Curcumin, a potential oral herbal male contraceptive: a review article

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ABSTRACT

Background: Worldwide, the population explosion and unintended pregnancies pose serious health issues. The family planning program is a vital element due to reducing population growth. Demographic data and family planning in Indonesia report that contraceptive use rates are 93.66% for women and 63.4% for men. Men’s participation in family planning programs remains low, with options limited to vasectomy and condoms. Limited contraceptive options may explain the low participation rate. WHO recommends traditional medicine as a cost-effective substitute for manufactured medicines. The primary ingredient in turmeric, Curcumin, has antiviral, antibacterial, anti-inflammatory, and anticancer activities. In both animal and human clinical trials, it has demonstrated a lack of toxicity. Little research has been done on how it affects the male reproductive.

Objective: This article reviews the literature regarding the effects of Curcumin in Curcuma Longa on male fertility.

Conclusion: Curcumin in Curcuma Longa causes noticeable changes in the male reproductive system that reverse when treatment is discontinued. Therefore, Curcumin may potentially control male fertility as a male contraceptive.

Keywords: anti-fertility, male contraceptive, curcumin.


INTRODUCTION

The World Population Prospect estimates that there are currently roughly 8.0 billion people on Earth. If current trends continue, that number will increase to 8.5 billion by 2030, 9.7 billion by 2050, and 11.2 billion by 2100. The impact of overpopulation on poverty, environmental degradation, natural resource depletion, and unemployment growth. Governmental and non-governmental organizations are working hard to manage the population, but the outcome has not been great. The limited choice of contraceptive alternatives could be one of the potential causes.1 Woman are the main gender who utilize contraceptives. Contraceptives developed for women successfully prevent unintended pregnancies, yet some women cannot use them related to side effects for health reasons, and the discovery of male contraceptives supports family planning.2,3

Until now, modern methods of male contraception are condoms and vasectomy. Around 8.9% of all contraceptive methods are used globally including condoms and vasectomy. According to a Population and Family Planning Agency survey in 2017, 93.66% of women and only 6.34% of males in Indonesia take contraceptives. Male participation in contraceptive use was still very low.4,5 Vasectomy and condoms as male fertility control methods have their limitations.4 Use of condoms is associated with psychological issues, including diminished sexual pleasure and increased failure rates.6 Vasectomy does not have complete reversibility after reversal surgery. Frightened of the side effects, such as impotence, makes male participation in family planning programs is very limited.8,9

Survey results indicate that over 80% of men think contraception is a collaborative effort and that 50% of men are looking to use male contraception options other than vasectomy and condoms. There was a demand for other contraceptive techniques among men who preferred them to vasectomy and condoms, but none were discovered.10 Men should be allowed to select a contraceptive method that is efficient, rapid, safe, and reversible. Additionally, it should not interfere with any other androgen-dependent processes. Furthermore, the application method should be easy and quite affordable.

The World Health Organization (WHO) has set up a working group program to look at the possibility of using natural medicines or herbs to create new and different forms of contraception. Traditional medicinal plants with effects on infertility must be acceptable to the community, safe, productive, reversible, and not affect with sexual intercourse.11,12 Since natural medications were believed to be healthier than synthetic ones, interest in using medicinal herbs and traditional medicine increased, and it began mostly in the last decade.

Indonesia has a large amount of biodiversity in all its tropical regions. Indonesia offers a range of plants that may be used as traditional herbal medicines because of its great biodiversity. With the fewest side effects and to avoid the negative effects of pharmaceutical drugs, herbs can be used as an alternative form of treatment and prevention for various illnesses or...
physical disorders. Turmeric and other Indonesian medicinal herbs have also been shown to affect male antifertility possibly.12-16

**Curcuma longa and curcumin**

For thousands of years, natural products have been used in traditional medicine and have proven to be a promising source of components for new drug development.14,15 Turmeric (Curcuma longa Linn) is cultivated worldwide in subtropical and tropical regions, stems from Indonesia, India, and Southeast Asia and belongs to the Zingiberaceae family.16 Curcuma longa’s rhizome is used to make spice turmeric.17 Turmeric powder is widely used in mustard and curry as a flavouring and coloring agent. The yellow colour of turmeric is due to polyphenolic pigments known as curcuminoids.18 Curcumin is the most important and active biological compound of Curcuma longa. It has been determined that curcumin is primary ingredient for Curcuma longa’s medicinal properties.19

Pharmacological effects of Curcumin have been reported, including antiprotozoal antimicrobial, antitoxin, antimalarial, anti-inflammatory, antitumor, antiproliferative, antiangiogenic, antioxidant, and antiaging.20-28 It has also been used to treat various skin conditions, ulcers, parasitic infections, immune disorders, and cold and flu symptoms.29 Curcumin has been shown to have anticancer effects due to free radical scavenging and its ability to increase glutathione levels and mitigate the hepatotoxicity of mutagens and carcinogens.30,31 Research results have shown that Curcumin has a beneficial effect on the gonads, testicles and ovaries, which may be due to its antioxidant, anti-inflammatory, cancer prevention agent, and apoptotic properties.32-35 The effects of Curcumin on conception and fertility have not been extensively studied.

The pharmacokinetics and toxicity of curcumin have just lately been clarified, despite the fact that turmeric has been included in traditional medicine for thousands of years. Curcumin’s safety has been proven in numerous trials.36 Several animal models, including mice, rats, and monkeys, have been used to investigate the toxicity of curcumin when given by different methods, including intramuscularly, intravenously, or intraperitoneally. It does not demonstrate toxicity in the examined animal models or in these ways.37-39 One study found that giving mice Curcumin intravenously, intraperitoneally, and orally had no negative effects.40

Several normal human cells, including oral and vaginal epithelial cells, human esophagus and fibroblasts, and bone marrow stromal cells, have all been studied in vitro with curcumin.41-44 It shows no toxicity. More than 13 human clinical trials are taking place in different countries. Phase I research has demonstrated that individuals may handle up to 8 g of curcumin per day without experiencing any negative side effects, providing a high dose for Phase II investigations. The US Food and Drug Administration and Food and Agriculture Organization (FAO) largely acknowledge its safety. A joint FAO/WHO expert committee on food additives has set its recommended daily intake at 0.1-3 mg/kg body weight.35,46

**Curcumin and antifertility**

Naz et al. investigated curcumin’s potential as a brand-new non-steroidal contraceptive. The in vitro effects of curcumin on mouse fertility and human sperm function were investigated using a mouse model.44 Sperm were collected and given Curcumin treatment to examine the effects of motility, capacitation/acrosome response, and in vitro fertilization (IVF). The effect on in vivo fertility was also examined using a mouse model. Sperm incubation with curcumin decreased capacitation, acrosome response, sperm motility, and IVF in a concentration-dependent way. Depending on the dose, sperm motility and function were completely blocked at higher concentrations (≥250 μM) for between 5 and 15 minutes. Both human and murine sperm significantly inhibited the acrosome reaction when incubated with Curcumin in a concentration-dependent manner. Even at a concentration (31.25 mM) that had no noticeable impact on forward motility, sperm capacitation/acrosome reaction was significantly inhibited, and IVF of murine oocytes was completely prevented. Without any adverse side effects, the administration of Curcumin, particularly intravaginally, significantly reduced fertility. Curcumin’s antifertility impact was entirely reversible. In a follow-up experiment, they examined whether Curcumin’s susceptibility to light could lower the dosage needed to suppress sperm motility. When a molecule is photosensitized at its maximum absorbance, it becomes more reactive to the target.47 Curcumin’s photosensitization reduced its concentration to block sperm forward motility by 25-fold totally.48 These interesting discoveries show how Curcumin’s sporicidal action dramatically rises following photosensitization. Curcumin impacts sperm function and motility, although the molecular mechanism by which it does so is yet unknown.

Another Naz et al. study looked at the signal transduction pathways and mechanisms by which curcumin affects sperm motility and function.49 It has been demonstrated that curcumin decreases sperm forward motility in a concentration-dependent manner in both human and mouse sperm. Additionally, it caused the intracellular pH of mouse and human sperm to decrease concentration-dependent. The plasma membrane was significantly hyperpolarized by Curcumin, which led to intracellular acidification and potential inhibition of sperm forward motility. Delineating the precise mechanism and signal transduction pathways.

These factors are believed to influence a number of chemicals and pathways, including tyrosine phosphorylation and Ca²⁺ influx, which are crucial for sperm function and motility.

The weights of the seminal vesicle, epididymis and testis, were dramatically reduced when an aqueous rhizome extract of Curcuma longa (600 mg/kg body weight per day for 56 and 84 days) was administered orally to Parkes (P) strain’s male mice. The seminiferous tubules underwent degenerative alterations as a result of the treatment. The fact that the Curcuma longa treatment had no effect on the body weight of the treated animals implies that the drug did not harm P mice systemically. Spermatozoa in the
cauda epididymitis had considerably decreased motility and viability. However, spermatozoa with morphological abnormalities were more common in the extract-treated group than in the control group. It implies that the Curcuma longa therapy interferes with mitotic and meiotic processes, which in turn suppresses spermatogenesis. Issues with epididymal function may have caused the changes in sperm viability, motility, and morphology, but the reduction in spermatozoa appeared to be due to the treatment with Curcuma longa’s suppressive effect on spermatogenesis, as the sperm number returned to normal levels after the treatment was stopped.

The quantities of sialic acid and fructose in the seminal vesicles, the seminal epithelium height, the seminiferous tubules size, and the amount of testosterone in the serum were all reduced by Curcuma longa extract in comparison to the control group. However, it thickened the muscular layer that surrounds the glandular epithelium. It is widely acknowledged that testosterone is essential for maintaining spermatogenesis. Therefore, it is likely that the Curcuma longa-induced decrease of spermatogenesis in the mice testes employed in this work was brought on by a testosterone deficit. However, the alterations in the reproductive indices returned to normal after 56 days of withdrawal therapy.

In mice, oral administration of a turmeric rhizome decoction at a concentration of 517.4 mg/kg body weight for a 30-day treatment period significantly reduced sperm motility and morphology. The asthenoteratozoospermia condition, caused by the turmeric rhizome decoction, affects mice’s sperm. The phytoconstituents in turmeric rhizome decoction entered Sertoli and epididymis cells, disrupted their functioning and caused these disorders. The decoction of turmeric rhizomes offers a good possibility for developing a male oral contraceptive.

The seminal pH of the cauda epididymis significantly decreases after being treated with Curcuma longa rhizome. Because spermatozoa are highly fragile at lower pH levels, this decrease in seminal pH also causes a reduction in sperm motility. Lower seminal pH and impaired spermatozoa motility may be the causes of the significantly greater spermatozoa mortality in mice treated with Curcuma longa rhizome.

Purohit et al. found that male rats’ serum levels of cholesterol, triglycerides, phospholipids, and fertility decreased after receiving Curcuma Longa extract (1 mg/kg body weight orally for 60 days). Furthermore, 80% of the fertility was negative. Reduced total cholesterol production and increased bile acid secretion, which result in androgen depletion and impaired spermatogenesis, may be responsible for the reduced cholesterol levels in the therapy group. Triglycerides are thought to be the source of energy for spermatozoa and an increase or reduction in them could indicate an unbalanced synthesis. Reduced phospholipids have been connected to sperm maturation and motility in the current investigation. By depletion of androgen levels, oral administration of Curcuma longa extract to male rats suppressed spermatogenesis. The unfavorable fertility results reflect spermatogenesis arrest and androgen deficiency. Additionally, Curcuma Longa exhibits antispermatic properties.

Furthermore, Purohit and Bhagat’s study demonstrated that treatment with aqueous and alcoholic extracts of the Curcuma Longa rhizome reduced the motility and density of spermatozoa in the rat cauda epididymis. After 60 days of therapy with an aqueous Curcuma longa rhizome extract at a dosage of 500 mg/kg body weight, the weight of the epididymis, seminal vesicle, ventral prostate, and testis reduced. The medicine also had an adverse effect on the Leydig cells, causing a dip in sperm count and motility, a rise in germ cell count, and a reduction in fertility. Leydig cell breakdown and decreasing Leydig cell nuclei are the two main causes of decreased androgen synthesis. As these organs are androgen-dependent, a reduction in the weights of the accessory sex structure and a decrease in the height of the epithelial cells in the caput and cauda epididymides also corroborate the theory of decreasing androgen level. Reduced spermatogenic components and spermatozoa may cause a decrease in testis weight. The anti-androgenic properties of the extract were thought to be responsible for these therapeutic results. These researchers also observed that two months after ceasing the curcumin therapy, the sperm count and motility in the epididymis of the treated rats rebounded.

Curcumin, an active biological compound of Curcuma longa, exhibits antifertility effects by lowering sperm counts, sperm motility, and seminal pH in male mice and significantly increasing spermatozoa mortality. As these factors are crucial in determining whether a male subject is fertile, any change in these seminal characteristics brought on by the medication has an antifertility effect and can be used as one of the oral contraceptives to limit fertility in male subjects. The Curcumin treatment causes noticeable
modifications in the male reproductive organs, reversible when treatment ends. As a result, Curcumin may have the ability to control male fertility as a contraceptive.

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REFERENCES
1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2022: Summary of Results. UN DESA/POP/2022/TR/NO. 2022