A pre-trial evaluation of blinding for a Chinese herbal medicine trial

Shohreh Razavy [*], John Lee, Christopher Zaslawski

School of Life Sciences, University of Technology Sydney, 2007, New South Wales, Australia

ABSTRACT

Background: Blinding is considered an important methodological characteristic in clinical trials to minimise bias and maximise the validity of a trial. Unlike pharmaceutical substances, most herbal medicines have distinctive sensory specifications, including odour and taste, which can be quite challenging when developing a placebo control to match the specific characteristics of herbal substances being examined. The present study was, therefore, designed to evaluate whether the participants could differentiate an active herbal capsule (Ganopoly combination) from a placebo material capsule. The aim of this study was to develop a suitable placebo substance for encapsulation to be used in a future herbal medicine clinical trial.
Methods: The current study was improved upon the previous investigation, and several modifications were made to the placebo substance in order to mimic the herbal substance characteristics. Prior to conducting the study, a refined placebo substance was developed using commonly consumed culinary agents. Sixty-two healthy volunteers participated in the study and were randomly provided one of the two substances. Individuals were asked to evaluate the three sensory characteristics of the allocated capsule (visual appearance, odour, and taste), and determine whether they believed the substance to be a 'herbal' or a 'placebo' substance.
Results: The study provided evidence on the success of blinding for only two sensory characteristics, namely, visual appearance (95% CI -0.15, 0.34) and odour (95% CI -0.34, 0.15). In contrast, the findings related to the taste indicated that participants correctly guessed the herbal substance compared to the placebo substance to a significantly higher proportion than would have been expected by chance alone (95% CI 0.14, 0.60).
Conclusion: The failure to blind participants for taste highlights the difficulties in preparing placebo herbal substances that match as closely as possible to a real herbal substance. Blinding is particularly challenging where herbal medicines have different sensory characteristics.

1. Introduction

Herbal medicines have become an essential part of healthcare globally [1,2]. Many clinicians and researchers believe traditional herbal medicine will play an increasing role in global health [3]. Among different herbal products, Chinese herbal medicine (CHM) is popular around the world although its effectiveness remains contentious [4]. Over the last several decades, the scientific evidence, including both experimental and clinical, has demonstrated the efficacy of some CHM for a range of illnesses and conditions [5]. Randomised controlled clinical trials (RCTs) are widely acknowledged as the criterion standard for unbiased assessment of the effect of the pharmacologic treatments [6]. In this regard, blinding is recognized as an important design feature, and the cornerstone of a rigorous evaluation in such trials [6,7]. Due to the importance of the blinding success, the CONSORT statement has incorporated this feature as one of 22 items (11a-b) when investigators

report their RCTs [8]. However, it is unclear what constitutes adequate evidence of blinding success [9]. Furthermore, the quality of the choice of control interventions within published trials has been repeatedly criticized [2,4,7,10]. Poor development and selection of control treatments is deemed to affect the success of blinding as well as the efficacy of the administered interventions [4,11]. High-quality RCTs are, therefore, required to further enhance and support acceptance of CHM [10].

Despite the importance of blinding, reporting of this critical feature is infrequent and often inadequately described in published studies [11–13]. In this respect, Hopton and MacPherson stated that the quality of a trial cannot be established unless the blinding is evaluated [14]. Others, however remain unconvinced that all trialists should conduct a blinding assessment exercise [15]. Nevertheless, blinding is widely acknowledged as an important methodological feature in RCTs [11,13, 16], and should be integrated into the study design whenever possible [13]. Methods of assessing and reporting the success of blinding,

however, is a controversial issue [16], and may be difficult to achieve in some situations [11,17]. While the magnitude of blinding is ascertained by directly asking participants and other associates at several stages during or at the end of a trial [11], evaluating the success of blinding is suggested to be more reliable when determined before the evaluation of the clinical trial outcome [15]. In a pre-trial assessment of blinding study, Walter and colleagues explained that "A pre-trial assessment can be based on establishing if one can reliably distinguish between the two types of medication, using some form of head-to-head comparison of their physical or other characteristics" [13].

Currently, research on herbal medicines poses various challenges including issues related to the ethical concerns, quality control, study design and more specifically, the selection of a control (placebo, usual care, or some form of an active intervention) [1]. The Council for International Organizations of Medical Sciences have defined placebo as "an inert substance or sham procedure is provided to research participants with the aim of making it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention" [18]. However, other research team have argued that a placebo cannot be defined in any logical way and, therefore, there is no commonly accepted definition of placebo [19,20].

Unlike pharmaceutical substances, most Chinese herbs have distinctive sensory characteristics which makes blinding very difficult. For instance, selecting a matching control in certain herbal products which contain ginger is a challenging task due to the unique odour of the herb [1]. To overcome this problem, researchers often encapsulate the herbal substance and the placebo substance. In our previous study, two experiments were undertaken to determine whether a credible placebo substance could be developed for use in a clinical trial for CHM. The study highlighted the difficulties involved in preparing placebo herbal substances that look, smell and taste as similar as possible to the real herbal substance [21].

The current study was, therefore, designed to determine whether a participant could identify a herbal capsule or a placebo capsule when randomised to receive one or the other. This study was also improved by modifying the taste and colour of the placebo substance used in our previous published study [21] to be as similar as possible to the herbal substance. It is noted that while this study did not involve a comparison comparable to the real-life situation of a clinical trial, the outcome of the current study will assist the development of suitable placebo substance for encapsulation which may eventually be used in a future clinical trial.

2. Materials and methods

2.1. Study overview

The study involved two substances, a refined placebo substance and a herbal substance. Participants were randomly provided one of the two substances and asked, using a questionnaire whether they believed the substance to be a 'herbal' or a 'placebo' substance. While the participants were blind to their capsule allocation (either herbal or placebo) no eye pad was necessary as there was no comparison with other substances which was the case in the previous published study.

2.2. Setting and participants

All data were collected on site at the University of Technology Sydney (UTS). Ethics approval was obtained from the UTS Human Research Ethics Committee (UTS HREC 2009–070) prior to commencing the study. Participants were sought from the local university environment and included undergraduate students. All participants were given an information sheet and asked to sign a consent form prior to participating in the study.

Sixty-two healthy participants, who were not taking any medication, were recruited by word of mouth, as the method involved the sample being drawn from a population that is "close at hand", that is readily available and convenient [22]. Participants were excluded if they had any food sensitivities or known food allergies.

2.3. Herbal substance

The herbal substance, Ganopoly combination, is derived from extracted material of two active ingredients, Ganoderma Lucidum (so-called *Lingzhi* mushroom) [23] and Cordyceps Sinensis *(Dong Chong Xia Cao)* which literally means 'winter worm-summer grass' [24]. The herbal supplement is currently manufactured by Alpha Bio-Tech Aust Pty Ltd (QLD, Australia) and is listed in the Australian Register of Therapeutic Goods (ARTG) with the following listed number-L71644. The capsule contained 500 mg of G. Lucidum (equivalent to dry 20 g) and 100 mg of C. Sinensis (equivalent to dry 200 mg) [25].

Both ingredients have a long history of use for a variety of health conditions [19,21]. Ganoderma Lucidum, a medicinal mushroom, has been used for promoting health and longevity in Asian countries [23, 26]. The G. Lucidum, medicinal mushroom, is purportedly considered beneficial for a broad range of conditions having a number of biological activities [27], and its growing popularity is reported to be due to its polysaccharides which have both anti-tumour and hypoglycemic activities [26]. In terms of taste, G. Lucidum is reported as bitter due to the high levels of triterpenes [28]. However, the triterpenes concentration is varied in the different parts and growing stage of the mushroom [29,30].

It should be noted that although it is a common practice to apply the originally European name 'Ganoderma lucidum' to G. Lucidum and G. Lingzhi fungi, the approach has been questioned by several taxonomists. In 2016, a research team investigated basidiocarp morphology and phylogenetic analyses of the two fungi and concluded that basidiocarp of Ganoderma lucidum is identified as G. lucidum s. str. whereas basidiocarp of Ganoderma Lingzhi represents G. Lingzhi. Further analysis also showed a higher diversity and higher amounts of ganoderic acids in G. lingzhi than in G. lucidum that probably are responsible for the bitter taste of the ethanol extract of the latter [31].

The other extract Cordyceps Sinesis, medicinal fungi, also has a long-standing use in China and other Asian countries for a variety of conditions, including treatment of infectious diseases [32]. Several bioactive constituents have been extracted from C. Sinesis such as cordycepin, polysaccharides, ergosterol, mannitol, and adenosine [33,34] with a wide range of pharmacological actions (e.g., nephroprotective, hepatoprotective, and inflammatory effects) [33]. Evidence from an vitro study indicated that C. Sinesis is an activator of innate immune responses that activates macrophages by engaging Toll-like receptors and inducing mitogen-activated protein kinase pathways characteristic of inflammatory stimuli [32]. C. Sinensis is described as sweet in taste and neutral in nature according to the theory of Chinese medicine [35,36].

2.4. Placebo substances

Prior to conducting the current study, a refined substance was developed based on the materials used for the placebo substance in our previous study [21]. While the placebo substances were required to have a strong flavour similar to that of the herbal substance, it also needed to be as therapeutically inert as possible. It should be highlighted that it is extremely difficult to have a substance that is physiologically inert once ingested, commonly used culinary agents that are frequently ingested in daily life were selected for the current study. The ingredients for the placebo material was comprised of (a) ground unprocessed (brown) rice; (b) food colouring agents (Queen brand) of yellow, red, and blue with a ratio of 6:9:6; (c) a mixture of black pepper (McKenzie's Ground Black pepper), curry powder (Masters of Spices brand) and ground rice with a ratio of 3:4:12 (Fig. 1).

It should be noted that the placebo materials used in the current study were modified and improved in three ways compared with the earlier published study [21]. First, ground rice was used instead of cornflour to give a grainier texture to the base material based on several

Fig. 1. Visual appearance of materials used (powder form); Note. A = placebo substance; B= Herbal substance.

Fig. 2. Visual appearance of materials used (encapsulated form); Note. A = Placebo substance; B= Herbal substance.

participants comments in the earlier published study that there was a difference between the cornflour based material and the real herbal substance. Second, a darker colouring agent was used to colour the placebo materials giving them a similar colour to the herbal substance. Lastly, the flavouring agents of black pepper and curry powder were used together in the placebo material to provide a more complex taste.

2.5. Study design and data collection procedures

The current study aimed to evaluate whether the participants could differentiate an active herbal capsule from a placebo material capsule. This design of the study regarding the intervention administration was different to the previous study in that during a two arm (active versus control placebo) clinical trial, a participant is only allocated to one treatment, either the herbal capsule or the placebo control capsule, unless of course, it is a cross over design. Participants were randomised using a permuted block of four participants and an envelope as the method of randomization to balance numbers for each type of capsule to receive either capsule A (placebo) or capsule B (herbal substance). To randomise the sequence of testing, 31 envelopes had the word placebo inside, and the remaining 31 had the word herbal. Each participant was asked to select one envelope from a block of four randomly chosen envelopes, and the participant was given the material that was indicted inside the envelope they had selected (A denoted placebo while B denoted herbal).

A simple self-designed questionnaire was developed and administered to all participants during the study. The questionnaire was consisted of three questions to evaluate the success of blinding with respect to visual appearance, smell and taste. Individuals were required to choose one of three response categories for each of the question and decide whether the allocated capsule was a 'herbal substance', a 'placebo substance'. The questionnaire also included a descriptor item, 'don't know' (DK), for participants if they were indecisive concerning the capsule provided. The method used in the study is the most prevalent method for obtaining the data needed for blinding assessment [37] and has been used in different studies [37–39]. Participants also needed to identify if they had previously ingested herbal medicine and methods of delivery (i.e. pill, granules, and decoction). In addition, an identical open-ended question was used for examination of the individual questions for the sensory characteristics (n = 3) to capture participants responses for the selected response choices. This assists in identifying what cues may have been important for the participants in discriminating the placebo from the herbal substance.

The materials were packed in transparent capsules (00 size) which were sealed by bringing the two halves of the capsule together (Fig. 2). The capsules were then placed in transparent plastic bottles.

The procedure for evaluating the capsule involved first asking each participant to visually examine the capsule, then smell the unopened capsule and then finally to break the capsule and taste with a wet fingertip the substance inside the capsule. Participants were required to complete the questionnaire only on one occasion.

3. Statistical analysis

To establish statistical power, it was estimated that a sample size of 62 participants would be required for this preliminary study considering potential drop-out or withdrawal cases. This was based on the condition that to test the null hypothesis, the proportion correctly choosing the herbal is 0.5 (i.e. indistinguishable from chance) versus the alternative hypothesis, and that the proportion was 0.7, given a power of 0.9.

Statistical analyses comprised of both descriptive statistics and a two-proportion hypothesis (z-test for the difference of proportions) to determine whether a statistically significant difference existed between the binomial proportions of the allocated groups. A sub-analysis (chi-square test for association) was also conducted to investigate if there was an association between the pre-experience of herbal medicine intake and participants' choice of responses. In a case where the expected cell counts identified below five, Fisher's Exact test was reported. Data analysis was performed using the statistical program, IBM SPSS Statistics Software (Version 26, USA). The null hypothesis (H_0) was set to test the observed number of correct guesses for each capsule, group A or group B at random, with a probability of 1/2 for each group due to a 1 in 2 chance. Under H_0, a similar percentage of individuals in each group should perceive that the substance they are observing, smelling and tasting was a herbal substance or a placebo substance with a two-tailed probability parameter equal to 0.5.

4. Results

A total of 62 healthy volunteers fulfilled the inclusion criteria and participated in the study with a mean age of 40.3 ± 14.1 years (range 15–68 years). Among participants, forty-one were females (66%) with an average age of 40.68 ± 13.78 (range 17–67 years), while twenty-one were males (33.9%) with an average age of 39.52 ± 14.97 (range 15–68 years). The homogeneity of age range was also evaluated by gender (male cf female). The results indicated that homogeneity of variances was met as assessed by Levene's test for equality of variances (p = 0.995). There was not a statistically significant difference in the age range between male and female participants in the study, t (60) = −0.305, p = 0.762.

Among participants, females (n = 40; 97.6%) reported greater experience in previously ingested herbal medicine compared to male participants (n = 17; 81%) (Table 1).

Of the 62 participants who reported previously taking herbal medicine in the study, 41.93% had used all three forms of herbal medicine, including pills, decoction, and granules (PGD). The remaining

Table 1
Participants' previous experience of herbal medicine by gender.

| | Gender, n (%) | |
	Female	Male
Taken herbs previously	40 (97.6)	17 (81.0)
Never taken herbs previously	1 (2.4)	4 (19.0)

Total valid participants (n = 62).

participants used other combinations, as shown in Fig. 3.

In the current study, the proportion of correct and incorrect responses were statistically compared and 'DK responses were excluded for further analysis given that DK respondents were genuinely uncertain about the status of their assigned capsule. One research team stated that most reports excluded data on participants answering DK from the statistical analysis [16]. Regarding this perspective, another research team stated that DK responses may be indicative of disagreement and, therefore, could be considered as a more favourable result since indicates a high magnitude of blinding [11]. It is worthwhile noting that in all the three examinations, correct guesses are least supportive of the blinding.

The results for visual appearance using a two-proportion hypothesis test showed that a similar proportion of participants (20 cf 17) believed they were receiving an herbal substance (p = 0.435) (Table 2).

A similar result was also obtained for odour, implying that the placebo substance was successful in blinding an equal proportion of participants (p = 0.443), those that received the herbal material and those that received the placebo material (13 cf 16) (Table 3).

In contrast, the results related to the taste implied that participants correctly judged the herbal substance versus placebo substance to a greater proportion than would have been expected by chance alone. Indeed, a statistically more significant proportion of participants in the herbal group believed they were tasting an herbal substance (p = 0.002) compared to the placebo substance (22 cf 10) (Table 4).

Participants were also asked to provide reasons for their choices concerning individual examinations. In most cases, no reasons were given (NRG) for each of the three examinations, visual appearance (12 out of 54), odour (10 out of 53), and taste (8 out of 52). A list of reasons for the individual type of responses were also thematically investigated, and the most frequent rational for the participants' choices were captured. Regarding the visual appearance of the capsules, 'herbal look' was the most frequent reasons identified by the participants (n = 6); however, five out of six incorrectly differentiated the capsules. Colour was the second most frequently reported reason (n = 4), where only two participants correctly identified herbal substances with an equal number of participants for DK and incorrect guess (n = 1). A similar pattern was
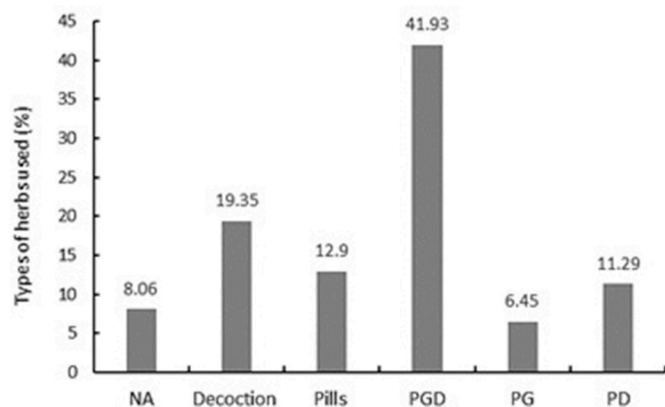

Fig. 3. Types of herbal delivery modes previously ingested among participants; NA = no answer; PGD = pills, decoction, granules; PG = pills, granules; PD = pills, decoction.

Table 2
Frequency of participants guesses by group assignment for visual appearance.

| | Participants guesses, n (%) | | |
Assignment	Correct	Incorrect	Don't know
Capsule B (Herbal substance)	20 (64.5)	3 (9.7)	8 (25.8)
Capsule A (Placebo substance)	5 (16.1)	17 (54.8)	9 (29.0)
	Z = 0.78; p = 0.435		
	95% CI [-0.15, 0.34]		

Total valid participants (n=62), with an equal number in each assignment (n=31).

Table 3
Frequency of participants guesses by group assignment for odour.

| | Participants guesses, n (%) | | |
Assignment	Correct	Incorrect	Don't know
Capsule B (Herbal substance)	13 (41.9)	13 (41.9)	5 (16.1)
Capsule A (Placebo substance)	11 (35.5)	16 (51.6)	4 (12.9)
	Z = −0.77; p = 0.443		
	95% CI [-0.34, 0.15]		

Total valid participants (n = 62), with an equal number in each assignment (n = 31).

Table 4
Frequency of participants guesses by group assignment for taste.

| | Participants guesses, n (%) | | |
Assignment	Correct	Incorrect	Don't know
Capsule B (Herbal substance)	22 (71.0)	7 (22.6)	2 (6.4)
Capsule A (Placebo substance)	15 (50.0)	10 (33.3)	5 (16.7)
	Z = 3.17; p = 0.002		
	95% CI [0.14, 0.60]		

Total valid participants (n = 61), number in Capsule B (n = 31) and Capsule A (n = 30); missing case (n = 1) in Capsule A.

also observed when participants assessed the odour of the capsules. Although 'herbal smell' was the most rational reason, in most cases, participants were incorrectly differentiating the capsule (8 out of 9).

In contrast, for the taste question, 'herbal taste' was the most identified reason. Indeed, three out of six respondents correctly identified the capsule with one respondent selecting the DK response. 'Pepper taste' was the second most rationale for participants choice and correctly guessed in most cases (4 out of 5) followed by 'bitter taste' (4 out of 4) (Fig. 4).

A further investigation was also conducted to explore the rationale for participants' selection of DK responses for the three sensory characteristics in both assignments. In most instances, participants did not provide any explicit reasons for the selection of the DK category. Indeed, participants' reasoning were predominantly synonymous which was interpreted as 'unable to identify' with the following ratios for individual characteristics; visual appearance (10 out of 15; 66.6%), smell (6 out of 8; 75%), and teste (2 out of 6; 33.3%).

Additionally, the results from Fisher's Exact test indicated no statistically significant association between the pre-experience of herbal medicine intake and participants' choice of responses (p = 0.056).

5. Discussion

The importance of blinding in clinical trials has been repeatedly highlighted by regulatory and advisory agencies such as FDA [40] to prevent potential sources of bias [17,41] in RCTs. Yet, blinding in clinical research on herbal medicine poses various challenges [1]. Several factors including colour, odour and taste of the herbs must be standardised prior to commencing a study to ensure that the substances being evaluated in both the active and control group are comparable and
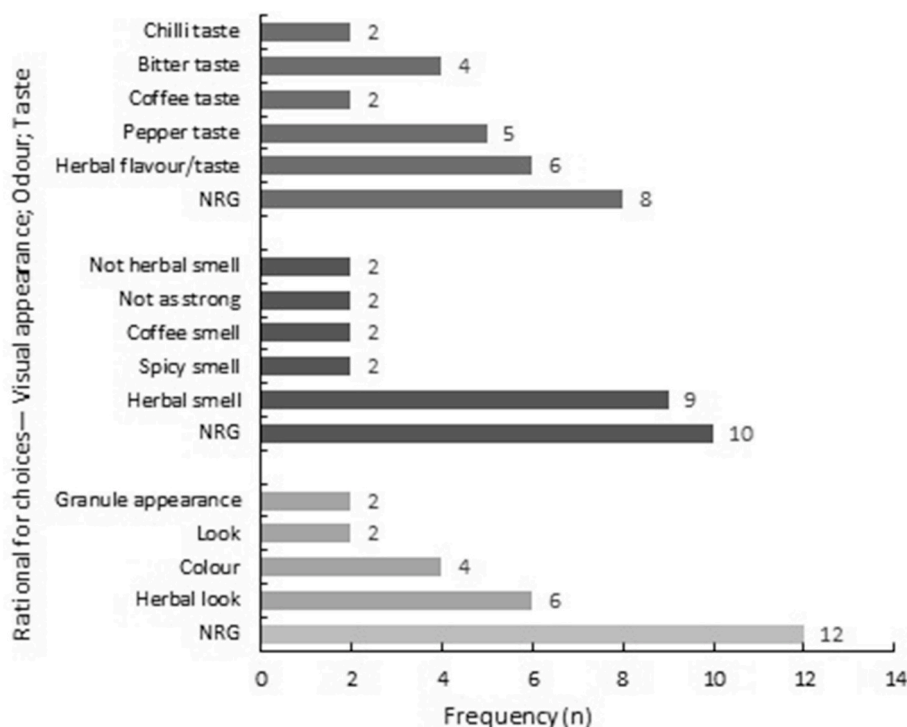
Fig. 4. Comparison of the most frequent rational for participants' choices (correct, incorrect, don't know) for the three examination (visual, odour, taste) regardless of participant allocation. NRG = no reason given.

have similar characteristics [1,17]. However, it is sometimes difficult or not feasible to design a flawlessly matched control [4] substance for some modalities of complementary medicine [19,42]. Another potential challenge is at what point in time during a trial, should participants be asked for their group allocation perception (i.e. asking before and/or during the early stage and/or at the end of the treatment phase) [42].

Currently, methods of assessing and reporting the success of blinding are contentious with no clear existing guidelines for adequately reporting the success of blinding [16]. Boutron et al. in a review of blinding in RCTs confirmed that the success of blinding is rarely described in reports [16]. In our previous research, a series of studies were developed aiming to identify important cues and features that may threaten participant blinding in an herbal medicine trial [21]. Similar to our previous study, a specific assessment approach was followed, including a visual appearance assessment, odour and taste evaluation. The current study attempted to improve upon the previous investigation, and therefore, several modifications were made to the placebo substance in order to mimic the herbal substance, as close as possible, in terms of texture, colour, and the flavour. The results of the current study indicated successful blinding for both visual and odour examinations as statistically similar proportions of participants believed they received herbal substances. However, this was not the case for the taste since a statistically greater proportion of participants correctly selected the herbal substance than the comparator substance. Additionally, the study findings indicated that previous experience of herbal medicine intake did not influence participants' choice of responses. However, the results should be interpreted with cautions due to small sample size.

One possible reason for unsuccessful blinding regarding taste could be that a sizeable proportion of participants had previous experience with ingesting herbal substances and had used all three forms of herbal medicine, including pills, decoction, and granules at some point in their lives. One may suggest recruiting participants who are herbal medicine naïve for future studies, although that is not the case in real practice. Herbal medicines are individualistic in approach [1], and often huge variations exist (i.e. source, preparation, dose and indication) in the way in which the medicines are used in herbal medicine practice. Hence, to

generalize the results from a structured and highly monitored trial to what will happen in the real world practice of the herbal medicine may be complicated [3]. In RCTs, the choice of a placebo control group is not simple [43] and the level of blinding of a trial [9] depends on the nature of the study. In addition, whether or not a substance is inert to some extent depends on the condition being evaluated (e.g. using a sugar pill for a patient in a trial for diabetes) [44].

It is also worth noting that while successful development of a control group (e.g., placebo substance) in a formal setting may assist others in the development of valid study design, this may not serve as an exact reference for future clinical trials. Matching placebo control substances cannot simply be purchased in an 'off-the-shelf' manner and its provision needs to be specific to each trial and the challenge is in the task of 'matching' [45]. In the current study, clear capsules were used for both assignments where participants could visually observe the substances in sealed capsules. Opaque or coated capsules are suggested in future herbal medicine trials to blind practitioners and practitioners from identifying which capsules contain the active medication or comparator product. However, this must conform to several regulations, one of which is a specific blinding feature that requires capsules to resists tampering and clearly reveal when tampering has occurred [46].

Nevertheless, it should be highlighted that research in herbal medicine must attempt to achieve a balance between internal validity (i.e. rigor) and external validity (i.e. generalizability) [3,43].

Other likely explanations for correctly guessing the herbal capsule are as follows: (1) participants were able to differentiate 'pepper taste' in the placebo substance; (2) participants expected the herbal substance to be bitter which could be partly explained due to higher dosage of G. Lucidum in each capsule. Similar to our previous study [21], the findings highlight that although not all herbal substances taste bitter, participants may expect the herbal substance to be bitter. It should be noted that differences in cultivation in different geographical locations under different climatic conditions and the natural genetic development (e.g., mutation, recombination) may affect the properties (i.e. taste) of individual species [28]. It is, therefore, an important factor to keep in mind when preparing and selecting placebo substances for future clinical

studies of herbal medicine.

5.1. Limitation and suggestion for future research

There are several limitations to this study that need to be acknowledged. Unlike pharmaceutical substances, CHM have special macroscopic, and sensory features including appearance, colour, odour and taste based on the origin of the constituents [47]. Hence, one major challenge was to develop a truly inert material with no, minimal or specific physiological effects and yet be identical to the characteristics of a herbal substance. Additionally, as discussed in our previous paper [21], culinary spices such as curry powder [48] and black pepper [49] which were used to develop the placebo substance in the current study have been reported to have some potential therapeutic value. However, this is always difficult as no substance, is truly physiologically inert once ingested [21]. Despite this, in order to improve blinding outcome, we suggest that placebo substances need to have a bitter taste, yet, smell as similar as possible to the real herbal substance being tested and smell less of culinary spices. Where possible, inert flavouring and colouring agents should also be used to avoid any undesirable therapeutic effect.

Furthermore, optional ancillary data could have been additionally collected from participants who declined to venture an opinion (i.e. don't know) by additionally requesting them to choose a capsule anyway in order to validate the responses. However, the major drawback associated with this approach is that participants would have been the coercive nature of the request.

6. Conclusion

A series of studies were undertaken to evaluate the success of blinding. The current study highlights the challenges involved in blinding participants in herbal RCTs. Despite all the attempts to blind participants concerning the examinations of all three sensory characteristics, the sense of taste remains difficult to blind. A potential problem for any herbal clinical trial would be that participants may break a capsule and taste the substances. Herbal medicines may exhibit a strong aroma or a distinguished taste which can be problematic when developing a control. Additionally, the relevance of blinding may vary based on the clinical trial context. While it may be unavoidable to use substances that have a physiological effect, every effort should be made to ensure that the placebo substance does not have an specific identifiable physiological effect on the condition being evaluated.

Funding

References

[1] A. Parveen, et al., Challenges and guidelines for clinical trial of herbal drugs, J. Pharm. BioAllied Sci. 7 (4) (2015).

[2] R. Guo, P.H. Canter, E. Ernst, A systematic review of randomised clinical trials of individualised herbal medicine in any indication, Postgrad. Med. 83 (984) (2007) 633.

[3] J.C. Tilburt, T.J. Kaptchuk, Herbal medicine research and global health: an ethical analysis, Bull. World Health Organ. 86 (8) (2008) 594–599.

[4] X. Zhang, et al., Placebo design in WHO-registered trials of Chinese herbal medicine need improvements, BMC Compl. Alternative Med. 19 (1) (2019), p. 299-299.

[5] C.C. Xue, Y. Lyu, Accelerating the comprehensive and systematic evaluation of clinical evidence for Chinese medicine using a whole-evidence approach, Global Health Journal 3 (2) (2019) 33–36.

[6] I. Boutron, et al., Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review, PLoS Med. 3 (10) (2006) e425.

[7] G.D. Qi, et al., Placebos used in clinical trials for Chinese herbal medicine, Recent Pat. Inflamm. Allergy Drug Discov. 2 (2) (2008) 123–127.

[8] C.W. Cheng, et al., CONSORT extension for Chinese herbal medicine formulas 2017: recommendations, explanation, and elaboration, Ann. Intern. Med. 167 (2) (2017) 112–121.

[9] J. Kolahi, H. Bang, J. Park, Towards a proposal for assessment of blinding success in clinical trials: up-to-date review, Community Dent. Oral Epidemiol. 37 (2009) 477–484.

[10] Z.X. Bian, et al., Improving the quality of randomized controlled trials in Chinese herbal medicine, part II: control group design, Zhong Xi Yi Jie He Xue Bao 4 (2) (2006) 130–136.

[11] H. Bang, L. Ni, C.E. Davis, Assessment of blinding in clinical trials, Contr. Clin. Trials 25 (2) (2004) 143–156.

[12] N.A. Desbiens, In randomized controlled trials, should subjects in both placebo and drug groups be expected to guess that they are taking drug 50% of the time? Med. Hypotheses 59 (3) (2002) 227–232.

[13] S.D. Walter, S. Awasthi, L. Jeyaseelan, Pre-trial evaluation of the potential for unblinding in drug trials: a prototype example, Contemp. Clin. Trials 26 (4) (2005) 459–468.

[14] A.K. Hopton, H. MacPherson, Assessing blinding in randomised controlled trials of acupuncture: challenges and recommendations, Chin. J. Integr. Med. 17 (3) (2011) 173–176.

[15] D.G. Altman, K.F. Schulz, D. Moher, Turning a Blind Eye: Testing the Success of Blinding and the CONSORT Statement, in: D.G. Altman (Ed.), 2004, p. 1135, author reply 1136-1135, author reply 1136.

[16] I. Boutron, C. Estellat, P. Ravaud, A review of blinding in randomized controlled trials found results inconsistent and questionable, J. Clin. Epidemiol. 58 (12) (2005) 1220–1226.

[17] L.L. Gluud, Bias in clinical intervention research, Am. J. Epidemiol. 163 (6) (2006) 493–501.

[18] Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Health-Related Research Involving Humans, fourth ed., CIOMS, Geneva, 2017.

[19] B. Brinkhaus, et al., Who controls the placebo? Introducing a placebo quality checklist for pharmacological trials, Contemp. Clin. Trials 29 (2) (2008) 149–156.

[20] A. Hróbjartsson, What are the main methodological problems in the estimation of placebo effects? J. Clin. Epidemiol. 55 (5) (2002) 430–435.

[21] B. Loyeung, et al., An experimental study in distinguishing an authentic herbal substance from sham herbal substances, Compl. Ther. Med. 39 (2018) 92–96.

[22] F.J. Fowler, Survey Research Methods, fourth ed., Sage Publications, Thousand Oaks, 2009.

[23] S. Wachtel-Galor, et al., Ganoderma Lucidum (Lingzhi or Reishi): A Medicinal Mushroom, in: I.F.F. Benzie, S. Wachtel-Galor (Eds.), Herbal Medicine: Biomolecular and Clinical Aspects, Nd, CRC Press/Taylor & Francis Llc, Boca Raton (FL, 2011).

[24] H.-C. Lo, et al., A systematic review of the mysterious caterpillar fungus ophiocordyceps sinensis in Dong Chong Xia Cao and related bioactive ingredients, Journal of traditional and complementary medicine 3 (1) (2013) 16–32.

[25] Australian Registry of Therapeutic Goods (ARTG), Ganopoly capsules. 1/10/2020. https://search.tga.gov.au/s/search.html?collection=tga-websites-web&query=71644&op=Search.

[26] X.-F. Bao, et al., Structural features of immunologically active polysaccharides from Ganoderma lucidum, Phytochemistry 59 (2) (2002) 175–181.

[27] E.K. Li, et al., Safety and efficacy of Ganoderma lucidum (lingzhi) and San Miao San supplementation in patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled pilot trial, Arthritis Rheum. 57 (7) (2007) 1143–1150.

[28] S. Wachtel-Galor, J. Yuen, J.A. Buswell, Ganoderma Lucidum (Lingzhi or Reishi): A Medicinal Mushroom, in: I.F.F. Benzie, S. Wachtel-Galor (Eds.), Herbal Medicine: Biomolecular and Clinical Aspects, Taylor and Francis Group, 2011.

[29] B. Boh, et al., in: M.R. El-Gewely (Ed.), Ganoderma Lucidum and its Pharmaceutically Active Compounds, in Biotechnology Annual Review, Elsevier, 2007, pp. 265–301.

[30] L. Packer, et al., Herbal and Traditional Medicine: Biomolecular and Clinical Aspects, second ed., CRC Press, New York, USA, 2004.

[31] F. Hennicke, et al., Distinguishing commercially grown Ganoderma lucidum from Ganoderma lingzhi from Europe and East Asia on the basis of morphology, molecular phylogeny, and triterpenic acid profiles, Phytochemistry 127 (2016) 29–37.

[32] J.L. Jordan, A.M. Sullivan, T.D. Lee, Immune activation by a sterile aqueous extract of Cordyceps sinensis: mechanism of action, Immunopharmacol. Immunotoxicol. 30 (1) (2008) 53–70.

[33] K. Yue, et al., The Genus Cordyceps: a Chemical and Pharmacological Review, Wiley Subscription Services, Inc., Bognor Regis, 2013, pp. 474–493.

[34] Y. Liu, et al., The Chemical Constituents and Pharmacological Actions of Cordyceps Sinensis vol. 2015, Evid Based Complement Alternat Med, 2015, 575063.

[35] B. Lin, S. Li, in: I.F.F. Benzie, S. Wachtel-Galor (Eds.), Cordyceps as an Herbal Drug, in Herbal Medicine :Biomolecular and Clinical Aspects, Taylor and Francis Group, 2011.

[36] D. Bensky, S. Clavey, E. Stöger, Chinese Herbal Medicine: Materia Medica, third ed., Eastland Press, Seattle, USA, 2004.

[37] H. Bang, et al., Blinding assessment in clinical trials: a review of statistical methods and a proposal of blinding assessment protocol, Clin. Res. Regul. Aff. 27 (2) (2010) 42–51.

[38] J. Kolahi, et al., Newly formulated chlorhexidine gluconate chewing gum that gives both anti-plaque effectiveness and an acceptable taste: a double blind, randomized, placebo-controlled trial, J. Int. Acad. Periodontol. 10 (2) (2008) 38–44.

[39] R.B. Bausell, et al., Is acupuncture analgesia an expectancy effect?: preliminary evidence based on participants' perceived assignments in two placebo-controlled trials, Eval. Health Prof. 28 (1) (2005) 9–26.

[40] US Food and Drug Administration, Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance, Health Qual. Life Outcome 4 (2006) 79.

[41] S.M. Zick, et al., Challenges in herbal research: a randomized clinical trial to assess blinding with ginger, Compl. Ther. Med. 13 (2) (2005) 101–106.

[42] J. Park, H. Bang, I. Cañette, Blinding in clinical trials, time to do it better, Compl. Ther. Med. 16 (3) (2008) 121–123.

[43] A.J. Vickers, A.J.M. de Craen, Why use placebos in clinical trials? A narrative review of the methodological literature, J. Clin. Epidemiol. 53 (2) (2000) 157–161.

[44] J. Stegenga, Care and Cure: an Introduction to Philosophy of Medicine, first ed., The University of Chicago Press, Chicago, 2018.

[45] M. Wan, et al., Blinding in pharmacological trials: the devil is in the details, Arch. Dis. Child. 98 (9) (2013) 656–659.

[46] M. Richardson, Over-encapsulation: Techniques and Challenges of Blinding Clinical Trial Materials, clinical trial materials, 2010.

[47] L.-L. Chen, et al., Effects of processing adjuvants on traditional Chinese herbs, J. Food Drug Anal. 26 (2) (2018) S96–S114. Supplement.

[48] D.M. Hossain, et al., Curcumin: the multi-targeted therapy for cancer regression, Front. Biosci. 4 (2012) 335–355.

[49] L. Hlavackova, et al., Piperine, active substance of black pepper, alleviates hypertension induced by NO synthase inhibition, Bratisl. Lek. Listy 111 (8) (2010) 426–431.