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A systematic review and meta-analysis on the effectiveness and safety of *Tribulus Terrestris* in male fertility problems: examining semen parameters and erectile function

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ABSTRACT

Objective. This study aimed to investigate the effectiveness and safety of *Tribulus Terrestris* (TT) in male fertility problems, the studied variables being semen parameters and erectile function.
Methods. In this systematic review and meta-analysis, all relevant articles were searched in the relevant databases, including ISI Web of science, Scopus, PubMed, Cochrane, SID, Magiran, IranDoc and Google Scholar, using the keywords which included (*Tribulus Terrestris* OR *Puncture Vine* OR Protodioscin) AND (sperm parameters OR Sperm Counts) AND (Oligozoospermia OR Azoospermia OR Erectile dysfunction OR Male Sexual Impotence OR Infertility). Risk of bias was assessed using Cochrane Collaboration's tool. The data were analyzed using STATA software version 11. To examine the heterogeneity, I2 index and Q test were used and the fixed effects model was applied to pool standardized mean differences (SMDs).
Results. A total of 10 articles were included in this study, some of which revealed that TT administration improved a number of semen parameters, such as sperm concentration, motility, liquefaction time, and normal acrosome reactions. However, some other studies did not report statistically significant differences in relation to other semen parameters, such as sperm morphology and ejaculate volume. The quantitative analysis showed a statistically significant effect of TT on erectile function (SMD: 0.54; interval confidence [95% CI]: 0.30 to 0.78; P < 0.001; heterogeneity: I2 = 0%, p = 0.98, the fixed effects model; 2 trials).

SOMMARIO

Obiettivo. Questo studio mira ad indagare l'efficacia e la sicurezza del *Tribulus Terrestris* (TT) nei problemi di fertilità maschile. Le variabili studiate sono i parametri dello sperma e la funzione erettile.
Metodi. In questa revisione sistematica e meta-analisi, tutti gli articoli pertinenti sono stati cercati nei database idonei, tra cui ISI Web of science, Scopus, PubMed, Cochrane, SID Magiran, IranDoc e Google Scholar, utilizzando le parole chiave che includevano (*Tribulus Terrestris* o *Puncture Vine* o Protodioscina) e (parametri spermatici o Conta spermatica) e (Oligozoospermia o Azoospermia o Disfunzione erettile o Impotenza sessuale maschile o Infertilità). Il rischio di bias è stato valutato utilizzando lo strumento di Cochrane Collaboration. I dati sono stati analizzati utilizzando la versione 11 del software STATA. Per esaminare l'eterogeneità sono stati utilizzati l'indice I2 e il test Q, e il modello a effetti fissi è stato applicato alle differenze medie standardizzate (SMD).
Risultati. In questo studio sono stati inclusi un totale di 10 articoli, alcuni dei quali hanno rivelato che la somministrazione di TT ha migliorato una serie di parametri dello sperma, come la concentrazione dello sperma, la motilità, il tempo di liquefazione e le normali reazioni acrosomiali. Tuttavia, altri studi non hanno riportato differenze statisticamente significative in relazione a ulteriori parametri dello sperma, come la morfologia dello sperma e il volume dell'eiaculato. L'analisi quantitativa ha mostrato un effetto statisticamente significativo del TT sulla funzione erettile (SMD: 0,54; intervallo di confidenza [IC

Conclusions. The findings of the present study indicated that TT improved some sperm parameters and also had a beneficial effect on erectile function. However, these findings should be interpreted with caution, due to the small sample size and some methodological differences among the studies. Therefore, further trials are still required to confirm these findings.

95%]: da 0,30 a 0,78; P < 0,001; eterogeneità: I2 = 0%, p = 0,98, il modello a effetti fissi; 2 prove).
Conclusioni. I risultati del presente studio hanno indicato che TT ha migliorato alcuni parametri dello sperma e ha anche avuto un effetto benefico sulla funzione erettile. Tuttavia, questi risultati dovrebbero essere interpretati con cautela, a causa della piccola dimensione del campione e di alcune differenze metodologiche tra gli studi. Pertanto, sono ancora necessari ulteriori studi per confermare questi risultati.

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Key words:
Tribulus Terrestris; sperm parameters; erectile function; systematic review; meta-analysis.

INTRODUCTION

Sexuality is an important part of human life and healthy sexual function plays an important role in improving individuals' and their families' health and quality of life. Sexual problems can ruin the health, quality of life, and general well-being, and cause marital problems, followed by emotional disturbances or family collapse (1-4).
One of men's most frequent sexual disorders is erectile dysfunction, defined as the inability to reach or maintain erection for satisfactory sexual activity. Several factors can affect men's erectile function, including cardiovascular diseases, diabetes, neurogenic factors, anatomical causes, hormonal problems, medical adverse effects, trauma, smoking, drug abuse, and psychological factors such as low self-esteem, tension, depression, feeling guilty, and relationship problems. The epidemiological data have shown high prevalence and incidence of erectile dysfunction (ED) worldwide. In one study, the overall prevalence of ED in men aged 40-75 years was 52%, and their mild, moderate, and complete ED were 2.17%, 2.25%, and 6.9%, respectively (5-7). Studies have shown that sexual problems such as ED reduce life satisfaction and also cause disorder in the mood and quality of relationship. In addition, men's ED and the relationship with their partners can affect emotional and physical self-esteem, associated with psychosocial outcomes such as depression, anxiety, denial of symptoms, sexual ban, disturbed relationship, and impaired life quality (8, 9). Given that sexual problems are not easily expressed in Iranian society due to cultural and religious reasons, these disorders may remain hidden and can reflect in daily behavior. Inappropriate treatment can cause chronicity of symptoms, anxiety, introversion, and feeling guilty as well as social problems, such as divorce and drug addiction (1, 10, 11). One of the most widely used treatments of ED is sildenafil citrate, a selective guanosine inhibitor, which has shown to be effective in treatment of erectile dysfunction. Despite its undeniable effects, it also has several adverse effects, the most important of which reported in various studies is visual impairment (12). In fact, synthetic drugs with favorable results in treatment of ED have adverse effects, indicating the necessity of alternative drugs with fewer complications (13). *Tribulus terrestris* (TT), also known as Aphrodite, is a herbal medicine containing chemical compounds such as resin, tannin, fixed oil, alkaloids, polyphenols, phallonoides, and minerals such as calcium, phosphorus, iron, sodium, potassium, sulfur, nitrogen, and chlorine and also sugars including glucose, arabinose as well as steroidal saponins. It has beneficial effects on enhancing sexual power and treatment of oligospermia, azoospermia, and men's infertility (14, 15). TT extract increases serum levels of testosterone and dihydrotestosterone, thereby increasing libido, arterial blood pressure, and the blood supply to the penis, resulting in increased erection and sexual behavior and thus reduced mating distance. Moreover, the histological and morphometric study of seminal tubes have proved the positive effects of TT on spermatogenesis probably through increase of thickness and num-

ber of seminal tubes (16, 17). Although numerous human and laboratory studies have been conducted to study the effect of TT on men's erectile function, the contradictory results necessitate a meta-analysis study to provide a clear and consistent result and a comprehensive conclusion. Therefore, this meta-analysis study aimed to investigate the effectiveness and safety of TT in male fertility problems focusing on semen parameters and erectile function.

MATERIALS AND METHODS

In this systematic review and meta-analysis, all the articles related to the purpose of the study were searched in the relevant databases including ISI Web of science, Scopus, PubMed, Cochrane, SID Magiran, IranDoc, and Google Scholar, from their inception up to February 2018 with no limitation for language. The keywords used in this study included (*Tribulus Terrestris* OR Puncture Vine OR Protodioscin) AND (sperm parameters OR Sperm Counts) AND (Oligozoospermia OR Azoospermia OR Erectile dysfunction OR Male Sexual Impotence OR Infertility), which were used separately and with all possible combinations. Furthermore, the reference section of relevant articles was screened to find further studies missed by electronic searching. The report of this meta-analysis was based on PRISMA checklist.

The inclusion criteria comprised both Persian and English articles contain one of the search strategic

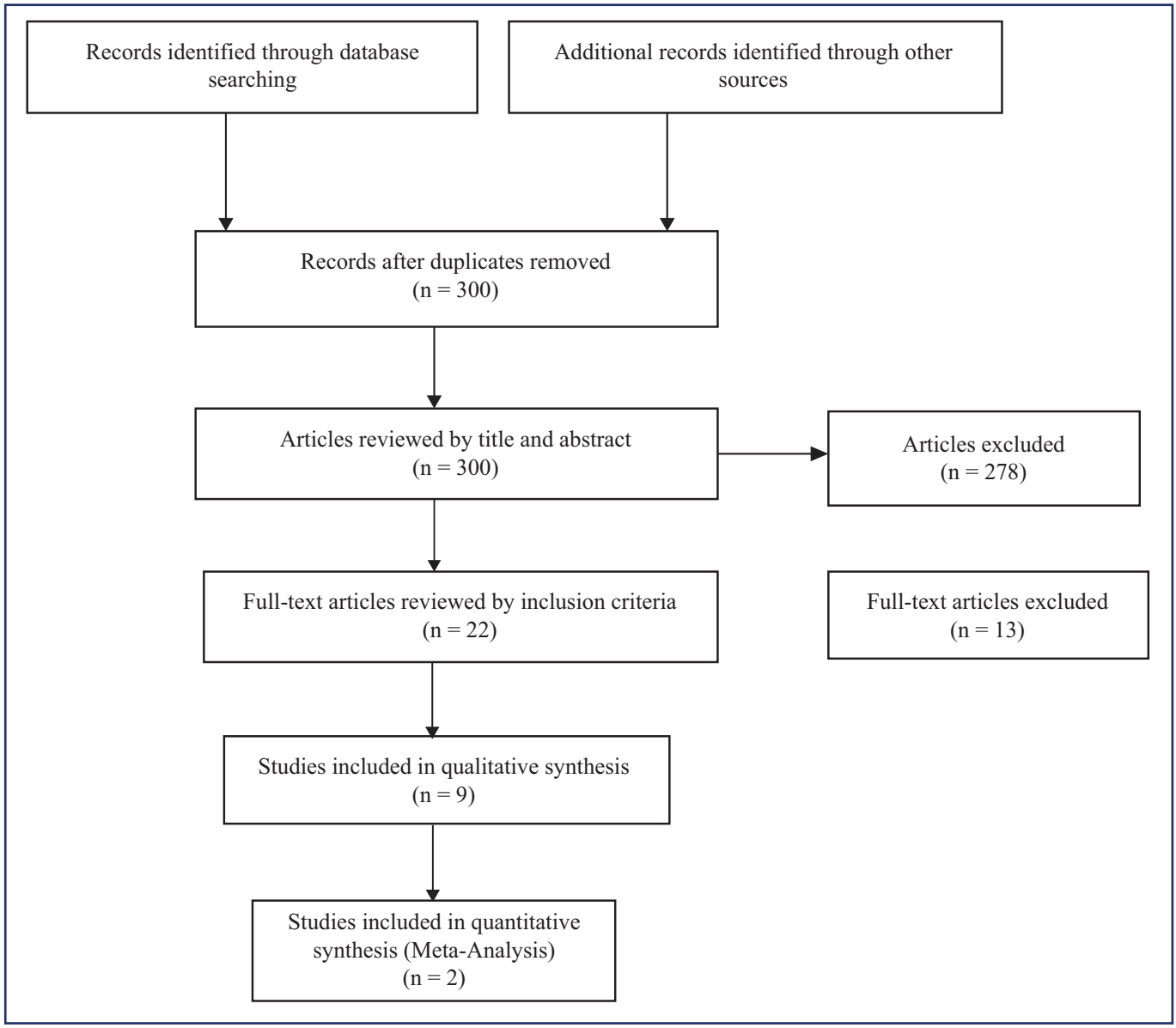

Figure 1. *PRISMA Flowchart of the study selection process.*

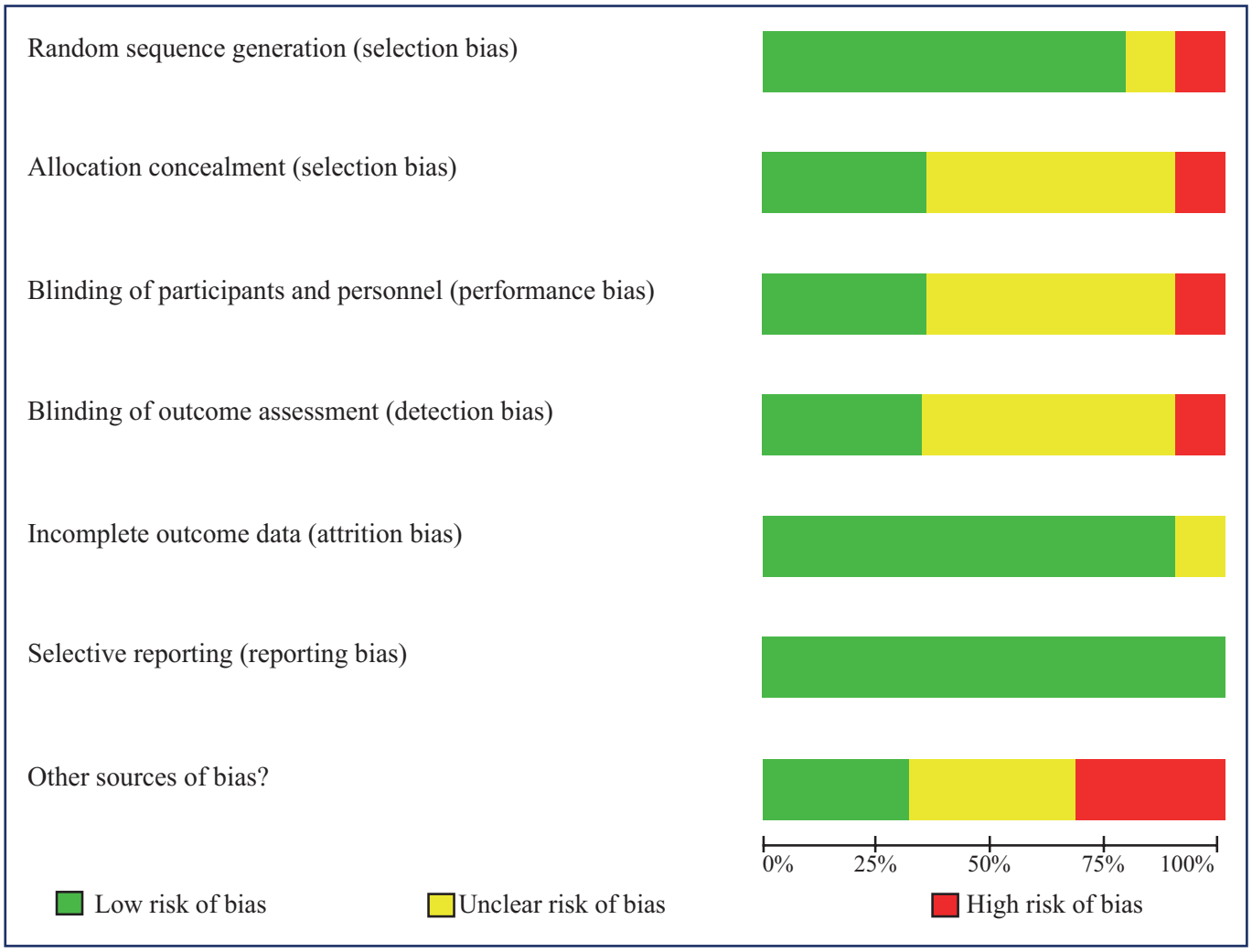

Figure 2. *Author's judgments of risk of bias presented as percentage across all the included studies.*

words in the title, abstract, and keywords related to the purpose of the study. The articles with incomplete and irrelevant data were excluded from the study. To select the related studies, their title, abstract, and keywords were evaluated and their eligibility criteria were reviewed. In the second step, full texts of all the articles were independently reviewed by two authors to check the eligibility and were discussed until reaching a consensus. The selection process of the studies is shown in **figure 1** using the PRISMA flowchart.

Moreover, two authors independently extracted the data from the full text articles using the data collection form. The extracted data were recorded in the relevant forms, including authors' names, yyear of publication, country, age, research design, patient, intervention, control, tools, blinding method, outcomes, and adverse events (**table I**).

The risk of bias in each study was assessed by two independent investigators using the Cochrane Collaboration's tool. This tool evaluates 6 types of bias, including selection bias (Random Sequence generation and Allocation concealment), performance bias (Blinding of participants, personnel), detection bias (Blinding of outcome assessment assessors), attrition bias (Incomplete outcome data), reporting bias (Selective reporting), and other sources of bias. Based on the bias rate for each type, the studies were reported with low, high, and uncertain risk (18, 19). It should be noted that in the case of disagreement between two investigators, a third researcher resolved this issue. Risk of bias of the studies assessed using the Cochrane Collaboration's tool is shown in **table I** and **figure 2**.

After data collection, the extracted data were reviewed. The data analysis was performed using STATA software version 11. To examine the heterogeneity among the studies, I^2 index and Q test were used. Given that no significant heterogeneity was found among the studies, the fixed effects model was used to combine the standardized mean differences in order to obtain the overall SMDs. In ad-

dition, the intervention and control groups reported the mean score of erectile function. The overall effect was evaluated by Z score. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 10 clinical trials met the inclusion criteria and only two trials were included in this meta-analysis. These 2 studies included a total of 210 males and were published as full text in 2014 and 2017, respectively. One study was from Bulgaria, and the other from Brazil. Both studies were published in English (20, 21). The summarized characteristics of the included studies are shown in **table II**. Risk of bias of the studies assessed using the Cochrane Collaboration's tool is shown in **figures 2** and **3**. The results of risk of bias assessment for these 2 studies showed low risk.
Since the number of included studies was less than 5, Funnel plot and Egger test were not used to test the publication bias.

The impact of TT on Semen Parameters

Five trials assessed the effect of TT on semen parameters (22-26).
One trial by Ramezani *et al*. in 2014 examined the effect of a herbal compound named ADOFON containing TT. The results revealed that the average number of sperm increased by 14.8% ($P < 0.05$), and also progressive mobility increased by 10.46% ($P < 0.001$), while no significant difference in sperm morphology was observed (22).
The other trial by Roaiah *et al*. (2016) evaluated the effects of TT on semen parameters in males with unexplained infertility. No statistically significant difference was found in semen parameters (sperm concentration or motility, or abnormal forms) before and after the treatment. Moreover, no statistically significant correlation was observed between testosterone (free and total) and LH and semen parameters before and after the treatment. Therefore, it was concluded that TT was ineffective in idiopathic infertility treatment (23).
The third trial by Salgado *et al*. (2016) assessed the effect of TT on semen quality. The complete semen analysis was perdormed at the end of the treatment and the findings demonstrated a significant increase in liquefaction time ($P = 0.01$), sperm concentration ($P = 0.007$), and sperm motility ($P < 0.001$) (24).

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other sources of bias
Kamenov *et al.* 2017	+	+	+	+	+	+	+
Punyawudho *et al.* 2013	+	?	?	?	+	+	?
Roaiah *et al.* 2016	+	?	?	?	+	+	-
Salgado *et al.* 2016	-	-	-	-	+	+	?
Santos *et al.* 2014	+	+	+	?	+	+	?
Sansalone *et al.* 2014	+	+	?	+	+	+	+
Ramezani *et al.* 2014	?	?	?	?	?	+	?
Sellandi *et al.* 2012	+	?	+	+	+	+	-
Shah *et al.* 2012	+	+	+	+	+	+	+
Setiawan *et al.* 1996	+	?	?	?	+	+	-

Table I. *Author's judgments of risk of bias items for each included study.*

In the fourth trial, Sellandi *et al*. (2012) studied the effect of TT on the management of Oligozoospermia. There was a significant difference in the total sperm count between the treatment and placebo groups ($P < 0.01$); however, regarding other semen parameters, there was no statistically significant difference ($P > 0.05$) (25).
The fifth trial by Setiawan (1996) revealed a significant increase in sperm motility in the TT group (1.666 ± 12.344) compared to the placebo group (-9.000 ± 10.889, $P < 0.05$). The quantity of sperms with normal acrosome reactions increased in the TT group (6.633 ± 6.282) compared to the placebo group (-0.333 ± 3.406, $P < 0.05$). Moreover, the quantity of immotile sperm in the TT group (-10.333 ± 16.198) significantly decreased compared to the placebo group (12.666 ± 21.865, $P < 0.05$). The volume of ejaculate, sperm concentration, morphology, and motility of rapid, progressive, and non-progressive sperms were not significantly different between the TT group and the placebo group (26).

The impact of TT on erectile function (International index of erectile function and its dimensions)

Six trials assessed the effect of TT on erectile function (20, 21, 25, 27- 29).
The first trial by Kamenov *et al*. (2017) showed that the International index of erectile function and its dimensions) (IIEF) score significantly improved in

Table II. *Characteristics of 10 clinical trials included in the study.*

Author year Country	Design	Age (Year)	Patient	Intervention	Control	Tools	Blinding method	Outcome(s)	Adverse events
Kamenov et al., 2017 Bulgaria (20)	RCT	18 to 65	180 men with mild or moderate ED for at least 6 months and/or secondary HSDD.	TT, 2 tablets (500 mg) orally 3 times daily, for 12 weeks	Tablets containing 250 mg placebo	IIEF	Double-blind	There was a significant difference (P<0.0001) between Tribestan and placebo	Not observed
Roaiah et al., 2016 Egypt (23)	Before and after study	30 to 50	30 male patients with idiopathic infertility	TT, 750 mg/day in 3 divided doses, for 3 months	-	Semen analysis	-	No statistically significant difference was observed in the levels of T (total and free), LH and semen parameters before and after the treatment. TT was ineffective in the treatment of idiopathic infertility	Not reported
Salgado et al., 2016 Brazil (24)	Clinical study	18 to 50	65 male patients with infertility	TT, 250 mg one capsule, q8h, for 12 weeks	-	Laboratory blood test, Semen analysis	-	There was an increase in DHT levels (P = 0.023), significant enhancement in sperm concentration (P =0 .007), motility (P <0 .001) and liquefaction time (P = 0.01)	Not reported
Santos et al., 2014, Brazil (21)	RCT	≥ 40	30 men who complaining of ED	TT, 800 mg, divided into two doses per day for 30 days	Placebo divided into two doses per day	IIEF	Double-blind	TT was not more effective than placebo on improving symptoms of erectile dysfunction or serum total testosterone	Not reported
Ramezani et al., 2014 Iran (22)	RCT	23 to 40	62 infertile men	ADOFON (multi-herb dry powder contains TT), 25 grams packets, 3 times a week for 3 months	Placebo 25 grams packets, 3 times a week, for 3 months	Semen analysis	Not reported	Number of sperm increased by 14.8%, which showed a significant correlation (P <0.05); Progressive mobility increased by 10.46% (P <0.001)	Not reported
Sansalone et al., 2014 Italy (28)	RCT	≥ 40	200 patients with mild-moderate ED	Tradamix, one tablet orally twice a day for 3 months	Placebo, one table twice a day	IIEF, MSHQ, SQoL-M	Single-blind	Therapy with Tradamix improves erectile and ejaculation function and sexual quality of life in patients with mild-moderate ED	Not observed
Punyawudho et al., 2013, Thailand (27)	RCT	35 to61	63 patients with mild or mild to moderate ED	minimum of 3 tablets of Cappra for 2-weeks	minimum of 3 tablets of Placebo, 3 tablets for 2-weeks	IIEF	Double-blind	There was an improvement of IIEF score for all domains in Cappra group compared to placebo group; The mean change of IIEF score from baseline for erectile function domain of Cappra was significantly higher than placebo (4.87 vs 3.44, P = 0.032)	Most common adverse events were dizziness (13.3% Cappra, 9.6% placebo), face numbness (1.6% Cappra, 0% placebo), and tachycardia (1.6% Cappra, 0% placebo) that were not serious.

Author year Country	Design	Age (Year)	Patient	Intervention	Control	Tools	Blinding method	Outcome(s)	Adverse events
Sellandi et al.,2012 India (25)	RCT	21 to 50	72 men with sperm count < 20 million/ml and Oligozoospermia	TT in granule form were given, 6 g twice daily, before food, in the morning and night, with warm water, for 60 days	Placebo in granule form was given, 6 g twice daily, before food, in the morning and night, with warm water, for 60 days	Laboratory test, Semen analysis, SQoL	Double-blind	TT is effective in the management of oligozoospermia, with lifestyle modification; TT have shown superior results in the management of oligozoospermia, as compared to placebo granules	Not observed
Shah et al.,2012 India (29)	RCT	25 to 50	78 men suffering from mild to moderate ED	VigRX (multi-herb supplement contains TT) at a dose of 2 capsules twice daily (each capsule containing 360 mg of active composition) for 12 weeks	Placebo at a dose of 2 capsules, twice daily (each capsule containing 360 mg of placebo composition) for 12 weeks	IIEF, EDITS, Laboratory test	Double-blind	VigRX was well tolerated and more effective than placebo in improving sexual function in men	The most common (7/23) adverse event was fever of mild severity, incidence of the event being similar in both.
Setiawan 1996 Indonesia (26)	RCT	25 to 40	30 primary and secondary infertile men	TT, oral 250mg , two tablets three times per day for 60 days	Placebo, two tablets, three times per day for 60 days	Semen analysis, frequency of sexual intercourse (per week)	Double-blind	The frequency of sexual intercourse, increased. Motility of sperm and sperms with normal acrosome reactions were increased significantly in the TT group ($P < 0.05$); The ejaculate volume, sperm concentration, morphology and motility of rapid, progressive and non-progressive sperms did not differ significantly	Not observed

T: testosterone.

q8h: every 8 hour.

DHT: dihydrotestosterone.

TT: Tribulus terrestris.

MSHQ: Male sexual health questionnaire-ejaculation disorder.

SQoL-M: Sexual quality of life.

Tradamix: alga Ecklonia bicyclis, Tribulus terrestris and glucosamine oligosaccharide.

ED: Erectile dysfunction.

HSDD: Hypoactive sexual desire disorder.

EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction.

IIEF: the international index of erectile function.

ADOFON: Tribulus terrestris, Orchis mascula, Amygdalus communis, Lepidium sativus, Allium ampeloprasum, Phoenix dactylifera pollen, Ficus carica.

Cappra: composed of Cervus Nippon Temminck, Epimedium Drevicornum Maxim, Cynomorium Songaricum Rupr., Carthamus Tinctorius and Cistanche Deserticola.

VigRX: Panax ginseng, Serenoa repens, Gingko biloba, Crataegus laevigata, Ptychopetalum olacoides, Erythroxylum catuaba, Cuscuta chinensis, and Epimedium sagittatum extract.

the TT group compared to the placebo group (P < 0.0001). For intention-to-treat (ITT), there was a statistically significant difference in changes of IIEF scores at baseline. The difference between TT and placebo was 2.70 (95% CI 1.40, 4.01) for the ITT population. A statistically significant difference was found between TT and placebo in terms of intercourse satisfaction (p = 0.0005), orgasmic function (P = 0.0325), sexual desire (p = 0.0038), and overall satisfaction (p = 0.0028) (20).

In the second trial, Punyawudho *et al*. (2013) evaluated the effectiveness of a combinational herbal medicine named Cappra containing TT. The results showed the improvement of IIEF score for all domains in Cappra group compared to placebo group. The mean changes of IIEF score at baseline for the erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domain in Cappra and placebo groups were 4.87 *vs* 3.44, 1.15 *vs* 0.81, 0.75 *vs* 0.52, 2.3 *vs* 1.82, and 1.49 *vs* 1.13, respectively. The mean change of erectile function domain score in Cappra group was significantly higher than the placebo group (4.87 *vs* 3.44, P = 0.032) (27).

In the third trial, Santos *et al*. (2014) evaluated the effects of TT in the treatment of erectile dysfunction. Prior to the treatment, the mean IIEF was 13.2 (minimum 5-21 maximum) in the intervention group and the mean IIEF was 11.6 (6-21) in the placebo group. After treatment, the mean IIEF was 15.3 (5-21) in the intervention group and 13.7 (6-21) in the placebo group. Therefore, TT was not more effective than placebo in improving the symptoms of ED (21).

The fourth trial by Sellandi *et al*. (2012) reported that the placebo group showed statistically significant results (P < 0.05) in terms of loss of penile erection (6.03%), loss of penile rigidity (9.41%), premature ejaculation (6.12%), and lack of orgasm (9.76%). However, the treatment group showed statistically significant results (P < 0.001) in terms of loss of penile erection (9.44%), loss of penile rigidity (17.02%), premature ejaculation (10.68%), and lack of orgasm (13.54%) (25).

In the fifth trial, Sansalone et al. (2014) assessed the effectiveness of oral administration of a combinational herbal medicine named Tradamix containing TT. They found significant changes of the IIEF in the therapy group (mean difference: 11.54; $P < 0.05$) during 3 months compared to the placebo group at the intergroup analysis (mean difference: 10.22; $P < 0.05$). IIEF-intercourse satisfaction ($P < 0.05$), IIEF-orgasmic function (mean $P < 0.05$), IIEF-sexual desire ($P < 0.05$), IIEF-overall satisfaction ($P < 0.05$), Male Sexual Health Questionnaire-Ejaculation Disorder (MSHQ-EjD) (mean difference: 1.21; $P < 0.05$), and quality of life instrument for men (SQoL-M) (mean difference: 10.2; $P < 0.05$) significantly changed in the treatment group compared to the baseline and placebo group. The findings showed that this treatment improved erectile and ejaculation functions and sexual quality of life in patients with mild-moderate ED (28).

In the sixth trial, Shah *et al*. (2012) examined the efficacy of a multi-herb supplement named VigRX Plus (VXP) for erectile dysfunction. In the treatment group, the IIEF scores significantly improved compared to the placebo group. After 12 weeks of therapy, the mean (sd) IIEF score at baseline increased from 16.08 (2.87) to 25.08 (4.56) in the treatment group in comparison to 15.86 (3.24) to 16.47 (4.25) in the placebo group ($P < 0.0001$). Similar results were observed in four domains of the IIEF (orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) (29).

Furthermore, in the trial by Sellandi et al. (2012), TT group showed 78.11% improvement in the quality of sexual health and the placebo group had 70.95% improvement (25). The other trial by Setiawan (1996) revealed that the subjects' sexual intercourse frequency with their partners significantly increased in the TT group (P < 0.05) (26).

Out of these six mentioned studies, two trials had sufficient data to be included in the meta-analysis (20, 21). Since the studies were homogeneous (I2 = 0, P = 0.98), the fixed effects model was applied. The results of these two above mentioned studies with a sample size of 210 males showed a significant effect of TT on erectile function (z = 4.7, $P < 0.0001$). The standard mean difference (SMD) between control and TT groups was estimated to be 0.54 (SMD 0.54; interval confidence 95% CI: 0.30 to 0.78). Moreover, the results of our meta-analysis showed that the estimated means of erectile function in the TT group (23.22, 12.02) and in the control group (20.47, 10.61) were 17.67 and 15.54, respectively (**figure 3**).

DISCUSSION

To the best of the authors' knowledge, the present study is the first systematic review and meta-analysis regarding the effects of oral administration of TT on semen parameters and erectile function in

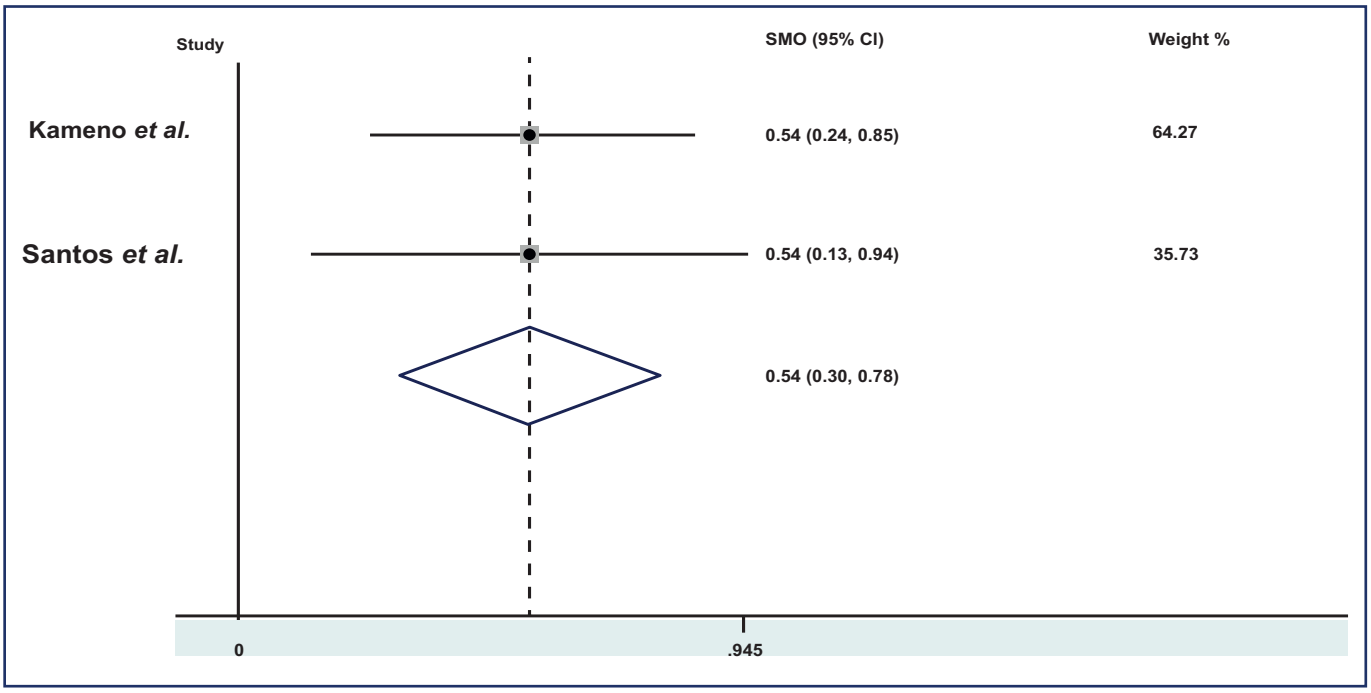

Figure 3. *The effects of TT on erectile function. The horizontal lines denote the 95% CI, ■ point estimate (size of the square corresponds to its weight); ♦ combined overall effect of the treatment.*

men. Overall, it seems that TT has beneficial effects on semen parameters and erectile function.

The impact of TT on semen parameters

Some studies revealed that TT administration improves the number of semen parameters including sperm concentration (22, 24, 25), motility (22, 24), liquefaction time (24) and normal acrosome reactions (26). However some other studies did not report a statistically significant difference in terms of other semen parameters like sperm morphology (22-26), sperm concentration or motility (23, 25, 26), and ejaculate volume (25, 26).

Some previous studies concerning the effect of TT extract on sperm motility showed that it could significantly increase sperm motility in mice (30, 31), which is consistent with the results of the present study. Likewise, Asadmobini *et al*. assessed the in-vitro effect of TT extract on human sperm parameters and concluded that TT extract increases the motility and viability of sperm (32). Another in-vitro study by Khaleghi *et al*. (2017) revealed that TT extract significantly enhanced total sperm motility, number of progressive motile spermatozoa, curvilinear velocity, and viability (33).

The exact mechanism through which TT extract enhances the sperm quality remaina unclear. However, TT extract is known to contain important chemical compounds acting as scavengers of free radicals, and may subsequently support the intercellular antioxidant system. These chemical compounds, such as saponins and alkaloids existing in this plant exhibit antioxidant activity. Reactive oxygen species (ROS) are among the factors damaging the sperm quality (34-36).

Oxidative stress is harmful to sperm function and impairs male fertility by affecting sperm viability. TT antioxidants components could prevent harmful effects of free radicals on the sperm by decreasing ROS (37). Also, TT extract contains total polyphenols, which include a wide class of components, such as phenolic acids and flavonols. These components are highly correlated to antioxidant activity as well (17, 31). Therefore, this extract with antioxidant compounds has an antioxidant activity which could be one possible reason for improving human sperm parameters. Furthermore, Nassar et al. suggested that a significant stimulatory effect of TT on human sperm parameters might have a relation to the trace elements, especially Ca2+ that is present in TT extract (38). Ca2+ could inhibit the enzyme phosphate diesterase, preventing cyclic adenosine monophosphate degradation and also enhancing the sperm motility (39). Zinc, another trace element in this extract, improves the sperm motility due to its involvement in protein synthesis and nuclear chromatin stabilization, which could be effective mechanisms in improving human sperm parameters (40).

Although TT has beneficial effects on semen parameters, this result should be interpreted with caution, since there was some bias in the design of two studies and also these studies had no control group (23, 24). Further trial studies are still required to confirm this finding.

The impact of TT on erectile function (International index of erectile function and its dimensions)

Out of six trials, five studies showed useful impacts of TT administration on erectile function in all 5 dimensions of IIEF, including erectile function, sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction (20, 25, 27-29). Only one study (21) concluded that TT was not more effective than the placebo in improving the symptoms of erectile dysfunction.

Out of these six studies, two trials had sufficient data to be included in the meta-analysis (20, 21). The findings revealed that TT had a significant effect on erectile function. In line with this finding, Adimoelja *et al*. (1997) concluded in a clinical trial that TT restores and enhances libido, erection, ejaculation, and orgasm during sexual intercourse possibly via significant increase in DHEA levels (41).

In relation to the mechanism of TT extract on erectile function, several studies have revealed that both nitric oxide (NOS) and opioid systems play a noteworthy role in the erectile function (42, 43). The study by Do *et al*. (2013) showed that TT extract caused relaxation of the corpus cavernous (CC) smooth muscle due to the contribution of the nitric oxide synthase pathway in the CC endothelium (44). Some authors proposed another hypothesis for erection improvement. They reported that erectile function improvement is due to the conversion of Protodioscin found in TT extract to dehydroepiandrosterone (DHEA) (41). A literature review by Neychev and Mitev (2016) revealed the effect of TT in treating ED and sexual desire problems. However, the empirical evidence to support the latter hypothesis in which the desirable effects are due to androgen enhancing properties of TT is still inconclusive and largely unknown (45).

One of the strengths of the present study is that it is the first systematic review and meta-analysis which specifically examined the effectiveness and safety of TT on semen parameters and erectile function.

The limits of this study consist the low number of clinical trials included in this meta-analysis, the lack of sample size for proper evaluation of TT effect on erectile function, and also the lack of data for subgroup analysis of IIEF dimensions.

Other limitations consist of the quality of the included studies in terms of general methodology and different methods of scoring. Therefore, it is suggested to perform more clinical trials with higher methodological quality in terms of allocation concealment (selection bias), blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias), as well as considering other sources of bias, such as performing intention-to-treat analysis in order to achieve greater robust evidence

Furthermore, there were some differences in design of the studies, including the treatment dose, the studied subjects, and duration of treatment. The therapeutic dose in two studies (24, 26) was 250 mg every 8 hours, in another study, it was prescribed in 25 grams packets 3 times a week (22), while others prescribed a dose of 500-800 mg (20, 21, 23). The duration of the treatments was at least 2 weeks (27) up to 3 months in different studies (20, 22-24, 28). It could be assumed that treatment duration is an important factor, since the interaction between treatment and visit time is not negligible and could lead to differences in the IIEF score between two groups. Moreover, the samples were different in these studies. In some studies, the studied population included infertile men (22-26) and in others, men who suffered from ED (20, 21, 27-29).

Furthermore, there are various content and composition of TT in several geographic regions of the world (22, 27). These variations may cause completely different bioactivities of TT and since the TT extract is composed of many chemical compounds rather than a single chemical compound (44). Therefore, due to the limitations of this study, more studies with a larger sample size and equal design are needed to achieve more accurate and reliable results.

CONCLUSIONS

The findings of the current study indicated that oral administration of TT improved some sperm parameters and also had beneficial effects on erectile function. Herbal medicines like TT could be appropriate alternatives to chemical medicines due to several reasons such as safety, tolerability, and lower adverse effects. Moreover, there is a high acceptance for herbal medicines among Iranians and their health care providers. However, these findings should be inter-

preted with caution due to the small sample size and some methodological differences among the studies. Therefore, it is necessary to conduct further clinical research studies to confirm these findings.

ETHICAL STATEMENT

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, *etc*.) have been completely observed by the authors.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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