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Meta-Analysis

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Investigate the Effect of *Cornus mas* or *Galega officinalis* on Sperm Parameters and Antioxidant Enzyme Levels in Diabetic Mouse Model: A Meta-analysis

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Abstract

Objectives: Diabetes mellitus decreases reproductive and sexual function in men by causing oxidative stress in testis cells and decreasing antioxidant enzymes. Several recent studies have found the effects of *Cornus mas* and *Galega officinalis* extracts on improving spermatogenesis dysfunction caused by diabetes. This meta-analysis study aimed to investigate the impact of *G. officinalis* and *C. mas* extract on testicular oxidative stress indices and sperm parameters in diabetic laboratory animals compared to healthy animals.

Methods: A search using Scopus, PubMed, Web of Science, and Google Scholar databases was conducted on studies that investigated the effects of plant extracts of *C. mas* and *G. officinalis* on testicular tissue and sperm indices in diabetic animals. The first part included the investigation of malondialdehyde (MDA) (nmol/mg), rate of catalase antioxidant activity, and superoxide dismutase. In contrast, the results of the second part included total sperm count ($\times 10^6$), total sperm motility (%), and immobility. The mean difference (MD) (95% confidence interval [CI]) was selected to express the effect size.

Results: Out of 154 identified articles, four studies on mice were included in the meta-analysis. The random effect size yielded an overall effect size for MDA (6.96) with a 95% confidence interval [-6.09; 20.00]. The random effect size yielded an overall effect size for SOD of -0.5076 with a 95% confidence interval [-0.62; -0.40]. The random effect size yielded an overall effect size for CAT of -1.68 with a 95% confidence interval [-1.88; -1.47]. Also, a significant decrease in total sperm count showed the random effect size yielded an overall effect size of -24.74 with a 95% confidence interval [-30.73; -18.74]. The random effect size yielded an overall effect size for sperm motility of -26.65 with a 95% confidence interval [-29.54; -23.76]. A significant increase was demonstrated in sperm immobile in diabetic animals compared to the control group. The random effect size yielded an overall effect size for this indicator is 6.5157 with a 95% confidence interval [-1.96; 14.99].

Conclusion: *G. officinalis* or *C. mas* extracts have reduced effects on MDA levels and tissue damage and increased antioxidant enzymes in laboratory animals with diabetes.

Keywords: Diabetes, *Galega officinalis*, *Cornus mas*, Sperm parameters

Introduction

Diabetes mellitus has adverse effects on the function and failure of various organs, including the male reproductive system (1). The effects of diabetes mellitus on male reproduction are manifested by reduced fertility and poor quality of sperm indices (2). In human and animal studies, degeneration of spermatogonia cells and Sertoli cells, reduction in the size of spermatic tubes, low sperm quality, and fertility decline have been demonstrated (3). The underlying mechanisms for diabetes' effect on human spermatogenesis have not yet been well understood. Several studies have shown that excessive amounts of reactive oxygen species (ROS) have been involved in reducing reproductive function in diabetic males (4). In fact, increasing glucose levels in the long-term leads to overproduction of ROS, which may upset the balance between antioxidant and antioxidant enzyme systems (1). It has been reported that the overproduction of ROS and oxidative stress causes the death of germ cells, which ultimately leads to an impaired spermatogenesis process (5). Several studies have been conducted on the treatment of spermatogenesis disorder in diabetes mellitus using chemical and hormonal drugs. However, the use of these types of medicines still leaves various adverse effects in the treatment of spermatogenic dysfunction. Therefore, the development of effective therapeutic drugs is an essential issue in the treatment of spermatogenic disorders caused by diabetes. It has been reported that herbal medicinal products have high therapeutic potential.

Galega officinalis has recently gained attention due to its therapeutic and traditional disease applications. The hydroalcoholic extract of *G. officinalis* contains

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compounds such as flavonoids, tannins, saponins, and steroids (6). In previous studies, it has been shown that compounds in this plant, including metformin, have anti-diabetic properties (7). Cornelian cherry herb, with the scientific name *Cornus mas*, is used in traditional medicine to treat diarrhea, fever, kidney stones (8), and kidney and bladder infections (9,10). Several studies have reported that C. *mas* has antibacterial (11), anti-allergenic (10), anti-diabetic (12), anti-inflammatory, and antioxidant properties (13). Several recent studies have shown that extracts of *G. officinalis* and *C. mas* improve diabetes, testicular oxidative damage, and sperm parameters caused by diabetes (14,15).

The present review used meta-analysis to investigate the effect of *C. mas* and *G. officinalis* on sperm parameters and antioxidant enzyme levels in a diabetic mouse model. Establishing the role and impact of plants' antioxidant properties on reproductive and sexual dysfunctions in mice can provide great insight into the mechanisms and effects of these antioxidant substances.

Methods

Search Strategy

Based on the review's meta-analysis structure, initial searches were conducted using words (spermatogenesis, *Cornus mas*, *Galega officinalis*, and diabetes) in four databases: PubMed, Scopus, Web of Science, and Google Scholar. Search strategies included MeSH search terms and keyword-related concepts. The "OR" or "AND" operator combined these terms into different combinations. The resources in the articles are also included. Search articles published from 30 March 2014 onwards are listed in English. The goal was to provide researchers with easier and better access to raw data. The study included only articles that reported animal models. In this study, we included articles containing herbal extracts of *C. mas* and *G. officinalis* on improving sperm indices function in spermatogenesis disorder caused by diabetes.

Selection Criteria

The inclusion criteria for the meta-analysis were as follows: 1) only in-vivo experiments conducted on rodent models, specifically mice and rats, were eligible for consideration; 2) plant extracts were required to be administered subsequent to the induction of diabetes; 3) the articles must provide data on sperm indices, including morphology, count, and motility, as well as measurements of antioxidant enzyme levels and lipid peroxidation.

The exclusion criteria for this meta-analysis were as follows: 1) published studies in the form of letters, editorials, abstracts, reviews, and conference proceedings, as well as non-animal studies, articles with incomplete information, redundant or repetitive research, and older articles lacking significance and credibility; 2) studies focusing solely on the effects of active ingredients derived from these plants; 3) a lack of sufficient data within the study; 4) in vitro studies and research involving non-rodent animal models were also excluded.

Selection of Studies

In the initial search, about 154 articles were found. After reviewing the titles and abstracts, seven duplicate articles and 136 reports were removed. The remaining studies (n=4) entered the study after further screening that met the entry criteria and were suitable for our meta-analysis. The screening process of the studies is shown in Figure 1.

Data Extraction

Initially, a detailed form of data extraction (4 articles) was extracted, which included: 1) Study characteristics, including the names of the authors, year of publication, sample size, type of intervention, type of administration of plant extract, dosage, duration of treatment, and the results of studies. Three authors (ES, IP, and HG) independently screened the titles and abstracts of the articles and excluded publications based on the established criteria. In cases of disagreement, consensus was achieved through discussion. The fourth author (SH) facilitated the resolution of inconsistencies through further discussion and consultation. Details regarding the interventions and comparisons, criteria for quality or risk of bias assessment, corresponding effect sizes, mean differences (MD), as well as the statistical models and I^2 values, were reported by two authors (ES and IP). The authors of these studies extracted the data using the form above. The results of these investigations are also reported in Table 1.

The studies were remained for meta-analysis that met the following criteria:

- The effects of plant extracts of *G. officinalis* or *Cornus mas* on testicular function, spermatogenesis, and reproduction in male rats
- SD, SEM, or mean values were available for the control and treatment groups with the extracts in the article.
- The constituent compounds in plant extracts have not been given to animals.

Statistical Analysis

Statistical analysis was performed using the R program (version 4.2). Statistical heterogeneity was calculated using Cochran's test and heterogeneity index (I^2), and $I^2 > 50\%$ indicated significant heterogeneity among the studies. The random method was used to compare the means. We evaluated the release bias using a funnel chart and the Egger regression test. The sensitivity analysis was also performed (16).

Results

Four articles out of 154 identified articles were included in the quantitative analysis. Figure 1 shows the study's flow chart according to the instructions. In this study, results

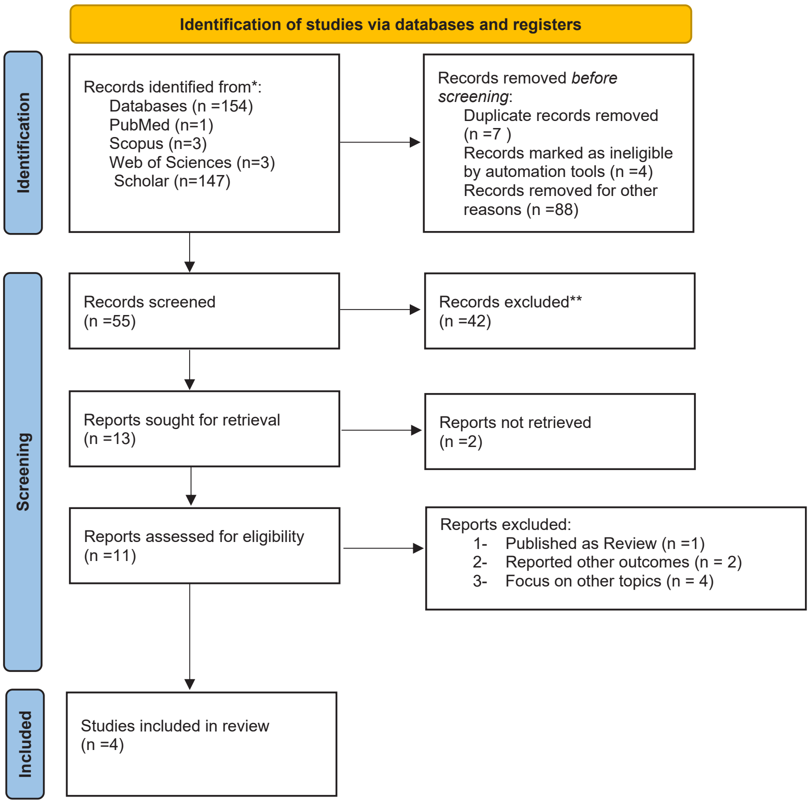

Figure 1. Flowchart for the Selection of Articles.

such as sperm concentration and ROS levels through the free radical scavenging test were not reported because the number of studies was insufficient for the forest diagram.

Malondialdehyde Concentration

Malondialdehyde (MDA) concentration was investigated in 3 studies with a sample size of 24. Significant heterogeneity was observed between the studies (I^2 = 98.4%). The heterogeneity test (Q test) was statistically significant ($P < 0.0001$). The results of both Egger tests did not show publication bias in the included studies ($P =$ 0.0883). The results showed that MDA levels significantly increased in laboratory animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract compared to healthy control animals. The random effect size yielded an overall effect size of (6.96) with a 95% confidence interval [-6.09; 20.00] (Figure 2).

Superoxide Dismutase Enzyme Activity

The activity level of the superoxide dismutase enzyme antioxidant was studied in 3 studies with a sample size of 24. The results of this section showed significant heterogeneity among the included studies (I^2 = 83.6%). The heterogeneity test (Q test) was statistically significant ($P > 0.0022$). The results of both Egger tests did not show a publication bias in the included studies ($P = 0.4710$). This enzyme's activity level was reduced in the animals with spermatogenesis disorder that received *C. mas* extract or *G. officinalis* compared to healthy animals. The random effect size yielded an overall effect size of -0.5076 with a 95% confidence interval [-0.62; -0.40] (Figure 3).

Catalase Enzyme Activity

The catalase enzyme's activity level was assessed in three studies with a sample size of 24. Heterogeneity analysis showed significant heterogeneity among the included studies ($I^2 = 69.0\%$). The heterogeneity test was statistically significant ($P > 0.0396$). The included studies did not demonstrate publication bias ($P = 0.1960$). The level of catalase activity in experimental animals that received *C. mas* extract or *G. officinalis* was decreased compared to the control animals. The random effect size yielded an overall effect size of -1.68 with a 95% confidence interval [-1.88; -1.47] (Figure 4).

Sperm Count

Sperm quality was evaluated for total sperm count and sperm motility. The sperm count level was also assessed in 3 studies with a sample size of 24. Significant heterogeneity was not observed between the included studies ($I^2 = 0.0\%$). The heterogeneity test was not statistically significant ($P < 0.7732$). Both Egger tests showed publication bias in the included studies ($P = 0.1895$). There was a significant decrease in total sperm count in animals receiving *G. officinalis* or *C. mas* extract compared to healthy control animals. The random effect size yielded an overall effect

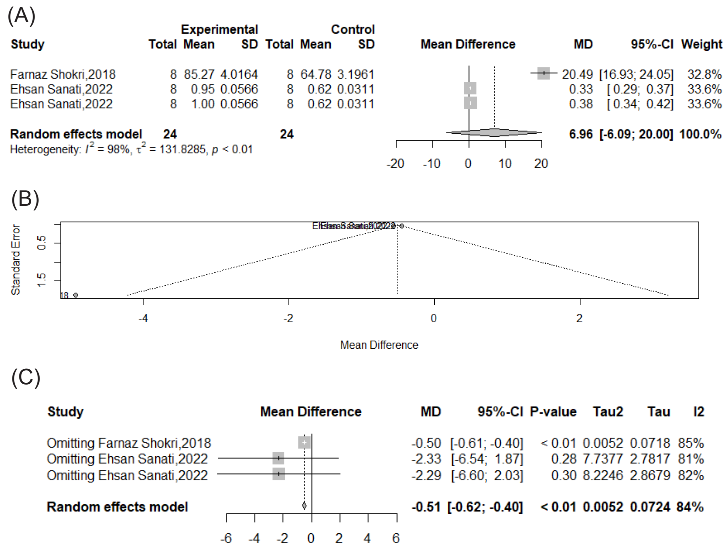

Figure 2. (A) Forest plot of the malondialdehyde concentration (MDA) in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract. (B) Funnel plot of the MDA in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. (C) Sensitivity analysis of the MDA in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. SD, standard deviation; MD, mean difference.

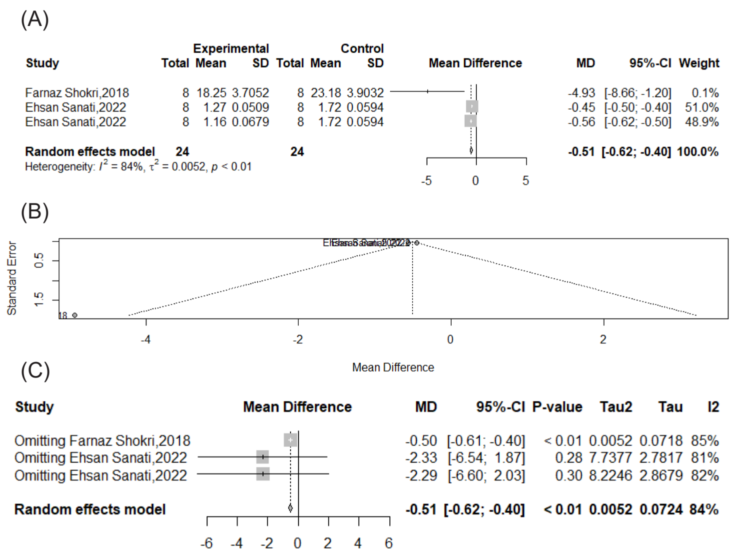

Figure 3. (A) Forest plot of the level of activity of the superoxide dismutase enzyme (SOD) in animals with spermatogenesis disorder treated with the extract of *C. mas* or *G. officinalis*. (B) Funnel plot of the SOD in animals with spermatogenesis disorder treated with the plant extract of *Cornus mas or G. officinalis*. (C) Sensitivity analysis of the SOD in animals with spermatogenesis disorder treated with plant extract of *Cornus mas* or *G. officinalis*. SD, standard deviation; MD, mean difference.

size of -24.74 with a 95% confidence interval [-30.73; -18.74] (Figure 5).

Sperm Motility

Heterogeneity analysis showed significant heterogeneity among the included studies (I^2 = 56.1%). The heterogeneity test (Q test) was statistically significant (P < 0.1313). Sperm motility in Sanati and colleagues' study was evaluated in two groups, *G. officinalis* or *C. mas*, with a sample size of 16. There was a statistically significant decrease in total sperm motility in experimental animals with spermatogenesis disorder that received *G. officinalis* or *C. mas* extract compared to control animals. The random effect size yielded an overall effect size of -26.65 with a 95% confidence interval [-29.54; -23.76] (Figure 6).

Immobile

Heterogeneity analysis showed no heterogeneity among the included studies (I^2 = 48.2%). The heterogeneity test (Q-test) was not statistically significant (P < 0.1453). Both Egger tests showed a propagation bias in the included studies (P = 0.4077). One study evaluated immobile rates

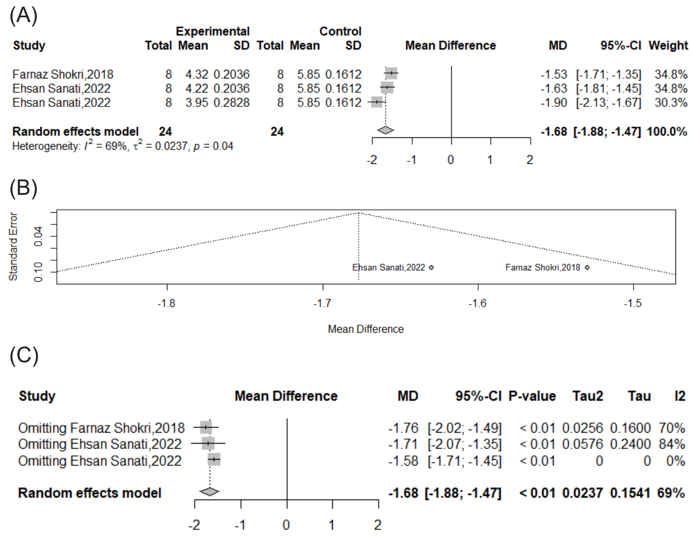

Figure 4. (A) Forest plot of the activity catalase enzyme (CAT) level in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract. (B) Funnel plot of the CAT in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. (C) Sensitivity analysis of the CAT in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. SD, standard deviation; MD, mean difference.

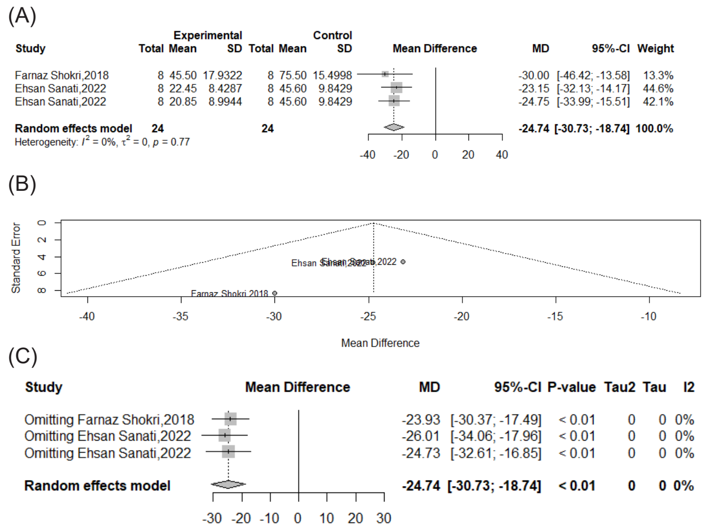

Figure 5. (A) Forest plot of the sperm counts in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract. (B) Funnel plot of the sperm counts in animals with spermatogenesis disorder treated with the plant extract of *C. mas* or *G. officinalis*. (C) Sensitivity analysis of the sperm counts in animals with spermatogenesis disorder treated with plant extract of *C. mas* or *G. officinalis*. SD, standard deviation; MD, mean difference.

in three doses of 250, 500 and 1000 of *C. mas* extract with a sample size of 24. There was a significant increase in immobile sperm in animals receiving *C. mas* extract at doses of 500 and 1000 mg/kg compared to the control group. The random effect size yielded an overall effect size of 6.5157 with a 95% confidence interval [-1.96; 14.99] (Figure 7).

Discussion

The overall results of this meta-analysis show that consumption of *G. officinalis* or *C. mas* extracts can significantly improve sperm function and sperm morphology in diabetic rats. It has been reported that diabetes mellitus causes physiological and functional disorders in different tissues of the body, especially reproductive and sexual systems (17). Several studies have shown that diabetes reduces reproductive function in men by causing oxidative stress in testis cells and reducing antioxidant enzymes, which can be due to the imbalance of redox/resuscitation in diabetic patients (18).

It is probable that compounds such as flavonoids and vitamins in *C. mas*, such as E, B2, B1, and C (19), as well as metformin in *G. officinalis* (6), have been able to act as one of the ways to treat hyperglycemia by increasing the expression of glucose-carrying proteins and reducing the harmful effects of oxidative stress on improving sperm

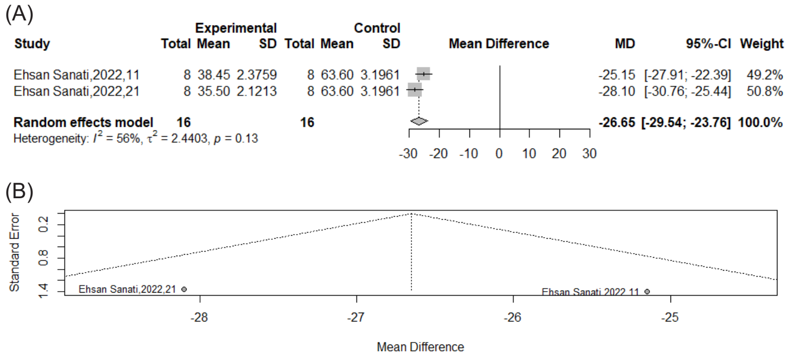

Figure 6. (A) Forest plot of the sperm motility in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract. (B) Funnel plot of the sperm motility in animals with spermatogenesis disorder treated with plant extract of *C. mas* or *G. officinalis*. SD, standard deviation.

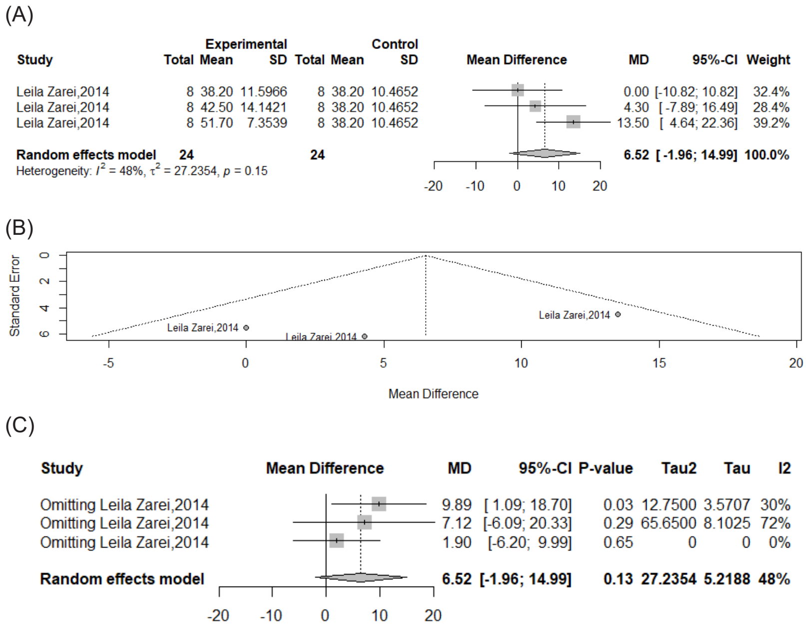

Figure 7. (A) Forest plot of the immobile rate in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* extract. (B) Funnel plot of the immobile rate in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. (C) Sensitivity analysis of the immobile rate in animals with spermatogenesis disorder treated with *C. mas* or *G. officinalis* plant extract. SD, standard deviation; MD, mean difference.

morphology and quality.

This meta-analysis study also showed that the plant extracts of *G. officinalis* and *C. mas* significantly reduced MDA levels in diabetic rats. MDA is a specific product of lipid peroxidation and acts as a marker of oxidative stress system (20). Oxidative stress caused by diabetes increases lipid peroxidation (21), which indicates a link between sexual function damage and oxidative stress levels (22). In Sanati et al and Shokri et al studies (14,15), treatment with *G. officinalis* was able to reduce MDA levels in mice with diabetes. It can be concluded that metformin in *G. officinalis* can lower blood sugar in diabetic rats in the first stage, which reduces oxidative stress and ultimately improves sperm function in sperm indices.

Also, in the current study, Sanati and colleagues' research shows that treatment with *C. mas* can reduce MDA and increase the superoxide dismutase and catalase enzymes (14). There is no precise mechanism for how *C. mas* reduces MDA concentration, but it has been suggested that *C. mas* extract modulates oxidative stress in diabetic rats and exerts mechanisms such as anti-radical and antioxidant properties (23). Also, in several studies, the authors hypothesize that all of the therapeutic effects of this herb are likely due to its antioxidant compounds. So far, in several pathological studies, antioxidant effects of *G. officinalis* and *C. mas* extracts have been reported in animals to prevent oxidative effects of protein and lipid by increasing the performance of antioxidant enzymes such as catalase and superoxide dismutase (24). Therefore, it can be generalized that the antioxidant properties of the extract of these two herbs may have a special and valuable therapeutic potential for treating various disorders related to oxidative damage of the testis caused by diabetes.

Also, the results of the meta-analysis study show that the plant extracts of *C. mas* and *G. officinalis* are associated with improvement in sperm index. Zarei et al (25) reported that administration of *C. mas* extract at doses of 1000 mg/kg and 500 mg/kg can have a beneficial effect on improving the quality of sperm indices. The effects and mechanisms of how *C. mas* affects sperm indices are unknown. However, it is possible that low doses of *C. mas* extract 250 mg/kg due to low bioavailability have not been able to have an optimal and beneficial effect on sperm motility. Therefore, the plasma concentration of *C. mas* extract at lower doses may not be sufficient to effectively regulate the function of spermatogenesis and improve the quality of sperm indices. According to the meta-analysis results, Sanati and colleagues' study showed that consuming *C. mas* extract in gavage can significantly improve sperm indices in a diabetic animal model. In fact, according to the above, determining the optimal dose of *C. mas* extract is very difficult, as Sanati and colleagues' study showed that at a dose of 100, it improved the performance and quality of sperm indices. In contrast, Zarei and colleagues' study at a dose of 250 did not show any improvement effects, which may be due to the different duration of treatment with the *C. mas* extract or the type of disease model in rats.

Limitations of the Study

The current study also has several inevitable limitations. Firstly, due to limited relative data, we could not further analyze the relationship between the amount of *G. officinalis* or *C. mas* extracts with an increase in antioxidant enzymes and an improvement in sperm indices performance. Second, we could not make a general assessment of all sperm indices in the animals that received these extracts because of inadequate data. In addition, the quality of the studies varied, and only two high-quality studies were found.

Conclusions

The results of our current analysis indicate that the consumption of *G. officinalis* and *C. mas* extracts significantly enhanced sperm function and morphology in rats, increased the levels of antioxidant enzymes (catalase and superoxide dismutase), and reduced free radical levels. These extracts may represent promising therapeutic agents for addressing reproductive and sexual dysfunctions associated with diabetes. However, the precise mechanisms of action require further verification through animal studies. Consequently, high-quality experimental research is encouraged to elucidate the relationship between the plant extracts of *G. officinalis* and *C. mas* and their effects on improving spermatogenesis indices in diabetic mouse models.

Authors' Contribution

Conceptualization: Ehsan Sanati.
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Resources: Ehsan Sanati, Iraj Posti.
Data curation: Ehsan Sanati, Iraj Posti, Hassan Gilanpour, Saeed Hesaraki.
Supervision: Iraj Posti.
Project Administration: Ehsan Sanati.
Writing–original draft: Ehsan Sanati.
Writing–review and editing: Ehsan Sanati, Iraj Posti.

Conflict of Interest

The authors declare they have no conflict of interest.

Ethical Approval

All the experimental processes of this research were approved by the Ethical Committee of Islamic Azad University, Tehran, Iran.

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