Ginseng for cognition (Review)
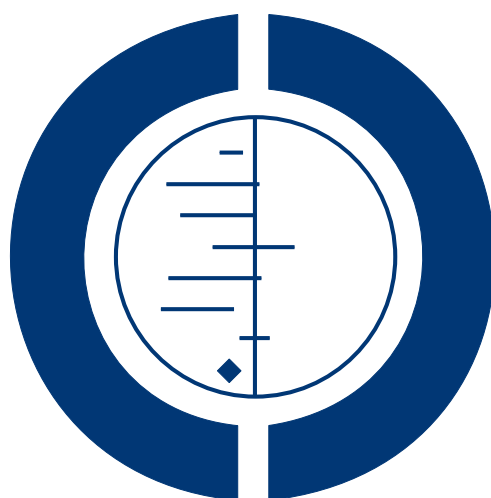
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[Intervention Review]

Ginseng for cognition

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A B S T R A C T

Background

Ginseng is a herbal medicine in widespread use throughout the world. Its effect on the brain and nervous system has been investigated. It has been suggested, on the basis of both laboratory and clinical studies, that it may have beneficial effects on cognitive performance.

Objectives

To evaluate the efficacy and adverse effects of ginseng given to improve cognitive performance in healthy participants, participants with cognitive impairment or dementia.

To highlight the quality and quantity of research evidence available.

Search strategy

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, clinical trials registries and grey literature sources were searched on 24 February 2009 using the following terms: ginseng* OR panax OR ginsan OR "Jen Shen"OR shinseng OR Renshen OR schinseng OR ninjin OR gingilone OR panaxoside* OR ginsenoside* OR protopanaxa* OR protopanaxadiol OR protopanaxatriol OR panaxagin OR ginsenol OR ginsenine and terms for dementia and cognition. The CDCIG Specialized Register contains records from all major health care databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many clinical trials registries and grey literature sources.

Selection criteria

All double-blind and single-blind randomized, placebo controlled trials assessing the effects of ginseng on cognitive function were eligible for inclusion. Interventions were considered to be ginseng if they were compounds containing ginseng or active agents of the Panax genus as the major component.

Data collection and analysis

Characteristics of each included trial were extracted independently by two reviewers using a self-developed data extraction form and entered into RevMan 5.0 software. Authors of identified trials were contacted for additional information and unpublished data. The effects of ginseng in healthy participants, participants with cognitive impairment or dementia were addressed independently.

Main results

Nine randomized, double-blind, placebo controlled trials meeting the inclusion criteria were identified. Eight trials enrolled healthy participants, and one was of subjects with age-associated memory impairment (AAMI).

Only five of the identified trials had extractable information and were included in the analysis. Four studies investigated the effects of ginseng extract and one assessed the efficacy of ginseng compound HT008-1. All of these trials investigated the effects of ginseng on healthy participants. Pooling the data was impossible owing to heterogeneity in outcome measures, trial duration, and ginseng dosage. Results of the analysis suggested improvement of some aspects of cognitive function, behavior and quality of life. No serious adverse events associated with ginseng were found.

Authors' conclusions

Currently, there is a lack of convincing evidence to show a cognitive enhancing effect of Panax ginseng in healthy participants and no high quality evidence about its efficacy in patients with dementia. Randomized, double-blind, placebo-controlled, parallel group trials with large sample sizes are needed to further investigate the effect of ginseng on cognition in different populations, including dementia patients.

PLAIN LANGUAGE SUMMARY

No convincing evidence of a cognitive enhancing effect of Panax ginseng.

Ginseng has been used to treat disease and to combat aging for thousands of years. Currently, ginseng occupies a prominent position in the herbal "best-sellers" list and is the most widely used herbal product throughout the world. This review aimed to identify all double-blind and single-blind randomized, placebo-controlled trials assessing the effects of ginseng on cognitive function. Five trials investigating the effects of ginseng on healthy participants had extractable information for efficacy and were included in the review. Ginseng appeared to have some beneficial effects on cognition, behavior and quality of life. More rigorously designed studies are needed on this important issue.

BACKGROUND

Description of the condition

Dementia is a syndrome characterized by progressive cognitive impairment, which leads to the decreased ability to perform activities of daily living and it is usually accompanied by the development of behavioral disturbances. There are several forms of dementia, with Alzheimer's disease (AD) being the most common form, accounting for 50% to 75% of cases (WHO 2004). Vascular dementia (VD), caused by impaired blood supply to the brain (Román 1993; DSM-IV), is the second most common form.
Dementia mainly affects older people. Above 65 years of age, the prevalence doubles with every five-year increment in age. It has

been estimated that the number of people affected will double every 20 years to 81.1 million by 2040, most of whom will live in developing countries (60% in 2001, rising to 71% by 2040) (Ferri 2005). Dementia causes an overwhelming financial burden to health care systems and is becoming a major public health issue across the world. The total worldwide societal cost of dementia, on the basis of a dementia population of 29.3 million people, was estimated to be US$315.4 billion in 2005, including US$105 billion for informal care (Wimo 2007). In the US, the 9.8 million family and other unpaid caregivers of people with AD and other dementias provided 8.4 billion hours of unpaid care, a contribution to the nation valued at $89 billion (Alzheimer's Association 2008). Moreover, caregivers of family members with dementia experience

significant emotional, physical and psychological burden (Maggio 2010; Miyamoto 2010). However, there is as yet no treatment that can delay or stop the deterioration of brain cells in dementia. Fortunately, pathological cognitive decline is not an inevitable consequence of aging, and prevention of dementia may be possible. Mild cognitive impairment (MCI) is a prevalent problem in the elderly, representing a transitional state between non-pathological brain aging and the severe cognitive pathology of dementia. Epidemiological studies suggested that some cases of MCI might be reversible. Some individuals experience memory loss that measurably exceeds that of their peers, although not severe enough to be diagnosed as MCI or AD, and are diagnosed with age-associated memory impairment (AAMI) (Kidd 2008).

Description of the intervention

Ginseng has been popularly referred to as an "adaptogen" in much of the alternative medicine literature. The term "adaptogen" implies a substance that increases resistance to physical, chemical, and biological stress and builds up general vitality including physical and mental capacity. Panax ginseng has been used for centuries as an important component of many Chinese prescriptions to treat disease and combat aging. Its medicinal efficacy was first documented in Shengnong Bencao Jing and was later summarised by Li Shizhen in Bencao Gangmu and Zhongyao Zhi (Chinese Materia Medica). More recently, ginseng has received much attention as a treatment claimed to enhance cognitive performance and well-being.

Ginseng commonly refers to species within the Panax genus in the family Araliaceae (Table 1). The two main species used in herbal medicines are Asian or Korean ginseng (Panax ginseng CA. Meyer) and American ginseng (*Panax quinquefolius*). The main active ingredients of the Panax genus are the so-called "ginsenosides", which belong to the chemical class of triterpene saponins. Other substances like some sugars and polysaccharides are also active agents.

Table 1. Species of Ginseng belonging to the genus Panax

Pinyin Name	English Name	Latin Name
Ren shen	Asian ginseng Asiatic ginseng Chinese ginseng Ginseng Korean ginseng Manchurian ginseng Oriental ginseng Red ginseng (steamed & dried peeled roots) White ginseng (sun-dried roots)	Panax ginseng
Xi yang shen	American ginseng Ginseng (USA) Wild American ginseng Occidental ginseng	Panax quinquefolius
Da ye san qi Ri ben ren shen Zhu jie shen	Japanese ginseng	Panax japonicus
Xia ye zhu jie shen Xia ye jia ren shen	Narrow-leaved Japanese ginseng	Panax japonicus
San qi	Notoginseng Sanchi ginseng (USA) San-qi ginseng (USA) South China ginseng Tien-qi ginseng Yunnan ginseng	Panax notoginseng

Table 1. Species of Ginseng belonging to the genus Panax   *(Continued)*

Jia ren shen	False ginseng Nepal ginseng Himalayan ginseng Pseudoginseng	Panax pseudoginseng
Xiu li jia ren shen	Elegant pseudoginseng Pearl ginseng	Panax pseudoginseng
Zhu zi shen	Pearl ginseng	Panax pseudoginseng
Bai san qi Ping bian san qi Tu san qi Ye san qi Zhu jie qi	Pingpien ginseng	Panax stipuleanatus
San ye ren shen	Dwarf ginseng Groundnut (USA)	Panax trifolius
Yue nan ren shen Ou mei san qi	Bamboo ginseng Vietnamese ginseng	Panax vietnamensis
Xia ye jia ren shen	Narrow-leaved pseudoginseng	Panax wangianus
Jiang zhuang san qi	Ginger ginseng Ginger-like pseudo-ginseng	Panax zingiberensis

Reference:
Court 2000
Multilingual multiscript plant name database
http://www.plantnames.unimelb.edu.au/Sorting/Panax.html#bipinnatifidus

How the intervention might work

With ginseng saponins or ginsenosides as major active components, the neuroprotective role of ginseng has been investigated. The anti-apoptotic action of panaxydol (PND) and panaxynol (PNN) may reduce neurodegeneration (Nie 2006; Nie 2008). Ginsenoside Re, Rg1, Rg3 and Rh2 may attenuate β-amyloid (Aβ) induced toxicity (Chen 2006; Shieh 2008). Ginsenoside Rg2 may have an anti-oxidative effect useful in treating AD (Li 2007), and may modulate the expression of proteins involved in apoptosis to treat VD or other ischaemic insults (Zhang 2008).

Why it is important to do this review

Ginseng occupies a prominent position in the herbal "best-sellers" list and is considered the most widely used herbal product throughout the world (Blumenthal 2001). According to data from different market research firms, in the Chinese market, ginseng accounted for over \$350 million in sales in 2006 (Heller 2008). It has been reported that among older adults living in a retirement community, 14% of herbal supplement users regularly or occasionally used ginseng (Weng 2004). Ginseng products are often purchased by consumers who believe that they will experience not only physical benefits, but also a positive effect on their cognitive performance and well-being (Kennedy 2003).

It is clearly widely believed that ginseng exerts a beneficial effect on cognitive performance. However, no systematic review of the

evidence has been done. We believe there is a need for a well-organised and up-to-date systematic review to evaluate the efficacy and safety of ginseng for cognition.

OBJECTIVES

The primary objective is to evaluate the efficacy and adverse effects of different types of ginseng (and compounds containing ginseng or active agents of the Panax genus as the major component) used by healthy participants, participants with cognitive impairment or dementia for cognition.

The secondary objective is to highlight the quality and quantity of research evidence available.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant double-blind and single-blind randomized placebo controlled trials assessing the efficacy of ginseng on cognitive function were included. There were no limitations to the language and publication type of trials. Two-period cross-over studies in healthy participants in the absence of carry-over effect also have been considered.

Types of participants

Trials involving healthy participants, participants with cognitive impairment or any type of dementia of any severity were included. Healthy participants were cognitively intact to exclude dementia and MCI. Cognitive impairment was diagnosed using validated rating scales. Dementia was diagnosed by validated and reliable diagnostic criteria such as American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-III; DSM-III-R; DSM-IV), National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-ADRDA: McKhann 1984), National Institute of Neurological Disorders and Stroke (NINDS-AIREN: Román 1993,) and the International Classification of Diseases (ICD-10: WHO 1992).

Types of interventions

Trials evaluating ginseng were included in the review regardless of dosage, administration mode and duration.
We intended to display trials as follows:
1. Ginseng versus placebo only;

2. Ginseng + routine treatment versus placebo + routine treatment. Routine treatment consisted of functional exercise, rehabilitation, nursing care and anti-dementia medications.
In addition, compounds containing ginseng or active agents of the Panax genus as a major component were considered. Compounds were drugs appearing on the market with claimed effects. This was to ensure that compounds included were likely to be manufactured to acceptable and reliable quality standards. We did not consider studies using a combination of ginseng and ginkgo, since ginkgo might comprise a relatively large proportion in the combination and exert a role in neuroprotection.

Types of outcome measures

Primary outcomes

The primary outcome measure was cognitive function (e.g. memory, concentration, immediate recall, calculation, speed of processing) as measured by psychometric tests such as Mini-Mental State Examination (MMSE) (Folstein 1975), Randt Memory Test (RMT) (Randt 1983), Cognitive Subsection of the Alzheimer's disease Scale (ADAS-Cog) (Rosen 1984) or acceptable alternatives.

Secondary outcomes

1. Behaviour disturbance (e.g., agitation, anxiety and restlessness) using validated rating scales such as the Neuropsychiatric Instrument (NPI) (Cummings 1994) and the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield 1996).
2. Performance of activities of daily living measured by validated rating scales (e.g., evaluated by Instrumental Activities of Daily Living (IADL) scales) (Lawton 1969).
3. Global impression of change (clinical change or changes in severity of disease) using global rating scales such as The Clinical Global Impression of Change (ADCS-CGIC) (Schneider 1997). Subjective perspective of family members or caregivers was also planned to be mentioned.
4. Quality of life (measured by recognised and validated quality of life scales or tools)
5. Caregiver burden
6. Institutionalisation
7. Death
8. Acceptability of treatment as measured by withdrawal from trials
9. Incidence and severity of adverse effects.
Trials which reported only physiological outcomes such as changes in plasma biological index, functional imaging or electroencephalography (EEG) were noted but not included and such outcomes did not contribute to the analysis. Outcomes of long-term follow-up in any of the included trials were also noted.

Search methods for identification of studies

Electronic searches

See Dementia & Cognitive Improvement Group methods used in reviews.

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 24 February 2009 using the search terms: ginseng, panax ginseng, ginsan, "Jen Shen", shinseng, Renshen, schinseng, ninjin, gingilone, panax*, ginsen*, panaxoside*, ginsenoside*, ginseng saponin, protopanaxa*, protopanaxadiol, protopanaxatriol, panaxagin, ginsenol, and ginsenine.

The Specialized Register at that time contained records from the following databases:

Healthcare databases
CENTRAL (The Cochrane Library 2009, Issue 1);
MEDLINE (1966 to 2008/07);
EMBASE (1980 to 2008/07);
PsycINFO (1887 to 2008/07);
CINAHL (1982 to 2008/07);
SIGLE (Grey Literature in Europe) (1980 to 2008/07)
LILACS (http://www.bireme.br/cgi-bin/wxislind.exe/iah/online/) (Latin American and Caribbean Health Science Literature): last searched July 2008.

Conference Proceedings
ISTP (http://portal.isiknowledge.com/portal.cgi) (Index to Scientific and Technical Proceedings) (to June 2008)
INSIDE (BL database of Conference Proceedings and Journals) (to June 2000).

Theses
Index to Theses (formerly ASLIB) (http://www.theses.com/) (UK and Ireland theses) (1716 to 11 August 2006);
Australian Digital Theses Program (http://adt.caul.edu.au/): (last update 24 March 2006);
Canadian Theses and Dissertations (http://www.collectionscanada.ca/thesescanada/index-e.html): 1989 to 28 August 2006);
DATAD - Database of African Theses and Dissertations (http://www.aau.org/datad/backgrd.htm);
Dissertation Abstract Online (USA) (http://wwwlib.umi.com/dissertations/gateway) (1861 to 28 August 2006).

Ongoing trials
UK
National Research Register (http://www.update-software.com/projects/nrr/) (last searched issue 3/2006);
ReFeR (http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home) (last searched 30 August 2006);
Current Controlled trials: Meta Register of Controlled trials (mRCT) (http://www.controlled-trials.com/) (last searched 30 August 2006):
ISRCTN Register - trials registered with a unique identifier

Action medical research
Kings College London
Laxdale Ltd
Medical Research Council (UK)
NHS Trusts Clinical Trials Register
National Health Service Research and Development Health Technology Assessment Programme (HTA)
National Health Service Research and Development Programme 'Time-Limited' National Programmes
National Health Service Research and Development Regional Programmes
The Wellcome Trust
Stroke Trials Registry (http://www.strokecenter.org/trials/index.aspx) (last searched 31 August 2006).
Netherlands
Nederlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) (last searched 31 August 2006).
USA/International
ClinicalTrials.gov (http://www.ClinicalTrials.gov) (last searched 31 August 2006) (contains all records from http://clinicalstudies.info.nih.gov/);
IPFMA
Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches http://www.controlled-trials.com/isrctn, http://www.ClinicalTrials.gov and http://www.centerwatch.com/. The ISRCTN register and Clinicaltrials.gov are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.
The IFPMA Trial Results databases searches a wide variety of sources among which are:
http://www.astrazenecaclinicaltrials.com (seroquel, statins)
http://www.centerwatch.com
http://www.clinicalstudyresults.org
http://clinicaltrials.gov
http://www.controlled-trials.com
http://ctr.gsk.co.uk
http://www.lillytrials.com (zyprexa)
http://www.roche-trials.com (anti-abeta antibody)
http://www.organon.com
http://www.novartisclinicaltrials.com (rivastigmine)
http://www.bayerhealthcare.com
http://trials.boehringer-ingelheim.com
http://www.cmrinteract.com
http://www.esteve.es
http://www.clinicaltrials.jp
This part of the IPFMA database is searched and was last updated on 4 September 2006;
Lundbeck Clinical Trial Registry (http://www.lundbecktrials.com) (last searched 15 August 2006);
Forest Clinical trial Registry (http://www.forestclinicaltrials.com/) (last searched 15 August 2006).

The search strategies used to identify relevant controlled trials on dementia for the Group's Specialized Register were combined with the terms listed in Appendix 1. See Appendix 2 for the sources searched and the numbers of hits retrieved for major source.

Searching other resources

In addition the following sources were searched for trial reports:
China National Knowledge Infrastructure (CNKI) (1979 to 2009)
VIP Chinese Science and Technique Journals Database (1989 to 2009)
Wanfang Data (1989 to 2009) which is an affiliate of Chinese Ministry of Science & Technology
The Chinese Clinical Trials Register (ChiCTR)
ProQuest Health and Medical Complete (1980 to 2009)
BIOSIS Previews (2001 to 2009)
Google up to February 2009
Any publications found were searched for additional sources. Authors of identified trials were contacted for additional information and unpublished data.

Data collection and analysis

Selection of studies

In accordance with the defined inclusion criteria, the title and abstract of each trial were screened by one reviewer to determine which studies require further assessment (Geng JS). Trials that did not meet the criteria were excluded. Following screening, the full texts of eligible citations were independently assessed by two reviewers (Jiang K and Geng JS). Reviewers' selection of trials and the final list of studies were reached by consensus. Disagreements were discussed and resolved between the two reviewers. A third member of the team was consulted (Wu TX) when consensus could not be reached.

Data extraction and management

Characteristics of each included trial including the methods of trial, participants (country, age, criteria used to diagnose MCI and dementia, inclusion and exclusion criteria), interventions and outcomes were extracted independently by two reviewers (Dong JC and Geng JS) using a self-developed data extraction form. Detailed data on adverse effects and drop-outs were also recorded. Data of included studies were extracted from the published reports where possible. We asked the authors for relevant information when additional data were required.

For continuous data, the summary statistics required for each trial and each outcome were the mean change from baseline to final assessment, the standard deviation of the mean change, and the number of participants for each group. When changes from baseline were not reported, the mean, standard deviation and the number of participants for each group at each time point were extracted.

For continuous data in crossover trials, we extracted the mean change from baseline to final assessment on each treatment. Where possible, we extracted the standard deviation or standard error of the participant-specific differences between the changes from baseline on each treatment. If this was not available, but a paired t-test had been conducted, then we extracted its t statistic or P value or confidence interval and calculated the standard error.

For dichotomous data, the numbers in each group and the numbers experiencing the outcome of interest at each time point were sought.

For an intention-to-treat analysis, data were collected for each outcome measure on every participant randomized, irrespective of compliance.

Assessment of risk of bias in included studies

Two reviewers (Wang GH and Geng JS) assessed the methodological quality of each trial according to the approaches described in "The Cochrane Handbook for Systematic Reviews of Interventions 5.0.1" (Higgins 2008) and "The concepts, design, practice and reports of allocation concealment and blinding" (Wu 2007). The standard checklist developed by Dementia & Cognitive Improvement Group was used to assess trial quality. The following characteristics were evaluated:

Methods of randomization: assessment of selection bias

A - Adequate methods of sequence generation achieved by referring to a published list of random numbers, or to a list of random assignments generated by a computer, central randomization, repeated coin-tossing, throwing dice, drawing of lots, shuffling cards or envelopes before the trial launch were considered as low risk of bias.

B - Insufficient information about the sequence generation process and which only mentioned 'random' were considered as uncertain risk of bias.

C - Some systematic or 'quasi-random' methods used in the sequence generation process such as date of birth, date of admission, hospital or clinic record number, were considered as high risk of bias.

Allocation concealment: assessment of selection bias

A - Adequate measures to conceal allocation such that participants and investigators enrolling participants could not foresee assignment, for instance, central randomization by a third party, sequentially numbered drug containers of identical appearance, or sequentially numbered, opaque, sealed envelopes, were considered as low risk of bias.

B - The methods of concealment were not described or not described in sufficient detail to allow a definite judgment were considered as uncertain risk of bias.

C - Any allocation procedure that could be foreseen before assignment, for instance, an open list of random numbers or assignments were considered as high risk of bias.

Trials falling into high risk of selection bias were excluded.

Blinding: assessment of performance bias and detection bias

A - No blinding, but the review authors judged that the outcome and the outcome measurement were not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias, were considered as low risk of bias.

B - Insufficient information to permit judgment of 'Yes' or 'No'; the study did not address this outcome, and were considered as uncertain risk of bias.

C - No blinding or incomplete blinding, and the outcomes or outcome measurements were likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias, were considered as high risk of bias.

Trials falling into high risk of performance and detection bias were excluded.

Drop-out/withdrawal/loss to follow-up: assessment of potential attrition bias

A - Low risk of bias: trials where an intention-to-treat analysis was possible and few drop-out/losses to follow-up were noted.

B - Moderate risk of bias: trials which reported the rate of exclusions was about 10% whatever intention-to-treat analysis was used.

C - High risk of bias: the rate of exclusion was at least 15% or wide differences in exclusions between groups regardless of whether intention-to-treat was used.

Trials falling into high risk of attrition bias were excluded.

Measures of treatment effect

The outcomes measured in clinical trials of dementia often arise from ordinal rating scales. Where rating scale data seemed to be approximately normally distributed or the parametric tests appeared to be appropriate, then the outcome measures were treated as continuous data.

For continuous outcomes, overall estimate of the treatment differences was the weighted mean difference (WMD) with 95% CIs when the pooled trials use the same rating scale or test to assess an outcome. Standardized mean difference (SMD) with 95% CIs was used to summarise results across studies with outcomes that were conceptually the same but measured in different ways.

Dichotomous outcome data arose when the outcome for every participant was one of two possibilities. Short ordinal scales such as Clinical Global Impression (CGI) was dichotomised and treated

as binary outcome measures. For dichotomous outcomes, the risk ratio (RR) with 95% CIs was used to measure treatment effect.

Unit of analysis issues

In cluster-randomized trials or group-randomized trials, during which groups of individuals rather than individuals were randomized to different interventions, meta-analysis using the generic inverse-variance method was intended to be adopted.

The duration of trials varied considerably. When the range seemed too great to combine all trials into one meta-analysis, it was divided into smaller time periods and a separate meta-analysis conducted for each time period. Some trials might contribute data to more than one time period if multiple assessments have been performed. When the outcome of interest was an event that occurred more than once, statistical methods for counts data were used.

For trials comparing more than two intervention groups, the relevant intervention group was assessed.

Dealing with missing data

Missing data and drop-outs were assessed for each included trial. Some studies that missed information on outcomes of interest, or missed summary data like sample sizes, numbers of events, standard errors, were included in the review but not considered in the meta-analysis. For individuals missing data such as drop-out or loss to follow-up, both an intention-to-treat analysis and an available case analysis were used whenever possible. We contacted the original investigators to request missing data if possible. The potential implications of missing data (e.g., loss to follow-up and no outcome obtained, receiving the wrong treatment, lack of compliance, or ineligibility) are addressed in the "Discussion" section.

Assessment of heterogeneity

A test for heterogeneity of the treatment effect between the trials using the I^2 statistic was performed. The interpretation of I^2 for heterogeneity was as follows:

0% to 40%: might not be important;

30% to 60%: might represent moderate heterogeneity;

50% to 90%: might represent substantial heterogeneity;

75% to 100%: might be considerable heterogeneity.

If no substantial or considerable heterogeneity has been indicated, then a fixed effect model was taken. Possible sources of heterogeneity were assessed by sensitivity and subgroup analyses as described below.

Assessment of reporting biases

Asymmetrical funnel plots might be considered as an indicator of publication bias when sufficient numbers of studies are available in the meta-analysis.

Data synthesis

We synthesized the results in meta-analysis when there was no important clinical heterogeneity. Separate analyses were conducted for different ginseng type, different populations (healthy individuals, MCI, dementia) and different dementia types (AD, VD, mixed dementia or other type). Results were presented visually with different populations on the same Forest plot to give an overall impression of the scope and number of studies. Combining of the trial data was carried out using Review Manager (version 5.0). In all cases the overall estimate from a fixed-effect model was presented and a test for heterogeneity using I^2 statistic was performed. If, however, there was evidence of heterogeneity of the treatment effect between trials then a random effects model was used. In this case the confidence intervals would be broader than those of a fixed-effect model. For low probability events, such as mortality, the Peto method of the typical odds ratio (OR) was applied.

For data from cross-over studies, we used the generic inverse variance method for the meta-analysis. Data from cross-over studies with those from parallel group trials were not combined because of the differences in characteristics between these two types of studies.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed for severity of dementia (mild, moderate, severe) and different treatment modalities (dosage, duration) to explore clinical heterogeneity in meta-analysis.

Sensitivity analysis

Sensitivity analysis was performed to assess the effect of:
including studies where there was some ambiguity as to whether they met the inclusion criteria
including studies with high risk of bias in one or more domains.
If the results observed remain unchanged, then the evidence would be considered as robust.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See: Characteristics of included studies; Characteristics of excluded studies

Included studies

Nine randomized, double-blind, placebo controlled trials (D'Angelo 1986; Neri 1995; Sotaniemi 1995; Sørensen 1996; Kennedy 2001; Reay 2005; Sünram-Lea 2005; Kennedy 2007; Kim 2008) meeting the inclusion criteria were identified. Eight enrolled healthy participants (D'Angelo 1986; Sotaniemi 1995; Sørensen 1996; Kennedy 2001; Reay 2005; Sünram-Lea 2005; Kennedy 2007; Kim 2008), and one was of subjects with age-associated memory impairment (AAMI) (Neri 1995).

Only five (D'Angelo 1986; Sørensen 1996; Sünram-Lea 2005; Kennedy 2007; Kim 2008) of the identified trials investigating the effects of ginseng on healthy participants had extractable information for efficacy and were included in the review. All of the trials were performed in the medical centers affiliated to universities. Sørensen 1996 was supported by a grant from Dansk Droge. The fourth author of Sünram-Lea 2005 was employed by Pharmaton SA, the producer of G115 used in the trial. Kim 2008 was supported by grants from Korea Plant Diversity Research Center of 21st Century Frontier Research Program, and by grants from the Seoul R&D Program and the Second Stage of Brain Korea 21 Project.

Three were parallel group studies (D'Angelo 1986; Sørensen 1996; Kim 2008), and two were two-period cross-over trials (Sünram-Lea 2005; Kennedy 2007). Two studies were conducted in UK (Sünram-Lea 2005; Kennedy 2007), one in Italy (D'Angelo 1986), one in Denmark (Sørensen 1996), and one in Republic of Korea (Kim 2008). The average age of participants in three studies ranged from 20 to 31.3 years (D'Angelo 1986; Sünram-Lea 2005; Kennedy 2007), and in the other two studies (Sørensen 1996; Kim 2008) ranged from 51.4 to 59.4 years.

One study compared the effects of HT008-1 (Neu Med, Seoul, Korea), the compound containing ginseng as a major component with placebo (Kim 2008). Four studies compared the effects of ginseng extract with placebo (D'Angelo 1986; Sørensen 1996; Sünram-Lea 2005; Kennedy 2007). Of these four studies, two assessed the effects of G115 (Pharmaton S.A., Switzerland) (D'Angelo 1986; Sünram-Lea 2005), one evaluated the effects of Gerimax Ginseng Extract (Dansk Droge, Denmark, currently Orkla ASA Gerimax) (Sørensen 1996), and one assessed the efficacy of Korean ginseng extract (Cheong Kwan Jang, Korea Ginseng Corporation, Seoul, Korea) (Kennedy 2007).

For all of the included trials, ginseng products were administrated orally. G115, Gerimax Ginseng Extract and Cheong Kwan Jang were capsules. HT008-1 was prepared as a liquid in a 30-ml pouch of solution. Details of ginseng products were presented in Appendix 3. The daily dose of ginseng extract ranged from 200 mg to 400 mg, whereas the daily dose of ginseng compound HT008-1 was 5200 mg. Four studies (D'Angelo 1986; Sørensen 1996; Kennedy 2007; Kim 2008) investigated the chronic effects of ginseng, with duration of treatment period varied from eight to twelve weeks. One study (Sünram-Lea 2005) evaluated the acute effects of ginseng, with treatment duration of merely two days.

Excluded studies

Fifteen reports were excluded because:

1. Data on effects of ginseng could not be extracted (Neri 1995; Sotaniemi 1995; Kennedy 2001; Reay 2005);
2. Not a randomized trial (Thommessen 1996);
3. Not a blinded trial (Heo 2008; Lee 2008);
4. Not a placebo controlled trial (Tian 2003b; Heo 2008; Lee 2008);
5. Compound containing ginseng or active agents of the Panax genus as a major component was not the drug appearing on the market with claimed effects (Tian 2003; Tian 2003a; Tian 2003b);
6. The Latin-square design cross-over trials compared other types of intervention besides ginseng were excluded (Kennedy 2004; Reay 2006);
7. Cognitive function was not tested (Wiklund 1994; Ellis 2002);
8. Only the abstract has been published and data were not obtainable from authors (Reay 2008).

Risk of bias in included studies

Allocation

The random number table was utilized to generate allocation sequence in D'Angelo 1986 (correspondence from Emilio Perucca on 28 May 2009). For Sørensen 1996, a randomization code was made by a pharmacist in the company and the detailed method of randomization was unclear. The randomization codes were withheld until all results were analyzed, not until then was the treatment allocation revealed. Meanwhile, members of the company were in no way involved in the conduct of the trial and had absolutely no access to participants or test procedures etc (correspondence from Jesper Sonne on 28 May 2009). A person not involved in the trial of Sünram-Lea 2005 carried out randomisation manually using a randomisation table. For Kennedy 2007, the computerized random number generator was used to allocate participants (correspondence from David Kennedy on 27 May 2009). All treatments were packaged and coded by a disinterested third party, who retained the emergency code break for use in the event of any serious adverse events. For Kim 2008, participants were randomly assigned through the online service of www.randomizer.org.

Blinding

All of the included trials used double-blinding method. The methods of blinding in three trials (D'Angelo 1986; Sünram-Lea 2005 Kennedy 2007) were acquired from authors (correspondence from Emilio Perucca on 28 May 2009; correspondence from Keith A. Wesnes on 21 July 2009; correspondence from David Kennedy on 27 May 2009). The blinding efficacy was tested to be adequate in one trial (Kim 2008).

Incomplete outcome data

For D'Angelo 1986, all participants completed the trial. The attrition rate (drop out of the trials) was 12% (15/127) in Sørensen 1996. Compliance in this study was assessed by querying the participants and by counting the tablets returned, and in no case did the returned tablets exceed 5% of the total number distributed to the participants. Detailed reasons for non-compliance were not provided. For Sünram-Lea 2005, exact number of participants completed the study was not stated. However, from the degree of freedom in the paired t-test we concluded that number of participants included in the statistical analysis were the same as the number of participants randomized. For Kennedy 2007, two participants failed to complete the trial, leaving 16 evaluable sets of data. Reasons for loss-to follow up were unrelated to treatment, for instance, simply dropped out of the trial. 19 participants (9 from HT008-1 group, 10 from placebo group) were excluded from Kim 2008. Reasons for exclusion were as follows: HT008-1 (4-lost to follow up, 1-adverse events, 4-protocol violations), Placebo (5-lost to follow up, 2-adverse events, 3-protocol violations). The attrition rate of this trial seemed to be relatively high (19/118). Nevertheless, 7 protocol violations were evidently not associated with the use of HT008-1 and placebo.

Carryover effects

No assessment was made of the risk of carryover in either of the two included cross-over trials (Sünram-Lea 2005; Kennedy 2007). Ginseng is one of the most complex plants, consisting of multiple components. The pharmacokinetics of ginseng, including elimination half-life, is poorly characterised in humans. Therefore, it is very difficult to judge the adequacy of the washout period. The possibility of carryover effects could not be entirely excluded and the effects would probably lead to an underestimate of the effect size.

A 'Risk of Bias Graph captures the review authors' judgments about each risk of bias item presented as percentages across all included trials see Figure 1 and a 'Risk of Bias Summary captures the review authors' judgments about each risk of bias item for each included trial see Figure 2.

Figure 1.   Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
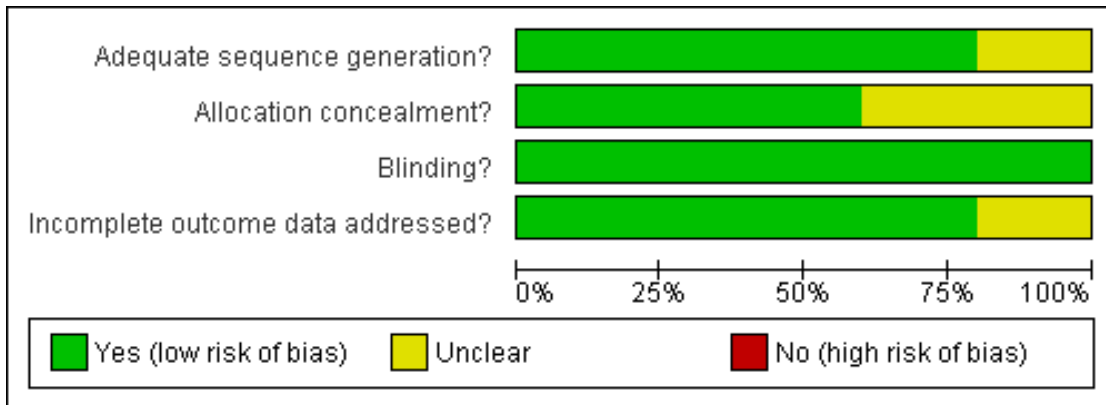
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Effects of interventions

For two parallel group trials (D'Angelo 1986; Kim 2008), we calculated the mean difference and standard deviation of change score from baseline to the final assessment since the mean change had not been suggested in the report. For two cross-over studies (Sünram-Lea 2005; Kennedy 2007), only outcomes where results from the paired t-test were available were included for analysis. We calculated the paired mean difference and standard error of change score from baseline to the final assessment.

Effects of ginseng extract on cognitive function of

healthy participants

• There was statistical significance in favour of 200 mg/day ginseng in working memory as assessed by the Speed of Carrying out 3-Back Task WMD -0.06 (95% CI -0.10 to -0.02, P = 0.004) at 4 weeks (Kennedy 2007). Nevertheless, no statistical significance was found between 200 mg/day ginseng and placebo in Corsi Block Digit span WMD 0.28 (95% CI -0.02 to 0.57, P = 0.07).

• There was significant statistical difference showing a benefit of 200 mg/day ginseng in working memory as assessed by the Speed of Carrying out 3-Back Task WMD -0.06 (95% CI -0.11 to -0.01, P = 0.02) at 8 weeks (Kennedy 2007).

• No statistically significant results in favour of 200 mg/day ginseng were found for 12 weeks on attention and concentration as measured by the Cancellation Test WMD 2.00 (95% CI -1.76 to 5.76, P = 0.30) (D'Angelo 1986).

• There was no statistically significant difference between 200 mg/day ginseng and placebo for 12 weeks in speed of processing as assessed by the Logical Deduction Test WMD 0.02 (95% CI -0.02 to 0.06, P = 0.37) and Digit Symbol Substitution Test WMD -1.00 (95% CI -5.32 to 3.32, P = 0.65) (D'Angelo 1986). However, results from Mental Arithmetic indicated a benefit for 200 mg/day ginseng compared with placebo WMD 0.12 (95% CI 0.03 to 0.21, P = 0.007).

• For psychomotor performance, there was a statistically significant difference in favour of 200 mg/day ginseng compared with placebo for 12 weeks in Choice Reaction Time WMD -0.01 (95% CI -0.02 to -0.01, P < 0.0001) and the Tapping Test WMD -8.00 (95% CI -14.66 to -1.34, P = 0.02) (D'Angelo 1986). However, no statistically significant differences were found in Simple Visual Reaction Time WMD 0.00 (95% CI -0.01 to 0.01, P = 1.00) and Simple Auditory Reaction Time WMD 0.00 (95% CI -0.01 to 0.01, P = 1.00).

• Results from Choice Reaction Time (CDR battery) suggested benefits for 400 mg/day ginseng for 2 days compared with placebo WMD -22.09 (95% CI -36.92 to -7.26, P = 0.004) (Sünram-Lea 2005). There was also a statistically significant difference in favour of 400 mg/day ginseng in Speed of Attention WMD -25.61 (95% CI -46.79 to -4.43, P = 0.02) in this study.

• No statistically significant differences were found between 400 mg/day ginseng and placebo for 2 days in the following outcome measures: Continuity of Attention WMD -0.32 (95% CI -1.65 to 1.01, P = 0.64), Quality of Memory WMD -2.28 (95% CI -28.57 to 24.01, P = 0.87), Speed of Memory WMD 28.17 (95% CI -82.25 to 138.59, P = 0.62), Working Memory WMD 0.05 (95% CI -0.02 to 0.12, P = 0.19), and Secondary Memory WMD -2.33 (95% CI -27.70 to 23.04, P = 0.86) (Sünram-Lea 2005).

• There were no benefits in favour of 400 mg/day ginseng for 8 to 9 weeks for improving attention and concentration as assessed by the D2 Test WMD 4.00 (95% CI -11.15 to 19.15, P = 0.60) (Sørensen 1996).

• No statistically significant differences were found when 400 mg/day ginseng for 8 to 9 weeks was compared with placebo on the psychomotor performance as measured by Simple Auditory Reaction Times (10 Percentile) WMD -6.60 (95% CI -15.72 to 2.52, P = 0.16), Simple Auditory Reaction Times (50 Percentile) WMD -9.80 (95% CI -22.69 to 3.09, P = 0.14), Simple Visual Reaction Times (10 Percentile) WMD -3.70 (95% CI -11.26 to 3.86, P = 0.34), Simple Visual Reaction Times (50 Percentile) WMD -2.20 (95% CI -11.63 to 7.23, P = 0.65), Finger-tapping

Test (Maximum) WMD -1.60 (95% CI -3.67 to 0.47, P = 0.13), and the Finger-tapping Test (50 Percentile) WMD -2.50 (95% CI -5.07 to 0.07, P = 0.06) (Sørensen 1996).

• Measures of learning and memory: 400 mg/day ginseng for 8 to 9 weeks significantly improved Selective Reminding over placebo; the results showed a WMD of 4.40 (95% CI 0.82 to 7.98, P = 0.02) (Sørensen 1996). However, no statistically significant differences were found between 400 mg/day ginseng and placebo on the following two tests: Logical Memory and Reproduction Test WMD 0.00 (95% CI -0.74 to 0.74, P = 1.00), and Rey-Oestrich Complex Figure Test WMD 0.20 (95% CI -1.46 to 1.86, P = 0.81).

Effects of ginseng compound on cognitive function of healthy participants

• No statistically significant differences were found between 5200 mg/day HT008-1 and placebo on cognition as measured by any aspects of Wechsler Memory Scale-III (WMS-III) (Kim 2008) at 8 weeks. Results were as follows: Logical Memory I WMD 0.20 (95% CI -0.62 to 1.02, P = 0.63), Logical Memory II WMD -0.09 (95% CI -0.95 to 0.77, P = 0.84), Verbal Paired Associates I WMD -0.46 (95% CI -1.22 to 0.30, P = 0.24), Verbal Paired Associates II WMD -0.60 (95% CI -1.31 to 0.11, P = 0.10, Letter-Number Sequencing WMD -0.76 (95% CI -1.52 to 0.00, P = 0.05), Spatial Span WMD -0.23 (95% CI -1.16 to 0.70, P = 0.63), and Auditory Recognition Delayed WMD 0.38 (95% CI -0.43 to 1.19, P = 0.36).

Effects of ginseng extract on behavior of healthy participants

• There were benefits associated with 200 mg/day ginseng compared with placebo in Calmness (Bond-Lader Visual Analogue Scales) WMD -9.31 (95% CI -14.29 to -4.34, P = 0.0002) (Kennedy 2007) at 4 weeks.

• The change in Calmness (Bond-Lader Visual Analogue Scales) was significantly better with 200 mg/day ginseng than with placebo WMD -5.91 (95% CI -7.96 to -3.85, P <0.00001) (Kennedy 2007) at 8 weeks.

• There were no statistically significant differences between 400 mg/day ginseng and placebo in the following aspects as assessed by Bond-Lader Visual Analogue Scales: Alertness WMD 1.20 (95% CI -4.68 to 7.08, P=0.69), Contentedness WMD -0.63 (95% CI -6.00 to 4.74, P = 0.82), and Calmness WMD -1.88 (95% CI -9.56 to 5.80, P = 0.63) (Sünram-Lea 2005) at 2 days.

Effects of ginseng extract on quality of life of healthy participants

• There were benefits associated with 200 mg/day ginseng compared with placebo in Social Relationships as measured by WHOQOL-BREF WMD 1.33 (95% CI 0.43 to 2.24, P= 0.004) (Kennedy 2007) at 8 weeks.

Effects of ginseng compound on quality of life of healthy participants

- There was statistical significance in favour of 5200 mg/day HT008-1 compared with placebo for improving Overall Quality of Life WMD 0.18 (95% CI 0.01 to 0.35, P = 0.04), General Health WMD 0.34 (95% CI 0.16 to 0.52, P = 0.0003), and Physical Health WMD 3.78 (95% CI 0.21 to 7.35, P = 0.04) as assessed by WHOQOL-BREF (Kim 2008) at 8 weeks. However, no significant differences were found in the following aspects: Psychological Health WMD 2.38 (95% CI -1.17 to 5.93, P = 0.19), Social Relationships WMD 4.02 (95% CI -0.42 to 8.46, P = 0.08), and Environment WMD 0.60 (95% CI -2.83 to 4.03, P = 0.73).

Adverse effects

- No adverse effects were identified in two trials (D'Angelo 1986; Sørensen 1996) according to the reports. No adverse effects were found in Kennedy 2007 based on information provided by the leading author (correspondence from David Kennedy on 27 May 2009). It should be mentioned that results from one study (Kim 2008) which investigated the efficacy of ginseng compound HT008-1 revealed some adverse effects in both the HT008-1 group and the placebo group including headache, dizziness, diarrhea, constipation, vomiting, gastric complaints, and dermatitis or eczema. However, no serious adverse events were reported during the study and no causal relationship was determined between the HT008-1 treatment and any adverse event.

DISCUSSION

This systematic review aimed to determine the effects of ginseng on cognition in healthy participants, participants with cognitive impairment and dementia. Five trials that intended to investigate the effects of ginseng on cognitive function of healthy volunteers were included in the review. Participants in three of the included trials were young volunteers, and in two were mid-aged people. Four trials investigated the effects of ginseng extract, and one assessed the efficacy of ginseng compound HT008-1.

Ginseng seemed to have beneficial effects for improvement of some aspects of cognitive function, behavior and quality of life in healthy participants. No serious adverse events caused by ginseng were found. For cognitive function, results of the data analysis suggested the improvement in one aspect of working memory as assessed by Speed of Carrying out 3-Back task following treatment with 200 mg/day ginseng for 4 weeks and 8 weeks, in one aspect of speed of processing as assessed by Mental Arithmetic following treatment with 200 mg/day ginseng for 12 weeks, in two aspects of psychomotor performance as assessed by Choice Reaction Time

and Tapping Test following treatment with 200 mg/day ginseng for 12 weeks, and in one aspect of learning and memory as assessed by Selective Reminding following treatment with 400 mg/day ginseng for 8 to 9 weeks. The acute cognitive beneficial effects of ginseng were evaluated by Choice Reaction Time and Speed of Attention following treatment with 400 mg/day ginseng for 2 days. For behavior, results of the analysis indicated the improvement in Calmness as measured by Bond-Lader Visual Analogue Scales following treatment with 200 mg/day ginseng for 4 weeks and 8 weeks. For quality of life, results of the analysis indicated the improvement in Social Relationships as measured by WHO-QOL-BREF following treatment with 200 mg/day ginseng for 8 weeks, and in Overall Quality of Life, General Health and Physical Health as measured by WHOQOL-BREF following treatment with 5200 mg/day ginseng compound HT008-1 for 8 weeks.

Results of the analysis should be interpreted with caution. Five trials with total of 289 participants provided data for the analysis. Small sample size might contribute to insufficient power to detect a difference, if one was present. Results were based on data from a single trial, which had not been duplicated by other trials. This may inevitably limit the strength of the evidence. There was a wide range of instruments utilized to measure various aspects of cognition within individual trials, which caused problems with the multiple comparisons of cognitive outcomes. No available data regarding some secondary outcome measures could be extracted from included trials, for instance, performance of activities of daily living, global impression of change and caregiver burden. Therefore, we were not able to draw conclusions about those outcomes. RCTs are needed to explore such important outcome measures. The effects of ginseng were observed in the short term, varying from 2 days to 12 weeks, which could not signify the efficacy of longer term benefit. Trials with longer duration of treatment and follow-up are needed to address this issue.

Three of the five included trials were at unclear risk of bias in at least one domain. The method of random sequence generation was unclear in one trial Sørensen 1996. Allocation concealment was not mentioned and whether the sequence was adequately concealed remained unclear in two trials (D'Angelo 1986; Sünram-Lea 2005). Therefore, uncertain risk of selection bias was considered for these three trials (D'Angelo 1986; Sørensen 1996; Sünram-Lea 2005). For Sünram-Lea 2005, the exact number of participants who completed the trial was missing and we did not know if any participants dropped out of the trial. As a result, the incomplete outcome data might pose an uncertain risk of attrition bias. A cross-over design is suitable to study cognition in healthy participants. However, carry over effects were not discussed in the reports of two included cross-over trials (Sünram-Lea 2005; Kennedy 2007). Thus whether carry over effects existed in these two trials was unknown.

The review aimed to assess the effects of ginseng for healthy participants, participants with cognitive impairment or any type of dementia of any severity. However, only young and mid-aged healthy

participants with extractable data for the analysis were included. As a result, conclusions about cognitive impairment and dementia that may be of interests to readers cannot be made. It should be noted that five excluded RCTs also examined the effects of ginseng on cognition. Participants in two excluded trials (Heo 2008; Lee 2008) were AD, in one trial (Tian 2003b) were dementia after stroke, in one trial (Tian 2003a) were elderly with mild cognitive impairment (MCI), and in one trial (Neri 1995) were age over 50 years and complained of memory impairments developing gradually. Ginseng appeared to exert some effects on cognitive function according to the results of these trials. Nevertheless, we should be aware of the limitations of these excluded studies as indicated before.

Potential biases in the review process

1. It was impossible to perform a funnel plot to assess the publication bias because of the limited number of included trials.

2. One study (Sørensen 1996) was supported by a grant from Dansk Droge A/S (Ishøj, Denmark). Whether other included studies might have conflicts of interests with pharmaceutical company remained unknown. The pharmaceutical industry might tend to discourage the publication of negative studies that it has funded (Higgins 2008). The lack of transparency could be amplified in part by sponsors' contractual requirements of their researchers (Williams 2007).

Agreements and disagreements with other studies or reviews

Lee 2009 aimed to assess the effects of ginseng for AD. Authors of this review searched 20 databases up to January 2009 using the term 'ginseng AND Alzheimer'. Two RCTs (Lee 2008; Heo 2008) were included in Lee 2009 but were excluded from our review. However, we agree with the conclusions of those authors that the evidence of ginseng for AD was scarce and inconclusive.
Major differences between Lee 2009 and our review existed in the study selection criteria and quality assessment methods. (1) Trials involving healthy participants, participants with cognitive impairment or any type of dementia were all included in our review, while Lee 2009 included only participants with AD. (2) Lee 2009 also considered ginseng as an adjunctive therapy to conventional drug therapy. Nevertheless, only double-blind and single-blind placebo controlled trials were included in our review. (3) The Jadad scale was adopted in Lee 2009 to assess the methodological quality of included trials, whereas 'General methods for Cochrane reviews' (Higgins 2008) were used to evaluate the quality of trials included in our review.

A U T H O R S '   C O N C L U S I O N S

Implications for practice

The small number of studies that have been done provided very limited evidence of beneficial effects of ginseng on cognitive function, behavior and quality of life in healthy participants. No serious adverse effects were caused by ginseng. No trustable evidence was revealed in this review for the effects of ginseng administration in participants with dementia and cognitive impairment. Given the potential efficacy of ginseng suggested by laboratory studies, better-designed, randomized, double-blind, placebo-controlled clinical studies are needed on this important issue.

Implications for research

The following features should be addressed in further research:

1. Clinical researchers should provide details of trial design (e.g., methods and process of randomization and blinding) and complete data (e.g., number and reasons of withdrawals or drop-outs, change score from baseline to the final assessment) to inform the public with authentic, transparent and unbiased information. Reporting of RCTs should be made according to the CONSORT Statement (Schulz 2010) or other internationally accepted clinical trial reporting standards.

2. Large sample sizes with the statistical power to detect a clinically significant difference should be used.

3. Given the chronic nature of cognitive impairment and dementia, the duration of treatment would be required for an extended length of time.

4. The efficacy of ginseng for cognition in different populations, especially in dementia participants, urgently needs to be addressed.

5. Validated instruments which are accepted internationally should be considered in measuring cognitive function.

6. RCTs are needed to explore other clinically important outcome measures (e.g. performance of activities of daily living, global impression of change and caregiver burden) as well as cognition to provide sufficient evidence.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

D'Angelo 1986

Methods	Randomized, double-blind, placebo controlled trial.
Participants	Country: Italy Setting: Single center, University of Pavia Number of participants randomized: 32 (male) Number of participants completed: 32 (male) Age (years): 21.9 ± 1.6 (treatment), 21.7 ± 1.6 (control) Weight (kg): 69.5 ± 8.4 (treatment), 69.6 ± 10 (control) Inclusion criteria: All participants were students at a local University College and were in good physical condition as assessed by a medical examination and conventional laboratory tests. Exclusion criteria: Not stated. Baseline performance were similar in the two groups as tested by psychometric tests except the choice reaction time. Choice reaction time was longer in the G115 group.
Interventions	Comparison: G115 versus placebo 1. G115® (GINSANA, Pharmaton S.A., Switzerland): One capsule twice a day, taken at 8:00 and 13:00, corresponding to a total daily dose of 200mg. 2. Placebo: Identical lactose-containing capsules 3. Duration of treatment: 12 weeks
Outcomes	1. Tapping test 2. Simple reaction time 3. Choice reaction time 4. Cancellation test 5. Digit symbol substitution test 6. Mental arithmetic 7. Logical deduction 8. Tolerability outcomes
Notes	1. This study was the first randomized, double-blind placebo-controlled study aimed at investigating the effect of G115 on some aspects of cognitive function in healthy volunteers. 2. Changes in psychometric test score from baseline to the final assessment were not suggested in the report. 3. The trial lacked an adequate description of methods of randomization and blinding. 4. We contacted Dr Emilio Perucca on 28 May 2009 for additional information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table

D'Angelo 1986 *(Continued)*

Allocation concealment?	Unclear	Allocation concealment was not mentioned and whether the sequence was concealed remained unclear.
Blinding? All outcomes	Yes	Both experimenters doing the tests and participants were blinded.
Incomplete outcome data addressed? All outcomes	Yes	All participants completed the study.

Sørensen 1996

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	Country: Denmark Setting: Single center, Department of internal medicine, Gentofte University Hospital. Number of participants randomized: 127 Number of participants completed: 112 (38 male) Age (years): 51.4 ± 7.9 (treatment), 51.5 ± 9.1 (control) Schooling (years): 10.5 ±1.9 (treatment), 10.2 ± 1.9 (control) Advanced education: 78% (treatment), 82% (control) Inclusion criteria: Healthy volunteers older than 40 years. Exclusion criteria: Serious illness, diseases of the central nervous system, and abuse of alcohol or drugs. Participants receiving psychoactive medication that might interact with ginseng. For all of the tests except the Selective Reminding Test, the baseline values for the two groups were similar and corresponded to the high end of expected values for normally functioning participants.
Interventions	Comparison: Gerimax Ginseng Extract versus placebo 1. Gerimax Ginseng Extract (Dansk Droge A/S, Ishøj, Denmark): 400 mg per day. 2. Placebo: Inactive, heavily soluble calcium preparation identical with the Gerimax. 3. Duration of treatment: 8 to 9 weeks
Outcomes	1. Simple Auditive Reaction Times Test 2. Simple Visual Reaction Times Test 3. Finger-Tapping Test 4. D2 Test 5. Fluency Test 6. Selective Reminding Test 7. Logical Memory and Reproduction Test 8. Rey-Oestrich Complex Figure Test 9. Wisconsin Card Sorting Test 10. Tolerability outcomes
Notes	1. The study was supported by a grant from Dansk Droge A/S (Ishøj, Denmark). 2. A comprehensive battery of cognitive tests was used to investigate cognitive function in healthy, middle-aged participants.

Sørensen 1996 (*Continued*)

3. The trial lacked an adequate description of methods of randomization.
4. Allocation concealment was not mentioned in the report.
5. We contacted Dr Jesper Sonne on 28 May 2009 for additional information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	A randomization code was made by a pharmacist in the company and the method of randomization code generation was unclear.
Allocation concealment?	Yes	The randomization code was kept under lock until all results had been analysed. Not till then was the treatment allocation revealed. Members of the company were in no way involved in the conduct of the trial and had absolutely no access to participants or test procedures etc.
Blinding? All outcomes	Yes	Both participants and study managers were blinded.
Incomplete outcome data addressed? All outcomes	Yes	15 (12%) dropped-out, 6 due to illness and 9 for unknown reasons. Compliance was assessed by querying the participants and by counting the tablets returned. In no case did the returned tablets exceed 5% of the total number distributed to the participants.

Sünram-Lea 2005

Methods	Randomised, double-blind, placebo-controlled, two period cross-over design
Participants	Country: UK Setting: Single University center Number of participants randomized: 30 (15 male) Number of participants completed: not given Age (years): 18-25 (Mean: 20) Inclusion criteria: Healthy undergraduate young volunteers taking no medication or herbal supplements. Of the 30 participants two were light smokers (<5 cigarettes per day and <2 per week, respectively). Participants agreed to refrain from smoking, and caffeine and alcohol consumption throughout each study day. No other dietary restrictions were implemented. Exclusion criteria: Not stated

Interventions	Comparison: G115 versus placebo 1. G115® (Pharmaton S.A., Switzerland): 400 mg 2. Placebo 3. Subjects received two capsules of identical appearance, each containing either 200mg G115 or an inert placebo, in a counterbalanced order, with a seven-day washout period between treatments. 4. Duration of treatment: 2 days
Outcomes	1. Primary outcome measures (a) Quality of memory factor (b) Speed of memory factor (c) Speed of attention factor (d) Accuracy of attention 2. Secondary outcome measures (a) Working memory sub-factor (b) Secondary memory sub-factor (c) CDR factor scores
Notes	1. The fourth author Petrini O was employed by Pharmaton SA, the producer of the standardised ginseng extract G115 used in the trial. 2. The trial aimed to evaluate the effect of ginseng (400 mg) administration on cognitive performance and mood in healthy young volunteers. 3. Methods of blinding and adverse effects of G115 were not stated in the report. 4. We contacted Professor Keith A. Wesnes on 21 July 2009 for additional information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A person not involved in the trial carried out randomisation manually using a randomisation table.
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Subjects and test administrators were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Exact number of participants completed the study was not stated. However, from the degree of freedom in the paired T-test we concluded that authors used number of participants randomized to calculate the results.

Kennedy 2007

Methods	Randomized, double-blind, placebo-controlled, two period cross-over design
Participants	Country: UK Setting: Single University center Number of participants randomized: 18 (5 male) Number of participants completed: 16 Age (years): 38.31 ± 10.3 Inclusion criteria: Healthy undergraduate young volunteers taking no illicit social drugs, and were free from "over the-counter" or prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Participants fasted overnight and were alcohol and caffeine free for 12 hours prior to all assessment sessions, and also abstained from psychoactive products during the testing day. Exclusion criteria: Heavy smokers (>5 cigarettes/day). No significant differences between all baseline assessments on all measures within the study.
Interventions	Comparison: Korean Panax ginseng extract versus placebo 1. Korean Panax ginseng extract (Cheong Kwan Jang, Korea Ginseng Corporation, Seoul, Republic of Korea): 200 mg 2. Placebo: Apparently identical with the intervention drug 3. Each participant took either ginseng or placebo for 8 weeks, with a 4 week placebo washout period between treatment arms. 4. Duration of treatment: 8 weeks
Outcomes	1. Cognitive Drug Research (CDR) computerised assessment battery 2. Working Memory Tasks (a) Corsi Block Tapping task (b) 3-back task (c) Alphabetic working memory 3. Subjective mood and 'quality of life' measures (a) Bond-Lader Mood scales (b) World Health Organisation Quality of Life questionnaire-BREF: (WHOQOL-BREF) 4. Blood glucose parameters
Notes	1. The effects of Korean ginseng extract (200 mg) on cognitive performance, gluco-regulatory parameters and ratings of subjective mood and 'quality of life' were investigated. 2. Detailed information of the Korean ginseng extract were not given in the report. 3. The report lacked an adequate description of randomization, blinding, reason of dropouts and adverse effects of Korean ginseng extract. 4. Authors did not analyse results of the first treatment period after randomization as it would have too little statistical power to be interpretable. 5. We contacted Professor David Kennedy on 27 May 2009 and Dr Jonathon Reay on 8 July 2009 for additional information.

Risk of bias

Item	Authors' judgement	Description

Kennedy 2007 *(Continued)*

Adequate sequence generation?	Yes	Random number generator allocating participants to two groups.
Allocation concealment?	Yes	All treatments were packaged and coded by a disinterested third party, who retained the emergency code break for use in the event of any serious adverse events.
Blinding? All outcomes	Yes	Participants and all experimenters were blinded.
Incomplete outcome data addressed? All outcomes	Yes	Two participants failed to complete the trial (16 evaluable sets of data). Reasons unrelated to treatment i.e. simply dropped out of the study, and as it was an extended treatment period they did not have time to replace them.

Kim 2008

Methods	A randomized, double-blind, fixed-dose, placebo-controlled, parallel group trial
Participants	Country: South Korea Setting: Single University center, Kyung Hee University Medical Center Number of participants randomized: 118 (42 male) Number of participants completed: 99 Age (years): 59.4 ± 5.1 (treatment), 59 ± 5 (control) Schooling (years): 12.2 ± 3.4 (treatment), 11.3 ± 2.9 (control) Inclusion criteria: Cognitively intact adults were required to have completed six or more years of education and have no difficulty reading or writing. A score≥borderline scores of 16.9 at ages 65 to 84 or 18.9 at ages 55 to 64 on the memory subscale of the Korean-Dementia Rating Scale (K-DRS) and a score of >24 on the Korean Version of the Mini Mental State Examination (MMSE-K). Exclusion criteria: Individuals who had histories of neurological disorders, including stroke, head injury, psychiatric disorders (mental retardation, schizophrenia, depression with ≥21 on the Beck's Depression Inventory (BDI) scores), drug abuse, alcohol dependence/abuse, or a disease or surgery that could influence drug absorption, were excluded from this study before the K-DRS test or MMSE-K test. Individuals who were being treated with hormones, antidepressants or other psychoactive medications, who had internal medical problems on blood test (except stable hypertension or diabetes mellitus with medication), who had an unstable medical state, were pregnant or would become pregnant, were undernourished, or who drank more than eight cups of coffee per day also were excluded. Participants who had participated in other clinical trials in the last month were also excluded. Participants were excluded from the study if they did not take more than 8 packs of study medicines in any 2-week period. No significant differences between all baseline assessments on all measures within the study.

Kim 2008 *(Continued)*

Interventions	Comparison: HT008-1 versus placebo 1. HT008-1 (Lot. No.001) (NeuMed Inc., Korea): two pouches daily with a daily dose of 5200mg (an average of 100 mg/ kg). In this clinical study, HT008-1 was prepared as a liquid containing 2600 mg of standardized extracts in a 30 ml pouch of solution. 2. Placebo: two pouches daily that did not differ in appearance (e.g., color, size, smell, or taste) from HT008-1. 3. Duration of treatment: 8 weeks
Outcomes	1. Wechsler Memory Scale-III (WMS-III) (a) Logical memory I (b) Logical memory II (c) Verbal paired associates I (d) Verbal paired associates II (e) Letter-Number Sequencing (f) Spatial span (g) Auditory recognition delayed 2. World Health Organization Quality of Life Assessment Instruments-BREF (WHO-QoL-Bref) (a) Overall quality of life (b) General health (c) Physical health (d) Psychological health (e) Social relationships (f) Environment 3. Tolerability outcomes
Notes	This work was supported by a grant (PF 0320201-00) of Plant Diversity Research Center of 21st Century Frontier Research Program (Ministry of Science and Technology, Korea) , and by grants from the Seoul R&D Program (10524) and the Second Stage of Brain Korea 21 Project (Ministry of Education, Korea).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Through the online service of www.randomizer.org.
Allocation concealment?	Yes	Through the online randomization service.
Blinding? All outcomes	Yes	To analyze the blinding efficacy, participants were asked to which group they belonged. It could be concluded that blinding was not broken from the testing result.
Incomplete outcome data addressed? All outcomes	Yes	Number (or %) of followed-up from each group: HT008-1 (50/59, 85%), Placebo (49/59, 83%); Reasons for loss: HT008-

Kim 2008 *(Continued)*

		1 (4-lost to follow up, 1-adverse events, 4-protocol violation), Placebo (5-lost to follow up, 2-adverse events, 3-protocol violation).

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Wiklund 1994	Randomized, double-blind, placebo controlled study to assess the effects of a combination of active substances including ginseng extract Gl15 on quality of life (QOL) in healthy, employed volunteers older than 25 years. Results: After 12 weeks of treatment, both the combination and placebo groups improved their general well being, but the improvement from baseline was more pronounced in those participants taking the combination of active substances (Gericomplex soft gelatin capsules containing 40 mg ginseng extract Gl15 and vitamins, minerals, and trace elements) twice daily. Conclusions: In healthy participants the combination of vital substances including Gl15 offered significant advantages over placebo treatment in terms of improvement in self-assessed feelings of vitality, alertness, less time urgency (that is, feeling more relaxed), and appetite. The beneficial effects appeared to be more pronounced in those participants who were at a disadvantage and worse off before the study started. Reasons for exclusion: Cognitive function was not tested.
Neri 1995	Randomized, double-blind, placebo controlled study to compares psychological well-being and perceived quality of life in participants with age-associated memory impairment (AAMI), who were administered Gegorvit® (Pharmaton S.A., Switzerland) or placebo for 9 months. Results: Drug-treated AAMI subjects differ from controls in part by improved scores on objective cognitive tests but even more so by modifications of the correlations among indexes of psychological well-being and quality of life. Conclusions: Ginseng might act on some of the mechanisms underlying AAMI and met the prerequisites as a candidate for drug therapy. Reasons for exclusion: Number (or %) of follow-up from each group was not stated. Therefore, relevant data could not be extracted.
Sotaniemi 1995	Randomized, double-blind, placebo controlled study to investigate the effect of ginseng on newly diagnosed non-insulin dependent diabetes mellitus (NIDDM) participants. Results: Ginseng 100 mg or 200 mg (Dansk Droge, Copenhagen) daily for 8 weeks elevated mood, improved mood, vigor, well-being, and psychomotor performance, but not memory, and reduced fasting blood glucose (FBG) and body weight. The 200 mg dose of ginseng improved glycated hemoglobin, serum aminoterminal-propeptide (PIIINP), and physical activity. The participants completed the study without any side effects. Conclusions: Ginseng might be a useful therapeutic adjunct in the management of NIDDM. Reasons for exclusion: Neither baseline results nor change from baseline values could be extracted.
Thommessen 1996	A double-blind, placebo controlled study to examine the effect of ginseng (Gericomplex, Pharmaton S.A., Switzerland) as an adjuvant to treatment and rehabilitation of geriatric participants. Results: After treated with two capsules of ginseng or placebo for 8 weeks, length of stay in hospital did not differ in the two groups. Both groups also improved to the same degree on the various functional outcome measures, except for the Kendrick Object Learning test, where the placebo group improved more markedly.

	Conclusions: No identifiable effects of ginseng as an adjuvant to treatment and rehabilitation of geriatric participants were observed. Reasons for exclusion: A clinical controlled study. "Randomization" was never mentioned in the paper. No additional information of sequence generation could be obtained from the first author.
Kennedy 2001	Randomized, double-blind, placebo-controlled, Latin square cross-over study to observe whether acute administration of Panax ginseng extract (G115®, Pharmaton SA) might have effects on mood and cognitive performance. Results: "Quality of Memory" and the associated "Secondary Memory" factor at all time points following 400mg of ginseng improved significantly. Both the 200 and 600mg doses were associated with a significant decrement of the "Speed of Attention" factor at later testing times only. Subjective ratings of alertness were also reduced 6h following the two lowest doses. Conclusions: Single doses of ginseng were capable of a dose dependent modulation of cognitive performance in healthy young adults. Reasons for exclusion: Data could not be extracted from the complicated Latin square cross-over study. We contacted Professor David Kennedy on 27 May 2009 for additional information.
Ellis 2002	Randomized, double-blind, placebo controlled study to assess the time-dependent effects of Panax ginseng on health-related quality of life (HRQOL) in healthy young volunteers. Results: After 4 weeks of therapy, higher scores in social functioning, mental health, and the mental component summary scales were observed in participants randomized to Panax ginseng (Ginsana), these differences did not persist to the 8-week time point. The incidence of adverse effects was 33% in the Panax ginseng group compared with 17% in the placebo group. Participants given Panax ginseng (58%) were more likely to state that they received active therapy than participants given placebo. Conclusions: Panax ginseng (Ginsana) improves aspects of mental health and social functioning after 4 weeks of therapy, although these differences attenuate with continued use. Reason for exclusion: Cognitive function was not tested.
Tian 2003a	Randomized, single-blind, placebo controlled study to evaluate the effect of King's Brain pill (Compound Chinese ginseng extract from herbs) on the treatment and the delaying of memory decline in the elderly with mild cognitive impairment (MCI) in a community by a year follow-up of neuropsychology. Results: Mean MMSE score increased after treated with 4 pills of King's Brain pill (1.5 g) thrice a day for 3 months, while decreased at one year follow-up point, but still higher than that in placebo group (P<0.05). Verbal Learning Test score was significantly increased at follow-up point in the King's Brain pill group , which was significantly higher than that in the placebo group (P<0.01). The total score of memory items on BNPT battery (Bristol Memory Disorders Clinic-Revised) was significantly increased at follow-up point in the King's Brain pill group, higher than that in Piracetam group (P<0.05) and the placebo group (P<0.01) . Conclusions: King's Brain spill had protective effect on cognitive and memory decline in elderly with MCI. Reasons for exclusion: King's Brain pill was a compound containing ginseng as a major component. Sales manager from Henan Wanxi Pharmaceutical Company said that King's Brain pill (Jin Si Wei) was not a compound on the market. Clinical information of King's Brain pill besides this study could not be found from academic database and the company.
Tian 2003b	This was a poster presentation at the American Stroke Association's 28th International Stroke Conference. A randomized, double-blind, pilot study to evaluate the effectiveness of a compound of Chinese ginseng tablet (King's Brain pill) in the treatment of memory impairment in participants with dementia after stroke. Results: After given one tablet of ginseng compound thrice a day for 12 weeks, a significant increase in mean scores on the HVLT and increase in total memory scores have been observed. There were greater improvements in episodic memeory function assessing story recall, delayed word recall, verbal learning and verbal recognition

(Continued)

and visual recognition in the compound Chinese ginseng group than in the duxil-controlled group.

Conclusions: Treatment with the compound of Chinese ginseng extract might improve memory function in participants with mild and moderate dementia after stroke and might warrant further research treatment strategies for VaD.

Reasons for exclusion: King's Brain pill was a compound containing ginseng as a major component. Not placebo controlled trial, since the comparison was Duxil.

Tian 2003	This was an abstract for the Asia Pacific scientific forum new discoveries in cardiovascular disease and stroke: Bench to bedside to community. It was the same as the abstract of Tian 2003a.
Kennedy 2004	Randomized, double-blind, counterbalanced, placebo-controlled study not only provided an examination of the cognitive and mood effects of guarana in healthy young volunteers, but also assessed the potential for additive or synergistic effects following the common, commercially available, combination of guarana with Panax ginseng. Results: In comparison to placebo, 75 mg of a dried ethanolic extract of guarana (approx 12% caffeine), 200 mg of Panax ginseng extract (G115®, Pharmaton SA), and their combination (75 mg/200 mg) resulted in improved task performance throughout the day. In the case of guarana, improvements were seen across 'attention' tasks (but with some evidence of reduced accuracy), and on a sentence verification task. While also increasing the speed of attention task performance, both ginseng and the ginseng/guarana combination also enhanced the speed of memory task performance, with little evidence of modulated accuracy. Guarana and the combination, and to a lesser extent ginseng, also led to significant improvements in serial subtraction task performance. Conclusions: These results provided the first demonstration in humans of the psychoactive effects of guarana, and confirmation of the psychoactive properties of ginseng. Reasons for exclusion: The Latin-square design cross-over trial compared other types of intervention besides ginseng was excluded since it was very difficult to evaluate the 'carry-over' effect due to other intervention. Data could not be extracted from the complicated Latin square cross-over study.
Reay 2005	Randomized, double-blind, placebo-controlled, Latin square cross-over study to investigate the effects of two separate single doses (200 mg and 400 mg) of Panax ginseng extract (G115®, Pharmaton SA) on changes in fasted blood glucose levels and performance during sustained mentally demanding tasks. Results: 200 mg ginseng could significantly improved Serial Sevens subtraction task performance and significantly reduced subjective mental fatigue throughout all (with the exception of one time point in each case) of the post-dose completions of the 10min battery. Conclusions: Panax ginseng could improve performance and subjective feelings of mental fatigue during sustained mental activity. Reasons for exclusion: Data could not be extracted from the complicated Latin square cross-over study. We contacted Professor David Kennedy on 27 May 2009 and Dr Jonathon Reay on 8 July 2009 for additional information.
Reay 2006	Randomized, double-blind, counterbalanced, placebo-controlled study to investigate the effects of single doses of Panax ginseng, glucose, and a combination of Panax ginseng and glucose on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. Results: Both Panax ginseng and glucose enhanced performance of a mental arithmetic task and ameliorated the increase in subjective feelings of mental fatigue experienced by participants during the later stages of the sustained, cognitively demanding task performance. Accuracy of performing the Rapid Visual Information Processing task (RVIP) was also improved following the glucose load. There was no evidence of a synergistic relationship between Panax ginseng and exogenous glucose ingestion on any cognitive outcome measure. Panax ginseng caused a reduction in blood glucose levels 1 hour following consumption when ingested without

(Continued)

	glucose. Conclusions: These results confirmed that Panax ginseng might possess glucoregulatory properties and could enhance cognitive performance. Reasons for exclusion: The Latin-square design cross-over trial compared other types of intervention besides ginseng was excluded since it was very difficult to evaluate the 'carry-over' effect due to other intervention. Data could not be extracted from the complicated Latin square cross-over study.
Reay 2008	Randomized, double-blind, placebo controlled, two-period cross-over study to assess the behavioural and mood effects of chronic ingestion of Panax ginseng (G115). Results: Results revealed improvements in working memory following a single acute dose of Panax ginseng have been observed, whereas, following chronic dosing results revealed both improvements and decrements in aspects of cognition and mood. Conclusions: An observed effect on a performance measure following chronic ingestion can be further modulated by that day's acute dose. Reasons of exclusion: Only the abstract has been published and data were not obtainable from the author.
Heo 2008	Randomized, open-label pilot study to evaluate the adjunctive effect of Korean red ginseng (KRG) in AD. Results: Participants in the high-dose (9 g/day) KRG group showed significant improvement on the ADAS and CDR after 12 weeks of KRG therapy when compared with those in the control group. Both low-dose (4.5 g/day) and high-dose (9 g/day) KRG groups showed improvement from baseline MMSE when compared with the control group, but this improvement was not statistically significant. Two participants in the low-dose KRG group complained of feeling feverish and two participants in the high-dose KRS group complained of nausea. Conclusions: KRG showed good efficacy for the treatment of AD; however, further studies with larger samples of participants and a longer efficacy trial should be conducted to confirm the efficacy of KRG. Reasons for exclusion: This was not a blinded study. The trial compared KRG as an adjuvant therapy to conventional anti-dementia medications, not placebo controlled trial.
Lee 2008	Randomized, open-label prospective study to evaluate clinical efficacy of Panax ginseng in the cognitive performance of AD participants. Results: After 12 weeks of the Panax ginseng powder (4.5 g/d) treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks. At 12 weeks after the ginseng discontinuation, the improved ADAS and MMSE scores declined to the levels of the control group. The adverse events (e.g. heat-sense, dizziness, nausea, anorexia, diarrhea and headache) were mild and transient. Conclusions: Panax ginseng was clinically effective in the cognitive performance of AD participants. Reasons for exclusion: This was an open-label trial with no blinding performed. Both Ginseng group and control group continued the conventional therapy, not placebo controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

Purdon 2007

Trial name or title	Cognitive, emotional, physical, and psychosocial effects of three weeks' prospective double-blind placebo controlled cross-over exposure to Panax Quinquefolius L (REMEMBER-fX), with optional six months' open label follow-up
Methods	Randomized, double-blind, placebo controlled, cross-over assignment trial

Purdon 2007   (*Continued*)

Participants	**Inclusion Criteria:** • Healthy men and women between the age of 35 - 75 • Women of child bearing capacity who agree to use an acceptable form of birth control during the trial (i.e. oral contraception, reliable use of a double-barrier method (e.g. condom and diaphragm, condom and foam, condom and sponge), IUD or tubal ligation) • Achievement Test (WRAT-III) score greater than 70 with a reading level within normal limits as defined by a Wide Range • Willing to adhere to the requirements of the protocol, including availability for follow-up visits • Willing and able to sign written informed consent **Exclusion Criteria:** • Medical conditions; • HIV/AIDS • Malignancy (under active observation or treatment) • Unstable cardiovascular disease (physician visit or hospitalization for unstable cardiovascular disease in the last 6 mo.) • Renal Abnormalities (serum creatinine known to be > 200umol/L) • Acute or active chronic liver disease • Diabetes • Neurologic or psychiatric disease (progressive or currently under treatment) • Active tuberculosis • Multiple sclerosis • Bleeding disorders
Interventions	HT1001 (Panax Quinquefolius L, REMEMBER-fX)
Outcomes	Primary outcome measures: Use of HT1001 will improve objective measures of psychomotor speed, sustained attention, working memory, declarative memory, and or executive skills. Secondary outcome measures: Use of HT1001 will be associated with no cognitive or physical adverse effects.
Starting date	July 2007
Contact information	Scot E Purdon, PhD, Department of Psychiatry, University of Alberta
Notes	Last visit took place on April 25, 2009.

DATA AND ANALYSES

Comparison 1. Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Attention and concentration, cancellation (No. of digits/2 min) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	2.0 [-1.76, 5.76]
2 Speed of processing, Mental arithmetic (correct responses/s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.03, 0.21]
3 Speed of processing, Logical deduction (correct responses/s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.02, 0.06]
4 Speed of processing, Digit symbol substitution (No. of symbols/90s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.32, 3.32]
5 Sensorimotor function, choice reaction time (s/10-no. of errors) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, -0.01]
6 Sensorimotor function, simple visual reaction time (s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Sensorimotor function, simple auditory reaction time (s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Pure motor function, tapping (taps/30s) (Change from baseline: week 12)	1	32	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-14.66, -1.34]

Comparison 2. Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Attention and concentration, D2 (total score) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	4.0 [-11.15, 19.15]
2 Learning and Memory, selective reminding (error index) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	4.4 [0.82, 7.98]
3 Learning and Memory, logical memory and reproduction (units lost) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Learning and Memory, Rey-Oestrich complex figure (units lost) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.46, 1.86]
5 Sensorimotor function, simple auditory reaction times (10 Percentile) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-6.60 [-15.72, 2.52]
6 Sensorimotor function simple auditory reaction times (50 Percentile) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-9.8 [-22.69, 3.09]
7 Sensorimotor function, simple visual reaction times (10 Percentile) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-3.70 [-11.26, 3.86]
8 Sensorimotor function, simple visual reaction times (50 Percentile) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-11.63, 7.23]
9 Pure motor function, finger-tapping (maximum) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-3.67, 0.47]
10 Pure motor function, finger-tapping (50 Percentile) (Change from baseline: week 8 to 9)	1	112	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-5.07, 0.07]

Comparison 3. Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wechsler Memory Scale-III (WMS-III), Logical memory I (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.62, 1.02]
2 Wechsler Memory Scale-III (WMS-III), Logical memory II (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.95, 0.77]
3 Wechsler Memory Scale-III (WMS-III), Verbal paired associates I (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-1.22, 0.30]
4 Wechsler Memory Scale-III (WMS-III), Verbal paired associates II (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.31, 0.11]
5 Wechsler Memory Scale-III (WMS-III), Letter-Number Sequencing (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-1.52, -0.00]
6 Wechsler Memory Scale-III (WMS-III), Spatial span (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-1.16, 0.70]
7 Wechsler Memory Scale-III (WMS-III), Auditory recognition delayed (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.43, 1.19]

Comparison 4. Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Crossover)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 4)	1		Mean Difference (Fixed, 95% CI)	-0.06 [-0.10, -0.02]
2 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 8)	1		Mean Difference (Fixed, 95% CI)	-0.06 [-0.11, -0.01]
3 Working Memory, Corsi Block Digit span (Change from baseline: week 4)	1		Mean Difference (Fixed, 95% CI)	0.28 [-0.02, 0.57]

Comparison 5.   Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Speed of attention (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-25.61 [-46.79, -4.43]
2 Continuity of attention (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-0.32 [-1.65, 1.01]
3 Quality of memory (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-2.28 [-28.57, 24.01]
4 Speed of memory (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	28.17 [-82.25, 138.59]
5 Working memory (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	0.05 [-0.02, 0.12]
6 Secondary memory (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-2.33 [-27.70, 23.04]
7 CDR battery, Choice Reaction Time (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-22.09 [-36.92, -7.26]

Comparison 6.   Ginseng extract (200mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 4)	1		Mean Difference (Fixed, 95% CI)	-9.31 [-14.29, -4.34]
2 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 8)	1		Mean Difference (Fixed, 95% CI)	-5.91 [-7.96, -3.85]

Comparison 7.   Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mood, Alertness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	1.2 [-4.68, 7.08]
2 Mood, Contentedness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-0.63 [-4.00, 4.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)	1		Mean Difference (Fixed, 95% CI)	-1.88 [-9.56, 5.80]

Comparison 8. Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WHOQOL-BREF, Overall quality of life (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.01, 0.35]
2 WHOQOL-BREF, General health (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	0.34 [0.16, 0.52]
3 WHOQOL-BREF, Physical health (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	3.78 [0.21, 7.35]
4 WHOQOL-BREF, Psychological health (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	2.38 [-1.17, 5.93]
5 WHOQOL-BREF, Social relationships (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	4.02 [-0.42, 8.46]
6 WHOQOL-BREF, Environment (Change from baseline: week 8)	1	99	Mean Difference (IV, Fixed, 95% CI)	0.60 [-2.83, 4.03]

Comparison 9. Ginseng extract (200mg/day) vs placebo for quality of life in healthy participants (Cross-over)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WHOQOL-BREF, Social relationships (Change from baseline: week 8)	1		Mean Difference (Fixed, 95% CI)	1.33 [0.43, 2.24]

Analysis 1.1. Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 1 Attention and concentration, cancellation (No. of digits/2 min) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 1 Attention and concentration, cancellation (No. of digits/2 min) (Change from baseline: week 12)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
D'Angelo 1986	16	7 (6.2769419)	16	5 (4.4271887)		100.0 %	2.00 [-1.76, 5.76]
Total (95% CI)	**16**		**16**			**100.0 %**	**2.00 [-1.76, 5.76]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.04 (P = 0.30)

```
        -10   -5    0    5    10
             Ginseng   Placebo
```
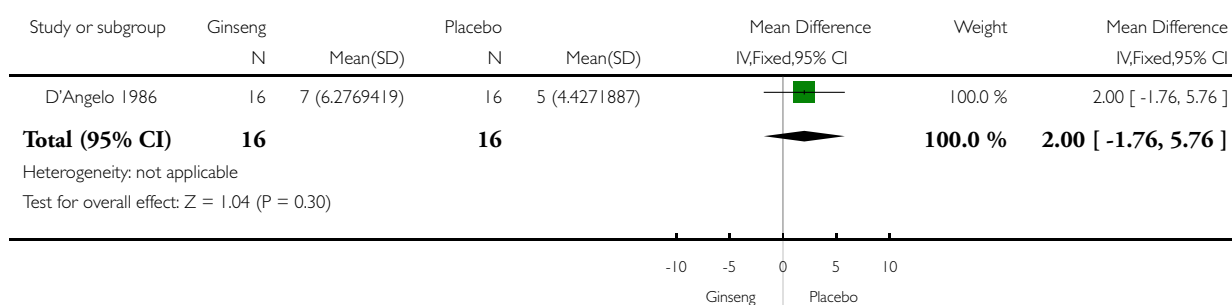
Analysis 1.2. Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 2 Speed of processing, Mental arithmetic (correct responses/s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 2 Speed of processing, Mental arithmetic (correct responses/s) (Change from baseline: week 12)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
D'Angelo 1986	16	0.12 (0.1456709)	16	0 (0.1032473)		100.0 %	0.12 [0.03, 0.21]
Total (95% CI)	**16**		**16**			**100.0 %**	**0.12 [0.03, 0.21]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.69 (P = 0.0072)

```
       -0.2   -0.1    0    0.1    0.2
              Ginseng   Placebo
```

Analysis 1.3.   Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 3 Speed of processing, Logical deduction (correct responses/s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 3 Speed of processing, Logical deduction (correct responses/s) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	16	0.06 (0.0608276)	16	0.04 (0.0664831)		100.0 %	0.02 [-0.02, 0.06]
Total (95% CI)	**16**		**16**			**100.0 %**	**0.02 [-0.02, 0.06]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.89 (P = 0.37)

```
      -0.2   -0.1    0    0.1    0.2
            Ginseng    Placebo
```

Analysis 1.4.   Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 4 Speed of processing, Digit symbol substitution (No. of symbols/90s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 4 Speed of processing, Digit symbol substitution (No. of symbols/90s) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	16	6 (6.9570109)	16	7 (5.4037024)		100.0 %	-1.00 [-5.32, 3.32]
Total (95% CI)	**16**		**16**			**100.0 %**	**-1.00 [-5.32, 3.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.45 (P = 0.65)

```
      -10    -5    0    5    10
            Ginseng    Placebo
```

Analysis 1.5.   Comparison I Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 5 Sensorimotor function, choice reaction time (s/10-no. of errors) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: I Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 5 Sensorimotor function, choice reaction time (s/10-no. of errors) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	-0.018 (0.0055317)		16	16	0 (0.0067082)	100.0 %	-0.01 [-0.02, -0.01]
Total (95% CI)	**16**		**16**			**100.0 %**	**-0.01 [-0.02, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.44 (P < 0.00001)							

-0.02   -0.01   0   0.01   0.02
Ginseng   Placebo

Analysis 1.6.   Comparison I Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 6 Sensorimotor function, simple visual reaction time (s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: I Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 6 Sensorimotor function, simple visual reaction time (s) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	16	0 (0.0126491)	16	0 (0.0228035)		100.0 %	0.0 [-0.01, 0.01]
Total (95% CI)	**16**		**16**			**100.0 %**	**0.0 [-0.01, 0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							

-0.05   -0.03   0   0.03   0.05
Ginseng   Placebo

Analysis 1.7. Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 7 Sensorimotor function, simple auditory reaction time (s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 7 Sensorimotor function, simple auditory reaction time (s) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	16	-0.02 (0.0184391)	16	-0.02 (0.0126491)		100.0 %	0.0 [-0.01, 0.01]
Total (95% CI)	**16**		**16**			**100.0 %**	**0.0 [-0.01, 0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							

$$-0.05 \quad -0.03 \quad 0 \quad 0.03 \quad 0.05$$

Ginseng   Placebo

Analysis 1.8. Comparison 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 8 Pure motor function, tapping (taps/30s) (Change from baseline: week 12).

Review: Ginseng for cognition

Comparison: 1 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 8 Pure motor function, tapping (taps/30s) (Change from baseline: week 12)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
D'Angelo 1986	16	0 (10.5261579)	16	8 (8.5906926)		100.0 %	-8.00 [-14.66, -1.34]
Total (95% CI)	**16**		**16**			**100.0 %**	**-8.00 [-14.66, -1.34]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.36 (P = 0.019)							

$$-20 \quad -10 \quad 0 \quad 10 \quad 20$$

Ginseng   Placebo

Analysis 2.1.   Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 1 Attention and concentration, D2 (total score) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 1 Attention and concentration, D2 (total score) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Srensen 1996	55	41.5 (41.9)	57	37.5 (39.8)		100.0 %	4.00 [-11.15, 19.15]
Total (95% CI)	**55**		**57**			**100.0 %**	**4.00 [-11.15, 19.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.52 (P = 0.60)

```
        -100    -50     0     50    100
              Ginseng      Placebo
```
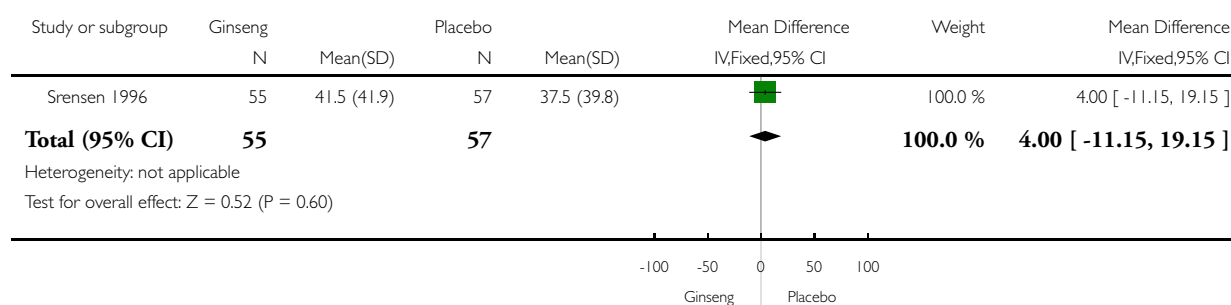
Analysis 2.2.   Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 2 Learning and Memory, selective reminding (error index) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 2 Learning and Memory, selective reminding (error index) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Srensen 1996	55	1.3 (8.9)	57	-3.1 (10.4)		100.0 %	4.40 [0.82, 7.98]
Total (95% CI)	**55**		**57**			**100.0 %**	**4.40 [0.82, 7.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.41 (P = 0.016)

```
        -20    -10     0     10    20
              Ginseng      Placebo
```
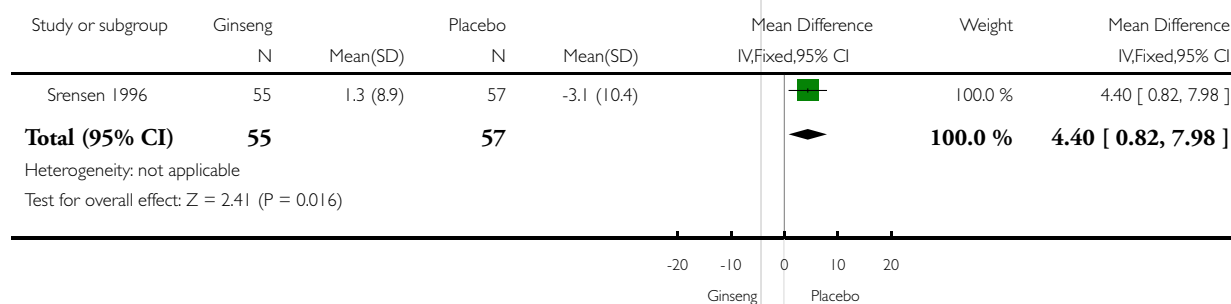
Analysis 2.3. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 3 Learning and Memory, logical memory and reproduction (units lost) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 3 Learning and Memory, logical memory and reproduction (units lost) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	0 (2)	57	0 (2)		100.0 %	0.0 [-0.74, 0.74]
Total (95% CI)	**55**		**57**			**100.0 %**	**0.0 [-0.74, 0.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							

```
        -4    -2    0    2    4
           Ginseng   Placebo
```
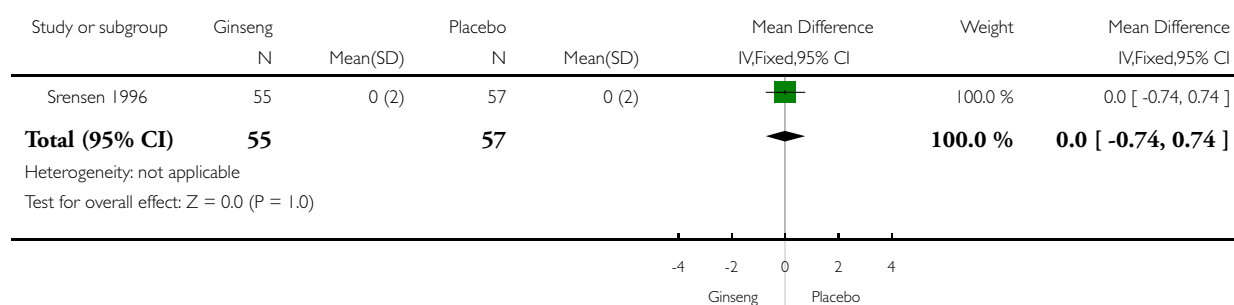
Analysis 2.4. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 4 Learning and Memory, Rey-Oestrich complex figure (units lost) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 4 Learning and Memory, Rey-Oestrich complex figure (units lost) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	-3.7 (5)	57	-3.9 (3.9)		100.0 %	0.20 [-1.46, 1.86]
Total (95% CI)	**55**		**57**			**100.0 %**	**0.20 [-1.46, 1.86]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							

```
        -10   -5    0    5    10
           Ginseng   Placebo
```
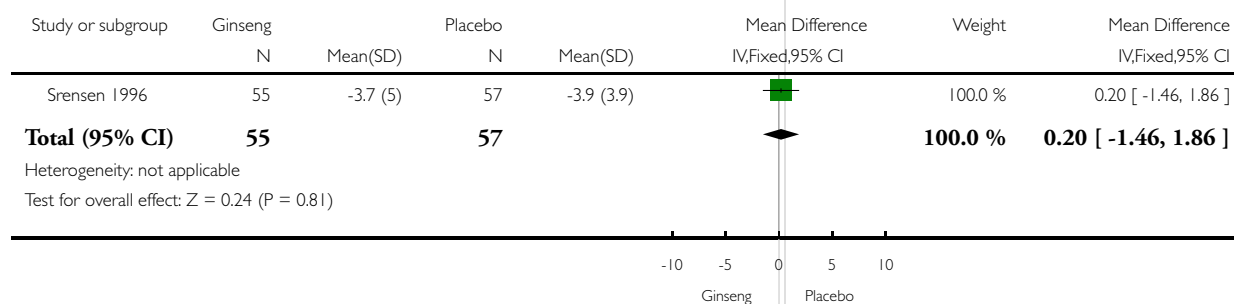
Analysis 2.5.   Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 5 Sensorimotor function, simple auditory reaction times (10 Percentile) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 5 Sensorimotor function, simple auditory reaction times (10 Percentile) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	0.8 (19.2)	57	7.4 (29.2)		100.0 %	-6.60 [-15.72, 2.52]
Total (95% CI)	**55**		**57**			**100.0 %**	**-6.60 [-15.72, 2.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.42 (P = 0.16)							

```
        -50   -25    0    25    50
             Ginseng     Placebo
```
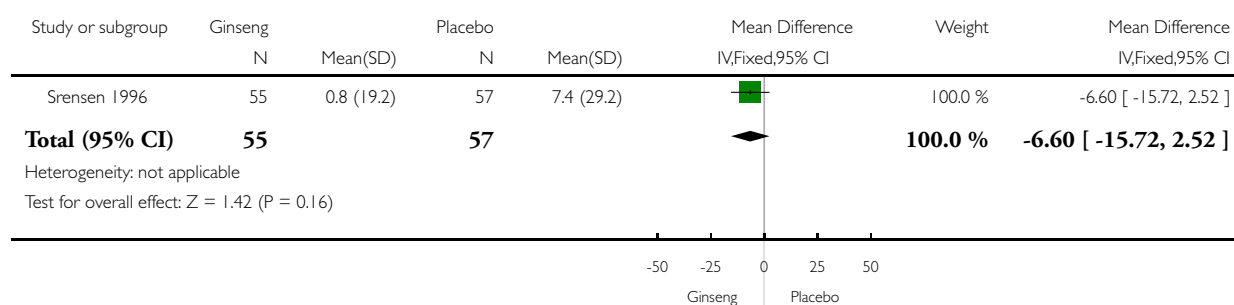
Analysis 2.6.   Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 6 Sensorimotor function simple auditory reaction times (50 Percentile) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 6 Sensorimotor function simple auditory reaction times (50 Percentile) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	-5.1 (37.3)	57	4.7 (32)		100.0 %	-9.80 [-22.69, 3.09]
Total (95% CI)	**55**		**57**			**100.0 %**	**-9.80 [-22.69, 3.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							

```
        -50   -25    0    25    50
             Ginseng     Placebo
```

Analysis 2.7. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 7 Sensorimotor function, simple visual reaction times (10 Percentile) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 7 Sensorimotor function, simple visual reaction times (10 Percentile) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	-4.6 (19.1)	57	-0.9 (21.7)		100.0 %	-3.70 [-11.26, 3.86]
Total (95% CI)	**55**		**57**			**100.0 %**	**-3.70 [-11.26, 3.86]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.96 (P = 0.34)

```
        -50    -25    0    25    50
              Ginseng    Placebo
```
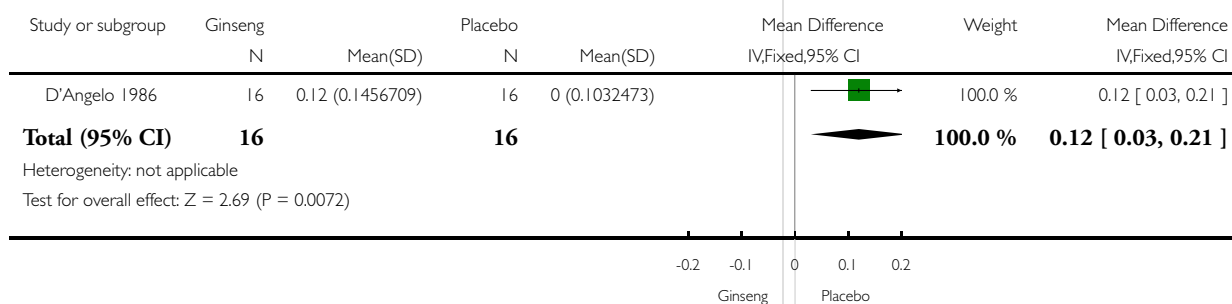
Analysis 2.8. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 8 Sensorimotor function, simple visual reaction times (50 Percentile) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 8 Sensorimotor function, simple visual reaction times (50 Percentile) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	-3.9 (24.3)	57	-1.7 (26.6)		100.0 %	-2.20 [-11.63, 7.23]
Total (95% CI)	**55**		**57**			**100.0 %**	**-2.20 [-11.63, 7.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.65)

```
        -50    -25    0    25    50
              Ginseng    Placebo
```
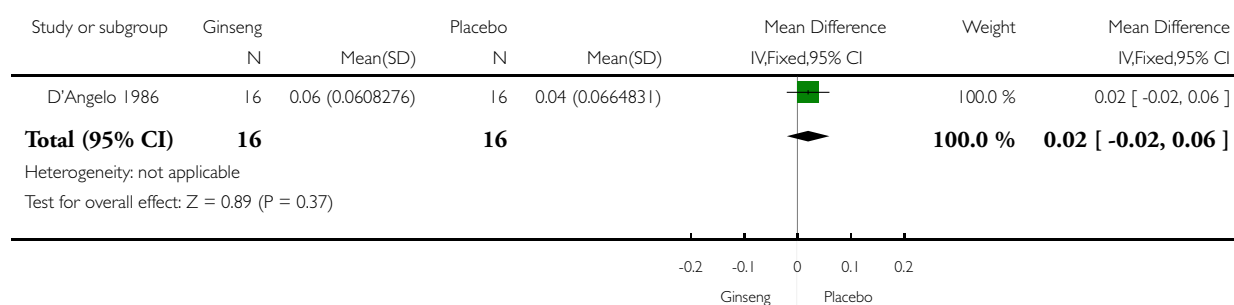
Analysis 2.9. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 9 Pure motor function, finger-tapping (maximum) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 9 Pure motor function, finger-tapping (maximum) (Change from baseline: week 8 to 9)

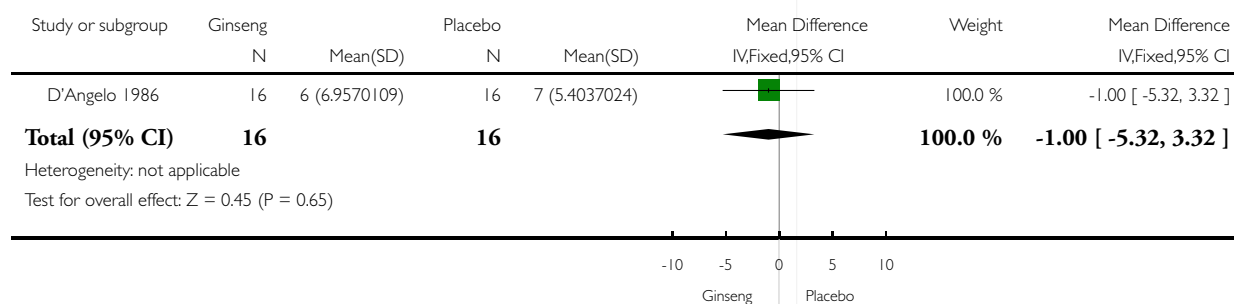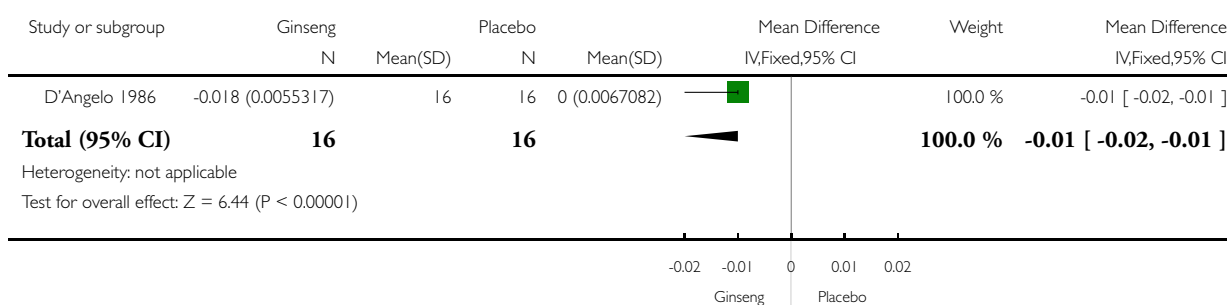| Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	0.9 (5.6)	57	2.5 (5.6)		100.0 %	-1.60 [-3.67, 0.47]
Total (95% CI)	**55**		**57**			**100.0 %**	**-1.60 [-3.67, 0.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.51 (P = 0.13)							

-10   -5   0   5   10
Ginseng   Placebo

Analysis 2.10. Comparison 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group), Outcome 10 Pure motor function, finger-tapping (50 Percentile) (Change from baseline: week 8 to 9).

Review: Ginseng for cognition

Comparison: 2 Ginseng extract (400mg/day) vs placebo for cognitive function healthy participants (Parallel Group)

Outcome: 10 Pure motor function, finger-tapping (50 Percentile) (Change from baseline: week 8 to 9)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Srensen 1996	55	1 (6.7)	57	3.5 (7.2)		100.0 %	-2.50 [-5.07, 0.07]
Total (95% CI)	**55**		**57**			**100.0 %**	**-2.50 [-5.07, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.90 (P = 0.057)							

-10   -5   0   5   10
Ginseng   Placebo

Analysis 3.1. Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 1 Wechsler Memory Scale-III (WMS-III), Logical memory I (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 1 Wechsler Memory Scale-III (WMS-III), Logical memory I (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	2 (2.1711748)	49	1.8 (1.9944924)		100.0 %	0.20 [-0.62, 1.02]
Total (95% CI)	**50**		**49**			**100.0 %**	**0.20 [-0.62, 1.02]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

```
      -4   -2    0    2    4
          Ginseng  Placebo
```
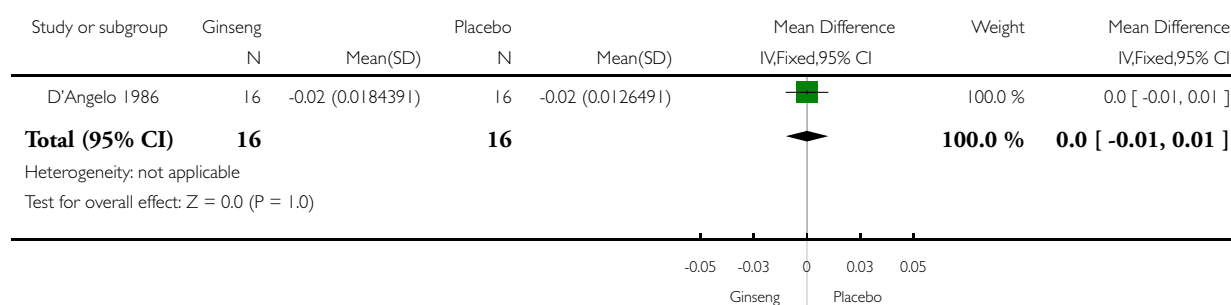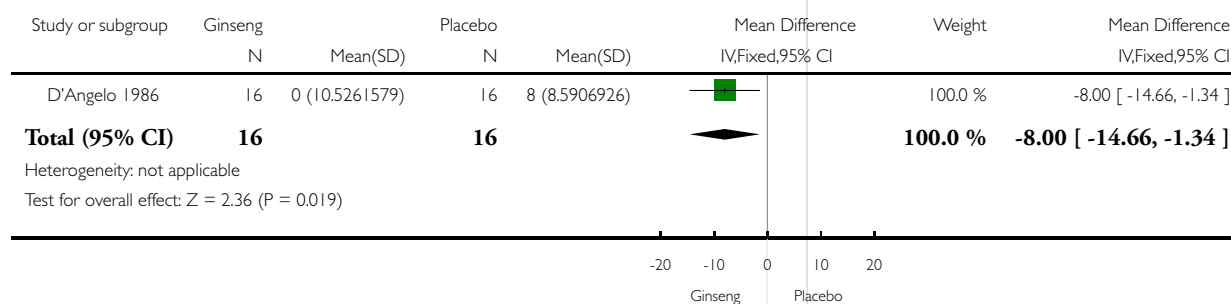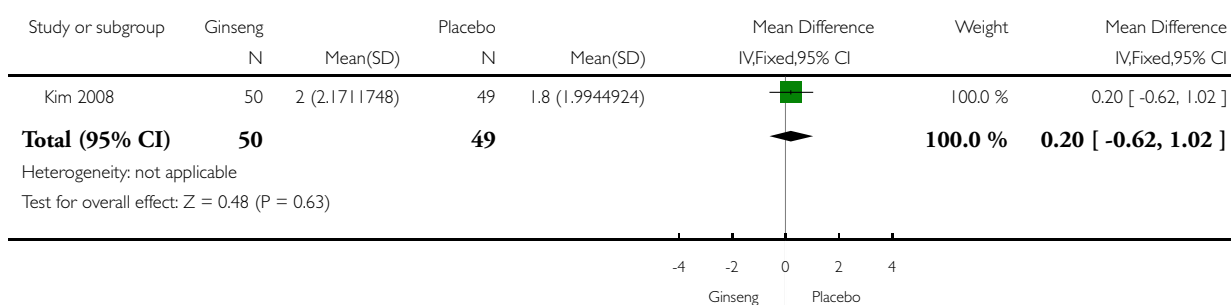
Analysis 3.2. Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 2 Wechsler Memory Scale-III (WMS-III), Logical memory II (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 2 Wechsler Memory Scale-III (WMS-III), Logical memory II (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	2.08 (2.2472205)	49	2.17 (2.1377558)		100.0 %	-0.09 [-0.95, 0.77]
Total (95% CI)	**50**		**49**			**100.0 %**	**-0.09 [-0.95, 0.77]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)

```
      -4   -2    0    2    4
          Ginseng  Placebo
```
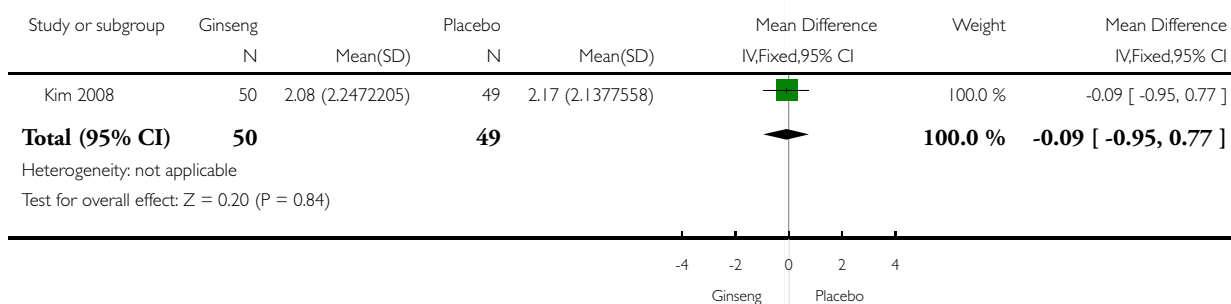
Analysis 3.3. Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 3 Wechsler Memory Scale-III (WMS-III), Verbal paired associates I (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 3 Wechsler Memory Scale-III (WMS-III), Verbal paired associates I (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	1.54 (1.9498718)	49	2 (1.9250974)	■	100.0 %	-0.46 [-1.22, 0.30]
Total (95% CI)	**50**		**49**		◆	**100.0 %**	**-0.46 [-1.22, 0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							

```
        -4    -2    0    2    4
           Ginseng    Placebo
```
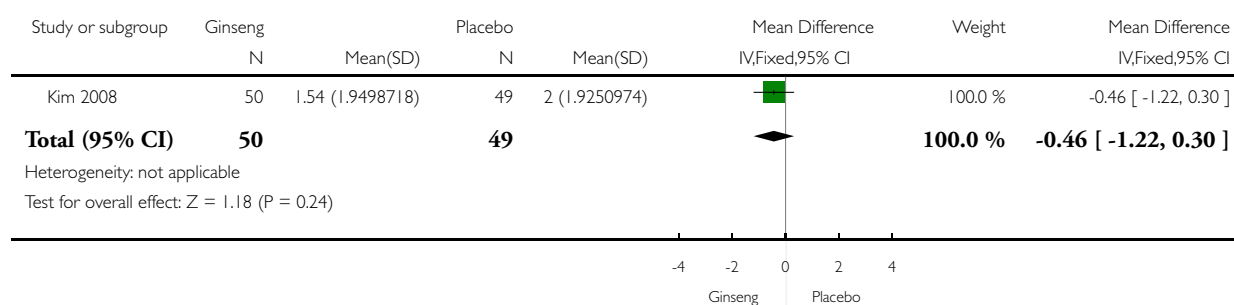
Analysis 3.4. Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 4 Wechsler Memory Scale-III (WMS-III), Verbal paired associates II (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 4 Wechsler Memory Scale-III (WMS-III), Verbal paired associates II (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	1.02 (1.9349419)	49	1.62 (1.6552945)	■	100.0 %	-0.60 [-1.31, 0.11]
Total (95% CI)	**50**		**49**		◆	**100.0 %**	**-0.60 [-1.31, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.097)							

```
        -4    -2    0    2    4
           Ginseng    Placebo
```
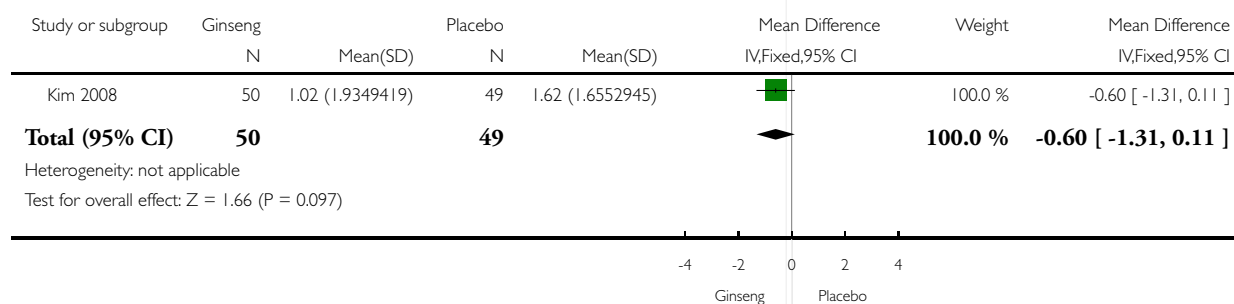
Analysis 3.5.   Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 5 Wechsler Memory Scale-III (WMS-III), Letter-Number Sequencing (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 5 Wechsler Memory Scale-III (WMS-III), LetterNumber Sequencing (Change from baseline: week 8)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2008	50	0.38 (1.8248288)	49	1.14 (2.0124612)		100.0 %	-0.76 [-1.52, 0.00]
Total (95% CI)	**50**		**49**			**100.0 %**	**-0.76 [-1.52, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.97 (P = 0.049)							

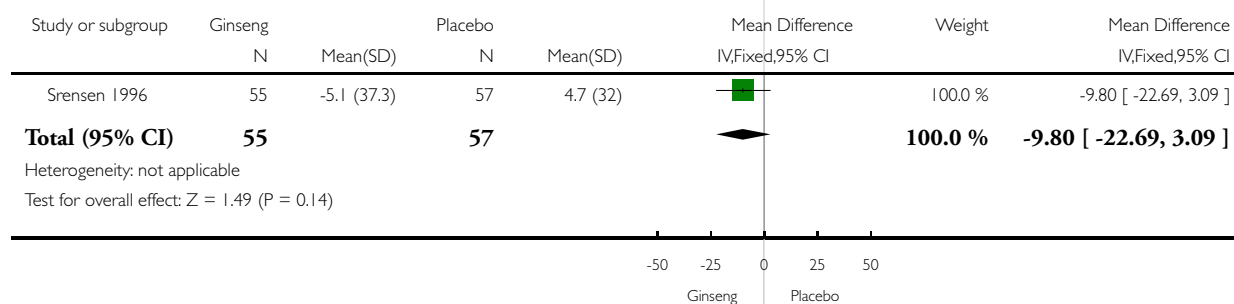-4   -2   0   2   4
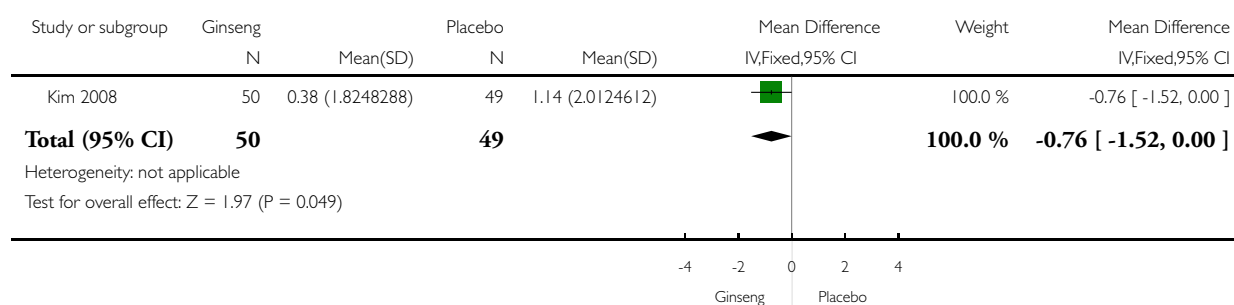
Ginseng   Placebo

Analysis 3.6.   Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 6 Wechsler Memory Scale-III (WMS-III), Spatial span (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 6 Wechsler Memory Scale-III (WMS-III), Spatial span (Change from baseline: week 8)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2008	50	0.14 (2.2631836)	49	0.37 (2.433105)		100.0 %	-0.23 [-1.16, 0.70]
Total (95% CI)	**50**		**49**			**100.0 %**	**-0.23 [-1.16, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							

-4   -2   0   2   4
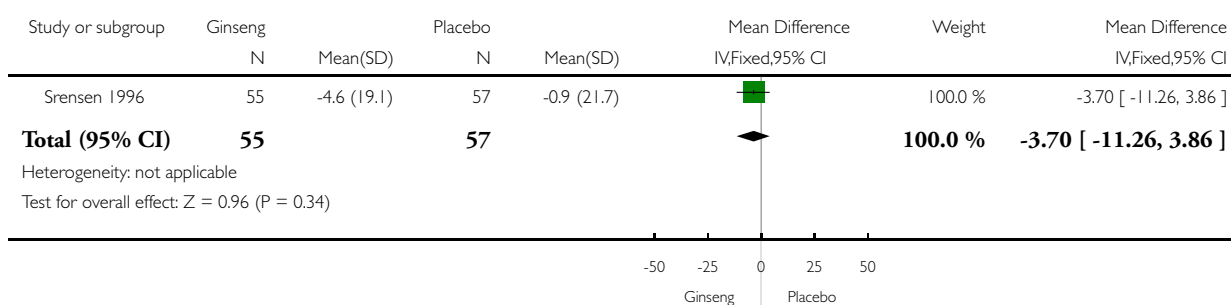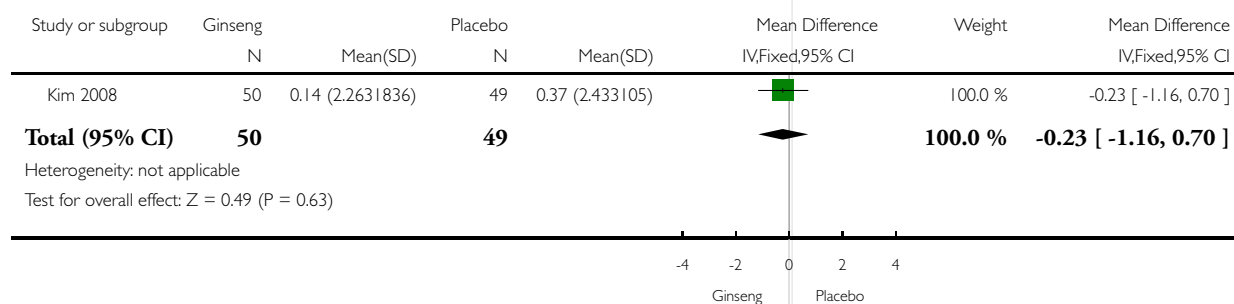
Ginseng   Placebo

Analysis 3.7.   Comparison 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group), Outcome 7 Wechsler Memory Scale-III (WMS-III), Auditory recognition delayed (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 3 Ginseng Compound HT008-1 (5200mg/day) vs placebo for cognitive function in healthy participants (Parallel Group)

Outcome: 7 Wechsler Memory Scale-III (WMS-III), Auditory recognition delayed (Change from baseline: week 8)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2008	50	2.18 (2.1377558)	49	1.8 (1.9864541)		100.0 %	0.38 [-0.43, 1.19]
Total (95% CI)	**50**		**49**			**100.0 %**	**0.38 [-0.43, 1.19]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

```
        -4    -2    0    2    4
           Ginseng    Placebo
```
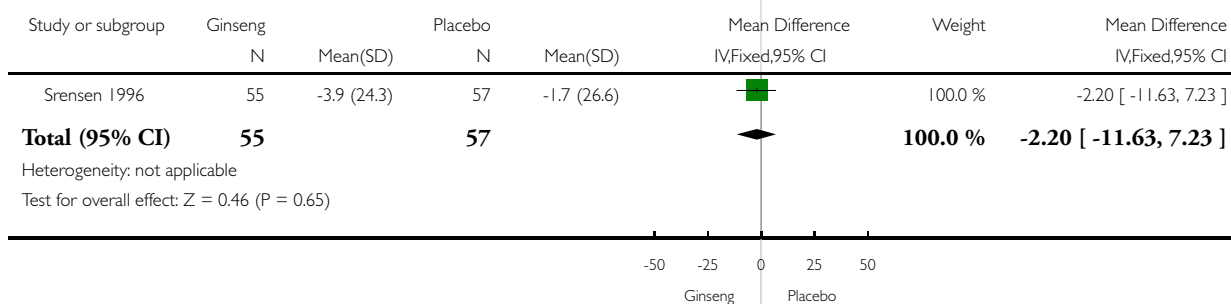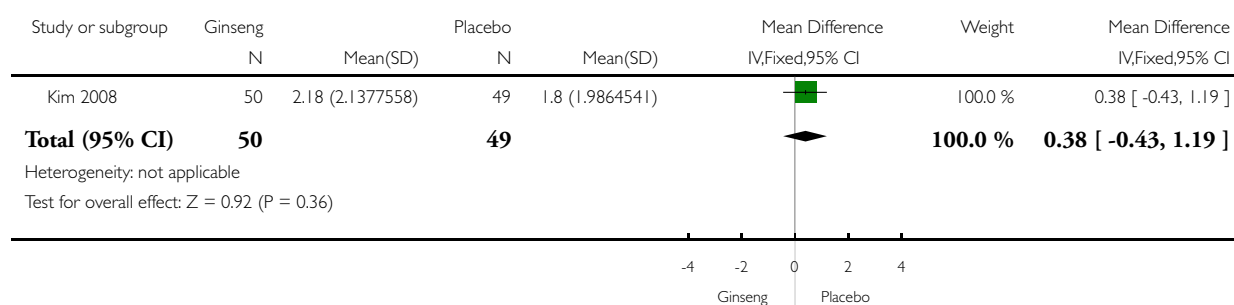
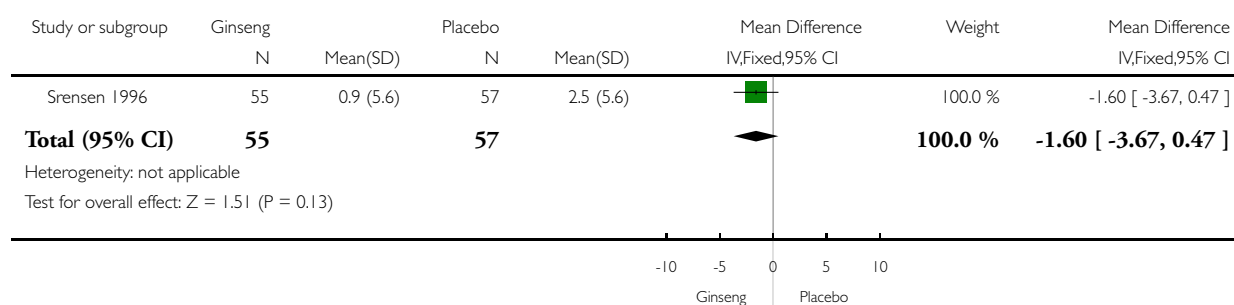**Analysis 4.1.   Comparison 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 1 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 4).**

Review: Ginseng for cognition

Comparison: 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 1 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 4)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	-0.06 (0.020747)		100.0 %	-0.06 [-0.10, -0.02]
Total (95% CI)			**100.0 %**	**-0.06 [-0.10, -0.02]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.89 (P = 0.0038)

```
     -0.2   -0.1   0   0.1   0.2
          Ginseng    Placebo
```
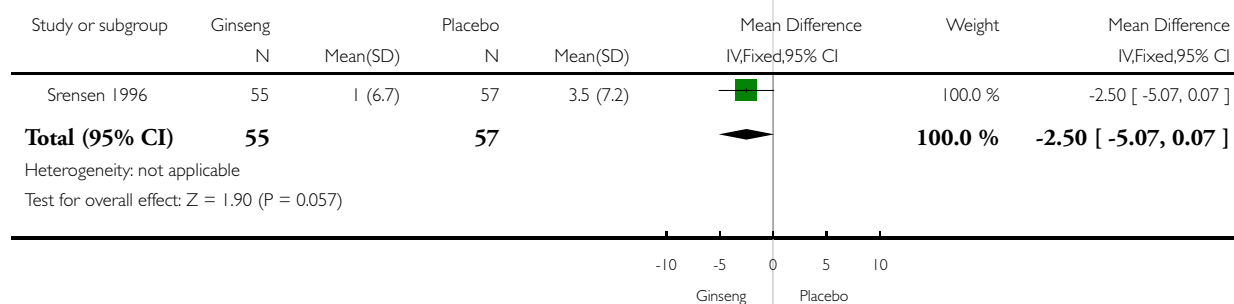
Analysis 4.2. Comparison 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 2 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 2 Working Memory, Speed of carrying out 3-Back task (Change from baseline: week 8)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	-0.062 (0.025801)		100.0 %	-0.06 [-0.11, -0.01]
Total (95% CI)			**100.0 %**	**-0.06 [-0.11, -0.01]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.40 (P = 0.016)				

-0.2 -0.1 0 0.1 0.2
Ginseng   Placebo

Analysis 4.3. Comparison 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 3 Working Memory, Corsi Block Digit span (Change from baseline: week 4).

Review: Ginseng for cognition

Comparison: 4 Ginseng extract (200mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 3 Working Memory, Corsi Block Digit span (Change from baseline: week 4)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	0.276 (0.151648)		100.0 %	0.28 [-0.02, 0.57]
Total (95% CI)			**100.0 %**	**0.28 [-0.02, 0.57]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.82 (P = 0.069)				

-1 -0.5 0 0.5 1
Ginseng   Placebo

Analysis 5.1.   Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 1 Speed of attention (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 1 Speed of attention (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-25.61 (10.80591)		100.0 %	-25.61 [-46.79, -4.43]
Total (95% CI)			**100.0 %**	**-25.61 [-46.79, -4.43]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.37 (P = 0.018)				

```
        -50    -25    0    25    50
              Ginseng    Placebo
```

Analysis 5.2.   Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 2 Continuity of attention (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 2 Continuity of attention (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-0.32 (0.680851)		100.0 %	-0.32 [-1.65, 1.01]
Total (95% CI)			**100.0 %**	**-0.32 [-1.65, 1.01]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.47 (P = 0.64)				

```
        -4    -2    0    2    4
              Ginseng    Placebo
```

Analysis 5.3. Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 3 Quality of memory (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 3 Quality of memory (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-2.28 (13.41176)		100.0 %	-2.28 [-28.57, 24.01]
Total (95% CI)			**100.0 %**	**-2.28 [-28.57, 24.01]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.17 (P = 0.87)				

```
     -100   -50    0     50    100
            Ginseng      Placebo
```
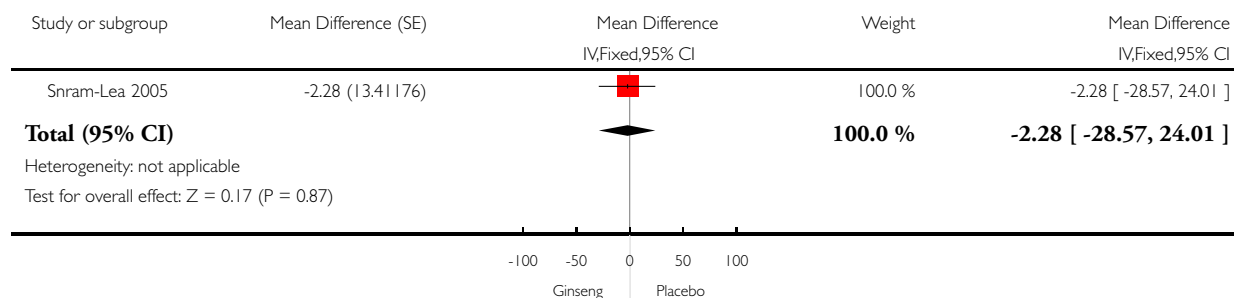
Analysis 5.4. Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 4 Speed of memory (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 4 Speed of memory (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	28.17 (56.34)		100.0 %	28.17 [-82.25, 138.59]
Total (95% CI)			**100.0 %**	**28.17 [-82.25, 138.59]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				

```
    -500  -250    0    250   500
           Ginseng      Placebo
```
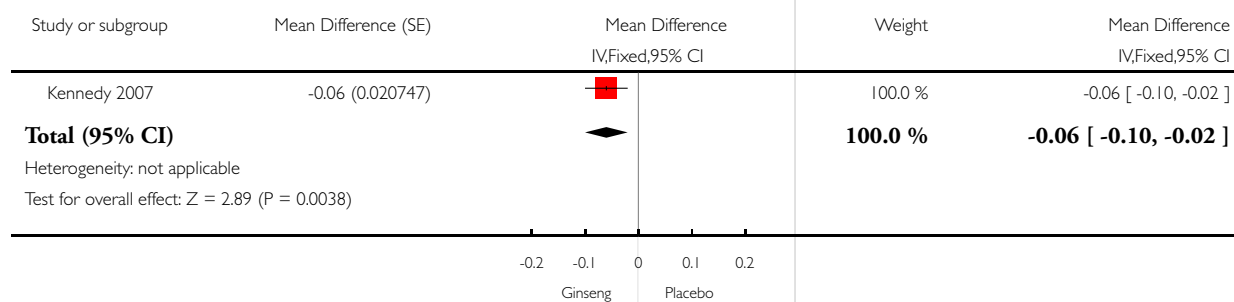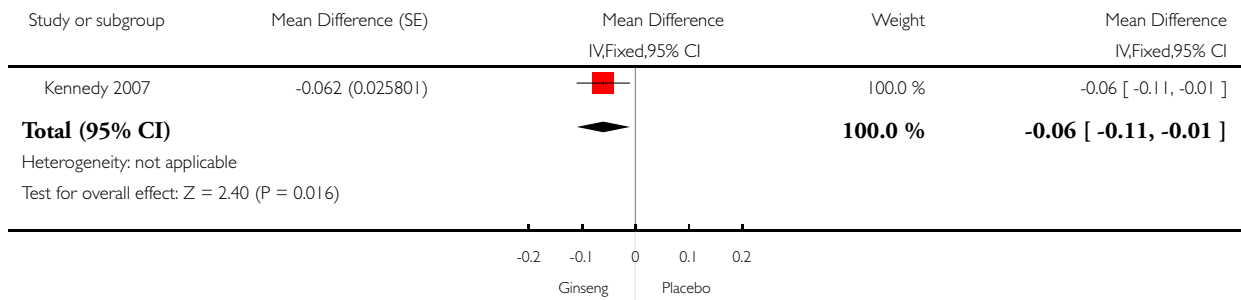
Analysis 5.5. Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 5 Working memory (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 5 Working memory (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	0.05 (0.037879)		100.0 %	0.05 [-0.02, 0.12]
Total (95% CI)			**100.0 %**	**0.05 [-0.02, 0.12]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.32 (P = 0.19)				

```
        -0.5   -0.25    0    0.25   0.5
               Ginseng      Placebo
```

Analysis 5.6. Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 6 Secondary memory (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 6 Secondary memory (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-2.33 (12.94444)		100.0 %	-2.33 [-27.70, 23.04]
Total (95% CI)			**100.0 %**	**-2.33 [-27.70, 23.04]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.18 (P = 0.86)				

```
        -100    -50    0     50    100
                Ginseng      Placebo
```
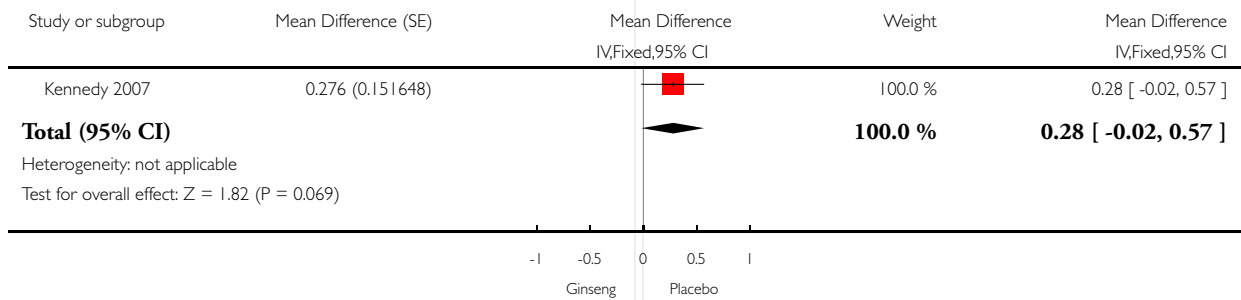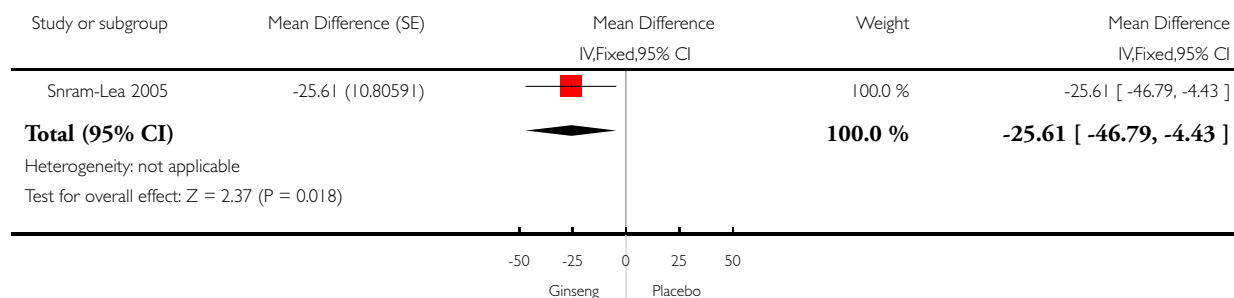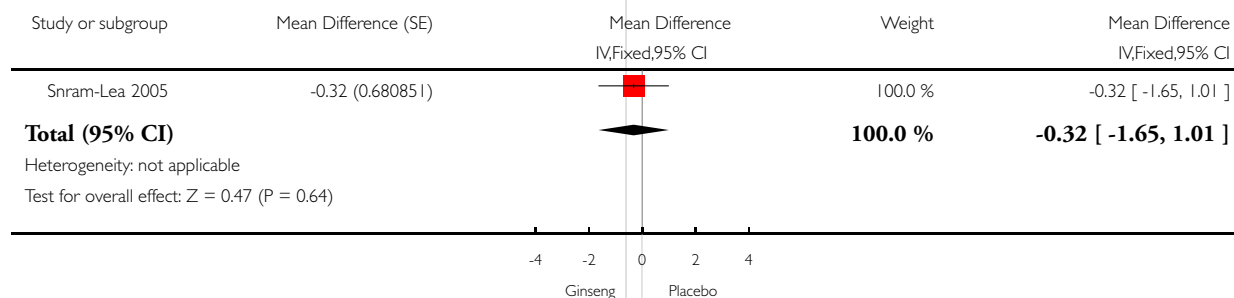
Analysis 5.7. Comparison 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over), Outcome 7 CDR battery, Choice Reaction Time (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 5 Ginseng extract (400mg/day) vs placebo for cognitive function in healthy participants (Cross-over)

Outcome: 7 CDR battery, Choice Reaction Time (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-22.09 (7.565068)		100.0 %	-22.09 [-36.92, -7.26]
Total (95% CI)			**100.0 %**	**-22.09 [-36.92, -7.26]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.92 (P = 0.0035)

```
       -50   -25    0    25    50
            Ginseng      Placebo
```

Analysis 6.1. Comparison 6 Ginseng extract (200mg/day) vs placebo for behavior in healthy participants (Cross-over), Outcome 1 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 4).

Review: Ginseng for cognition

Comparison: 6 Ginseng extract (200mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome: 1 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 4)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	-9.313 (2.539678)		100.0 %	-9.31 [-14.29, -4.34]
Total (95% CI)			**100.0 %**	**-9.31 [-14.29, -4.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.67 (P = 0.00025)

```
       -20   -10    0    10    20
            Ginseng      Placebo
```

Analysis 6.2. Comparison 6 Ginseng extract (200mg/day) vs placebo for behavior in healthy participants (Cross-over), Outcome 2 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 6 Ginseng extract (200mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome: 2 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: week 8)

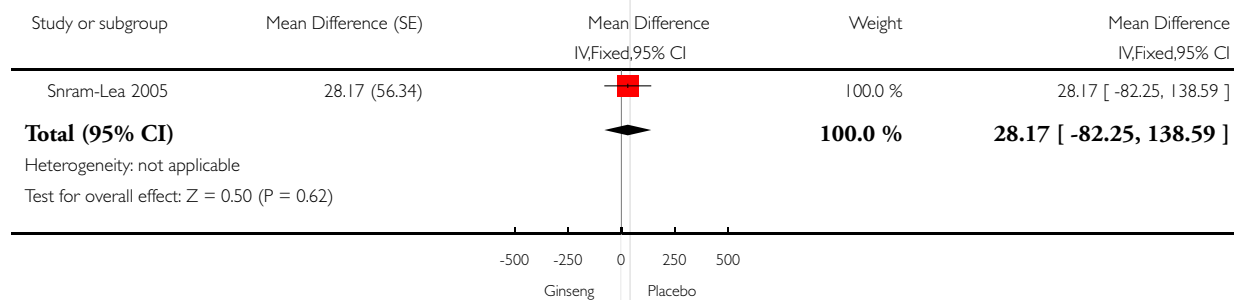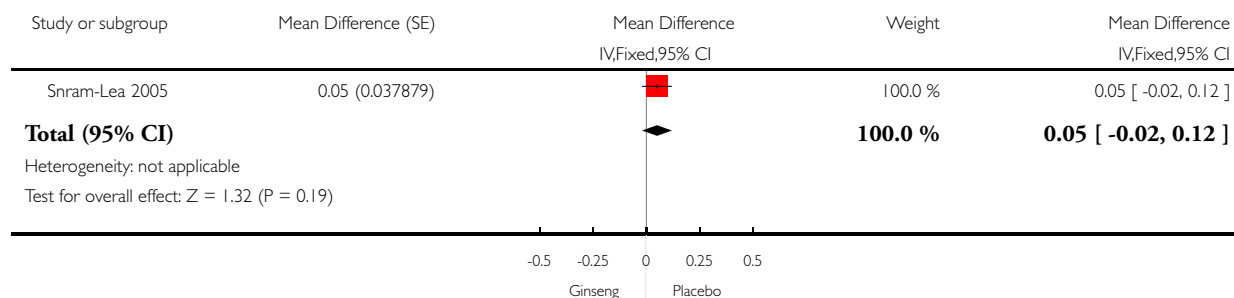| Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	-5.906 (1.047163)		100.0 %	-5.91 [-7.96, -3.85]
Total (95% CI)			**100.0 %**	**-5.91 [-7.96, -3.85]**
Heterogeneity: not applicable				
Test for overall effect: Z = 5.64 (P < 0.00001)				

```
        -10   -5   0   5   10
            Ginseng   Placebo
```
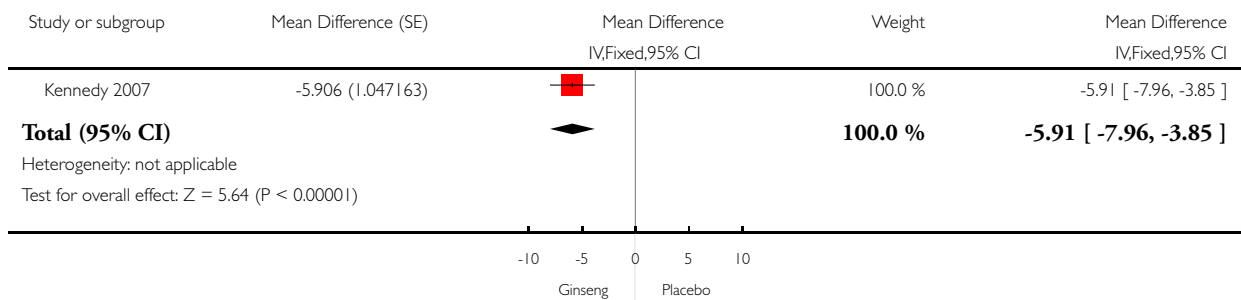
Analysis 7.1. Comparison 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over), Outcome 1 Mood, Alertness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome: 1 Mood, Alertness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)

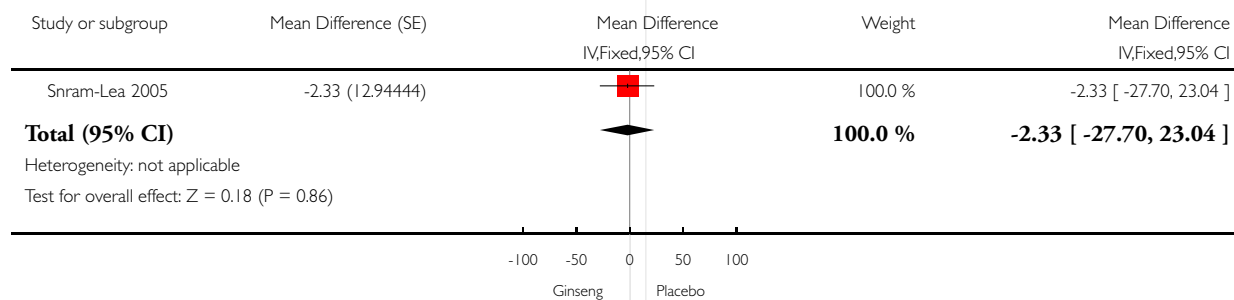| Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	1.2 (3)		100.0 %	1.20 [-4.68, 7.08]
Total (95% CI)			**100.0 %**	**1.20 [-4.68, 7.08]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.40 (P = 0.69)				

```
      -20   -10   0   10   20
            Ginseng   Placebo
```
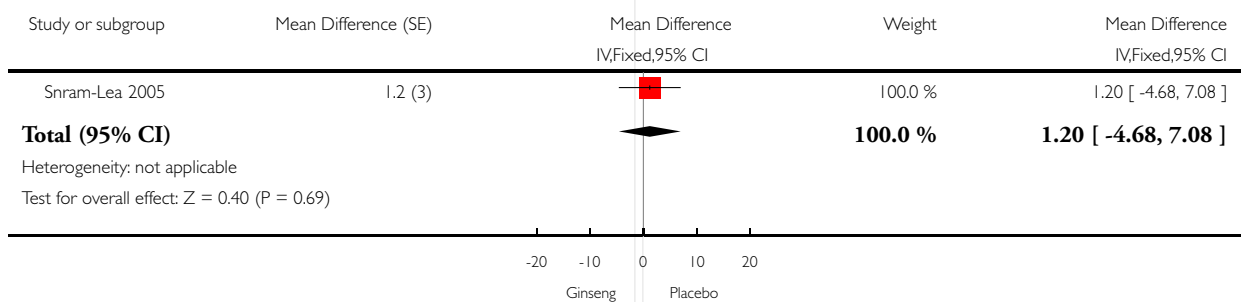
Analysis 7.2.   Comparison 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over), Outcome 2 Mood, Contentedness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome: 2 Mood, Contentedness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-0.63 (2.73913)		100.0 %	-0.63 [-6.00, 4.74]
Total (95% CI)			**100.0 %**	**-0.63 [-6.00, 4.74]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.23 (P = 0.82)

```
        -20   -10    0    10    20
              Ginseng    Placebo
```
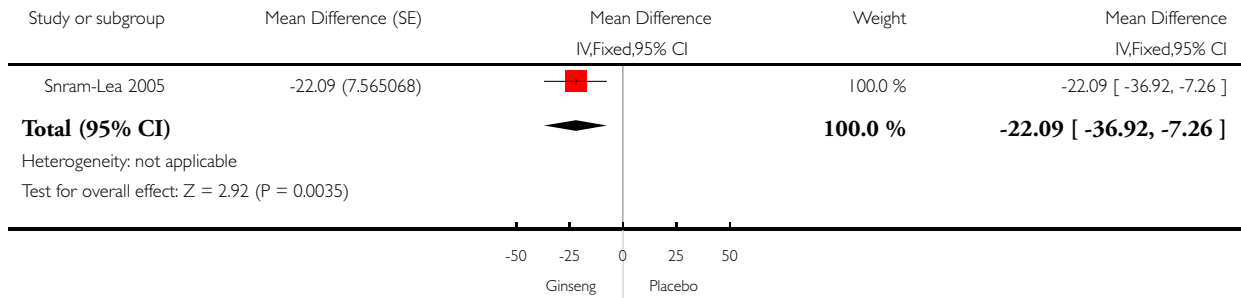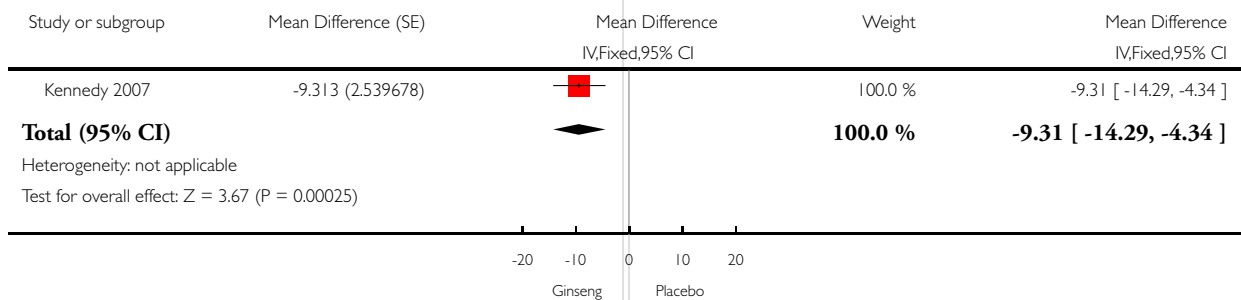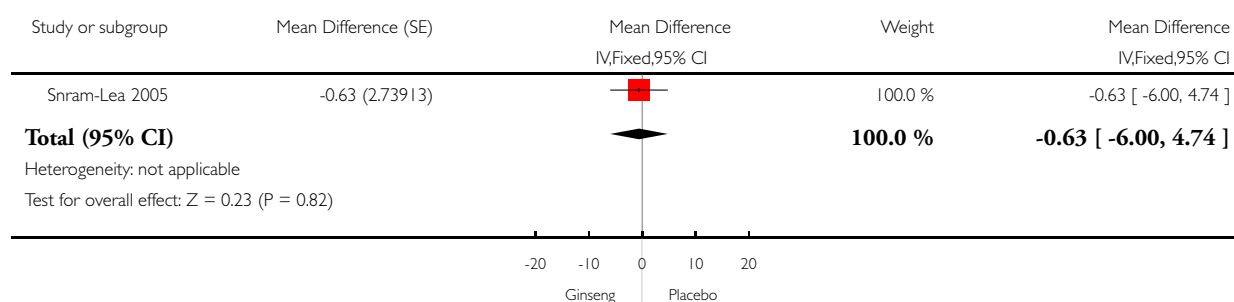
Analysis 7.3.   Comparison 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over), Outcome 3 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2).

Review: Ginseng for cognition

Comparison: 7 Ginseng extract (400mg/day) vs placebo for behavior in healthy participants (Cross-over)

Outcome: 3 Mood, Calmness (Bond-Lader Visual Analogue Scales) (Change from baseline: day 2)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Snram-Lea 2005	-1.88 (3.916667)		100.0 %	-1.88 [-9.56, 5.80]
Total (95% CI)			**100.0 %**	**-1.88 [-9.56, 5.80]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

```
        -50   -25    0    25    50
              Ginseng    Placebo
```
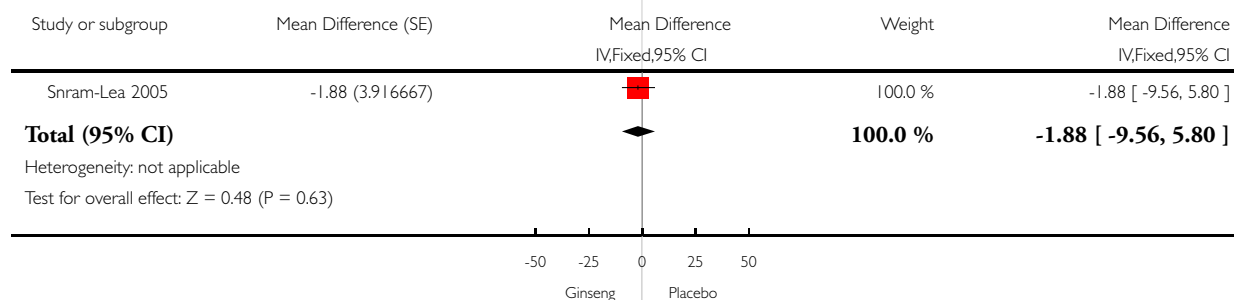
Analysis 8.1. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 1 WHOQOL-BREF, Overall quality of life (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 1 WHOQOL-BREF, Overall quality of life (Change from baseline: week 8)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2008	50	0.18 (0.3794733)	49	0 (0.4816638)		100.0 %	0.18 [0.01, 0.35]
Total (95% CI)	**50**		**49**			**100.0 %**	**0.18 [0.01, 0.35]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.06 (P = 0.039)

```
          -1    -0.5    0    0.5    1
              Ginseng      Placebo
```

Analysis 8.2. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 2 WHOQOL-BREF, General health (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 2 WHOQOL-BREF, General health (Change from baseline: week 8)

Study or subgroup	Ginseng N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2008	50	0.12 (0.4219005)	49	-0.22 (0.5059644)		100.0 %	0.34 [0.16, 0.52]
Total (95% CI)	**50**		**49**			**100.0 %**	**0.34 [0.16, 0.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.63 (P = 0.00029)

```
          -1    -0.5    0    0.5    1
              Ginseng      Placebo
```

Analysis 8.3. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 3 WHOQOL-BREF, Physical health (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 3 WHOQOL-BREF, Physical health (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	2.44 (8.6452299)	49	-1.34 (9.4573781)	■	100.0 %	3.78 [0.21, 7.35]
Total (95% CI)	**50**		**49**		◆	**100.0 %**	**3.78 [0.21, 7.35]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.07 (P = 0.038)

```
         -10    -5    0    5    10
              Ginseng   Placebo
```
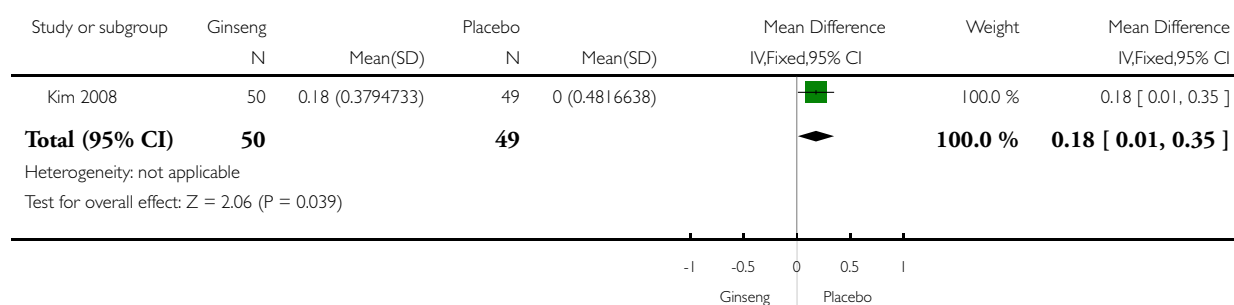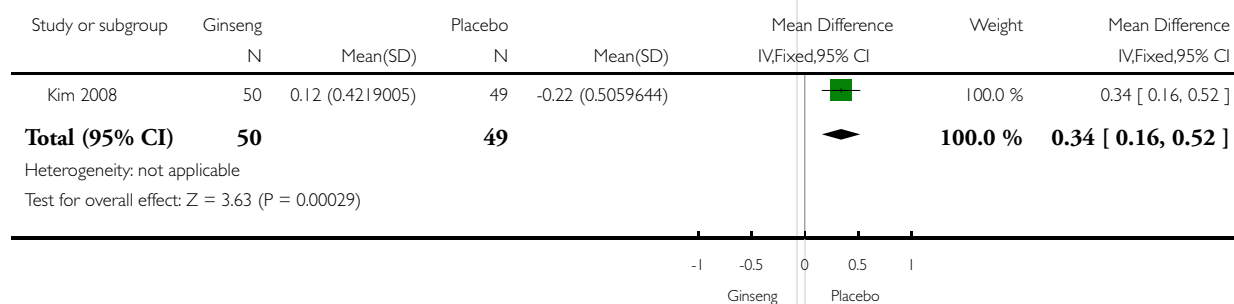
Analysis 8.4. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 4 WHOQOL-BREF, Psychological health (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 4 WHOQOL-BREF, Psychological health (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	5.62 (8.211699)	49	3.24 (9.7229625)	■	100.0 %	2.38 [-1.17, 5.93]
Total (95% CI)	**50**		**49**		◆	**100.0 %**	**2.38 [-1.17, 5.93]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

```
      -20   -10    0    10    20
            Ginseng   Placebo
```
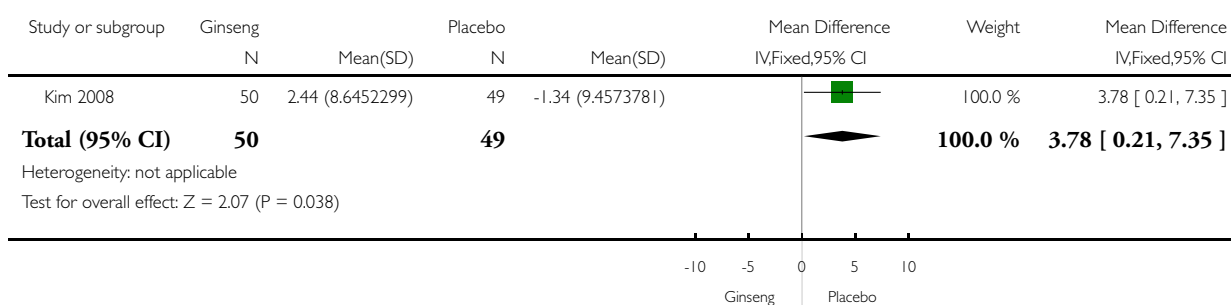
Analysis 8.5. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 5 WHOQOL-BREF, Social relationships (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 5 WHOQOL-BREF, Social relationships (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	6.94 (12.564235)	49	2.92 (9.8608316)		100.0 %	4.02 [-0.42, 8.46]
Total (95% CI)	**50**		**49**			**100.0 %**	**4.02 [-0.42, 8.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.77 (P = 0.076)							

```
        -20   -10    0    10    20
             Ginseng    Placebo
```
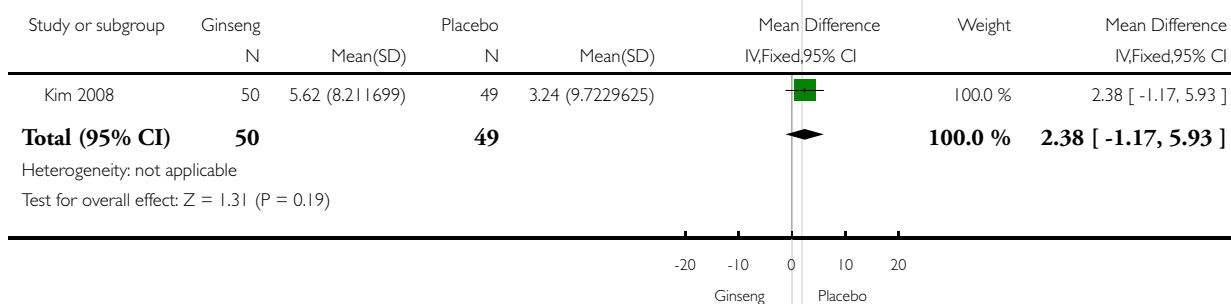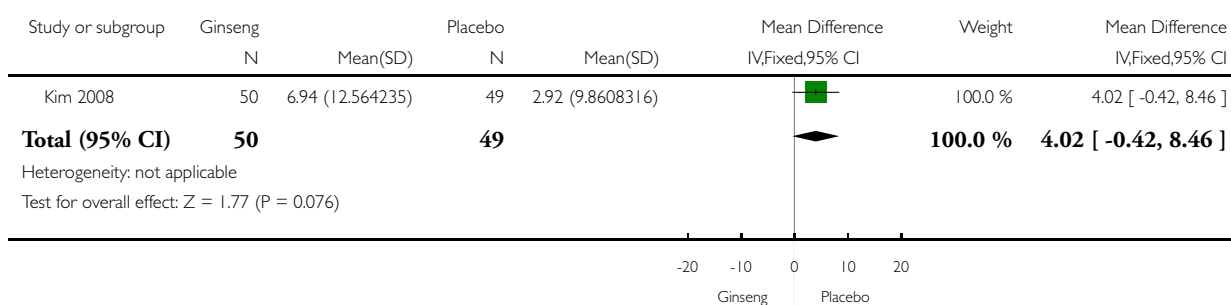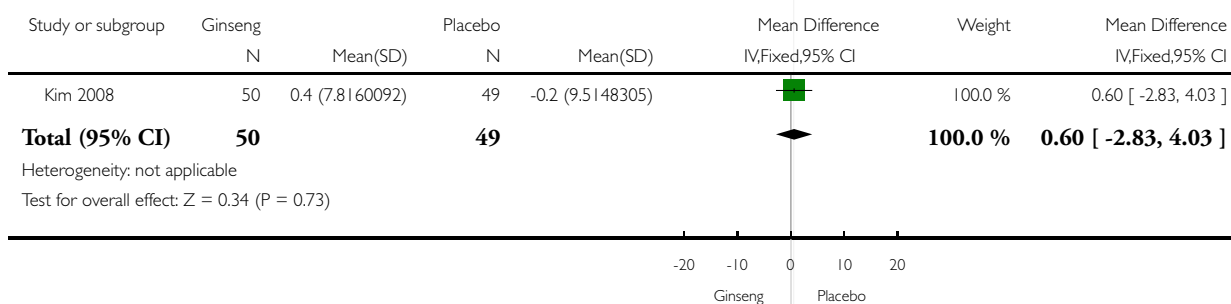
Analysis 8.6. Comparison 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group), Outcome 6 WHOQOL-BREF, Environment (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 8 Ginseng Compound HT008-1 (5200mg/day) vs placebo for quality of life in healthy participants (Parallel Group)

Outcome: 6 WHOQOL-BREF, Environment (Change from baseline: week 8)

Study or subgroup	Ginseng		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Kim 2008	50	0.4 (7.8160092)	49	-0.2 (9.5148305)		100.0 %	0.60 [-2.83, 4.03]
Total (95% CI)	**50**		**49**			**100.0 %**	**0.60 [-2.83, 4.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							

```
        -20   -10    0    10    20
             Ginseng    Placebo
```
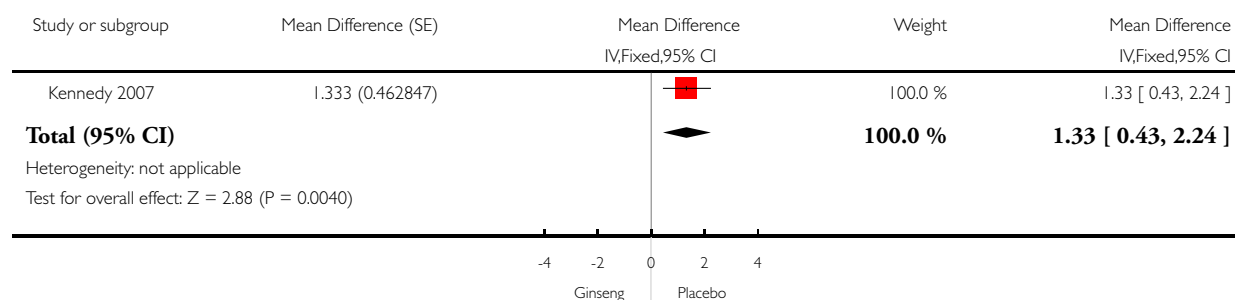
Analysis 9.1. Comparison 9 Ginseng extract (200mg/day) vs placebo for quality of life in healthy participants (Cross-over), Outcome 1 WHOQOL-BREF, Social relationships (Change from baseline: week 8).

Review: Ginseng for cognition

Comparison: 9 Ginseng extract (200mg/day) vs placebo for quality of life in healthy participants (Cross-over)

Outcome: 1 WHOQOL-BREF, Social relationships (Change from baseline: week 8)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kennedy 2007	1.333 (0.462847)		100.0 %	1.33 [0.43, 2.24]
Total (95% CI)			**100.0 %**	**1.33 [0.43, 2.24]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.88 (P = 0.0040)				

```
        -4   -2    0    2    4
            Ginseng   Placebo
```

APPENDICES

Appendix 1. MEDLINE search strategy

1	see CDCIG module text for all dementia-related search terms (Cochrane Dementia and Cognitive Improvement Group)
2	Ginsen* ti, ab
3	Panax ginseng ti, ab
4	Ginsan ti, ab
5	Jen Shen ti, ab
6	Shinseng ti, ab
7	Renshen ti, ab
8	Shinseng ti, ab
9	Ninjin ti, ab
10	Gingilone ti, ab

11	Panax* ti, ab
12	Panaxoside* ti, ab
13	Ginsenoside* ti, ab
14	Ginseng saponin ti, ab
15	Protootopanaxadiol ti, ab
16	Panaxagin ti, ab
17	Ginsenol ti, ab
18	Ginsenine ti, ab
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	randomized controlled trial*.ti, ab, pt
21	randomised controlled trial* ti, ab
22	controlled clinical trial* ti, ab, pt .
23	Randomi* ti, ab .
24	(double blind* or single blind* or triple blind*) ti, ab
25	(crossover or cross-over)ti, ab
26	20 or 21 or 22 or 23 or 24 or 25
27	19 and 26
28	Limit 27 to Humans

Appendix 2. Sources searched and number of hits retrieved

Source	Date range searched	Hits retrieved
Medline (Pubmed)	Up to 24 feb 09	7
Embase (Ovid SP)	Up to 26 Feb 09	6

(Continued)

PsycInfo (Ovid SP)	Up to 26 Feb 09	2
Cinahl (Ovid SP)	Up to 26 Feb 09	7
Lilacs (bireme)	Up to 24 Feb 09	0
CDCIG SR*	Searched 24 Feb 09	17
CENTRAL (The Cochrane Library)	Issue 1 2009	23
ISTP Conference Proceedings http://portal.isiknowledge.com/portal.cgi	Up to 26 Feb 09	12
Australian Digital Theses Program http://adt.caul.edu.au/	Searched 26 Feb 09	0
Canadian Theses and Dissertations http://www.collectionscanada.ca/thesescanada/index-e.html	Searched 26 Feb 09	0
WHO trials register	Searched 26 Feb 09	0
Current Controlled trials: Meta Register of Controlled trials (mRCT) http://www.controlled-trials.com/	Searched 26 Feb 09	1
ISRCTN Register	Searched 26 feb 09	//
Nederlands Trial Register http://www.trialregister.nl/trialreg/index.asp	Searched 26 Feb 09	0
ClinicalTrials.gov http://www.ClinicalTrials.gov	Included in WHO portal	//
IPFMA Clinical Trials Register www.ifpma.org/clinicaltrials.html	Searched 26 Feb 09	1
UMIN Japan Trial Register http://www.umin.ac.jp/ctr/	Searched 26 Feb 09	1
OPENsigle	Searched 26 Feb 09	1
Ageline	Searched 26 Feb 09	1
China National Knowledge Infrastructure (CNKI)	Searched 28 Feb 09	6

(Continued)

VIP Chinese Science and Technique Journals Database	Searched 28 Feb 09	6
Wanfang Data	Searched 28 Feb 09	6
The Chinese Clinical Trials Register (ChiCTR)	Searched 28 Feb 09	0
ProQuest Health and Medical Complete	Searched 28 Feb 09	1
BIOSIS Previews	Searched 28 Feb 09	2
Google	Searched 28 Feb 09	5

Appendix 3. Additional information of Panax ginseng products included in the review

1. G115® (Pharmaton S.A., Switzerland) is made from the fine rootlets of the plant Panax ginseng. Every batch of G115® ginseng extract always contains 4% ginsenosides. Ginsana® is based on the standardised G115® Ginseng extract. G115® is sold in combination with vital vitamins, minerals and trace elements as Ginsana® Gold Blend in the United States and Gericomplex® in Europe. Three similar products also produced by Pharmaton (Geriatric Pharmaton®, Gegorvit®, Pharmaton® Capsules) contained an additional ingredient, deanol (dimethylaminoethanol bitartrate).

2. Gerimax® (Dansk Droge) was launched in Denmark in 1981, and is today one of Europe's leading ginseng products. Gerimax® range consists of various product types, but common to all is that they contain the unique and patented Gerimax® Ginseng Extract. Gerimax® Ginseng Extract is characterized as containing 4 percent ginsenosides. Gerimax® is the market leader in the Nordic countries and sold in more than 25 countries. Dansk Droge was acquired by Orkla ASA and became part of this grouping in 2006. The combined company (Möller-Collett and Dansk Droge) renamed Axellus in 2007.

3. Cheong-Kwan-Jang is the official brand for the six-year-old red ginseng roots manufactured by Korean Ginseng Corporation (Korea), a government subsidized company. The Cheong-Kwan-Jang red ginseng contains 31 varieties of ginsenosides. Found in Cheong-Kwan-Jang red ginseng are 8 additional, unique substances of red ginseng including maltol and ginsenoside Rh2.

4. HT008-1 (Neu Med, Seoul, Korea) is the Korean ginseng complex comprising the roots of Panax ginseng and other components like Scutellaria baicalensis, Angelica sinensis, and Acanthopanax senticosus.

Reference:

Barrett 2004

Pharmaton product Ginseng G115®. http://www.pharmaton-proactive.ch/com/Main/Product/Ginseng/G115/index.htm

Gerimax - When you need extra energy http://www.axellus.no/no/c-51-Gerimax.aspx

What is Cheong - Kwan - Jang? http://www.kgc.or.kr/new˙eng/

HT008-1 Korean Ginseng Complex http://newmede.subnara.info/shop/eng/shop/content.php?co˙id=e33; http://neumed.en.ec21.com/Brain˙Care--4010677˙4011113.html

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 12, 2010

CONTRIBUTIONS OF AUTHORS

Geng JS - All correspondence; drafting protocol and review versions; search for trials; selection of trials for inclusion/exclusion; extraction of data; interpretation of data analyses; updating review.

Dong JC - Drafting review versions; extraction of data; updating review.

Ni HJ - Obtaining copies of trial reports; updating review.

Wu TX - Methodology expert; arbiter of selection of trials for inclusion/exclusion.

Jiang K - Search for trials; selection of trials for inclusion/exclusion; updating review.

Zhou AL - Updating review.

Wang GH - Interpretation of data analyses; entry of data; updating review.

Contact Editor - Krista Lanctot

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Evidence based medicine centre, Medical School of Nantong University, Jiangsu, China.

External sources

- Chinese Cochrane Center, China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The inclusion of two-period cross-over studies was not specified in the previously published protocol. This change in methods was made to bring the methods in line with the recommendations in the latest edition of the Cochrane Handbook and to ensure that potentially valuable information was not lost from the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Panax [adverse effects]; *Phytotherapy; Cognition [*drug effects]; Cognition Disorders [*drug therapy]; Nootropic Agents [adverse effects; *therapeutic use]; Plant Extracts [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans; Middle Aged