytes are maturing, enzymatic antioxidants such as MnSOD and Cu-ZnSOD help maintain a balance of ROS. Local inflammation, fibrosis, tissue malfunction, and infertility are all potential outcomes of an imbalance between ROS and antioxidants. This is despite the fact that ROS also play crucial physiological roles [15, 16]. Excessive antioxidants in pre-ovulatory follicles restrict LH-stimulated production of progesterone and the synthesis of ovulation-related genes [17]. ROS are generated in preovulatory follicles due to the oscillation of prostaglandins, cytokines, proteolytic enzymes, and steroids, leading to changes in blood flow and ultimately follicle rupture [18].

Ovulation

Ovulation is a complex process resembling an inflammatory response, characterized by increased vascular permeability, leukocyte infiltration, and tissue remodeling. Ovulation happens under the stimulus of luteinizing hormone (LH), primarily through the activation of NADPH oxidase enzymes when the preovulatory follicle is produced [19]. LH-induced

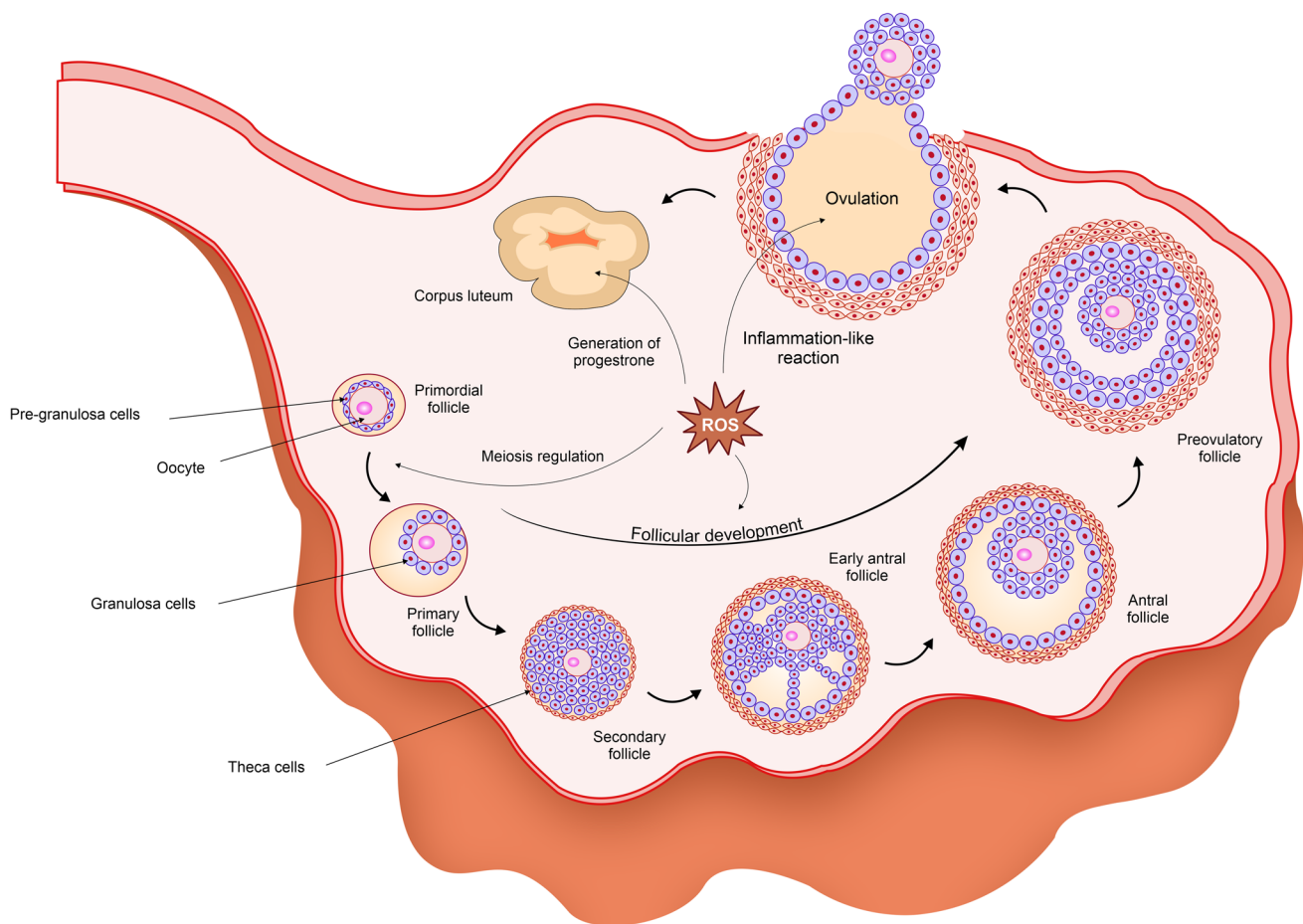


Fig. 1 This figure illustrates the multifaceted roles of reactive oxygen species (ROS) in the female reproductive system across various stages of the ovarian cycle. During pre-ovulation, physiological levels of ROS are involved in follicular development, steroidogenesis, and oocyte maturation. At ovulation, ROS contribute to the inflammatory-like processes leading to follicle rupture via activation of signaling pathways such as EGFR/MAPK. In the post-ovulatory (luteal)

phase, ROS play critical roles in corpus luteum function and luteolysis. Excessive ROS can lead to oxidative stress, negatively impacting oocyte quality, endometrial receptivity, and implantation. The figure emphasizes the balance between ROS and antioxidant systems in maintaining reproductive health and highlights how disruptions in this balance may contribute to infertility (Figure illustrated using Corel Draw v. 2020)

epidermal growth factor receptor (EGFR) transactivation is a critical step in triggering of LH-induced signaling pathways and is required for ovulation. In addition, the activation of MAPK in granulosa and cumulus cells that is regulated by EGFR signaling and stimulated by LH is responsible for the enlargement of cumulus and the maturation of oocytes [20].

ROS play a significant role in the activation of the EGFR through the inhibition of either EGFR-specific phosphatases (PTPs) or mitogen-activated protein kinase phosphatases (PPs). The activation of EGFR triggers a signaling cascade that results in the phosphorylation of p42/44 MAPK [21]. Moreover, ROS act as signaling molecules to promote the expression of ovulation-related genes, such as prostaglandin-endoperoxide synthase 2 (Ptgs2), which is essential for follicular rupture. Inhibiting ROS production during this phase can impair ovulation. For instance, the administration of antioxidants like N-acetyl cysteine (NAC) or butylated

hydroxyanisole (BHA) in animal models reduced ovulation rates, highlighting the indispensable role of ROS in this process [20].

Post-ovulation

Post-ovulation is the beginning of the luteal phase, which is characterized by changes in hormone levels. These changes include decreasing levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as higher levels of estrogen and progesterone. This phase is distinguished by the development of the corpus luteum as well as the hormonal modulation of uterine modifications that are conducted so as to promote implantation [22]. By way of the fallopian tube, the zygote makes its way to the uterine lining in preparation for implantation after fertilization has taken happened [23]. A decrease in the number of hormones produced by

the corpus luteum and the shedding of the endometrium are the two signs that indicate the end of the luteal phase in the absence of pregnancy [24].

ROS continue to play a role in this luteal phase by modulating steroidogenesis. At the end of the luteal phase, if pregnancy does not occur, the corpus luteum undergoes regression in a process called luteolysis. ROS are key mediators of luteal regression process. They induce apoptosis in luteal cells by activating pro-apoptotic signaling pathways, such as caspase activation. Excessive ROS promote lipid peroxidation and damage to mitochondrial membranes, further driving luteal cell death.

Oxidative stress and inflammation in female fertility

The dynamic interplay between antioxidants and ROS in the ovary is sophisticated. In meiosis, reactive oxygen species and antioxidants are essential for the precise regulation of oocyte meiosis pause and restart. Monthly, a singular dominant oocyte undergoes meiosis I, coinciding with elevated ROS levels and suppressed antioxidant synthesis [25]. Dietary antioxidants play a significant role in modulating oxidative stress. Higher consumption of antioxidant-rich foods has been associated with a reduced risk of female infertility, emphasizing the importance of oxidative balance in reproductive health [26].

OS occurs when ROS levels exceed the capacity of antioxidant defense systems, leading to molecular damage. For example, studies have shown that ROS levels above 80 $\mu\text{mol/L}$ in follicular fluid are associated with a 30% reduction in fertilization rates [27]. Inflammation, often associated with oxidative stress, contributes to reproductive disorders such as endometriosis and polycystic ovary syndrome (PCOS). These conditions are characterized by chronic inflammatory states that disrupt normal ovarian function, leading to infertility. In the female reproductive system, OS has been implicated in various infertility-related conditions, including endometriosis, polycystic ovary syndrome (PCOS), and unexplained infertility [28]. Excessive ROS can damage oocytes and follicles, disrupt implantation, harm the endometrium, and affect endocrine function. This damage may result in low-quality embryos, reduced implantation rates, miscarriages, and placental anomalies [29].

A specific level of oxidative stress is essential during initial embryonic evolution: sperm-oocyte combination, embryo separation, or blastocyst emergence. The mitochondria facilitate oxidative phosphorylation, hence producing ROS in the fetus. The primary sign of OS is SOD, while its non-enzymatic antioxidant equivalent is glutathione [27]. The elevated amounts of ROS in endometriosis result from both the severe inflammation related to the disorder and an

improper regulation of ROS removal pathways. An increase in hydrogen peroxide generation due to mitochondrial SOD activity, coupled with a decrease in catalase activity, was observed to raise ROS levels in lesions of endometrium [30]. OS may facilitate the formation of vessels in ectopic endometrial implants through the upregulation of a growth factor associated with vascular endothelial creation [31].

Lifestyle factors such as extremes of body weight, cigarette smoking, alcohol use, and exposure to environmental pollutants can promote excess free radical production, potentially affecting fertility. Additionally, obesity has been associated with higher levels of circulating triglycerides and inflammatory markers, leading to lipotoxicity, which can impair follicular development and disrupt implantation [32].

Flavonoids: structure, sources, and biological functions

Flavonoids are a diverse group of polyphenolic compounds prevalent in various fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. They are renowned for their health benefits and are integral to numerous nutraceutical, pharmaceutical, medicinal, and cosmetic applications [33].

They share a basic structural framework of a 15-carbon skeleton (C6-C3-C6), comprising two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic ring (C). This structure allows for extensive variability, leading to several subclasses, including flavones, flavonols, flavanones, flavanols (catechins), isoflavones, and anthocyanidins, each differing in the degree of oxidation and pattern of substitution [34].

Flavonoids are abundant in a wide range of plant-based foods and beverages. Fruits such as berries, apples, and citrus fruits; vegetables like onions and kale; grains; as well as beverages like tea and red wine are rich sources of flavonoids. For instance, flavonols are present in a variety of fruits and vegetables, with daily intake estimates ranging from 20–50 mg per day in Western populations [35].

Flavonoids exhibit a broad spectrum of biological activities that contribute to their health-promoting effects. They are well-known for their antioxidant properties, scavenging free radicals and thereby reducing oxidative stress. Additionally, flavonoids possess anti-inflammatory, anti-cancer, and anti-allergic activities. Their role in modulating key cellular enzyme functions and improving vascular health has been documented, with potential benefits in preventing cardiovascular diseases [36]. In plants, flavonoids serve essential functions, including UV filtration, symbiotic nitrogen fixation, and acting as chemical messengers. They are crucial for flower pigmentation, attracting pollinators, and providing defense mechanisms against pathogens [37].

The diverse structures and widespread availability of flavonoids in the human diet underscore their significance in both plant biology and human health.

Despite promising *in vitro* findings, the clinical application of flavonoids is often limited by poor bioavailability. Quercetin, for instance, has an oral bioavailability of less than 20%, primarily due to poor solubility and rapid metabolism. Strategies such as nanoparticle encapsulation, co-administration with piperine, or the use of prodrugs are being explored to enhance absorption and systemic retention [35].

Hormonal regulation of flavonoids

Flavonoids have garnered attention for their potential to modulate hormonal balance and support ovarian function in females. Their interactions with estrogen and progesterone pathways are particularly noteworthy.

Certain flavonoids can interact with estrogen and progesterone receptors (ERs and PRs), thereby modulating endocrine pathways relevant to reproductive health. Isoflavones, particularly genistein, exhibit selective binding to ER β , influencing estrogen-mediated gene expression and signaling.

In addition, Apigenin, a flavonoid present in various fruits and vegetables, suppressed the proliferation of breast cancer cells through interaction with ER [38]. Apigenin exhibits limited bioavailability; however, it is more bioavailable than other prevalent flavonoids, including quercetin and luteolin. Also, it has been identified as a modulator of progesterone receptors (PR), which is potentially eliciting progestin-like effects and may influence reproductive functions [39]. The antioxidant and antiapoptotic characteristics of apigenin are likely responsible for its capability

to enhance the maturity of oocytes and the growth of embryos [40]. Apigenin has showed that it can promote both of these processes. Apigenin helps to maintain the functionality and viability of oocytes by reducing the amount of oxidative damage that occurs and by providing support for the pathways that are involved in cell survival [41]. Both progesterone and estrogen are required for a normal function of the menstrual cycle and for promoting pregnancy [42]. Apigenin has the potential to modulate the levels of both of these hormones. It is possible for apigenin to have a role in the regulation of hormonal levels by interacting with estrogen receptors and altering the signaling pathways that they initiate, which ultimately helps to promote normal reproductive activities [43]. Boosting the generation of antioxidant enzymes and lowering the development of proinflammatory chemicals in ovarian cells are two of the ways that apigenin improves the capacity of cells to withstand harm caused by a variety of factors [44].

Antioxidant properties of flavonoids

Flavonoids are renowned for their antioxidant capabilities, which enable them to neutralize free radicals and reduce oxidative stress. This activity is crucial in preventing cellular damage linked to various chronic diseases. The antioxidant effect is primarily due to their ability to donate hydrogen atoms or electrons and their metal-chelating properties [45]. Arikian et al. [46], analyzed effect two flavanols, quercetin and kaempferol on growth and antioxidant mechanisms of wheat leaves in exposure to arsenic (As) stress. They showed that the applications of quercetin and kaempferol enhance the performance of antioxidant enzymes such as ascorbate peroxidase, superoxide dismutase, and peroxidase. Another study by Al-Zharani and his colleagues showed antioxidant properties of quercetin in detoxifying lead-induced oxidative stress in Wistar rats [47].

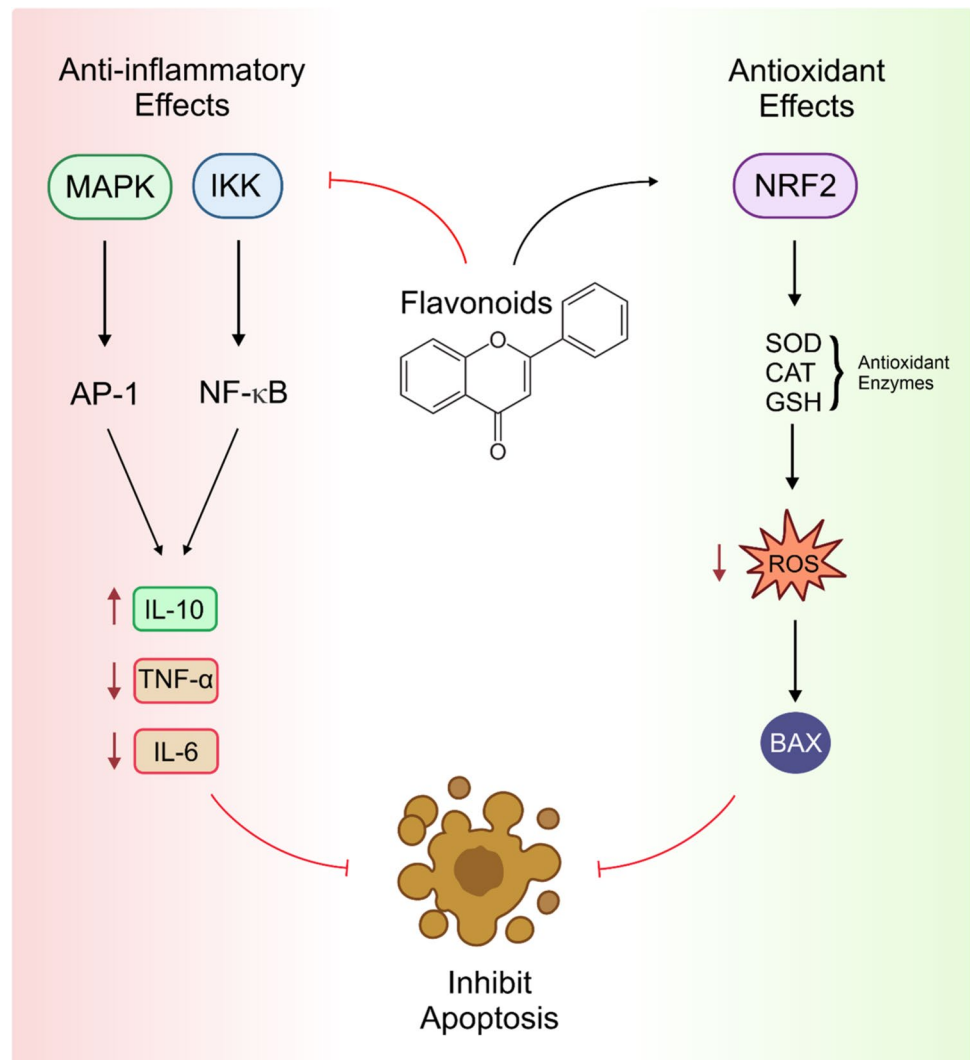
In addition, these compounds exhibit significant anti-inflammatory properties by modulating key signaling pathways and inhibiting the production of pro-inflammatory mediators. Flavonoids can suppress enzymes such as cyclooxygenase and lipoxygenase, reducing the synthesis of inflammatory eicosanoids. Additionally, they influence the activity of transcription factors like NF- κ B, leading to decreased expression of inflammatory cytokines [48].

Anti-inflammatory properties of flavonoids

Inflammation is a fundamental biological response essential for protecting the body against infections and injuries by promoting healing and tissue repair. However, dysregulated or chronic inflammation can lead to various diseases, including autoimmune disorders, cardiovascular conditions, and cancer [49]. For example, targeting inflammation in cancer is a promising strategy due to its critical role in tumor development and progression. Chronic inflammation fosters genetic instability, angiogenesis, and immune suppression, creating a tumor-friendly microenvironment [50–52]. Anti-inflammatory therapies, including cytokine inhibitors and immune checkpoint blockers, can disrupt these processes and enhance the effectiveness of traditional treatments. This approach not only aids in combating tumor growth but also offers potential for cancer prevention in individuals with chronic inflammatory conditions [53–55].

Inflammation is often triggered by an imbalance in the immune system, leading to the release of pro-inflammatory cytokines such as interleukin (IL)–6, tumor necrosis factor (TNF)- α , and C-reactive protein (CRP) [56, 57] (Fig. 2). Chronic low-grade inflammation is associated with impaired ovarian function, altered follicular development, and disrupted endometrial receptivity, all of which can hinder successful conception [58]. Flavonoids, a diverse group of plant-derived polyphenolic compounds, have garnered

Fig. 2 This schematic representation demonstrates how flavonoids exert their protective effects in the female reproductive system through anti-oxidant and anti-inflammatory pathways. Flavonoids neutralize excessive ROS, upregulate antioxidant enzymes (e.g., superoxide dismutase, catalase), and prevent oxidative stress-mediated cellular damage such as follicular atresia and oocyte degeneration. In addition, flavonoids modulate inflammatory signaling by suppressing nuclear factor-kappa B (NF- κ B) activation and inhibiting the production of pro-inflammatory cytokines such as TNF- α and IL-6. These actions help preserve follicular integrity, improve endometrial receptivity, and support successful embryo implantation (Figure illustrated using Corel Draw v. 2020)



attention for their potential to modulate inflammatory pathways, offering a promising therapeutic avenue for improving reproductive health in women [59].

Inflammation plays a critical role in the pathophysiology of many female reproductive conditions, including PCOS, endometriosis, and uterine disorders [58]. This inflammation can disrupt key reproductive processes, such as ovulation, fertilization, and embryo implantation. Studies have demonstrated that elevated levels of inflammatory cytokines in the follicular fluid and serum are associated with poor oocyte quality and impaired embryo development in women undergoing in vitro fertilization (IVF). Moreover, inflammation has been linked to poor endometrial receptivity, which is essential for successful embryo implantation [60].

Inflammation activates the eicosanoid pathway via the enzymatic and non-enzymatic the oxidative process of arachidonic acid (AA), which synthesized by phospholipase A2 (PLA2) from membrane phospholipids. AA is subsequently metabolized by cyclooxygenases (COXs), lipoxygenases

(LOXs), and nitric oxide synthase (NOS), resulting in various oxidation products, including prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), and lipoxins (LXs). Cytokines induce the up-regulation of COX-2 expression, leading to increased COX-2-dependent prostaglandin E2 (PGE2) biosynthesis in the peritoneal fluid of endometriosis patients in comparison with normal endometrium [61, 62].

Flavonoids in specific infertility conditions

Flavonoids exert their anti-inflammatory effects through various molecular mechanisms, including the modulation of pro-inflammatory cytokine production and the inhibition of key inflammatory enzymes. These compounds are known to inhibit the nuclear factor-kappa B (NF- κ B) pathway, a central regulator of inflammation. NF- κ B controls the transcription of genes involved in immune and inflammatory responses, and its dysregulation is

commonly observed in conditions like endometriosis and PCOS. By suppressing the activation of NF- κ B, flavonoids can reduce the expression of inflammatory cytokines and

chemokines, ultimately mitigating the inflammatory cascade that impairs fertility (Table 1).

Table 1 Summary of some studies investigating the anti-infertility effects of flavonoids

Infertility Condition	Population/Model	Intervention	Findings	Refs.
EMS	ESCs	Apigenin	Apigenin inhibited TNF α -induced proliferation of ESCs through the modulation of IL-8 gene and protein expression. The addition of apigenin resulted in a reduction of phosphorylated I κ B α protein production	[85]
EMS	VK2/E6E7 and End1/E6E7 cells	DMF	DMF caused a decrease in mitochondrial membrane potential, disrupted intracellular calcium levels, and increased ROS production, leading to accelerated apoptosis	[86]
OC	1. Human ovarian cancer cell line (SKOV3) 2. rodent-induced ovarian cancer	Curcumin	CUR treatment enhanced indicators of the biogenesis of mitochondria, including PGC-1 α and TFAM, and mitigated the increase of ET-1-mediated renal fibrosis and apoptosis in kidneys isolated from CIS-treated ovarian cancer rats	[87]
OC	SKOV3/DDP cells	Apigenin	Apigenin decreased expansion, reduced cell cycle progress, and increased SKOV3 cell death	[88]
POF	Rats and granulosa cell model	TFSC	The integration of TFSC and LIPUS has the potential to reduce POF through the modulation of cell autophagy and apoptosis	[89]
PCOS	Rat	Punica granatum (pomegranate)	The incorporation of pomegranate juice led to positive alterations in female sex hormones among patients with PCOS	[90]
PCOS	Rat	WS and TT	The combination of drugs resulted in a reduction of ovarian mass, and uterine size was restored to normal scales	[91]
PCOS	Rat	Green tea (<i>Camellia sinensis</i>)	The green tea extract proved effective in addressing letrozole-induced PCOS in the rats by enhancing the function of the antioxidant enzymes	[92]
Acrylamide- Induced Infertility	Rat	Lycium shawii seeds extract	Lycium shawii seeds may serve as a potential nutraceutical agent for enhancing infertility diseases, inflammatory conditions, and OS	[93]
Acrylamide- Induced Infertility	Rat	Lepidium sativum seeds	Lepidium sativum seed oil reduced ovarian injury and may serve as a new supplementary agent for addressing female infertility	(94)

DMF 5,7-dimethoxyflavone, ESCs Endometriotic stromal cells, LIPUS Low intensity pulsed ultrasound, OC Ovarian cancer, POF Premature ovarian failure, TFSC Total flavonoids from semen cuscutae, TT Tribulus terrestris, WS Withania somnifera

Polycystic ovary syndrome (PCOS)

The most prevalent gynecological endocrinopathy is PCOS, a polygenic endocrine condition that is thought to impact 5–20% of women of reproductive age [63]. Symptoms associated with PCOS also diminish the quality of life by impacting the psychiatric dimensions of a patient's experience [64]. Women diagnosed with PCOS show a higher prevalence of various chronic conditions such as obesity, hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), and heart disease [65]. Research indicates that women with PCOS, regardless of their body weight, predominantly show insulin resistance, which is a significant risk factor for the onset of metabolic issues like impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) [66]. Recent studies indicate that oxidative stress serves as a trigger in the onset of PCOS and its associated signs, including elevated production of androgen and infertility. The therapeutic effects of quercetin on PCOS were investigated in a systematic review by Tabrizi et al. [65]. They concluded that quercetin was administered in doses ranging from 15 to 50 mg/kg/day in rodent models, improving ovarian histomorphology and decreasing testosterone levels by up to 40%. Reports have indicated the impact of quercetin on lowering testosterone, LH, and insulin resistance levels. While quercetin demonstrated an improvement in dyslipidemia, it did not show a significant impact on weight loss. The advantages of quercetin appear to be more associated with its antioxidant and anti-inflammatory properties than with its potential for weight reduction.

Endometriosis (EMS)

EMS is a prevalent estrogen-dependent gynecological condition that results in the proliferation of cells of the endometrium outside the uterus, usually referred to as “endometriosis implants” [67, 68].

Genetic, immune-mediated, and external factors are recognized as critical contributors to the emergence of EMS [69, 70]. Its pathogenesis is unknown, however various studies concur that it is characterized by alterations in progesterone (P4) and estradiol (E2) receptor activity, which disrupts their dependent pathways and causes E2 reliance and P4 resistance. These circumstances appear to have a strong correlation with symptoms and fertility problems in women who have EMS [70, 71]. It has been shown that the metabolic changes of sex hormones E2 and P4 impact the mesothelium-infiltrating, migration, and proliferation of endometriotic cells. Additionally, they facilitate the release of inflammatory mediators, which are essential in the development of disease [72, 73].

The surgical removal of ectopic endometriosis lesions is the preferred treatment, typically succeeded by long-term

pharmacological therapy involving NSAIDs and contraceptive pills [74, 75]. To prevent the generation of EMS-dependent PGs, NSAID therapy is typically initiated a few days prior to the menstrual cycle thereby alleviating inflammation and pain. NSAIDs hinder the formation of PGE2 by reversibly blocking the COX-1 and COX-2 enzymes, which primarily lead to the breakdown of arachidonic acid into prostaglandins. Non-selective NSAIDs, such as ibuprofen (IBF) or naproxen (NAP), inhibit both COX-1 and COX-2 enzymes, whereas selective NSAIDs, like celecoxib (CXB), specifically inhibit only the COX-2 enzyme [76].

Oral contraceptives result in hypoestrogenemia and also inhibit tissue growth and the inflammation [77]. Progestins combined with gonadotropin-releasing hormone agonists (GnRH) that induce amenorrhea represent an additional approach for decreasing systemic estrogen levels, thereby alleviating symptoms associated with the disease [78, 79]. The traditional therapies may demonstrate poor effectiveness for many patients, attributable to various adverse effects such as symptoms associated with the perimenopausal phase, osteoporosis, alterations in lipid profiles, and a failing liver [74, 75].

The phosphoinositide 3-kinase (PI3-K)/Akt/mammalian target of the rapamycin (mTOR) pathway plays a crucial role in tumor formation, angiogenesis, tumor expansion, and metastasis [80]. Research indicates that QRC blocks the AKT/mTOR pathway, demonstrating anti-cancer effects through decreasing cancer cell survival and promoting cell death and autophagy. Additionally, QRC has been shown to inhibit cell growth and stimulate arrest of the cell cycle and apoptosis in endocervical cell lines VK2/E6E7 and End1/E6E7. QRC also exhibits anti-inflammatory effects linked to the blocking AA and manufacturing of inflammatory agents such as PGs and leukotrienes, which contribute to in regulating uterine contractile characteristics [81]. So, flavonoids have been shown to exert anti-inflammatory effects in endometriosis by suppressing the activity of inflammatory mediators such as IL-6, TNF- α , and prostaglandins.

Uterine health and implementation

Implantation is the initial phase of pregnancy during which the blastocyst attaches to the uterine wall. Proper blastocyst attachment necessitates a sequence of molecular and structural alterations in the uterus at the beginning of pregnancy to accommodate the conceptus. The initial phase of blastocyst implantation is particularly susceptible to metabolic disruptions. Consequently, examining the embryo-maternal communication during the implantation period may be a crucial method for comprehending the detrimental impact of metabolic disturbances on implantation [82]. Increase of OS can affect the implantation process. Bolouki et al. showed that treatment with quercetin increased implementation sites and

serum level of estradiol in diabetic mice [83]. In another study, quercetin treatment increased expression of *IGF1R*, integrin $\alpha\beta3$, and *COX2* genes in diabetic mice. Also, *caspase (Casp)3* gene decreased after treatment with quercetin [84]. So, quercetin can preserve preimplantation embryos against the detrimental effects of diabetes. Flavonoids present a significant therapeutic potential for improving uterine health and implantation due to their anti-inflammatory, antioxidative, and angiogenic characteristics. Addressing the root causes of endometrial dysfunction, these natural compounds may significantly enhance fertility outcomes, especially for women facing implantation challenges related to inflammation.

Conclusion

The rising tide of female infertility calls for novel strategies to battle the underlying causes, such as oxidative stress and chronic inflammation. Flavonoids are among the most promising therapeutic agents since they are strong antioxidants and anti-inflammatory compounds. Modulating both oxidative and inflammatory pathways, flavonoids prevent damage in reproductive tissues and improve oocyte quality and maintain proper hormonal balance. Evidence underpins their potential in the management of conditions such as PCOS and endometriosis, as well as in supporting uterine health and implantation processes. While promising, the application of flavonoids in reproductive health is limited by gaps in our understanding of their long-term safety, inter-individual responses, and efficacy in human populations. Further clinical trials with standardized flavonoid formulations and clearly defined endpoints are needed. Flavonoids represent a significant step toward personalized and nutraceutical-based solutions for improving female reproductive health and bridging gaps in current infertility management.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Consent for publication Not applicable.

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