

Vitamins combined with traditional Chinese medicine for male infertility: A systematic review and meta-analysis

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Abstract

Background: Male infertility is a tough problem in medicine. This article aims to provide the latest evidence for the efficacy and safety of traditional Chinese medicine (TCM) combined with vitamins in the treatment of male infertility.

Method: All randomized controlled trials (RCTs) that used TCM combined with vitamins for male infertility treatment were included in databases of China National Knowledge Infrastructure (CNKI), Wanfang, VIP Database, China Biology Medicine disc (CBM), MEDLINE, EMBASE, and Cochrane Library. The quality of the included articles was evaluated using the Cochrane Reviewer's Handbook 5.3, and meta-analysis was performed using Stata 15.

Results: A total of 14 eligible studies with 1488 patients were included in this meta-analysis. The results suggested that, compared with vitamin E or vitamin E + C alone, combination of TCM with vitamins increased significantly sperm concentration, sperm motility, sperm viability, liquefaction time of semen, the activity of acrosome enzyme, and the pregnancy rate of patients with male infertility. Three kinds of TCM (Shengjing capsule, Huanshao capsule, and compound Xuanju capsule) showed significant improvement for male infertility in terms of pregnancy rate, sperm concentration, or sperm motility. In addition, the results of the publication bias test demonstrated that no significant bias occurred.

Conclusion: Traditional Chinese medicine combined with vitamins has significant efficacy in the treatment of male infertility with no increase in side effects. The specific implementing regulations still need more long-term, multicenter, randomized, and double-blind clinical trials.

KEYWORDS

male infertility, meta-analysis, traditional Chinese medicine, vitamins

1 | INTRODUCTION

Infertility is a disease of the reproductive system defined as the failure to achieve conception after 1-2 years of regular unprotected sexual intercourse,¹ which impacts an estimated 15% of couples globally. A recent study suggested that male factor contributes to

20%-70% of overall infertility problems.² According to this report, a total of 48.5 million couples worldwide suffer from infertility with the highest rates observed in Africa and central/eastern Europe. Previous evidence suggested that many different causes are responsible for male infertility, including urogenital infections,³ genitourinary dysplasia, immune system-related factor,⁴ chromosomal

abnormalities,^{4,5} unhealthy lifestyle,⁶ alteration in reproductive hormone,^{7,8} and abnormal levels of biochemical components of seminal plasma.^{9,10} At present, the main clinical drugs for treating male infertility are hormones,^{9,10} antioxidants,¹¹ L-carnitine,¹² pentoxifylline,¹³ and other drugs.

It was reported that approximately 30%-80% of male infertility is thought to be partly because of the negative effects of oxidative stress on spermatozoa.¹⁴ Oxidative stress, which damage lipids, proteins, and DNA, occurs when reactive oxygen species (ROS) overwhelm the semen's innate antioxidant defenses.¹⁴ The damage of sperm's DNA caused by oxidative stress can result in reduced sperm motility, acrosome membrane damage, and sperm disability in fertilizing oocyte and eventually cause fertility decline.¹⁵ Antioxidants such as vitamin C, vitamin E, and coenzyme Q10 can effectively scavenge oxygen free radicals to protect spermatozoa from the effects of oxidative stress and thereby increase sperm quality. Previous study suggested that vitamin C effectively ameliorates sperm quality in patients with male infertility and increases male fertility.¹⁶ Proper supplementation of vitamin E effectively alleviates the damage of sperm DNA, and its therapeutic effect increases with age.¹⁷ In addition, clinical studies have found that the combined use of vitamin E with clomiphene citrate effectively increases sperm motility, sperm concentration, and fertility.^{18,19}

A number of studies have revealed that traditional Chinese medicine (TCM) has an important role in the enhancement of the parameters of spermatozoa, including sperm count, viability, motility, and morphology.²⁰⁻²² Not only can it treat male infertility but it also improves the symptoms of other diseases, such as premature ejaculation,²³ erectile dysfunction.²⁴ In terms of sperm quality, studies show that the total sperm motility of patients who had received TCM combined with vitamins for twelve weeks is better than those who only received vitamins.²⁵ Combined therapy has synergistic effects,²⁵ and how to exploit the full spectrum of advantages of a potential combinatorial strategy in the treatment of male infertility has become a primary focus for healthcare professionals, in China and elsewhere. The aim of this analysis was to evaluate the efficacy and safety of combination therapy using TCM and vitamins, based on the published literature,

2 | METHOD

2.1 | Literature searching strategies

A systematic search was made through the electronic databases of MEDLINE, PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure Database (CNKI), Wanfang Database, China Biology Medicine Database (CBM), VIP Science Technology Periodical Database, Cochrane Library. Related Randomized controlled trials (RCTs) were collected and selected from the beginning to January 12, 2020, without any language restriction.

The search strategy used combined MeSH terms and keywords and was based on the following keywords: "male infertility"

or "oligozoospermia", "oligoasthenozoospermia", "spermatozoa" or "semen" or "sperm" AND "traditional Chinese medical" or "Chinese herbal medicine" AND "Vitamin" or "L-carnitine" were used. Appropriate adjustments of the search strategy were applied to fit the different databases. The Chinese form of the above terms was used in Chinese search. The reference lists of the retrieved articles were screened manually for potentially missing literature. The authors were contacted for missing data, and data were independently extracted by two authors.

2.2 | Inclusion and exclusion criteria

The assessment of eligible articles was performed by two independent researchers according to the following inclusion and exclusion criteria, and discrepancies between them were resolved via negotiation. The inclusion criteria were as follows: (a) only randomized controlled trials (RCTs) were included; (b) male patients with a diagnosis of infertility, aged 18 to 60 years, according to the European Association of Urology guidelines on Male Infertility, 2012 edition²⁶ or other authoritative standards were considered; (c) In the treatment group, patients were treated with TCM combined with vitamins, while patients in the control group were only treated with vitamins; (d) outcomes: pregnancy rate and sperm parameters (concentration, motility, viability). Exclusion criteria included: (a) animal experiments, reviews, and fundamental studies; (b) studies with self-control or without control group; (c) incomplete or incorrect data.

2.3 | Data extraction and quality evaluation

Two researchers independently examined all eligible studies and extracted carefully the essential information, including the author, year, sample, intervention, and outcomes. Risk of bias was evaluated for the included studies by two reviewers independently according to the guidelines of the Cochrane Collaboration Handbook version 5.3. When the evaluation results were inconsistent, it shall be settled by a third researcher.

2.4 | Statistical methods

The meta-analysis was performed using STATA/SE 15 (Stata Corporation). The pooled effect of continuous variables is represented by standardized mean difference (SMD) or weighted mean difference (WMD); the combined effect of the dichotomous variables was expressed in relative risk (RR) or odds ratio (OR). The combined effect amount was represented by 95% confidence interval (CI), and Z-test was used for hypothesis testing. A test of heterogeneity among the included studies was analyzed by the chi-squared test and I^2 statistics. The fixed-effect model was used if $I^2 > 50\%$ and $P > .05$. Otherwise, the random-effect model was used. Sensitivity analysis was performed by omitting one study in each turn.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 1058 studies were retrieved using the abovementioned strategy, 583 articles were selected after deleting the duplicate papers. Among these, 424 were judged not pertinent after reading the abstract because of the study aim and 139 of the study design. The remaining 21 full texts were assessed for eligibility. Seven papers were removed, and 14 eligible papers with 1488 individuals matched the inclusion criteria were included in the meta-analysis, including 763 cases in the treatment group and 725 cases in the control group.²⁷⁻⁴⁰ Studies characteristics are shown in Table 1, the articles were filtered as shown in Figure 1, and evaluation of the quality of included studies is shown in Figure 2.

3.2 | Effect of TCM plus vitamins on pregnancy rate compared with vitamins alone

Ten literatures reported the effect of TCM plus vitamin treatment on pregnancy rate. The results showed that the pregnancy rate was significantly higher in patients treated with TCM plus vitamins compared with vitamins alone (RR = 3.701; 95%CI: 2.480-5.523). No inter-study heterogeneity was found ($I^2 = 0.0\%$, $P = .860$). Subgroup analysis was performed based on the treatment of the control group and the different kinds of TCM. The results suggested that compared with the single use of vitamin E, the combination therapy of TCM and vitamin E had a statistically significant further improvement on the pregnancy rate ($I^2 = 0.00\%$, $P = .887$; $Z = 3.98$, $P < .001$; RR = 2.758, 95%CI: 1.673-4.546). In addition, the pregnancy rate was significantly higher in patients treated with TCM plus vitamin E + C compared with those treated with vitamin E + C alone ($I^2 = 3.9\%$, $P = .353$; $Z = 4.77$, $P < .001$; RR = 3.563; 95%CI: 2.114-6.005) (Figure 3). Moreover, the combination of HSC (RR = 2.24; 95%CI: 1.09-4.59), SJC (RR = 2.77; 95%CI: 1.18-6.50), and other kinds of TCM (RR = 3.67; 95%CI: 2.27-5.93) with vitamins had a significant improvement on the pregnancy rate based on the results of subgroup analysis (Figure 4).

3.3 | Effect of TCM plus vitamins on sperm parameters compared with vitamins alone

Three articles were involved in regards of the sperm volume. Heterogeneity tests were conducted on the included literatures ($\text{Chi}^2 P = .157$, $I^2 = 46.0\%$). Fix-effect model was used to calculate the combined effect: WMD = 0.25, 95%CI: (-0.19,0.68), $Z = 1.62$, $P = .106$, Figure 5. Heterogeneity test was performed on two studies involving the liquefaction time: chi-square value = 3.45, $P = .063$, I-square = 71.0%. Random-effect model was used to calculate the combined effect: WMD = -14.888, 95%CI: (-20.058, -9.719), $Z = 5.64$, $P < .001$, Figure 6. The acrosome enzyme activity

was reported in two articles. The combined effect (WMD = 15.61, 95%CI: 11.45-19.77) was calculated using random-effect model. Inter-study heterogeneity was observed ($\text{Chi}^2 P < .001$, $I^2 = 92.9\%$) (Figure 7).

There are twelve studies reporting the effect of TCM plus vitamins treatment on the sperm concentration and motility, with eight studies using vitamin E as control and four articles using vitamin E + C as control. The combined effect value (WMD = 12.91, 95%CI:6.37-19.44) for sperm concentration was calculated using random-effect model ($Z = 3.87$, $P < .001$). Subgroup analysis showed that the combined effect value for those with vitamin E as the control group was: WMD = 11.71, 95%CI: (4.13-19.29), while the pooled effect was: WMD = 15.27, 95%CI: (1.28-29.25) for those with vitamin E + C as control (Figure 8). The combined effect value for those with HSC, CXJC, and other kinds of TCM combined with vitamins as the treatment group were as follows: WMD = 19.31, 95%CI: (6.42-32.20); WMD = 11.55, 95%CI: (-11.02, 34.13); WMD = 10.00, 95%CI: (1.61-18.40), respectively (Figure 9). For sperm motility, random-effect model was applied to obtain the pooled effect value (WMD = 13.74, 95%CI:8.89-18.60) owing to the presence of heterogeneity ($\text{Chi}^2 P < .001$, $I^2 = 97.4\%$). Subgroup analysis demonstrated that the combined effect values from the random-effect model for those with vitamin E or vitamin E + C as control were (WMD = 16.85, 95%CI: 10.57-23.14) and (WMD = 7.85, 95%CI:5.61-10.08), respectively (Figure 10). The pooled effect for those with HSC (WMD = 17.34, 95%CI:5.38-29.30), CXJC (WMD = 6.61, 95%CI:5.33-7.89), SJC (WMD = 23.50, 95%CI:14.59-32.40), and other kinds of TCM (WMD = 10.83, 95%CI:9.31-12.34) combined with vitamins as treatment were also calculated using random-effect model (Figure 11). In addition, six studies included the sperm viability data. The combined effect value (WMD = 22.39, 95%CI: 13.11-31.66) was calculated using random-effect model, and subgroup analysis based on the treatment of the control group (Figure 12) and the different kinds of TCM (Figure 13) were also performed.

3.4 | Publication bias and sensitivity analysis

Publication bias were tested for pregnancy rate (Begg's test: 0.210; Egger's test: 0.950), sperm concentration (Begg's test: 0.283; Egger's test: 0.034), sperm motility (Begg's test: 0.837; Egger's test: 0.012), sperm viability (Begg's test: 0.260; Egger's test: 0.220), respectively, suggesting that no statistical significance existed. Sensitivity analysis was used to evaluate the stability and reliability of the results of pregnancy rate and sperm parameters (concentration, motility, and viability) by omitting one study in each turn, and the result showed that: (a) for pregnancy rate (Figure S1), viability (Figure S2), or sperm concentration (Figure S3), the combined RR/WMD is stable; (b) for sperm motility (Figure S4), the combined WMD was significantly affected, which mainly caused by the reference.³¹ After removing the reference, the I-square of sperm motility (92.3%) is lower than before, and the adjusted combined effect value for sperm motility (WMD = 12.26, 95%CI: 9.07-15.46) was also recalculated.

TABLE 1 Literature characteristics

First author	Year	T/C sample	Interventions		Period (week)	Observation target
			Treatment group	Control group		
Wang Y	2017	65/55	TCM (Gujing Maisiha Tablets)+ Vitamin E	Vitamin E (100 mg, b.i.d)	12	Sperm motility; percentage of progressively motile sperm (PMS); pregnancy rate
Song B	2012	24/26	TCM (Compound Xuanju Capsule) + Vitamin E	Vitamin E (100 mg, b.i.d)	12	Sperm volume; Sperm concentration; PMS; dna fragmentation indexes (dfi); pregnancy rate
Zeng YX	2017	40/40	TCM (Shengjing Capsule)+ Vitamin E	Vitamin E (100 mg, t.i.d)	12	Sperm concentration and count; sperm total motility; sperm viability; liquefaction time; superoxide dismutase (sod); malondialdehyde (mda); pregnancy rate
Men B	2017	30/30	TCM (Yishen Tongluo Decoction) + Vitamin E	Vitamin E (100 mg, b.i.d)	12	Sperm viability; semen volume, sperm concentration; dfi
Wang WJ	2017	61/57	TCM (Shengjing Capsule)+ Vitamin E	Vitamin E (5 mg, t.i.d)	12	Sperm volume; Sperm concentration; sperm viability; liquefaction time; pregnancy rate
Zhu JW	2017	56/54	TCM (Bushen Shengjing decoction) + Vitamin E	Vitamin E (50 mg, t.i.d)	12	Sperm concentration; PMS (grade a); sperm motility
Qin DH	2017	61/55	TCM (Huanshao Capsules) + Vitamin E	Vitamin E (5 mg, t.i.d)	12	Sperm volume; sperm concentration; PMS(grade a); PMS(a + b); sperm viability; liquefaction time;
Chen GZ	2015	45/45	TCM (Huanshao capsule)+ Vitamin E	Vitamin E (100 mg, bid)	12	Sperm concentration; PMS (a + b); pregnancy rate
Jiang X	2014	36/35	TCM (Xianlu oral liquid) + Vitamin E	Vitamin E (100 mg, tid)	12	Sperm concentration; PMS (a); PMS (b)
Wei H	2016	45/45	TCM (Huanshao Capsules) + Vitamin E	Vitamin E (100 mg, tid)	12	Sperm concentration; sperm motility; pregnancy rate;
Zhu JW	2018	54/50	TCM (Shengjing Guben Decoction) + Vitamin E + C	Vitamin E (100 mg; b.i.d) + Vitamin C (100 mg, t.i.d)	12	Sperm density; pregnancy rate
Lu SX	2013	160/160	TCM (Shengjing San)+ Vitamin E + C	Vitamin E (100 mg, t.i.d) + Vitamin C (200 mg, t.i.d)	12	Sperm density; sperm viability; sperm motility; pregnancy rate
Gui Q	2018	47/47	TCM (Compound Xuanju Capsule) + Vitamin E + C	Vitamin E (100 mg; t.i.d) + Vitamin C (100 mg, t.i.d)	12	Sperm motility; sperm density; acrosome enzyme activity; pregnancy rate
Pu JB	2016	39/26	TCM (Compound Xuanju Capsule) + Vitamin E + C	Vitamin E(100 g, b.i.d) + Vitamin C (100 g, t.i.d)	12	Sperm density; Sperm viability; sperm motility; liquefaction time; acrosome enzyme activity

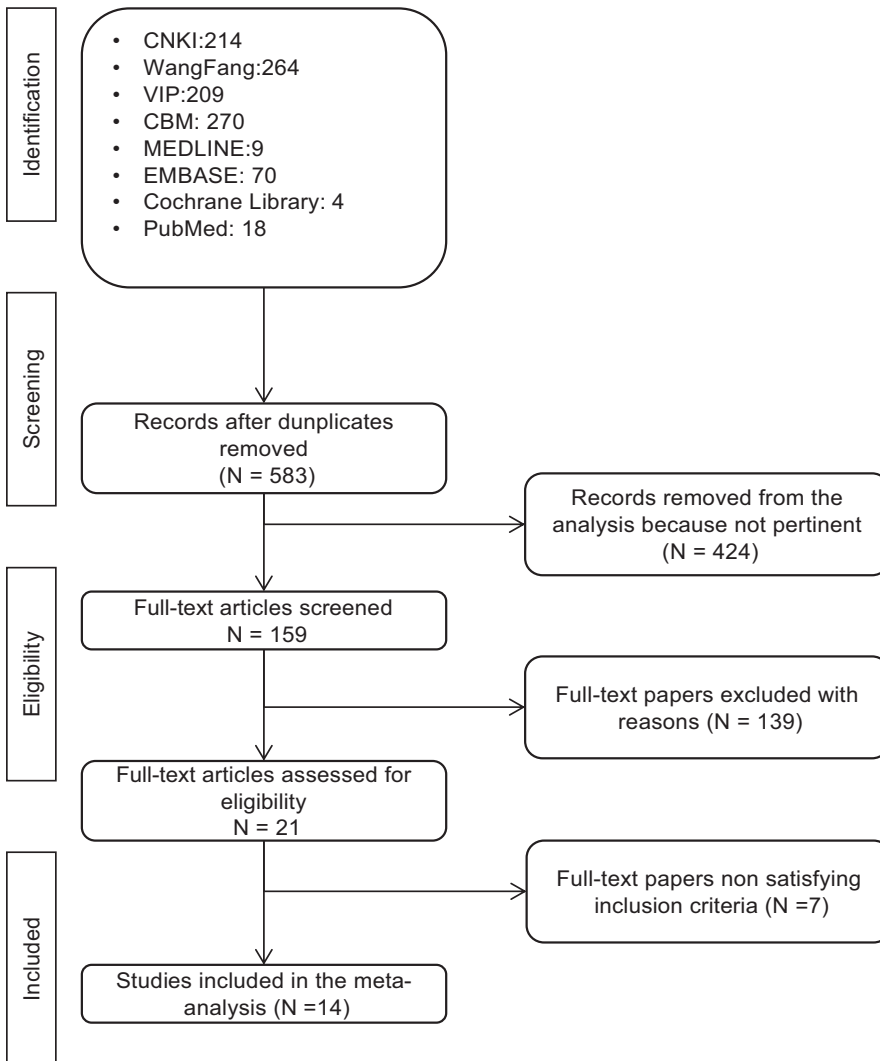


FIGURE 1 Flowchart of the studies included in the meta-analysis

4 | DISCUSSION

With the development of global industrialization and the influence of smoking, drug abuse, alcohol abuse, sexually transmitted diseases, environmental pollution, drug abuse, and other factors, male fertility has decreased significantly.⁴¹ Jorgensen et al found that the sperm concentration of 20% of young people is lower than the recommended level of the World Health Organization, and the sperm concentration of 40% of young people cannot reach the optimal level.⁴² A good testicular environment is a necessary condition for sperm production and development. The feedback system consisting of the hypothalamus, the pituitary, and the testes is responsible for the correct secretion of male hormone and for normal spermatogenesis.⁴³ The pathogenesis of asthenospermia is related to changes and/or destruction of the internal environment of spermatogenesis.⁴⁴ Abnormal spermatozoa resulted from impaired spermatogenesis and maturation, obstruction of sperm transport ducts and abnormal gonads, accounting for the most common causes of male infertility. Unbalanced ratio of oxidant and antioxidant in seminal plasma make spermatozoa vulnerable to damage. Related studies have shown that the damage caused by the oxidation reaction

depends on the balance between the activity of ROS and intracellular antioxidants.⁴⁵ Excessive accumulation of reactive oxygen in the body can break the balance and result in damages to germ cells and spermatozoa, eventually leading to male infertility.

Consequently, oxidative stress has undoubtedly become an important target for treating male infertility. Vitamin E is one of the most important antioxidants in the body. Being a free radical scavenger and fat-soluble antioxidant, it mainly targets the free radicals generated by lipid peroxidation, stabilizing and protecting biofilms. Meanwhile, vitamin E is considered to be the most fundamental component of the sperm antioxidant system and plays a role in the pathogenesis of male infertility.^{46,47} It inhibits peroxidation of polyunsaturated fatty acids (PUFA), which is important in spermatozoon because of their high PUFA content.⁴⁸ In vitro experiments have shown that vitamin E can effectively scavenge reactive oxygen, while in vivo studies have found that vitamin E supplementation can improve semen quality.⁴⁹⁻⁵¹ In addition, vitamin E supplementation can reduce sperm DNA fragmentation⁵² and benefit to in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).^{53,54} It was believed that vitamin E has a role in promoting the synthesis of testosterone by Leydig cells,⁵⁵ and testosterone decrease was

FIGURE 2 Risk of bias item for each included study

	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 bias
Chen 2015	?	?	-	-	+	+	?
Gui 2018	+	?	-	-	+	+	?
Jiang 2014	+	?	-	-	+	+	?
Lu 2013	?	?	-	-	?	+	?
Men 2017	?	?	-	-	-	+	?
Pu 2016	?	?	-	-	+	+	?
Qin 2017	?	?	-	-	+	+	?
Song 2012	?	?	-	-	+	+	?
Wang 2017	+	?	-	-	-	+	?
Wang WJ 2017	?	?	-	-	-	+	?
Wei 2016	+	?	-	-	+	+	?
Zeng 2017	?	?	-	-	+	+	?
Zhu 2017	?	?	-	-	+	+	?
Zhu 2018	?	?	-	-	-	+	?

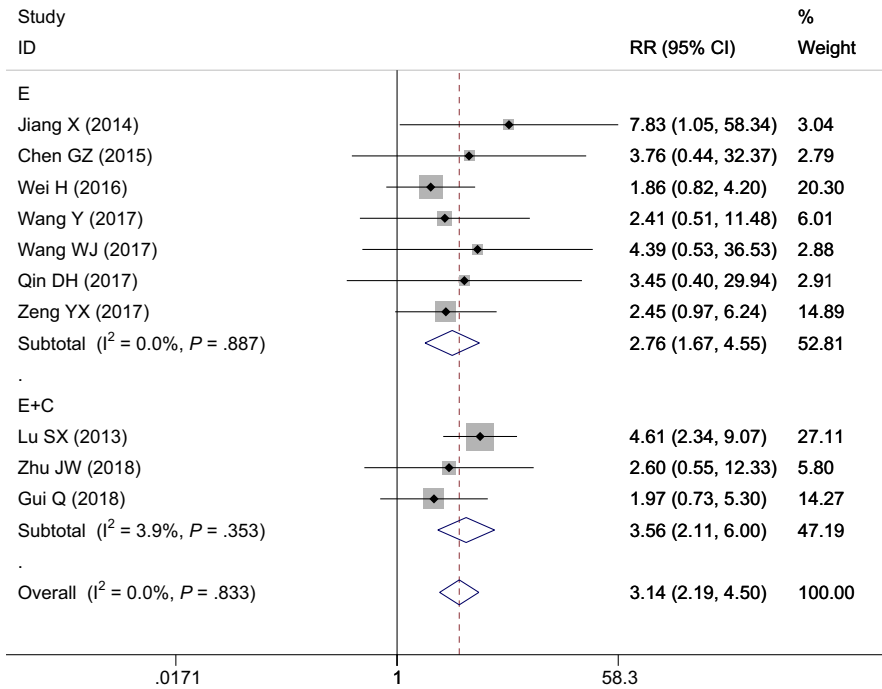


FIGURE 3 Subgroup analysis of the effect of combined treatment of TCM and vitamins on pregnancy rate in comparison with the treatment of vitamins alone based on the treatment of the control group

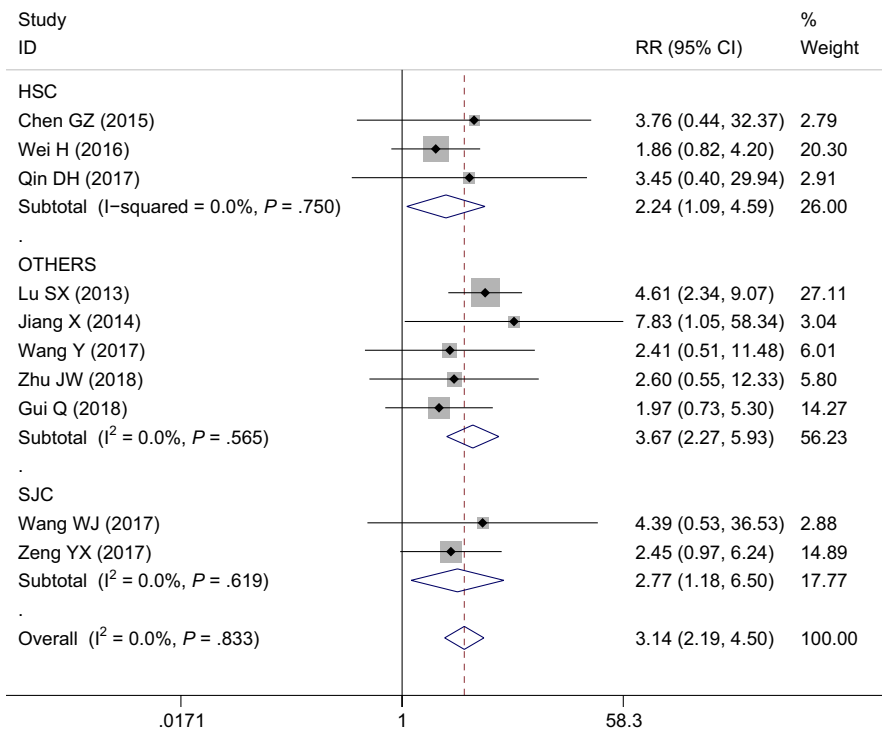


FIGURE 4 Effect of combined treatment of TCM and vitamins on sperm volume in comparison with the treatment of vitamins alone

associated with mental disorders,⁵⁶ sexual dysfunction,⁵⁶ and cognitive impairment.⁵⁷

The viewpoints of TCM define male infertility as a multifactorial disease whose pathogenesis is associated with kidney, liver and spleen disorders. Except for kidney and spleen deficiency,⁵⁸ liver disorder-induced pathological factor (nonalcoholic fatty liver disease) was also revealed to be associated with severe male reproductive organ impairment.⁵⁹ Modern research suggests that

the multisystemic approach of TCM can explain its positive outcome in the treatment of male infertility, which benefits of the multiple targeting strategy often provided by TCM remedies. For example, *Shenjing* capsule, consists of velvet antler, ginseng, epimedium, cordyceps sinensis, and some other Chinese herbs, can improve the microcirculation and spermatogenic function, promote the development of the reproductive system, enhance the metabolism ability, and improve the sperm quality, density and

FIGURE 5 Effect of combined treatment of TCM and vitamins on liquefaction time in comparison with the treatment of vitamins alone

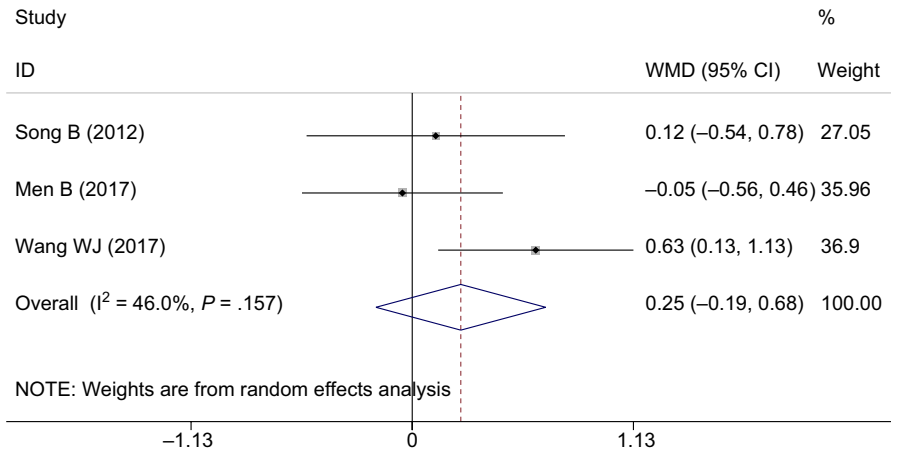


FIGURE 6 Effect of combined treatment of TCM and vitamins on acrosome enzyme activity in comparison with the treatment of vitamins alone

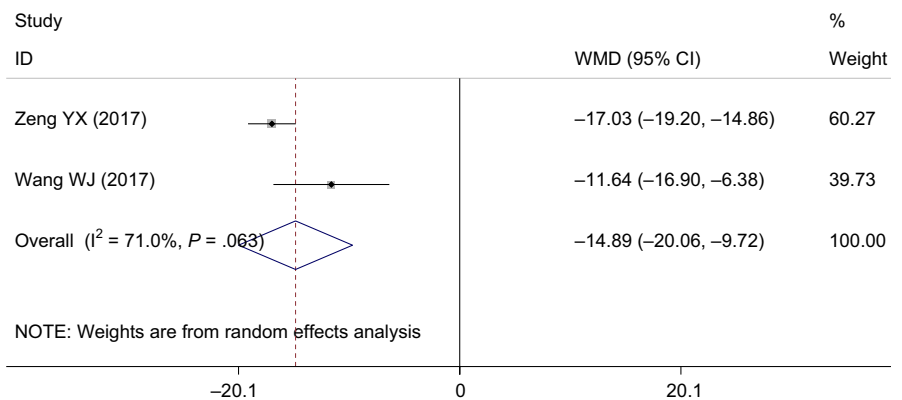
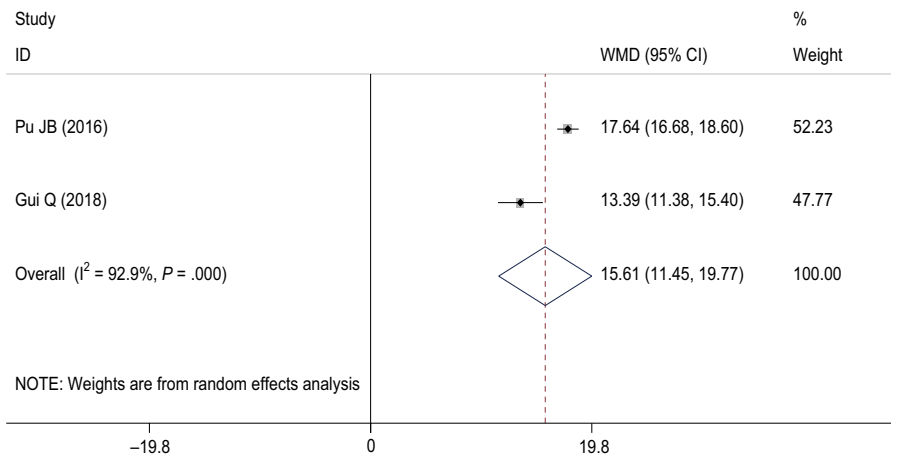


FIGURE 7 Subgroup analysis of the effect of combined treatment of TCM and vitamins on pregnancy rate in comparison with the treatment of vitamins alone based on the different kinds of TCM used in the treatment group



vitality.^{35,60} Recent studies found the therapeutic function of velvet antler polypeptide⁶¹ and total flavonoids of Epimedium⁶² for reproductive system, which may be responsible for the clinical efficacy of *Shenjing* capsule for male infertility. In addition, growing evidence has revealed that TCM can not only regulate the reproductive endocrine system,⁶³ but it can also regulate luteinizing hormone levels,⁶⁴ raise testosterone levels,⁶⁵ boost the function of Sertoli cells and Leydig cells,⁶⁶ prevent oxidative stress,^{67,68}

modulate the proliferation and apoptosis of germ cells,^{67,68} and supplement trace elements.⁶⁹ With the continuous exploration of integrated TCM and Western medicine therapy, its advantages in male infertility treatment will be further highlighted. The aim of this meta-analysis was to provide the latest evidence on the efficacy of TCM combined with vitamins for the treatment of male infertility. The results demonstrated that the combination of TCM with vitamins effectively improved the pregnancy rate and sperm

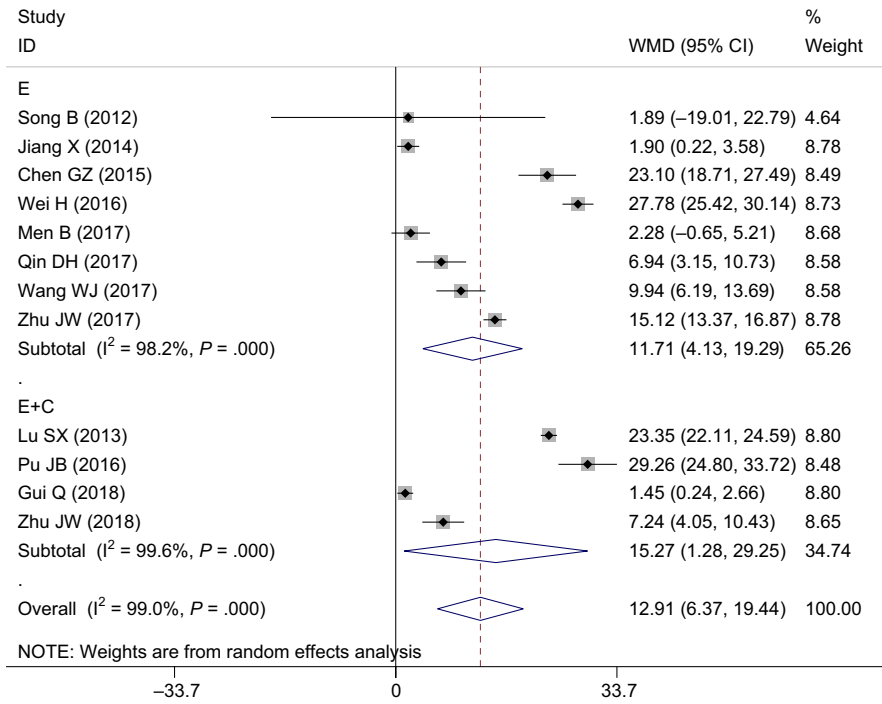


FIGURE 8 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm concentration in comparison with the treatment of vitamins alone based on the treatment of the control group

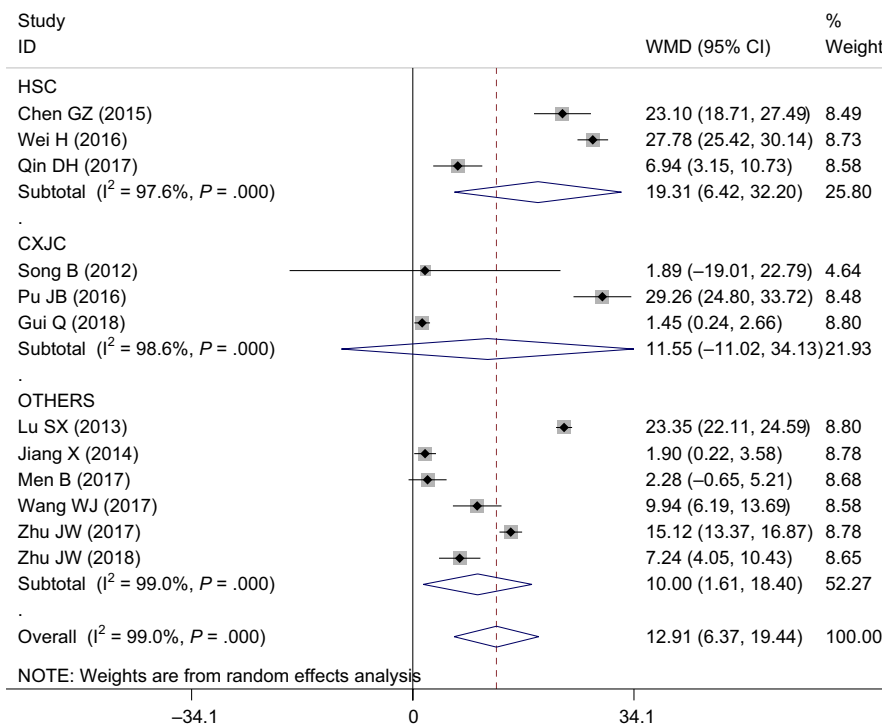


FIGURE 9 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm concentration in comparison with the treatment of vitamins alone based on the different kinds of TCM used in the treatment group

parameters (sperm concentration, sperm viability) when compared with vitamin E alone or vitamin E + C.

Subgroup analysis based on the different kinds of TCM used in the treatment group demonstrated that *Shengjing* capsule, *Huanshao* capsule, and compound *Xuanju* capsule can improve clinical symptoms of male infertility patients. Although the molecular mechanism

for male infertility of these TCM are not fully understood, several studies have been performed to investigate the function of specific herbs or ingredients of TCM for male infertility. For example, *Lycii Fructus* is the common herbs of SJC, HSC and CXJC, and *Lycii Fructus polysaccharides* was proved to protect cultured seminiferous epithelium against time and hyperthermia-induced damage⁵.

FIGURE 10 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm total motility in comparison with the treatment of vitamins alone based on the treatment of the control group

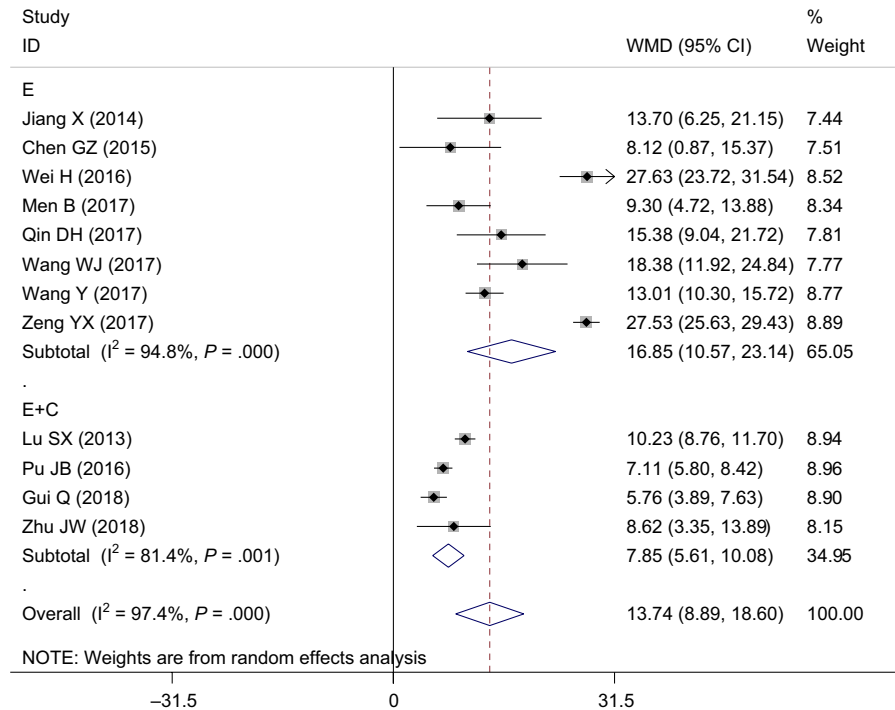
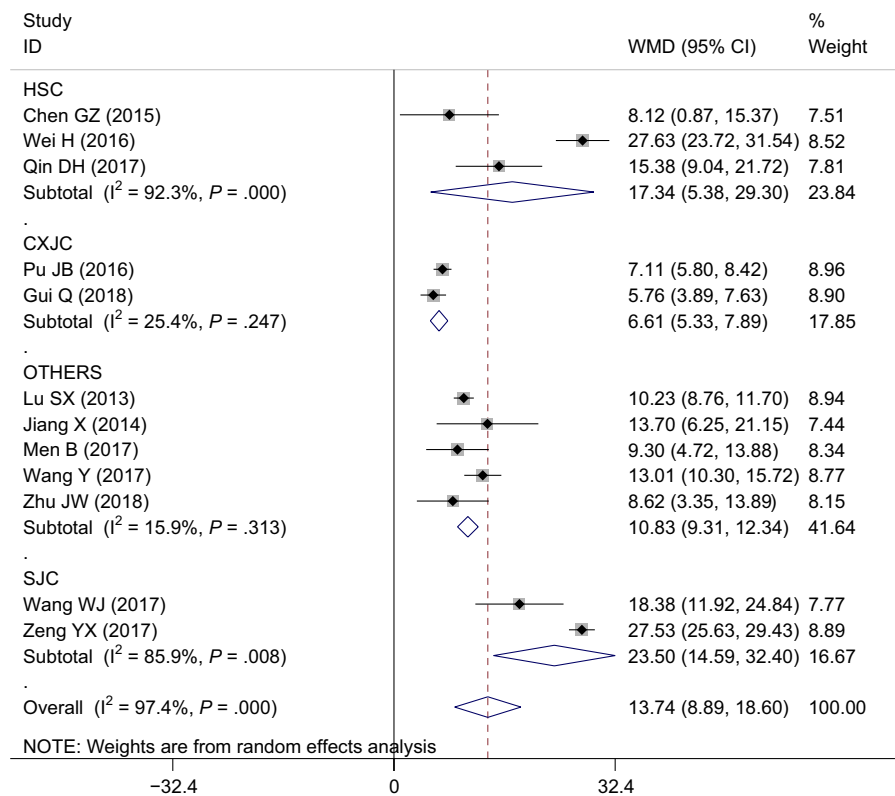


FIGURE 11 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm total motility in comparison with the treatment of vitamins alone based on the different kinds of TCM used in the treatment group



Eucommiae Cortex, a common component of SJC and HSC, is able to enhance the male reproduction function by increasing sperm production.⁷⁰ In addition, function and mechanism of specific herbs of these TCM are also explored. Cornu Cervi Pantotrichum (CCP), the core herbs of SJC, was revealed that the therapeutic mechanism of CCP for treatment of kidney-yang deficiency infertility associated with the increase of acrosomal enzyme level and the regulation of

sexual hormones. Panax ginseng, another herbs of SJC, has a wild therapeutic function for many kinds of disorders, such as cancer, cardiovascular diseases,⁷¹ neurodegenerative disorders,⁷² and reproductive system disorders.⁷³ Ginseng has a abundant of phenolic acids, flavonoids and vitamins,⁷⁴ which may contribute to the therapeutic function on male infertility owing to the antioxidative activity of these compounds.

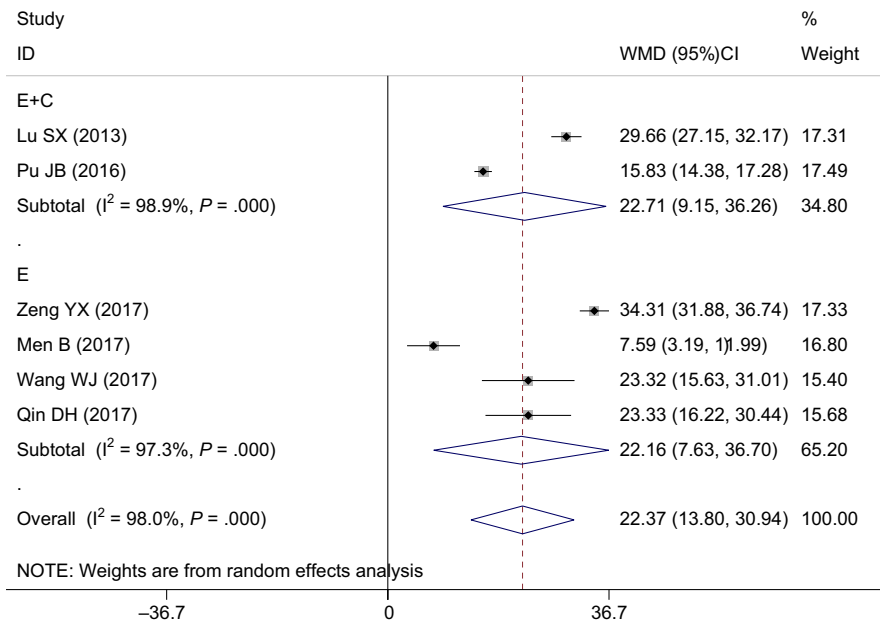


FIGURE 12 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm viability in comparison with the treatment of vitamins alone based on the treatment of the control group

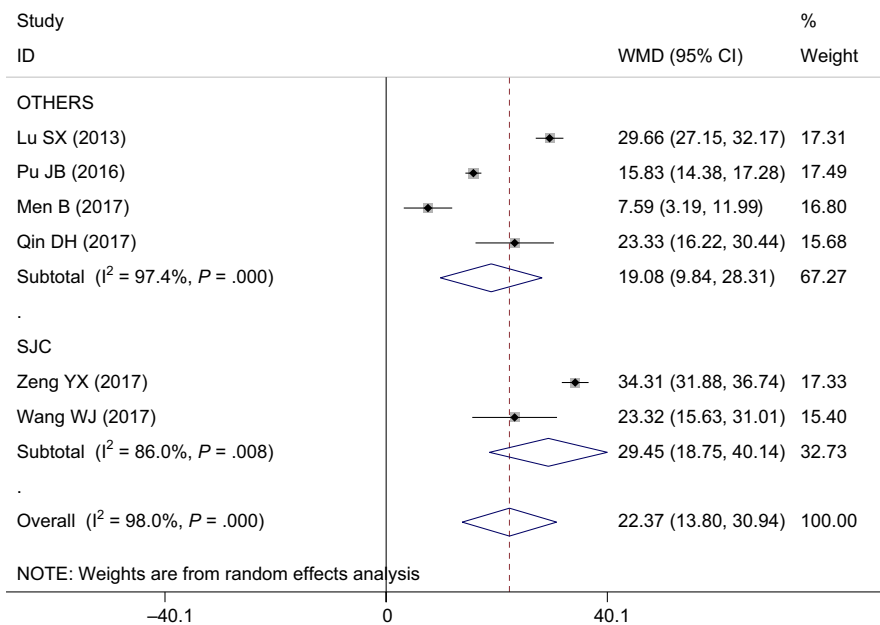


FIGURE 13 Subgroup analysis of the effect of combined treatment of TCM and vitamins on sperm viability in comparison with the treatment of vitamins alone based on the different kinds of TCM used in the treatment group

There are several limitations in this meta-analysis. Firstly, different criteria were adopted to define oligozoospermia in the eligible studies. Specifically, oligozoospermia was classified in terms of values of sperm concentration for total sperm count, respectively, of 5 out of 15 million/mL,⁷⁴ 7 out of 20 million/mL,^{27,29,31,32,35,37,40} and one out of 30 million/mL.⁷⁵ Secondly, this meta-analysis presents obvious heterogeneity, which may be caused by the following: (a) different types of traditional Chinese medicine used in the experimental group; (b) different doses used in the control group, especially in the combination of vitamin C and E, which may contribute to more heterogeneity. Therefore, further studies focused on a specific TCM combined with vitamins are required to confirm the efficiency of the combined strategy, considering the quantitative dose-effect of vitamins.

5 | CONCLUSION

According to the meta-analysis, compared with vitamins alone, the combined use of TCM and vitamins for the treatment of male infertility have more advantages in terms of pregnancy rate and sperm parameters. TCM combined with vitamins is a new regimen worth of further multicenter, larger sample, and long-term clinical studies to explore the best parameters for the strategy.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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