JoP Journal of Pharmacopuncture

Journal of Pharmacopuncture 2024;27(2):82-90
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2024.27.2.82

Original Article



# The Effect of the Combination of Ginseng, Tribulus Terrestris, and L-arginine on the Sexual Performance of Men with Erectile Dysfunction: a randomized, double-blind, parallel, and placebo-controlled clinical trial

**Reza Tahvilian[1], Mohammad Amin Golesorkhi[2], Farajollah Parhoudeh[3], Fatemeh Heydarpour[4], Hossein Hosseini[5], Hojjat Baghshahi[5]*, Hossein Akbari[6], Mohammad Reza Memarzadeh[5], Mehdi Mehran[5], Hosna Bagheri[2]**

[1]School of Pharmacy, Pharmaceutical Sciences Research Center, Research Institute for Health, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2]Kermanshah University of Medical Sciences, Kermanshah, Iran
[3]School of Medicine Imam Reza Hospital Kermanshah University of Medical Sciences, Kermanshah, Iran
[4]School of Health, Medical Biology Research Center, Research Institute for Health Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran
[5]Barij Essence Medicinal Plants Research Center, Kashan, Iran
[6]Social Determinants of Health (SDH) Research Center, Department of Biostatistics and Epidemiology, School of Public Health, Kashan University of Medical Sciences, Kashan, Iran

**Received** August 16, 2023
**Reviewed** November 21, 2023
**Accepted** April 22, 2024

***Corresponding Author**
Hojjat Baghshahi
Barij Essence Medicinal Plants Research Center, Mashhad Ardehal, Kashan 8715985131, Iran
Tel: +98-915-903-1196
E-mail: Baghshahi_h1989@yahoo.com

**Objectives:** Nitric oxide is the most important mediator of penile erection after the onset of sexual excitement. It activates cyclic guanosine monophosphate (cGMP), increasing penile blood flow. Most pharmaceutical medications prevent enzyme phosphodiesterase type 5 (PDE-5) from breaking down cGMP, thus keeping its level high. However, due to the adverse effects of pharmacological therapies, herbal drugs that improve sexual function have gained attention recently. This study aimed to investigate the combined effects of *ginseng*, *Tribulus terrestris*, and L-arginine amino acid on the sexual performance of individuals with erectile dysfunction (ED) using the 5-item version of the International Index of Erectile Function (IIEF-5) questionnaire.

**Methods:** Over three months, 98 men with erectile dysfunction were randomly assigned to receive either 500 mg of herbal supplements or placebo pills. Each herbal tablet contained 100 mg of protodioscin, 35 mg of ginsenosides, and 250 mg of L-arginine.

**Results:** The results showed that the changes in the average scores of ILEF-5 within each group before and after the intervention indicated that all parameters related to the improvement of sexual function in patients with erectile dysfunction improved in the herbal treatment group ($p < 0.001$). The herbal group significantly improved IIEF-5 scores in non-diabetics ($p < 0.05$). However, there was no significant difference in the changes of IIEF-5 scores between the two intervention and control groups in diabetic patients.

**Conclusion:** In conclusion, *ginseng*, *Tribulus terrestris*, and L-arginine have properties that increase energy and strengthen sexual function, making them suitable for patients with sexual disorders.

**Keywords:** penile erection, herbal medicines, international index of erectile function, erectile dysfunction, traditional medicine

## INTRODUCTION

Erectile dysfunction (ED) is one of the most common sexual disorders among men worldwide. It is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1]. The prevalence of ED increases with age and is more common in older men. However, it can also be a health concern among young men [2]. While ED is not a life-threatening disease [3], it is a psychological threat to patients and can impact various aspects of mental and physical health, as well as the quality of life [4, 5].

Penile erection is a complex physiological process that involves the coordination of multiple systems including the vascular, nervous, and endocrine systems [6]. Research has shown that nitric oxide released from parasympathetic neurons increases cyclic guanosine 3',5'-cyclic monophosphate (cGMP) production. cGMP causes relaxation of cavernous smooth muscles and dilation of arterioles, resulting in increased penile blood flow and erection [7].

The enzyme, phosphodiesterase 5 (PDE-5), breaks down cGMP and causes an erection to subside [8]. Standard medications for improving penile erection work by inhibiting PDE-5, to maintain a high level of cGMP [9]. However, these medications can lead to resistance in some patients, increase the cost of care, and have side effects, such as headache, dizziness, indigestion, heartburn, flushing, and vasodilation [10, 11]. For these reasons, researchers are increasingly interested in finding alternatives [12]. Medicinal plants have been used for a long time in traditional medicine across different countries and cultures worldwide to enhance sexual function in both men and women. In recent years, numerous studies have investigated the properties of medicinal plants in reducing and treating ED [13-15].

*Panax ginseng* belongs to the *Araliaceae* family. In traditional medicine, ginseng is used to enhance physical and sexual strength, reduce stress and fatigue, and has anti-inflammatory and antioxidant properties [16]. Studies have found that ginseng compounds increase nitric oxide in vascular endothelial cells [17].

*Tribulus terrestris* (TT) belongs to the *Zygophyllaceae* family. In traditional medicine, this plant is used to treat various diseases, such as cardiovascular diseases, diabetes, tumors, stomach problems, and urinary infections. Research has shown that TT compounds, particularly steroidal saponins, play a crucial role in the biological processes of male reproduction by increasing testosterone [18]. Moreover, the amino acid, L-arginine, acts as a precursor to nitric oxide, increasing the availability of NO and cGMP [19].

This study aimed to investigate the combined effects of *Panax ginseng*, *Tribulus terrestris*, and L-arginine under the brand name of Highsense® (Barij-Essence Pharmaceutical Company), on the quality of erection in patients with ED using the 5-item version of the IIEF-5 questionnaire (IRC in Iran = 2421155422024155).

## MATERIALS AND METHODS

### 1. Plant collection

The *Tribulus terrestris* plants were harvested and dried for 72 hours in a shaded and well-ventilated location. Voucher number 247-1 was assigned to the dried *Tribulus terrestris* and it was stored in the herbarium of Barij Medicinal Plants Research Center in Iran. The *Panax ginseng* dry extract used in this study was purchased from Jiaherb Company in China.

### 2. Extraction and preparation of extract

The extraction process involved grinding one kilogram of dried aerial parts of *Tribulus terrestris* and extracting it with 50% ethanol using the percolation method. The liquid extract was concentrated at 40℃ using a rotary apparatus, and then, dried at 120℃ using the Dorsa spray dryer (Model: DSD-02, Iran).

### 3. Formulation preparation

The liquid extract was blended with L-arginine, microcrystalline cellulose (Avicel® PH-101), polyvinyl pyrrolidone, and other ingredients. Blending was performed for 10 minutes in a tumbler. After that, 1% magnesium stearate was added, and the mixture was stirred for an additional five minutes. Finally, the combination was compressed into tablets using a mono-punch tablet machine press, with an 18 mm-diameter oblong punch set.

### 4. Standardization

To standardize the composition of the tablets, protodioscin, a steroidal saponin found in *Tribulus terrestris*, was measured.

Methanol was used to prepare protodioscin at four standard concentrations, ranging from 100 to 400 μg/mL, and the absorbance was read at 510 nm.

### 5. Method and features of the device

UV analysis was performed using a PerkinElmer UV spectrophotometer apparatus. A test tube filled with 5 mL of the sample solution and 5 mL of p-dimethylaminobenzaldehyde reagent was placed in a 58℃ water bath for two hours. The sample solutions were read at wavelengths ranging from 400 to 700 nm using the UV-Vis Spectrophotometer.

### 6. Study design

This study was conducted as a randomized, double-blind, parallel, and placebo-controlled clinical trial at the specialized clinic, Bustan, affiliated with Kermanshah University of Medical Sciences in Kermanshah, Iran. A total of 137 patients with ED, aged 38-64 years, were selected by a urology specialist who had been practicing medicine for approximately 12 years in Iran, and was interested in prescribing herbal medicines and their natural effects.

All participants were instructed not to change their current herbal supplement or diet during the study. The herbal tablets and placebo tablets were prepared in identical packages, sizes, shapes, and colors. The treatment group was instructed to take 500 mg of the herbal tablets (with at least 100 mg total saponin, 30 mg total ginsenosides, and 150 mg L-arginine in each tablet), twice daily after a meal, for three months, while the control group received placebo tablets and the same instructions. Before the study, the study purpose was explained to patients with ED and an informed consent to participate in the study was signed. The clinical features of the patients, including age, high blood pressure, diabetes, dyslipidemia, lower urinary tract disorders, drug usage, and side effects, were assessed in both groups. The IIEF-5 questionnaire (lower scores = a higher rate of ED) was completed by all participants. Additionally, the patients completed a questionnaire regarding their age, history of drug and alcohol use, underlying disorders (such as diabetes, high blood pressure, and genitourinary conditions), and previous consumption of other herbal compounds. Exclusion criteria included severe underlying disorders, simultaneous use of other drugs, and/or consumption of other interfering substances. Throughout the study, phone calls were made to facilitate communication with the participants and results were recorded. Three months after the start of the study, the IIEF-5 questionnaire was administered again to determine each participant's sexual desire index. The five subdomains of this questionnaire were Q1: erectile function, Q2: orgasm function, Q3: sexual desire, Q4: sexual pleasure, and Q5: total satisfaction. The score for each subdomain ranged from 1 to 5.

### 7. Sample size

The sample size was calculated based on the results from examining the effect of *Tribulus terrestris* extract on increasing sexual desire relative to the placebo. According to the mentioned study, the mean and standard deviation of the increase in orgasm score in the intervention group were 0.33 and 0.49, respectively. In the placebo group, these numbers were 0.07 and 0.26, respectively. Considering a 95% confidence level and 80% power of the test, the minimum required sample size of 34 participants in each group was determined [20].

### 8. Size of randomized blocks

In this study, the 4-block randomization method was used. One individual, who was not involved in the recruitment and evaluation processes, created a random sequence using https://www.sealedenvelope.com, and 25 blocks of 4 were created. Another individual was responsible for blindly allocating participants to the different groups. All participants and investigators were blinded to the patient allocation process. The type of medicine was also unknown to the patients, physicians, drug delivery personnel, and data analysts. Only the pharmacists had access to the membership data of the groups.

### 9. Ethical considerations

This clinical trial was registered with the Iranian Registry of Clinical Trials (IRCT) under approval number IRCT20130722014106N8. Furthermore, this protocol was validated by the Kermanshah University of Medical Sciences Ethics Committee in Iran under code number IR.KUMS.REC.1399.568. All participants were aware of the protocol and provided written informed consent. All stages of proposal writing, implementation, data collection and analysis, and manuscript preparation were performed according to the checklist of the 4 Items for Reporting Randomized, Controlled Trials of

 https://doi.org/10.3831/KPI.2024.27.2.82

Herbal Medicine Interventions guideline [21].

### 10. Statistical analysis

The statistical analyses were performed using SPSS Statistics, version 25 (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test was conducted to assess the normality of the variables. The effects of each treatment group were assessed using the Wilcoxon signed-rank test and Fisher's exact tests. The Chi-square test was used to compare qualitative variables, while the independent T and Mann-Whitney tests were applied for quantitative variables. Additionally, analysis of covariance (ANCOVA) was used to examine multivariate effects. A p-value less than 0.05 was considered statistically significant.

## RESULTS

### 1. Standard curve

Each herbal pill contains 100 mg of protodioscin, 35 mg of ginsenosides, and 250 mg of L-arginine.

### 2. Formulation uniformity

Formulation uniformity was assessed by analyzing physical properties, such as color, appearance, mass uniformity, hardness, and dissolution test over a six-month period under accelerated conditions (75% humidity and 40℃). The results showed no significant changes throughout the storage period.

### 3. Microbial control

Microbial control tests conducted on the tablets at zero, third, and sixth months showed consistent results. The total aerobic microbial count and total yeast and mold counts were both N ≤ 10. *Salmonella* and *Escherichia coli* tests were also negative.

### 4. Eligible participants

Of the 137 eligible participants enrolled in the study, 17 men were excluded because they did not meet the inclusion criteria, while 6 other men declined to participate. The remaining 114 patients were randomly assigned to 2 groups: 1) the herbal medicine group (n = 57) and 2) the placebo group (n = 57).

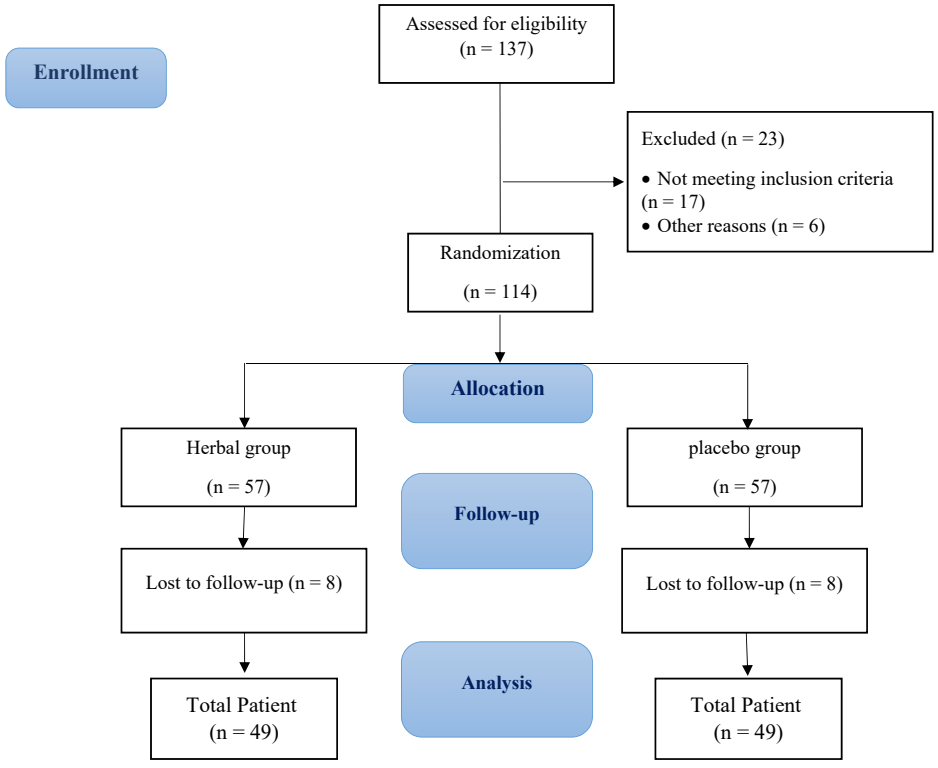


**Figure 1.** Consort flow diagram of the study.

Finally, data from 49 participants in the herbal medicine group and 49 participants in the control group were analyzed (Fig. 1).

## 5. Basic clinical features

Baseline characteristics were similar between the two groups, except for the ratio of patients with diabetes. Twelve participants in the herbal treatment group and 10 in the placebo group have diabetes (p = 0.628, Table 1).

Changes in the average ILEF-5 scores before and after the intervention within each group indicated that all parameters that were indicative of sexual function improved in the herbal treatment group (p < 0.001). In contrast, none of the IIEF-5 questionnaire items showed a statistically significant change before and after treatment in the control group (Table 2).

The IIEF-5 questionnaire item scores between the herbal medicine and placebo groups did not differ before the intervention. However, after the intervention, the between-group comparisons of the mean IIEF-5 scores revealed that the parameters associated with ED significantly improve in the herbal group (Table 3). These results indicate that, on average, the herbal group reported a total score difference of 3.22 ± 2.42 after the intervention compared to before the intervention, while the placebo group had a difference of 0.23 ± 0.7 (p < 0.05) (Table 3).

Table 4 compares the mean IIEF-5 scores for diabetic and non-diabetic individuals before and after the intervention. The findings show a significant difference between the two groups (diabetic vs. non-diabetic) for every item. In particular, the IIEF-5 scores increased significantly among the non-diabetics in the herbal treatment group (p < 0.05). The overall difference in IIEF-5 scores between the herbal and placebo groups was 3.27 ± 2.45 and 0.11 ± 0.52, respectively (p < 0.05). However, the

**Table 1.** Comparison of basic characteristics of the participants between the two groups before the intervention

| Variables | | Intervention group (n = 49) | Placebo group (n = 49) | p-value |
|---|---|---|---|---|
| Age (year) (mean ± S.D) | | 51 ± 12.30 | 49.20 ± 10.63 | 0.439 |
| Hypertension, n (%) | Yes | 6 (12.2) | 7 (14.3) | 0.766 |
| | No | 43 (87.8) | 42 (85.7) | |
| Diabetes, n (%) | Yes | 12 (24.5) | 10 (20.4) | 0.628 |
| | No | 37 (75.5) | 39 (79.6) | |
| Dyslipidemia, n (%) | Yes | 2 (4.1) | 3 (6.1) | 0.695 |
| | No | 47 (95.9) | 46 (93.9) | |
| Lower urinary tract diseases, n (%) | Yes | 2 (4.1) | 1 (2) | 0.785 |
| | No | 47 (95.9) | 48 (98) | |
| Drug abuse, n (%) | Yes | 13 (26.5) | 11 (22.4) | 0.638 |
| | No | 36 (73.5) | 38 (77.6) | |
| Reported Side effects, n (%) | Yes | 8 (16.3) | 7 (14.3) | 0.779 |
| | No | 41 (83.7) | 42 (85.7) | |

p < 0.05 shows a statistical significant difference.

**Table 2.** Comparison of mean IIEF-5 scores before and after the intervention within each group

| Item | Herbal (mean ± S.D) | | | Placebo (mean ± S.D) | | |
|---|---|---|---|---|---|---|
| | Before | After | p-value | Before | After | p-value |
| Q1 | 2.02 ± 0.91 | 2.62 ± 1.07 | < 0.001 | 1.80 ± 0.85 | 1.86 ± 0.85 | 0.083 |
| Q2 | 2.30 ± 0.79 | 2.77 ± 0.94 | < 0.001 | 2.17 ± 0.97 | 2.19 ± 0.98 | 0.317 |
| Q3 | 2.17 ± 0.81 | 2.67 ± 0.99 | < 0.001 | 2.43 ± 1.22 | 2.43 ± 1.22 | N.S |
| Q4 | 2.35 ± 1.12 | 2.82 ± 1.15 | < 0.001 | 2.32 ± 1.23 | 2.36 ± 1.21 | 0.157 |
| Q5 | 1.90 ± 1.00 | 3.07 ± 1.11 | < 0.001 | 1.97 ± 0.99 | 2.08 ± 1.02 | 0.25 |
| Total | 10.75 ± 3.66 | 13.97 ± 4.72 | < 0.001 | 10.71 ± 4.51 | 10.95 ± 4.54 | 0.37 |

N.SM, not significant; S.D, standard deviation.

 https://doi.org/10.3831/KPI.2024.27.2.82

**Table 3.** Comparison of mean IIEF-5 scores before and after the intervention between groups

| Time | Item | Herbal (mean ± S.D) | Placebo (mean ± S.D) | p-value |
|---|---|---|---|---|
| Before intervention | Q1 | 2.02 ± 0.91 | 1.80 ± 0.85 | 0.264 |
| | Q2 | 2.30 ± 0.79 | 2.17 ± 0.97 | 0.716 |
| | Q3 | 2.17 ± 0.81 | 2.43 ± 1.22 | 0.414 |
| | Q4 | 2.35 ± 1.12 | 2.32 ± 1.23 | 0.776 |
| | Q5 | 1.90 ± 1.00 | 1.97 ± 0.99 | 0.677 |
| | Total | 10.75 ± 3.66 | 10.71 ± 4.51 | 0.994 |
| After intervention | Q1 | 2.62 ± 1.07 | 1.86 ± 0.85 | < 0.001 |
| | Q2 | 2.77 ± 0.94 | 2.19 ± 0.98 | < 0.001 |
| | Q3 | 2.67 ± 0.99 | 2.43 ± 1.22 | < 0.001 |
| | Q4 | 2.82 ± 1.15 | 2.36 ± 1.21 | < 0.001 |
| | Q5 | 3.07 ± 1.11 | 2.08 ± 1.02 | < 0.001 |
| | Total | 2.62 ± 1.07 | 10.95 ± 4.54 | < 0.001 |
| Difference | ΔbQ1 | 0.60 ± 0.63 | 0.06 ± 0.24 | < 0.001 |
| | ΔQ2 | 0.47 ± 0.59 | 0.02 ± 0.14 | < 0.001 |
| | ΔQ3 | 0.50 ± 0.59 | 0.00 ± 0.00c | < 0.001 |
| | ΔQ4 | 0.47 ± 0.59 | 0.04 ± 0.20 | < 0.001 |
| | ΔQ5 | 1.17 ± 0.74 | 0.10 ± 0.31 | < 0.001 |
| | ΔTotal | 3.22 ± 2.42 | 0.23 ± 0.70 | < 0.001 |

S.D, standard deviation.

**Table 4.** Comparison of the mean IIEF-5 score for diabetic and non-diabetic individuals before and after the intervention

| Diabetic type | Item | Herbal (mean ± S.D) | Placebo (mean ± S.D) | p-value |
|---|---|---|---|---|
| Non-diabetic | n | 37 | 39 | - |
| | ΔQ1 | 0.59 ± 0.64 | 0.02 ± 0.16 | < 0.001 |
| | ΔQ2 | 0.48 ± 0.60 | 0.00 ± 0.00 | < 0.001 |
| | ΔQ3 | 0.51 ± 0.60 | 0.00 ± 0.00 | < 0.001 |
| | ΔQ4 | 0.48 ± 0.60 | 0.02 ± 0.16 | < 0.001 |
| | ΔQ5 | 1.18 ± 0.73 | 0.05 ± 0.23 | < 0.001 |
| | ΔTotal | 3.27 ± 2.45 | 0.11 ± 0.52 | < 0.001 |
| Diabetic | n | 12 | 10 | - |
| | ΔQ1 | 0.66 ± 0.57 | 0.20 ± 0.42 | 0.140 |
| | ΔQ2 | 0.33 ± 0.57 | 0.10 ± 0.31 | 0.345 |
| | ΔQ3 | 0.33 ± 0.57 | 0.00 ± 0.00 | 0.068 |
| | ΔQ4 | 0.33 ± 0.57 | 0.10 ± 0.31 | 0.345 |
| | ΔQ5 | 1.00 ± 1.00 | 0.30 ± 0.48 | 0.169 |
| | ΔTotal | 2.66 ± 2.30 | 0.70 ± 1.05 | 0.140 |

$\Delta Q = (Q_{\text{after intervention}}) - Q_{\text{before intervention}}$.

$p < 0.05$ shows a statistical significant difference.

IIEF-5 scores among patients with diabetes in the herbal and placebo groups did not significantly differ. Furthermore, 16.3% of patients in the intervention group and 14.3% in the control group reported at least one side effect and the difference was not statistically significant (p = 0.779).

## DISCUSSION

ED is a complex disorder primarily caused by reduced nitric oxide formation due to impaired neural and endothelial function of the corpus cavernosum of the penis [22]. However, there are other pathophysiological mechanisms, such as high blood pressure, androgen deficiency, arteriosclerosis, high cholesterol levels, diabetes mellitus, prostate diseases, and anatomical deformation of the penis [23, 24]. Due to the negative consequences associated with chemical and hormonal drugs, the use of medicinal herbs and natural bioactive components to treat and lessen the severity of ED has attracted attention in recent years [12]. In this study, we investigated the combined effect of *Panax ginseng*, *Tribulus terrestris*, and L-arginine on increasing sexual performance using the IIEF-5 questionnaire. The IIEF is validated for evaluating the effectiveness of ED therapy [25, 26]. Andrade et al. (2007) found that using 1,000 mg of Korean red ginseng three times a day dramatically increased the erectile IIEF score in men with ED [27]. According to Choi et al. (2013), taking Korean ginseng berry tablets reduced premature ejaculation and slightly improved penile erection [28]. Ginseng contains various ginsenosides that promote NO production [29-32]. Intraperitoneal injections of ginsenoside Rg1 have been shown to increased serum testosterone concentration, NO release, and cGMP accumulation in the corpus cavernosum of male rats [32]. Additionally, ginsenoside Rg3 inhibits corporal phosphodiesterase, thus, increasing cAMP and cGMP levels in smooth muscles [33]. These findings support the use of *Panax ginseng* for treating ED. Additionally, the combined effect of ginseng with vitamin E has also been shown to improve erectile function [34].

Kamenov et al. (2017) reported that TT at a standardized dose, with 250 mg of the saponin furostanol, taken for 12 weeks, improved sexual function in men with mild to moderate ED. Importantly, TT was well tolerated by patients with ED [35]. Gauthaman et al. (2008) showed that an intravenous administration of TT extract increased plasma testosterone, dihydrotestosterone, and dehydroepiandrosterone sulfate in primates. An oral administration of TT extract in rabbits and rats also increased dihydrotestosterone levels. Protodioscin, a saponin-like compound found in TT, may trigger testosterone synthesis by the Leydig cells [36]. Administering TT to rabbits results in a rise in cAMP and a relaxing effect on the corpus cavernosum, suggesting that TT affects the erectile process through the NOS pathway [37]. Moreover, Zhang et al. (2019) demonstrated a reparative effect of impure saponins on the endothelial function of a type 2 diabetes mouse model. Furthermore, gross saponins of *Tribulus territories* increased NO levels and decreased reactive oxygen species in the penile tissue of mice, as well as increased the cGMP level [38].

A meta-analysis previously reported that arginine supplementation substantially increased IIEF sub-domain scores of overall satisfaction, sexual satisfaction, orgasmic function, and erectile function [39]. Furthermore, L-arginine significantly improved their erectile performance [40].

## CONCLUSION

In conclusion, the combination of *Panax ginseng*, *Tribulus terrestris*, and L-arginine has the potential to improve erection in patients with ED. Further research is needed to fully understand the exact mechanisms and the overall benefits of these herbal components.

## LIMITATIONS

In this study, the IIEF-5 questionnaire was used to measure erectile function, which may be regarded as unideal. In the future, to improve study quality, erectile function should be assessed by measuring plasma hormones, especially free testosterone, blood flow in the internal pondal artery using Doppler ultrasound, and blood pressure in the genitals using penile thermography, as well as nighttime swelling of the genitals via prostate ultrasound, especially in males, aged over 50 years old.

## ACKNOWLEDGEMENTS

This study was conducted using Highsense Barij® tablets manufactured by Barij Essence Company in Iran, and this company was supported all financial support.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

 https://doi.org/10.3831/KPI.2024.27.2.82

## FUNDING

This study was supported by a research grant from the Barij Essence Pharmaceutical Research Center, Kashan, Iran.

## SUPPLEMENTARY MATERIALS

Supplementary data is available at https://doi.org/10.3831/KPI.2024.27.2.82.

## ORCID

Reza Tahvilian, https://orcid.org/0000-0001-6376-986X
Mohammad Amin Golesorkhi, https://orcid.org/0000-0001-6062-4585
Farajollah Parhoudeh, https://orcid.org/0000-0002-8995-9191
Fatemeh Heydarpour, https://orcid.org/0000-0002-2441-7332
Hossein Hosseini, https://orcid.org/0000-0002-6484-0725
Hojjat Baghshahi, https://orcid.org/0000-0003-0540-471X
Hossein Akbari, https://orcid.org/0000-0001-7486-8580
Mohammad Reza Memarzadeh, https://orcid.org/0000-0001-5965-9182
Mehdi Mehran, https://orcid.org/0000-0002-3460-7367
Hosna Bagheri, https://orcid.org/0009-0004-4863-443X

## REFERENCES

1. Adam DR, Alem MM. Erectile dysfunction: pharmacological pathways with understudied potentials. Biomedicines. 2022;11(1):46.
2. Heruti R, Shochat T, Tekes-Manova D, Ashkenazi I, Justo D. Prevalence of erectile dysfunction among young adults: results of a large-scale survey. J Sex Med. 2004;1(3):284-91.
3. Sin VJ, Anand GS, Koh HL. Botanical medicine and natural products used for erectile dysfunction. Sex Med Rev. 2021;9(4):568-92.
4. Wang H, Zhao M, Zhang J, Yan B, Liu S, Zhao F, et al. The efficacy of acupuncture on patients with erectile dysfunction: a review. Evid Based Complement Alternat Med. 2022;2022:4807271.
5. Shankhwar SN, Mahdi AA, Sharma AV, Pv K. A prospective clinical study of a prosexual nutrient: Nano Leo for evaluation of libido, erection, and orgasm in Indian men with erectile dysfunction. Evid Based Complement Alternat Med. 2020;2020:4598217.
6. Sangiorgi G, Cereda A, Benedetto D, Bonanni M, Chiricolo G, Cota L, et al. Anatomy, pathophysiology, molecular mechanisms, and clinical management of erectile dysfunction in patients affected by coronary artery disease: a review. Biomedicines. 2021;9(4):432.
7. Irwin GM. Erectile dysfunction. Prim Care. 2019;46(2):249-55.
8. Castela Â, Costa C. Molecular mechanisms associated with diabetic endothelial-erectile dysfunction. Nat Rev Urol. 2016;13(5):266-74.
9. Hatzimouratidis K, Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, et al. Pharmacotherapy for erectile dysfunction: recommendations from the fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016;13(4):465-88.
10. Ückert S, Kuczyk MA, Oelke M. Phosphodiesterase inhibitors in clinical urology. Expert Rev Clin Pharmacol. 2013;6(3):323-32.
11. Panahi Y, Akhavan A, Sahebkar A, Hosseini SM, Taghizadeh M, Akbari H, et al. Investigation of the effectiveness of Syzygium aromaticum, Lavandula angustifolia and Geranium robertianum essential oils in the treatment of acute external otitis: a comparative trial with ciprofloxacin. J Microbiol Immunol Infect. 2014;47(3):211-6.
12. Masuku NP, Unuofin JO, Lebelo SL. Promising role of medicinal plants in the regulation and management of male erectile dysfunction. Biomed Pharmacother. 2020;130:110555.
13. Chauhan NS, Sharma V, Dixit VK, Thakur M. A review on plants used for improvement of sexual performance and virility. Biomed Res Int. 2014;2014:868062.
14. Taghizadeh M, Ostad SN, Asemi Z, Mahboubi M, Hejazi S, Sharafati-Chaleshtori R, et al. Sub-chronic oral toxicity of Cuminum cyminum L.'s essential oil in female Wistar rats. Regul Toxicol Pharmacol. 2017;88:138-43.
15. Taghizadeh M, Farzin N, Taheri S, Mahlouji M, Akbari H, Karamali F, et al. The effect of dietary supplements containing green tea, capsaicin and ginger extracts on weight loss and metabolic profiles in overweight women: a randomized double-blind placebo-controlled clinical trial. Ann Nutr Metab. 2017;70(4):277-85.
16. Zhang H, Abid S, Ahn JC, Mathiyalagan R, Kim YJ, Yang DC, et al. Characteristics of *Panax ginseng* cultivars in Korea and China. Molecules. 2020;25(11):2635.
17. Kim JY, Lee HJ, Kim JS, Ryu JH. Induction of nitric oxide synthase by saponins of heat-processed ginseng. Biosci Biotechnol Biochem. 2005;69(5):891-5.
18. Hossein M, Hossein A, Mohsen T, Jamileh J, Mohadese M, Mahnaz M. Evaluation of the effects of capsules containing Tribulus terrestris extract and L-carnitine on treatment of oligospermia in males. J Evol Med Dent Sci. 2018;7(29):3266-70.
19. Gunarathne R, Nadeeshani H, Lu A, Li J, Zhang B, Ying T, et al. Potential nutraceutical use of *Tribulus terrestris* L. in human health. Food Rev Int. 2022;39(8):5326-55.

20. Santos CA, Reis LO, Destro-Saade R, Luiza-Reis A, Fregonesi A. Tribulus terrestris versus placebo in the treatment of erectile dysfunction: a prospective, randomized, double blind study. Actas Urol Esp. 2014;38(4):244-8.
21. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med. 2006; 144(5):364-7.
22. Zou H, Zhang X, Chen W, Tao Y, Li B, Liu H, et al. Vascular endothelium is the basic way for stem cells to treat erectile dysfunction: a bibliometric study. Cell Death Discov. 2023;9(1):143.
23. Aversa A, Bruzziches R, Pili M, Spera G. Phosphodiesterase 5 inhibitors in the treatment of erectile dysfunction. Curr Pharm Des. 2006;12(27):3467-84.
24. Papagiannopoulos D, Khare N, Nehra A. Evaluation of young men with organic erectile dysfunction. Asian J Androl. 2015; 17(1):11-6.
25. Jurys T, Burzynski B, Potyka A, Paradysz A. Post-radical prostatectomy erectile dysfunction assessed using the IIEF-5 questionnaire - a systematic literature review. Int J Sex Health. 2021;34(1):55-64.
26. Su H, Lu Y, Ma C, Li H, Su X. Impact of atorvastatin on erectile dysfunction: a meta-analysis and systematic review. Andrologia. 2022;54(6):e14408.
27. de Andrade E, de Mesquita AA, de Almeida Claro J, de Andrade PM, Ortiz V, Paranhos M, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. Asian J Androl. 2007;9(2):241-4.
28. Choi YD, Park CW, Jang J, Kim SH, Jeon HY, Kim WG, 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(2):45-50.
29. Qi LW, Wang CZ, Yuan CS. Isolation and analysis of ginseng: advances and challenges. Nat Prod Rep. 2011;28(3):467-95.
30. Yu J, Eto M, Akishita M, Kaneko A, Ouchi Y, Okabe T. Signaling pathway of nitric oxide production induced by ginsenoside Rb1 in human aortic endothelial cells: a possible involvement of androgen receptor. Biochem Biophys Res Commun. 2007;353(3): 764-9.
31. Leung KW, Cheng YK, Mak NK, Chan KK, Fan TP, Wong RN. Signaling pathway of ginsenoside-Rg1 leading to nitric oxide production in endothelial cells. FEBS Lett. 2006;580(13):3211-6.
32. Wang X, Chu S, Qian T, Chen J, Zhang J. Ginsenoside Rg1 improves male copulatory behavior via nitric oxide/cyclic guanosine monophosphate pathway. J Sex Med. 2010;7(2 Pt 1):743-50.
33. Kang YJ, Sohn JT, Chang KC. Relaxation of canine corporal smooth muscle relaxation by ginsenoside saponin Rg3 is independent from eNOS activation. Life Sci. 2005;77(1):74-84.
34. Najafabadi BT, Jafarinia M, Ghamari K, Shokraee K, Tadayyon F, Akhondzadeh S. Vitamin E and ginseng combined supplement for treatment of male erectile dysfunction: a double-blind, placebo-controlled, randomized, clinical trial. Adv Integr Med. 2021;8(1):44-9.
35. Kamenov Z, Fileva S, Kalinov K. Evaluation of the efficacy and safety of Tribulus terrestris in male sexual dysfunction - a prospective, randomized, double blinded, placebo-controlled clinical trial. Maturitas. 2015;81(1):P208.
36. Gauthaman K, Ganesan AP. The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction--an evaluation using primates, rabbit and rat. Phytomedicine. 2008;15(1-2):44-54.
37. Kam SC, Do JM, Choi JH, Jeon BT, Roh GS, Hyun JS. In vivo and in vitro animal investigation of the effect of a mixture of herbal extracts from Tribulus terrestris and Cornus officinalis on penile erection. J Sex Med. 2012;9(10):2544-51.
38. Zhang H, Tong WT, Zhang CR, Li JL, Meng H, Yang HG, et al. Gross saponin of *Tribulus terrestris* improves erectile dysfunction in type 2 diabetic rats by repairing the endothelial function of the penile corpus cavernosum. Diabetes Metab Syndr Obes. 2019;12:1705-1716.
39. Rhim HC, Kim MS, Park YJ, Choi WS, Park HK, Kim HG, et al. The potential role of arginine supplements on erectile dysfunction: a systemic review and meta-analysis. J Sex Med. 2019; 16(2):223-34.
40. Klotz T, Mathers MJ, Braun M, Bloch W, Engelmann U. Effectiveness of oral L-arginine in first-line treatment of erectile dysfunction in a controlled crossover study. Urol Int. 1999;63(4): 220-3.


 https://doi.org/10.3831/KPI.2024.27.2.82