

Curcumin and Its Nanoformulations: Exploring Therapeutic Potential in Female Reproductive Health

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Abstract

This review explores the potential therapeutic benefits of curcumin and its nanoformulations for treating common reproductive health problems in women, including polycystic ovary syndrome (PCOS), endometriosis, and premenstrual syndrome (PMS). Curcumin is a bioactive compound sourced from turmeric that possesses analgesic, antioxidant, and anti-inflammatory effects. These characteristics position it as a strong candidate for helping to relieve symptoms related to various health conditions. Nanoformulations enhance curcumin's bioavailability and therapeutic efficacy, allowing for better absorption and targeted action. Additionally, the review discusses the role of curcumin in reducing toxicity within the female reproductive system, highlighting its impact on hormone regulation and cellular health. Overall, this review highlights the importance of conducting additional research to thoroughly understand the mechanisms behind curcumin and its nanoformulations in female reproductive health, suggesting they may provide valuable synergistic approaches to complement conventional treatments of female reproductive disorders.

Keywords: Curcumin, PMS, PCO, Endometriosis, Antioxidant

1. Introduction

Numerous studies have highlighted the positive impact of various plants and their derivatives on reproductive health (1). Traditional medicine across cultures has long utilized botanical compounds for their therapeutic properties, emphasizing enhancing reproductive function and addressing related disorders (2, 3).

Medicinal plants containing bioactive compounds contribute to female reproductive health through hormone regulation, cell membrane support, anti-inflammatory effects, and menstrual cycle regulation (4). These plants help balance hormones, facilitate communication and function in reproductive tissues, reduce inflammation that can disrupt ovulation, and promote regular menstrual cycles, making them valuable for treating conditions such as endometriosis, polycystic ovary syndrome (PCOS), and menstrual irregularities (5-8).

In conclusion, the integration of plant-based therapies

and their derivatives into reproductive health can offer holistic support and preventative measures. While modern medicine plays a crucial role in treating reproductive disorders, exploring these natural alternatives can provide additional benefits (9). Cumulatively, the diversity of plants and their bioactive compounds underscores their potential to foster reproductive health and address various reproductive system challenges (10, 11). Continued research into these natural remedies will advance our understanding and application of plants in optimizing reproductive wellness.

One of these notable plant-derived compounds is curcumin. Curcumin has multifaceted benefits, which can enhance ovarian function, support hormonal balance, and protect reproductive tissues from damage (12, 13). Its potential to improve overall reproductive health makes curcumin a valuable addition to the array of botanical solutions promoting female reproductive wellness (12).

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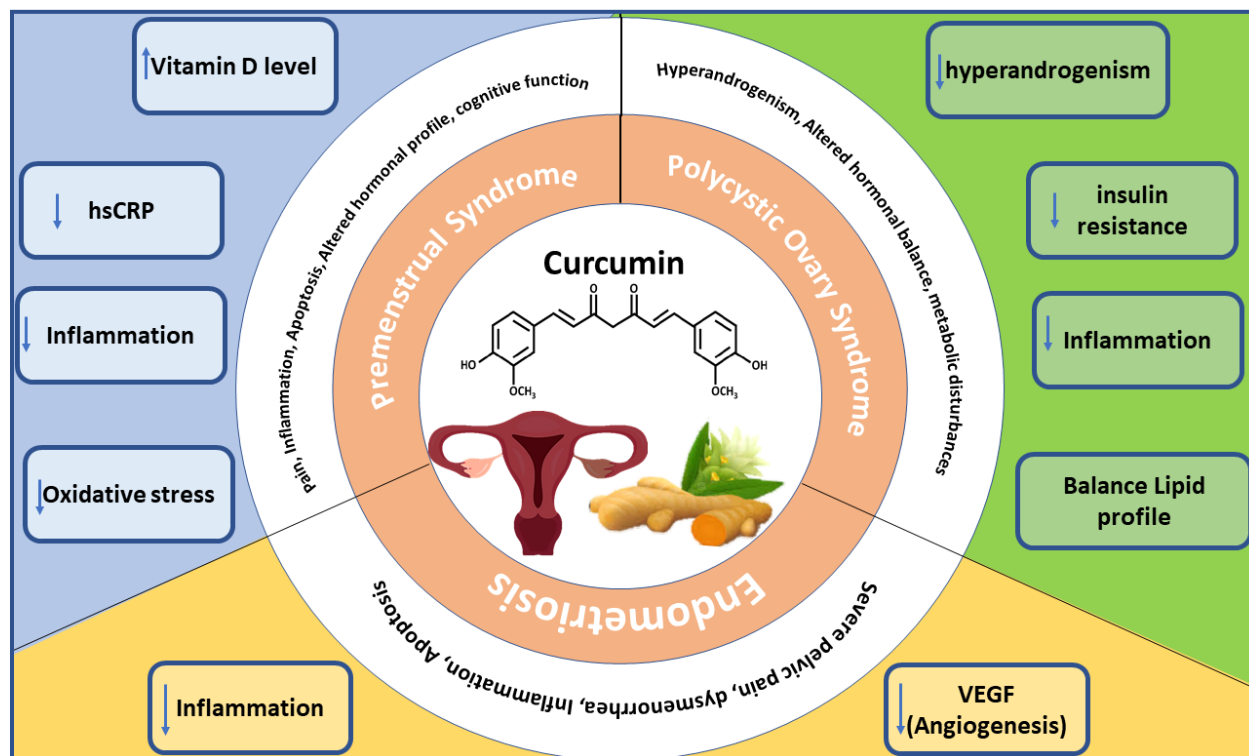


Figure 1. The mechanisms of Curcumin's beneficial effect on PCOS, endometriosis, and PMS

2. Source and Definition of Curcumin

Curcumin is a naturally occurring polyphenolic compound obtained from the rhizome of the plant *Curcuma longa*, commonly known as turmeric. It is well-known for its bright yellow hue, which contributes to its role as both a spice and a food preservative in various culinary applications (14). Beyond these applications, curcumin has gained significant attention in medicine and nutrition because it has a broad range of biological activities (15). The compound's chemical structure, featuring a diketone group, enables it to interact with various cellular targets, making it a subject of interest in numerous health studies (15).

3. Curcumin's Pharmacological Properties

Curcumin exhibits a wide range of bioactivities that have garnered significant interest in scientific research (16). Curcumin's beneficial effects include combating oxidative stress, associated with chronic diseases such as cancer, diabetes, and heart disease (17, 18). Its anti-inflammatory action is crucial for managing inflammatory conditions like arthritis, contributing to symptom relief and enhanced quality of life (19, 20). Additionally, research indicates that curcumin may improve cognitive function and provide neuroprotective benefits, therefore reducing the risk of neurodegenerative disorders (21). Its role in regulating blood sugar and enhancing insulin sensitivity highlights its potential in managing type 2 diabetes (22).

In summary, this multifaceted compound positions curcumin as a powerful natural agent with the potential to enhance overall health and wellness across multiple systems

in the body.

This review aims to investigate curcumin's influence on the disorders of the female reproductive system. As illustrated in Figure 1, curcumin affects various conditions of the female reproductive system through multiple mechanisms. Additionally, the study will examine curcumin's protective role against reproductive toxicity, and assess safety and toxicity considerations. Finally, the study will determine the mechanism of curcumin.

4. Effects of Curcumin on PCOS in Animal and Clinical Studies

Polycystic ovary syndrome is characterized by a combination of clinical, hormonal, and metabolic disturbances, including hyperandrogenism, irregular menstrual cycles, insulin resistance, and infertility (23, 24). These metabolic irregularities often increase the risk of developing long-term health issues such as dyslipidemia, cardiovascular diseases, and type 2 diabetes (24, 25). Consequently, the management of PCOS is crucial not only for fertility but also for improving overall health and reducing the risk of metabolic and cardiovascular complications (24, 26).

Traditional treatments for PCOS focus primarily on symptom management, with the use of ovulation-inducing drugs, anti-androgens, insulin-sensitizing agents such as metformin, and oral contraceptives (27). However, these therapies often come with side effects and do not always affect all hormonal and metabolic of PCOS (27). This

limitation has led to increasing interest in alternative therapies, particularly those that provide a more holistic approach to treatment (28, 29). Herbal medicine, with its variety in bioactive compounds, has gained significant attention for treatment and managing PCOS (30, 31). Animal and human studies reveal that natural remedies modulate various pathways in the syndrome's pathophysiology, offering a promising adjunct or alternative to conventional treatments (32, 33). Due to the multifaceted nature of PCOS and its varying presentations, extensive research has utilized animal models to explore different aspects of the syndrome, including its pathophysiology, diagnostic criteria, and potential treatment modalities (34-37).

Curcumin has garnered attention for modulating key pathophysiological processes associated with PCOS (38). Recent studies demonstrate that curcumin may reduce insulin resistance, alleviate hyperandrogenism, improve lipid profiles, and regulate menstrual cycles, offering a multi-targeted approach to managing PCOS (29, 39-42). Although research on curcumin has been expanding, its effectiveness remains uncertain, as clinical and preclinical studies have yielded inconsistent results.

Reddy et al. (2016) explored curcumin's effects in a rat model of PCOS induced by letrozole, showing that curcumin treatment at doses of 100 mg/kg and 200 mg/kg for a duration of fifteen days restored hormonal balance, improved glucose metabolism, and resolved ovarian cysts, suggesting its protective effects comparable to clomiphene citrate (5).

Zhang et al. delved deeper into curcumin's molecular mechanisms by focusing on its impact on granulosa cells in hyperandrogen-induced PCOS. Administration of curcumin at 200 mg/kg for 56 days, alleviated hyperandrogen-induced granulosa cell apoptosis and endoplasmic reticulum stress by activating the PI3K/AKT and modulating the IRE1 α -XBP1 signaling pathway. Therefore, by mitigating the cellular stress commonly seen in ovarian granulosa cells curcumin could serve as an effective treatment for PCOS (43). In another study, they combined curcumin with aerobic exercise to investigate the effects on endoplasmic reticulum stress and granulosa cell apoptosis. The results indicated that curcumin and exercise together mitigated endoplasmic reticulum stress and downregulated genes related to follicular development, suggesting that the combined therapeutic approach could benefit ovarian function in PCOS (44).

Curcumin administration in PCOS rats at 100 and 200 mg/kg improved insulin levels, fasting blood glucose, body weight, and gene expression of GLUT4 and estrogen receptor alpha (Er α), indicating its potential role in managing metabolic disturbances commonly seen in PCOS (45). Mosa, Jasim et al. (2023) also demonstrated that curcumin treatment in DHEA-induced PCOS rats resulted in increasing progesterone, estradiol, ghrelin, and reduction in the levels of leptin, LH testosterone, further supporting curcumin's role in regulating hormonal imbalances in PCOS (46).

Further studies demonstrated curcumin treatment reduced levels of reactive protein and Interleukin-6 as pro-inflammatory cytokines in PCOS animal models (42). Nanoparticles of Curcumin-loaded super-paramagnetic iron

oxide (SPIONs) in a PCOS mouse model resulted in reduced ovarian damage, lowered apoptosis, and enhanced expression of anti-apoptotic markers such as Bcl2 while reducing BAX and CASP3 expression. These findings highlight the potential of nanoparticle-mediated curcumin delivery for mitigating ovarian damage in PCOS (47).

It is demonstrated that Curcumin and nano curcumin differ in efficacy and bioavailability. On a more targeted note, Raja, Maldonado et al. (2021) synthesized curcumin encapsulated in chitosan-based nanoparticles and compared in effects in alleviating PCOS. While curcumin reduces testosterone and increases progesterone levels, enhancing cycle regularity and ovarian health, nano curcumin, with its smaller particle size, demonstrates more pronounced effects, including greater reductions in testosterone and significant increases in progesterone, leading to better regulation of estrous cycle phases. Additionally, nano curcumin results in more substantial decreases in insulin levels and improved metabolic restoration than curcumin, along with notable enhancements in ovarian histology, such as well-formed follicles and more corpus lutea (48).

A significant body of human research has explored the effects of curcumin on metabolic disturbances in PCOS, particularly insulin resistance, hyperglycemia, and lipid abnormalities (29, 40, 49). Clinical trials have demonstrated consistent improvements in glycemic control following curcumin supplementation. Significant reductions in fasting glucose, body weight, body mass index, serum insulin, insulin resistance (HOMA-IR), and improvements in insulin sensitivity were observed in women with PCOS who received 500 mg/day of curcumin for 12 weeks. Moreover, a favorable shift in the lipid profile, reducing total cholesterol, and LDL cholesterol, and improving HDL cholesterol levels were observed after curcumin supplementation (49).

Studies like those by Sohaei et al. (2019) and Heshmati et al. (2021) also support these findings, reporting reductions in dehydroepiandrosterone, insulin levels, and fasting plasma glucose, resulting in insulin resistance improvements following curcumin supplementation. However, these studies did not show significant effects on all metabolic parameters, such as triglycerides and HDL levels, emphasizing the need for larger trials to fully understand curcumin's metabolic effects (50, 51).

Research has shown that curcumin supplementation significantly reduced insulin levels and fasting blood sugar, along with improving the HOMA-IR, indicating enhanced insulin sensitivity. Additionally, high-sensitivity C-reactive protein (hs-CRP), a critical marker of systemic inflammation, was notably decreased in individuals with polycystic ovary syndrome (PCOS), highlighting the intervention's potential anti-inflammatory benefits (29, 40).

Ghanbarzadeh-Ghashti et al. (2023) reported improvements in menstrual cycles, with reduced rates of amenorrhea and oligomenorrhea in the PCOS patients who received 500 mg curcumin tablets for twelve weeks (52). Curcumin's effects may be enhanced when combined with other treatments. Sohrevardi et al. (2021) investigated the synergistic effects of metformin, a commonly used drug, and curcumin for managing insulin resistance in PCOS. The study showed that daily receiving of an 80 mg capsule of

curcumin nano micelle with 500 mg metformin three times a day for three months led to remarkable improvements in fasting insulin, testosterone levels, and HOMA-IR along with better lipid profiles. This finding supports the idea that curcumin may have a complementary role in managing PCOS, particularly when combined with conventional treatments like metformin (53).

Collectively, animal and human studies suggest that curcumin shows promise in managing PCOS through mechanisms such as regulating ovarian function by modulating inflammation, improving insulin sensitivity, and reducing oxidative stress (54). Whether used alone or with treatments like metformin, it may help alleviate PCOS symptoms and enhance reproductive and metabolic health. Advanced formulations like curcumin-loaded nanoparticles could further improve its bioavailability. While clinical evidence supports curcumin's safety and benefits in improving insulin resistance and metabolic parameters, more large-scale, well-designed human trials should be carried out to confirm its long-term efficacy role for integrated PCOS management.

5. Curcumin as a Therapeutic Agent in Endometriosis Treatment: Insights from In Vitro and In vivo Studies

Endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterus, leading to inflammation, pain, and often infertility (55). This disorder affects many women globally and can affect their quality of life (56). The exact cause of endometriosis remains unclear, but it is linked to immune dysfunction, hormonal imbalances, and genetic predisposition (56). Common symptoms include severe pelvic pain, dysmenorrhea, painful intercourse, and gastrointestinal discomfort. Traditional treatment options, such as hormonal therapy and surgery, aim to alleviate symptoms but may have significant side effects and recurrence rates (57, 58).

In recent years, there has been growing interest in the use of complementary and alternative medicine, particularly herbal remedies, to manage endometriosis (6, 59-61). Herbal medicine offers a holistic approach that can help reduce inflammation, modulate immune responses, and provide pain relief with fewer side effects (58, 62). Compounds such as flavonoids, polyphenols, and antioxidants found in various herbs play a role in mitigating the oxidative stress and inflammatory pathways involved in endometriosis (60, 61, 63).

Curcumin has shown significant promise in the treatment of endometriosis. Known for its potent anti-inflammatory and antioxidant properties, curcumin inhibits pro-inflammatory cytokines, reduces the expression of enzymes such as COX-2, and modulates pathways such as NF- κ B (13, 64).

Studies have demonstrated that curcumin can reduce lesion size and improve pain in endometriosis (63, 65, 66). Its ability to downregulate inflammation and support immune function makes curcumin a compelling candidate for integrative approaches to managing endometriosis,

potentially enhancing the efficacy of conventional treatments while minimizing adverse effects (13).

Various studies have explored how curcumin can ameliorate these harmful effects in both in vitro and in vivo models.

One study evaluated the impact of curcumin on the expression of several growth factors and inflammatory mediators in bovine cumulus-oocyte complexes cultured with peritoneal fluid from infertile women suffering from endometriosis. The addition of curcumin significantly enhanced the expression of Growth Differentiation Factor-9 and Kit Ligand. Notably, a marked decrease in Tumor Necrosis Factor-alpha (TNF- α) expression was also observed, indicating that curcumin may improve factors essential for folliculogenesis (67).

Further investigations have demonstrated that curcumin can inhibit critical inflammatory mediators involved in the pathogenesis of endometriosis. One study reported that curcumin suppresses vascular endothelial growth factor (VEGF) secretion in a dose-dependent manner and induces apoptosis in endometriotic epithelial cells (68).

In a study by Kim et al. (2012), the effects of curcumin on endometriotic stromal cells were investigated in a laboratory setting. The findings revealed that curcumin significantly reduced the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) at both the mRNA and protein levels in response to TNF- α . This inhibitory effect was observed to be dependent on the concentration of curcumin used. Additionally, curcumin notably diminished the production of several pro-inflammatory cytokines, specifically interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1). The research also indicated that curcumin plays a role in suppressing the activation of the transcription factor nuclear factor-kappa B (NF- κ B) within these endometriotic cells (69). Another in vitro study investigated the effects of curcumin on the eutopic endometrium of individuals with endometriosis (EESC) compared to normal endometrial stromal cells (NESC). The results indicated that curcumin treatment led to a significant and dose-dependent reduction in the secretion of chemokines and cytokines in both EESC and NESC over time. Curcumin also significantly inhibited the phosphorylation of several key signaling pathways, including IKK α / β , NF- κ B, STAT3, and JNK, under the experimental conditions tested (70).

Moreover, curcumin has been shown to affect the proliferation of endometriotic stromal cells. In studies involving endometrial stromal cells from endometriosis patients, treatment with curcumin resulted in reduced cell survival and significant alterations in cell cycle distribution, suggesting an anti-proliferative effect (71). Additionally, curcumin was found to lower estradiol levels, emphasizing its role in hormonal regulation, which is crucial given the hormone-resistant nature of endometriosis-afflicted tissues (72).

Besides in vitro studies, curcumin's therapeutic potential in managing endometriosis has been widely investigated through various preclinical studies employing animal models.

The studies by Kizilay et al. (2017) conducted in a rat model of endometriosis induced by autologous transplantation of endometrial tissue, and Rajeswari et al. (2017), using diethylstilbestrol (DES)-induced endometriosis rat model, highlighted curcumin's impact on reducing endometrial implant size and improving reproductive outcomes (73, 74). Kizilay et al. observed that treatment with 100 mg/kg of curcumin significantly decreased endometrial lesion size and reduced proliferative markers, showcasing its capacity to inhibit the growth and progression of ectopic endometrial tissue (73). Similarly, Rajeswari et al. reported improved body weight gain and successful implantation rates, demonstrating curcumin's restorative influence on reproductive homeostasis (74).

Curcumin's anti-inflammatory role is further elucidated by studies focusing on its effects on specific molecular markers. Swarnakar and Paul (2009) conducted their work using a mouse model of surgically induced endometriosis, showing that curcumin reduced MMP-9 activity in endometriotic tissues, which was associated with lower TNF- α levels, reflecting its inflammation-modulating properties (75). Jana, Rudra et al. (2012) used an in vitro approach with human endometrial stromal cells and an in vivo rat model to add that curcumin inhibited MMP-2 activity through the upregulation of TIMP-2 and downregulation of MT1MMP, delaying endometriosis progression. The regulation of MMPs, key enzymes in tissue remodeling, suggests that curcumin can mitigate the invasive nature of endometrial cells, thereby stabilizing disease pathology (76).

In a network pharmacology analysis combined with an in vivo mouse model of endometriosis, it was revealed that curcumin modulates the inflammatory signaling pathway, impacting hypoxia and inflammation and reducing lesion size and adhesion (77).

The studies by Zhang et al. (2011), using a rat model of endometriosis induced by autologous transplantation, and Hendarto et al. (2010), employing a cyclosporine A-induced rat model, corroborated curcumin's anti-angiogenic properties by reducing VEGF expression in endometriotic tissue (67, 78).

Innovative drug delivery systems have been explored to optimize curcumin's efficacy. Curcumin-loaded nanofibers made from poly ϵ -caprolactone and polyethylene glycol (PEG) in a rat model of endometriosis induced by uterine tissue transplantation reduced endometrial gland size and lower inflammatory cell infiltration (79). Another study involving an in vivo rat model of endometriosis showed that nano curcumin significantly reduces oxidative stress markers and improves folliculogenesis, reinforcing the compound's role in enhancing reproductive health (80).

In contrast to the mentioned studies, a clinical trial conducted in 2022 involved 68 women with endometriosis who received curcumin supplementation (500 mg twice daily for 8 weeks). The results showed no significant differences in pain reduction or quality of life between the intervention and control groups, suggesting that curcumin did not provide measurable benefits for managing endometriosis symptoms (65).

In conclusion, the collective evidence from these studies suggests that curcumin exerts a complex therapeutic effect

against endometriosis. Its multi-targeted actions include anti-inflammatory, anti-angiogenic, anti-proliferative, and apoptosis-inducing pathways, where curcumin reduces inflammatory cytokine levels and alleviates oxidative stress. By enhancing growth factor expression crucial for folliculogenesis and inhibiting the survival of endometriotic cells, curcumin presents potential as a natural treatment option for managing endometriosis symptoms and supporting fertility. Furthermore, advanced delivery mechanisms may enhance its effectiveness. Despite these promising findings, further clinical investigations are warranted to deepen the understanding of curcumin's efficacy and mechanisms in endometriosis treatment.

6. Curcumin and Premenstrual Syndrome

Curcumin has been studied for its potential benefits in alleviating the symptoms of premenstrual syndrome (PMS) and dysmenorrhea (81). Both conditions are prevalent among women of reproductive age, causing significant discomfort and disruption to daily life (82). The mechanism through which curcumin exerts its effects involves its anti-inflammatory, antioxidant, and neuroprotective properties, which may help reduce pain, improve mood, and enhance cognitive function (82).

Several studies have highlighted the positive effects of curcumin supplementation on PMS and dysmenorrhea symptoms. In a randomized, triple-blind, placebo-controlled trial by Arabnezhad et al. (2022), curcumin supplementation significantly increased serum vitamin D levels, a factor often associated with menstrual health, and improved liver enzyme function in women with PMS and dysmenorrhea. However, the study did not report any significant effects on blood glucose levels, suggesting that curcumin's influence on PMS symptoms may be unrelated to metabolic changes (83). Curcumin also appears to benefit cognitive function in women suffering from PMS and dysmenorrhea. In another study, curcumin supplementation was associated with significant improvements in memory, inhibitory control, and selective attention. This suggests that curcumin might not only reduce physical discomfort but also mitigate cognitive impairments often associated with PMS (81).

Furthermore, curcumin's impact on inflammation has been explored in multiple studies. Talebpour et al. (2023) demonstrated that curcumin reduced serum levels of high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, without significantly affecting iron metabolism or other inflammatory biomarkers. This reduction in inflammation may contribute to curcumin's ability to alleviate pain and other PMS-related symptoms, as inflammation is thought to play a key role in the pathophysiology of these conditions (84).

Therefore, curcumin's multifaceted effects—ranging from inflammation reduction and vitamin D levels—make it a promising candidate for managing PMS and dysmenorrhea. While results are generally positive, further research with larger sample sizes, longer durations, and optimal dosing is needed to establish definitive clinical guidelines for curcumin use in treating these common gynecological complaints.

7. Beneficial effects of curcumin in Premature ovarian failure and ovarian aging

Curcumin has shown promising protective effects against premature ovarian failure (POF) in both rat and mouse models through its ability to mitigate oxidative stress and restore ovarian function. In a study by Melekoglu et al. (2018), curcumin was administered to rats following cyclophosphamide-induced POF, resulting in significant improvements in hormonal profiles, including increased serum estradiol and anti-Müllerian hormone (AMH) levels, alongside decreased FSH and LH levels. Histopathological assessments also indicated restoring ovarian tissue integrity with less inflammation and damage (85).

Similarly, a mouse model of POF induced by D-galactose demonstrated that curcumin treatment improved ovarian function by elevating progesterone and estrogen levels while decreasing FSH, LH, and malondialdehyde levels, indicative of reduced oxidative stress. Furthermore, curcumin treatment increased the proportion of primordial follicles and reduced apoptosis in granulosa cells (86).

Also, curcumin has significant protective effects on ovarian aging. Curcumin treatment in aging (7-8 months) FSH receptor haploinsufficient mice significantly improved ovarian health, particularly in the context of mild hyperandrogenemia, by enhancing the immunolocalization of bone morphogenetic protein-15 and indicating a better environment for oocyte health and development. Additionally, remarkable structural improvements in the zona pellucida were observed, suggesting a restoration of ovarian integrity (87).

Also, Azmi et al. demonstrated that curcumin treatment (100 mg/kg/day) in aging female mice significantly reduced oocyte apoptosis and necrosis enhanced ovarian volume, increased follicle count, and improved hormonal profiles at 12 and 33 weeks. Also, the expression of key genes related to oocyte maturation and anti-aging was upregulated (88).

Ischemia-reperfusion injury is a well-recognized condition that occurs when blood supply to tissues is temporarily blocked and then restored. This pathological process can significantly damage tissues and organs, including the ovaries. Sak et al. demonstrated that the administration of curcumin before ischemia and subsequent reperfusion injury led to a marked reduction in oxidative stress markers and tissue damage (89). Also, female Albino rats with unilateral ischemia/reperfusion treated with curcumin (200 mg/kg) during reperfusion exhibited a substantial increase in the levels of AMH (90).

Besides, nano curcumin showed significantly improved tissue recovery compared to those treated with conventional curcumin rats with ovarian ischemia-reperfusion injury demonstrating the enhanced bioavailability and efficacy of nano curcumin in reducing oxidative damage by enhancing antioxidant enzymes such as Superoxide Dismutase, Glutathione Peroxidase, and Glutathione-S-Transferase (91).

A study demonstrated that Curcumin 100 mg/kg/day curcumin administration for 50 days following tubal ligation in rats mitigates the decline in ovarian reserve, as evidenced by stable AMH levels, histological preservation of ovarian follicles and reduced apoptosis in granulosa cells (92).

Together, these studies highlight the multifaceted protective roles of curcumin in ovarian health, particularly in the context of reproductive system disorders. Curcumin's antioxidant and anti-inflammatory properties, as well as its ability to modulate key signaling pathways, position it as a promising therapeutic for preserving ovarian function and improving reproductive outcomes making it a promising candidate for further research in female reproductive health.

8. Curcumin as a Shield: Protective Effects Against Reproductive Toxicity Induced by Environmental and Pharmacological Agents

Curcumin has been extensively studied for its protective effects against reproductive toxicity induced by environmental and pharmacological agents. Research highlights its ability to mitigate oxidative stress, apoptosis, and hormonal imbalances in animal models exposed to various toxic substances (93, 94). For instance, in mice exposed to ionizing radiation, curcumin demonstrated anti-apoptotic properties, reducing follicular atresia and supporting granulosa cell proliferation (95). Similarly, it normalized hormonal imbalances and oxidative markers caused by lamotrigine an antiepileptic drug, while improving ovarian and uterine tissue architecture (94). Moreover, curcumin showed significant potential in countering toxicity induced by endocrine disruptors such as Bisphenol AF, where it restored cellular viability, suppressed apoptosis, and modulate oxidative stress pathways (96). In cases of chlorpyrifos exposure, a pesticide known for its oxidative and inflammatory effects, curcumin and its nanoformulations reduced inflammatory cytokines and enhanced antioxidant defenses across reproductive tissues (93).

Environmental toxins like sodium arsenite and acrylamide also induced reproductive damage, including oxidative stress and histological alterations in ovarian tissues. Curcumin alleviated these effects by restoring antioxidant enzyme activity and normalizing hormonal profiles (97, 98). Additionally, in chemotherapy-induced ovarian damage by cisplatin, curcumin preserved follicular structures, reduced apoptosis, and restored anti-Müllerian hormone levels, showcasing its therapeutic promise in reproductive health (99). These findings collectively underscore curcumin's broad-spectrum protective effects against diverse reproductive toxicants.

9. Curcumin's Safety Profile: Side Effects and Toxicological Considerations

While curcumin is generally considered safe for most people when used in moderate amounts, especially as a spice in cooking, it can have some adverse effects, particularly when taken in high doses as a concentrated supplement or with prolonged use (100). Understanding these effects is crucial for ensuring their safe application in clinical and therapeutic settings.

High doses can lead to gastrointestinal issues such as stomach upset, nausea, diarrhea, or indigestion, though these are often mild and subside once the supplement is discontinued or the dose is reduced (100). Curcumin may

also have anticoagulant properties, increasing the risk of bleeding, particularly for those taking blood-thinning medications like warfarin or aspirin; consulting a healthcare provider is crucial before use in such cases (17, 101).

Also, its potential hormonal effects could interfere with hormonal therapies or conditions, as curcumin may exhibit estrogenic activity, necessitating caution for individuals with hormone-sensitive conditions (101, 102). Additionally, curcumin can interact with various medications, altering their effectiveness or increasing side effects, making it essential to seek medical advice before starting supplementation, especially for those on prescription drugs (102).

10. Conclusion

Curcumin and its nanoformulations hold significant promise in enhancing female reproductive health by addressing key conditions such as PMS, PCOS, and endometriosis. With their potent anti-inflammatory, antioxidant, and hormone-regulating properties, these compounds present a holistic approach to managing reproductive disorders. Nanoformulations further amplify curcumin's efficacy by improving bioavailability and targeted delivery, offering innovative therapeutic avenues. However, while preclinical and clinical evidence underscores curcumin's safety and potential, the variability in outcomes highlights the necessity for further large-scale, well-designed studies to establish definitive guidelines. Advancing research into curcumin's mechanisms and exploring synergistic approaches with conventional treatments will be pivotal in maximizing its full therapeutic potential for female reproductive health.

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