

The Influence of Turmeric and Curcumin on Female Reproductive Processes

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ABSTRACT

The present review summarizes the available knowledge concerning the action of curcumin, the best-known polyphenol among the rhizomes of *Curcuma*, on female reproductive processes and their dysfunctions. Curcumin affects a number of physiological processes, including female reproduction (puberty, reproductive aging, ovarian folliculogenesis and oogenesis, and fecundity). Curcumin can affect these processes via changes in the release and reception of pituitary and ovarian hormones, growth factors and cytokines. Furthermore, it can influence the response of ovarian cells to these substances and external environmental factors. Finally, curcumin can affect oxidative processes within the ovary and numerous intracellular signalling pathways related to ovarian cell proliferation and apoptosis. These effects suggest the applicability of curcumin for stimulation of female reproductive processes *in vivo* and *in vitro*, as well as for the prevention, mitigation, and treatment of various reproductive disorders from ovarian insufficiency and infertility to polycystic ovarian syndrome and ovarian cancer.

Introduction

Curcuma/turmeric is a popular spice. Its health-promoting effects have already been described in several reviews [1–5]. On the other hand, only one publication [6] reviewed curcuma action on reproductive processes, though it was focused on cancerogenesis and not on curcuma action on a healthy reproductive system. The present publication is the first attempt at summarizing the available information concerning the action of curcuma and its constituents on a healthy female reproductive system, as well as of the data concerning their ability to prevent and to treat reproductive disorders.

A search of the literature was performed in agreement with PRISMA-ScR criteria [7]. To find related articles, Pubmed, Web of Science, and SCOPUS databases were searched for articles published between the years 2000 and 2021. In cases of repeated or conflicting information or references, the most recent source was

used. Words used in the search were curcumin, turmeric, review, health, metabolism, fertility, ovarian, and mechanisms.

Provenance and Properties

The herbs that belong to the genus *Curcuma* (Zingiberaceae) are currently cultivated in tropical and subtropical areas of Asia, Australia, and South America. Approximately 93–100 species of *Curcuma* are described now. These herbs are widely used for the coloring and flavoring of food, for preparation of food additives (the most known is curry powder), dyes, perfumes, and cosmetics as well as in folk medicine. The most known and useful *Curcuma* species are *Curcuma longa* (Indian turmeric) and *Curcuma zedoaria* (zedoary). Turmeric is native to Southeast Asia but is now cultivated extensively worldwide. Zedoary originated from India and Indonesia but it is cultivated in many subtropical regions around

the world. The rhizome is the most commonly used part of these plants.

Turmeric rhizome typically contains carbohydrates (69.4%), protein (6.3%), fat (5.1%), and minerals (3.5%). The main active components of the rhizome are the non-volatile curcuminoids and the volatile oil [3]. A main biologically active component of *C. longa* L. is curcuminoids curcumin, which is chemically known as diferuloylmethane [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-epitadiene-3,5-dione], and its polyphenolic derivatives and metabolites, demethoxycurcumin and bisdemethoxycurcumin [1]. The major components of curcuma oils are sesquiterpenoids and monoterpenoids [3,4].

Mechanisms of Action

Curcumin has antioxidant, anti-inflammatory, antimicrobial, proapoptotic, antiproliferative, antiangiogenic, and antimutagenic activities [2,4,8–10], which determine its physiological and therapeutic effects. For example, the antioxidant action of curcumin defines its ability to prevent oxidative stress, DNA, and protein damage [10]. Common molecular intracellular targets and mediators of curcuma action could be cytokines and transcription factors promoting inflammatory processes, some protein kinases, and enzymes. Curcumin can affect a number of signaling molecules like Nrf2, β -catenin, NF- κ B, p38 MAPK, DNA (cytosine-5)-methyltransferase-1, COX-2, TNF- α , 5-lipoxygenase, PGE2, FOXO3, generation nitric oxide and reactive oxygen species, cyclin D1, VEGF, glutathione, cytosolic PLA2, and p-Tau (p-t). For example, curcumin can suppress inflammatory processes through the downregulation of intracellular promoters of inflammation such as Nrf2, NF- κ B, STAT3, reactive oxygen species, and COX-2 (see [2] for review). On the other hand, curcumin can boost the functions of immunocompetent cells, the production of inflammatory cytokines, and reparative processes [11,12]. Furthermore, curcumin can suppress cancerogenesis [10,13] and other illnesses [14] targeting microRNAs and long non-coding RNAs. The physiological action of turmeric oils could be explained by their ability to inhibit reactive oxygen species, COX-2, and other signaling molecules as well [3]. This ability of turmeric molecules to modulate many extra- and intracellular signaling pathways related to various dysfunctions and diseases suggests that it is a polyphenol with many targets and physiological and medicinal actions [2,4].

Physiological and Therapeutic Actions

The current literature describes anti-inflammatory, antioxidant, anticancer, antimutagenic, antimicrobial, anti-obesity, hypolipidemic, cardioprotective, wound healing, and neuroprotective properties of curcumin [4,5,11,15]. Curcumin-containing *Curcumas* are popular in Asian folk medicine to treat pneumonia, bronchitis, leucorrhea, diarrhea, dysentery, infectious wounds or abscesses, and insect bites. In this context, curcumin is applicable as a carminative, digestive aid, stomachic, anthelmintic, appetizer, tonic, and laxative. It is also used as a treatment against fever, gastritis, dysentery, infections, hypercholesterolemia, hypertension, chest congestion, arthritis, jaundice, liver and gall bladder problems, cough, urinary tract infections, skin diseases, dia-

betic wounds, and menstrual discomfort [3,4]. It can be a potent immunostimulator and anticancer drug [11]. Many reports indicate that curcumin can regulate blood sugar levels, decrease blood pressure, protect nerve cells, and enhance immunity. Therefore, curcumin may be especially beneficial for the elderly in the prevention and treatment of age-related disorders like diabetes and diabetic complications as well as neurodegenerative and cardiovascular diseases [5].

As mentioned above, polyphenol curcumin has antioxidant, anti-inflammatory, anticancer, antiangiogenic, wound healing, and antimicrobial properties. Due to these properties, curcumin has been shown to be efficient for the treatment of numerous chronic diseases including various types of cancers, diabetes, obesity, and cardiovascular, pulmonary, neurological, infectious, and autoimmune diseases [2,8,9,16]. Furthermore, curcumin can be a synergist to other plant polyphenols with therapeutic action like resveratrol, catechins, piperine, quercetin, and genistein [2].

Curcuma essential oils, like curcumin, possess a number of biological and medicinal properties, including anti-inflammatory, anticancer, antiproliferative, hypocholesterolemic, antidiabetic, antihepatotoxic, antidiarrheal, diuretic, antirheumatic, hypotensive, antioxidant, antimicrobial, antiviral, insecticidal, larvicidal, antivenomous, carminative, and antithrombotic effects. These oils can promote functions of the immune system, blood circulation, detoxication, and digestion (see [3,4,16] for reviews).

Curcuma longa extracts possess renal protective, hepatoprotective, cardioprotective, antidiabetic, neuroprotective, and gonadoprotective effects [2,4,6].

Moreover, curcumin can mitigate or prevent the harmful action of environmental contaminants [15]. For example, it has been shown to reduce genotoxicity, nephrotoxicity, hepatotoxicity, skin diseases, angiogenesis, reproductive toxicity, neurotoxicity, and immunotoxicity of arsenic [10]. Either no or no substantial negative curcumin side effects have been observed [4,16].

Effect on Female Reproductive Processes

Effect on reproductive organs

Feeding rats curcumin did not affect weight of their ovaries or size of their litters [17]. On the other hand, an artificial pegylated curcumin analogue inhibited rat ovarian follicle development, sexual maturation, and fecundity [18]. Curcumin promoted ovarian growth, folliculogenesis [19], and mitigated the age-dependent suppression of ovarian functions in mice [20], d-galactose-induced ovarian failure in mice [21] and ovarian failure induced by cyclophosphamide in rats [22]. Dietary curcumin promoted ovarian folliculogenesis and ovulation in the fish *Pseudotropheus socofofi* [23]. The plant additive containing curcumin promoted ovarian follicle development in the buffalo as well [12]. On the contrary, Destici Isgoren et al. [24] did not observe an effect of the curcuma extract on rat ovarian follicle development. Feeding rabbits turmeric powder did not influence their ovarian size or weight, but it increased the number and diameter of ovarian follicles. It did not affect rabbit fecundity but increased the viability of their pups [25].

Tossetta et al. [15] presented evidence that curcumin can be useful for managing pregnancy complications (preeclampsia, gestational diabetes mellitus, fetal growth retardation, preterm birth, and response to toxins and pathogens).

Therefore, the data listed above suggest curcumin can both up- and downregulate puberty, ovarian folliculogenesis, and fecundity, as well as prevent complications during pregnancy. The character of its effect depends on the animal species and experimental model.

Effect on ovarian cell functions

One *in vitro* study showed a suppressive effect of curcumin on basic healthy ovarian cell functions. In a study by Kádasi et al. [26], the addition of curcumin reduced proliferation and viability and promoted apoptosis in cultured porcine ovarian granulosa cells. Numerous studies on ovarian cancer cells showed the ability of curcumin to inhibit the cell cycle and to promote apoptosis [8, 13, 17, 27–35].

In vivo studies have shown the opposite, stimulatory action of curcumin and its analogue on murine ovaries. In these studies, curcumin stimulated proliferation and inhibited apoptosis in murine [21, 35–37] and rat [24] ovarian cells. Moreover, curcumin stimulated ovarian oogenesis in mice [19, 36, 37]. Therefore, the available publications demonstrate the curcumin has an influence on ovarian cell mitosis, meiosis, apoptosis, and viability.

Effect on reproductive hormones

In vivo experiments demonstrated the ability of curcumin to decrease the concentration of gonadotropins FSH (follicle stimulating hormone) and LH (luteinizing hormone) in rat serum [19, 22]. Surprisingly, a decrease in gonadotropin release was associated with a rise in the serum level of estradiol and anti-mullerian hormones [19, 22], which should be upregulated by gonadotropins [38]. Rabbits fed curcumin had an increase in the ovarian production of progesterone but a decrease the ovarian release of testosterone and leptin. Moreover, feeding rabbits curcumin altered the response of ovarian cells to LH, as LH reduced leptin release by ovarian cells of the control rabbits but increased leptin release by ovarian cells of rabbits fed curcumin [25].

In vitro experiments also showed the stimulatory influence of curcumin on progesterone and testosterone release by cultured porcine granulosa cells [26], and its inhibitory action on progesterone release by cultured luteal cells from rat ovaries [39].

Some experiments, however, did not show any curcumin influence on FSH, progesterone, or estradiol [17] or anti-mullerian hormones [24] in rat plasma. Moreover, they demonstrated a curcumin-induced increase in LH and a decrease in prolactin concentration in the plasma of rats fed curcumin [17]. Thus, the performed studies demonstrated that curcumin influences (1) the release of gonadotropins by pituitary cells, (2) the release of hormones by ovarian cells, and (3) the response of ovarian cells to gonadotropins.

Mechanisms of action on female reproductive processes

It can be easily noted that the curcumin effects observed in *in vivo* and *in vitro* studies are different, and sometimes contradictory.

This fact indicates the action of curcumin directly on ovarian cells and on their upstream regulators. The best-known endocrine and paracrine/autocrine regulators of reproductive and other physiological actions are hormones. It is well documented that fecundity is defined by the growth, development, and atresia of follicles in the ovary, and that these processes are under the control of gonadotropins, ovarian steroids, and peptide hormones [38]. The previous sections of this review have demonstrated that curcumin can influence pituitary and ovarian hormones, which can mediate curcumin action on reproductive processes.

Curcumin as a phytoestrogen [40] can interact with the steroid hormones and their receptors, affect the hypothalamo-hypophysial-ovarian axis, and treat some reproductive disorders [41]. For example, in mouse ovaries, curcumin can suppress androgen receptors and stimulate 3-beta-hydroxysteroid dehydrogenase [20], although it does not affect aromatase [42]. Furthermore, curcumin mitigated the action of dehydroepiandrosterone on mouse ovarian cell apoptosis [35]. Therefore, the influence of curcumin on ovarian functions and state could be mediated by its action on ovarian steroid hormone receptors.

There are indications that curcumin action on the ovary (at least the ovary suffering from polycystic ovarian syndrome) can be mediated by its suppressive action on inflammation [6] and inflammation-related cytokine interleukin-6, tumor necrosis factor- α , C-reactive protein [43], growth factors GDF-9 and BMP-15 [19, 44], and vascular endothelial growth factor [6].

Furthermore, the influence of curcumin on intracellular regulators of the cell cycle and apoptosis in healthy [21, 26, 35, 36, 45] and cancer [6, 13, 28, 30, 33, 34] cells suggests that these regulators could be mediators of curcumin action on ovarian cell functions. Viability, proliferation, and apoptosis of ovarian cells should affect their hormone release as mentioned above, although the opposite effect of steroid and peptide hormones on ovarian cell proliferation and apoptosis has also been documented [35, 38].

Curcumin action on ovarian cell mitosis and apoptosis can be mediated by its action on transcription factor p53, which stops the cell cycle, promotes DNA reparation, and induces apoptosis in defect or cancer ovarian cells [6]. On the other hand, there is evidence that p53 does not mediate the stimulatory action of curcumin on apoptosis in ovarian carcinoma cells. Evidence has shown that curcumin can activate proliferation promoter p38 mitogen-activated protein kinase (MAPK) and downregulate anti-apoptotic peptides Bcl-2 and survivin and Akt signaling [28]. The involvement of MAPK in mediating curcumin action has also been demonstrated for healthy ovarian cells [39].

The results of other studies have indicated that curcumin action on ovarian cancer cells or ovarian cells suffered from polycystic ovarian syndrome could be mediated by transcription factor STAT, matrix metalloproteinase-9 [6], sarco/endoplasmic reticulum Ca²⁺ ATPase [30], 5' AMNe-activated protein kinase, NF- κ B, heat shock protein 70 [33, 36], PI3K/Akt and Nrf2/HO-1 [21], AKT/mTOR/p70S6K [13], Wnt/ β -catenin signaling pathways [33], and enzymes SIRT-1 and SIRT-3 [44].

The antioxidant curcumin can bind reactive oxygen species and, therefore, prevent peroxidation and degradation of nucleic acids, peptides, lipids, and the consequent apoptosis, aging or malignant transformation of healthy cells, but not cancer cells [6,

19, 44]. It is not to be excluded that the protective effect of curcumin against pregnancy complications could also be due to its antioxidant properties [15]. Recently, the involvement of some micro-RNAs and long non-coding RNAs in regulating various types of cancer cells and curcumin action on these cells have been indicated [13, 33].

Application in Reproductive Biology and Medicine

The available reports regarding curcumin's effect on reproductive processes allows for outlining possible areas of its application. The ability of curcumin to promote ovarian folliculogenesis and fecundity in laboratory rodents [18, 19, 21, 35–37] and rabbits [25] *in vivo* indicates its potential applicability as a natural biostimulator of reproduction in large farm animal production. Furthermore, its ability to improve oocyte maturation, quality, and developmental capacity [19, 36, 37, 45] suggests that its addition could be beneficial for *in vitro* oocyte maturation, fertilization, and embryo production.

Furthermore, evidence suggests its applicability for the prevention, mitigation, and maybe even treatment of some age-dependent reproductive disorders including late sexual maturation [19, 20], reproductive aging, ovarian insufficiency and failure [5, 20–22, 24, 36, 37], complications during pregnancy [15], and a prolonged postpartum period [12]. Moreover, its potential to prevent, mitigate, and treat signs of ovarian cancer [8, 11, 13, 17, 27–34], polycystic ovarian syndrome [35, 43, 44], and adverse effects of immunological shock [36], hypoxia [46], ionizing irradiation [45], ischemia [47], oxidative stress [44, 48], mykotoxins [48], and arsenic [10] on ovarian functions suggests the large therapeutic potential of curcumin and its molecules.

It is, however, necessary to note that wider application of curcumin can be limited by its relatively low solubility, bioavailability, bioabsorption [1, 29, 49], and stability in light and in organisms [34]. To improve these physicochemical and therapeutic characteristics, the following approaches have been tested:

1. Synthetic curcumin analogues with enhanced bioabsorption and a higher ability to block reactive oxygen species and cancer development [29].
2. Application of curcumin nanoparticles with higher absorption, transport through cell membranes and accumulation in the ovary [49], with increased stability and a proapoptotic effect on cancer cells [34], or with enhanced antiparasitic properties [16].
3. A combination of chemical modifications of curcumin and the generation of nanoparticles from the modified curcumin [32].
4. The application of lipid [9, 16, 31] or metal [35] nanoparticles as carriers for curcumin transport.

The chemical modifications of curcumin and its carriers could expand the possibilities and efficiency of its application in animal production, biotechnology, and human and veterinary medicine.

Conclusion and Possible Directions of Further Studies

Rhizomes of *Curcumas* contain various biologically active substances, the best-known of which is polyphenol curcumin, which has a wide array of biological and medical effects. Its influence on female reproduction (puberty, reproductive aging, ovarian folliculogenesis and oogenesis, and fecundity) has been well documented. Curcumin can affect these processes via changes in the release and reception of pituitary and ovarian hormones, growth factors and cytokines. Furthermore, it can influence the response of ovarian cells to these substances and external environmental factors. Finally, curcumin can affect oxidative processes within the ovary and numerous intracellular signalling pathways related to ovarian cell proliferation and apoptosis. These effects described in the details above suggest the applicability of curcumin for stimulation of female reproductive processes *in vivo* and *in vitro*, as well as for the prevention, mitigation, and treatment of various reproductive disorders from ovarian insufficiency and infertility to polycystic ovarian syndrome and ovarian cancer.

On the other hand, numerous aspects of *Curcumas'* influence and application in the control of female reproduction require further studies. Previous investigations were focused mainly on curcumin, whilst reproductive effects of other constituents of *Curcumas*, including curcumin derivatives and curcuma oils, remain not studied as of yet. Hierarchical interrelationships between numerous mechanisms of curcumin action on reproduction require further elucidation. It could help to understand the causes of different actions of curcumin *in vivo* and *in vitro* on healthy cells and cancer cells. The available information concerning the effect and potential applicability of curcumin listed above was obtained mainly during animal and *in vitro* experiments, while clinical studies remain rare and insufficient. Increased bioavailability and efficiency of curcumin requires further efforts of specialists in chemistry and medicine. Nevertheless, the available information demonstrates that curcumin can be a promising, inexpensive, accessible, and efficient natural regulator, protector, and medicine for animal and human female reproductive processes.

Contributors' Statement

The manuscript has been generated by one author.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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