Ganoderma lucidum for the treatment of cardiovascular risk factors (Protocol)

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[Intervention Protocol]

Ganoderma lucidum for the treatment of cardiovascular risk factors

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this systematic review is to evaluate the effectiveness of *Ganoderma lucidum* for treatment of pharmacologically modifiable risk factors of cardiovascular disease in adults. This will include determining size, direction, and uncertainty of effect for each risk factor (blood pressure, glucose, cholesterol and triglycerides), and the consistency of effects between studies. The strength and consistency of evidence for adverse events will also be evaluated.

BACKGROUND

Description of the condition

The importance of cardiovascular disease is well recognised for its medical, economic, social and personal burden. The World Health Organisation estimates at least 17 million deaths per year, worldwide, are due to cardiovascular disease (WHO 2005). This includes coronary heart disease, independently the world's leading cause of death and stroke. Stroke also has the highest prevalence rates for disability in many countries (WHO 2005). With rates of diabetes and obesity rapidly increasing in both the developed and developing world, it is expected that morbidity and mortality rates for cardiovascular disease will continue to rise (Hossain 2007).

Cardiovascular disease is multi-factorial in causation. Over 300 risk factors have been identified as likely contributors to vascular pathogenesis and, in combination, may have complex and cumulative metabolic effects. Tobacco, alcohol, high blood pressure, high cholesterol, high blood glucose and obesity remain the primary modifiable risk factors (Hossain 2007), and novel markers are being increasingly researched for their predictive ability and role in the development of cardiovascular disease. These include homocysteine, markers of inflammation, such as C-reactive protein, and markers of abnormal coagulation, including fibrinogen (Pearson 2003).

Description of the intervention

Ganoderma lucidum, also known as LingZhi or Reishi, is a mushroom that has been consumed for its broad medicinal properties in China and wider Asia for 2000 years, and has more recently been introduced to western society. As with most herbal interventions, it is regarded as both medicine and food to bring the body 'into balance', promote health, prolong life and prevent and cure many systemic diseases (Willard 1990). The potential of *Ganoderma lucidum* to safely and effectively treat multiple primary risk factors for cardiovascular disease, as a single medication, has greatly increased interest in this medicinal mushroom. Clinical trials have indicated that *Ganoderma lucidum* can lower blood pressure, cholesterol, and glucose in humans (Gao 2004a; Gao 2004b; Jin 1996; Kanmatsuse 1985; Wachtel-Galor 2004a; Wachtel-Galor 2004b). In these trials, no abnormalities in haematological and biochemical (including hepatic and renal) safety biomarkers, and no moderate, serious or severe adverse events were reported for the participants. Data from animal and in vitro studies suggest that the constituents, either individually or synergistically, produce beneficial effects of being anti-oxidant, anti-inflammatory, anti-hyperglycaemic, anti-atherogenic and immune-protective (Chen 2004; Lakshmi 2003; Yang 2002; Zhang 2004).

How the intervention might work

Unlike many synthetic medicines, knowledge of medicinal mushrooms' modes of action, and evidence and guidelines for use are not well established. There is no agreed dosage for *Ganoderma lucidum* treatment, however, most recommended amounts vary between 1.5 g and 9 g of dried extract per day (Chang 2000;Teow 1996). The Ganoderma mushroom contains pharmacologically active variables and the effects and effectiveness of the whole product are likely to differ from any single component acting alone. The constituents of *Ganoderma lucidum* include polysaccharides (including beta-D-glucans, heteropolysaccharides and glycoproteins), triterpines, germanium, essential and non-essential amino acids, sterols, lipids, anti-oxidants, vitamins B1, B2, B6, iron, calcium, and zinc (Huie 2004; McKenna 2002).

Why it is important to do this review

Human trials which have evaluated *Ganoderma lucidum* vary greatly with regard to level and quality of evidence, internal and external validity, and in particular, the analyses and reporting of results. This provides a challenge to health professionals to determine effectiveness for cardiovascular risk factor management from an evidence-based perspective. A systematic review of this increasingly popular complementary medicine is required for both eastern and western medical practice. This review will evaluate the effectiveness of *Ganoderma lucidum* for the management of pharmacologically modifiable cardiovascular risk factors.

OBJECTIVES

The objective of this systematic review is to evaluate the effectiveness of *Ganoderma lucidum* for treatment of pharmacologically modifiable risk factors of cardiovascular disease in adults. This will include determining size, direction, and uncertainty of effect for each risk factor (blood pressure, glucose, cholesterol and triglycerides), and the consistency of effects between studies. The strength and consistency of evidence for adverse events will also be evaluated.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, controlled clinical trials (as defined by Higgins 2006), and randomised cross-over studies, for which only the first phase data will be included. Comparison must be against placebo or alternative pharmacological or non-pharmacological treatment .

Types of participants

Any person taking *Ganoderma lucidum* for management of at least one cardiovascular risk factor listed as a primary outcome measure

in this review. The cardiovascular risk factor must be evaluated in the context of prevention or treatment of a cardiovascular-related disease (e.g. blood pressure changes evaluated in a cancer trial would be excluded).

Types of interventions

As with most complementary medicines, a range of strains, herb products and active ingredients may be expected from the same product name. Therefore a degree of heterogeneity must be expected. Co-intervention will be allowed as long as all arms of the randomised trial received the same co-intervention. *Ganoderma lucidum:*

- must be the only new intervention;
- may include teas, decoctions, powders in any form;
- may be raw or extract product;
- may include any part of the mushroom;
- may be of any dose (dosage equivalence between types of intervention is difficult to determine);
- may be of any duration greater than 21 days;
- may be an isolated active compounds e.g. *Ganoderma lucidum* polysaccharide extract may be included.

Types of outcome measures

Primary outcomes

One primary outcome measure is required for study inclusion in the systematic review. Primary and secondary outcomes measures must be outside normal range at baseline.

- Change in blood glucose level (fasting blood glucose/ HbA1c (glycosylated haemoglobin)/ postprandial glucose test).
- Change in blood pressure (systolic/ diastolic/ mean blood pressure).
- Change in lipid profile (total triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol).
- Change in incidence rates of any of the above.

Secondary outcomes

- Change in obesity measures (waist circumference, hip-waist ratio, fat percentage, bodyweight, body-mass index).
- Change in inflammatory markers (Hs C or C-reactive protein, apolipoprotein).
- Change in insulin (fasting insulin, pro-insulin, homeostasis model assessment [HOMA-IR]).
- Fibrinogen.
- Homocysteine.
- Health-related quality of life.

Adverse events

- Adverse event symptoms and signs attributable to treatment.
- Evidence of liver dysfunction.
- Evidence of renal dysfunction.

Search methods for identification of studies

Electronic searches

Health databases

The Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*
PubMed Entrez (inclusive of MEDLINE)
Science Direct
EMBASE
MD Consult
Stat!Ref-Medical
Biomed Central
Scopus
CINAHL
Current contents
Blackwell Synergy
Australasian Medical Index (AMI)
Expanded Academic
Health and Medical Complete
Science Citations Index
BIOSIS
The search strategies for CENTRAL and EMBASE are detailed in Appendix 1. These will be adapted as appropriate for other databases. All searches will cover the time period from the inception of the database until the last issue. No language restrictions will be applied. Published or unpublished studies, including those only available as abstracts, will be eligible for inclusion.

Databases of ongoing trials

Current controlled trials
Australian register of clinical trials
UK National Research Register
CentreWatch Clinical Trials Listing Service (USA)
National Institutes of Health (USA)
Clinical trials.gov

Complementary medicine databases

Allied and Complementary Medicine Database (AMED)
Centralized Information Service for Complementary Medicine (CISCOM)
Chinese Biomedical Literature Database (CBM)
Chinese Medical Current Contents (CMCC)
Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS)
Chinese Dissertation Database (CDDB)
Chinese Academic Conference Papers (CACP)
China Medical Academic Conference (CMAC)
System for Information on Grey Literature in Europe (SIGLE)

Searching other resources

- All relevant papers found electronically will have reference lists hand searched
- Personal communication with authors in the relevant field
- Personal communication with medicinal mushroom research centres
- Personal communication with relevant pharmaceutical companies
- International Journal of Medicinal Mushrooms

Data collection and analysis

Selection of studies

Two reviewers will independently evaluate the titles and abstracts (where available) (NK and FH). Full text versions will be retrieved for all potentially relevant studies (NK). Authorship and results will not be blinded as the effectiveness of applying this process has not been established by empirical evidence (Higgins 2006). Any disagreement will be resolved by discussion between reviewers (NK and FH) and as needed, arbitration by a third reviewer (SG).

Data extraction and management

One reviewer (FH) will extract data using a preprepared and pilot tested data extraction form. Data extraction forms will be checked independently by two reviewers (NK and FH). Any differences of opinion about data collection will be resolved by discussion between reviewers (NK and FH) and as needed, arbitration by a third reviewer (SG). The following data will be extracted.

- General information: title, authors, contact details, country, sponsor.
- Verification of meeting inclusion criteria.
- Publication details: published or unpublished, abstract only or not, publication type, language, standard referencing details, duplicate publications.
- Trial characteristics: design (parallel or cross-over), recruitment procedures, method of randomisation, allocation concealment, blinding (participants, intervention administrators, outcome assessors), evaluation of blinding by trialists, setting, quality appraisal.
- Participants: inclusion and exclusion criteria, total number and number in comparison groups, baseline characteristics.
- Interventions: the composition or ingredients; preparation method, dose, route, and duration of intervention; comparison intervention; co-intervention; and expertise of practitioner.
- Outcomes: outcomes specified above and adverse events.
- Follow up: length of follow up, reason and number of dropouts and withdrawals, compliance, and intention-to-treat analysis.

Assessment of risk of bias in included studies

Methodological quality of included trials will be rated independently by two reviewers (NK and FH) using the following criteria, as described in the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2006):

1. Randomisation;
2. Concealment of allocation;
3. Blinding of intervention provider;
4. Blinding of participants;
5. Blinding of outcomes assessment;
6. Handling of withdrawals and losses (analysis by intention-to-treat);
7. Completeness of follow up.

Within this review, there are two essential criteria for intention-to treat (ITT) analyses, as defined by the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2006):

1. Trial participants are analysed in the groups to which they were randomised; regardless of which (or how much) treatment they received; AND,
2. All participants are included in analyses; regardless of whether their outcomes were actually collected.

When only the first of the two criteria is fulfilled, this will be termed available case analysis. When trials based analyses only on those participants for whom outcomes were measured and who complied with their allocated treatment, this will be termed per protocol analysis (also known as treatment received analysis) (Higgins 2006).

Each criterion, excluding allocation concealment, will be assigned a yes/no/unclear classification. Allocation concealment will be classified as: adequate (A), unclear (B), inadequate (C), not used (D) (Maxwell 2006).

Assessment of quality will be according to the three-category ranked system as recommended by Higgins and Green (Higgins 2006) to describe risk of bias.

- Low: all individual quality criteria met.
- Moderate: one or more criteria partially met.
- High: one or more criteria not met.

Measures of treatment effect

Mean endpoint scores will be used for inter-group comparisons. For continuous data, weighted mean differences with 95% confidence intervals (CI) will be calculated if measurement scales are the same. If different measurement scales are used, standardised mean difference analyses will be performed. The conservative random-effects model will be used unless the degree of heterogeneity is readily explainable, or when the measure of heterogeneity I^2 is less than 25% in which case the fixed-effect model will be used (Higgins 2006). All quantitative analyses will adhere to intention-to-treat models where appropriate, whereby the participant is analysed according to the original group to which they were assigned. Relative risk (RR) or odds ratios (OR) with 95% CI will be calculated for dichotomous data.

Unit of analysis issues

Cross-over trials will be included, however as there is minimal data on the effectiveness of washout periods for *Ganoderma lucidum*, only the first phase of intervention will be included.

Dealing with missing data

Where possible, data will be extracted from intention-to-treat analyses. If data is missing, the first or corresponding author will be contacted for further information, which will be italicised in data extraction forms and clearly indicated in the review text.

Assessment of heterogeneity

Heterogeneity will be assessed and if trials are sufficiently clinically homogenous for participants, interventions and outcomes, they will be included for meta-analysis. The heterogeneity of included trials will be evaluated visually by inspecting forest plots to evaluate overlap of confidence intervals, then using the chi-squared test for heterogeneity, the I^2 statistic will be obtained to describe the proportion of the variability.

Data synthesis

Statistical analyses will be performed with the Cochrane statistical package, Review Manager 5. One reviewer (FH) will be responsible for entering data and this will be checked by a second reviewer (NK) using the double data entry facility.

Subgroup analysis and investigation of heterogeneity

Meta-analysis of subgroups will follow the same method as primary analysis. Subgroup analysis will be performed by:

1. Dosage where comparable and possible;
2. Duration of treatment;
3. Severity of illness;
4. Age.

Sensitivity analysis

Sensitivity analysis will be performed by repeating the analysis excluding: (1) unpublished studies; and (2) studies with low to moderate risk of bias. If all trials are found to have a high risk of bias, the sensitivity analysis will be performed excluding studies which did not have adequate allocation concealment or participant blinding. If one or more outliers are found to contribute to heterogeneity, and a reason for the outlying result is apparent, an analysis of trials without outliers will be performed.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor Ganoderma explode all trees
#2 ganoderma in All Text
#3 Ling-Zhi in All Text
#4 lingzhi in All Text
#5 Reishi in All Text
#6 (chinese in All Text near/6 mushroom* in All Text)
#7 (medicinal* in All Text near/6 mushroom* in All Text)
#7 (#1 or #2 or #3 or #4 or #5 or #6)

EMBASE

1 exp ganoderma/
2 Ganoderma Lucidum Extract/
3 ganoderma.tw.
4 Reishi.tw.
5 ling-zhi.tw.
6 lingzhi.tw.
7 (chinese adj5 mushroom$).tw.
8 (medicinal$ adj5 mushroom$).tw.
9 or/1-8

10 limit 9 to human

HISTORY

Protocol first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

Securing funding for review: DC, HK, AB

Concieving and coordinating review: NK

Data management in RevMan: NK

Designing review: NK, DC, SG, HK, AB, CS

Submission of protocol: NK

Undertaking searches: NK

Reviewing titles and abstracts NK, FH

Retrieval of articles: NK, FH

Screening search results for inclusion: NK, FH (SG 3rd reviewer)

Data extraction and quality evaluation: NK, FH (SG 3rd reviewer)

Data analysis: NK, FH

Writing the review: NK, DC, SG, HK, AB, CS

Guarantor and first author: NK

DECLARATIONS OF INTEREST

NK, DC and HK are involved in an ongoing clinical trial which might be eligible for inclusion in future review updates.

SOURCES OF SUPPORT

Internal sources

- Centre for Complementary Medicine Research, Australia.

External sources

- Cardiac Health Institute, Australia.