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Beyond the Spice Rack: The Therapeutic Benefits of Curcumin for Male Reproductive Health

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Abstract:

Turmeric, derived from the rhizome of Curcuma longa, is a widely utilized spice. It is characterized by a warm and slightly bitter flavor, and is often employed to enhance the taste and color of curry powders. The active compound, curcumin has been the subject of extensive research due to its anti-inflammatory, antioxidant, and potential anticancer properties, among others. This review explores the therapeutic potential of curcumin, the active ingredient in turmeric, for male reproductive health, going beyond its culinary uses. The articles used for this narrative review were obtained from some search engines including National Library of Medicine (PubMed), Science Alert, Google Scholar, Excerta Medical database (EMBASE) and Cumulated Index to Nursing and Allied Health Literature (CINAHL). It summarizes the current scientific evidence regarding curcumin's effects on various aspects of male fertility, including sperm quality. It also highlights curcumin's antioxidant, anti-inflammatory, anti-apoptotic properties and how these contribute to its potential benefits in addressing male reproductive issues. Evidence from the overview of existing literature suggests the potential benefits of curcumin supplementation in alleviating male infertility. An avenue for future investigations into curcumin's role in maintaining and improving male reproductive health in human is widely open.

1. INTRODUCTION

Throughout history, various cultures have embraced plant-based therapies. The use of medicines derived from plants is widespread, with many countries dedicating 40% to 50% of their total healthcare budgets to the development of new pharmaceuticals. Herbal remedies are often viewed as beneficial for health, typically associated with few or no side effects [1]. The genus Curcuma has a rich history of medicinal use, comprising around 133 species worldwide. Notable species include *C. longa* (commonly known as Haridra), *C. aromatica Salisb* (known as Vana Haridra), *C. angustifolia Roxb., C. zanthorrhiza Roxb., C. amada Roxb* (referred to as Amaragandhi Haridra), *C. caesia Roxb* (called Kali Haridra), and *C. zedoaria Rosc* (commonly known as Zedoary), which are found in various regions across the globe. Curcuma longa Linn. (*C. longa*) is a prominent tall herb that flourishes in tropical climates including Africa.

Curcumin, the active compound found in the rhizomes of *Curcuma longa*, commonly known as turmeric, has long been known for its potent bioactive properties. As a polyphenolic compound, curcumin is primarily responsible for the characteristic yellow color of turmeric. It has been the subject of extensive research due to its anti-inflammatory, antioxidant, and potential anticancer properties, among others [2]. It has been used in traditional medicine for thousands of years, particularly in South Asian and Southeast Asian cultures, where it has played a role in both culinary and therapeutic practices [3].

In some cultures, turmeric has been utilized for the alleviation of conditions such as urticaria, dermatitis, hepatitis infections, inflammatory joint disorders, sore throats, and wounds. Historical texts in Hindu mythology reference its use as an aromatic stimulant and carminative agent. A common home remedy involves the combination of turmeric powder with calcium hydroxide, which is frequently employed to address sprains and swelling resulting from injuries, often applied directly to the affected area. Throughout history, traditional medicine has harnessed dried curcumin powder for the treatment of various ailments. Curcuma longa is recognized for its potential antitoxic, anticancer, antibacterial, anti-inflammatory, and antioxidant properties [4]. The sources of curcumin are primarily derived from turmeric, though small quantities of curcumin can also be found in other plants of the *Zingiberaceae* family, such as *Curcuma aromatica* and *Curcuma zedoaria* [5]. Curcumin is extracted from the rhizomes of turmeric, which are typically harvested, boiled, and dried before being ground into a powder. This powder is then used in various forms, including in cooking, supplements, and in medicinal formulations. Despite its natural abundance in turmeric, curcumin constitutes only about 3% of turmeric by weight [6].

The previous studies have exhibited certain deficiencies, particularly in their failure to adequately address the therapeutic potential of C. longa in ameliorating male infertility. In response to these gaps, we aim to present a comprehensive analysis that emphasizes the existing knowledge voids in both traditional and scientific literature regarding C. longa and its curcumin content, specifically in the context of its potential to mitigate male infertility.

2. METHODS

A comprehensive literature search was conducted utilizing various electronic databases, including Google Scholar, National Library of Medicine (PubMed), Excerta Medical database (EMBASE), Cumulated Index to Nursing and Allied Health Literature (CINAHL), and African Journal Online (AJOL). The search employed specific terms and combinations, notably "Beyond the Spice Rack: The Therapeutic Benefits of Curcumin for Male Reproductive Health." The inclusion criteria were met by original research articles, review papers, and meta-analyses that investigated the therapeutic effects of curcumin. From each selected study, pertinent information was extracted, encompassing participant demographics, statistical methodologies, and key findings. The gathered data was then synthesized and analyzed to uncover prevalent themes, discrepancies, and gaps within the existing literature. A thorough evaluation was performed to assess the methodological soundness, limitations, and potential biases of the studies included. Furthermore, the clinical relevance of the findings from the included research was critically appraised.

3. OVERVIEW OF MALE INFERTILITY AND ITS IMPACT

In Nigeria, male infertility accounts for approximately 40 to 50% of all infertility cases, although this figure can differ by region, with male factors being the sole cause in 20–30% of cases globally [7]. The underlying causes of male infertility often relate to deficiencies in semen quality, which serves as a proxy for assessing male reproductive capability [8]. The global decline in semen quality is attributed to a variety of factors, necessitating a thorough investigation into these influences to develop effective therapeutic and preventive strategies. Increasingly, environmental factors and lifestyle choices are acknowledged as critical contributors to infertility, as they can disrupt the normal endocrine environment that affects both semen quality and male fertility [9]. The condition is defined as the inability of a man to contribute to conception after one year of regular, unprotected intercourse.

Male infertility can stem from multiple factors, which are generally classified into three main categories: sperm production issues, sperm transport problems: and sperm function issues: Common causes include hormonal imbalances, genetic abnormalities, testicular dysfunction, and lifestyle factors such as smoking, alcohol use, and exposure to environmental toxins [9,10].

Male infertility often leads to profound psychological distress, including depression, anxiety, and a diminished sense of masculinity [11]. The stigma associated with infertility can exacerbate feelings of inadequacy, particularly in cultures where parenthood is closely linked to social status. From a physiological perspective, conditions such as varicocele, hypogonadism, and infections are frequently implicated, necessitating targeted treatments like varicocelectomy, hormone therapy, or assisted reproductive technologies [12].

4. THE ANTIOXIDANT PROPERTIES OF CURCUMIN

4.1. The Chemical Structure and Antioxidant Properties of Curcumin

Curcumin exhibits a unique molecular architecture characterized by two methoxyphenolic rings interconnected by a seven-carbon chain that incorporates a β-diketone functional group. Its molecular formula is $C_{21}H_{20}O_6$, with a molecular weight of 368.39 g/mol. This structural configuration facilitates the formation of a conjugated system, which is thought to play a significant role in its antioxidant properties. The antioxidant capabilities of curcumin are primarily ascribed to the electron-rich characteristics of its phenolic groups, which are capable of donating electrons to counteract reactive oxygen species (ROS). Additionally, the molecular structure of curcumin enhances its capacity to interact with metal ions and influence various biochemical pathways [13].

The principal functional groups present in curcumin's structure include the β-diketone group and the aromatic rings, which are substituted with hydroxyl and methoxy groups. The enol form of the β-diketone group allows curcumin to engage with a range of biological molecules, including enzymes and receptors, through the formation of hydrogen bonds. The hydroxyl and methoxy substitutions on the aromatic rings further augment its potential for molecular interactions, rendering curcumin a multifaceted compound in therapeutic contexts [14].

From a chemical standpoint, curcumin is categorized as a diferuloylmethane, comprising two aromatic rings linked by a seven-carbon chain. Its hydrophobic properties confer solubility in lipids while limiting its solubility in aqueous environments, which has implications for its bioavailability.

4.2. The Mechanisms of Action of Curcumin as an Antioxidant

Curcumin serves as a powerful antioxidant by counteracting reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby safeguarding cells from damage. Research conducted by Li *et al.* (2022) highlighted curcumin's capacity to mitigate oxidative stress through the modulation of critical transcription factors, including NF-kB and Nrf2, which play significant roles in the body's antioxidant defense mechanisms. Comparative studies have shown that curcumin's antioxidant effectiveness can surpass that of conventional antioxidants such as vitamins C and E in specific contexts, attributed to its ability to regenerate other antioxidants and its diverse molecular actions [15].

The active component of turmeric, curcumin, has attracted considerable interest due to its antioxidant capabilities, which may underlie its therapeutic potential. Antioxidants are essential molecules that neutralize detrimental free radicals, thereby alleviating oxidative stress associated with numerous chronic conditions [16]. The mechanisms through which curcumin exerts its antioxidant effects are complex, warranting extensive investigation.

A well-established mechanism by which curcumin operates as an antioxidant is its ability to scavenge free radicals. These highly reactive molecules pose a threat to cellular integrity, affecting lipids, proteins, and DNA. Research indicates that curcumin can directly engage with several types of free radicals, including superoxide, hydroxyl, and peroxyl radicals. Studies have revealed that the phenolic structure of curcumin is vital for its free radical scavenging capabilities. This interaction is instrumental in preventing cellular damage and lowering the likelihood of diseases linked to oxidative stress, including cancer and neurodegenerative conditions [17-19].

4.2.1. Activation of Antioxidant Enzymes

Curcumin significantly bolsters the body's intrinsic antioxidant defense mechanisms. Research indicates that it promotes the upregulation of essential antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase. Studies have demonstrated that curcumin elevates the levels of these enzymes in cells subjected to oxidative stress, thereby elucidating a cellular basis for its antioxidant properties. The enhancement of these enzymes plays a crucial role in neutralizing reactive oxygen species (ROS) and preserving redox equilibrium within cells. This finding implies that the antioxidant capabilities of curcumin extend beyond mere scavenging of free radicals to encompass the activation of cellular protective systems [20,21].

4.2.2. Inhibition of Enzymes that Cause Oxidative Damage

Beyond its function in promoting antioxidant enzymes, curcumin has been identified as an inhibitor of enzymes that facilitate oxidative damage. Notably, it affects lipoxygenase (LOX) and cyclooxygenase (COX), which are involved in generating inflammatory mediators and reactive species. By blocking cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOs), and lipoxygenase (COX), curcumin reduces inflammation. Three important enzymes that mediate inflammatory processes are INOs, LOX, and COX. The physiopathology of several inflammatory illnesses has been discovered to be associated with the improper up-regulation of COX-2 and/or ins. By modulating these enzymes, curcumin influences the oxidative-inflammatory cascade, thereby providing a dual approach to mitigating oxidative stress [22,23].

4.2.3. The Impact of Curcumin on the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Pathway

The Nrf2 pathway serves as a vital cellular mechanism for initiating antioxidant responses. Research indicates that curcumin activates the Nrf2 signaling pathway, which in turn promotes the transcription of genes associated with antioxidant activity. This pathway is instrumental in regulating the synthesis of phase II detoxifying enzymes, thereby safeguarding cells against oxidative damage. Accordingly, curcumin may raise the levels of cellular antioxidants like SOD, GPx, and CAT by activating the Nrf2 pathway. It may also directly or indirectly reduce the production of ROS and inflammation by promoting the expression of HO-1 (Heme Oxygenase-1), a Nrf2-regulated gene involved in preventing vascular inflammation [24,25]. By influencing this pathway, curcumin bolsters the body's inherent defense systems against oxidative stress.

4.2.4. Curcumin's Role in Mitochondrial Protection

Mitochondria are crucial organelles within cells, primarily responsible for energy production, yet they also represent a significant source of reactive oxygen species. Curcumin has demonstrated protective effects on mitochondria against oxidative damage by regulating their function and decreasing the production of reactive oxygen species. This process is essential for permitting DNA repair or encouraging senescence to stop damaged cells from proliferating. The upregulation of p53 and p21 in irradiated rats highlighted the potential of curcumin nanoparticles in modulating these pathways as well as their functions as indicators of radiation-induced cellular senescence [26]. Curcumin nanoparticles may lessen the prolonged activation of p53-p21 signaling by reducing oxidative stress and maintaining mitochondrial integrity. This would alleviate mitochondrial dysfunction and slow the progression of senescence. This showed that curcumin preserves mitochondrial integrity through the modulation of mitochondrial biogenesis and the reduction of oxidative damage. This protective effect on mitochondria is particularly significant in the context of aging and neurodegenerative diseases, where mitochondrial dysfunction and oxidative stress play critical roles in the progression of these conditions [27,28].

4.3. Comparison of Curcumin to other Antioxidants

4.3.1. Curcumin vs. Vitamin C

Vitamin C is recognized as a prominent water-soluble antioxidant, celebrated for its ability to neutralize free radicals and regenerate other antioxidants. Nonetheless, its antioxidant effectiveness is constrained by its swift metabolism and elimination from the body [29]. In contrast, curcumin exhibits a prolonged antioxidant effect, as it can engage with various cellular targets, thereby providing protection against extended oxidative stress. Recent comparative research indicated that curcumin demonstrates greater efficacy in reducing oxidative damage to lipids and proteins than vitamin C in both in vitro and in vivo studies [29].

4.3.2. Curcumin vs. Vitamin E

Vitamin E is primarily recognized for its protective role in safeguarding lipid membranes from oxidative damage, functioning as a fat-soluble antioxidant. Curcumin, being lipophilic, shares similar protective properties for cellular membranes but possesses the additional advantage of functioning effectively in both aqueous and lipid environments [30,31]. Research has indicated that curcumin, in comparison to vitamin E, offers more extensive protection against oxidative stress due to its ability to modulate inflammatory pathways, which are frequently linked to oxidative damage [32]. This characteristic endows curcumin with a wider therapeutic potential relative to vitamin E.

4.3.3. Curcumin vs. Other Plant-Based Antioxidants

Polyphenols, particularly those derived from fruits, vegetables, and tea, represent another category of antioxidants that have been extensively investigated for their capacity to mitigate oxidative stress. However, curcumin has demonstrated a higher binding affinity for specific enzymes and proteins associated with oxidative damage, thereby enhancing its bioavailability and antioxidant properties [33]. Unlike polyphenols, curcumin's distinctive ability to influence redox-sensitive signaling pathways further underscores its potential as a therapeutic antioxidant, especially in conditions marked by chronic inflammation.

5. THE ROLE OF OXIDATIVE STRESS AND LIPID PEROXIDATION IN MALE INFERTILITY

Oxidative stress (OS) has emerged as a crucial factor contributing to male infertility. OS refers to the imbalance between the productions of reactive oxygen species (ROS) and the antioxidant defense mechanisms in the body. In the context of male reproduction, OS can negatively affect sperm function, including motility, viability, and DNA integrity. Studies have shown that elevated ROS levels in seminal fluid are associated with reduced sperm quality and male infertility [34]. The main sources of ROS in the male reproductive tract include mitochondria, leukocytes, and defective spermatozoa [35,36]. Research has highlighted a significant relationship between mitochondrial enzyme activity and sperm motility, indicating that effective motility is contingent upon optimal mitochondrial performance. Additionally, mitochondrial dysfunction adversely affects sperm vitality. Mitochondria play a critical role in the regulation of cellular apoptosis; thus, any impairment in their function can disrupt this regulatory mechanism. Mitochondrial dysfunction, particularly when induced by oxidative stress, can amplify apoptotic signaling and lead to programmed cell death in sperm, ultimately reducing their vitality and viability. This situation may result in decreased sperm counts and diminished reproductive potential [37,38].

These interrelated mechanisms underscore the substantial impact of oxidative stress on male reproductive health. The processes of lipid peroxidation within sperm cell membranes, along with protein oxidation and DNA damage, contribute to decreased sperm motility, lowered reproductive capacity, and heightened risk of infertility. A comprehensive understanding of these pathways is essential for clarifying the role of oxidative stress in male infertility [39,40]. It is imperative to develop strategies aimed at mitigating oxidative damage to enhance reproductive outcomes.

Lipid peroxidation (LP) is one of the key consequences of oxidative stress in spermatozoa. The plasma membrane of sperm cells is rich in polyunsaturated fatty acids, making it particularly vulnerable to lipid peroxidation when ROS levels are elevated. Peroxidation of membrane lipids leads to the formation of aldehydes, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), which are toxic to sperm cells and can compromise sperm integrity. Studies have demonstrated that increased lipid peroxidation in semen samples correlates with poor sperm quality and male infertility. Moreover, lipid peroxidation has been implicated in the disruption of sperm membrane integrity, a key factor for successful fertilization [41,42].

5.1. Oxidative Stress has Implications that Reach Beyond Fertility Issues

Elevated oxidative stress in males can adversely affect female fertility, leading to increased rates of miscarriages and a higher likelihood of genetic abnormalities in their children. Specifically, heightened oxidative stress in sperm is associated with a greater incidence of pregnancy loss in females and an increased risk of genetic disorders in offspring. This highlights the necessity of recognizing the extensive consequences of male oxidative stress on reproductive success [44].

Children conceived through assisted reproductive technologies may be at an elevated risk for certain childhood illnesses, potentially linked to oxidative stress present in the paternal system [45,46].

Oxidative stress can lead to hormonal disruptions. Evidence has indicated the complex effects of oxidative stress which extends to the regulation of hormones, and may contribute to broader reproductive health issues [47]. In summary, maintaining a delicate equilibrium between reactive oxygen species (ROS) and antioxidants in the male reproductive system is crucial not only for the health of sperm but also for overall male reproductive health and the well-being of future generations. As the understanding of this relationship evolves, it becomes increasingly important to investigate both diagnostic and therapeutic approaches to mitigate oxidative stress, with the goal of improving reproductive outcomes [38].

6. THE POTENTIAL THERAPEUTIC BENEFITS OF CURCUMIN FOR MALE REPRODUCTIVE HEALTH

6.1. Curcumin and Spermatogenesis

Spermatogenesis, the process of sperm production, is sensitive to oxidative stress, which can disrupt normal functioning and lead to infertility. Curcumin's antioxidant properties have shown promise in enhancing spermatogenesis. In an experimental study, Amusan and Emokpae [48] demonstrated that curcumin administration in cadmium induced testicular injury and oxidative stress resulted in a significant increase in sperm count and motility, suggesting its protective effect against oxidative damage. Other authors have reported similar findings where curcumin's protective effects on the seminiferous tubules were evident, supporting its potential role in improving sperm quality [49]. One possible mechanism for providing protection is by preventing oxidative stress. This is because albino rats given 20g/Kg of cadmium solution in that study had substantially lower serum and semen antioxidant levels than the control group. Serum MDA, on the other hand, was greater than negative controls. Serum antioxidant levels were considerably higher in rats given curcumins daily for 28 days in a dose-dependent manner after supplementing with different concentrations of the compound. Supplementing with curcumin raised the activity levels of glutathione reductase, catalase, superoxide dismutase, and glutathione peroxidase (GPx), but it also decreased MDA and hydrogen peroxide levels [48].

It has been reported that curcumin can improve the decline in testicular spermatogenesis and sperm quality brought on by a low-carb diet. It was established that a low-carb diet resulted in decreased sperm quality and damaged testicular histology in animals fed a low-carb diet and supplemented with curcumin. By reducing oxidative stress, inflammation, and apoptosis, curcumin supplementation may help sperm and testis function [50].

Another study conducted to compare curcumin and curcumin nanoemulsion on high-fat, high-fructose diet-induced impaired spermatogenesis in rats, it was observed that curcumin nanoemulsion outperformed curcumin powder, especially in terms of increasing the percentage of spermatozoa that were able to move forward, normalizing the essential and non-essential amino acids in semen, normalizing the levels of testosterone and leptin in the serum, and normalizing the oxidative and nitrosative parameters. Additionally, it also demonstrated an increased testicular cellular energy while decreasing testicular DNA fragmentation. The histological analysis of the seminiferous tubules revealed that the highest level of spermatogenesis was induced by curcumin nanoemulsion given at a dose of 10 mg/kg. The negative effects of an HFHF on spermatogenesis were successfully mitigated by curcumin nanoemulsion given at a dose of 10 mg/kg [51].

According to one study that evaluated the ameliorative effects of curcumin nanomicelle (CUR-n) on testicular damage in the mouse model of multiple sclerosis, it was reported that CUR-n (100 mg/kg) considerably raised the levels of LH, FSH, testosterone, and TAC while lowering MDA. Additionally, it enhanced sperm count, morphology, viability, and motility; it raised testis weight and volume; it increased the number of spermatogonia, spermatocytes, round spermatids, and long spermatids, and it improved the amount of germinal epithelium. Additionally, following intervention with CUR-n (100 mg/kg), a significant reduction in the amount of wrinkling and disruption of the germinal epithelium was noted. In addition, there was a noticeable rise in germ cells when compared to the group that received chlorpromazine (CPZ). According to the study, CUR-n may be a treatment for reducing the negative effects of multiple sclerosis on the testes [52].

6.2. Curcumin as a Potential Antioxidant in Stress Regulation

In a research investigation by Atef *et al.* [53], it was demonstrated that curcumin possesses the capability to mitigate hepatic oxidative stress in rabbits subjected to aflatoxin B1 (AFB1) exposure. This effect was substantiated by an elevation in the levels of antioxidant enzymes, including glutathione (SGH), catalase (CAT), and superoxide dismutase (SOD), alongside a reduction in free radical presence. Nonetheless, it is important to acknowledge that curcumin may exhibit genotoxic properties contingent upon its concentration [54]. In a related study, the oral administration of curcumin to mice revealed protective effects against the adverse impacts of AFB1 on renal function, enhancing renal antioxidant capacity while decreasing blood urea nitrogen (BUN), uric acid, and creatinine levels [55,56].

Additionally, exposure to agricultural pesticide; cypermethrin (CPM) is associated with various health risks, including neurotoxicity, reproductive toxicity, and molecular toxicity, marked by increased in malondialdehyde (MDA) and protein carbonyl (PC) levels in serum, liver, and brain tissues. Curcumin supplementation in the exposed subjects led to a significant decreased oxidative stress in serum and brain tissues. Ziada-Reem *et al.* [57] highlighted those phytochemicals from plants, such as vitamin C and curcumin, provide a protective effect against oxidative stress induced by cypermethrin in serum, brain, and liver. Beyond its antioxidative and free-radical-scavenging properties, curcumin also enhances the efficacy of other antioxidants [57]. Furthermore, heavy metals like cadmium (Cd) can inflict damage on various organ systems in animals following prolonged exposure. For example, in Kunming mice, Cd exposure notably impaired semen quality, reduced serum testosterone levels, and decreased the number of spermatogenic cells and mature spermatozoa. However, intervention with curcumin was observed to ameliorate these oxidative injuries by activating the Nrf2 signaling pathway [58]. Similarly, the administration of nickel nanoparticles (NiNPs) at a dosage of 50 mg/kg over 28 days resulted in liver damage in rats, but curcumin at doses of 150 mg/kg or 300 mg/kg was shown to mitigate this toxic effect [54].

6.3. Curcumin and Male Hormonal Regulation

Male reproductive health is also governed by hormonal balance, particularly the levels of testosterone. Curcumin has been shown to influence various hormones, including testosterone, by modulating the expression of key enzymes involved in hormone synthesis. In a study by Arunasree *et al.* [59], curcumin supplementation in male rats led to a significant increase in serum testosterone levels, potentially due to its ability to inhibit aromatase activity. This finding points to curcumin's potential to improve testosterone-dependent aspects of male reproductive function, such as libido and sexual performance. Tsao *et al.*[50] reported that a replacement of a normal diet supplemented with curcumin in experimental animal models improved semen quality and testosterone levels by reducing oxidative stress. The researchers assessed testosterone levels and the expression of proteins associated with the testosterone biosynthesis pathway in experimental animal models. The findings indicated that testosterone concentrations in animals subjected to a low-carbohydrate diet were significantly lower compared to those on a standard diet, which showed an increase. Additionally, the results revealed that the low-carbohydrate group exhibited reduced protein expression of 17β-hydroxysteroid dehydrogenase relative to the normal diet group. When this was supplemented with curcumin, an increased levels of serum testosterone was observed[50]. Furthermore, Sharma *et al.* [60] designed a study using rat model to investigate the effects of insecticides and xenobiotics, wherein the animals were supplemented with curcumin and quercetin. Their study demonstrated that these compounds could mitigate the adverse effects of insecticides and xenobiotics on sperm count, testosterone levels, and the activities of enzyme 3β-HSD (3beta-hydroxysteroid dehydrogenase/isomerase) and 17β-HSD (17beta hydroxysteroid dehydrogenase), as well as oxidative damage. The observed increases in lipid peroxidation and oxidative stress in may have contributed to the declines in both sperm count and testosterone concentration. Conversely, it is plausible that negative feedback inhibition within the hypothalamic–pituitary–gonadal axis may also play a role in the observed reduction of testosterone levels [50].

6.4. Curcumin and Testicular Function

Testicular function can be compromised by inflammation and oxidative damage, often leading to decreased fertility. Curcumin's anti-inflammatory properties may help counteract these effects. A study by Shah *et al.* [61] found that curcumin treatment in rats with induced testicular damage reduced inflammation and oxidative stress markers, thereby improving testicular function. Furthermore, the histological analysis showed a reduction in cellular damage within the testes, highlighting curcumin's potential as a therapeutic agent in conditions such as testicular torsion or ischemia [61].

Recent research it was reported that curcumin nanomicelle could mitigate oxidative stress, enhance sperm quality-specifically in terms of sperm count, motility, morphology, and viability and increase the population of spermatogenic cells in a multiple sclerosis model. Additionally, curcumin nanomicelle was observed to elevate levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone. Notably, it significantly reduced the wrinkling and disruption of the germinal epithelium in testicular tissue caused by the induction of multiple sclerosis [52,62]. However, the authors recommended that further extensive studies are necessary to validate these findings. Future research should aim to investigate additional potential benefits of nano-curcumin on various male fertility parameters, as well as its effects on inflammatory markers and the positive implications of nano-curcumin in addressing other complications associated with multiple sclerosis in different tissues.

6.5. Curcumin's Effect on Sperm DNA Integrity

Sperm DNA integrity is critical for successful fertilization and embryo development. Curcumin has been shown to protect against DNA fragmentation in sperm cells. A study by Nair *et al.* [63] demonstrated that curcumin supplementation in a mouse model with induced oxidative stress resulted in a significant reduction in sperm DNA damage, suggesting its potential to improve sperm quality by safeguarding genetic material. This aspect of curcumin's action could be particularly beneficial in addressing male infertility issues associated with DNA fragmentation [64].

Certain researchers have demonstrated that the inclusion of curcumin in cryopreservation media offers protective benefits for human sperm characteristics and DNA, effectively mitigating oxidative damage associated with the freeze-thaw cycle [65].

In other animal studies, curcumin has been shown to alleviate the detrimental effects of testicular ischemia and enhance the quality of sperm chromatin in mice. The integrity of sperm DNA is crucial for successful fertilization and the proper development of embryos. Although the precise molecular mechanisms through which curcumin supports optimal sperm function remain to be elucidated, it is hypothesized that its antioxidant properties, attributed to the presence of β-diketone, methoxy, and phenolic functional groups, play a significant role in improving sperm parameters [66].

6.6. Curcumin as an Adjunct to Conventional Treatments

While curcumin shows potential on its own, it may also complement conventional treatments for male reproductive issues. A clinical trial by Kianbakht *et al.* [67] suggested that curcumin, when used alongside assisted reproductive technologies (ART), improved the outcomes in infertile men by enhancing sperm quality and motility. The synergistic effects observed in the study point to curcumin as a promising adjunct in the management of male infertility

7. THE IMPACT OF OXIDATIVE STRESS AND LIPID PEROXIDATION ON MALE INFERTILITY

Reactive oxygen species (ROS) are highly reactive molecules produced during cellular metabolism, especially within the mitochondria. While ROS are crucial for various cellular signaling pathways, their overproduction can result in oxidative stress, which has been associated with numerous pathophysiological conditions, including male infertility. In the realm of male reproductive health, ROS adversely affect sperm quality by compromising sperm motility, viability, DNA integrity, and morphology, all of which are critical factors in infertility [68].

In the male reproductive system, ROS are predominantly generated during sperm metabolism, particularly in the mitochondria of sperm cells. Various factors, including infections, varicocele, smoking, environmental pollutants, and aging, can increase ROS levels in the testes and seminal fluid. An overproduction of ROS disrupts the balance between ROS and the antioxidant defense mechanisms, leading to oxidative stress. Prolonged oxidative stress inflicts considerable damage on sperm cells and other components of the male reproductive system, thereby contributing to infertility[69].

Excessive ROS can hinder sperm functionality through multiple pathways. Initially, ROS can induce lipid peroxidation, resulting in the degradation of polyunsaturated fatty acids in sperm membranes, which adversely affects sperm motility and structural integrity. Additionally, ROS can oxidize proteins, impairing the function of enzymes and structural proteins essential for sperm operation [70]. Notably, DNA damage in sperm cells, particularly the oxidation of guanine bases, has been extensively documented as a significant outcome of ROS-induced injury. These detrimental effects can lead to reduced fertilization rates and compromised embryonic development, ultimately contributing to male infertility[71].

8. THE EFFECTS OF LIPID PEROXIDATION ON SPERM FUNCTION

One of the most critical consequences of lipid peroxidation on sperm functionality is the impairment of motility. The integrity of the sperm membrane is essential for sustaining motility, and lipid peroxidation disrupts this integrity, resulting in diminished flagellar activity and overall motility. Studies have indicated that sperm exhibiting elevated levels of lipid peroxidation demonstrate a significant reduction in forward motility, which is vital for successful fertilization [72]. A decline in motility is often associated with the extent of oxidative damage inflicted on the sperm membrane [70,73].

Lipid peroxidation negatively influences this function by compromising the structural integrity of the sperm membrane. Oxidative stress induces the oxidation of phospholipids within the sperm membrane, thereby disrupting both the fluidity and functionality of membrane proteins. Consequently, sperm motility is hindered, and their capacity to navigate towards the oocyte is adversely affected. Numerous studies conducted in 2022 have underscored this relationship, particularly emphasizing the oxidative modification of lipids as a key contributor to reduced motility in cases of male infertility [74,75].

Furthermore, lipid peroxidation has been demonstrated to hinder capacitation by modifying the structure and functionality of sperm membranes. This alteration obstructs the necessary signal transduction pathways required for effective capacitation, ultimately leading to a diminished potential for fertilization. Recent research by Silva *et al.* [76], illustrated how oxidative stress can modify membrane cholesterol levels, disrupting the mechanisms of sperm capacitation and resulting in fertilization failures.

Additionally, the acrosomal reaction, which is crucial for sperm penetration of the egg's zona pellucida, is also adversely affected by lipid peroxidation. Oxidative damage to lipids within the acrosomal membrane can hinder the acrosomal reaction, thereby obstructing successful fertilization. Recent investigations have established a strong correlation between lipid peroxidation and a deterioration in acrosomal integrity, consequently diminishing the sperm's ability to effectively fertilize oocytes[77].

9. ANALYSIS OF THE SAFETY AND TOLERABILITY OF CURCUMIN

Extensive research has been undertaken to assess the safety profile of curcumin, with findings from both animal and human studies suggesting that curcumin is generally well tolerated at typical supplementation doses. The majority of reported adverse effects are mild and transient, predominantly manifesting as gastrointestinal discomfort, particularly at elevated doses [78].

Clinical trials have demonstrated that curcumin is relatively safe when administered within the recommended dosage parameters. A comprehensive review of various studies revealed that daily doses of up to 8 grams do not exhibit significant toxicity in healthy individuals. Nonetheless, some individuals may experience mild side effects, including nausea, diarrhea, or headaches, which are often linked to higher doses or extended use. These side effects are typically reversible upon cessation of supplementation [79]. Furthermore, other researchers indicated that curcumin is generally well tolerated when used in conjunction with other medications, although caution is warranted when co-administering it with drugs that affect bile secretion or gastrointestinal motility [80].

A significant concern regarding the safety of curcumin pertains to its bioavailability. Curcumin exhibits poor absorption when ingested orally, raising questions about whether its potential therapeutic benefits justify its low bioavailability. Nevertheless, researchers have investigated various strategies to enhance its absorption, such as the combination of curcumin with piperine (an alkaloid found in black pepper), which has been shown to increase bioavailability by as much as 2000%. This enhancement not only improves the efficacy of curcumin but also its safety profile, allowing for the achievement of therapeutic doses without considerable risk of toxicity [81]. Despite its limited bioavailability, curcumin continues to be regarded as a promising candidate for clinical application, supported by a robust safety profile across diverse populations.

Some investigations have focused on the long-term safety of curcumin, particularly concerning chronic usage. Research involving extensive follow-up periods is essential to fully understand the implications of prolonged curcumin supplementation.

10. FUTURE DIRECTIONS

Curcumin, a bioactive compound derived from turmeric (Curcuma longa), has gained attention for its antioxidant, anti-inflammatory, and anti-apoptotic properties. Studies suggest that oxidative stress plays a crucial role in male infertility by impairing sperm function and DNA integrity. Curcumin's ability to neutralize reactive oxygen species (ROS) and regulate oxidative stress may offer potential benefits in mitigating infertility issues caused by oxidative damage [78]. Despite its promising properties, the bioavailability of curcumin remains a significant challenge. Most studies indicate that oral curcumin exhibits poor absorption and rapid metabolism, limiting its therapeutic efficacy. Recent advancements, such as the development of nanoformulations and curcumin conjugates, aim to enhance its stability and bioavailability. These innovations could pave the way for more effective treatments targeting male infertility[82].

Another critical area for investigation is the effect of curcumin on hormone regulation. Testosterone and other reproductive hormones play a vital role in male fertility, and some evidence suggests that curcumin may influence hormone levels. However, comprehensive clinical studies are required to understand these effects fully and to determine whether curcumin supplementation could support hormonal balance in infertile men [83]. Additionally, curcumin's anti-inflammatory properties may be beneficial in cases of male infertility associated with inflammatory conditions such as varicocele or epididymitis. Preclinical studies have shown that curcumin can suppress pro-inflammatory cytokines and modulate immune responses, which might improve testicular health and sperm quality. Further research is essential to confirm these findings in human populations [84].

Lastly, while in vitro and animal studies highlight curcumin's potential in improving sperm motility, count, and morphology, clinical trials involving human subjects are scarce. Future research should focus on large-scale, randomized controlled trials to establish curcumin's safety and efficacy in managing male infertility. Furthermore, exploring its interactions with conventional treatments, such as assisted reproductive technologies, may provide insights into integrated therapeutic strategies [85].

10.1. Challenges and Limitations of using Curcumin for Male Infertility

10.1.1. Bioavailability Challenges

A significant obstacle in utilizing curcumin for the treatment of male infertility is its low bioavailability. The absorption of curcumin in the body is limited, characterized by a rapid metabolic rate and swift elimination. Research indicates that when administered orally, curcumin's bioavailability may be as low as 1% [85]. This limitation significantly undermines the potential of curcumin as an effective standalone therapy for male infertility. Various strategies, such as the formulation of curcumin with other compounds like piperine, have been investigated to improve its absorption; however, the results have been inconsistent.

10.1.2. Absence of Standardized Dosage

Another challenge in employing curcumin for male infertility treatment is the lack of a standardized dosage. Different clinical trials and studies have utilized varying dosages, which complicates the identification of an optimal therapeutic regimen [86]. The absence of a consensus on dosing, coupled with significant variability in individual responses, hinders the practical application of curcumin in clinical environments. Additional research is essential to develop a definitive dosing protocol that guarantees both safety and efficacy.

10.1.3. Limited Clinical Evidence

Despite preclinical studies indicating potential benefits of curcumin in enhancing male reproductive health, there is a notable deficiency of large-scale, rigorously controlled human clinical trials [87]. Most existing research on curcumin and male infertility is either small-scale or conducted on animal models, which may not translate effectively to human applications. To substantiate the efficacy of curcumin in treating male infertility and to ensure its long-term safety, larger and more methodologically sound clinical trials are imperative.

10.1.4. Safety and Side Effects

While curcumin is generally regarded as safe, it may lead to side effects, particularly when administered in high doses or over prolonged periods. Common adverse effects include gastrointestinal issues such as nausea and diarrhea [88]. Additionally, there are concerns regarding the interaction of curcumin with other medications and its overall safety profile.

CONCLUSION

Curcumin, the active compound in turmeric, has been studied for its potential therapeutic effects on male reproductive health. Research indicates that curcumin may offer several benefits including Improved sperm quality, antioxidant effects due to its capacity to reducing oxidative damage, curcumin may protect sperm DNA integrity and improve overall reproductive function. It can influence hormone levels, potentially restoring balance in cases of hormonal imbalances affecting male fertility. Curcumin has been shown to protect against testicular damage caused by conditions like testicular torsion. It can improve sperm chromatin quality and reduce apoptosis (cell death) in testicular cells, thereby preserving fertility potential. While these findings are promising, most of these studies have been conducted in animal models. Further clinical trials in humans are necessary to confirm curcumin's efficacy and safety for male reproductive health. As with any supplement, it's advisable to consult a healthcare professional before starting curcumin supplementation, especially for individuals with existing health conditions or those taking other medications.

Finally, curcumin's multifaceted therapeutic benefits, ranging from antioxidant and anti-inflammatory properties to hormonal regulation and protection against cell apoptosis, make it a promising natural treatment for male infertility. Further clinical trials and studies are needed to better understand the full extent of its efficacy and mechanisms in fertility treatment in humans.

AUTHOR CONTRIBUTIONS

Conceptualization, MAE; Data Curation, MAE, TAA; Methodology, MAE, TAA; Project Administration,

MAE, Resources, MAE, TAA; Software, MAE, TAA; Supervision, MAE; Writing—Original Draft, TAA;

Writing—Review and Editing, MAE. All authors have read and agreed to the published version of the manuscript.

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