



Traditional Chinese Medicine as a Remedy for Male Infertility: A Review

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Male infertility (MI) is a complex multifactorial disease, and idiopathic infertility accounts for 30% of cases of MI. At present, the evidence for the effectiveness of empirical drugs is limited, and *in vitro* fertilization is costly and may increase the risk of birth defects and childhood cancers. Therefore, affected individuals may feel obliged to pursue natural remedies. Traditional Chinese medicine (TCM) may represent a useful option for infertile men. It has been demonstrated that TCM can regulate the hypothalamic-pituitary-testicular axis and boost the function of Sertoli cells and Leydig cells. TCM can also alleviate inflammation, prevent oxidative stress, reduce the DNA fragmentation index, and modulate the proliferation and apoptosis of germ cells. Furthermore, TCM can supply trace elements and vitamins, ameliorate the microcirculation of the testis, decrease the levels of serum anti-sperm antibody, and modify epigenetic markers. However, the evidence in favor of TCM is not compelling, which has hindered the development of TCM. This review attempts to elucidate the underlying therapeutic mechanisms of TCM. We also explore the advantages of TCM, differences between TCM and Western medicine, and problems in existing studies. Subsequently, we propose solutions to these problems and present perspectives for the future development of TCM.

Keywords: Infertility, male; Medicine, Chinese traditional; Therapeutics

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INTRODUCTION

Infertility is defined as no conception after at least of 12 months of unprotected intercourse. Infertility affects up to 15% of couples, and male fertility has been found to be deficient in no fewer than 50% of infertile couples [1]. According to the 2012 publication of the European Association of Urology Guidelines on Male Infertility (MI), 30% of infertile men suffer from idiopathic infertility [2]. However, evidence-based data are limited in the empirical use of drugs for idiopathic MI

[3], and some drugs have obvious side effects.

The treatment of MI has been revolutionized by advances in assisted reproductive technology, including intrauterine insemination, *in vitro* fertilization (IVF) and even intracytoplasmic sperm injection (ICSI). However, IVF and ICSI procedures are costly and traumatic. Additionally, the use of IVF and/or ICSI techniques may increase the risk of birth defects and childhood cancers in the offspring. Therefore, seeking effective natural remedies to enhance fertility is still the principal alternative for most people affected by infertile-

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ity. In China, Traditional Chinese medicine (TCM) has been employed to treat MI for more than 2000 years, which has influenced the opinions of people in surrounding areas and has made it increasingly appealing to people with infertility. Holism and treatments based on syndrome differentiation are the essence and the basic characteristics of TCM, and utilizing this theory for treating MI yields satisfactory results.

However, the theory of TCM is abstract, and the therapeutic mechanism of TCM is obscure, which has impeded its popularization and aroused skepticism among Western scientists regarding its potency. This review sheds light on the potential therapeutic mechanisms of TCM and includes information regarding the advantages of TCM, the differences between TCM and Western medicine, and problems with existing studies. Subsequently, we propose solutions to the problems and present perspectives for the future development of TCM.

POTENTIAL THERAPEUTIC MECHANISMS OF TRADITIONAL CHINESE MEDICINE

1. Regulation of the reproductive endocrine system

In the theory of TCM, the kidney stores an individual's essence and governs growth, development, and reproduction. TCM regards the kidney as the prenatal source of life; therefore, the fundamental pathogenesis of MI is kidney deficiency, and supplementing the kidney is recognized as the essential therapy for MI. The hypothalamic-pituitary-testicular (H-P-T) axis is a major positive- and negative-endocrine feedback system that regulates testis function. Hormone levels that are either too high or too low are detrimental to spermatogenesis. Modern research has demonstrated that kidney deficiency often manifests with the dysfunction and impaired structure of the H-P-T axis [4]. Experiments have shown that kidney-supplementing formulas could repair the structure and restore the function of the H-P-T axis [5], bidirectionally regulate the hormone levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and eventually increase the level of testosterone (T) to improve the quality of semen.

1) Enhancement of follicle-stimulating hormone levels, regulation of luteinizing hormone levels

Recent studies have indicated that a Chinese herbal monomer regulates the levels of FSH and LH. *Lycium barbarum*, a traditional Chinese medicinal herb, has been used to enhance male fertility for thousands of years, and *L. barbarum* polysaccharide (LBP) is the major active component isolated from *L. barbarum*. Animal experiments have shown that LBP could significantly raise FSH and LH levels in heat-induced model rats [6]. Ginsenosides and their monomers of Rb1 and Rg1 were able to stimulate cultured anterior pituitary cells to secrete FSH and LH *in vitro* [7]. Additionally, semen *Cuscutae* extracts significantly improved FSH and LH levels in adenine-induced model rats [8]. Chinese herbal compounds also have had the same effect. Studies have found that the *liuwei dihuang* pill significantly increased FSH and LH levels in kidney-yin-deficient infertile men [9]. Furthermore, the *wuzi yan-zong* pill (WYP) was found to promote the secretion of FSH and to simultaneously reduce LH levels through a negative feedback pathway [10]. Low levels of FSH imply hypospermatogenesis, and kidney-supplementing and replenishing herbal medicines heightened testicular function in spermatogenesis through upregulation of FSH.

2) Reducing follicle-stimulating hormone levels, regulating luteinizing hormone levels

Previous data suggest that *Schizandra chinensis* polysaccharide extracted from *S. fructus* reduced FSH and LH levels in cyclophosphamide-induced model rats [11]. In addition, animal experiments confirmed that the *jingui shenqi* pill remarkably lowered FSH and LH levels in adenine-induced kidney-yang-deficiency rats [12]. Moreover, the *liuwei dihuang* decoction was capable of decreasing FSH levels and increasing LH levels in model rats treated with gossypol acetate [13]. Abnormally high FSH and LH levels suggest injured spermatogenesis in the testis, and kidney-supplementing and essence-replenishing herbal medicines can repair the damaged histologic structure of the seminiferous epithelium and stimulate spermatogenesis by down-regulating FSH levels.

3) Raising testosterone levels

In addition to regulating the H-P-T axis to raise T levels [8-13], modern pharmacological studies have

shown that echinacoside extracted from *Cistanche tubulosa* and *Cistanche tubulosa* itself significantly enhanced testosterone biosynthesis by increasing the expression of key steroidogenic enzymes, including steroidogenic acute regulatory protein (StAR), cytochrome P450 side chain cleavage (CYP11A1), 3 β -hydroxysteroid dehydrogenase (HSD), 17 β -HSD, and CYP17A1 [14]. This suggests that kidney-supplementing herbal medicines elevate T levels *via* multiple targets and pathways.

4) Regulating follicle-stimulating hormone and luteinizing hormone levels bidirectionally

A prospective controlled study showed that the *bushen shengjing* pill increased LH levels in kidney-yang-deficient infertile men, and decreased FSH levels in kidney-yin-deficient and kidney-yin and -yang-deficient men [15]. The results from this study and the studies mentioned in the previous sections suggest that TCM regulates FSH and LH level bidirectionally, maintaining endocrine homeostasis.

2. Boosting the function of Sertoli cells and Leydig cells

Sertoli cells (SCs) play a central role in spermatogenesis. A reduction in the number of SCs leads to a proportional decrease in the number of germ cells and Leydig cells (LCs), with detrimental effects on fertility [16]. SCs secrete androgen-binding protein under the regulation of FSH, while LH stimulates LCs to synthesize T. These 2 processes cooperate to maintain normal spermatogenesis. Experiments have shown that TCM promoted the proliferation of SCs and LCs, elevated the levels of inhibin B and T, and eventually facilitated the progression of germ cells to spermatozoa.

The WYP is an essential formula for the treatment of MI. Previous studies have demonstrated that the WYP could dramatically enhance the activity of cytochrome c oxidase in SCs [17] and inhibit the overexpression of Cox7a2 in SCs [18]. Additionally, the WYP prominently elevated levels of serum inhibin B in model rats induced by multiglycosides of *Tripterygium wilfordii* Hook F [19]. WYP treatment also increased vimentin expression and repaired the cytoskeleton in SCs [20], and additionally activated the Akt signal transduction pathway and upregulated p-Akt expression to induce proliferation of SCs [21]. Notably, *liuwei dihuang* pill extract was also capable of stimulating SCs to proliferate [22].

Previous studies have suggested that *yangjing* capsule (YC) extract could significantly upregulate testosterone synthesis in LCs *via* the Nur77 pathway [23]. Moreover, icariin treatment significantly reduced apoptosis and promoted the proliferation of LCs [24]. Meanwhile, icariin was found to stimulate the proliferation of SCs by activating the ERK1/2 signal pathway and upregulating the mRNA expression of FSH receptor and claudin-11 in SCs [25,26].

3. Preventing oxidative stress

In recent decades, problems including infection, environment pollution, and lifestyle have increased, and cellular damage caused by oxidative stress (OS) has attracted attention. Excessive reactive oxygen species (ROS) attack the membrane and DNA of sperm cells, leading to decreased fluidity and impeded permeability of the sperm plasma membrane. This results in an augmented DNA fragmentation index (DFI) and apoptosis rate, ultimately resulting in infertility. TCM has been demonstrated to scavenge ROS, improve the antioxidant capacity of the seminal plasma, lower sperm DFI, and protect the male reproductive system from the lesions induced by ROS.

Pharmacological studies have indicated that *Morinda officinalis*, semen *Cuscutae*, *Lycii fructus*, and *Schisandrae fructus* could increase superoxide dismutase (SOD) levels and reduce the malondialdehyde (MDA) content in the testis to protect the sperm from OS [27-30]. *Wuzi yanzong* compound extract improved the survival rate of SCs, elevated the activity of SOD, and reduced the MDA content in SCs injured by H₂O₂ [31]. The *jinkui shenqi* pill increased the activity of SOD and decreased MDA levels in serum from model rats with infertility induced by hydrocortisone [32]. Furthermore, experiments by Zhou et al [33] and Weng et al [34] on rats induced by cadmium chloride and cigarette smoke indicated that kidney-supplementing and blood-quickening formulas were capable of significantly raising the activity of SOD and glutathione reductase (GSH) in the testis, while lowering MDA levels and sperm DFI [33,34].

OS is a common consequence of spermatogenic damage, and TCM remedies MI by means of antioxidation.

4. Modulating the proliferation and apoptosis of germ cells

SCs are the paracrine regulators of spermatogenesis

and secrete glial cell line-derived neurotrophic factor (GDNF), which is an important growth factor that modulates the differentiation and self-renewal of spermatogonia [35]. Animal experiments have shown that *Cynomorium songaricum* extracts dramatically increased the expression of GDNF (mRNA and protein) in SCs [36]. *In vitro* cell culture experiments indicated that YC extract could act on GDNF to upregulate POU3F1 expression by triggering the activation of the PI3K/AKT pathway, ultimately stimulating spermatogonial stem cell proliferation [37]. Furthermore, matrimony vine treatment was able to facilitate the division and differentiation of spermatogonia and propagation of primary spermatocytes [38].

Apoptosis is commonly known as programmed cell death. The apoptosis of germ cells is an important testicular self-regulation process. However, high levels of apoptosis cause MI. Researchers have suggested that LBP decreased the expression levels of caspase-3, increased the Bcl-2/Bax-43 ratio and the testicular antioxidant enzyme activity of SOD and GSH, and eventually inhibited the apoptosis of testicular germ cells in streptozotocin-induced diabetic mice [29]. The *jingui shenqi* pill reduced the expression of Fas/FasL to inhibit germ cell apoptosis in a kidney-yang-deficiency mice model [39]. Furthermore, *wuzi yanzong* formula treatment downregulated protein expression levels of Bax and caspase-3 [40], and upregulated the expression of Bcl-2, which modulates the p53 signal pathway and the H-P-T axis. Ultimately, T levels were increased, inhibiting apoptosis in germ cells [41,42].

Therefore, TCM prompts the proliferation of spermatogonia and inhibits the apoptosis of germ cells to treat MI.

5. Supplementing trace elements

Zinc and selenium are essential trace elements for testicular development and spermatogenesis. Zinc is a component of SOD and plays an important role in antioxidation [43], DNA repair mechanisms, and maintaining genomic stability [44]. Selenium is a critical component of phospholipid hydroperoxide glutathione peroxidase, which shields membrane lipids from oxidation. Selenium is also a constituent of the mitochondrial sheath of spermatozoa [45]. Manganese is also an essential trace element that acts as a potent trigger of sperm motility by increasing adenylate cyclase activity [46]. Substantial evidence has demonstrated that

infertile men are likely to have a zinc or selenium deficiency, and moderate supplementation of zinc and selenium improved the semen quality of infertile men [47,48]. Domestic studies have shown that kidney-supplementing herbal medicines such as *Epimedium* and *Curculigo* were rich in zinc and manganese [49], while cooked *Rehmannia* had high levels of selenium [50]. Therefore, TCM supplements zinc, selenium, and manganese to remedy MI.

6. Ameliorating the microcirculation of the testis

Spermatogenesis is a highly metabolic process that is susceptible to disruptions in the supply of nutrients and oxygen. Sufficient blood supply for the testis is a prerequisite for normal spermatogenesis. Previous studies have advanced the concept of treating male disease from the perspective of blood stasis [51]. Zhou and Xie [51] insisted that blood-quickening medicines ameliorated the microcirculation and metabolism of the testis and ensured an adequate nutrient supply for the testis. Blood-quickening medicine alleviated inflammatory effusion and inflammation and unblocked the vas deferens.

Animal experiments have suggested that *bushen huoxue* formulary treatment could upregulate the protein expression of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2) and Rous sarcoma oncogene (Src) *via* the VEGF/VEGFR2 pathway to facilitate testicular microcirculation in cyclophosphamide model mice [52]. A randomized controlled trial of 128 infertile men indicated that kidney-supplementing and blood-quickening methods dramatically raised sperm concentration and motility more effectively than other therapeutic methods [53]. Kidney-supplementing and blood-quickening formulas also improved semen quality and pregnancy rate.

7. Improving semen quality and the pregnancy rate

1) Improving seminal plasma quality

Fructose and alpha-glucosidase are the major components of seminal plasma. Fructose is the energy source for sperm; it is metabolized into adenosine triphosphate by glycolysis and is associated with sperm motility. Alpha-glucosidase can catalyze the degradation of the glycogen stores of sperm in the epididymis, supplying

energy for the maturation and motion of sperm. Studies by Chen et al [54] found that *jiawei wuziyanzong* decoction treatment increased fructose levels in seminal plasma in infertile men with asthenozoospermia. We thought that seed herbal medicines contained numerous vitamins and fructose and could elevate the fructose level in seminal plasma, consequently improving sperm motility. Another study showed that *shengjing* prescription treatment significantly increased the levels of seminal plasma alpha-glucosidase and fructose [55]. Therefore, TCM can elevate sperm motility by increasing fructose and alpha-glucosidase levels in seminal plasma.

2) Improving sperm quality

A randomized controlled study showed that both *jiawei wuzi yanzong* decoction and *liuwei dihuang* pill treatments improved sperm vitality and motility in kidney-yin-deficient infertile men [9], which is consistent with previous studies. A multicenter study found that both the *qilin* pill and the WYP could effectively improve the seminal concentration and sperm motility in oligoasthenozoospermia patients, which is in accordance with the results from treatment with the *shengjing* prescription [56]. In addition, *shengjing* prescription treatment improved normal sperm morphology and acrosin activity, reducing sperm DFI [55]. Because of the differences in basic features of the included studies, 2 meta-analyses yielded inconsistent results. One meta-analysis suggested that TCM could improve sperm concentration, sperm motility, and the pregnancy rate more effectively than Western medicine [57]. However, another meta-analysis indicated that TCM and Chinese-Western combined therapy significantly enhanced the pregnancy rate. That study only performed a descriptive analysis on semen parameters due to the high heterogeneity of the included studies [58]. In terms of the efficacy of acupuncture, a meta-analysis showed that acupuncture was able to increase grade A sperm motility and sperm concentration, but had no significant impact on the pregnancy rate [59].

8. Others

1) Alleviating inflammation

Mycoplasma and *Chlamydia* infections of the male genital tract are a common etiology of MI [60], resulting in decreased sperm motility and increased abnor-

mal sperm counts. Inflammation leads to leukocyte infiltration into the seminal plasma, and the leukocytes release excessive ROS, which attack the plasma membrane and DNA of sperm. Experiments have shown that *Phellodendron*, *Scutellaria*, and *Taraxacum* were effective at killing mycoplasma and chlamydia *in vitro*, while *zhibai dihuang* decoction treatment increased protein and mRNA expression levels of interleukin-2 and inhibited the protein and mRNA expression of tumor necrosis factor alpha in rats infected by *Ureaplasma urealyticum* [61]. Hence, TCM not only kills pathogenic microorganisms directly, but also regulates cytokine secretion to treat infections indirectly.

2) Decreasing the level of anti-sperm antibody

Sperm is a specific antigen that causes the human body to generate anti-sperm antibody (AsAb) when the immune system is exposed to it. AsAb decreases sperm motility [62], impedes sperm from undergoing capacitation and acrosome reactions, and interferes with sperm-oocyte recognition and fusion [63]. Animal experiments have suggested that *zhibai dihuang* decoction treatment could remarkably reduce serum levels of AsAb in rats [64]. While the concrete mechanism is obscure, TCM may eliminate testicular immunological complexes and regulate the ratio of CD₄/CD₈ T cells to cure immune-induced infertility [65,66].

3) Modifying epigenetic markers

Epigenetics is the study of modification of gene expression without changing the DNA sequence, and epigenetic processes include DNA methylation, histone modification, and chromatin remodeling [67]. Normal H19 gene expression is crucial to spermatogenesis, and many patients with oligoasthenoteratozoospermia had hypomethylation at the H19 locus [68]. A study by Lian et al [69] indicated that *shengjing* formula treatment could improve sperm concentration, motility and clinical pregnancy rate by reducing the loss rate of the H19 imprinted gene. Research into TCM in the field of epigenetics is limited and needs to be strengthened.

CONCLUSIONS

Overall, the effectiveness of TCM for MI has been confirmed by numerous studies, but many problems exist in these studies. The advantages of TCM and the differences between TCM and Western medicine, as

Table 1. Potential therapeutic mechanisms of TCM

Function of TCM	Chinese herbal medicines and monomers	Potential therapeutic mechanisms of TCM
Regulating the reproductive endocrine system		
Enhancing FSH levels, regulating LH levels	Ginsenosides and Rb1, Rg1 LBP, <i>semen Cuscutae</i> extract <i>Liuwei dihuang</i> pill WYP	Stimulated cultured anterior pituitary cells to secrete FSH and LH <i>in vitro</i> Significantly increased FSH and LH levels Promoted the secretion of FSH and simultaneously reduced LH levels
Reducing FSH levels, regulating LH levels	<i>Schizandra chinensis</i> polysaccharide <i>Jingui shenqi</i> pill <i>Liuwei dihuang</i> decoction	Reduced FSH and LH levels Decreased FSH levels and increased LH levels
Raising T levels	<i>Cistanche tubulosa</i>	Enhanced testosterone biosynthesis by increasing the expression of key steroidogenic enzymes, including StAR, CYP11A1, 3 β -HSD, 17 β -HSD, and CYP17A1
Regulating FSH and LH levels bidirectionally	<i>Bushen shengjing</i> pill	Increased LH levels in kidney-yang-deficient infertile men, and decreased FSH levels in kidney-yin-deficient and kidney-yin and -yang-deficient men
Boosting the function of SCs and LCs	WYP <i>Liuwei dihuang</i> pill extract YC extract Icariin	Enhanced the activity of cytochrome c oxidase, inhibited the overexpression of Cox7a2 in SCs, repaired the cytoskeleton of SCs, upregulated p-Akt expression Stimulated SCs to proliferate Upregulated testosterone synthesis in LCs <i>via</i> the Nur77 pathway Reduced apoptosis and promoted the proliferation of LCs, stimulated the proliferation of SCs by activating the ERK1/2 signal pathway and upregulating the mRNA expression of FSH receptor and claudin-11 in SCs
Preventing oxidative stress	<i>Morinda officinalis</i> , <i>Cuscutae semen</i> <i>Lycii fructus</i> , <i>Schisandrae fructus</i> Wuzi yanzong <i>Jinkui shenqi</i> pill Qilin pill	Increased SOD levels, reduced the MDA content in the testis Elevated the activity of SOD, and reduced the MDA content in SCs Increased the activity of SOD and decreased MDA levels in serum Raised the activity of SOD and GSH in the testis, lowered the MDA level and the sperm DFI
Modulating the proliferation and apoptosis of germ cells		
Prompting the proliferation of spermatogonia	<i>Cynomorium songaricum</i> extracts Matrimony vine YC extract	Increased the expression of GDNF (mRNA and protein) in SCs Facilitated the division and differentiation of spermatogonia and propagation of primary spermatocyte Activated the PI3K/AKT pathway, upregulated POU3F1 expression, ultimately stimulated the spermatogonial stem cells proliferation
Inhibiting the apoptosis of germ cells	LBP <i>Jingui shenqi</i> pill <i>Wuzi yanzong</i> formula	Decreased the expression of caspase-3, increased the Bcl-2/Bax 43 ratio, and the testicular enzyme activity of SOD, GSH Reduced the expression of Fas/FasL Downregulated the protein expression of Bax and Caspase-3, upregulated the expression of Bcl-2, modulated p53 signal pathway, enhanced T levels
Supplementing trace elements	<i>Epimedium</i> , <i>Curculigo</i> Cooked <i>Rehmannia</i>	Were rich in zinc and manganese Had high levels of selenium

Table 1. Continued

Function of TCM	Chinese herbal medicines and monomers	Potential therapeutic mechanisms of TCM
Ameliorating the microcirculation of the testis	<i>Bushen huoxue</i> formular	Upregulated the protein expression of VEGFR2 and Src via the VEGF/VEGFR2 pathway
	<i>Shengjing</i> decoction II	Ameliorated the microcirculation of the testis and ensured an adequate nutrient supply for the testis
Improving the semen quality and pregnancy rate		
Improving seminal plasma quality	<i>Jiawei wuziyanzong</i> decoction	Increased fructose and alpha-glucosidase levels in seminal plasma
	<i>Shengjing</i> prescription	
Improving sperm quality	<i>Qilin</i> pill, WYP, <i>Shengjing</i> prescription	Improved sperm concentration, motility, normal sperm morphology, acrosin activity, and reduced sperm DFI
Others		
Alleviating the inflammation	<i>Phellodendron</i> , <i>Scutellaria</i> , <i>Taraxacum</i>	Were effective at killing <i>Mycoplasma</i> and <i>Chlamydia</i> <i>in vitro</i> Increased the protein and mRNA expression of IL-2, inhibited the protein and mRNA expression of TNF- α
	<i>Zhibai dihuang</i> decoction	
Decreasing the level of anti-sperm antibody	<i>Zhibai dihuang</i> decoction	Remarkably reduced serum level of AsAb
	<i>Mianbu</i> formula I	Eliminated testicular immunological complex
	Acupuncture	Regulated the ratio of CD ₄ /CD ₈ T cell
Modify epigenetic markers	<i>Shengjing</i> formula	Reduced the loss rate of H19 imprinted gene

TCM: Traditional Chinese medicine, FSH: follicle-stimulating hormone, LH: luteinizing hormone, T: testosterone, LBP: *Lycium barbarum* polysaccharide, WYP: *wuzi yanzong* pill, StAR: steroidogenic acute regulatory protein, CYP11A1: cytochrome P450 side chain cleavage, HSD: hydroxysteroid dehydrogenase, SCs: Sertoli cells, LCs: Leydig cells, YC: *yangjing* capsule, SOD: superoxide dismutase, MDA: malondialdehyde, GSH: glutathione reductase, DFI: DNA fragmentation index, GDNF: glial cell line-derived neurotrophic factor, VEGFR2: vascular endothelial growth factor receptor 2, Src: Rous sarcoma oncogene, VEGF: vascular endothelial growth factor, IL: interleukin, TNF: tumor necrosis factor, AsAb: anti-sperm antibody.

well as unsolved problems and solutions, are summarized below.

1. Advantages of Traditional Chinese medicine and potential mechanisms

We propose the following potential mechanisms of TCM treatments of MI: regulation of the H-P-T axis, boosts to the function of SCs and LCs, alleviation of inflammation, prevention of OS, and reduction of the DFI. TCM also acts to modulate the proliferation and apoptosis of germ cells, supply trace elements and vitamins, ameliorate the microcirculation of the testis, decrease AsAb levels, and modify epigenetic markers (Table 1, Fig. 1). TCM has effects on multiple targets, systems, and pathways to improve sperm parameters and the pregnancy rate. The therapy of TCM focuses on overall balance by improving the condition of the body and regulating the testis, instead of complementing a certain hormone directly. Moreover, natural products have few side effects. This may be the underlying mechanism for the bidirectional effects of TCM on disordered hormone levels.

2. Problems and insufficiency

At present, however, the evidence in favor of TCM is not compelling. The studies of TCM for MI are almost all domestic and contain small sample sizes. They are also not blinded randomized controlled trials, and do not contain detailed descriptions of the methods of random sequence generation and allocation concealment; therefore, the overall quality score for methodology is low. The absence of uniform standards for the evaluation of TCM efficacy causes considerable heterogeneity. In addition, most TCM studies lack reports of adverse effects and mainly target infertile men with oligoasthenozoospermia, neglecting patients with azoospermia and teratozoospermia. Additionally, the extraction of effective components and reforms in the preparation of herbal medicines are lagging, which hinder its development and popularization.

3. Solutions and outlook

In our view, evidence-based-medicine methods must be applied to assess the efficacy of TCM in modern times. The refinement of herbal medicine needs to be promoted. Large-scale, multicenter, and nationalized

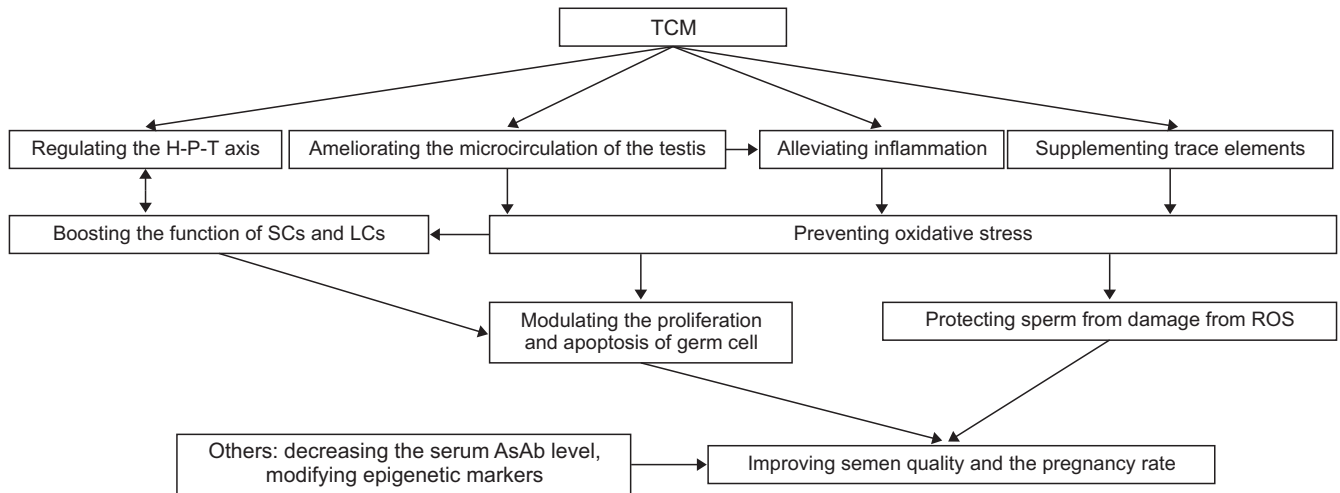


Fig. 1. Potential therapeutic mechanisms of TCM. TCM: Traditional Chinese medicine, H-P-T: hypothalamic-pituitary-testicular, SCs: Sertoli cells, LCs: Leydig cells, ROS: reactive oxygen species, AsAb: anti-sperm antibody.

rigorous randomized controlled trials and further investigations of Chinese herbal monomers will elucidate their therapeutic mechanisms at the molecular and cellular levels, verifying the effectiveness of TCM.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization, Design and Methodology: Zhou SH. Writing-original draft and Editing: Deng YF. Writing-review: Deng YF. Critical revision of the manuscript: all authors. Approval of final manuscript: all authors.

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