Commentary

Study designs of randomized controlled trials not based on Chinese medicine theory are improper

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Abstract

Current biomedical research methods to evaluate the efficacy of Chinese medicine interventions are often conceptually incompatible with the theory and clinical practice of Chinese medicine. In this commentary, we (1) highlight the theory and principles underlying Chinese medicine clinical practice; (2) use ginseng as an example to describe clinical indications in Chinese medicine; (3) propose a framework guided by Chinese medicine theory for the evaluation of study designs in Chinese medicine research; and (4) evaluate 19 randomized, double-blind, placebo-controlled trials of ginseng. Our analysis indicates that all 19 trials with both positive and negative results confirm the specific effects of ginseng indicated by Chinese medicine theory. Study designs guided by Chinese medicine theory are necessary to validate and improve future randomized controlled clinical trials in Chinese medicine.

Background

Chinese medicine remains popular in China where traditional herbal preparations are estimated to account for 30–50% of the total medicinal consumption [1]. Chinese medicine has also been gaining popularity in the West [1-3]. However, Chinese medicine lacks funding and leading scientists to conduct scientific research (e.g. randomized controlled trials) [4].

The study of ginseng provides an example of the research challenges in Chinese medicine. Highly valued in the Chinese medicine classics and widely used in China for more than two thousand years, ginseng has yet to prove its safety and efficacy through clinical trials [5,6], which, many investigators believe, may be attributed to a paradigm conflict and the poor quality of some clinical trials [7,8].

We found that this paradigm conflict may be resolved by using study designs guided by Chinese medicine theory.

Chinese medicine theory

Chinese medicine is a syndrome-oriented holistic medical system that is conceptually distinct from its Western counterpart. According to Chinese medicine theory, a syndrome is a group of associated signs and symptoms described in terms of Yin and Yang, Qi, and Xue (blood) [9]. All illnesses fall into eight principal categories used to guide the prevention and treatment of illnesses [10]. These categories are Yin and Yang, Biao (exterior) and Li
immune resistance, leading to various diseases. The man-

Considered the premium Qi-tonifying herb to treat five major syn-
dromes [16] caused by Qi-deficiency. Therefore, we argue that only studies in which participants are diagnosed with Qi-deficiency are valid to evaluate ginseng’s efficacy [22-25].

Herbal species
While at least eight species of ginseng are commercially available [26], only two major species, namely Panax ginseng (Chinese or Korean ginseng) and Panax quinquefolius (American ginseng), are used as medicinal herbs world-
wide. According to Chinese medicine theory, the proper-
ties and functions of these two species are quite different [16]. While P. ginseng enhances Yang, P. quinquefolius nourishes Yin. A search for randomized controlled trials of ginseng in PubMed (7 September 2008) found that about one-third of the studies did not mention the gin-
seng species used and that very few studies addressed the species issue.

Herbal quality
Herbal quality may affect research results. Different batches of P. ginseng [27,28] or P. quinquefolius [29] pro-
duced opposing study results respectively on acute post-
prandial glycemia. The primary active ingredients in
ginseng are ginsenosides. G115, a ginsenoside-based standard-
ized extract of P. ginseng, may help assess the efficacy and safety of ginseng. In fact, G115 was used in most P. ginseng (single herb) trials reviewed in this paper.

Herbal formulae
In Chinese medicine, herbs are often formulated to
achieve increased therapeutic effects and reduced toxicity
or side effects [16]. Results from clinical trials on herbal
formulae confirm this practice. A Japanese trial found that
a 7-herb formula was effective in preventing liver cancer in
cirrhosis patients [30]. Two British trials showed that a 10-
herb formula was effective in treating a severe atopic
eczema [31,32]. No single herbal ingredient explains the
efficacy in these studies [33]. Furthermore, ginseng herbal
formulae were shown to be effective in treating chronic
pulmonary disease [22,34], congenital heart disease
[35,36], mild cognitive impairment [37], coronary heart
disease [38] and nasopharyngeal carcinoma [39].

Herbal safety
Certain Chinese medicine herbs are toxic and others may
have adverse effects when used improperly [16]. A condi-
tion known as the ginseng abuse syndrome is character-
ized by heart palpitations, heaviness in the chest, high
blood pressure, dizziness, insomnia, agitation, restless-
ness, nausea, vomiting, abdominal pain and/or bloating,
diarrhea, possible upper digestive tract bleeding, edema,
and red skin rash [40]. Most of these reported adverse
effects are common manifestations of Qi-excess and Qi-

(i)nterior), Han (coldness) and Re (heat), and Xu (defi-
cency) and Shi (excess). Western medicine, however,
views a disease or syndrome as pathological changes of
specific biological processes [1]. As a result, the syn-
dromes in Chinese medicine do not always correspond
with Western classifications of diseases and syndromes.
For instance, hypotension may be related to syndromes of
Gan (liver) Yang ascending, Yin deficiency of liver and
kidney, flaming liver fire, stagnation of phlegm, Xue stasis
and/or dual Yin/Yang deficiency [11]. Conversely, Qi-
deficiency syndrome is related to chronic obstructive pul-
monary disease [12], lung cancer [13], coronary heart dis-
eease [14] and persistent allergic rhinitis [15].

Herbal medications
In Chinese medicine, medicinal herbs are categorized
according to the concepts of Yin, Yang, Qi, Xue, Jing
(essence) and Jin (body fluid) [16]. In general, ‘tonics’ are
used to treat deficiency and ‘clear-ups’ are used to treat
excess [9].

Considered the premium Qi-tonifying herb to treat vari-
ous illnesses [16], ginseng is thought to have the major indica-
tions as follows:

(1) Impalpable pulse caused by severe Qi-deficiency;

(2) Shortness of breath, feeble voice, spontaneous sweat-
ing and a weak pulse caused by Fei (lung) Qi-deficiency;

(3) Fatigue, anorexia and loose bowels caused by Pi
(spleen) Qi-deficiency;

(4) Fever and strong thirst caused by Qi-deficiency;

(5) Palpitation, insomnia and forgetfulness caused by
dual deficiency of Qi and Xue.

Study design compatible with Chinese medicine theory
Research topics
Instead of evaluating the efficacy of ginseng in all patients
suffering from a single disease, researchers should focus
on those patients with Qi-deficiency syndrome. Qi-defi-
cency causes decreased visceral functions and lowered
immune resistance, leading to various diseases. The mani-
festations of Qi-deficiency include lassitude, shortness of
breath, feeble voice, dizziness, spontaneous perspiration,
susceptibility to cold, pale tongue and weak pulse [10].

Participants
Chinese medicine practitioners prescribe herbal medica-
tions to rectify disharmony in a patient’s system [16].
Healthy individuals should not participate in treatment
groups in Chinese medicine studies. This explains the neg-
ative results from the ginseng studies in which healthy
individuals participated [17-21].

Ginseng is a Qi-tonifying herb to treat five major syn-
dromes [16] caused by Qi-deficiency. Therefore, we argue that only studies in which participants are diagnosed with Qi-deficiency are valid to evaluate ginseng’s efficacy [22-25].

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Herbal quality
Herbal quality may affect research results. Different batches of P. ginseng [27,28] or P. quinquefolius [29] produced opposing study results respectively on acute post-prandial glycemia. The primary active ingredients in ginseng are ginsenosides. G115, a ginsenoside-based standardized extract of P. ginseng, may help assess the efficacy and safety of ginseng. In fact, G115 was used in most P. ginseng (single herb) trials reviewed in this paper.

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Herbal safety
Certain Chinese medicine herbs are toxic and others may have adverse effects when used improperly [16]. A condition known as the ginseng abuse syndrome is characterized by heart palpitations, heaviness in the chest, high blood pressure, dizziness, insomnia, agitation, restlessness, nausea, vomiting, abdominal pain and/or bloating, diarrhea, possible upper digestive tract bleeding, edema, and red skin rash [40]. Most of these reported adverse effects are common manifestations of Qi-excess and Qi-
stasis. While all clinical trials should document adverse effects, only one trial did so [41].

**Re-examination of equivocal ginseng trial results**

To exemplify our framework of experimental study design, we searched and analyzed randomized controlled trials of ginseng in PubMed. The inclusion criteria were single herb ginseng trials with a sample size of ≥20. We selected trials of single herb ginseng because the majority of the trials belonged to this category. Nineteen clinical trials were selected for analysis according to the inclusion criteria (Table 1) [42-46]. Most of the trials were considered good based on a trial quality evaluation scale [47].

| Negative results | Trial quality* | Research topic | Participants (n) | Herb species | Chinese medicine theory | Reference |
|------------------|----------------|----------------|------------------|--------------|------------------------|-----------|
| Allen JD et al. (1998) | 4 | Exercise performance | Healthy young (28) | *P. ginseng* | No Qi-deficiency | [17] |
| Cardinal BJ et al. (2001) | 4 | Psychological well-being | Healthy young adults (83) | *P. ginseng* | No Qi-deficiency | [18] |
| Caron MF et al. (2002) | 3 | Cardiovascular function | Healthy adults (30) | *P. ginseng* | No Qi-deficiency | [42] |
| Dowling EA et al. (1996) | 3 | Exercise performance | Highly trained distance runners (20) | *Acanthopanax senticosus* | No Qi-deficiency | [43] |
| Engels Hj et al. (1997) | 3 | Physiologic and psychological responses | Healthy adults (36) | *P. ginseng* | No Qi-deficiency | [21] |
| Engels Hj et al. (2001) | 3 | Exercise & short-term recovery | Healthy active women (24) | *P. ginseng* | No Qi-deficiency | [20] |
| Engels Hj et al. (2003) | 3 | Physical performance heart rate recovery | Active healthy adults (38) | *P. ginseng* | No Qi-deficiency | [19] |
| Stavro PM et al. (2006) | 3 | Blood pressure and renal function | Hypertension (52) | *P. quinquefolius* | Inappropriate herb species | [49] |
| Wiklund IK et al. (1999) | N/A | Quality of life & physiological parameters | Symptomatic postmenopausal women (384) | *P. ginseng* | Inappropriate herb species | [51] |

| Positive results | Trial quality* | Research topic | Participants (n) | Herb species | Chinese medicine theory | Reference |
|------------------|----------------|----------------|------------------|--------------|------------------------|-----------|
| Cicero AF et al. (2004) | 2 | Quality of life | Elderly hypertensive and digitalized (20) | *Acanthopanax senticosus* | Appropriate herb species | [53] |
| de Andrade E et al. (2007) | 2 | Sexual function | Erectile dysfunction (60) | *P. ginseng* | Qi-Deficiency | [44] |
| Ellis JM et al. (2002) | 5 | Quality of life | Healthy young (30) | *P. ginseng* | Marginal Qi-deficiency | [48] |
| Gross D et al. (2002) | N/A | Respiratory function | Chronic Obstructive Pulmonary Disease (COPD) (92) | *P. ginseng* | Qi-Deficiency | [22] |
| Hong B et al. (2002) | 3 | Sexual function | Erectile dysfunction (45) | *P. ginseng* | Qi-Deficiency | [45] |
| Kim JH et al. (2006) | 3 | Quality of life | Cancer (53) | *P. ginseng* | Qi-Deficiency | [23] |
| Liang MT et al. (2005) | 3 | Endurance exercise | Untrained adults (29) | *P. notoginseng* | Appropriate Qi-deficiency | [54] |
| McElhaney JE et al. (2004) | 3 | Acute respiratory illness | Sub healthy seniors (198) | *P. quinquefolius* | Qi-Deficiency | [24] |
| McElhaney JE et al. (2006) | 3 | Acute respiratory illness | Sub healthy adults and seniors (43) | *P. quinquefolius* | Qi-Deficiency | [46] |
| Predy GN et al. (2005) | 5 | Cold | Sub healthy adults (323) | *P. quinquefolius* | Qi-Deficiency | [25] |

*Trial quality evaluation scale [47]
0–2: poor quality
3–5: high quality
N/A: full text unavailable for quality evaluation
life in a healthy young adult population. In this case, the participants had marginal Qi-deficiency as young adults are at the stage of ‘gradual filling of Qi and Xue’ [9] according to Chinese medicine theory.

**Herbal species/safety**

The species of ginseng may be a confounding factor in the interpretation of trial results, which is illustrated by four trials as follows (Table 1).

Stavro et al. [40] enrolled 52 hypertensive participants to evaluate the long-term effects of *P. quinquefolius* on blood pressure [49]. Long-term use of ginseng was reported to be associated with the development of hypertension, which was refuted by Stavro et al. In Chinese medicine practice, however, *P. quinquefolius*, unlike its cousin *P. ginseng*, is in fact used to treat hypertension in some cases.

Wiklund et al. [50] reported a trial in which 384 symptomatic postmenopausal women were assessed for the effects of *P. ginseng* on the quality of life and physiological parameters. Postmenopausal symptoms such as hot flashes are often regarded as Shen (kidney) Yin-deficiency [51] and are treated with *P. quinquefolius* rather than *P. ginseng*. Moreover, the use of *P. ginseng* in this study was contraindicated and might have produced adverse effects.

Cicero et al. [52] studied 20 elderly hypertensive and digitalized patients treated with *Acanthopanax senticosus* (Siberian ginseng) which is a mild Qi-tonic for an unspecified feeling of fatigue, a sign of Qi-deficiency [53]. Hypertension is manifested in five syndromes [11], of which Qi-deficiency is only a minor one. The positive results from this trial were due to the fact that *A. senticosus*, an alternative Qi-tonic, was used [16].

Liang et al. [54] found that *P. notoginseng* improved endurance time to exhaustion and lowered mean blood pressure in 29 untrained young adults during an endurance exercise. *P. notoginseng* is another important ginseng species classified as homeostatic medicine to arrest bleeding and removes stagnant Xue.

**Conclusion**

Our analysis of 19 randomized controlled clinical trials of single herb ginseng shows that all the trials with both negative and positive results confirm the specific effects of ginseng indicated by Chinese medicine theory. Therefore, study designs guided by Chinese medicine theory are necessary to validate and improve future randomized controlled trials in Chinese medicine.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

JY conceived the idea of the manuscript. VFE modified the idea and edited the manuscript. YXH and YJ collected references and participated in the discussions. WKG helped draft the manuscript. JY finalized the manuscript. All authors read and approved the final version of the manuscript.

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