Original Article

Effect of Carob and Ginseng Supplements on Semen Analysis Parameters, Sexual Function, and Sex Hormones in Infertile Men: Double-Blind, Randomized Controlled Trial Study

Abstract

Background: Infertility is one of the most common problems in the world; there is a growing demand for herbal medicines to treat infertility-related problems. **Materials and Methods:** A randomized controlled trial with three groups was conducted, each with 30 participants. The first group was administered 1.5 grams of Carob daily, the second group was administered 1.5 grams of Ginseng daily, and the third group received a placebo. The treatment was administered for 12 weeks, and before and after the intervention, semen parameters, testosterone, prolactin, luteinizing hormone, follicle-stimulating hormone, thyroid hormones, and sexual function were evaluated. Sexual function was assessed using the International Index of Erectile Function Questionnaire. **Results:** The mean (SD) age of participants was 34.83 (6.22), 34.60 (5.78), and 33.67 (5.82) years in Carob, Ginseng, and Placebo groups, respectively. The results showed that in the Carob group, the normal volume of semen ($Z_{133} = 3.05$, $p = 0.02$) and the normal shape of sperm ($Z_{134} = 2.97$, $p = 0.01$) increased significantly compared to the control group. In the Ginseng group, the normal volume ($Z_{133} = 3.90$, $p = 0.001$) and the normal viscosity of semen ($Z_{133} = 2.36$, $p = 0.01$) increased significantly compared to the control group.The Carob group showed a significant increase in normal sperm counts and testosterone hormone levels ($Z_{131} = 2.81$, $p = 0.05$). The Ginseng group demonstrated a significant improvement in orgasm function ($H_2 = 6.14$, $p = 0.04$) and the total score of the International Index of Erectile Function (IIEF) ($H_2 = 5.8$, $p = 0.05$). **Conclusions:** Carob supplements are suggested to enhance some semen parameters and male sex hormones. For infertile men, Ginseng can be beneficial in improving sexual function.

Keywords: *Herbal medicine, infertility, locust bean gum, Panax, sexual dysfunctions*

Shamim Pilehvari[1], Seyedeh Zahra Masoumi[2], Tayebeh G. Bahar[2], Farideh Kazemi[2], Shirin Moradkhani[3], Parvin Maleki[2]

[1]Fertility and Infertility Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, [2]Mother and Child Care Research Center, Midwifery and Reproductive Department, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran, [3]Department of Pharmacognosy, School of Pharmacy, Medicinal Plants and Natural Products Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

Introduction

According to the World Health Organization (WHO) definition, infertility is the inability of a couple to conceive after one year of unprotected intercourse. It is one of the most common problems worldwide, affecting about 15% of couples. In 50% of infertility cases, there are male causes and sperm problems.[1] The prevalence of male infertility in Iran, Hamadan, was 43.9%. The most common cause of male infertility was an abnormality in semen fluid. Infertility has both male and female causes. The male factor is involved in about half of all infertility cases.[2] The most important causes of male infertility include congenital or acquired abnormalities of the genitourinary system.[3] The presence of the malefactor is often based on abnormal sperm parameters.[4] Impaired sperm production and function and damage to the spermatogenesis process are among the most common causes of male infertility.[5] Leukocytes overproducing reactive oxygen species (ROS) have emerged as a leading cause of male infertility in recent years. The resulting oxidative stress leads to abnormal semen parameters.[6]

Studies have shown that infertile men have a lower antioxidant capacity than fertile men. The researchers claimed that they could reduce motility, increased mortality, and DNA damage by oxidative stress in infertile people by using antioxidants. Plants were considered the most important source of medicine for treating the disease about half a century ago.[7,8] Ginseng is an aromatic and durable medicinal plant belonging to the genus

How to cite this article: Pilehvari S, Masoumi SZ, Bahar TG, Kazemi F, Moradkhani S, Maleki P. Effect of Carob and Ginseng supplements on semen analysis parameters, sexual function, and sex hormones in infertile men: Double-blind, randomized controlled trial study. Iran J Nurs Midwifery Res 2024;29:113-9.

Submitted: 08-Dec-2021. **Revised:** 23-Sep-2023. **Accepted:** 03-Oct-2023. **Published:** 09-Jan-2024.

Address for correspondence:
Dr. Seyedeh Zahra Masoumi, Fahmideh Ave, Hamadan University of Medical Sciences, School of Nursing and Midwifery, Hamadan, Iran. E-mail: zahramid2001@gmail.com

Access this article online

Website: https://journals.lww.com/jnmr

DOI: 10.4103/ijnmr.ijnmr_460_21

Quick Response Code:

Panax and Araliaceae family. The medicinal properties of Ginseng are related to its root. The root of this plant contains triterpene saponins, essential oils, polyacetylene, polysaccharides, peptidoglycans, nitrogen compounds, fatty acids, carbohydrates, and phenolic compounds. This plant's most crucial active ingredient is saponins with a triterpene structure; Ginseng's pharmacological activities are related to this compound.[9] Carob is another plant antioxidant that is native to the Mediterranean region and is found in southern Syria.[10] Studies on the chemicals of Ceratonia siliqua seeds show that it has high fiber, polyphenols, arachidonic acid, lignin, fats, proteins, carbohydrates, calcium, potassium, and phosphorus.[11] They also contain aspartic acid, glutamic acid, linolenic acid, linoleic acid, vitamin E, beta-sitosterol, silica, iron, and magnesium. Carob antioxidant activity is associated with phenolic compounds and the presence of substances. In a small number of studies, the effects of Carob on improving semen quality parameters have been investigated.[12] There are two hypotheses regarding the effects of antioxidants on fertility. The first one proposes that these compounds enhance sperm quality. The second hypothesis suggests that antioxidants boost testosterone levels by positively affecting spermatogenic and Sertoli cells, which are responsible for maintaining the reproductive system's health in men and promoting spermatogenesis.[13]

Adaptogens, such as Ginseng and Carob, possess antioxidant properties that enhance the body's resistance to stressors, trauma, anxiety, weakness, and fatigue. These plants also act as a mental stimulant and tonic. Their extracts impact the central nervous system, leading to the dilation of blood vessels in the circulatory system and activation of the hypothalamic–pituitary–adrenal axis.[14] Following infertility, sexual function is sometimes impaired. Antioxidants may affect improving sexual function. Sexuality has a profound effect on marital life and its cohesion and stability. The WHO recognizes sexual health as the integration and harmony between the mind, the senses, and the body.[15] Various studies found that red Ginseng improves erection in males but does not improve the sexual experience in general.[16] The effect of antioxidants on sexual function is not yet fully understood in studies.[7,16] Infertility medications often result in complications such as dizziness, gastrointestinal disorders, bloating, hot flashes, nausea, and headache. However, side effects are significantly reduced with the use of herbal medicines. Traditional medicine has recently explored the use of Carob and Ginseng in treating male infertility. However, there is limited research on their effectiveness, which means that the findings of review studies and clinical trials may not accurately reflect the true impact of treatments for male infertility. As a result, this study was conducted to address the observed sexual dysfunction and adverse effects associated with the chemical drugs currently used in male infertility treatment. The present study aimed to analyze the impact of Carob seed and Ginseng root intake on sperm parameters, sex hormone levels, and sexual function in men with infertility issues. The findings could potentially contribute to the treatment of male fertility.

Materials and Methods

This study was conducted in a randomized, three-group, double-blind, placebo-controlled clinical trial (IRCT20120215009014N284) in infertile men from June 2019 to September 2020. The sample size was determined using the Sampsi module in Stata 13 software. Using the data from Mahdiani *et al*.'s article[7] and considering M1 = 17, M2 = 21, Sd1 = 4, Sd2 = 1.5, $\alpha = 0.05$, power = 0.90, and 25% attrition, the sample size was calculated for each group of 30 men. At the start of the study, an allocation sequence was generated by an individual not involved in the research team. The participants were then assigned to the Carob, Ginseng, or Placebo groups using balanced block randomization [Figure 1]. The study included men under 40 with primary infertility who did not have infertility caused by female factors or sexual dysfunction in women. Participants were required to have at least one abnormal parameter of semen (volume, concentration, number of sperm, motility, and morphology of sperm) according to the WHO definition; they could not have chronic diseases, a body mass index over 30, consume alcohol, psychiatric disorders, take drugs that interfere with spermatogenesis and pituitary suppressors or use medicines that cause ejaculation failure and erectile dysfunction. Participants also could not have a history of testicular and vasodilator surgery, contact with pesticides, heavy metals, and solvents, or use antioxidant supplements in the last 3 months.

Initially, male participants provided a semen sample while receiving 10 ml of blood to assess their sex hormones (luteinizing hormone, follicle-stimulating hormone, prolactin, and testosterone) and Thyroid-Stimulating Hormone (TSH) levels at the start of the research. The capsules were packaged and labeled as A, B, and C by an individual not affiliated with the researchers. The researcher and the patient were blind to the study groups in this study. The three drugs administered had a similar appearance, and the participants were not informed about the specific type of drug they were receiving. The first group was given 1.5 grams of Carob seed powder capsules, the second group received 1.5 grams of Ginseng, and the third group was given a Placebo daily. It is important to note that all three groups received the same routine infertility treatments during the 12-week study period. The levels of Luteinizing Hormone (LH), FSH, serum testosterone, prolactin, and TSH were measured using the enzyme-linked immunosorbent assay method.

The study examined the sexual function of men in three groups before and after the intervention, using the International Index of Erectile Function (IIEF) questionnaire.

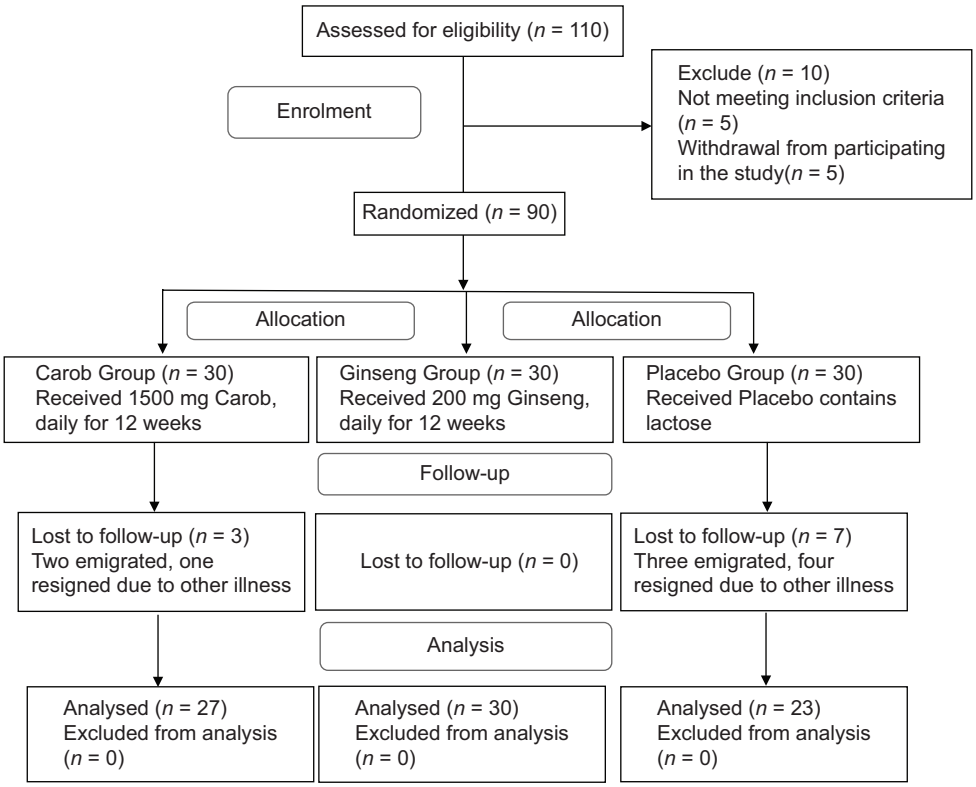

Figure 1: Flowchart of sampling

The questionnaire comprised 15 questions, divided into five categories: erectile and orgasm function, sexual desire, sexual satisfaction, overall satisfaction, and International Erection Performance Index. Previous studies have confirmed that the questionnaire's reliability, measured by Cronbach's alpha, was 0.85%. Furthermore, sexual function is classified as low for scores between 15 and 25, moderate for scores between 25 and 50, and high for scores above 50.[17] Following the intervention, a second round of tests was conducted to measure semen analysis, hormones, and sexual function. The distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Data analysis involved the use of one-way analysis of variance, Wilcoxon test, Kruskal–Wallis, Chi-square, Fisher's exact test, and multivariable regression. A p value less than 0.05 was deemed statistically significant. Stata-13 software was utilized for statistical analysis.

Ethical considerations

This research was approved by the Ethics Committee of Hamadan University of Medical Sciences under code (IR.UMSHA.REC.1398.155). Written informed consent was obtained from all the study participants. The objectives of the study and the procedure taken to conduct it were explained to the participants. Moreover, they were reassured about the anonymity and confidentiality of their information and the right to leave the study if they wished.

Results

The Placebo, Ginseng, and Carob groups had a mean (SD) age of 34.83 (6.22), 34.60 (5.78), and 33.67 (5.82) years, respectively. There was no significant difference in demographic variables observed among the three groups. The multivariate analysis results indicated that before the intervention, the Carob group had a 9% lower normal semen volume than the placebo group ($Z_{133} = 3.05$, $p = 0.02$) when semen parameters were controlled. Similarly, the Ginseng group had a 30% lower normal semen volume than the placebo group ($Z_{133} = 3.90$, $p = 0.001$) and a 28% decrease in normal viscosity compared to the placebo group ($Z_{133} = 2.36$, $p = 0.01$). Conversely, in the Carob group, the normal volume of semen ($Z_{133} = 3.05$, $p = 0.02$) and the normal shape of sperm ($Z_{134} = 2.97$, $p = 0.01$) increased significantly compared to the placebo group [Table 1].

There were no significant differences ($p > 0.05$) in the mean scores of all areas of the IIEF questionnaire among the three groups in the pre-intervention stage, except for sexual satisfaction ($H_2 = 9.13$, $p = 0.01$). Similarly, in the after-intervention stage, there were no significant differences ($p > 0.05$) in the mean scores of all areas of the IIEF questionnaire among the three groups, except for orgasm function ($H_2 = 6.14$, $p = 0.04$) and the total score of IIEF ($H_2 = 5.8$, $p = 0.05$)). The orgasm function was compared pairwise, revealing statistically significant differences between placebo and Ginseng ($W_2 = -2.16$, p-value = 0.03) and Carob and Ginseng ($W_2 = -2.18$, p-value = 0.03). Similarly, a pairwise comparison of the IIEF scores demonstrated a statistically significant difference between placebo and Ginseng ($W_2 = -2.22$, p-value = 0.02) [Table 2].

Table 1: Comparison of semen analysis results after intervention between groups*

Variables	Placebo group[a] *n* (%)	Ginseng group[b] *n* (%)	Carob group[c] *n* (%)	Statistical result of a/b**		Statistical result of a/c**	
				RR*** (95% CI****)	*p*	RR*** (95% CI****)	*p*
Volume							
≤1.5	21 (91.30)	19 (63.33)	25 (92.59)	0.70 (0.59, 0.84)	0.001	0.91 (0.86, 0.96)	0.02
>1.5	2 (8.70)	11 (36.67)	2 (7.41)				
Viscosity							
Normal	19 (82.61)	16 (53.33)	25 (92.59)	0.72 (0.55, 0.94)	0.01	1.15 (0.99, 1.33)	0.29
Abnormal	4 (17.39)	14 (46.17)	2 (7.41)				
Sperm count per ml (million)							
≤15	18 (78.26)	23 (76.67)	23 (85.19)	0.97 (0.81, 1.16)	0.59	0.99 (0.85, 1.17)	0.88
>15	5 (21.74)	7 (23.33)	4 (14.81)				
Fast or slow progressive movement							
≤32%	14 (60.87)	20 (66.67)	20 (74.07)	0.96 (0.73, 1.25)	0.77	1.07 (0.84, 1.37)	0.48
>32%	9 (39.13)	10 (33.33)	7 (25.93)				
Normal shape							
≤4%	19 (82.61)	23 (76.67)	27 (100.00)	0.95 (0.81, 1.12)	0.51	1. 17 (1.05, 1.30)	0.01
>4%	4 (17.39)	7 (23.33)	0				
WBC number							
Normal	23 (100.00)	30 (100.00)	27 (100.00)	-	-	-	-
Abnormal	0	0	0				

*In each item of hormones, the reference group was an abnormal outcome. **Binomial regression (by controlling before intervention values), reference: control group (a). ***RR: Risk ratio, ****CI: confidence interval

Table 2: Comparison within and between groups of the total score of sexual function domains before and after the intervention

Domains	Placebo[a] Mean (SD)		Ginseng[b] Mean (SD)		Carob[c] Mean (SD)		Analysis results of a, b, and c Before intervention		Analysis results of a, b, and c After intervention	
	Before	After	Before	After	Before	After	Statistic test* (H)	*p*	Statistic test* (H)	*p**
Erectile function	22.96 (4.31)	23.80 (3.78)	24.34 (4.53)	24.94 (4.92)	22.81 (6.63)	22.72 (7.89)	2.06	0.35	2.66	0.26
Statistic test**(W)	-1.25		-0.28		-0.74					
p	0.21		0.77		0.45					
Orgasm function	7.85 (1.53)	8.20 (1.29)	8.70 (0.95)	9.00 (1.00)	7.73 (2.11)	7.84 (2.24)	4.58	0.10	6.14	0.04
Statistic test** (W)	-0.87		-0.36		-0.44					
p	0.38		0.71		0.65					
Sexual desire	7.50 (1.47)	7.76 (1.30)	7.51 (1.45)	7.84 (1.34)	7.34 (1.43)	7.61 (1.09)	0.24	0.88	0.44	0.80
Statistic test** (W)	-1.09		-0.86		-0.68					
p	0.27		0.38		0.49					
Sexual satisfaction	10.03 (2.06)	10.12 (1.89)	11.56 (2.47)	11.52 (2.01)	9.45 (3.52)	9.73 (3.84)	9.13	0.01	4.94	0.08
Statistic test** (W)	-0.09		-1.34		-0.28					
p	0.92		0.17		0.77					
Overall satisfaction	9.00 (1.26)	8.32 (1.97)	8.89 (1.89)	9.26 (1.09)	8.04 (1.98)	8.57 (1.53)	4.10	0.12	2.64	0.26
Statistic test** (W)	1.58		-0.06		-0.98					
p	0.11		0.95		0.32					
International Erection Performance Index	56.51 (9.56)	58.12 (7.54)	60.33 (8.78)	62.57 (8.55)	54.95 (13.09)	56.52 (14.65)	4.28	0.11	5.80	0.05
Statistic test** (W)	-1.27		-0.31		-0.45					
p	0.20		0.75		0.64					

*Kruskal–Wallis, **Wilcoxon

The results of multivariate analysis compared to the placebo group showed that by controlling the levels of hormones in the pre-intervention stage, in Carob users, the probability of normal levels of LH, prolactin, and testosterone were, respectively, 18%, 37%, and 40% higher than that of abnormal levels. However, this difference was only statistically significant for testosterone ($p = 0.05$) [Table 3].

Discussion

A comparison between the Carob, Ginseng, and Placebo groups in the current study showed that the number of normal sperm increased in the Carob group. Protecting cells, particularly in sperms, against free radicals is a crucial function of antioxidants. A decrease in the activity of antioxidants within the body's physiological system may lead to a decline in the quality of sperm cells. Studies indicate that ROS can significantly impact sperm parameters, such as morphology and motility. Sperm's plasma membrane's high content of unsaturated fatty acids is believed to cause its high sensitivity to ROS.[8] Carob is an herb known for its antioxidant properties. Carob extract in animal studies has been effective in cAMP production and enzyme activity involved in the steroidogenesis of rat testis. Studies by Alsalman *et al*. in 2014[8] and Elsheikh MG *et al*. in 2015[18] showed that the consumption of antioxidants improves sperm quality. In the study of Mahdiani *et al*.,[7] in 2018, in the group receiving Carob, the mean total antioxidant capacity and plasma malondialdehyde concentration changes were significant. As the results of our study, Faramarzi *et al*.,[19] in 2020, showed an increase in the progressive motility of sperm after administration of Carob.

Our study revealed that the Carob group had a higher level of normal testosterone following the intervention compared to the other groups. Carob is a nutrient-dense food that contains essential minerals such as iron, calcium, sodium, potassium, phosphorus, and vitamins E, C, D, niacin, folic acid, and pyridoxine. Additionally, Carob powder is rich in 11 phenolic compounds, including pyrogallol, catechol, and chlorogenic acid, with smaller amounts of other phenolic compounds, such as coumarin, cinnamic, ferulic, and gallic acid. The substance comprises 17 fatty acids, with oleic, linoleic, palmitic, and stearic acids being the most prominent. These components, along with vitamins and minerals, influence the body's natural production of sex hormones and, consequently, male fertility.[20] However, these studies have not explored the impact of antioxidant supplements on adrenal androgens. In 2020, Sadeghzadeh *et al*.[21] examined the potential effects of Carob seeds on FSH, LH, testosterone and dihydrotestosterone levels, testicular tissue, and improved fertility in male rats. The results showed that consumption of Carob seed extract caused a significant increase in the concentration of testosterone and dihydrotestosterone and decreased LH levels in the experimental groups, which was similar to the results of our study. Aghajani's research and our own both revealed an increase in testosterone levels following Carob consumption. However, unlike our study, Aghajani's findings showed a reduction in normal LH levels, which may be attributed to the difference in Carob dosage.[22] The increase in testosterone by Carob is due to its direct effect on Leydig cells and in testosterone biosynthesis.[20]

These effects are implemented by stimulating PGE2 synthesis. In addition, Carob seeds contain gamma-linolenic acid and alpha-linolenic acid, which can be converted to dihomo-gamma-linolenic acid and PGE2, ultimately increasing the production of cyclic adenosine monophosphate and stimulating testosterone production.[23]

Table 3: Comparison of hormones levels after intervention between groups*

Variables	Placebo group[a] *n* (%)	Ginseng group[b] *n* (%)	Carob group[c] *n* (%)	Statistical result of a/b		Statistical result of a/c	
				RR*** (95% CI****)	*p***	RR*** (95% CI****)	*p***
LH							
Normal	12 (52.20)	19 (63.30)	25 (92.60)	1.00 (0.76, 1.30)	0.80	1.18 (0.94, 1.47)	0.11
Abnormal	11 (47.80)	11 (36.70)	2 (7.40)				
FSH							
Normal	18 (78.30)	18 (60.0)	21 (77.80)	0.88 (0.73, 1.07)	0.11	1.04 (0.91, 1.20)	0.86
Abnormal	5 (21.70)	12 (40.0)	6 (22.20)				
Prolactin							
Normal	10 (43.50)	11 (36.70)	18 (66.70)	0.87 (0.55, 1.37)	0.49	1.37 (0.95, 1.99)	0.20
Abnormal	13 (56.50)	19 (63.30)	9 (33.30)				
Testosterone							
Normal	14 (60.90)	19 (63.30)	21 (77.80)	1.27 (0.97, 1.65)	0.40	1.40 (1.10, 1.78)	0.05
Abnormal	9 (39.10)	11 (36.70)	6 (22.20)				
TSH							
Normal	21 (91.30)	22 (73.30)	23 (85.20)	0.86 (0.73, 1.00)	0.11	0.97 (0.86, 1.08)	0.89
Abnormal	2 (8.70)	8 (26.70)	4 (14.80)				

*In each item of hormones, the reference group was an abnormal outcome. **Binomial regression (by controlling before intervention values), reference: control group (a). ***RR: Risk ratio, ****CI: confidence interval

Our study revealed a significant increase in both the mean score of orgasm and the overall score of IIEF in the Ginseng group following the intervention. This improvement can be attributed to the antioxidant properties of Ginseng herbal medicine and the active compounds called Ginsenosides. These compounds have the ability to synthesize nitric oxide in endothelial cells and nerves around the arteries, thereby increasing the sensitivity of vascular smooth muscle cells to nitric oxide.[24] Choi *et al*.[25] (2013) showed that Ginseng effectively improves sexual dysfunction in men. Dordin *et al*.[26] (2015) showed that the root of a species of Ginseng reduces the sexual side effects of specific serotonin reuptake inhibitors. Our study's results were consistent with the results of these studies. Lee *et al*.[27] conducted a systematic review study in 2021, which found that Ginseng has a noteworthy impact on enhancing male sexual function, specifically in orgasm and sexual satisfaction. In our study on the comparison of other areas of IIEF between the three groups, such as sexual satisfaction, erectile function, and overall satisfaction, no statistically significant difference was observed. These herbal supplements may not have a clinically statistically significant effect on erectile function and sexual satisfaction, but their effects have been without increasing side effects. Infertile men with erectile dysfunction have expressed in self-reports that they have an improved ability to have intercourse compared to placebo.

There were limitations to this study. The use of a nonparametric test meant that the effect on sexual satisfaction could not be controlled before the intervention, despite being significant. Additionally, the limited number of participants due to time constraints during sampling restricts the generalizability of the results to the broader population. These limitations should be taken into consideration. Future studies should compare the effects of Carob with other antioxidants, such as vitamin E, and explore different dosages.

Conclusion

According to the results of this study, Carob supplements can enhance some semen parameters, including the normal shape of sperm and testosterone levels. Additionally, Ginseng supplements have been shown to improve sexual function in infertile men. As a result, it is recommended that Carob supplements be used to enhance semen parameters and Ginseng supplements be used to improve sexual function in infertile men.

Acknowledgments

The present study results from a research thesis approved by Hamadan University of Medical Sciences. Thus, the authors would like to express their heartiest gratitude to the Research Department of Hamadan University of Medical Sciences and the men in the infertility clinic in Fatemieh Hospital, whose contributions were vital to conducting the present study (No. 9805013364).

Financial support and sponsorship

Hamadan University of Medical Sciences

Conflicts of interest

Nothing to declare.

References

1. Taylor HS, Pal L, Sell E. Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th ed. Lippincott Williams and Wilkins; United States. 2019.
2. Masoumi SZ, Parsa P, Darvish N, Mokhtari S, Yavangi M, Roshanaei G. An epidemiologic survey on the causes of infertility in patients referred to infertility center in Fatemieh Hospital in Hamadan. Iran J Reprod Med 2015;13:513-6.
3. Abdoli S, Masoumi SZ, Kazemi F. Adverse quality of life style and risk of infertility: A systematic review study. Curr Womens Health Rev 2020;16:169-81.
4. Barratt CL, Björndahl L, De Jonge CJ, Lamb DJ, Osorio Martini F, McLachlan R, *et al*. The diagnosis of male infertility: An analysis of the evidence to support the development of global WHO guidance—challenges and future research opportunities. Hum Reprod Update 2017;23:660-80.
5. Semet M, Paci M, Saïas-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H, *et al*. The impact of drugs on male fertility: A review. Andrology 2017;5:640-63.
6. Alahmar AT. Role of oxidative stress in male infertility: An updated review. J Hum Reprod Sci 2019;12:4-18.
7. Mahdiani E, Khadem Haghighian H, Javadi M, Karami AA, Kavianpour M. Effect of Carob (Ceratonia siliqua L.) oral supplementation on changes of semen parameters, oxidative stress, inflammatory biomarkers and reproductive hormones in infertile men. Sci J Kurdistan Univ Med Sci 2018;23:56-66.
8. Alsalman ARS, Almashhedy LA, Alta'ee AH, Hadwan MH. Effect of zinc supplementation on urate pathway enzymes in spermatozoa and seminal plasma of Iraqi asthenozoospermic patients: A randomized controlled trial. Int J Fertil Steril 2020;13:315-23.
9. Siddiqi MZ, Shafi SM, Im W-T. Complete genome sequencing of arachidicoccus ginsenosidimutans sp. nov., and its application for production of minor ginsenosides by finding a novel ginsenoside-transforming β-glucosidase. RSC Adv 2017;7:46745-59.
10. Papaefstathiou E, Agapiou A, Giannopoulos S, Kokkinofta R. Nutritional characterization of carobs and traditional carob products. Food Sci Nutr 2018;6:2151-61.
11. Goulas V, Hadjisolomou A. Dynamic changes in targeted phenolic compounds and antioxidant potency of carob fruit (Ceratonia siliqua L.) products during *in vitro* digestion. LWT 2019;101:269-75.
12. Abidar S, Boiangiu RS, Dumitru G, Todirascu-Ciornea E, Amakran A, Cioanca O, *et al*. The aqueous extract from Ceratonia siliqua leaves protects against 6-hydroxydopamine in zebrafish: Understanding the underlying mechanism. Antioxidants 2020;9:304. doi: 10.3390/antiox9040304..
13. Shojaeepour S, Sharififar F, Haghpanah T, Iranpour M, Imani M, Dabiri S. Panax ginseng ameliorate toxic effects of cadmium on germ cell apoptosis, sperm quality, and oxidative stress in male Wistar rats. Toxin Rev 2022;41:389-401.
14. Wenhao S, Quanwei W, Wenwen F, Ce Z, Tian W. The role of ginsenosides in myocardial ischemic injury-A systematic review. Asian J Pharm Res Dev 2022;10:61-70.
15. World Health Organization. Sexual health and its linkages to reproductive health: An operational approach. 2017.

Available from: https://www.who.int/reproductivehealth/publications/sexual_health/sh-linkages-rh/en/. [Last accessed on 2023 Nov 23].

16. Lee HW, Kil K-J, Lee MS. Ginseng for improving semen quality parameters: A systematic review. World J Mens Health 2020;38:377-84.
17. Babazadeh S, Habibi M, Sadeghi-Firoozabadi V, Gohari-Derakhshande N. Study of psychometric properties of the international index of erectile function (IIEF) in substance dependent men. Q Appl Psychol 2020;14:435-57.
18. ElSheikh M, Hosny M, Elshenoufy A, Elghamrawi H, Fayad A, Abdelrahman S. Combination of vitamin E and clomiphene citrate in treating patients with idiopathic oligoasthenozoospermia: A prospective, randomized trial. Andrology 2015;3:864-7.
19. Faramarzi A, Aghaz F, Bakhtiari M, Khazaei M. *In vitro* application of Ceratonia siliqua improved sperm parameters and chromatin quality after vitrifacation in normozoospermic aged men. Middle East Fertil Soc J 2020;24:1-5. doi: 10.1186/s43043-019-0007-9.
20. Mekhoukhe A, Kicher H, Ladjouzi A, Medouni-Haroune L, Brahmi F, Medouni-Adrar S, *et al*. Antioxidant activity of carob seeds and chemical composition of their bean gum by–products. J Complement Integr Med 2019;16. doi: 10.1515/jcim-2017-0158.
21. Sadeghzadeh F, Sadeghzadeh A, Changizi-Ashtiyani S, Bakhshi S, Mashayekhi FJ, Mashayekhi M, *et al*. The effect of hydro-alcoholic extract of Ceratonia Silique L. on spermatogenesis index in rats treated with cyclophosphamide: An experimental study. Int J Reprod Biomed 2020;18:295-306.
22. Aghajani MMR, Mahjoub S, Mojab F, Namdari M, Gorji NM, Dashtaki A, *et al*. Comparison of the effect of ceratonia siliqua L.(Carob) syrup and vitamin E on sperm parameters, oxidative stress index, and sex hormones in infertile men: A randomized controlled trial. Reprod Sci. 2021;28:766-74.
23. Javanmard F, Bidmeshkipour A, Yadegari JG. Ceratonia siliqua L improved cryodamage of asthenozoospermic specimens: An experimental study. Int J Reprod Biomed 2022;20:1029-38.
24. Sengupta P, Dutta S. Panax ginseng as reproductive medicine in male infertility: With a brief focus on herb-drug interaction. Chem Biol Lett 2022;9:279.
25. Choi Y, Park C, Jang J, Kim S, Jeon H, Kim W, *et al*. Effects of Korean ginseng berry extract on sexual function in men with erectile dysfunction: A multicenter, placebo-controlled, double-blind clinical study. Int J Impot Res 2013;25:45-50.
26. Dording CM, Schettler PJ, Dalton ED, Parkin SR, Walker RSW, Fehling KB, *et al*. A double-blind placebo-controlled trial of maca root as treatment for antidepressant-induced sexual dysfunction in women. Evid Based Complement Alternat Med 2015;2015:949036. doi: 10.1155/2015/949036.
27. Lee HW, Lee MS, Kim T-H, Alraek T, Zaslawski C, Kim JW, *et al*. Ginseng for erectile dysfunction. Cochrane Database Syst Rev 2021;4. doi: 10.1002/14651858.CD012654.pub2.