



## An experimental study in distinguishing an authentic herbal substance from sham herbal substances



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### ABSTRACT

**Objectives:** An unblinded randomised trial can result in biased treatment effect estimates and lead to erroneous conclusions on the efficacy of the therapeutic intervention. Unlike pharmaceutical substances, Chinese herbal medicines have special characteristics including texture, colour, odour and taste as the origin of these constituents are different. In addition, its distinctive odour makes blinding of Chinese herbal medicine RCTs very difficult, as the placebo substance needs to match the special characteristics of the herbal substance being investigated. For these reasons, two studies were undertaken to evaluate whether a participant could distinguish a herbal intervention capsule (Ganopoly combination) when compared to three types of capsules containing culinary materials following a visual, odour and taste evaluation.

**Design:** Study One, was a pilot involving eleven participants ( $n = 11$ ) while Study Two, involved eighty one participants ( $n = 81$ ) and was conducted to make improvements on Study One. For both studies, participants were asked to identify which of four capsules were a herbal substance following a visual, smell and taste evaluation.

**Results:** For study One it was found that for both odour ( $p = .484$ ) and visual appearance ( $p = .077$ ) the number of participants selecting the herbal substance was not significantly different from what may have been selected by chance. This was not the case for taste where significantly more participants selected capsule B as the herbal substance ( $p = .004$ ). For Study Two test it was found that all three evaluations for odour, visual appearance and taste significantly more participants selected the herbal substance ( $p < .0001$  in all cases). This indicates that the participant guesses were not evenly distributed across the four choices and suggests a failure to blind.

**Conclusion:** The failure to blind participants highlights the difficulties in preparing sham herbal substances that look, smell and taste like the real herbal substance.

### 1. Introduction

Randomised Controlled Trials (RCTs) are currently the “gold standard” experimental design for assessing the efficacy of a therapeutic intervention.<sup>1</sup> There are three important aspects to RCTs which are (a) randomization, (b) use of a comparator, usually a placebo or sham intervention and (c) blinding of various parties involved in the trial. The placebo effect refers to the phenomenon in which some people experience some type of benefit after the administration of a placebo. The expectations of the patient play an important role in the placebo effect; the more a person expects the treatment to work, the more likely he or she will exhibit a placebo response.<sup>1,2</sup> Participant blinding is thus a very important aspect to consider when designing and conducting an RCT. For any successful controlled clinical trial, the use of a placebo plays an important role with respect to controlling for subject expectation. An unblinded randomised trial can result in biased treatment effect

estimates and lead to erroneous conclusions on the efficacy of the therapeutic intervention.<sup>3</sup> Successful blinding therefore ensures that these expectations are distributed evenly across the two or more groups, and not necessarily eradicated, as it controls for participant bias such as demand characteristics and motivation.<sup>4</sup> The use of a placebo intervention in pharmaceutical RCTs is common practice and uncomplicated as the placebo intervention is easy to produce, for example a sugar pill.<sup>5</sup>

Unlike pharmaceutical substances, Chinese herbal medicines have special characteristics including texture, colour, odour and taste as the origin of these constituents are different. In addition, its distinctive odour makes blinding of Chinese herbal medicine RCTs very difficult, as the placebo substance needs to match the special characteristics of the herbal substance being investigated. To overcome this problem researchers often make the herbal substance and placebo substance into tablets or capsules. Even though the encapsulation of the herbal

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substance is made more palatable, herbal medicines still possess special qualities such as taste, odour, colour and texture. In a study evaluating the blinding of the encapsulated ginger and placebo substances, the authors reported that participants were able to distinguish the ginger capsule in comparison to the placebo tablet by the odour that accumulated in the bottle prior to opening.<sup>6</sup> In another study assessing whether volunteers who received either placebo or tea tree oil ointment could determine their treatment allocation, the finding was that 50% correctly identified their allocation status.<sup>7</sup>

For these reasons, a series of experiments were undertaken to determine whether a credible sham substance could be developed for use in a clinical trial for Chinese herbal medicine. It is important to highlight the deliberate use of the word ‘sham’ rather than ‘placebo’. This is because, while the materials used to make the sham substance were commonly used culinary products, they are not inert and therefore could possibly have some physiological effect when ingested. Therefore the word sham was chosen to denote a mock or imitation, rather than placebo which refers to an inert substance. The two studies reported in this article were undertaken in sequential order, with the second study attempting to address any shortcomings or flaws of the former.

The aim of the two studies was to evaluate whether a participant could distinguish a herbal intervention capsule (Ganopoly combination) when compared to three types of capsules containing culinary materials following a visual, odour and taste evaluation.

## 2. Materials and methods

### 2.1. Overview of the two studies

The initial study, Study One, was a pilot involving eleven participants (n = 11). The aim of this study was to test the data collection process and determine whether the selected materials for producing a sham were suitable for the study. The latter study, Study Two, involved eighty one participants (n = 81) and was conducted to make improvements on Study One. These included: (a) an increase in participant numbers (b) the use of an opaque eye pad during the tasting phase to effectively blind the participant, and (c) improved colour matching between the sham and udy, Study Two, involved eighty one participants (n = 81) and was conducted to make improvements on Study One. These included: (a) an increase in participant numbers (b) the use of an opaque eye pad during the tasting phase to effectively blind the participant, and (c) improved colour matching between the sham and herbal substance compared to Study One.

### 2.2. Setting

All data were collected on site at the University of Technology Sydney (UTS) Chinese Medicine clinic. Prior to commencing the study ethics approval was obtained from the University of Technology Sydney (UTS) Human Research Ethics Committee (UTS HREC 2009-070).

### 2.3. Participants

Healthy volunteers who were not taking any medication were included in the study while those with severe food sensitivities or known food allergies were excluded. Recruitment of participants was advertised through word of mouth and those meeting all the inclusion criteria gave written informed consent prior to participating in the study. Eleven participants (n = 11) were recruited in Study One and a larger sample size of eighty one participants (n = 81) was recruited for Study Two.

### 2.4. Herbal substance (capsule B)

The herbal substance used in all three studies is marketed as “Ganopoly combination” and is manufactured by Alpha Healthcare, a

New Zealand company. The granulated herbal extract is derived from the extracts of two herbal substances, *Ganoderma lucidum* and *Cordyceps sinensis*. The product used is currently approved by the Therapeutic Goods Administration (TGA) as a herbal supplement and has the listed number AUST L71644.

*Ganoderma lucidum*, or Ling Zhi in Chinese literally means “spiritual mushroom”. It is an edible mushroom that is commonly consumed in China and clinical studies have reported its protective effects against oxidative damage<sup>8</sup> and immune enhancing effects.<sup>9</sup> The other extract, *Cordyceps sinensis*, is known in Chinese medicine as Dong Chong Xia Cao which literally means “winter worm summer grass”, a fungus that also has had long usage in China. Recent studies have shown that it enhances endurance and reduces resistance to fatigue,<sup>10</sup> inhibits the proliferation of lung cancer,<sup>11</sup> and can also inhibit oxidative stress.<sup>12</sup>

### 2.5. Sham ingredients for study one and two (capsules A, C and D)

#### 2.5.1. Study one

The sham substances for the first study were developed based on a trial of different food ingredients. The sham substances had to have a strong flavour, similar to that of the herbal substance, but it also needed to be as therapeutically inert as possible. This is always difficult as no substance, even a sugar pill, is physiologically inert once ingested. Therefore we chose commonly used culinary agents including, chilli powder, curry powder and chocolate cake mixture that are consumed frequently in daily life. The base material chosen was wheaten cornflour (Fielders brand), which was selected for its neutral taste and similar granule size to the herbal material. To this base material, some flavouring agents were added. The composition of the three sham capsules in Study One was:

- Sham Capsule A – cornflour and curry powder (Master of Spices brand) with a ratio of 100:16 (cornflour:curry powder);
- Sham Capsule C – cornflour only;
- Sham Capsule D – cornflour, chilli powder (Master of Spices brand) and chocolate cake mixture (White Wings – Moist chocolate cake) with a ratio of 100:3:50 (cornflour:chilli powder:chocolate cake mixture).

The materials were mixed thoroughly and used to fill transparent (00 size) capsules, which were sealed by bringing the two halves of the capsule together.

**Fig. 1** Visual appearance of sham substances used in the Study One (note that capsule B contains the actual herbal substance)

#### 2.5.2. Study two

In Study Two, the ingredients were modified because the sham substances in Study One were different in colour compared to the herbal substance. A combination of food colourings were used to darken the cornflour, and the chocolate cake mixture was removed as it was found that some participants in Study One could identify the taste. Below are the ingredients for the three sham capsules for Study Two (**Fig. 2**).

- Sham capsule A – cornflour and curry powder (Master of Spices brand) with a ratio of 100:16 (cornflour:curry powder);
- Sham capsule C – cornflour, food colouring (red:blue, 4:1) and Black Pepper (McKenzie’s Ground Black pepper) with a ratio of 50:10:1 (cornflour:food colouring: black pepper);
- Sham capsule D – cornflour flour, food colouring (yellow: red: blue, 6:4:1) and chilli powder with a ratio of 81:29:0.7 (cornflour:food colouring:chilli powder).

As in Study One, the ingredients were mixed thoroughly, used to fill transparent (00 size) capsules, and sealed by bringing the two halves of the capsule together. Several batches of capsules were made for each

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