REVIEW ARTICLE

Quercetin and Male Fertility: A Literature Review

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Abstract

Background: Infertility causes social and psychological distress and has negative economic effects on healthcare systems. Infertility is the incapability to conceive after at least 12 months of unprotected regular sexual intercourse. Finding the impacts of herbal antioxidants can result in new visions for enhancing male fertility. Quercetin belongs to the bioflavonoids family, and many nutritionists, scientists, and researchers have investigated its pharmacokinetic and pharmacodynamic properties in their studies.

Methods: In this review, the authors summarized the protecting role of quercetin against oxidative damage and toxic metals stimulating male infertility by searching in PubMed, Web of Science, Scopus, and Embase via the keywords "male infertility", "quercetin", "male fertility", "oxidative stress", "toxic metals", "environmental contaminants", and "heavy metals" without language or date restrictions.

Results: Due to insufficient antioxidant defenses and inadequate cell repair systems, spermatozoa are predominantly susceptible to oxidative stress and toxic agents, especially heavy metals. Reactive oxygen species mediate several other cellular mechanisms, such as apoptosis. Previous research has highlighted quercetin and polyphenols' positive and negative impact on male fertility.

Conclusion: Quercetin exerts its beneficial functions through its antioxidant capacity by scavenging ROS and chelating toxic heavy metals and other environmental contaminants; thus, it can prevent male infertility.

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Introduction

There has been a growing interest in using bioflavonoids as antioxidants in human health and disease.[1-3] Flavonoids, a group of natural substances with variable phenolic structures, are found in fruits, vegetables, tea, grains, flowers, stems, roots, bark, and wine.[4-8] Herbal flavonoids and their potential to improve fertility have been recently investigated in humans and animals.[9, 10] Finding the impacts of herbal antioxidants can result in new visions for enhancing male fertility.[11] Quercetin has an anti-cancer role and also has improving effects on metabolic diseases and male infertility.[12] Oxidative stress and inflammation play important roles in the human body[13-15] and are important factors in infertility and the male reproductive system.[16] With antioxidant and anti-inflammatory properties, quercetin can be a potential supplementary treatment for male infertility.[12]

Several previous studies have investigated the effects of quercetin on male fertility and infertility. Oxidative stress, inflammatory situations, air pollutants, and heavy metals are the main reasons for human infertility. Quercetin has been reported to act as an antioxidant and anti-inflammatory agent and can chelate heavy toxic metals. Hence, in this review, we intend to focus on the ameliorative impact of quercetin on male fertility and its mechanisms of action.

Male Fertility and Spermatogenesis

The male version of gametogenesis is spermatogenesis. This process leads to the production of spermatozoa (sperm), which are the mature male gametes in humans and can fertilize the counterpart female gamete. Spermatogenesis occurs in the seminiferous tubules located in the testes, and final maturation occurs in the epididymis.[17, 18] The process is under hormonal control; the most important hormones are testosterone, follicle-stimulating, and luteinizing. Testosterone production in Leydig cells is related to LH function, and androgen-binding protein production in Sertoli cells depends on the follicle-stimulating hormone. Testosterone is concentrated through binding to the ABP and facilitates spermatogenesis. Any hormonal or spermatogenic disorder can cause infertility in men.[17, 19, 20]

Methods

In this review, we summarized the protecting role of quercetin against oxidative damage and toxic metals stimulated by male infertility. The search was performed in Scopus, PubMed, Embase, and Web of Science via the keywords "male infertility", "quercetin", "male fertility", "oxidative stress", "heavy metals", "toxic metals", and "environmental contaminants" without date and language limitations. The title and abstract of all articles recognized and those reporting the impact of quercetin on male infertility were finally selected.

Results

Male Infertility

The infertility definition is the incapability to conceive after at least 12 months of unprotected, regular sexual intercourse.[21] Eight to twelve percent of couples of reproductive age are estimated to suffer from infertility. Infertility causes social and psychological distress and has a significant economic impact on healthcare systems and patients.[22] Male infertility is a multifactorial condition, and several idiopathic, acquired, and congenital reasons can be involved in its occurrence.[23, 24] Idiopathic risk factors include alcohol, smoking, obesity, advanced paternal age, dietary factors, psychological stress, recreational drugs, and environmental or occupational exposure to toxins.[25, 26] Acquired factors consist of varicocele, urogenital tract obstruction, germ cell tumors, acquired hypogonadotropic hypogonadism, testicular torsion, recurrent urogenital infections, post-inflammatory conditions, testicular trauma, exogenous factors (medications, radiation, heat, chemotherapy), anti-sperm antibodies, systemic diseases (renal failure, live cirrhosis), surgeries, and sexual dysfunction.[25, 27] Congenital factors include congenital obstruction, genetic endocrinopathy, chromosomal or genetic abnormalities, Y chromosome microdeletions, cryptorchidism, congenital absence of vas deferens, and anorchia.[25]

Quercetin

Herbal products technology has progressed in recent decades, and using phytochemicals for human health has attracted much attention.[28] Quercetin belongs to the bioflavonoids family, and many nutritionists, scientists, and researchers have investigated its pharmacokinetic and pharmacodynamic properties in their studies.[29, 30] Quercetin originates from the Latin - *quercetin*, which means oak forest, *Quercus* oak. Prof. Stephan C. Bischoff, a German nutritionist, believes that quercetin is one of the major complementary medications for preventing and treating diseases.[31]

Absorption, Metabolism, and Excretion of Quercetin

In the colon and small intestine, bacterial enzymes remove the carbohydrate part of quercetin and facilitate its absorption.[31] It metabolizes in the intestine and the liver. Intestinal microorganisms metabolize the unabsorbed parts of quercetin, while the liver plays an important role in the absorbed quercetin metabolism. The anaerobic bacterium of the intestine cleaves the quercetin ring structure into 3,4-dihydroxyphenylacetic acid. Quercetin biotransformation occurs in the liver through sulfonylation, methylation, hydroxylation, and glucuronidation. Some parts of glucuronidation take place when it passes through the epithelium.[32] Within two days after sulfate and glucuronide conjugation, quercetin exerts into urine and the bile. Simultaneous administration of quercetin with high-fat foods delays its exertion through urine and the bile.[31]

Quercetin's Mechanisms of Action

Quercetin can scavenge reactive oxygen species and heavy metals and has a powerful antioxidant capacity.[33] It can prevent the peroxidation of lipids.[34] Free radicals attack fatty acids, steal their electrons, and convert them to free radicals.[35] Since the formed fatty acid radicals are unstable, they react with oxygen and produce peroxyl-fatty acid radicals. Peroxyl-fatty acid radicals accelerate this chain by acting as free radicals and more peroxyl-fatty acid radicals. Quercetin is a strong antioxidant that eliminates oxygen radicals and prevents peroxyl fatty acid formation. Quercetin exerts its antioxidant potential through the 2,3-double bond, 4-oxo, and 3-hydroxyl groups, hydroxyl groups of ring B, and 5,7-dihydroxyl groups of ring A (Figure 1).[32]

Quercetin and Male Fertility

Plant-derived compounds as dietary supplements have been previously examined for their capacity to

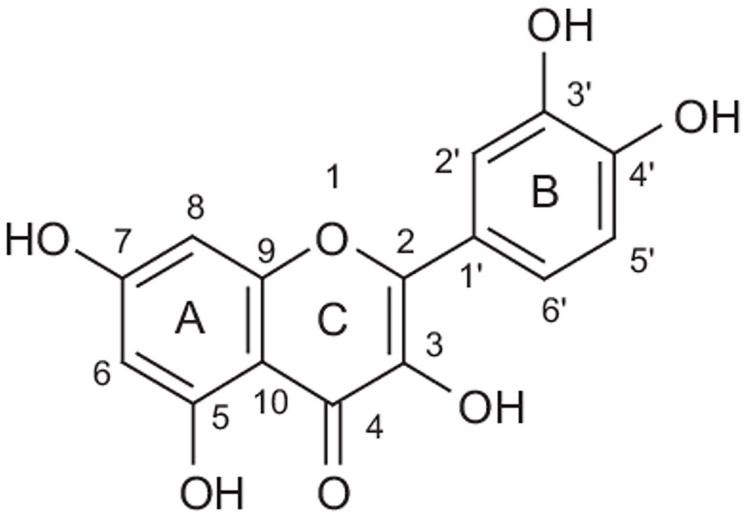

Figure 1: Quercetin chemical structure. Quercetin exerts its antioxidant potential through 2,3-double bond, 4-oxo, and 3-hydroxyl groups in ring C, hydroxyl groups of ring B, and 5,7-dihydroxyl groups of ring A

improve fertility in humans and animals.[10] Previous research has highlighted quercetin and polyphenols' positive and negative impacts on male fertility. Most reports have reported quercetin's anti-oxidative capacity and its impacts on male infertility prevention and treatment.[36] However, other improving properties of quercetin, including anti-inflammatory, protective effects against toxic agents and heavy metals, and protective effects against environmental contaminants, have also been reported.[37]

Discussion

Protective Effects Against Oxidative Stress

Mammalian sperm are vulnerable to reactive oxygen species attack since polyunsaturated fatty acids are abundantly found in their structure. Oxidative stress may result in rapid loss of ATP, causing morphology defects and reduction in sperm viability. One of the key mechanisms of sperm oxidative damage is lipid peroxidation of its membrane.[37-39] Due to insufficient antioxidant defenses and inadequate cell repair systems, spermatozoa are predominantly prone to oxidative damage.[38] Sperm fertilization potential, motility, and viability are disturbed by oxidative stress, evidenced by the existence of markedly higher levels of reactive oxygen species in the semen of infertile men.[40] Several other cellular mechanisms, such as apoptosis, are mediated by reactive oxygen species.[12]

Quercetin is a phytoestrogen and flavonoid in many fruits and vegetables, such as citrus fruits, apples, onions, parsley, sage, tea, and red wine. It has attracted increasing attention because of its antioxidant, anti-carcinogenic, anti-obesity, antiviral, anti-inflammatory, and antibacterial effects. This great antioxidant capability of quercetin is due to the existence of 3 functional rings in its structure.[41] Based on previous reports, quercetin can improve the longevity of spermatozoa and sperm quality and prevent reactive oxygen species formation in spermatozoa through non-enzymatic and enzymatic cellular systems.[42]

Quercetin is noteworthy in preventing oxidative stress-induced DNA damage, improving the sperm antioxidant system, and decreasing hydrogen peroxide production.[43] Quercetin can ameliorate oxidative damage, followed by Diethylstilboestrol (DES) administration by inducing glutathione peroxidase and superoxide dismutase activity.[44] DES is an artificial estrogen used to investigate the harmful effects of estrogenic endocrine defects on male animals.[44] DES exerts its deteriorating effects by reducing superoxide dismutase, glutathione peroxidase, glutathione reductase, and an increase in lipid peroxidation.[45] Moretti et al. investigated the effects of quercetin alone and quercetin-loaded liposomes on oxidative stress presentation in human sperm. Sperm viability and motility were improved dose-dependently. Compared to quercetin alone, quercetin-loaded liposomes had less toxicity on sperm motility and viability.[11] Zribi et al. studied DNA integrity and survival during cryopreservation and thawing in human sperm by adding quercetin to the cryoprotective media. They reported that 50 µM of quercetin enhanced sperm viability and motility and reduced DNA damage of sperm after thawing.[43] In many other studies, quercetin has been reported to improve oxidative defense in testicular tissue through increasing antioxidant enzymes and decreasing oxidative stress-related products such as malondialdehyde.[46]

Protective Effects Against Heavy Metals

Male fertility can be affected by the accumulation of heavy metals in the body and reproductive organs.[47]

Heavy metals, including mercury (Hg), aluminum (Al), lead (Pb), cadmium (Cd), cobalt (Co), and arsenic (As), are extremely toxic and can result in irreversible effects on male fertility.[48] Exposure to heavy metals typically happens unintentionally via consumption of some drugs, contaminated water and food, and inhalation of polluted air.[49] Heavy metals may cross the blood testicular barrier and exert deteriorating effects on spermatogenesis, characterized by decreased sperm density and motility, increased morphological abnormalities, and subsequent male infertility.[50]

Heavy metal poisoning affects the function and morphology of reproductive organs and fertility by inhibiting defense mechanisms against free radicals and other cytotoxic mechanisms.[50] Several studies have shown that quercetin reduces heavy metal toxicity by scavenging and chelating reactive oxygen species and other cytotoxic agents.[51] Quercetin improves the function and morphology of the male reproductive system by increasing sperm number, tubular epithelial height, and proliferative capacity.[52] In a study by Al-Omair et al. (2017), it was reported that quercetin, when compared to the lead acetate-treated group, increased sperm motility and count while reducing the percentage of abnormal sperm in rats.[53] It has been found that quercetin can protect goat preimplantation embryos and sperm from cadmium-induced oxidative toxicity.[54] Cadmium-induced abnormal changes reversed after quercetin co-treatment, indicating its protective activities of it.[55]

Quercetin administration improves male fertility through hormonal changes. A marked increase in intratesticular and serum testosterone was seen following quercetin administration in sodium arsenite poisoning.[56] This may be due to the inhibition of reactive nitrogen species and ROS generation stimulated by arsenic toxication or induction of androgenic enzymes 3ß-HSD and 17ß-HSD activity.[52] Cadmium suppresses sexual behavior and steroidogenesis, negatively affecting sexual behavior and penile erection. By reversing these changes, quercetin has beneficial effects on male fertility.[57]

Other Protective Mechanisms

Quercetin prevents reproductive defects induced by environmental contaminants, including 3- methyl-4 nitrophenol,[58] 3-methyl-4-nitrophenol,[59] 4-nitro-3-phenlyphenol,[60] and polychlorinated biphenyls.[60] It also facilitates the destructive effects of environmental poisons such as 2,4-dichlorophenoxyacetic acid and strengthens the antioxidant defense in testicular cells.[61]

Limitation

The use of isolated quercetin as a dietary supplement should be cautiously advised. It has been reported to enhance nephrotoxic effects in the pre-damaged kidney or to promote tumor development, especially in estrogen-dependent cancers. Also, there is a lack of adequate safety data from human intervention studies regarding a supplemental intake of quercetin for pregnant and breastfeeding women and children. Quercetin administration may show interactions with some drugs and change the drug's bioavailability based on previous reports.[62]

Conclusion

In summary, the results of the current study indicated that quercetin administration in males improves reproductive function. Quercetin exerts its beneficial functions through its antioxidant capacity by scavenging ROS and chelating toxic heavy metals and other environmental contaminants; thus, it can prevent male infertility. However, more research is needed, especially clinical trials, to find quercetin's exact mechanism and adverse effects on male fertility.

Conflict of Interest: None declared.

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