



Effectiveness of Ginseng in Treating Erectile Dysfunction: A Review Paper

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Abstract

Early identification and treatment of erectile dysfunction (ED) and ED related comorbidities, including hypertension, diabetes mellitus, and hyperlipidemia is crucial in improving the quality of life of men and their partners. To date, the main treatment options for ED can be divided into pharmacological and surgical interventions. These treatments include oral phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil), intraurethral or intracavernosal alprostadil, vacuum devices and penile prosthesis. Although considerable advances have been made, there seems to be a high dropout rate of the above treatment due to cultural restrictions and taboos. Subsequently, these patients would seek herbal dietary supplements such as ginseng as an alternative. Even though several studies have proved that ginseng is ideal in treating ED, the published trials on humans were not robust, and there is a lack of exploration of subjective outcomes. This literature review aimed to synthesize and critically appraise clinical and scientific literature on the effects of ginseng in managing ED. In total, 7 studies were included and reviewed. It was concluded that ginseng is a feasible alternative to currently available practices in treating ED due to a significant improvement in International Index of Erectile Function (IIEF)-5 scores and its safety profile. There is a higher likelihood to consider ginseng as an alternative therapy if more studies with larger-scaled clinical trials and higher standards on the safety and efficacy of ginseng are conducted in the future.

Subject Areas

Andrology

Keywords

Erectile Dysfunction, Ginseng, Effectiveness, Treatment

1. Introduction

Interest surrounding erectile dysfunction and its treatments has been persistent throughout centuries as penis erection has always represented man's sexual prowess. Erectile dysfunction (ED) is the recurrent or persistent incapacity to maintain or achieve an adequate penile erection to obtain satisfactory sexual performance [1]. Worldwide, around 150 million men are unable to either obtain or sustain an erection. Age is proven to have the strongest association with ED. Research showed that the occurrence of moderate ED doubles from 17% to 34% and that severe ED triples from 5% to 15% in men aged 40 to 70 [2]. ED is often caused by psychogenic and organic factors, where 80% of cases have an organic aetiology [1]. Atherosclerotic disease such as diabetes mellitus, hypertension and heart disease is reckoned to account for 40% of cases [3] [4] [5]. Sexual dysfunctions are also common in haemodialysis patients and male kidney transplant recipients [6]. From a clinical point of view, ED also acts as an indicator of systemic endothelial dysfunction, where ED may be used as an early marker for cardiovascular events [1] [5]. Therefore, it is important for a primary care physician to identify ED early as other modifiable risk factors and comorbidities could be treated simultaneously when a patient presents with ED [7]. The quality of life of men and their partners could be improved with the early intervention [8].

Reflexogenic and psychogenic are the two distinct central erection mechanisms of the penile erection. Reflexogenic erection is achieved by exteroceptive stimulation of the penile shaft and is regulated by a sacral spinal nerve mechanism. Psychogenic erection utilizes the limbic system of the brain and is initiated by sensory and imaginative stimuli [1] [9] [10].

Relaxation of intracavernosal smooth muscle is an essential process in penile erection. The corpora cavernosa becomes engorged with blood, compressing on the emissary veins, thus decreasing venous outflow from the penis [11]. When there is sexual stimulation, excitatory signals originate in the brain, and the signals travel through the parasympathetic nervous system to parasympathetic nerves of the S2-S4 sacral plexus. The signals travel to cavernosal nerves in the penis from the sacral plexus, which release nitrous oxide (NO) from its terminal end. This nitrous oxide initiates an erectile process, whereas nitrous oxide from endothelial cells are responsible to maintain it. When nitrous oxide enters the intracavernosal smooth muscle, the muscle relaxes, causing an arterial flow to increase with concurrent veno-occlusive activity. All these result in a rigid erection. When corporal smooth muscle contracts again, the process reverses. ED arises if pathology from any of the above processes arises [12].

Currently, the main treatment options for ED can be divided into pharmacological and surgical interventions [13] [14]. Examples of pharmacotherapy include oral phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil), and the surgical interventions, namely intraurethral or intracavernosal alprostadil, vacuum devices, and penile prosthesis [15] [16] [17] [18]. PDE5-inhi-

bitors act as a first-line therapy as they have favourable safety profiles and are highly effective [19]. Most of the patients respond well to the drug reactions [20]. These drugs prevent cyclic GMP from being neutralised by PDE5 enzyme, thus lengthening the penile erection [20] [21]. Studies demonstrated no significant difference in safety and efficacy among the different types of PDE5-inhibitors [15].

However, treatment failure due to patient and clinician issues and drug allergic reactions forces patients to opt for second-line therapies such as alprostadil and vacuum devices [15] [20]. Alprostadil relaxes the cavernosal smooth muscle through cyclic AMP synthesis, leading to penile erection [22] [23] [24]. Alprostadil remains an excellent treatment option, but fear of needles and severe adverse event, which is penile fibrosis, can limit patient acceptance [15] [17]. Vacuum constriction devices, which are relatively safe, are usually offered to the elders with satisfaction rates ranging between 27% and 94% [15] [16] [17]. The reasons for a low acceptance rate among younger patients include the unnatural erection and delay in erection [15] [17]. Penile prosthesis remains as a last resort in treating ED. It is only recommended when all the medical treatments have failed and when patients have developed a severe allergic reaction to the medication. Due to its invasiveness, high cost, risk of recurrent infections and other complications such as changes in sensation during erection and ejaculation, reduction in and penile length and urethral injury, the penile implant remains as a third-line therapy for ED [15] [17] [25] [26].

Although considerable advances have been made, there seems to be a group of patients who are reluctant to comply with western treatments due to cultural restrictions and taboos, resulting in a high dropout rate of the above treatment [27] [28]. Subsequently, these patients would seek alternatives such as herbal dietary supplements [18]. Among the wide range of herbal products, ginseng, which has a rich medicinal history of over 2000 years, has garnered popularity in treating ED and other ED related comorbidities, including hypertension, diabetes mellitus, and hyperlipidemia [29]. Ginsenosides (GS), the major primary active agents in ginseng, have been shown to enhance nitric oxide (NO) production, thus improving vascular endothelial abnormalities. Research studies postulated that with enhanced nitric oxide synthesis in the endothelium of lung, heart, kidney and corpus cavernosum, ginseng possesses antioxidant and organ-protective action in the human body [30]. Several studies also showed that ginsenosides cause a dose-dependent relaxation of corpus cavernosal smooth muscle in rabbits through the release of nitrous oxide [11] [31] [32] [33] [34]. Choi *et al.* (1995) also concluded that ginseng significantly improved patient satisfaction and penile girth [35].

Nevertheless, insufficient evidence is available to evaluate the exact efficacy of ginseng as the published trials on humans were not robust, and there is a lack of exploration of subjective outcomes. Therefore, we conducted this review aiming to synthesize and critically appraise clinical and scientific literature on the effects of ginseng in managing ED.

2. Efficacy of Ginseng in ED-Related Comorbidities

We analyzed the efficacy of Ginseng in ED-related comorbidities including hypertension, diabetes mellitus and hyperlipidemia.

2.1. Hypertension

Hypertension can be a risk factor for ED; similarly, ED can be one of the early signs of hypertension. During hypertension, vasculature structural changes such as increase in collagen deposition and decrease in lumen diameter can be seen. These vascular changes may affect penile vasculature, resulting in diminished blood supply to the penis. Impairment in the balance between vasodilators and vasoconstrictors due to sustained release of procontractile agents could also be found during hypertension. These agents widely affect the erectile structures as there will be a widespread release of reactive oxygen species, which is detrimental to endothelium and smooth muscle [36] [37].

Research demonstrated that consumption of ginseng causes transient vasodilation and in some cases, it is followed by vasoconstriction, culminating in a rise in blood pressure. While ginseng can elevate blood pressure, this generally occurs with low blood pressure, which helps to restore blood pressure to normal. Blood circulation has been shown to be improved with the vasodilation action of *Panax ginseng*. Korean red ginseng, which has lower doses of GS, has an antihypertensive effect. GS activates eNOS activation, therefore, causing a surge in NO production. Research proposed that GS activates the calcium-activated potassium channels in vascular smooth cells, which decreases calcium influx, thus vasodilation occurs [38]. Furthermore, when aqueous extracts of *Panax notoginseng* and *salvia miltiorrhiza* were mixed together, the mixture demonstrated antihypertensive effects by inhibiting arterial myogenic responses. In a nutshell, ginseng improves blood circulation and normalizes blood pressure [39].

2.2. Diabetes Mellitus

ED is common in diabetic men with a prevalence of $\geq 50\%$ [40]. In diabetes-induced erectile dysfunction (DIED), elevated advanced glycation end-products (AGEs) lead to atherosclerosis and vascular thickening. Moreover, sustained release of oxygen free radicals give rise to oxidative cell damage and smooth muscle relaxation impairment. Levels of NO synthesis are significantly impaired in DIED, culminating in cavernosal and smooth muscle dysfunction. Diabetes is known to manifest microvascular complications, mostly peripheral and autonomic neuropathy [41]. This situation is documented by longer latency in abnormal bulbar urethral and urethroanal reflexes [42].

The hypoglycemic effect of ginseng's active ingredient has been known since the 1980s. GS was revealed to activate adenosine monophosphate-activated protein kinase (AMPK), which suppresses hepatic gluconeogenesis. AMPK causes a surge in glucose uptake into skeletal or adipose tissue and stimulates glucose

metabolism by improving mitochondrial biogenesis, where people with type 2 diabetes have mitochondrial function deficit. Excess amounts of triglyceride in muscles, which is associated with insulin resistance, could be reduced through activation of AMPK. Besides, ginseng increases insulin production and ensures cell viability in pancreatic islet cells [43]. Recent animal studies revealed that ginseng enhances glucose transporter-2 proteins in the livers of mice and glucose uptake into sheep red blood cells [44]. In short, ginseng holds promise as a therapeutic agent for diabetes treatment.

2.3. Hyperlipidemia

The lipid profile in ED patients predominantly shows high levels of total cholesterol/high-density lipoprotein (TC/HDL) and low levels of high-density lipoprotein (HDL). Higher levels of HDL appeared to be beneficial as it carries cholesterol away from tissues to the liver, where it can be excreted. Hyperlipidemia causes arterial stenosis and occlusion, which further exacerbates ED. The peripheral nerves, endothelial cells, and smooth muscles for penile erection are further damaged by hyperlipidemia [45]. Hyperlipidemia is also linked to decrease in NO production, followed by impairment of endothelium relaxation, leading to failure of penile relaxation during erection [46].

Studies have shown that ginseng improves lipid profile by lowering serum total cholesterol, LDL, and triglyceride levels while elevating serum HDL levels [47]. AMPK, which is activated through a rise in intracellular AMP: ATP ratio, plays a role in ameliorating hyperlipidemia. AMPK activation increases ketogenesis and fatty acid oxidation with concurrent inhibition of fatty acids, hepatic lipogenesis and cholesterol synthesis. The action of ginseng in improving lipid profile can be seen in an animal study. The study, conducted by Yuan *et al.* (2010), showed that saponins increase cholesterol excretion through acid bile formation, thus decreasing blood cholesterol levels in prolonged cholesterol-fed rabbits [48]. Another animal study showed that saponins as GS promote the synthesis of LDL receptors in rats, thus increasing LDL receptors. Furthermore, present results reported that long-term administration of ginseng in obese patients improved HDL level while cholesterol level was decreased [49]. After all, ginseng has beneficial effects as an anti-hyperlipidemic agent.

3. Efficacy of Ginseng in Treating ED

We review seven studies [2] systematic reviews and 5 randomized controlled trials (RCTs)] to examine the efficacy of ginseng in treating ED. Most of these trials were conducted in Asian populations, mainly Korean. In these trials, the efficacy of ginseng on ED was determined using the International Index of Erectile Function (IIEF) [27] [50]-[55], Rigiscan [27] [51], questionnaires related to erectile function [51] [54], global assessment questionnaire (GAQ) [53] and premature ejaculation diagnostic tool (PEDT) [52]. The main findings and conclusion is presented in **Table 1**.

Table 1. List of included articles in this review with main study findings and conclusion.

Study, year, country	Design	Participant characteristics	Intervention	Main outcomes	Author's conclusion
systematic review/Meta-analysis					
Jang <i>et al.</i> [54], 2008 Korea	Systematic review	7 relevant trials which evaluated 363 men aged from 24 - 70 years old who had ED for 1 to 30 years	In 4 trials: 600 mg red ginseng 3 times daily In 2 trials: 900 mg red ginseng In 1 trial: 1000 mg red ginseng	<ul style="list-style-type: none"> • International Index of Erectile Function (IIEF) • Watts sexual function questionnaire • global efficacy question (mainly for erection sufficient for normal satisfaction) • author made structural interview questionnaires related to erectile function 	6 RCTs showed therapeutic efficacy of red ginseng compared with placebo control.
Borrelli <i>et al.</i> [50], 2018 Italy	Systematic review and meta-analysis	2080 patients with ED	12 mono preparations: 5 ginseng, 3 saffron, 1 Pinus pinaster 1 Lepidium meyenii, 2 Tribulus terrestris, 7 evaluated formulations, 5 dietary supplements with pure compounds	International Index of Erectile Function [IIEF]-5 or IIEF-15	Ginseng significantly improved ED. <i>P. pinaster</i> and <i>L. meyenii</i> showed positive results, and saffron and T. terrestris treatment produced mixed results. Several herba formulations were associated with a decrease of IIEF-5 or IIEF-15.
Randomised controlled trials (RCTs)					
Andrade <i>et al.</i> [53], 2007 Brazil	Double-blind, placebo-controlled study (RCT)	60 patients with mild or mild to moderate ED	1000 mg of Korean Red Ginseng(KRG) or a placebo 3 times daily	<ul style="list-style-type: none"> • International Index of Erectile Function [IIEF]-5 • global assessment questionnaire (GAQ) 	The IIEF-5 score after the treatment was significantly higher in the KRG group compared with that before the treatment. There was no difference before and after the treatment in the placebo group. As for the GAQ, there were significant improvements in erection in the treatment group as compared to placebo.
Choi <i>et al.</i> [51], 1995 Korea	RCT	33 patients with borderline organic and psychogenic ED	Korean red ginseng (daily) or a placebo for 3 months	<ul style="list-style-type: none"> • Questionnaire to survey self-reported status of libido, erection, ejaculation, sexual performance, satisfaction rate of intercourse • Rigiscan 	All parameters surveyed have shown improvements compared to the controls. 4 out of 6 patients showed rigidity of more than 70% after consumption of ginseng.
Choi <i>et al.</i> [52], 2012 Korea	multicenter, placebo - controlled, double-blind clinical study (RCT)	119 men with mild-to-moderate ED	4 tablets of either standardized Korean ginseng berry (berry SKGB, 350 mg ginseng berry extract per tablet), or placebo, daily, for 8 weeks	<ul style="list-style-type: none"> • International Index of Erectile Function (IIEF)-15 • premature ejaculation diagnostic tool (PEDT) 	IIEF-15 score increased significantly in the SKGB by the 8th week. PEDT scores significantly improved in the SKGB group after 4 and 8 weeks of treatment.

Continued

Kim <i>et al.</i> [55], 2009 Korea	double-blind, placebo-controlled study (RCT)	143 patients with ED	1000 mg of tissue-cultured mountain ginseng extract (TGME) or 1000 mg of placebo twice a day for 8 weeks	Korean version of International Index of Erectile Function (IIEF) questionnaire	The scores of 5 domains of IIEF after medication were significantly higher than baseline scores in the group treated with TGME. No significant improvement was observed in the placebo group.
Hong <i>et al.</i> [27], 2002 Korea	double-blind, placebo controlled, crossover study (RCT)	45 patients with ED	900 g of Korean red ginseng or placebo 3 times daily (8 weeks on treatment, 2 weeks of washout and 8 weeks on treatment)	<ul style="list-style-type: none"> • International Index of Erectile Function (IIEF) • Rigiscan • Penile duplex ultrasonography 	Mean IIEF scores were significantly higher in patients treated with Korean red ginseng than in those who received placebo. Among other variables, penile tip rigidity on Rigiscan showed significant improvement for ginseng versus placebo.

Jang *et al.* (2008) conducted a systematic review in 2008 evaluating the effectiveness of red ginseng for treating ED. The systematic review was conducted on 7 RCTs, including 363 men from 24 - 70 years old with ED that lasted for 1 to 30 years. Among the seven trials, four trials, two trials, and one trial adopted 600 mg ginseng three times daily, 900 mg once daily, and 1000 mg once daily, respectively. Six of the included trials compared the therapeutic efficacy of red ginseng with placebo. The meta-analysis indicated that red ginseng is superior to placebo [n = 349, risk ratio (RR), 2.40; 95% CI of 1.65, 3.51, p < 0.00001]. Moreover, subgroup analyses also revealed beneficial outcomes of red ginseng in patients with psychogenic ED (n = 135, RR, 2.05; 95% CI of 1.33, 3.16, p = 0.001). All these RCTs showed that red ginseng is effective in treating erectile dysfunction. However, a more rigorous study is necessary due to the small sample size [54].

In the study by Borrelli *et al.* (2018), 2080 patients with ED were recruited, and 12 types of mono preparations were introduced to them. These mono preparations included 5 ginsengs (n = 399), 3 saffron (n = 397), 2 *Tribulus terrestris* (n = 202), 1 *Pinus pinaster* (n = 21) and 1 *Lepidium meyenii* (n = 50). Besides, 5 investigated dietary supplements with pure compounds (n = 410) and 7 evaluated formulations (n = 544) were involved. The IIEF-5 score was significantly improved by ginseng (140 for ginseng, 96 for placebo) with standardized mean difference of 0.43 (95% confidence interval [CI] 0.15 - 0.70, P < 0.01). Saffron and *T. terrestris* showed mixed results, whereas *P. pinaster* and *L. meyenii* produced positive preliminary results. With these encouraging results, ginseng may be an effective herbal treatment for ED. However, more rigorous research in the field is required before a firm conclusion can be drawn. A degree of familiarity with the safety and efficacy of ginseng used in ED should be established to ensure the patients are being properly counselled and treated [50].

De Andrade *et al.* (2007) assessed the efficacy of Korean Red Ginseng (KRG) using IIEF-5 and GAQ. In the KRG group, the IIEF-5 score after the treatment was significantly improved compared with that before the treatment (16.4 ± 2.9

to 21.0 ± 6.3 , $P < 0.0001$). On the other hand, in the placebo group, there was no difference before and after the treatment (17.0 ± 3.1 to 17.7 ± 5.6 , $P > 0.05$). Besides, the total score for questions 3 and 5 in IIEF-5 improved significantly after treatment, with $P < 0.001$ and $P < 0.0001$, respectively. In the global efficacy question, 20 patients (66.6%) in the KRG group appeared to have improved erection which was significant ($P < 0.01$), while there was no difference in the placebo group. With these results, KRG plays a beneficial role in treating ED [53].

In a previous study done by Choi *et al.* (1998), a questionnaire that surveyed the self-reported status of libido, erection, ejaculation, sexual performance and satisfaction rate of intercourse was used to determine the efficacy of KRG in patients with borderline psychogenic and organic erectile dysfunction. Besides, Rigiscan was also used to determine the outcome. On an objective questionnaire, the clinical efficacy of KRG was 66.7% and 72.2% on subjective analysis. All parameters included in the questionnaire were enhanced compared to the placebo. After evaluating erectile function using Rigiscan, 4 out of 6 patients treated with KRG showed penile rigidity greater than 70%. In conclusion, KRG has been proven effective in Koreans as it has beneficiary action on male erectile functions with minimal adverse events [51].

A multicenter placebo-controlled, double-blind clinical study which was conducted in 2012 established the efficacy of standardized Korean ginseng berry (SKGB) using IIEF-5 and PEDT. By 8th week of treatment, the total scores and each domain score of IIEF-5 in the SKGB group have significantly improved from 40.95 ± 7.05 to 46.19 ± 12.69 ($P < 0.05$). The domain score for erectile function improved slightly from 17.17 ± 2.57 to 18.59 ± 5.99 for those who had consumed SKGB. On the other hand, PEDT, which evaluates ejaculatory function, increased slightly from the baseline score of 9.14 ± 4.57 to 7.97 ± 4.4 and 7.53 ± 4.26 , respectively, after 4 and 8 weeks of treatment ($P < 0.05$). Therefore, ginseng can be used as an alternative treatment for ED [52].

In 2009, Kim *et al.* conducted a double-blind, placebo-controlled study in Korea on 143 patients experiencing ED. IIEF was applied to gauge the efficacy of tissue-cultured mountain ginseng extract (TMGE). After two months of treatment, the total IIEF score of the TMGE group had significantly improved from 29.78 ± 13.14 to 39.86 ± 15.29 ($P < 0.001$). The improvement observed in the placebo group was not statistically significant as it only increased slightly from 29.71 ± 10.58 to 33.33 ± 10.17 ($P > 0.05$). In the TMGE group, the domain score for intercourse satisfaction and overall satisfaction improved to 6.83 ± 2.95 and 5.74 ± 1.93 respectively after eight weeks of medication ($P = 0.001$ for both). On the other hand, the placebo group showed no statistical significance of increment for both domains. Based on these results, the authors concluded that TMGE could be utilized for improving erectile function in male patients [55].

Hong *et al.* (2002) conducted a double-blind crossover study which included 45 patients with ED. Korean version of IIEF, Rigiscan, and penile duplex ultra-

sonography were used to determine the efficacy of KRG. After treatment, the mean IIEF scores were significantly improved in patients receiving ginseng than in those who received placebo where in the KRG group the total IIEF scores increased to 38.1 ± 16.6 versus 30.9 ± 15.7 in the placebo group ($p < 0.01$). Domain scores for erectile function, sexual desire and intercourse satisfaction also significantly improved after treatment. Nevertheless, the mean scores for orgasmic function and overall satisfaction domains showed no significant difference after treatment. On Rigiscan, there was a significant improvement in penile tip rigidity after treatment with ginseng with a baseline of $34.27\% \pm 33.11\%$ and $44.5\% \pm 28.84\%$ versus $40.42\% \pm 30.21\%$ ($p < 0.05$). On penile duplex ultrasonography, the mean end-diastolic velocity changed from 4.15 ± 3.94 to 3.82 ± 3.79 versus 4.08 ± 3.38 with ginseng and placebo, respectively ($p = 0.708$). On the other hand, the mean peak systolic velocity on duplex ultrasonography increased from 35.39 ± 19.13 to 39.48 ± 22.29 and 37.45 ± 20.01 in treatment and placebo groups, respectively ($p = 0.534$). All in all, this study proved that Korean red ginseng could be used as an alternative for treating ED [27].

4. Discussion

Ginseng has been used as an adaptogen to boost health and a popular aphrodisiac to enhance ED and sexual performance for thousands of years [56]. In this review, all these trials reached a similar conclusion: ginseng is ideal in treating ED where IIEF-5 scores were significantly improved after treating with ginseng [27] [50] [52] [53] [54] [55]. Similar to multiple study findings, Borrelli *et al.* also revealed a positive outcome of ginseng on four of the five IIEF-15 domains: improving sex desire ($P < 0.01$), erectile function ($P = 0.01$), erection maintenance ($P < 0.01$) and overall satisfaction ($P = 0.01$). However, domain scores such as orgasmic function showed no significant improvement after treatment ($P = 0.06$) [28]. Khera and Goldstein (2011), which reviewed *Panax ginseng* data from six RCTs, concluded that approximately 58% of men who consumed ginseng experienced sexual function improvement as compared with 20% of patients who received placebo [2]. Ernst *et al.* (2011) also arrived at a similar conclusion as Khera and Goldstein (2011) where the experts concluded that *Panax ginseng* was the only herbal supplement test that received a cautiously positive conclusion without apparent safety issues [2] [57]. Another subgroup analysis again showed ginseng had a significant positive effect on the psychogenic aetiology of sexual dysfunction ($P = 0.001$) and reported no significant side effects [12]. Similarly, a study conducted among Japanese adult patients with low domain scores for erectile function and low libido concluded that the intercourse satisfaction, libido and penile circumference were significantly improved with ingestion of Sanchi ginseng extract capsules [58]. No major safety concerns were reported with the consumption of ginseng in this study.

In this review, we also observed that ginseng can also treat ED-related comorbidities such as hypertension, diabetes mellitus and hyperlipidemia. Evidence

has shown that the action of GS in ginseng enhances vascular endothelial abnormalities and possesses organ-protective action, especially in lungs, heart, and corpus cavernosum [59]. In a human study that included 26 patients with essential hypertension, ginseng has been shown to significantly lower the systolic blood pressure ($p = 0.03$), whereas the diastolic pressure remained unchanged ($p = 0.17$) [38] [60]. Wood *et al.* (1964), who conducted an animal study, found approximately 25 mmHg of transient reduction in blood pressure after a bolus injection of ginseng extract into the dogs [61]. A reduction in blood pressure can reduce the risk of myocardial infarction by at least 16% and stroke by 35% - 40% [62] [63]. Sotaniemi *et al.* (1995) proposed that 200 mg of ginseng reduced fasting blood glucose and improved HbA1c [64]. Another study conducted by Vuksan *et al.* (2018) also resulted in similar conclusion as Sotaniemi *et al.* where ginseng decreased HbA1c and fasting blood glucose levels with p value of 0.041 and 0.008 respectively [65].

Another animal study showed positive outcomes of ginseng in treating diabetes mellitus where it was found that the antioxidant effect of ginseng prevents ED from occurring in non-insulin-dependent diabetes mellitus rats as oxidative stress is one of the chief factors in causing ED in diabetics [66]. In an animal study, Bakircioglu *et al.* (2000) demonstrated that rats treated with Chinese herbal medicine have increased levels of caveolin-1 expression, protecting the penile smooth muscles from detrimental effects of high cholesterol level thus resulting in better erectile response [67]. Kim *et al.* (2003) concluded that the triglyceride, total cholesterol level and low-density lipoprotein levels were reduced after two months of ginseng administration [49]. Besides that, weight and fat mass have been reduced significantly after the consumption of ginseng [68].

In terms of the safety of ginseng, the US National Institutes of Health to the US National Toxicology Program nominated *Panax* ginseng to assess its carcinogenic potential. Tumorigenicity, safety, and chronic toxicity of ginseng were examined in multiple studies in mice and rats. In the 2-week, 3-month, or 2-year gavage studies, no significant safety issues were reported. Therefore, researchers concluded that even when ginseng was administered at a dose of 5000 mg/kg, it was neither tumorigenic nor toxic [69]. No safety issues of concern have been noted in the past laboratory studies exploring the effect of *Panax* ginseng on sexual function. For instance, the researchers reported that even with doses up to 20 g/kg, there was no animal mortality in the most recent investigation. Besides, in another ancillary study by this same group, the beagle dogs showed no signs of toxicity when treated with a primary ginsenoside (Rg1) at a dose of 500 mg/kg by mouth daily for five months [69].

Moreover, the consistency of safety data from human studies is derived from different sources and is notable. For instance, a 2002 analysis included all articles with original data on adverse events and drug interactions with *Panax* ginseng. Information was also requested from twelve manufacturers regarding preparations of ginseng, national drug safety bodies, and the World Health Organiza-

tion. The incidence of side effects of ginseng was found to be similar to that of placebo. An update to this manuscript, which was done in 2009, came to a similar conclusion and stated that the potential for drug-ginseng interactions is “low” [69].

5. Conclusion

Based on this review, it is shown that ginseng improved IIEF-5 scores, normalized blood pressure, blood glucose level, and lipid profile. Ginseng as a mono-preparation showed a safe profile with no significant differences between the ginseng and placebo groups in terms of the symptoms and frequency of side effects in RCT studies with a small number of subjects with various conditions for each patient. Therefore, ginseng could be a popular and useful alternative therapy considering that many patients are reluctant to use potentially invasive pharmaceutical drugs to achieve an erection. However, due to the small sample sizes, and methodological quality of preliminary trials, the possible utility of ginseng in everyday clinical practice would be reduced. On that account, more studies with larger-scaled clinical trials and higher standards on the safety and efficacy of ginseng are needed to develop more definite factual information about ginseng as complementary medicine to the consumers. More trials which involved Caucasian populations and comparison of ginseng with other established ED interventions are also worth to be considered.

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Conflicts of Interest

The authors declare no conflicts of interest.

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List of Abbreviation (Sorted Alphabetically)

95% CI	95% Confidence Interval
AGEs	Advanced Glycation End-products
AMP: ATP	Adenosine Monophosphate:Adenosine Triphosphate
AMPK	Adenosine Monophosphate-activated Protein Kinase
Cyclic AMP	Cyclic Adenosine Monophosphate
Cyclic GMP	Cyclic Guanosine Monophosphate
DIED	Diabetes-induced Erectile Dysfunction
ED	Erectile Dysfunction
eNOS	Endothelial Nitric Oxide Synthase
GAQ	Global Assessment Questionnaire
GS	Ginsenosides
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
IIEF	International Index of Erectile Function
IIEF-5	International Index of Erectile Function -5
IIEF-15	International Index of Erectile Function -15
KRG	Korean Red Ginseng
LDL	Low-Density Lipoproteins
n	Number
NO	Nitrous Oxide
P	Probability
PDE5	Phosphodiesterase Type 5
PEDT	Premature Ejaculation Diagnostic Tool
RCTs	Randomized Controlled Trials
Rg1	Ginsenoside Rg1
RR	Risk Ratio
S2	Sacral Spine Nerve 2
S4	Sacral Spine Nerve 4
SKGB	Standardized Korean Ginseng Berry
TC/HDL	Total Cholesterol/High-Density Lipoprotein
TMGE	Tissue-cultured Mountain Ginseng Extract
US	United States