

Review Article

## Curcumin and Pregnancy Problems: a Narrative Review of Curcumin's Effect on Preeclampsia

Marzieh Zanganeh<sup>1</sup>, Seyedeh Narges Mazloomi<sup>2\*</sup>, Ebrahim Alijanpour<sup>3</sup>, Ali Jabbari<sup>4,5,6</sup>

1. Department of Gynecology and Midwifery, Golestan University of Medical Sciences, Gorgan, Iran
2. Department of Food Science and Technology, Gorgan University of Agricultural and Natural Sciences, Gorgan, Iran
3. Department of Anesthesiology and Critical Care Medicine, Babol University of Medical Sciences, Babol, Iran
4. Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran
5. Department of Anesthesiology and Critical Care Medicine, Golestan University of Medical Sciences, Gorgan, Iran
6. Clinical Research Development Unit, 5 Azar Hospital, Golestan University of Medical Sciences, Gorgan, Iran

\* **Correspondence:** Seyedeh Narges Mazloomi, Department of Food Science and Technology, Gorgan University of Agricultural and Natural Sciences, Gorgan, Iran  
Email: [samira.mazloomi@yahoo.com](mailto:samira.mazloomi@yahoo.com)

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### Abstract

Curcumin is a bright yellow chemical produced by *Curcuma longa*, a member of the ginger family (Zingiberaceae). This compound is mainly extracted from fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin has been used as an herbal supplement, cosmetic ingredient and spice. Curcumin may be useful in the prevention and treatment of inflammation-associated adverse pregnancy outcomes mainly due to its anti-inflammatory properties, which are exerted through reduction of pro-inflammatory factors, macrophage infiltration and NF- $\kappa$ B activation. This review provides a brief overview of the efficacy of curcumin for treatment of preeclampsia.

**Keywords:** Curcumin; Pregnancy; Preeclampsia; Anti-Inflammatory

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## INTRODUCTION

Herbal medicine has contributed greatly to the commercial drug preparations today (1). Although herbs benefit from general acceptance of people worldwide, a limited number of them are proven to be beneficial in well-designed scientific studies (2). In addition, some people may suffer from side effects of medicinal herbs, which are usually not taken into consideration carefully (3). The World Health Organization (WHO) has recommended evaluation of effective plants for different disorders with limited effective, chemical medications (4). The current trend of the medical world is toward using natural compounds in disease prevention and treatment (5). Ethnobotanical and ethnopharmacological surveys intend to document traditional knowledge of medicinal plants for potential use in pharmacological sciences (6). Recently, a great deal of attention has been given to finding drugs with minimal side effects and high biocompatibility (7).

The use of medicinal herbs in obstetrics may affect the course and outcome of pregnancy. In gynecology, the situation can be even more alarming since these herbs may sometimes worsen certain conditions including infertility, uterine fibroids and malignancies (8). Curcumin is a polyphenol extracted from the rhizomes of turmeric (*Curcuma longa*). This compound is commonly used in cooking and cosmetic industry. Chemically, curcumin is a diarylheptanoid belonging to curcuminoids, which are natural phenols responsible for turmeric's yellow color. This tautomeric compound exists in enolic form in organic solvents and in keto form in water (9). Curcumin incorporates several functional groups whose structures were first identified in 1910. Curcumin has a diverse range of

molecular targets, including transcription factors, growth factors and related receptors, cytokines, enzymes and proteins that regulate cell proliferation and apoptosis (7-9). The phenols are connected by two  $\alpha,\beta$ -unsaturated carbonyl groups. The diketones form stable enols and are readily deprotonated to form enolates; the  $\alpha,\beta$ -unsaturated carbonyl group is a good Michael acceptor and undergoes nucleophilic addition (7-10). Curcumin also exhibits multiple pharmacological activities including antioxidant, anti-inflammatory, antibacterial and antiviral activities that makes it suitable as a potential therapeutic for cardiovascular disease, cancer and Alzheimer's disease. In other hand the clinical use of Curcumin has not confirmed in some studies; since it has poor bioavailability and is unstable. (10-13).

In this review, we summarize experimental, cellular and clinical information related to curcumin's potential in treatment of preeclampsia.

Various basic and clinical databases including the Cochrane Library, Database of Abstracts of Reviews of Effectiveness (DARE), TRIP, MEDLINE, EMBASE, Science Citation Index, Social Science Citation Index and NHS were searched. The reference list of the relevant review articles were also checked to find additional studies.

### **Anti-inflammatory activity of curcumin**

Curcumin is a compound found in *Curcuma longa*(14). possessing many biological activities, such as anti-inflammatory and antioxidants properties. Thus, it can be potentially used for treatment of oxidative stress and inflammatory diseases (14). Hansson et al. proposed that curcumin can be utilized as an alternative therapy for preeclampsia due to its ability in inhibiting regulator protein likeNF $\kappa$ B (15).

A recent study found that curcumin reduced malondialdehyde level as well as NF $\kappa$ B expression in rat model of preeclampsia (16). Curcumin has been studied recently in the treatment of preeclampsia. Curcumin treatment in various doses could decrease significantly pro-inflammatory cytokines levels in monocyte cultures exposed to preeclamptic plasma. According to studies, curcumin treatment significantly decreases nuclear NF- $\kappa$ B p50 and increases peroxisome proliferator-activated receptors (PPARs) (17, 18). In another study, Lipopolysaccharides (LPS) -curcumin treatment decreased blood pressure and urinary protein level, which was comparable to the control group. Moreover, curcumin treatment significantly lowered the increased TLR4, NF- $\kappa$ B and IL-6 and MCP-1 level in the LPS-treated group (19). It is suggested that curcumin can reduce inflammatory responses through NF- $\kappa$ B suppression by blocking the inhibitor of  $\kappa$ -kinase activation (20, 21). Curcumin also decreases inflammation by acting as an agonist of PPAR-c (15). Factors that limit the bioactivity of curcumin or its analogs include chemical instability, water insolubility, absence of potent and selective target activity, low bioavailability, limited tissue distribution and extensive metabolism (15,16). Curcumin is mostly excreted in feces without notable change, while very little amounts may escape the gastrointestinal tract. If curcumin enters plasma in reasonable amounts, there is a high risk of toxicity since it is promiscuous and interacts with several proteins including hERG, cytochrome P450s and glutathione S-transferase (15-17).

### **Effect of curcumin on preeclampsia**

In a rodent model of sepsis, intravenous administration of curcumin resulted in down-regulation of tumor necrosis factor-a

(TNF-a) and markers of tissue damage (17). In an animal study, adverse pregnancy outcomes were generated by daily administration of LPS to pregnant mice from gestation day 13.5 to 16.5. There is a dramatic blood pressure increase following LPS treatment, which may be due to excessive maternal inflammation resulting in endothelial dysfunction, alteration of maternal hemostasis and vasoconstriction (22). In addition to hypertension, LPS also increases proteinuria in pregnant mice. This is likely due to the LPS-induced renal damage. It was observed that the kidney of LPS-treated animals have extensive endothelial swelling as well as narrowing and occlusion of capillary lumen. Moreover, lower fetal and placental weight in LPS-treated animals is in agreement with the previous findings in humans showing fetal loss and fetal growth restriction (FGR) in Gram-negative bacterial infections. These findings suggest that inflammation is a key mechanism in the pathogenesis of LPS-induced adverse pregnancy outcomes (22, 23).

Clinical studies have shown that curcumin may have beneficial anti-inflammatory effects for the treatment of inflammatory bowel disease, acute respiratory distress syndrome, postoperative inflammation, knee osteoarthritis and chronic kidney disease (14, 24). Although the use of curcumin in pregnancy period is not well documented, phase I clinical trials have shown that curcumin is safe in humans even at high doses (12 g/day) (25). In another study, curcumin had no adverse effect on reproductive performance in two successive generations in a two-generation reproductive toxicity study in Wistar rats (26).

Some studies have shown that curcumin is not toxic to humans. However, there were a severe allergic reaction and a death caused by injection of a curcumin emulsion product

Two preliminary clinical studies in cancer patients consuming high doses of curcumin (up to 8 g/day for 3–4 months) reported no toxicity, but some subjects had experienced mild nausea or diarrhea. Curcumin is also safe for embryos, as one study found that curcumin inhibits methylglyoxal-induced apoptosis in mouse ESC-B5 cells and blastocysts by blocking reactive oxygen species formation (27, 28).

A growing body of evidence shows that modulation of inflammation may have therapeutic benefit in the prevention and management of pregnancy complications. For example, aspirin and vitamin D3 which has been shown to exert anti-inflammatory actions (28), can reduce the risk of preeclampsia and important adverse perinatal health outcomes when used with low dose in early gestation (29). Curcumin is another chemical with potential anti-inflammatory function. Recent researches now support the anti-inflammatory, anti-diabetic, antioxidant, and cardiovascular protective properties of curcumin (30). Numerous studies have shown that dietary curcumin reduces inflammation and delays or prevents obesity-induced insulin resistance and associated complications, including atherosclerosis and immune-mediated liver disease (31).

Studies have shown that excessive inflammatory response plays an important role in the pathogenesis and pathology of embryonic resorption, Fetal growth restriction and preeclampsia (32). As one of the most powerful bacterial virulence factors in terms of pro-inflammatory properties, LPS has been widely used to induce FGR and preeclamptic symptoms in rat and mouse models of pregnancy (27, 33).

The anti-inflammatory effects of curcumin are exerted through reduction of pro-inflammatory factors (TNF- $\alpha$ , IL-1 $\beta$  and MCP-1), macrophage infiltration and NF- $\kappa$ B

activation. Due to its anti-inflammatory property, curcumin may be useful in the prevention and treatment of inflammation-associated adverse pregnancy outcomes (27–29). Fadinie et al. reported that curcumin administration significantly decreases Cyclooxygenase-2 (COX-2) level in patients with preeclampsia, which led to a decrease in visual analog scale (VAS), shorter clotting time and lower thrombocyte count. Moreover, they found a significant correlation between clotting time and bleeding time at T2 in patients with preeclampsia (34, 35). Perioperative curcumin administration had no significant effect on the level of IL-10 and COX-2 in patients with preeclampsia undergoing caesarean section (36–38). Although there is no evidence that dietary consumption of turmeric as a spice adversely affects pregnancy or lactation, the safety of curcumin supplements in pregnancy and lactation has not been established (28,34).

## CONCLUSION

Curcumin is well-tolerated and has low toxicity in humans even at high doses. However, the use of curcumin in pregnancy is not well-documented. By inhibiting the expression of pro-inflammatory factors and macrophage infiltration in the placenta, curcumin can ameliorate the LPS-induced adverse pregnancy outcomes. More studies are required to evaluate effects of curcumin on pregnancy outcomes.

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## Ethics approvals and consent to participate

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## Conflict of interest

The author declares that there is no conflict of interest regarding publication of this article.

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