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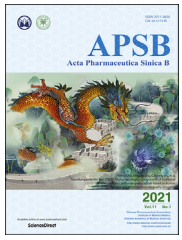

POLICY FORUM

Botanical drug clinical trial: Common issues and future options

Yu Sun[a], **Jiahua Qian**[b,*]

[a]*Department of Traditional Chinese Medicine and Ethnopharmaceuticals, Center for Drug Evaluation, National Medical Products Administration, Beijing 100022, China*
[b]*Center for Drug Evaluation, National Medical Products Administration, Beijing 100022, China*

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Abstract In order to understand this disparity between human use and drugs approved by regulatory agencies, we analyzed botanical drug clinical trials registered at ClinicalTrial.gov to detect trends in current trials and guide future trials. A total of 195 botanical drug clinical trials were registered from 2016 to 2019, of which 81 are phase II or phase II/III. 95% of all phase II and II/III studies were designed with 100 or less participants per arm, indicating a more observational nature due to the limited power to detect differences in outcomes between treatment and control groups. Due to the limited number of participants, efficacy outcome from results may be highly subjective. 14% of the total trials were phase I studies. For botanical drugs with well-documented or extensive history of human use, phase I may not provide significant additional information, and may, therefore, not be necessary. For the trial design, we suggest added-on studies when botanical drugs are used as part of a combination treatment. Additionally, we believe standardized data collection methods and criteria are critical to utilizing the vast collection of human experience as quality evidence to support regulatory approval.

*Corresponding author.
E-mail address: qianjweb@outlook.com (Jiahua Qian).

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1. Introduction

Botanical drugs are plant-derived, complex mixtures which may have synergistic effects beyond and be more affordable than their purified analogs. In the Democratic Republic of Congo, dried leaves of the *Artemisia* plant were given to 18 malaria patients who failed the standard malaria therapy. Five days later, all of them fully recovered[1]. Although limited in sample size, the study's success offers hope for not only drug-resistant malaria, but also supports the use of plant-derived mixtures as new drugs for the treatment of human diseases. Additionally, plant-derived complexes are more affordable due to less manipulation and processing. Despite a long history of human use, few botanical drugs have been approved. In this review article, we analyze the common issues in clinical trial designs of botanical drugs and discuss options for plant-derived complexes, some of with unclear active ingredients.

A botanical drug, as defined by the U.S. Food and Drug Administration (FDA), is "a product that contains as ingredients vegetable materials, which may include plant materials, algae, microscopies fungi, or combinations of that is used as a drug"[2]. The same definition of "botanicals" does not include[2]: 1) products that contain animals or animal parts, except when these are a minor component in a traditional botanical preparation (*e.g.*, traditional Chinese medicine, Ayurvedic medicine); 2) materials derived from genetically modified botanical species; 3) products produced by fermentation of yeast, bacteria, plant cells, or other microscopic organisms; 4) highly purified substances derived from a naturally occurring source (*e.g.*, paclitaxel) or chemically modified (*e.g.*, estrogens synthesized from yam extracts).

Although there are differences among botanical drugs, chemical drugs, and biological products pharmacologically, there is no difference in current requirements for clinical trials to demonstrate safety and efficacy for regulatory approval. Botanical drug clinical trial design is impeded by the limited number of approvals by FDA and European Medicines Agency (EMA). Thus, there is currently no consensus on how to conduct clinical trials for botanical drugs to accommodate the complexity of plant-derived mixtures where mechanism of action may differ from that of a single molecule. With this in mind, we analyzed botanical drug clinical trials registered at ClinicalTrial.gov in hopes of providing insight on current trials and inciting potential improvements in the near future.

2. Methods

We searched ClinicalTrial.gov website over a three-year period (4/30/2016 to 4/30/2019) using key words: TCM, traditional Chinese medicine, traditional medicine, herbal, botanical, and extract. TCM stands for "traditional Chinese medicine." Both "TCM" and "traditional Chinese medicine" were used as key words due to the lack of standardization in botanical drug trial registry. Results were filtered by study type [interventional studies (clinical trials)] and phase (not including phase 4). Trials were excluded from our study if they were plant-derived single molecular entities (*e.g.*, cannabidiol and curcumin) or the combination of the highly purified substances (*e.g.*, cannabidiol plus Δ9-tetrahydrocannabinol), registered as a dietary supplement, or a phase 4 study.

3. Geographic distribution of botanical drug clinical trials

Of 1782 trials meeting our search criteria, 195 trials met our inclusion criteria as botanical drug clinical trials. On average there were 65 entries per year and no meaningful increase or decrease during the three-year period. China, United State, Egypt and Korea were the top four countries in botanical drug trial registration (Table 1). China had 101 of 195 registered botanical trials.

4. Trial design

A trial depends largely on the type of disease; therefore, we analyzed indications of 195 registered trials using the code structure for the ICD-11 in Supporting Information Table S1. The indications were widely spread into 81 categories. All the 195 registered trials did not intend to treat rare diseases defined as fewer than 1 per 1500 people.

Table 2 shows the trial designs from single arm to eight-arm studies. 39 of 195 trials (20%) did not specify the trial phase and thus are displayed as "not applicable". 4 of 195 trials (2%) did not provide the number of participants. Two-arm studies were the majority with 134 of 195 trials (69%). 27 of 195 trails (14%) were registered as phase I studies. The purpose of a phase I study is to evaluate safety, tolerability and pharmacokinetics for the first in-human use. Since most botanical products have a prior human experience, one may question the necessity of phase I studies. Previous human experience may be used to support beginning with phase II clinical trials[2].

We analyzed 175 trials from 2 arms to 8 arms studies. 98 of 175 trials (56%) were placebo control studies. Randomized-controlled studies (RCT) are the gold standard in clinical trial design. The double blinded, single blinded and unblinded studies were analyzed in Table 3. 57 of 175 trials (32.5%) were designed as randomized, double-blinded and controlled studies. 82 of 175 trials (46.9%) were single-blind studies. 34 trials (19.4%) were randomized and controlled but not blinded studies. Only 2 of 195 trials (1.1%) were not controlled. 173 of 195 studies (88%) were RCT studies.

The purpose of phase II and III studies is to demonstrate an effectiveness of investigational products. Sufficient sample size is an important factor in trial design. Fig. 1 demonstrates trial size of these studies. 159 of 191 (81.6%) trials had 100 or less participants per arm. 85 trials were registered as phase II and phase II/III, among which 77 of 85 studies (90.5%) were designed with 100 or less participants per arm. Among phase III studies, 14 out of 28 studies (50%) had 100 or less participants per arm.

The trial size of 2-arm studies was further analyzed, since 2-arm studies constituted 131 of 191 (68.5 USD) of eligible trials. In Fig. 2,

Table 1 Geographic distribution of botanical clinical trials.

Country	Number of trials per country
China Mainland/China Taiwan/China Hong Kong	84/12/5
United States	22
Egypt, Korea	12
Brazil, India	5
Canada, Iran, Thailand	4
Bangladesh, Singapore, Switzerland	3
Indonesian, Israel, Malaysia	2
France, Germany, Japan, Lebanon, Mexica, Pakistan, Saudi Arabia, Sweden, Tunisia, United Kingdom, Vietnam	1

Table 2 Trial design.

Study design	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase not specified	Number of participants not specified	Total
1 arm	9	3	4	0	0	0	4	20
2 arms	14	9	33	21	26	3	28	134
3 arms	2	4	8	4	2	1	3	24
4 arms	1	0	7	1	0	0	3	12
5 arms	0	0	1	0	0	0	1	2
6 arms	1	0	1	0	0	0	0	2
8 arms	0	0	1	0	0	0	0	1
Total	27	16	55	26	28	4	39	195

Table 3 Multi-arm trial design.

Trial design	Total	Randomized/double blinded/controlled	Randomized/single blinded/controlled	Randomized/controlled	Not controlled	Total
2 arms	134	45	64	24	1	83
3 arms	24	7	100	6	1	15
4 arms	12	4	6	2	0	8
5 arms	2	0	1	1	0	1
6 arms	2	1	0	1	0	1
8 arms	1	0	1	0	0	1
Total	175	57	82	34	2	175

we grouped participants into 3 groups; 20 or less, 21 to 100 and more than 100 per group. In 20 or less participants per arm group, there were 6 trials for phase I/II study, and 2 trials for each phase II/III and III studies (Fig. 2). Among phase II studies, 30 of 33 trials were designed with 100 or less participants per arm. From our analysis trial sizes was a common issue in botanicals clinical trial design.

5. Thought and suggestions

The history of botanical drug usage differs greatly between countries. In China, botanical drugs have been used for thousands of years[3]. Information on these drugs has been passed through generations as individual experiences. The difficulty lies in transforming individual experience into transparent, auditable, and reproducible data for supporting regulatory approval. We need standards for data entry and collection, which would allow us to collect data from a variety of sources. Only high-quality data, known as real-world data (RWD), can be analyzed to generate safety and efficacy evidence, known as real-world evidence, to be used for regulatory approval. It will be a challenge to generate efficacy evidence from random data. To standardize the data, FDA guidance on standardizing electronic source data are good references[4,5]. A promising sign is that China, which holds over 50% registered botanical drug clinical trials, is implementing an Electronic Medical Record (EMR) system to standardize data fields[6]. We believe this is the first step in translating botanical clinical use data to actionable knowledge in the near future.

For many botanical drugs with human experience, we think the safety data could be obtained from real-world experience. With known safety profiles, non-clinical and phase I safety studies might not be necessary.

We also recommend a special add-on clinical trial design when a botanical drug could be added on as a part of a combination therapy, potentially reducing risk and improving outcome. For corona virus disease 2019 (COVID-19), patients who received a

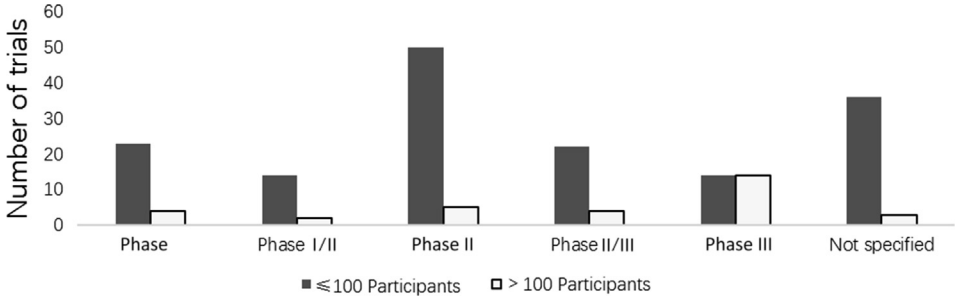

Figure 1 Analysis of participant's number in phase I to III studies. 191 of 195 trials were used excluding 4 trials which did not register the number of participants.

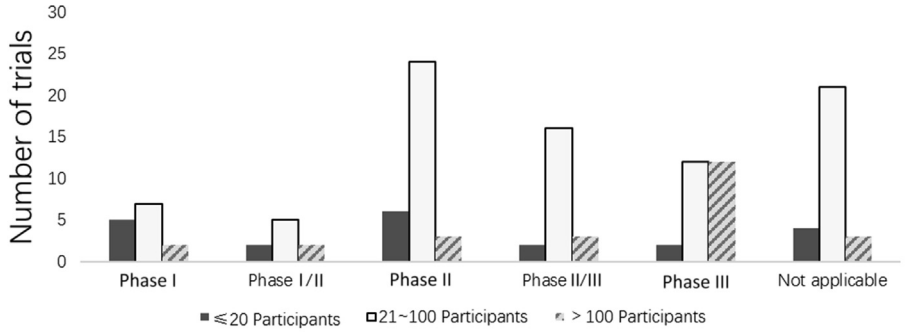

Figure 2 Analysis of participants' number in 2 arms study. Total of 131 trials for 2 arms study were used in the analysis.

combination therapy of botanicals from traditional Chinese medicine and standard care had shortened times to recover compared to patients who received standard care alone[7].

For botanical drugs with known active ingredients, RCTs may be a preferred choice. The advantages of an RCT are the familiarity of regulatory agencies with this trial design, relatively limited sample size, and short follow-up time. RCTs are designed for products with a known active chemical or molecular structure. Knowledge of target binding sites and biological interactions creating a difference between the treatment and control is the basis in determining inclusion criteria and the measurable endpoint.

For botanical drugs with unknown active ingredients, it is a challenge to determine appropriate inclusion/exclusion criteria and trial size. We suggest conduct a large sample size, prospective, and controlled observational phase II/III study. This trial design could broaden eligibility criteria and increase enrollments to include different types of evidence, which may increase the understanding the botanicals' benefit−risk profile. By increase the power of botanical drug clinical trials, we can better assess the benefit of these drugs in treatment outcomes, including improving quality of life.

To date, the FDA has approved two botanical drugs, Veregen (sinecatechins, 2006) and Fulyzaq (crofelemer, 2013)[8], from several hundreds of botanical product Investigational New Drug (IND) applications. The FDA recognizes that many botanical drugs have previous human experiences, which may provide sufficient safety data to support the early phase of study under INDs[2]. The FDA suggested to reduce or delayed the testing botanical products in animals if human experience demonstrated reasonable safety of products[2]. The FDA guidance on botanical drug development emphasized adequate and well-controlled clinical trials are necessary for marketing botanical products in US[2].

We hope the article illustrates lessons in trial design to inform an improved trial design in the future, and our suggestions on potential trial designs may initiate discussion for the development of new and affordable botanical drugs for the treatment of unmet medical needs.

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Author contributions

Jiahua Qian was responsible for the conception and design of the review. Yu Sun drew the figures. Jiahua Qian and Yu Sun drafted and revised the manuscript.

Conflicts of interest

Yu Sun and Jiahua Qian declare that they have no conflict of interest or financial conflicts to disclose. Dr. Jiahua Qian, currently, is an independent consultant, Maryland, USA.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2020.08.003.

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