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MANFORT: A DIETARY SUPPLEMENT FOR SEMEN PARAMETERS QUALITY IMPROVEMENT IN LOW SPERM COUNT AND AZOOSPERMIA PATIENTS

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ABSTRACT

Background: The production of healthy sperms from testicular tissues which able to successfully fertilize the mature egg is the main target of the recent studies. Recently dietary supplements composed from multi-natural products extracted from medicinal herbs are used for sperm parameters improvement compared with chemically-based synthesized drugs. This traditional method of treatment is safe, effective and low costed compared with the chemical-based synthesized drugs treatment.

Objectives: We will investigate the efficacy of Manfort on a total number of 33 patients (n = 33) suffering from low sperm count or azoospermia. It is expected that Manfort will improve the semen parameters qualities.

Materials and methods: In this study we prepared a dietary supplement called "Manfort" composed from multi-active antioxidants and anti-inflammatory ingredients.

Results: The semen parameters of patients treated with Manfort showed an improvement in most of semen parameters. Compared with the semen parameters before treatment, the semen volume significantly increased 1.4 times in the patients consumed Manfort. The sperm concentration of low sperm counts and azoospermia patents increased 5.2 times and 0.5 times respectively. Sperm motility also elevated into 2.1 times as compared with same data before Manfort consumption. Additionally, the number of white blood cells in the semen significantly decreased in the treated patients with Manfort.

Conclusion: The data obtained from this study introduced important information about nature products extracted from medicinal herbs and its role in the infertility treatment.

This study recommends the use of dietary supplements which contain multi-active antioxidants ingredients to improve semen parameters.

1. Introduction

Infertility usually is known as failure to get pregnant, even the couples have continual and unprotected sex for more than one year (1). Previous studies reported that, above 70 million couples complain from infertility around the world. Furthermore, infertility was reported in 8% to 12% of couples throughout the world, based on previous studies (2). In specific, male infertility is an argumentative problem in all world populations. Through the past century, the treatment of infertility disorders with the medicinal herbs is more effective, safe, agree with patient's ideology (3,4).

There are many medical benefits (especially disorders concerned with male infertility) of antioxidants, such as flavonoids and polyphenols, found in the medicinal herbs. There are different varieties of flavonoids; for example, but not limited, hesperetin flavonoid has the ability to reduce the testicular damage and inflammation in mice. The protective role of this hesperetin is due to the oxidative stress inhibition (5). Additionally, flavonoids found in epimedium extract highly reduce the damage of DNA in testicular tissue of rats (6). Also, *Cymbopogon citratus*, *Colocasia esculenta* and chrysin extracts ameliorates testicular dysfunction and reduced the testicular fail (7,8,9). In addition to flavonoids, polyphenols consider as a group of chemical substances that is popular in medicinal herbs. Therefore, polyphenols such as tea leaves consider as one of the most famous antioxidants used in human dietary supplement used for infertility treatment (10,11,12).

It well known that, the dietary supplements which contain antioxidant, can improve effectively the quality of semen parameters in men who are suffering of infertility disorders (13,14,15,16,17). For example, extracts from parsley seed, green tea (15,17), leaf of *Cardiospermum halicacabum* (16) showed positive improvement of the semen parameters especially sperm concentration after administration for long time. Sperm motility is crucial that sperm move through the vaginal tract, uterus and fallopian tube to reach and fertilize mature egg there. Flavonoids have many positive characteristics such as antioxidant and anti-inflammatory. For example, rutin, naringin, and kaempferol, catechin and citrus extracted flavonoids decreased the inflammation and disorders in the testicular tissues and increased sperm motility (18,19,20).

Polyphenols also have important role in the male infertility treatment. The higher concentration of polyphenols such as glutathione in seminal plasma act as natural antioxidants (21,22). For example, superoxide dismutase and selenium (23-25) and green tea extracts (26,27) have the ability to remove reactive oxygen species and improve sperm motility. Testicular tissue inflammations might produce lower quality of semen parameters therefore, antioxidants including polyphenols can protect against the inflammation or WBCs increase of reactive oxygen species (28,29).

Previously we prepared a dietary supplement composed from different medicinal herbs. The experimental animals treated with Manfort supplement showed no obvious side effects, improvement in the testosterone levels and testicular tissues (30). Recently the clinical trial about Manfort was published in ISRCTN registry under trial registration number: ISRCTN15796121 (https://doi.org/ 10.1186/ ISRCTN 1579 6121). Therefore, this study aimed to evaluate the role of Manfort dietary supplement to evaluate the semen parameters improvement of some patients characterized with low sperm count or azoospermia. The data from this study will introduce important information for treatment of patient with fertility disorders using natural produced-based supplement.

MATERIALS AND METHODS

This study was a case report study performed in Jannat Hospital at Sohag governorate Egypt, and under supervision

of Egypt Innovate for Development and Training Foundation, Cairo, Egypt from June 2018 to July 2020.

1.1. Manfort supplement preparation

Similar to the previously published report by Hussein ME, 2020, Manfort dietary supplement was papered from several medicinal plant powders mixed with ginger powder and high quality honey bee. Briefly, to prepare the Manfort supplement, some medicinal plants, which known by its effects on the infertility treatment, were collected from Sohag governorate, Egypt. These plants were dried and grinded separately. A specified amount of each plant was determined and mixed together with the powder of the ginger. Finally, the powders of all plants were mixed together with a high quality honey in a ratio of 1:3. The prepared product was similar to brownish paste. Some of the prepared Manfort was used to investigate the smell, color, appearance and safety. The Manfort dietary supplement was approved by Egyptian National Research Center, Cairo, and the Ministry of Health and Population, National Nutrition institute, Food Registration Unit Cairo, Egypt (Patent no: 7156/2017) (30).

1.2. Manfort supplement chemical ingredients evaluation

To detect the effective ingredients, some of the papered Manfort supplement was used for further chemical analysis using infra-red spectra analysis. The Manfort supplement was analyzed for the main active chemical ingredients such as alkaloids, polyphenols, saponins, tannins, glycoside, steroids, coumarins, carbohydrates, terpenoids and flavonoids. In this method we analyzed the supplement according to standard methods in which we used hexane, ethyl acetate, 70% ethyl alcohol or water as solvents of the supplement. Consequently, phytochemical screening for each solvent including Manfort supplement was determined (30).

1.3. Patients inclusion criteria

In this study the age of the patients ranges from 36 years to 46 years. The body wighet of all patients ranges from 56kg to 95 kg. As much as possible the age and the semen parameters of each group showed the same profiles. All patients are married and don't have any children. Additionally, patients suffering from other diseases such varicocele were exempted from this study. Patients who intake medications were exempted from this study to prevent semen analysis disturbance. After informed consents, a total of 33 patients were involved in this study and were divided into two groups. The first group was 15 patients (n = 15) with low sperm total count (17 million) and the second group was 18 patients (n = 18) with azoospermia (no sperm).

1.4. Semem analysis test

More than 33 participant patients are randomly selected in Jannat Hospital at Sohag governorate. The participants then were divided into two groups based on the semen analysis test. The low sperm count patients were assigned as the first group (n = 15). While the azoospermia patients was assigned as the second group (n = 18). All semen specimens were collected by the staff of Janat Hospital, Sohag governorate, Egypt, during the period from June 2018 to May 2020. Before Manfort supplement intake start, during two weeks two semen specimens were collected by masturbation after 4 days of last sexual abstinence. The specimens were processed for analysis within 1 h after ejaculation in the same andrology laboratory to keep the quality of the semen specimen according to World Health Organization sample collection criteria. Semen examinations were applied to analyze semen parameters such as volume, sperm concentration/mL of semen, total sperm count/ejaculate, sperm motility and white blood cells count in the semen. Sperm motility percentage was evaluated according to World Health Organization slandered criteria (31). After 15 days from the first semen sample collection and during 4 months both low sperm count and azoospermia patients were administrated orally three times daily with 5gm from Manfort dietary supplement after each meal. After treatment time finished another two semen specimens were collected from the patients under similar criteria of the samples without treatment.

1.5. Ethical consideration

This study has been done under the guidelines and approved by the ethical committee of the Egypt Innovate for Development and Training Foundation, Cairo, Egypt. All participants gave informed consent being included in the study.

1.6. Statistical analysis

All semen parameters were analyzed using ANOVA with Tukey's tests and the significance grad was evaluated at $p < 0.05$.

2.Results

2.1.Manfort characteristics

Morphologically, Manfort is a brownish paste with acceptable smell and taste. The honey bee expressed 75% of the paste. Chemically, the infra-red spectrum analysis of Manfort showed that the main ingredients in the Manfort supplement is flavonoids, polyphenols, carbohydrates, steroids, coumarins, terpenoids, glycosides. The phytochemical analysis showed that Manfort supplement has higher concentrations from carbohydrates, flavonoids, and polyphenols. The ratio of flavonoids was 1.98 mg/gm while polyphenols was 3.43 mg/gm as reported previously (30). Furthermore, the antioxidant activity of Manfort supplement was evaluated using 2, 2-diphenyl-1-picrylhydrazyl standard method. The antioxidant activity experiment showed that, the inhibition percentage of Manfort supplement elevated by increasing the concentration of Manfort supplement. The inhibition ratio of Manfort at concentration 7.25 mg/ml was about 42%. Additionally, the antioxidant activity of Manfort supplement showed that, the IC50 was 8.93 mg/ml compared with antioxidant activity of ascorbic acid as a standard antioxidant (0.3 mg /ml) (30)

2.2.Semen volume and Manfort supplement

As shown in figure 1, the treated patients (33 cases) with sperm low count (15 cases; 76%) and azoospermia (18 cases; 24%) with Manfort dietary supplement for 4 months showed significant increase in the semen volume. From 33 cases a total of 4 cases (12%) showed no change in the semen volume, 2 cases (6%) showed decrease in the semen volume and 27 cases (82%) showed increase in the semen volume after 4 months of Manfort administration. The average increase in the semen volume was 1.4 times higher from the non-treated cases with Manfort supplement. The increase of the semen volume after treatment with Manfort supplement indicated the positive effects of the Manfort ingredients to activate the spermatogenic cells, leydig cells, and prostate gland which responsible to produce the semen contents.

2.3. Sperm number and Manfort supplement

All patients (33 cases) including 12 case (36%) with low sperm count and 20 cases (64%) with azoospermia are characterized with the presence of spermatogenic cells.

2.3.1.Low sperm count cases

The low sperm count patients (12 case; 36%) showed a decrease in the sperm concentration and total sperm count in each ejaculate. Before Manfort supplement treatment of low sperm count cases, the lower total sperm count was 20,000 sperm/ejaculate and the higher total sperm count was 17,400,000 sperm/ejaculate. While, the lower semen concentration was 10,000 sperm/mL and the highest sperm concentration was 5,800,000 sperm/mL. After treatment of low sperm count cases with Manfort supplement, the sperm

total count and concentration significantly increased compared with the non-treated cases. Interestingly, the lower total sperm count was 6,000 sperms/ejaculate, but the highest total sperm count was 210,000,000 sperm/ejaculate. Additionally, the lower concentration of the semen sample was 30,000 sperms/mL and the highest sperm concentration was 7,000,000 sperms/mL (Figure 2).

2.3.2.Azoospermia cases

The azoospermia cases (20 cases; 64%) showed different profiles in the sperm count when treated with Manfort supplement as compared with the low sperm count cases. Obviously, in the treated cases of azoospermia with Manfort supplement, the lower total sperm count was 15,000 sperms/ejaculate, while the highest total sperm count was 60,000,000 sperms/ejaculate. Furthermore, the lower concentration of the sperm was 10,000 sperm/mL and the highest sperm concentration was 12,000,000 sperms/mL (Figure 2).

The above mentioned data showed a significant increase in the sperm counts after Manfort supplement treatment of both cases low sperm count as well as azoospermia cases. In general, the treatment of low sperm counts cases with Manfort for 4 months significantly increased the total sperm count and sperm concentration into 7.8 times and 5.2 times respectively compared with the non-treated cases. While the treatment of the azoospermia cases with Manfort supplement increased the total sperm counts into 1.4 times, while the sperm concentration increased only into 0.5 times compared with the non-treated cases.

2.4. Sperm motility and Manfort supplement

The treatment of total 33 cases of patients with Manfort supplement showed significant increase in the sperm motility (Figure 3). From the total number of 33 cases there were 17 cases (52%) didn't showed any change in the sperm motility, 12 (36%), case showed an increase of the sperm motility and 4 (12%) case showed decrease in the sperm motility. The 12 cases which showed an increase in the sperm motility included 8 cases with zero sperm motility before Manfort supplement treatment. In general, the sperm motility after treatment with Manfort supplement increased 2.1 times as compared with non-treated cases. This data indicated that Manfort treatment could increase the sperm motility of low or zero sperm motility cases (Figure 3).

2.5. Semen WBCs and Manfort

As shown in figure 4, the treatment of patients with Manfort supplement for 4 months consequently, showed a remarkable decrease in the number of the WBCs in the semen. From the total number cases (33 patients) there were 22 cases (67%) showed significant decrease in the total number of WBCs, 9 cases (27%) did not show any change in the number of the WBCs and 3 cases (6%) showed an increase in semen WBCs number. In general, the average number of the WBCs in the semen samples of patients who treated with Manfort supplement was significantly lower than those of non-treated patients.

3. DISCUSSION

Production of a high quality sperm that can move for long distance in the female genital tubes depends on many disorders. For example, there are disorders that can prevent spermatogonia from growing into spermatids and sperms. Other problems can prevent mature and healthy sperms from reaching the site of the egg. Furthermore, the temperature of the male scrotum may affect production of high quality sperms. The previous mentioned disorders consider as the main causes of male infertility. More specifically the most common problems that prevent sperms to reach the ova are low sperm number or even no sperms (azoospermia), distortion in the sperm shape and low sperm motility.

Previously to overcome of these problems, there are many chemical-based drugs that can treat some of previous mentioned sperm disorders, but these drugs have several side effects on other tissues in addition to the testicular tissue. Recently natural products-based drugs are the most effective and safe without side effects when it used for infertility treatment. Flavonoid and polyphenols as antioxidants are the most important natural products that can be used for increase the semen parameters and overcome of the fertility disorders (3).

Recently many dietary supplements were prepared from natural products antioxidants to overcome of the above mentioned infertility disorders. One of the most recent dietary supplements, which prepared from medicinal herbs, is the Manfort dietary supplement. This supplement contains many varieties of effective ingredients with antioxidant properties which extracted from medicinal plants (30). Manfort supplement composed mainly from a mix of medicinal herbs extracts which mixed with a high quality grade of honey bee. Based on the chemical structure of Manfort supplement, the main effective ingredients in Manfort supplement are flavonoids, polyphenols, coumarins, terpenoids and glycosides which consider as rich-antioxidant ingredients (30). Of note, polyphenols and flavonoids consider as groups of natural macromolecules that have variable phenolic structures, several beneficial properties such as antioxidants and anti-inflammatory, and have several protective and ameliorative roles against male genital system disorders (3,32-34). Interestingly, the treatment of experimental animals with Manfort supplement didn't show any disorders such as mortality, toxicities and blood parameters changes. Additionally, serum testosterone levels of treated animals with Manfort supplement elevated the non-treated animals. Furthermore, the histological observations of the testicular tissues improved in the treated animals with Manfort supplement (30). The interesting data about the efficacy of Manfort obtained from the animal experiments encouraged us to apply this supplement on some patients suffering from low sperm count and azoopspermia.

In this study the treatment of both low sperm count and azoospermia patients with Manfort supplement for 4 months significantly increased the average semen volume 1.4 times, when it compared with the non-treated cases. The volume of the semen is very important parameter which can elevate the chance of sperm to reach the mature egg site. It is well known that, honey is a valuable dietary supplement that can improve the quality of human semen. From this point of view Manfort supplement composed of 75% of honey, which is the key role to increase the semen ingredients and liquid media. Our data is in consistent with several previous reports which confirmed the important role of honey to increase the quality and volume of semen. Honey is a source of antioxidant, anti-inflammatory characteristics. Additionally, honey elevates the serum testosterone level and sperm count (35). Furthermore, long-term nutrition of pure honey has a crucial effect on semen parameters and volume improvement (36,37).

The sperm concentration is another parameter for successful fertilization of the mature egg. Higher sperm concentration increases the chance to produce healthy and high quality sperm. In this study, low sperm count patients treated with Manfort significantly showed an increase in the total sperm count/ejaculate and sperm concentration/mL into 7.8 times and 5.2 times respectively. While azoospermia patients treatment with Manfort increased the total sperm count/ ejaculate into 1.4 times, but the sperm concentration/ mL increase only into 0.5 times compared with the non-treated patients. It is well known that antioxidants are important to remove the reactive oxygen species from the testicular tissues. Polyphenols and flavonoid as antioxidant found in a higher ratio in Manfort supplement ingredients. These two

antioxidants have the ability to improve the semen parameters when consumed for long time. Previously polyphenol in the leaves of green tea, showed anti-inflammatory properties, prevents tissue damage and improve testicular spermatogenesis (38). Furthermore, long-term consumption of green tea leaves is safe and improved sperm concentration (39). Flavonoids such as quercetin, is well known as anti-inflammatory. Of note, quercetin can improve the semen parameters such as sperm concentration (40). For more evidence about the role of antioxidant to improve the fertility, olive leaves extract as a source of antioxidants and polyphenols, ameliorate the induced toxicity by busulfan in rat testicular tissue and improved sperm concentration (41). Furthermore, in vivo administration of melatonin or ghrelin as antioxidants could be effective to improve egg fertilization and sperm concentration (42).

It is well known that, the healthy sperm that can forward progressions more than 25 µm per second is defined as normal sperm motility. In this study the sperm motility significantly improved in 36% of total patient number after treatment with Manfort supplement. The increase in the sperm motility was 2.1 times higher when it compared with the non-treated patients. Manfort composed from active ingredients such as carbohydrates, polyphenols and flavonoids that can increase sperm motility. In general, flavonoids have a role to decrease the toxic lipid peroxidation levels in the serum. Therefore, previously flavonoids in dietary supplements was used to improve semen quality especially sperm motility in infertile men with low sperm count (43). For example, quercetin as flavonoid increased sperm motility when administrated for long time and used in asthenozoospermia treatment (44). Furthermore, selenium, Zinc, carthinine, arginine and vitamin B-12, which contain many antioxidants have been shown to elevate sperm motility (45).

The treatment of 33 patients with Manfort supplement decreased semen WBCs number in 67% of the patients into the half. The ginger which present in the Manfort supplement, has a crucial role as anti-inflammatory ingredient. Therefore, ginger may have a role to reduce inflammation in the testicular tissues which due to improvement of semen quality produced by the testis. It is well known that, ginger is rich phytochemistry and has anti-inflammatory and antioxidant properties (46). Therefore, ginger has a beneficial effect on semen quality, and this is attributable to increased levels of testosterone hormones, and decreased oxidative damage to testicular tissues (47). Additionally, ginger was effective in lowering sperm DNA fragmentation in the low sperm count cases (48).

4.CONCLUSION

Male infertility disorders are a big problem facing many couples. It is crucial to overcome of these disorders using effective, safe and low coast treatments. To improve the quality of sperm parameters of infertility suffering patients we used a dietary supplement called "Manfort" in this study. The Manfort supplement is safe and effective to improve testosterone and testicular tissues in the mice. While Manfort supplement consumption by low sperm count and azoospermia patients showed an improvement in the semen parameters such as volume, sperm concentration and sperm motility. Based on the data obtained from this study, it is recommended to use dietary supplements contain effective materials against sperm disorders rather that chemically-based synthesized drugs.

Acknowledgment

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Figure legends

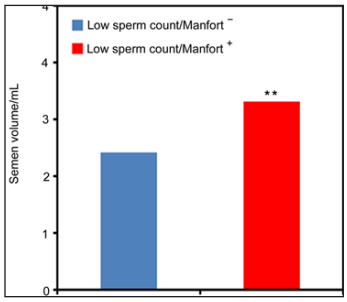

Figure 1: Quantitative analysis of semen volume of low sperm count patients of non-treated and treated patients with Manfort dietary supplement. The treatment with Manfort increase the average volume of the semen significantly compared with non-treated patients. These data are expressed as mean ± SEM. (n=33). ** indicate p value of < 0.001 (one-way ANOVA with Tukey's test).

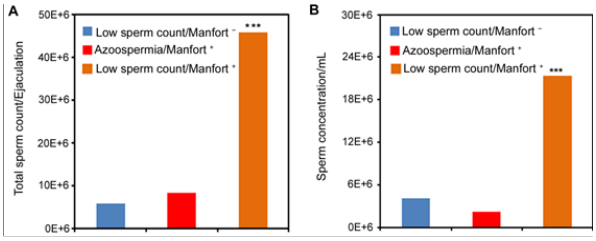

Figure 2: Graphs showing the quantitative analysis of (A), total sperm count in all ejaculated semen and (B) sperm concentration in a milliliter of semen in low sperm count patients and azoospermia patients treated with Manfort supplement. The total number of sperms significantly increased when low sperm count and azoospermia patients treated with Manfort. The sperm concentration significantly increased after treatment of low sperm count with Manfort, while sperm concentration slightly increased in azoospermia cases after treatment with Manfort. These data are expressed as mean ± SEM. (n=13 and 20 for low sperm count and azoospermia respectively). *** indicate p value of < 0.0001 (one-way ANOVA with Tukey's test).

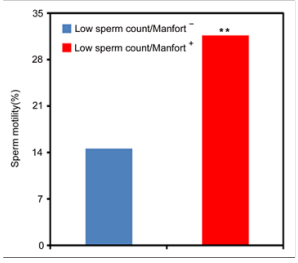

Figure 3: Quantitative analysis of sperm motility of low sperm count patients after 4 months of Manfort treatment. The motility of sperm increased significantly after treatment with Manfort. These data are expressed as mean ± SEM. (n=12). ** indicate p value of < 0.001 (one-way ANOVA with Tukey's test).

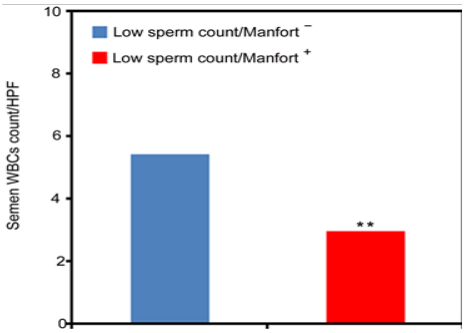

Figure 4: Quantitative analysis of WBCs numbers in the

semen of low sperm count or azoospermia patients after treatment with Manfort. The WBCs number in the semen decreased significantly after treatment with Manfort. These data are expressed as mean ± SEM. (n=26). ** indicate p value of < 0.001 (one-way ANOVA with Tukey's test).

Conflict of Interest

The authors have no financial or non-financial conflicts of interest.

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