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Exploring the Role of Curcumin in Supporting Reproductive Health and Infertility- Focus on ROS Scavenging Ability

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ABSTRACT

Attention toward traditional medicine is increasing in recent years. Curcumin as an herbal polyphenolic compound has a therapeutic potential in supporting reproductive health and infertility. The effect of free radicals on male and female reproductive disorders is clear, and many of these problems lead to infertility. As a non-toxic substance, curcumin has antioxidant, anti-cancer و anti-inflammatory, etc. properties. Curcumin can neutralize free radicals and improve the quality of the target tissue. So it seems that the usage of curcumin and its analogs can be effective in treating many male and female reproductive diseases.

Introduction

Todays, much attention is paid to the usage of medicinal plants, and since the active ingredients of herbal medicines are biologically balanced with other substances found in their combination, they do not accumulate in the body and have few side effects and in this respect they are significantly better than chemical drugs. (1). Turmeric, with the scientific name "*Curcuma longa*", from the "*Zingiberaceae*" family, is one of the oldest plants that has been used in traditional medicine for a long time and has been used for blood purification, arthritis treatment, food digestion, liver protection as well as an anti-inflammatory agent (2-4). Its ground powder has been used for centuries as a seasoning, food preservative and coloring agent. The color of turmeric is due to a substance called Curcumin 1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-hepadiene-3,5-dione) ($C_{21}H_{20}O_6$), which makes up 3 to 4% of it (5). Curcumin is a bright yellow seed and one of the main polyphenolic compounds obtained from turmeric rhizome. Curcumin

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was isolated for the first time in 1842 by "Vogel" (6, 7) and its chemical structure was determined by "Milobedeska" and Colleagues in 1910 (7). This valuable seed was introduced to the Western world in the 14th century and is still used today. In ancient India "Ayurveda" that was the substance made from turmeric and had been used in the treatment of eye infection and inflammation, as well as healing injuries caused by burns, bites and other skin problems (4).

Owing to the therapeutic potentials that were mentioned about Curcumin as a medicinal plant, usage of this precious natural substance has widely increased and one of its important targets is reproductive organs.

Free Radicals and Male Infertility

Oxidative stress is one of the main causes of male infertility, and many infertile men have high levels of (Reactive Oxygen Species) ROS in their sperm. The main site of free radical production and target in the male reproductive system is the mitochondria (8). Production of reactive oxygen species activates various redox-dependent signaling pathways and induces mitochondria to regulate sperm function. Thus, ROS production in spermatozoa is a physiological process that plays an important mediating role in signaling mechanisms, sperm capacitation, facilitating the acrosome reaction and sperm oocyte fusion (9), but because the sperm plasma membrane contains a large amount of unsaturated fatty acids and the cytoplasm has few scavenging enzymes, it is susceptible to damage caused by oxidative stress under non-physiological conditions (10). High concentrations of hydrogen peroxide cause lipid peroxidation and eventually lead to cell death. Peroxidation of unsaturated fatty acids in the head and midsection of the sperm causes changes in sperm morphology, decreased motility and ineffectiveness of the sperm-oocyte fusion reaction (11).

ROS damage can include depletion of sperm ATP causing disruption of the phosphorylation process, lipid peroxidation, and ultimately loss of sperm motility and longevity. Decreased motility may be associated with steps that ultimately lead to a reduction in phosphorylation of axonemal proteins and sperm motility (3, 12), both of which are accompanied by a decrease in membrane fluidity, and that fluidity is essential for sperm-oocyte connection. Moreover DNA damage caused by excessive levels of ROS can accelerate apoptosis and lead to reduced sperm count, which is associated with male infertility (3). Clear reasons indicate that human spermatozoa produce oxidizing agents. The amount of ROS produced by sperm is inversely related to sperm quality (11).

When sperm formation is disrupted in the presence of a large amount of ROS, the spermatozoa that are released from the germinal layer have damaged cytoplasm (13). Under these conditions, the released spermatozoa are immature and practically incomplete. These sperms have redundant cytoplasm, which is an accumulation of cytoplasm in the middle region of the sperm. Cytoplasmic accumulation in spermatozoa is certainly related to ROS production, and this relationship is through the mechanisms directed by the enzyme glucose 6-phosphate dehydrogenase (G6PD) (10, 13). The amount of this enzyme increases in the middle part of the spermatozoon. This enzyme regulates the amount of glucose flow throughout the hexose monophosphate pathway and thus controls the amount of NADPH. Spermatozoa use NADPH as an electron source that stimulates the production of ROS by an enzyme system known as NADPH-oxidase (9). Mitochondria are the main source of intracellular ROS production. Conjugation of electron transport with oxidative phosphorylation causes the maintenance of high membrane potential in mitochondria, which requires ATP production in somatic cells. This process in sperm is damaged by overproduction of ROS and therefore the mitochondrial membrane potential is reduced (14).

Nitric oxide is a kind of free radical molecules which produced by the enzyme nitric oxide synthases (NOSs) (15). Although NO in low concentrations have essential roles in the

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male reproductive system, its excessive production can have many negative effects on the quality of testes tissue and sperm parameters. Since sperm have a large amount of unsaturated fatty acids in plasma membrane (16) and it's cytoplasm has little scavenger. It is sensitive to the damage caused by oxidative stress that occurs in non-physiological conditions. Reactive nitrogen species (RNS) can cause damage to all biomolecules in the cell, especially mitochondria, and causes a decrease in mitochondrial membrane potential (MMP). Besides, the effect of high concentration of nitric oxide in apoptosis induction in many cells, including epithelial, endothelial and mesangial cells, has been shown (17, 18).

Studies demonstrated that the production of ROS causes disturbances in the transfer of electrons in the mitochondria inner membrane. The transfer of electrons and oxidative phosphorylation in sperm keeps the mitochondrial membrane potential (MMP) at a high level (19, 20). In a study conducted on the correlation between MMP, sperm quality with fertility, it was shown that high MMP is an indicator of normal sperms with proper motility (21). Studies indicated that MMP decreases in patients with varicocele (22), which can be a reason for decreased sperm motility in these individuals. High MMP is required for ATP production and consequently for sperm motility and since it is an important indicator for determining the health and function of the cell, so it has been carefully considered (21).

Free Radicals and Female Infertility

ROS level and antioxidants in a physiological condition have vital roles in reproductive processes such as oocyte maturation, fertilization, and endometrial shedding. But under pathological condition, over production of ROS and consequently imbalance between oxidant and antioxidant level leads to reproductive system dysfunction that resulted in infertility (23). ROS are known as a double-edged sword and since many authors reported the presence of oxidative stress (OS) markers in the serum and follicular fluid of IVF patients, it is clear that the presence of a large amount of free radicals could be the major cause of female infertility (24).

Since the ovaries are metabolically active, they are constantly affected by various types of stress. OS affects various functions of the ovary, including egg maturation, ovulation, and luteal function (25).

Studies have shown that changes in superoxide dismutase (SOD) and ROS levels can cause endometrial disability in the late phase of secretion (23).

Polycystic ovary syndrome (PCOS) is considered as the most common endocrine disorders in women of reproductive age (26). In these patients, OS is considered as a reason of increased androgen production in the ovary, the creation of abnormal follicles, damage to the DNA in ovarian epithelium cells, and cell apoptosis. Furthermore, this disease is related to raising in mitochondrial dysfunction and decreasing in antioxidant levels (26, 27).

Endometriosis is an identified benign and estrogen-dependent disease that is known to be directly associated with female infertility (28). Although many theories are existed related to this multifactorial and complex disorder but retrograde menstruation is most likely mechanism that is explained (29). It has been shown that iNOS activity and NO production from the peritoneal macrophages were considerably increased in endometriosis. Radical metabolism is closely related to the inflammatory process and the development of endometriosis complications. Furthermore, peritoneal fluid nitrite and nitrate content in endometriosis is higher than normal (30). Beside, many studies have reported oxidative stress markers in patients with endometriosis (29).

Pelvic adhesions that is one of the major cause of infertility in female, are fibrous adhesions between tissue surfaces in non-anatomical areas that can involve nerves and blood vessels and are often seen after surgery, infection, inflammation (31, 32). It has been suggested that ROS could be involved in the formation of post-surgery adhesions. Free

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radicals are probably generated locally in the peritoneal tissue during laparoscopy as a result of the ischemia/reperfusion process; in part, their development may be related to exposure to a hyperoxic environment (room air) during laparotomy. It has therefore been hypothesized that the susceptibility to infection is due to increased activity of either free radicals or scavenger molecules (23, 32). Preeclampsia is a complex disease that occurs in 3% -14% of pregnancies worldwide and presents as a rise in blood pressure. Preeclampsia represents a high level of OS markers than normal pregnancies. Early-initiation of Preeclampsia is coincidence with increased levels of protein carbonyls, lipid peroxides as well as DNA oxidation, all indicators of placental dysfunction.(29).

Many studies demonstrated that higher level of total antioxidant capacity (TAC) in follicular fluid (FF) of women undergoing IVF is associated with successful fertilization (33, 34).

Properties of Curcumin

Antioxidant effects

Curcumin can act as a free radical scavenger through breaking the chain reaction of free radical production. And consequently improve reproductive tissue quality by increasing the expression of antioxidant genes (3, 12). Studies have shown that curcumin inhibits the production of nitric oxide and free radicals by macrophages (35). Curcumin interacts with protein kinase C and calcium. It is claimed that an increase in cytosolic calcium may cause an increase in ROS level (36). It has been determined that the antioxidant effect of Curcumin is to inhibit calcium entry and inhibit protein kinase C. The antioxidant effect of Curcumin is equal to the effects of vitamin C and E. Curcumin also stimulates the activity of enzymes that play a role in the synthesis and change of unsaturated fatty acids to saturated fatty acids. Therefore, it is possible that Curcumin modulates the natural fluidity of the cell membrane.

Many studies indicated that Curcumin inhibits the production of nitric oxide as well. In fact, Curcumin inhibits iNOS production in activated macrophages. In addition, Curcumin reduces the level of iNOS protein by decreasing the mRNA expression of iNOS. The exact mechanism of inhibition of iNOS production by Curcumin is not precisely known. According to one theory, Curcumin inhibits the production of protein kinase C and tyrosine kinase, and inhibiting both, leads to the prevention of iNOS production.

Anti-inflammatory properties

The anti-inflammatory potential of Curcumin is because of its polyphenolic structure. Curcumin compounds could interact with several pro-inflammatory molecules and inhibited inflammation mechanism by eliminating molecular targets (37). Curcumin reduces protein responses associated with inflammatory processes, such as interleukin-1 (IL-1), IL-2, IL-6, IL-8 and IL-12 as well as tumor necrosis factor alpha (TNF-α). TNF-α is a key mediator of inflammation that finally resulted in many chronic disorders. The existence of TNF-α, starts up nuclear factor (NF)-κB and leads to inflammatory responses. Researches have been shown that Curcumin could suppress TNF-α activation of the NF-κB pathway (4).

Anti-cancer activity

Curcumin inhibits cancer growth both in vivo and in vitro. It prevents cell proliferation in several cancer cell lines and prevents tumor growth. There are several mechanisms of action that how Curcumin impacts on cancer cells: in addition to mitotic inhibition in different kind of tumor cells, G1/S arrest and induction of apoptosis have been reported. Furthermore, experimental studies detect many molecular targets, such as transcription factors, cell cycle proteins, enzymes, adhesion molecules, as well as cytokines (38).

Anti-Infection activity

Antiviral activity about Curcumin has been reported in different studies. Several studies have shown that Curcumin could present anti-HIV potential by targeting the proteins of

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virus. In addition, Curcumin inhibits the hepatitis virus so can be effective in the treatment of liver-related diseases. Curcumin also could exhibit inhibitory activity against Influenza, and herpes viruses (22).

Effects of Curcumin on Reproductive Health

Impact of Curcumin on Male Reproductive Health

Exploring the reports presented regarding the medicinal effect of Curcumin on the male reproductive system, shows that this herbal non-toxic substance has healing effects on sperm parameters, which can be due to the its antioxidant properties. Curcumin stops oxidative changes in sperm and testicular membrane, which ultimately resulted in increased sperm motility and reduced spermatozoa defects (39).

In one study, Curcumin has been shown to decrease serum level of triglyceride, cholesterol, and phospholipids and also fertility in male rats (40).

In another study, it was revealed that Curcumin reduced nitrate-induced reproductive changes as indicated by normalized lipid peroxidation, testicular antioxidant components (including glutathione (GSH) superoxide dismutase (SOD) and γ-glutamyl trans peptidase (γ-GT)), total proteins, DNA and RNA contents in serum and testis and sperm count in male wistar rats (41).

p53 is an important factor in suppressing tumor cells, which could induce apoptosis process. Curcumin application for the treatment of human ovarian cancer cell line (Ho-8910) was shown to increase total p53 levels. In addition, Curcumin treatment has depleted the levels of anti-apoptotic agents such as Bcl-2 and Bcl-XL and grew the levels of pro-apoptotic factor Bax in these cells (42).

In a study it was found that Curcumin plays a supportive role against the harmful effects of cadmium chloride applied to the sperm parameters of adult mice (43). In fact, Curcumin as a potent radical scavenger could decrease oxidative stress and ameliorate adverse effects of cadmium chloride on lipid oxidation and sperm plasma membrane integrity considerably (44).

Sharma and Singh assessed the role of Curcumin administration on adverse effects of pesticide lindane on the testis. They found that Curcumin could improve sperm parameters like count and motility and also ameliorate testis and epididymis weight in male Wistar rats after reproductive toxicity caused by lindane. Curcumin also improved antioxidants components such as catalase, superoxide dismutase and glutathione-s-transferase activity in treatment groups (45).

In another study, sodium arsenite caused destructive effects on sperm count and testicular tissue structure of adult mice and it was reported that Curcumin could have a defensive role against the changes caused by this environmental pollutant (46). Another study showed the preservative role of Curcumin in the colonization of spermatogonial stem cells of rats under radiation therapy (39). Curcumin also have been shown to act as an antioxidant protecting roles on spermatozoa under oxidative stress in cattle.

This natural product can adjust several signaling pathways and impact different molecular targets. And due to its safety, efficiency, diverse molecular targets, not high cost, Curcumin has been predicted as a promising product for preventing the effects of various substances and diseases in male reproductive system (47, 48).

Impact of Curcumin on Female Reproductive Health

Curcumin has useful impacts on ovarian diseases, which can be achieved by its antioxidant, anti-apoptotic and anti-inflammatory properties. Curcumin has been reported to reduce ovarian ischemia/reperfusion injury by reducing markers of OS (49). The potential of Curcumin in the treatment of PCOS has been investigated. One study demonstrated that Curcumin has an ameliorating effect on PCOS complications caused by letrozole in female Wistar rats and is suggested to be widely used in the treatment of this syndrome (50, 51). In a study by Mohammadi et al. in

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2017, it was found that Curcumin had anti-inflammatory properties and a supportive role in the treatment of PCOS by influencing TNF and IL-6 levels and modulating endocrine disorders (52). Furthermore, one of the major symptoms of PCOS is elevated androgen levels. Curcumin has been reported to decrease high androgen levels in PCOS (4).

HSV-2 (Herpes simplex virus type 2) is one of the most common sexually transmitted viruses and is an identified risk factor for HIV infection in the female genital tract (FGT). In a research study, Curcumin has been found to inhibit HSV-2 infection and inhibit the inflammatory cytokines and chemokine production in genital epithelial cells in vitro.(53).

Different in vitro and in vivo research studies indicate that estrogens may raise the risk of endometrial and breast cancer (BC) through various molecular mechanisms, such as cell growth activation, reduction of apoptosis and DNA fragmentation (54, 55). There is evidence that Curcumin and its several analogs may present chemo preventive and antitumor action against reproductive tract cancers in both males and females due to their ability to regulate androgen - and/or - estrogen related pathways (56).

Many clinical trial studies have indicated that Curcumin could prevent d-galactose-induced OS, apoptosis, and ovarian damage. Furthermore, decreased MDA and increased SOD levels were observed in the Curcumin-treated groups (57). In addition, in one study Curcumin has been shown to increases the protein expression level of NF-E2-related factor-2 (Nrf2) and HO-1, which are proteins that are involved in the removal mechanism of ROS. Nrf2 could bind to antioxidant response elements (ARE) in the promoter region of Nrf2 target genes, which used sequential HO-1 enzymatic processes to scavenge ROS (57, 58)

Impact of Curcumin in suppressing apoptosis on the ovary has been found in diverse clinical trial studies. Administration of Curcumin reduced granulosa cell apoptosis and protein expression levels of cleaved caspase-3 and -9 in D-galactose-induced premature ovarian failure mice. Curcumin also could decrease PCNA (proliferating cell nuclear antigen) and its mRNA, increase both Bax and its mRNA, and also decreases cell viability in porcine ovarian granulosa cells in *in vitro* study (59).

In another study, effect of Curcumin on toxicity impacts of Chlorpyrifos (CPF) on mice ovarian tissue and uterus tissue examined and also OS levels evaluated. Results revealed that Curcumin could improve antioxidants level and histopathology index of ovarian tissue after chlorpyrifos administration (60).

Primary dysmenorrhea (PD) and Premenstrual syndrome (PMS) are popular gynecologic complaints among youthful women. Different reasons have been shown to be associated to these disorders. Since the exact etiology is uncertain, treatment is generally symptomatic (61, 62). Curcumin because of ability to regulate neurotransmitters and biomolecule, and acting as antioxidant and anti-inflammation compound and also decreasing oxidative stress (OS) could ameliorate psychosomatic symptoms in these patients (63). Furthermore, Curcumin has been shown to have anti-anxiety and anti-depressant effects by increasing norepinephrine, serotonin and dopamine levels in the brain (64), thus, Curcumin administration could be efficient in decreasing PMS symptoms in patients. Moreover, in a research study, pain reduction in more PD patients have been reported dramatically (63). PD pain is related to the increased levels of Prostaglandin E2 (PGE2) and PGF2α. PGE2 stimulates cervical constriction, uterine hyper contraction and increased vasopressin release and in the following, uterine hypoxia, ischemia, and pain is occurred (65). Increased PG levels cause severe uterine contractions and this pain may be alleviated with PGs or Cyclooxygenase (COX) enzyme inhibitors. It has been reported that Curcumin reduces COX-2 expression by inhibiting PG production (66) and because of anti-inflammatory properties of Curcumin, this herbal compound is able to inhibit PG

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synthesis (67).
Curcumin has been found to attenuate abnormal maternal inflammation in preeclampsia by attenuating Nuclear factor kappa B (NF-κB) (master regulator of inflammation) activation, which reduce pro inflammatory cytokines including Tumor necrosis factor-α (TNF-α), IL-6, IL-1β, and chemokines such as Macrophage Inflammatory Protein-1 (MIP-1). and monocyte chemoattractant protein-1 (MCP-1) released from trophoblasts, decidual and chorioamnion cells in vivo and in vitro (37).

Conclusion

Free radicals are known as one of the main causes of reproductive system disorders. Curcumin, the active ingredient of turmeric, is a polyphenol compound and it has long been used in the treatment of various diseases, especially reproduction due to its antioxidant, anti-inflammatory, anti-cancer and anti-infection properties. Therefore, it plays a very effective role in eliminating free radicals, infection, as well as tumorogenic agents, etc. Thus curcumin with multiple properties could be a good choice in the treatment of the male and female reproductive disorders.

Abbreviation

ROS: reactive oxygen specious
MMP: mitochondrial membrane potential
OS: oxidative stress
PCOS: polycystic ovary syndrome
Nrf2: NF-E2-related factor-2
PCNA: proliferating cell nuclear antigen
PGE2: Prostaglandin E2
COX: Cyclooxygenase
NF-κB: Nuclear factor kappa B
MIP: Macrophage Inflammatory Protein
MCP-1: monocyte chemoattractant protein-1

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Conflicts of interest

There is no competing interest to this study.

Authors' contributions

Conceptualization and Investigation: Melika Izadpanah
Writing–original draft: Melika Izadpanah & Zeinab Vahidinia
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