



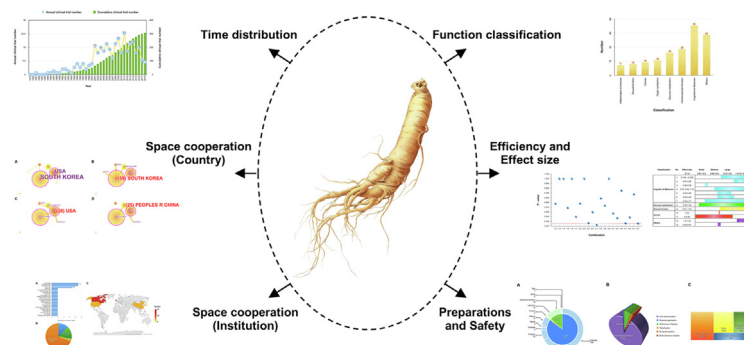
Ginseng: A bibliometric analysis of 40-year journey of global clinical trials



Weijie Chen¹, Peifen Yao¹, Chi Teng Vong, Xiuzhu Li, Zhejie Chen, Jianbo Xiao, Shengpeng Wang*, Yitao Wang*

State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao SAR, China

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Ginseng has a long history of widespread use and remarkable effects as traditional medicine, adjuvant and dietary supplement. The therapeutic value, diverse functionalities and rapid development of ginseng have driven a significant increase in the number of ginseng clinical trials, ranging from its use in various ailments, formulation to safety concerns. Despite the persistent interest in ginseng clinical research, the medical effectiveness of ginseng is inconclusive and there is a lack of bibliometric analysis of the hundreds of ginseng clinical trials.

Aim of Review: This review aims to provide an extensive overview of ginseng clinical trials over the past 40 years (1979–2018) in combination with a qualitative and quantitative analysis. The annual clinical trial analysis of time distribution, country and institution network analysis for space cooperation, statistical analysis for various functions, as well as efficiency and effect size were performed for global ginseng clinical trials. Besides, preparation categories, administration routes, and the safety of ginseng clinical trials were also investigated.

Key Scientific Concepts of Review: The 40-year journey of ginseng clinical trials has experienced emerging, boom, and stable or transitional stages. The global network of ginseng clinical trials has relevant regional distribution in Asia, North America and Europe. South Korea makes a great contribution to building up large research clusters and strong cooperation links. Universities are the key contributors to ginseng clinical trials. The development of ginseng products could be focused on the clinical trial in diseases with higher effectiveness or effect size, such as sexual function and cognitive & behavior and require rigorous

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* Corresponding authors at: University of Macau, Avenida da Universidade, Taipa, Macao SAR 999078, China.

E-mail addresses: swang@um.edu.mo (S. Wang), ytwang@um.edu.mo (Y. Wang).

¹ Weijie Chen and Peifen Yao share co first authorship.

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investigations and evidence to evaluate safety. More attention should be paid to different effects from different preparations. We believe this review will provide new insights into the understanding of global ginseng clinical trials and identifies potential future perspectives for research and development of ginseng.

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Introduction

Ginseng is a time-honored herb internationally that belongs to the *Araliaceae* family, and it is commonly referred as the ginseng family. There are several species that are under the same name ginseng, such as *Panax ginseng* C. A. Mey. (*P. ginseng*) (Asian ginseng), *Panax quinquefolius* L. (PQ) (American ginseng), and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Siberian ginseng). According to the processing methods, ginseng can also be classified into the following types: fresh ginseng (less than 4 years old, eaten fresh), white ginseng (4–6 years old, peeled and dried in an oven or air), sun ginseng (SUG) (white ginseng steamed at a high temperature and pressure), and red ginseng (RG) (6 years old, unpeeled and steamed) [1,2].

Tracing back to thousands of years ago, China was the first country to use and record ginseng accurately and reliably. In Shen-nong's Herbal Classic, the earliest existing monograph of Chinese medicine, ginseng was recorded as traditional medicine for calming the mind, stopping palpitations and brightening the eyes. Ginseng has also attracted attentions of the western countries and is approved by the German Commission E and the World Health Organization (WHO) as an adaptogen and tonic, as well as an anti-fatigue and anti-stress herb [3]. It is well known for consisting of high contents of ginsenosides (e.g. Rb1, Rb2, Rc, Rd, Re, and Rg1), which endorse ginseng with diverse bioactivities, including ameliorating cardiovascular functions [4], regulating glucose metabolism [5], benefiting cognitive and behaviors [6], and improving sexual functions [7].

The therapeutic value, diverse application and rapid development of ginseng have driven the increase of ginseng clinical trials significantly [8]. Despite the persistent interest in ginseng clinical research, the medical effectiveness is inconclusive and there is a lack of systematic analysis for the hundreds of ginseng clinical trials through qualitative and quantitative analysis in this field. Bibliometric analysis is widely used to investigate academic research shift and burst, explore current research frontiers and hotspots, and predict future research focuses and achievements [9–11]. It has been applied to understand the global and longitudinal trends of ginseng research [12,13]. Meanwhile, CiteSpace is one of the most common and powerful software designed for the detection, analysis and visualization of the patterns and trends in scientific and systematic literatures [14,15].

In this sense, the combination of bibliometrics and CiteSpace can deal with the large and complex ginseng clinical data, as well as provide special perspectives and meaningful conclusions. In this review, we intend to provide an extensive overview and analysis of global ginseng clinical trials over the past 40 years (1979–2018): Section I (Data collection and analysis) introduces the methodology and software used to analyze ginseng clinical trials; Section II (Time distribution of ginseng clinical trials) analyzes the annual number of ginseng clinical trials and summarizes these clinical trials into three stages; Section III (Space cooperation of ginseng clinical trials) visualizes the country and institution network and discusses a landscape of the global trend in ginseng clinical trials; Section IV (Function classification of ginseng clinical trials) divides the clinical trials into 8 different function classifications and analyzes the efficiency and effect size of ginseng clinical trials; Section V (Ginseng preparations in clinical trials) describes the preparations

and administration routes of ginseng; Section VI (Ginseng safety in clinical trials) presents the situations of side effects in ginseng clinical trials; finally, some concluding remarks are provided in the Conclusion and perspectives. We believe this study will shed light on the understanding of global ginseng clinical trials and identify potential future perspectives of ginseng research and development.

Data collection and analysis

The following search strategies were applied based on the PubMed advanced search tutorial: (((Ginseng) OR (Ginsenoside)) OR (Ginseol)) OR (Ginsana) in full fields. "Clinical Trial" was selected, which met the inclusion criteria: 1) published before 2019, 2) related to ginseng individual or compound herbal medicines, 3) written in English, 4) involved human clinical trials, 5) provided sufficient data for analysis. In addition, there were no criteria set for gender, age or ethnicity. In other words, the clinical trials that do not meet these criteria were excluded. Fig. 1 presents the flow chart in details.

CiteSpace software (Version 5.3.R4) was used to analyze the time distribution and space cooperation. The parameters were imported into the software as follows: 1) Time slicing: 1979–2018, 2) Years per slice: 1 year as the length of a single time slice, 3) Node type: country/institution, 4) Links: cosine was used for the connection strength and scope was used for the within slices, 5) Selection criteria: select all items from each time slice, 6) Pruning and Visualization: pathfinder, pruning sliced networks, cluster view-static and show merged network were selected. Function classification was analyzed by SPSS software (Version 21) for statistical analysis, including Fisher's exact probability test, Chi-square test and Bonferroni correction.

Time distribution of ginseng clinical trials

As shown in Fig. 1, 308 ginseng clinical trials were identified in the time distribution during the past 40 years (from 1979 to 2018). The average annual number of ginseng clinical trials was near to 8. The first clinical trial of ginseng was published in 1981. The second one was completed in 1985 and then ginseng clinical trials were conducted in each subsequent year. It was shown that there were decreases in 14 years compared to the last year (1988, 1992, 1993, 1996, 1998, 2002, 2004, 2006, 2007, 2010, 2012, 2015, 2017, and 2018), which accounted for 35% of the entire period. However, there was an overall growth trend according to the cumulative clinical trial number, with a distinct surge in 2001 and 2011. Moreover, the chain growth rates in the year 1987, 1990, 1994, and 2001 were twice or more than twice, with a significant increase. In 2012, it was the first time that the chain growth rate was near to negative 0.5 (Fig. 2).

From this aspect, the duration of the past 40 years can be preliminarily divided into three stages according to the tendency. Stage I (1979–2000) can be regarded as the emerging stage with muted growth. It suggests the initial development of ginseng clinical trials. Stage II (2001–2011) is called the boom stage, due to a rapid and apparent increase of ginseng clinical trials. Practically, the number peaked in 2011, which implied that there was a con-

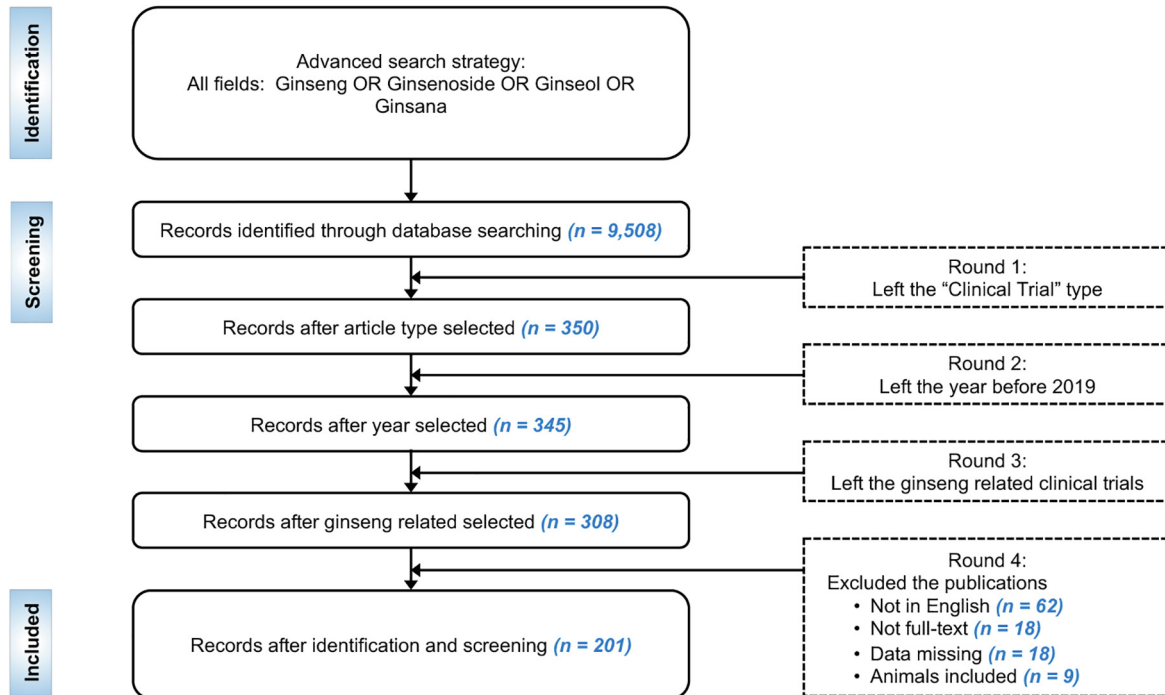


Fig. 1. The flow-chart summary of the searching process.

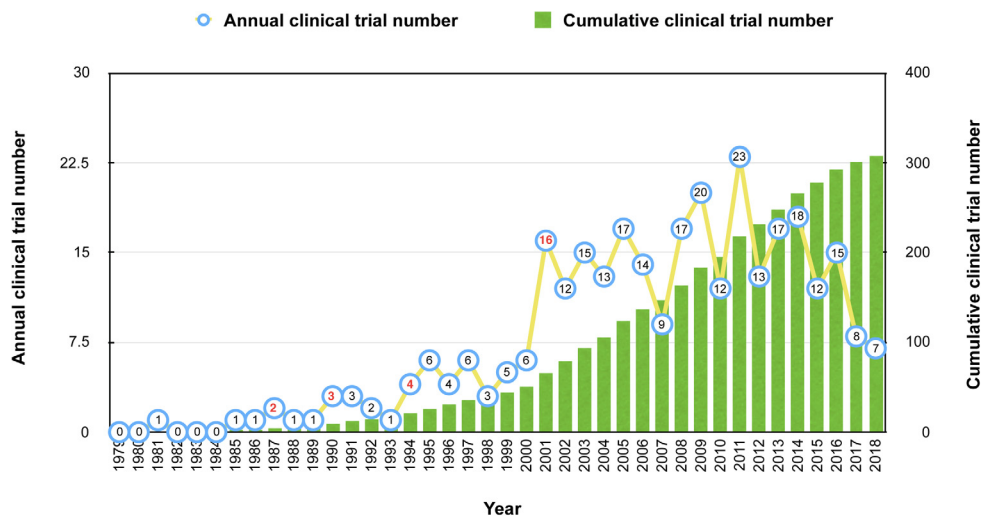


Fig. 2. The annual and cumulative clinical trial number of ginseng from 1979 to 2018. The blue circle represents the annual clinical trial number. The blue circle with red number represents the chain growth rate of the annual clinical trial number ≥ 1 . The green column represents the cumulative clinical trial number. The yellow line represents the fluctuation.

siderable interest in the ginseng clinical trial field at that time. Stage III (2012–2018) is recognized as the downtrend. This implicates that this field may have entered into a stable or transitional period.

Space cooperation of ginseng clinical trials

Country and institution network visualize a landscape of the global trend of research cooperation involved in the ginseng clinical trials. After the screening and exclusion, 201 clinical trials were selected for this analysis. Fig. 3A presents the network for all the countries with 7 nodes. The diameter of each line circle represents the intensity of the clinical trial number of the country. The thick-

ness of the connecting line represents the intensity of country cooperation. Apparently, South Korea occupies the largest global share with nearly one third of the ginseng clinical trials (59) (Fig. 3B), which is followed by the USA (38) (Fig. 3C) and China (25) (Fig. 3D). The top 3 countries cooperate closely with each other and with other countries, such as Canada, Croatia, and Australia. Nevertheless, England displays isolated nodes with no connections. In Fig. 3B–3D, it shows that South Korea is connected with 4 countries, whereas the USA is connected with 4 countries, and China is connected with 3 countries.

The number of clinical trials conducted in institutions was also analyzed. In total, 25 different institutions are shown in Fig. 4A, according to that the clinical trial number is equal to or greater

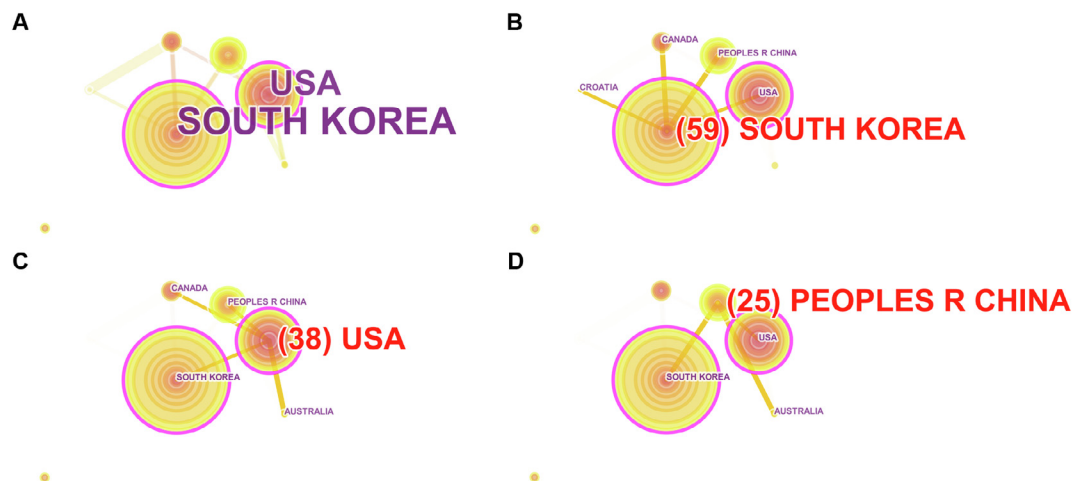


Fig. 3. Country relationship networks of ginseng clinical trials. (A) Network for all the countries. (B) South Korea network. (C) The USA network. (D) The People's Republic of China network.

than two. The University of Toronto and St Michaels Hospital have the largest number of clinical trials, which is followed by North Umbria University and Yonsei University. In addition, there are 4 classifications for institutions: University (17), Research institute (4), Hospital (3), and Company (1), as shown in Fig. 4B. In terms of the countries of the institutions, they are from South Korea (29), Canada (22), the UK (10), China (6), the USA (6), and Japan (2). All the institutions are in the colored countries (Fig. 4C). The institution with more clinical trials is presented in darker red color. Obviously, South Korea can be identified as the most productive country.

Among these countries, South Korea has the most ginseng clinical trials and the closest cooperation with other countries. Meanwhile, the institutions from South Korea are ranked the first on the global country map, which is consistent with the trend described in a study in 2010 [12]. Therefore, South Korea makes a great contribution to the ginseng clinical trials by playing a leader role in working together to build up large research clusters and strong collaboration links. As a whole, Asia, North America and Europe are identified as the active research areas with the power of research distribution. The ginseng clinical trial global network has relevant regional distribution, which may be linked to the existence of different origins of ginseng species. In Asia, China is famous for Northeast ginseng and Siberian ginseng. Besides, Korean red ginseng (KRG) is also popular globally. In North America and Europe, PQ is the predominant ginseng [1]. In relation to institution types, it should be emphasized that universities are the key contributors to the number of clinical trials, and this phenomenon also exists in other research areas, such as global regulatory T-Cell research [16], global molecular modeling of cyclodextrins research [17], and global liposome research [18].

Researchers from China have published thousands of ginseng clinical research in the CNKI database (a key national research and information publishing institution in China). However, no institutes from China are ranked in the world top 10 ginseng clinical trial institutes. Consequently, it is necessary to enhance cooperation among countries and institutions, especially Chinese universities. Regional cooperation plays a vital role in enhancing more research outputs, and could effectively reduce the cost of clinical trials and improve research qualities and efficiencies [19,20]. In addition, the governmental and financial supports, and the development of information and communication technologies are also indispensable. Therefore, we believe that the cooperation network will become more complicated with faster development and more communication between countries and institutions.

Function classification of ginseng clinical trials

Two authors extracted the data independently in a predefined and standardized manner. The authors discussed the discrepancies and met to achieve a consensus on the data (title, objective, trial design, trial length, sample size, patients entered, function classification, medicine details (name, formulation, ingredients/position, manufacturer), intervention process (administration route, dosage), and main results (effects, side effect, and effect size)). All the clinical trials were sorted according to the clinical functions: inflammation & immune (11), sexual function (12), cancer (14), organ symptoms (16), glucose metabolism (24), cardiovascular function (28), cognitive & behavior (53), and others (43) (Fig. 5A).

Cognitive & Behavior

The application of ginseng in the past serves as a platform for its modern clinical trials. In the ancient, ginseng was used to tranquilize mind and promote intelligence. Now, it can ameliorate mental health, improve social behavior, and benefit memory performance, such as secondary memory, quality of memory, and working memory, as shown in Supplementary Table 1. Moreover, the modern clinical effects of ginseng on improving cognitive function and behavioral symptoms in patients with moderately severe Alzheimer's disease (AD) have also been proved [6].

Cardiovascular function

The current evidence does not support the use of ginseng to prevent or reduce cardiovascular risks. Ginseng contributes to the improvement in cardiac function and is beneficial for cardiovascular health, especially chronic heart failure (CHF) [21], and hypertension [22], as shown in Supplementary Table 2. Therefore, the pharmacological properties and molecular mechanisms of ginseng should be further investigated in the area of cardiovascular research.

Glucose metabolism

It has been confirmed by several clinical trials that ginseng can regulate glucose metabolism [23,24]. As shown in Supplementary Table 3, all the clinical trials have similar conclusions, suggesting that ginseng may have beneficial effects on the prevention of diabetes. However, due to the inconsistent standardization of

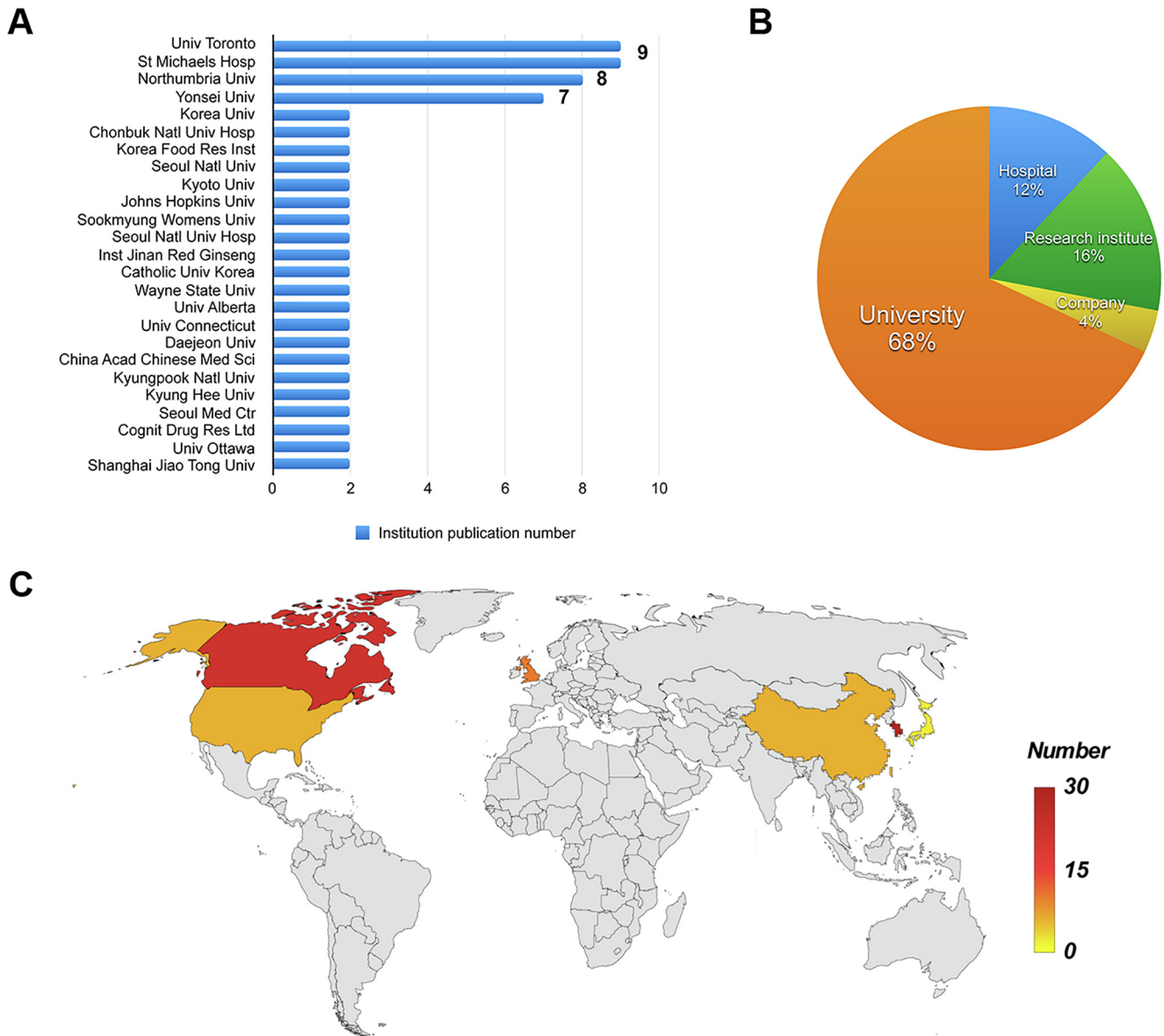


Fig. 4. Institution relationship networks of ginseng clinical trials. (A) The bar chart shows the clinical trial numbers for each of the institutions. (B) The pie chart shows 4 institution classifications with percentages of the total number of clinical trials. (C) The map shows the geographic distribution of the global institutions.

methodology and limited data from clinical trials, a definitive conclusion could not be made, which was consistent with the conclusion from a study in 2011 [25]. Thus, future studies must be focused on standardized methodologies, powerful calculation procedures and rigorous treatment regimens to reach a conclusive agreement.

Organ symptoms

Ginseng has been reported to ameliorate the symptoms occurring in organs, as shown in Supplementary Table 4. For example, ginsenoside Rb1 (GS-Rb1) can reduce oxidative stress and inflammation in chronic kidney disease (CKD) patients [26]. Shenmai injection (SMI) containing ginseng possesses a better protective effect on mitigating pulmonary gas exchange dysfunction in patients who were scheduled for lower extremity surgery [27]. Combined Ninjin-to can improve gastrointestinal motility and mucosal blood flow [28]. While KRG can protect subjects from con-

tracting acute respiratory illness (ARI) [29]. In addition, KRG is regarded as a complementary therapy for chronic hepatitis B and an adjuvant for patients undergoing bile acid dissolution therapy for gallstones [30,31]. Taken together, ginseng has considerable and potential clinical applications in treating organ symptoms.

Cancer

Ginseng has an excellent potential as an adjuvant for patients with cancer and cancer-related symptoms. There are 12 ginseng clinical trials in cancer, shown in Supplementary Table 5. Among all types of cancer, non-small cell lung cancer (NSCLC) accounted for the most studied cancer with a 25% share [32–34]. It is shown that ginseng is used frequently in combination with chemotherapy for adjuvant effects, and this reduces the side effects of the anti-cancer drugs for NSCLC patients. In addition, ginseng can improve cancer-related fatigue (CRF), as well as the overall quality of life [35,36].

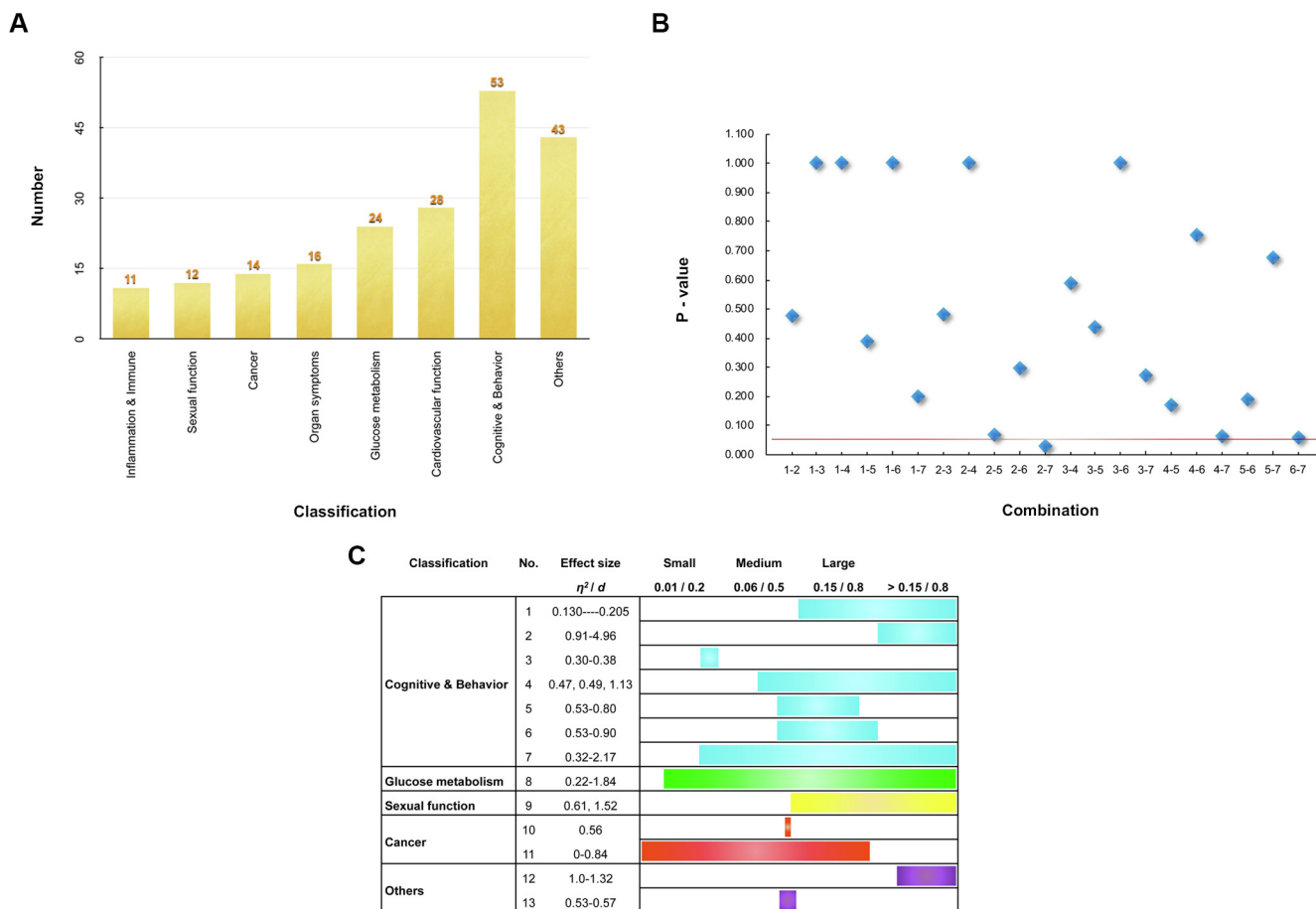


Fig. 5. The analysis of function classifications, efficiency and effect size of ginseng clinical trials. (A) The bar chart shows 8 function classifications with their total clinical trial numbers. (B) The scatter chart shows P values between two classifications, including 21 combinations: 1–2 (Inflammation & Immune-Sexual function), 1–3 (Inflammation & Immune-Cancer), 1–4 (Inflammation & Immune-Organ symptoms), 1–5 (Inflammation & Immune-Glucose metabolism), 1–6 (Inflammation & Immune-Cardiovascular function), 1–7 (Inflammation & Immune-Cognitive & Behavior), 2–3 (Sexual function-Cancer), 2–4 (Sexual function-Organ symptoms), 2–5 (Sexual function-Glucose metabolism), 2–6 (Sexual function-Cardiovascular function), 2–7 (Sexual function-Cognitive & Behavior), 3–4 (Cancer- Organ symptoms) and 3–5 (Cancer-Glucose metabolism), 3–6 (Cancer-Cardiovascular function), 3–7 (Cancer-Cognitive & Behavior), 4–5 (Organ symptoms-Glucose metabolism), 4–6 (Organ symptoms-Cardiovascular function), 4–7 (Organ symptoms-Cognitive & Behavior), 5–6 (Glucose metabolism-Cardiovascular function), 5–7 (Glucose metabolism-Cognitive & Behavior), and 6–7 (Cardiovascular function-Cognitive & Behavior). The blue dots represent the P-value, whereas the red line represents the P-value that is equal to 0.05. (C) The bar chart shows the effect size in different classifications. The blue column represents Cognitive & Behavior. The green column represents Glucose metabolism. The yellow column represents Sexual function. The red column represents Cancer. The purple column represents Others.

Sexual function

As presented in Supplementary Table 6, ginseng has different effects on different genders. On one hand, ginseng can treat infertility [37], and erectile dysfunction (ED) [38] in male patients. On the other hand, it is proved to improve sexual arousal, enhance sexual life, satisfy sexual desire, reduce vaginal dryness, and increase the frequency of sexual intercourse, orgasm and clitoral sensation in menopausal and postmenopausal women [39,40]. Although notable improvements and positive effects were observed, the clinical trial data remains insufficient to make a consistent conclusion. As a result, ginseng is only treated as an alternative medicine or supplement in clinical trials, related to sexual function. All in all, clinical trials should be conducted to produce sufficient, novel and strong evidence, and ginseng with alternative effects in sexual function should be further developed, which has also been suggested by some evidence-based systematic reviews and meta-analysis [41,42].

Inflammation & Immune

Among all the clinical trials of ginseng, the function of inflammation & immune has the smallest number of clinical trials, as

shown in Supplementary Table 7. Importantly, it was shown that the ginseng and one of the active constituents of ginseng displayed the same effects. Regarding to inflammation, it was demonstrated that Ren Shen Yang Rong Tang (RSYRT) (a formulation product with ginseng) could decrease chronic inflammation [43], and ginsenoside compounds might inhibit inflammatory responses [44]. For the immune effects, RG [45] and ginseng polysaccharide (Y-75) [46] were reported to enhance immune function. For this reason, activity markers should be used more and more significantly in the further research on ginseng, and animal studies may provide important evidence to screen some potential markers for the study of clinical benefits of ginseng [47,48].

Others

In addition to the above 7 classifications, ginseng clinical trials have been studied in diverse research areas, and were shown to exert a large number of functions, such as cellular DNA protection [49], menopausal syndrome transition [50], skin anti-aging function [51], CD4⁺ T cell slow depletion (in human immunodeficiency virus type 1-infected patients) [52], alcohol hangover symptom relief [53] and so on (Supplementary Table 8).

Table 1

The count, expected count and percentage of each classification for the effective and ineffective.

No.	Classification	Item	Effect		Total
			Ineffective	Effective	
1	Inflammation & Immune	Count	1	10	11
		Expected Count	2.3	8.7	11.0
		% within Classification	9.1%	90.9%	100.0%
2	Sexual function	Count	0	12	12
		Expected Count	2.5	9.5	12.0
		% within Classification	0.0%	100.0%	100.0%
3	Cancer	Count	2	12	14
		Expected Count	2.9	11.1	14.0
		% within Classification	14.3%	85.7%	100.0%
4	Organ symptoms	Count	1	15	16
		Expected Count	3.3	12.7	16.0
		% within Classification	6.3%	93.8%	100.0%
5	Glucose metabolism	Count	7	17	24
		Expected Count	5.0	19.0	24.0
		% within Classification	29.2%	70.8%	100.0%
6	Cardiovascular function	Count	4	24	28
		Expected Count	5.8	22.2	28.0
		% within Classification	14.3%	85.7%	100.0%
7	Cognitive & Behavior	Count	18	35	53
		Expected Count	11.1	41.9	53.0
		% within Classification	34.0%	66.0%	100.0%
8	Total	Count	33	125	158
		Expected Count	33.0	125.0	158.0
		% within Classification	20.9%	79.1%	100.0%

Efficiency and effect size analysis of ginseng clinical trials

Although most clinical trials of ginseng show obvious or potential effects, 20% of the clinical trials fail to achieve consistent outcomes in the several areas, including electrocardiograph values, blood pressure (BP), platelet function, arterial stiffness, renal function, glucose and insulin levels, impaired glucose tolerance, postprandial hypoglycemic, cognitive improvement, mood, stress, exercise performance, driving performance, fatigue, CRF, breast cancer survivors (BCSs), immune, human immunodeficiency virus, fibromyalgia, and ischemic stroke. The results were not consistent, either effective or ineffective (Table 1). Fisher's exact probability test was shown pictorially among the 7 classifications with $p < 0.05$ (exact significance (2-sided) = 0.037), indicating that there was a significant difference. This value makes it necessary to use the four-fold table test to compare two classifications. The P values showing the differences between the two classifications, namely 21 combinations, are shown in Fig. 5B. The P values with $p > 0.007$ were considered to be insignificant between two classifications, according to the Bonferroni correction.

According to the analysis, there is a significant difference in all the classifications of the ginseng clinical trial effects. Sexual function has the highest effective rate, which means that ginseng could potentially be investigated in this area. However, it may be limited due to the sample size. The effective rate is ranked as Sexual function > Organ symptoms > Inflammation & Immune > Cancer > Cardiovascular function > Glucose metabolism > Cognitive & Behavior, so this provides a complete picture on the therapeutic value of ginseng clinical trials, which is beneficial for drug development. In contrast, a comparison that shows no significant difference suggests that the differences in clinical trial effects are focused on the integrated pattern, and are not mutually independent. Hence, the effects of ginseng clinical trials should be conducted at larger size and multi-classifications.

Effect size is used to evaluate the power of effect, including Cohen d and η^2 . Meanwhile, $d = 0.2$, $d = 0.5$ and $d = 0.8$ correspond to the small, medium and large effect sizes, respectively. Similarly, $\eta^2 = 0.01$, 0.06, 0.15 are considered to be small, medium, and large

in effect sizes, respectively. Among all the clinical trials, only 13 of them [36,54–65] provided this information, as shown in Fig. 5C.

Most clinical trials were conducted in the medium-large range. In other words, these clinical trials have an intermediate level effect of power. However, the classification Cognitive & Behavior is in the large range mostly, which possesses potential effect of power for ginseng medical applications. Only 6% of all clinical trials presented the d or η^2 parameters. Notably, very few clinical trials analyze the effect size. It is important to emphasize that this information should not be ignored. Moreover, the 6th edition of the American Psychological Association (APA) guideline reported in 2010 that it is necessary to record and report the effect size. Therefore, we suggest that the effect size may be a potential parameter to evaluate the effects of clinical trials and to help ginseng development.

Ginseng preparations in clinical trials

Fig. 6A and 6B show the preparations and administration routes in a pie chart and a 3D pie chart, respectively. The inner-circle is divided into three dosage forms, namely solid (172), semi-solid (2), and liquid (27). The solid dosage form includes capsule (67%), powder (8%), granule (2%), tablet (1%) and others (7%). On the other hand, the liquid dosage form includes 4 types, injection (6%), drink (1%), tea (1%), and aqueous solution (6%). The least commonly used dosage form is the semisolid cream (1%). Moreover, oral administration was shown to be the most common administration route, which was used by 188 clinical trials and the capsule is also widely used in ginseng clinical trials. Besides, Chinese medicine injection is also used but with a few shares (9).

For *P. ginseng*, drink preparation does not have a significant impact on the BP parameters [66]. However, capsule [67] and powder [68] preparations have opposite effects. Considering the major active components of ginseng, each capsule of ginseng extract (100 mg) is standardized to contain 4% ginsenosides. 1 g powder consists of ginsenosides Rb1 (3.77 mg), Rg1 (0.57 mg), Re (1.86 mg), Rf (12.3 mg), Rb2 (1.24 mg), Rh1 (41.5 mg), Rc

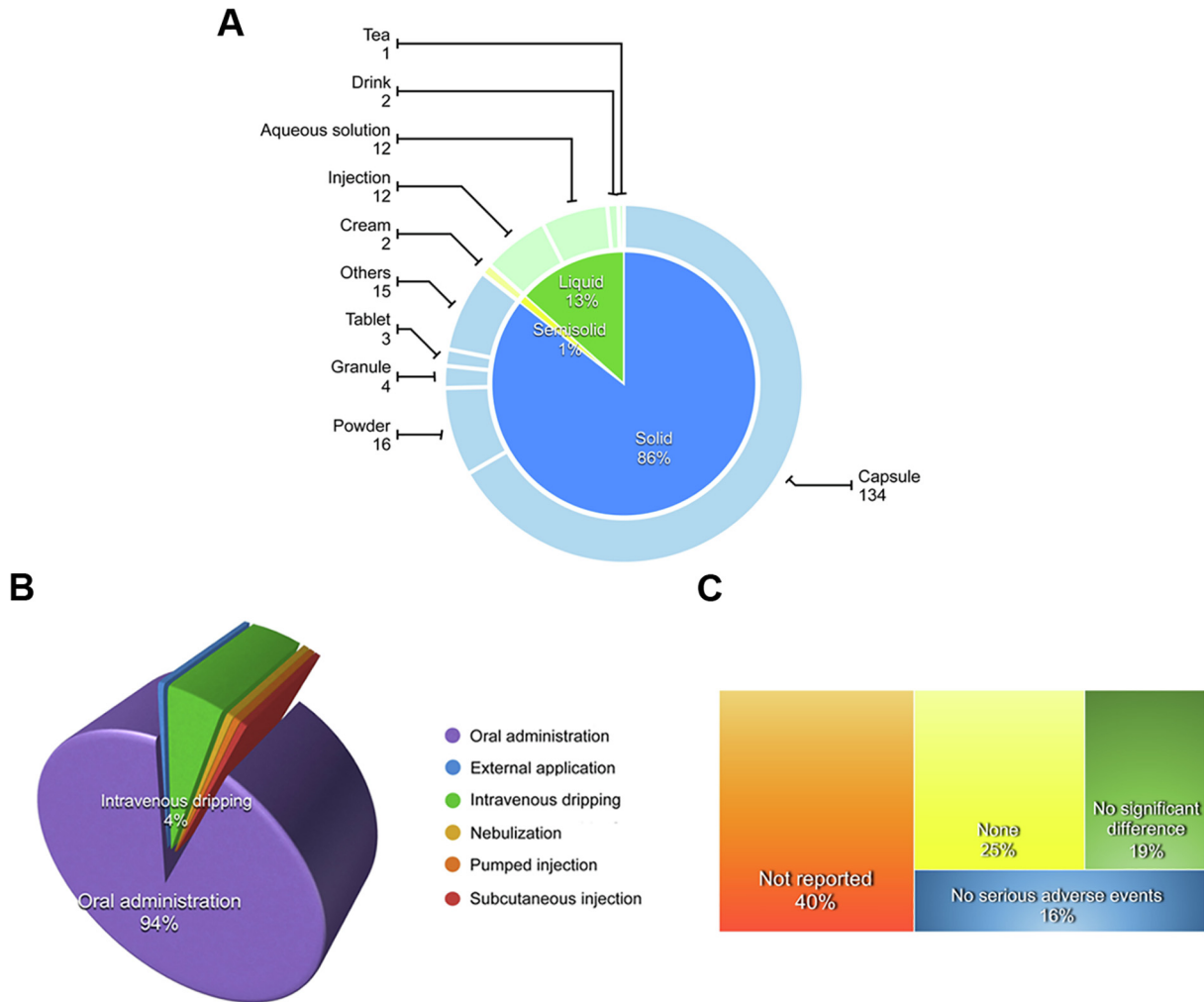


Fig. 6. The analysis of preparation categories, administration routes and side effects of ginseng clinical trials. (A) The pie chart shows the percentages of clinical trial number and the total number of clinical trials for different ginseng preparations. (B) The 3D pie chart shows the percentages of clinical trials tested for side effect. (C) The tree diagram shows the percentages of clinical trial number for different administration routes.

(0.99 mg) and Rg3 (100 mg). Nevertheless, ginsenoside profiles are limited for the drink preparation.

Based on the available clinical trials, different preparations have different and even opposite effects on BP, and not all the preparations provide information about the constituents and ratio of major active components of ginseng. Therefore, we suggest that ginseng preparations and its major active components should be reported in a standard way to achieve the accurate therapeutic effects of ginseng.

Ginseng safety in clinical trials

The tree diagram (Fig. 6C) shows the situation for recording side effects in ginseng clinical trials. Clinical adverse effects are categorized as no serious adverse events (16%; mild or slight side effects but not serious), no significant difference (19%; no statistically significant difference between groups), none (25%; no side effects), and not reported (40%; missing data for this part).

In total, 35% of clinical trials reported side effects of ginseng. The adverse effects included both physiological and psychological symptoms in humans. The mild and slight symptoms include dizziness, facial flushing, headaches, transient anxiety, diarrhea, insomnia, hypoglycemia, nausea, dyspepsia, stomach discomfort, body

rash and pruritus, palpitation, urticarial condition, vomiting, fever, nervousness, and constipation with no regularities.

Most of the ginseng clinical trials have an important safety concern. 60% of the ginseng clinical trials were examined to be safe. However, it was shown that 40% of the clinical trials did not report any side effects in details, especially for Chinese medicine injection, and 50% of the clinical trials were lack of safety evaluation, such as Shenmai injection [69], Shenfu Injection [70], and Ginseng polysaccharides Injection [34]. With limited clinical trial information for safety evaluation, it is hard to make a definitive conclusion for the safe use of ginseng. Therefore, clinical trials must be designed specifically to test the adverse effects or toxicity in order to provide complete data for safety considerations, which can also enhance the significance of increasing quality of research. Meanwhile, safety is also the key factor for international development of Chinese medicine.

Conclusion and perspectives

In the past 40 years, the journey of ginseng clinical trials has experienced into three stages: emerging stage, boom stage, and stable or transitional stage. The global network of ginseng clinical trials has relevant regional distribution in Asia, North America and

Europe. In particular, South Korea makes a great contribution to building up large research clusters and strong cooperation links with other countries. Moreover, universities are the key contributors to ginseng clinical trials, which contribute more than research institutes, hospitals or companies. There are 7 main function classifications of ginseng clinical trials. In terms of efficiency, ginseng shows potential medical effectiveness in various ailments, with the highest effectiveness in sexual function and the highest effect size in cognitive & behavior. Interestingly, different ginseng preparations display different and even opposite effects with the same condition.

Despite that ginseng plays an important role in both East and West of the world, the clinical efficacy of ginseng remains to be established. Based on the analysis of ginseng clinical trials, the development of ginseng products could be focused on the clinical trial in diseases with higher effectiveness or effect size, such as sexual function and cognitive & behavior. Meanwhile, more attention should be paid to the different effects from different preparations. Moreover, 35% of the clinical trials reported some side effects of ginseng, so it is warranted that ginseng products require more rigorous investigations and evidence to evaluate its safety, especially for the safety evaluation of herbal injections. In particular, ginseng clinical trials should be analyzed via a set of standardized ways and an unbiased assessment of their qualities. The CONSORT (Consolidated Standards of Reporting Trials) statement is a useful standardization for the design of clinical trials. Furthermore, the effect size, preparations with its major active components, and side effects should be used as potential parameters to evaluate the quality of ginseng clinical trials.

Although we conducted a global whole picture of ginseng clinical trials, the search strategy was limited to clinical outcomes published in English. Besides, the screening criteria did not include the evaluation of the quality of these ginseng clinical trials. Thus, the future direction should be focused on the evaluation of the quality of the ginseng clinical trials, which can provide better clinical trial analysis for ginseng based on more stringent principles and regulations.

Compliance with Ethics Requirements

This review does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors have declared no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jare.2020.07.016>.

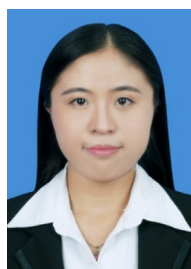
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Weijie CHEN obtained her bachelor degree from China Pharmaceutical University in 2015, and master degree from University of Macau in 2017. She is a PhD candidate in Institute of Chinese Medical Sciences in University of Macau currently. She focuses on ginseng research, molecular dynamics, and data analysis.



Peifen YAO obtained her bachelor degree from Shandong University of Traditional Chinese Medicine in 2008, and master degree from Sun Yat-sen University in 2011. After then, she became a Ph.D candidate in University of Macau. Her research primarily focuses on the quality control and international standards of medicinal herbs.



Chi Teng VONG received her bachelor and master degrees from King's College London, UK in 2008 and 2009, and obtained doctoral degree from University of Macau in 2017. She has been working as a research assistant at King's College London for 3 years, and is currently working as a postdoctoral fellow at University of Macau. Her research interests are focused on the drug discovery and development for inflammatory diseases including Type 2 Diabetes and Inflammatory Bowel Disease.



Jianbo XIAO obtained his PhD in nutritional science from Okayama Prefectural University, Japan (2009). He worked as Humboldtian at University of Wuerzburg, Germany (2013-2015), prior to join University of Macau in 2015. Dr. Xiao has published over 100 papers on international journals. Prof. Xiao has been selected as 2016 and 2017 Clarivate Analytics Highly Cited Researcher (HCR) in agricultural science. Dr. Xiao is currently the associate editor of *Phytochemical Analysis* (Wiley) and *Journal of Berry Research* (IOS), the editorial boards of several international journals. He was the chairman of several international conferences.



Xiuzhu LI received her bachelor degree from South China Agricultural University of Food Science and Engineering in 2012. Now she is a master candidate of Institute of Chinese Medical Sciences in University of Macau. Currently, her research primarily focuses on the evaluation of clinical trials of herbal medicines.



Shengpeng WANG received his bachelor degree from Chengdu University of Traditional Chinese Medicine in 2010 and obtained his doctoral degree from University of Macau in 2016. He is currently an Assistant Professor of Institute of Chinese Medical Sciences in University of Macau. Dr. WANG primarily focuses on drug discovery from Chinese medicine for prevention and treatment of cancer and inflammatory bowel disease, as well as development of novel delivery systems and health products of Chinese medicine.



Zhejie CHEN obtained his bachelor degree of Pharmaceutical Engineering from Xihua University in 2015, and Master degree of Pharmaceutics from Chengdu University of Traditional Chinese Medicine in 2018. Since then, he became a Ph.D candidate of Institute of Chinese Medical Sciences in University of Macau.



Yitao WANG is the founding Director of the Institute of Chinese Medical Sciences and Chair Professor at University of Macau as well as the Director of the State Key Laboratory of Quality Research in Chinese Medicine. He is also the Chief Scientist of Chinese Academy of Chinese Medical Sciences and the Director of International Research Centre of Medicinal Administration at Peking University. He is known internationally for his pioneering contributions to the modernization of Chinese medicine, with an emphasis on systematic evaluation and quality control of Chinese medicine. He has a long-standing interest in efficacy, safety, stability and controllability evaluation of Chinese medicine.