

A Systematic Review of the Efficacy of Herbal and Nutritional Medicines for Improving Cognition in Older Adults With and Without Subjective Cognitive Impairment

Adele E. Cave

Western Sydney University

Dennis H. Chang

Western Sydney University

Gerald W. Münch

Western Sydney University

Genevieve Z. Steiner-Lim (✉ g.steiner@westernsydney.edu.au)

Western Sydney University <https://orcid.org/0000-0002-8708-6104>

Research Article

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Abstract

Background: Subjective cognitive impairment (SCI), is conceptualised as the preclinical phase of dementia, and is characterised by a worsening of cognitive functioning, particularly within the area of memory. Due to the increased risk of developing future objective decline, and the lack of pharmacological interventions available to treat SCI, complementary medicines (CMs) are becoming more widely used by older adults, particularly herbal and nutritional medicines. The aim of this systematic review was to describe the study characteristics, methodologies, and intervention efficacy of studies on herbal and nutritional medicines for older adults with and without SCI.

Method: Four databases (Cochrane, MEDLINE, CINAHL, and PsycInfo) were searched from database inception until 20 February 2022. Articles were included in the review if they met the following criteria: study population of older adults with and without SCI, herbal and nutritional medicines as an intervention, evaluated cognitive outcomes, and were randomised control trials.

Results: Data was extracted from 20/6,006 eligible full-text articles, and risk of methodological bias in accordance with the Cochrane review process for randomised trials, (ROB 2) was assessed. Nine studies used an SCI population, with the remaining eleven, older adults without SCI. Most studies employed parallel, randomised, placebo-controlled designs, and were 12 weeks in length. Sixteen out of twenty studies used a herbal supplement, with most of these using a form of *Ginkgo biloba* or *Bacopa monnieri*. Measures of cognition varied across the studies, with 13/20 studies reporting improvements in at least one area of cognitive functioning across time, in the intervention group (compared to placebo). A total of 14/20 studies were deemed as having an overall high methodological risk of bias, 5/20 had some concerns, and only one study (using an SCI population) was assessed as having a low risk of methodological bias.

Conclusions: This was the first review to conduct an extensive search of randomised control trials using herbal and nutritional medicines, to improve cognitive functioning in older adults with, and without SCI. Further work needs to be done in classifying and understanding SCI, before future studies can more accurately determine the efficacy of these interventions.

1. Introduction

Subjective cognitive impairment (SCI) is a self-perceived worsening of cognitive functioning, particularly in the area of memory, that cannot be verified by neuropsychological tests (1, 2). SCI lies on a continuum of healthy cognitive ageing and is conceptualised as the preclinical phase of dementia (healthy cognitive ageing, to preclinical SCI, followed by prodromal mild cognitive impairment (MCI), then dementia) (2, 3). Importantly, SCI carries a three-fold increased risk of future objective decline.

It is estimated that the prevalence of SCI is 1 in 4 older adults aged 60 years and above, worldwide, with these numbers increasing rapidly each year (2). Currently there are no approved pharmacological interventions available, with many older adults experiencing SCI seeking alternative treatments (4). Further difficulty lies with the assessment of SCI, as current diagnostic tools have been developed for MCI or dementia (4, 5). Further, inconsistencies in the categorisation of SCI (namely the division between healthy adults without SCI, and those with SCI), is apparent in research (4, 5). Due to the increased risk of dementia and high prevalence of SCI, high quality research into effective treatments to improve cognitive functioning and prolong further decline is needed.

A review and meta-analysis conducted in 2018, investigated a variety of interventions (group psychological, cognitive, lifestyle, and complementary and alternative medicines) for the treatment of SCI, and their efficacy on psychological well-being, metacognition, and objective cognitive performance (5). The authors found that studies were generally of low quality, hence no firm conclusions could be made about the efficacy of the interventions employed (5). Whilst this review/meta-analysis is of great importance to furthering SCI treatment research, it did not explore the efficacy of single interventions on cognitive functioning, nor did they investigate this usage and efficacy in older adults without SCI.

Complementary medicines (CMs) are defined as a broad range of health care approaches, that are not thought to be a part of conventional medical care (6, 7). CMs are classified into three primary categories of delivery: nutritional (e.g. herbs, dietary supplements), psychological (e.g. meditation, relaxation therapy) and physical (e.g. acupuncture, massage) (6). CMs are becoming more widely available and used by older adults, particularly herbal and nutritional medicines for the treatment of chronic health conditions including, cardiovascular disease (8) and diabetes (9). Herbal medicines contain herbal substances or herbal preparations, with nutritional supplements/medicines containing vitamins, minerals and in combination formulas, herbal substances/preparations as well (7, 10). The natural properties of these medicines make them attractive to individuals wanting to improve their general health and well-being (7).

The aim of this review was to describe the study characteristics, methodologies, and intervention efficacy of studies on herbal and nutritional medicines for older adults with and without SCI. The secondary aim was to assess study quality and risk of methodological bias (ROB). This is the first review, to our knowledge, that has investigated the use of herbal and nutritional medicines for older adults with and without SCI, in depth.

2. Methods

This review is structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11) and registered with PROSPERO international database of systematic reviews on 7 May, 2021 (#CRD42021244631). A protocol was not published for this review.

2.1 Eligibility Criteria

A scoping review was conducted in line with study eligibility criteria which were determined as per the PICOS principles for systematic reviews (12):

1. Population: older adults with and without subjective cognitive impairment

2. Intervention: herbal and nutritional medicines
3. Comparisons: appropriate control group
4. Outcome: measures of cognition
5. Study design: randomised control trials (parallel or cross-over)

Inclusion criteria: chronic dosing studies over a period of 2 weeks or more, peer reviewed articles fully accessible online and written in English that met the above PICOS criteria. *Exclusion criteria:* reviews, case studies, editorials, conference proceedings, preclinical studies (both *in vitro* and *in vivo*), trial protocols, trial registrations, book chapters, abstracts only, peer-reviewed articles in which the study population had a diagnosis of mild cognitive impairment or dementia, did not include cognition as a primary endpoint, did not utilise herbal or nutritional medicines as an intervention, and/or employed a co-intervention such as cognitive training.

2.2 Search Strategy

Two researchers (AEC, GZS) reviewed the search strategy prior to commencement of scoping. Four databases were searched for peer reviewed articles: Cochrane, MEDLINE, CINAHL, and PsycInfo, from inception of each database until 4 August 2018. The database alerts for new articles were established until article finalisation on 20 February 2022. A full list of keywords is detailed below in Table 1. The only modification to the search strategy was the exclusion of non-randomised controlled trials from the Cochrane database to reduce the number of records for screening. Reference lists of included studies were also searched to identify any further eligible studies.

Table 1
Keywords forming the search strategy of the review utilised for all four databases.

Area & Search Number	Search Terms
Subjective Cognitive Impairment (S1)	"subjective cognitive impairment" OR "SCI" OR "subjective cognitive complaint*" OR "SCC" OR "subjective memory complaint*" OR "SMC" OR "cognitive decline" OR "preclinical dementia" OR "preclinical Alzheimer*" OR "age associated cognitive decline" OR "age related cognitive decline" OR "age associated memory impairment"
Older Adults Without Subjective Cognitive Impairment (S2)	"healthy ageing" OR "healthy aging" OR "cognitive decline" OR "older adult"
Intervention (S3)	"herbal medicine" OR "Chinese medicine" OR "complementary medicine" OR "alternative medicine" OR "natural medicine" OR "vitamin*" OR "nutraceutical" OR "nutritional supplement" OR "Chinese herbal medicine" OR "traditional Chinese medicine" OR "ginkgo" OR "ginseng" OR "alpha-lipoic acid" OR "lipoic acid" OR "bacopa monnier*" OR "brahmi"
(S4)	S1 OR S2 AND S3

2.3 Data Extraction and Appraisal

All titles and abstracts were first screened by one author (AEC) for inclusion or exclusion from the review. If there were uncertainties regarding suitability for inclusion, the second reviewer (GZS) would assist to collaboratively make a final decision. Full-text articles were reviewed by the two authors with disagreements of acceptability resolved by discussion. Study characteristics were then extracted for each full-text article. These characteristics included: author(s) and study location, aim, study population (group, sex, mean age, standard deviation and range), diagnosis criteria/global cognition measure, study design and outcome measurement frequencies, intervention, dose & duration, measures of cognition and results (cognition, retention, adherence and adverse events).

A methodological risk of bias assessment was conducted in accordance with the Cochrane review process for randomised trials (ROB 2) (13). Quality of trial design, conduct, and reporting of the included studies was assessed. Separate risk of bias assessments were conducted for parallel (14–32) and cross-over design studies (33). The risk of bias tool evaluates five domains: bias arising from the randomisation process, deviations from intended interventions (effect of assignment and adherence to intervention), bias due to missing outcome data and in the measurement of the outcome, and bias in selection of the reported result (13). A sixth domain of bias arising from period and carryover effects, was also evaluated for the cross-over study (13). One author (AEC) independently conducted the risk of bias assessment, with the second author (GZS), reviewing the outcomes.

Individual studies were assessed as *low risk*, *some concerns* regarding methodology, and *high risk* based on each of the above-mentioned domains. Studies with one or more domains assessed as high risk or with some concerns for multiple domains, were deemed overall as high risk. Those with at least one domain with some concerns were evaluated in this category. The risk of bias process was conducted to evaluate the quality of reporting across all included studies in this review. A qualitative synthesis approach to this review was taken due to the large variation of interventions and cognitive assessments utilised across the studies, for each of the populations.

3. Results

3.1 Study Selection

Figure 1 outlines the study selection process, with twenty studies meeting the eligibility criteria (14–33). Nine studies involved older adults with SCI (14–16, 20, 22, 27, 29, 31, 32), and the remaining eleven, older adults without SCI (17–19, 21, 23–26, 28, 30, 33).

3.2 Study Characteristics

Table 2 details a summary of the characteristics for the nine (14–16, 20, 22, 27, 29, 31, 32) SCI studies, and Table 3 details the eleven studies in older adults without SCI (17–19, 21, 23–26, 28, 30, 33). Both tables outline: study aim, population (group, sex, mean age, standard deviation and range), diagnosis/global cognition measure, design, intervention and dose, duration, measures of cognition and results (cognitive outcomes, retention and adherence, and adverse events).

Table 2
Summary of characteristics for studies involving older adults with subjective cognitive impairment.

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition
Ban et al., 2018 <i>Korea</i>	To examine the efficacy and safety of oral administration of <i>Tremella fuciformis</i> in individuals with Subjective Cognitive Impairment	Community dwelling adults (65F:10M) with subjective cognitive complaints aged $m = 53.83(\pm 5.5)$ years, range 40–65 years with 26F:4M in the HD group and 26F:4M in the LD group and 13F:2M in the placebo group	MMSE (> 25), clinical dementia rating scale ≤ 0.5	Randomised, double-blind placebo control trial, outcomes at 0, 8 weeks	<i>Tremella fuciformis</i> (species of fungus) 1) HD = 1200mg daily (2 capsules, 3 × per day) 2) LD = 600mg daily (2 capsules, 3 × per day). 3) Matched placebo (2 capsules, 3 × per day) N.R = placebo ingredients	8 weeks	Immediate recall from the pattern recognition memory task and the spatial span task (CANTAB), Executive function (WCST)
Barbhaiya et al., 2008 <i>India</i>	To evaluate the clinical efficacy, safety and tolerability of BacoMind® on impaired memory in elderly individuals	Adults with memory complaints for one year with no major cognitive deficits (AAMI) aged $m = 64.98(\pm 9.37)$ years, range 50–75 years with 23F:42M	MMSE (≥ 24)	Randomised, double-blind placebo control trial, outcomes at 0, 12, 24 weeks	BacoMind® (standardised extract of <i>Bacopa monnieri</i> with bioactive constituents) 1 × 450mg capsule daily. Matched placebo 1 × capsule daily, N.R = ingredients in placebo, only states 'matched without actives'	12-week intervention period then a 12-week withdrawal period	Digit span forward & backward (WAIS), Digit cancellation test, Serial subtraction test, list learning (RAVLT) immediate and delayed recall, passages (WMS-1) immediate and delayed recall, paired associates-similar and dissimilar pairs-immediate and delayed recall, visual retention 1 (based on designs), visual retention 2 (based on pictures), digit symbol (WAIS)

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition
Brautigam et al., 1998 <i>The Netherlands</i>	To determine the efficacy and tolerance of two dosages of an alcohol/water extract of <i>Ginkgo biloba</i> versus placebo in the elderly with memory and/or concentration complaints	Elderly adults with self-reported memory and/or concentration complaints $m = 68.96 (\pm 7.77)$ years, range 55–86 years with 31 males and 46 females in a high dose group, 50F:32M in a low dose group and 47F:35M in the placebo group	MMSE (≥ 20), & memory loss of known origin	Randomised, double-blind placebo control trial, outcomes at 0, 6, 12, 24 weeks	<i>Ginkgo biloba</i> alcohol/water extract (composition: <i>Ginkgo biloba</i> leaf, folium, ethanol, flavone glycosides) 1) High dose (40 drops, 1.9ml undiluted 3 × daily) 2) Low dose (40 drops (1.9ml extract with placebo 3 × daily) 3) Placebo (40 drops, 1.9ml 3 × daily) (water-soluble chlorophyll powder dissolved in an alcohol/water mixture, (water insoluble chlorophyll was dissolved in alcohol) both solutions were mixed together, taste and colour of all 3 dosages similar	4 weeks washout then 24 weeks treatment	EMCT (measuring attention and concentration), Benton test of visual retention-revised (short-term visual memory), Rey test parts 1 & 2 (short-term verbal memory and learning, long term memory)
Cicero et al., 2017 <i>Italy</i>	To evaluate the effects of a rational assemblage of nutraceuticals on cognitive functions in a sample of 30 elderly subjects	30 older adults ($m = 66 (\pm 3)$ years of age), (N.R = range, sex), with self-perceived cognitive decline	MMSE (20–27), self-perceived cognitive decline without known diagnosis of cognitive decline or dementia	Randomised, double-blind placebo control trial, outcomes at 0, 8 weeks	Combination of <i>Bacopa monnieri</i> dry extract 320mg, L-Teanina 100mg, <i>Crocus sativus</i> 30mg, vitamin B6 9.5mg, Biotine 450mcg, Folic acid 400mcg, Vitamin B12 33mcg, Vitamin D 25mcg, Copper 2mg, capsule form, 1 per day. Matched placebo, 1 × capsule per day, N.R = placebo ingredients	8 weeks	MMSE
Herrlinger et al., 2018 <i>U.S.A</i>	To investigate effects of supplementation with a spearmint extract on cognitive performance, sleep and mood in individuals with AAMI	Adults with AAMI (based on National Institute of Mental Health criteria) aged $m = 59.4 (\pm 0.6)$ years, range 50–70 years with 30 participants in each group (placebo, 600mg spearmint and 900mg spearmint), (overall 30M:60F)	MMSE (≥ 24), MAC-Q (≥ 25), WMS (≤ 29 on VPA-1), WMS (≤ 9 on VPA-2)	Randomised, double-blind placebo control trial, outcomes at 0, 45, 90 days (average on each day) (participants arrived on testing day fasting from product/food and were assessed 15mins prior to ingestion of intervention or placebo, then 30 mins, 2, 4, 6 hours after ingestion. Average of scores across testing day equiv. to overall score for that day)	1) 600mg spearmint extract (<i>Mentha spicata</i> L.)/day (2 × capsules total) 2) 900mg spearmint extract (<i>Mentha spicata</i> L.)/ day (2 × capsules total). 3) Placebo capsules contained microcrystalline cellulose, /day (2 × capsules total), N.R = if matched on taste, appearance, smell	90 days	CDR- with 11 tasks investigating attention and information processing, episodic and working memory, executive function & tracking (motor control)

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition
Macpherson et al., 2012 <i>Australia</i>	To investigate the effects of 16 weeks supplementation of a multivitamin and herbal formula on cognition in community dwelling, elderly women	Women reporting subjective memory complaints Multivitamin group ($m = 71.9(\pm 4.8)$ years, placebo group ($m = 70.3(\pm 4.3)$ years, range 64–82 years with 28 participants in each group	MMSE (≥ 24), memory questionnaire to screen for SMCs, & medical exam with a medical practitioner to determine whether participants were in good health	Randomised, double-blind placebo control trial, outcomes at 0, 16 weeks	Swisse Women's Ultivite 50 + TM tablet (combination formula with 46 ingredients, with the largest quantities being from: <i>Silybum marianum</i> Dry Fruit (St. Mary's thistle), <i>Ginkgo biloba</i> , and <i>Vitis vinifera</i> Dry Seed (grape seed), 1 tablet each day with breakfast. Placebo tablet matched on appearance of intervention, contained starch and 2mg of Riboflavin (vitamin B2), 1 tablet taken with breakfast	16 weeks	Swinburne University computerized cognitive assessment battery (SUCCAB) & CVLT-2 (word list learning)
Neri et al., 1995 <i>Italy</i>	To determine the influence of treatment (intervention) on two major domains of well-being and their interrelationships (psychological well-being-affection & cognitive functioning, and perceived quality of life)	Older adults ($m = 60.45(\pm 3.9)$ years, range 51–65 years) with AAMI, 21F:9M in the intervention group and 21F:9M in the placebo group	MMSE (≥ 24)	Randomised, double-blind placebo control trial, outcomes at 15 days, 3, 6, 9 months (only first and last session analysis conducted)	Standardised ginseng extract G115 (N.R = dose) (from the root of <i>Panax ginseng</i>), dimethylaminoethanol bitartrate, minerals & vitamins (not specified)- two capsules daily (one after breakfast, one after lunch). Placebo 'identical' to study drug- two capsules daily (one after breakfast, one after lunch), N.R = placebo ingredients	9 months	RMT- (memory index, acquisition recall & deferred memory)
Raghav et al., 2006 <i>India</i>	To study the efficacy of SBME in subjects with AAMI	Forty adults with AAMI, range 55–70 years, N.R = mean age ($\pm$ SD), (3F:37M) with 20 participants in each group	MMSE (≤ 24), & WMS (< 6)	Randomised, double-blind placebo control trial, outcomes at 0, 4, 8, 12, 16 weeks	125mg of SBME twice a day, N.R = type of administration. Placebo twice daily, N.R = administration, ingredients	12 weeks, then following 4 weeks of a placebo period	Mental control, logical memory, digit forward, digit backward, visual reproduction, paired associate learning (WMS)

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition
Zhu et al., 2016 <i>China</i>	To evaluate the safety and effectiveness of short-term administration of BrainPower Advanced, a multi-ingredient dietary supplement on SMCs in older adults	Community volunteers with SMCs aged $m = 67.1 (\pm 10.5)$ years, range 47.28–88.43 years including: 33F:14M in the intervention group & 34F:17M in the placebo group (ages and participant numbers calculated after withdrawals)	No reports of hypomnesia, forgetfulness, memory loss or impaired attention/concentration as determined by a standard medical questionnaire, constructed and validated for a Chinese population, participants scoring 1:(no SC or occasional slight SC) or 2:(slight/mild SC) were combined as 'slight SC group', 3:(moderate severe) 4:(severe) and 5:(very severe) were categorised as 'severe SC group', N.R = name of questionnaire	Randomised, double-blind placebo control trial, outcomes at 0, 12 weeks	BrainPower Advanced (Phosphatidylserine, Catharanthus roseus, Huperzia serrata (whole plant), <i>Ginkgo biloba</i> , Vitamin B6, Vitamin B12, L-Tyrosine, L-Pyroglutamic acid, Green tea extract (<i>Camellia sinensis</i> leaf), Acetyl-L-carnitine, Cola nut extract (<i>kola nitida</i>), Choline bitartrate, L-Glutamine, L-Phenylalanine & L-Cysteine) (2 capsules with meals daily). Matched placebo, mainly containing flour, N.R = specific dose measurements for active & placebo (states 2 capsules with meals p/day), or additional placebo ingredients	12 weeks	Visual/auditory memory, abstracting & memory recall

Table 3
Summary of characteristics for studies involving older adults without subjective cognitive impairment.

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition	Re-
Burns et al., 2006 <i>Australia</i>	To extend on previous research in order to determine the efficacy of 120mg ginkgo, to benefit performance of healthy older and young adults on cognitive outcomes	Healthy older adults $m = 61.7(\pm 5.5)$ range 55–79 years: 50 males (26 males in placebo, 24 in ginkgo) & 43 females (21 females in placebo, 22 in ginkgo). Younger adults also included in this study however analysed separately	Medical questionnaire- medical history & current medications, POMS, N.R = global cognition measure & names of medical questionnaires	Randomised, double-blind placebo control trial, outcomes at 0, 12 weeks	Ginkgoforte™ (<i>Ginkgo biloba</i>) 120mg per day (3 tablets daily of 40mg each- 1 per meal). Matched placebo (3 tablets per day- 1 per meal), N.R = placebo ingredients	12 weeks	Woodcock-Johnson Psycho-educational battery-revised (fluid ability, crystallised ability, short-term memory, cognitive processing speed, long-term storage and retrieval, delayed recall, spot-the word (vocabulary), self-ordered pointing (executive function), odd-man-out (both movement and decision time), inspection time	Co- im- ter- ret- gin Re- 13 wit pre ad- as pai cor Ad- rep pai wit gin to l dis
Calabrese et al., 2008 <i>U.S.A</i>	To evaluate the effects of <i>Bacopa monnieri</i> (whole plant standardised dry extract) on cognitive function and its affect, safety and tolerability in healthy elderly participants	54 healthy older adults (60% women) living independently aged 65 years or older $m = 73.5$ years, N.R = range, S.D, (27 participants in each group)	BOMC & no complaints of memory impairment, POMS, N.R = BOMC cut-off	Randomised, double-blind placebo control trial, outcomes at 0, 6, 12 weeks	Standardised <i>Bacopa monnieri</i> extract, 300mg/day (1 tablet daily). Matched placebo (1 tablet daily), N.R = placebo ingredients	6 weeks of placebo for control group, and 12 weeks of <i>Bacopa monnieri</i> for treatment group	Delayed recall score from RAVLT. Additionally, Stroop task assessing ability to ignore irrelevant information, the DAT, and the WAIS letter digit test of immediate working memory	Co- im- RA & S the grc Re- 6 p wit in 1 3.9 tat no bet Ad- pla int- rep syr dig
Carlson et al., 2007 <i>U.S.A</i>	To determine if a <i>Ginkgo biloba</i> -containing supplement improves cognitive function and quality of life, alters primary hemostasis, and is safe in healthy, cognitively intact older adults	Healthy, cognitively intact older adults: ginkgo group (21F:21M 73.1($\pm$ 4.8) years range 65–84 years), placebo group (15F:21M, 72.1($\pm$ 6.0) years, range 65–83 years)	MMSE (24–29)	Randomised, double-blind placebo control trial, outcomes at 0, 4 months	<i>Ginkgo biloba</i> -based supplement containing: 160mg of <i>Ginkgo biloba</i> , 68mg of <i>Gotu kola</i> , 180mg of DHA, a bioflavonoid concentrate (100mg), and vitamin A (300 IU) as beta carotene, three capsules/day with meals. All participants were also given a once-daily multivitamin/multimineral supplement (Nutralite Daily). Matched placebo three capsules/day with meals, N.R = placebo ingredients	4 months	Benton visual retention, controlled oral word association, judgement of line orientation, modified mini mental screening, list learning easy, list learning strict, symbol digit modalities	Co- im- list tas grc Re- 3 p Gir fro drc ad- pai Ad- of rep on- the ing mc bei nai up- two hex diz

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition	Re:
Crews et al., 2005 U.S.A	To conduct the first known clinical trial of the short-term efficacy of cranberry juice on the neuropsychologic functioning of cognitively intact older adults	Cognitively intact older adults (> 60 years of age): Cranberry group (25 adults) $m = 69.17(\pm 7.11)$ years placebo group (25 adults) $m = 69.39(\pm 5.80)$ (N.R = range, sex)	MMSE (≥ 24), & reporting no history dementia or significant neurocognitive impairment	Randomised, double-blind placebo control trial, outcomes at 0, 6 weeks	32 ounces/day (2×16 ounces) of a beverage containing 27% cranberry juice sweetened with Sucralose. Matched placebo beverage 32 ounces/day (2×16 ounces), N.R = specific placebo ingredients	6 weeks	Selective Reminding Test, WMS-3 (Faces 1 and Faces 2 subtests), Trail Making Test (parts A and B), SCWT the WAIS- 3 Digit Symbol-Coding subtest	Co sig imj nei tes Rei 3 p exc an: cor adl Ad ser eff by mii
Lewis et al., 2014 U.S.A	To extend the evaluative process of nutritional therapies through a randomised, double-blind, placebo controlled clinical trial assessing a regimen of dietary supplements' efficacy	Healthy older adults Ginkgo synergy® plus Choline $m = 67.6(\pm 6.3)$ years, range 58–82 years, with 25F:8M; OPC Synergy® plus Catalyn group $m = 68.5(\pm 6.7)$ years, range 59–83 years, with 24F:7M; placebo group $m = 70.3(\pm 8.3)$ years, range 60–93 years, with 21F:12M	MMSE (≥ 23), SPMSQ, WMS-Story A, no AD or related disorders, not living in a nursing facility	Randomised, double-blind placebo control trial, outcomes at 0, 3, 6 months	1) Ginkgo Synergy® (2 capsules/day-120mg/day total) and Choline (4 tablets/day-700mg/day total) 2) OPC Synergy® (2 capsules/day) and Catalyn (4 tablets/day). 3) Placebo containing cellulose, lactose & beet powder N.R = placebo administration method/type, dose	6 months	MMSE, SCWT, the TMT Parts A and B, COWA, the Digit Symbol subtest of the WAIS, and the HVLT-R	Co to 1 the sho from mc cor as: scc inc Gir ba: an: from mc Rei reti inc rep adl eve pai syr dia ulc sho eni pai syr rep on: pai ins hei nig
Mix et al., 2000 U.S.A	To examine the relatively short-term (i.e., 6 weeks) efficacy of <i>Ginkgo biloba</i> extract EGB 761 on the cognitive functioning of cognitively intact persons over the age of 55 years via a diverse battery of neuropsychologic tests and measures	Cognitively intact healthy older adults, 55–86 years of age: ginkgo group $m = 67.5(\pm 9.23)$ years, placebo group $m = 68.65(\pm 6.95)$ years, 24F:24M	MMSE (≥ 24), & no history of significant neurocognitive dysfunction, considered cognitively intact (self-reported)	Randomised, double-blind placebo control trial, outcomes at 0, 6 weeks	<i>Ginkgo biloba</i> EGB 761 (180 mg/day = 60mg $\times$ 3 capsules per day). Matched placebo $\times$ 3 capsules per day (methylcellulose), N.R = additional placebo ingredients	6 weeks	SCWT (parts A and B) and the WMS-revised, Logical Memory 1 and 2 and Visual Reproduction 1 and 2 subtests	Co imj int: ac: nai the Wc to j tria Rei 21 fer the pai cor > 2 ren me = 0 Ad ad: rep pai

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition	Re:
Mix et al., 2002 U.S.A	To conduct the first known, large-scaled clinical trial of the efficacy of <i>Ginkgo biloba</i> extract (EG 761) on the neuropsychological functioning of cognitively intact older adults	Cognitively intact older adults, 60 $\geq$ years of age: ginkgo group $m = 66.97(\pm 6.12)$ years, placebo group $m = 68.60(\pm 6.96)$ years, (N.R = range), with 262 participants in total in the study, after withdrawals/non-compliance, 147F:102M remained in the study	MMSE (≥ 26), & no history of dementia or significant neurocognitive impairment (self-reported)	Randomised, double-blind placebo control trial, outcomes at 0, 6 weeks	<i>Ginkgo biloba</i> EGB 761 (180 mg/day = 60mg $\times$ 3 tablets per day). Matched placebo tablets $\times$ 3 per day, N.R = placebo ingredients	6 weeks	SRT, WAIS-3 block design, Digit Symbol-Coding subtests, WMS-3 Faces 1 & 2 subtests	Co: pa intu (cc pla imj tas del an vis Re: 24' cor prc pla intu we stu adl 20' = o Ad: of : inc lim ga: ner res rea boi ser pla intu
Morgan et al., 2010 Australia	To investigate the effectiveness of <i>Bacopa monnieri</i> Linn. for improvement of memory performance in healthy older persons	Healthy older adults from the general population $m = 65(\pm 7.53)$ years, range 55–86 years Bacopa group = 24F:25M, placebo group = 28F:21M	MMSE (≥ 24), & absence of depression (≤ 12) on HAMD	Randomised, double-blind placebo control trial, outcomes at 0, 12 weeks	<i>Bacopa monnieri</i> (BacoMind™) 300mg/day (one tablet daily). Matched placebo tablet, N.R = dose, ingredients	12 weeks	Audio-verbal and visual memory performance measured by RAVLT, the Rey-Osterrieth CFT, and the Reitan TMT, subjective complaints measured by the MAC-Q	Co: sig imj lea acc del lea reti intu Re: 81, cor N.F Ad: tre: pla eff sig tre: inc fre an cra
Perry et al., 2018 U.K	To evaluate for the first time the effects of a combination of sage, rosemary and Melissa- traditional European medicines on verbal recall in normal healthy subjects	Healthy older adults $m = 61(\pm 9.26)$ years (Divided into 2 groups: younger (43–62), older (63–80)) 38F:6M total (older group numbers: 4 males = 2 in intervention group and 2 in placebo 14 females = 10 in intervention and 4 placebo)	No reported current or previous clinical diagnosis of cognitive impairment or dementia, N.R = global cognition measure	Randomised, double-blind placebo control trial, outcomes at 0, 2 weeks	5ml of SRM (<i>Salvia officinalis</i> L., <i>Rosmarinus officinalis</i> L. and <i>Melissa officinalis</i> L.) ethanol extract or 5ml placebo (50% fresh sweet cicely (<i>Myrrhis odorata</i> (L.)), 1% Lyles Black Treacle & 1g/ml 45% EtOH, diluted in water) twice per day, N.R = specific time of day for dose, or matched on smell, taste	2 weeks	Pen & paper immediate and delayed recall tests of verbal episodic memory	Co: sig dif tre: grc to imi rec Re: 1 p cor (44 an do: old boi spe Ad: ad rep pai

Author & Study Location	Aim	Study Population	Diagnosis Criteria/Global Cognition Measure	Design	Intervention/Control & Dose	Duration	Measures of Cognition	Re:
Solomon et al., 2002 <i>U.S.A</i>	To evaluate whether ginkgo improves memory in elderly adults as measured by objective neuropsychological tests and subjective ratings	Community-dwelling volunteer older adults (total of 132F:98M, 115 in each group), aged between 60–82 years. Ginkgo group $m = 68.7(\pm 4.7)$ years, with 65F:46M, placebo group $m = 69.9(\pm 5.4)$ years with 63F:45M (assignment to intervention numbers, F:M ratio and ages calculated after withdrawals)	MMSE (≥ 26), & in generally good health	Randomised, double-blind placebo control trial, outcomes at 0, 6 weeks	Ginkgo (Ginkoba) 40mg 1 tablet, taken 3 times per day. States matched placebo (lactose gelatin), 1 capsule 3 × per day. Note: active is a tablet, placebo is a capsule	6 weeks	Learning, memory, attention, concentration, expressive language tested utilising: the CVLT, the Logical Memory subscale of the WMS-revised, the Visual Reproduction subscale, digit symbol subscale of the WAIS-revised), the digit span (WMS-R) and mental control (WMS-R) controlled category fluency test, Boston naming test	Co sig dif tre: an' me turr Rei 4 g pla cor pai cor no dif grc cor pai gin in i cor me N.F adl Ad mc stu
Tohda et al., 2017 <i>Japan</i>	Investigate the effects of a diosgenin-rich yam extract on cognitive enhancement in healthy volunteers	Healthy adults (16F:12M) $m = 46.5(\pm 18.67)$ years, range 20–81 years (subgroup for analysis of older adults 60–81 years) (ages and participant numbers calculated after withdrawals)	Overall good physical and mental health, no diagnosis of AD or related disorders, N.R = global cognition measure	Randomised, double-blind placebo control, crossover trial, outcomes at 0, 12, 30 weeks	Diosgenin-rich yam extract diopower 15 containing 8mg diosgenin, 672mg olive oil, glycerol fatty acid ester, vitamin E derivative, & white beeswax (2 capsules/day = 50mg), N.R = when doses taken. Placebo (2 capsules/day) containing olive oil (672mg), glycerol fatty acid ester, vitamin E derivative, & white beeswax, N.R = when doses taken, if placebo was matched in colour, smell & taste to active	12 weeks intake, with a 6-week washout period separating the crossover period	RBANS, MMSE-J (Japanese version)	Co inc bet an' enr per flu ind bui (sig 81 an: sig 60 Rei 3 p wit stu N.F Ad rep pai

Across both populations, all studies were randomised, double-blind, placebo-controlled trials (14–33). Nineteen studies employed a parallel design (14–32), and one study utilised a cross-over design (33). Three studies utilised the same intervention with two different doses (three comparison groups in total, including placebo) (14, 16, 22), and one study utilised two different interventions compared to a single control (23).

Eight studies were conducted in the United States (18, 19, 21–25, 30), three in Australia (17, 26, 32), two each in India (15, 29), and Italy (20, 27), and one each in Korea (14), the Netherlands (16), United Kingdom (28), China (31), and Japan (33). Two studies were published from 1995 to 1998 (16, 27), ten published between 2000 and 2010 (15, 17–19, 21, 24–26, 29, 30), with the remaining eight between 2012 and 2018 (14, 20, 22, 23, 28, 31–33).

Fourteen studies reported methods of recruitment (14, 16–20, 22, 23, 26, 29–33), with twelve studies conducted in community settings (audio, visual, and print media, universities) (14, 17–19, 22, 23, 26, 29–33), and two in clinical settings (general practice and outpatient clinics) (16, 20).

Tables 2 & 3 about here.

3.3 Participants

Across the included studies, the total sample size (at baseline) was $N = 1,811$, with 18/20 studies reporting participant sex ($N = 1,718$; 61% were female) (14–19, 22–33). The mean age of participants reported across 19/20 studies was 65.61 years (14–28, 30–33), $SD_{pooled} = 14.33$ (for 16 studies) (14–17, 19, 21–27, 30–33). Individual studies ranged from 28 (33) to 262 participants (25). A total of 755 participants were from the nine SCI studies (14–16, 20, 22, 27, 29, 31, 32), compared to 1,056 from the eleven studies in older adults without SCI (17–19, 21, 23–26, 28, 30, 33).

3.4 Eligibility Criteria and Global Cognition Measures

All twenty studies utilised cognitive scales or tests (14–16, 19–27, 29, 30, 32), medical questionnaires (17, 31), self-reports of cognitive function (16, 18, 20, 21, 23–25, 28, 33), or clinical questionnaires (17, 18, 26, 32), to determine eligibility for their respective study. Fourteen studies utilised the Mini-Mental State Exam (MMSE), as a measure of global cognition (14–16, 19–27, 29, 30, 32). The MMSE cut-off score for participant inclusion varied between studies, and populations. For SCI studies, one utilised a cut-off of ≥ 20 (16), another a range of 20–27 (20), one with ≤ 24 (29), four studies with a cut-off of ≥ 24 (15, 22, 27, 32), and one of > 25 (14). For studies on older adults without SCI, one reported a cut-off of ≥ 23 (23), one with a range of 24–29 (19), three with a cut-off of ≥ 24 (21, 24, 26), and two ≥ 26 (25, 30). Overall, studies with an SCI population, reported lower cut-off scores and ranges for participant inclusion.

Other scales included the Blessed Orientation Memory Scale (BOMC) (18), Weschler Memory Scale (WMS) (22, 23, 29), Clinical Dementia Rating (CDR) scale (14), Memory Complaint Questionnaire (MAC-Q) (22), and the Short Portable Mental Status Questionnaire (SPMSQ) (23). Overall, three studies utilised a global cognition measure as their primary or secondary outcome measure, with two of these using the MMSE (20, 23), and one the WMS (logical subset score of < 6) (29).

3.5 Intervention and Control Type

Sixteen out of twenty studies used a herbal supplement (15, 17–20, 22–27, 29–33) with most studies utilising a form of *Ginkgo biloba* (17, 19, 23–25, 30–32) or *Bacopa monnieri* as a primary ingredient in their intervention (15, 18, 20, 26, 29). One of these sixteen studies used a combination formula (containing *Ginkgo biloba* and 45 other herbs, minerals, and vitamins) specifically made for women (32). In addition, one study each, used a spearmint extract (*Mentha spicata* L.) (22), a standardised ginseng extract (G115) (27), a Diosgenin-rich yam extract (diopower 15) containing vitamins, oils, and beeswax, (33), and one used a nutritional supplement (OPC Synergy® plus Catalyn) containing buckwheat, teas, and fruit and vegetable extracts, as a secondary intervention (23).

Two of the remaining four studies, studies utilised a herbal combination via a liquid solution (*Ginkgo biloba*, alcohol/water solution (16), and SRM [*Salvia officinalis* L., *Rosmarinus officinalis* L. and *Melissa officinalis* L.]) (28), one study utilised a nutrient based juice (sweetened cranberry juice) (21), and one study used an oral capsule containing a type of fungus (*Tremella fuciformis*) (14). Nineteen out of twenty studies reported a method of administration (14–28, 30–33) with ten administering the intervention orally via capsule (14, 15, 19, 20, 22–24, 27, 31, 33), six utilised tablets (17, 18, 25, 26, 30, 32), and three a liquid solution (16, 21, 28).

In terms of the control groups, all studies utilised a form of placebo. Eighteen out of twenty studies detailed the type of placebo employed (14–22, 24–28, 30–33), with ten studies utilising a capsule (14, 15, 19, 20, 22, 24, 27, 30, 31, 33), five a tablet (17, 18, 25, 26, 32), and three an oral liquid (16, 21, 28). Seven out of twenty studies (35%) provided some information on the ingredients contained in the placebo (16, 22, 23, 28, 30–32). Four of these studies used a form of placebo containing active herbal or nutritional ingredients (16, 23, 28, 32), with the remaining three using a placebo containing inert substances (22, 30, 31). Overall, 16/20 studies stated that they matched their placebo with the intervention (14–21, 24–27, 30–33). Eighteen out of the twenty studies sufficiently detailed the dose of intervention (14–26, 28–30, 32, 33), and sixteen detailed the dose of placebo (14–16, 18–22, 24, 25, 27, 28, 30–33).

Total duration of studies ranged from 2 weeks (28) up to 9 months (27). Majority of studies were 12 weeks (15, 17, 18, 26, 29, 31), 6 weeks (21, 24, 25, 30), or 8 weeks (14, 20) in length. Three studies employed a washout or withdrawal period; one before the trial began (16), one between two cognitive testing periods (midpoint-12 weeks, and endpoint-24 weeks) (15), and one for 6 weeks separating the intervention cross-over period (33). One study utilised a 6 week placebo intake period for the control group, with 12 weeks of intervention for the treatment group (18).

3.6 Primary and Secondary Measures of Cognition

Measures of cognition varied across the included studies. The most common were the Wechsler Adult Intelligence Scale (WAIS; $n = 6$) (15, 18, 21, 23, 25, 30), the Weschler Memory Scale (WMS; $n = 6$) (15, 21, 24, 25, 29, 30), the Rey Auditory Verbal Learning Test (RAVLT; $n = 4$) (15, 16, 18, 26), the Stroop Color and Word Test (SCWT; $n = 4$) (18, 21, 23, 24), the Trail Making Test (TMT; $n = 3$) (21, 23, 26), and the Mini Mental State Examination (MMSE; $n = 3$) (20, 23, 33).

3.7 Retention and Adherence

Eighteen of twenty studies consistently reported on retention, with an average retention rate of 92% across the studies (14–20, 22, 24–32, 32, 33). Comparatively, only 7/20 studies reported treatment adherence, with an overall average of 93% across both intervention and placebo usage (14, 16, 18, 20, 22, 27, 32, 32).

3.8 Risk of Bias Within and Across Studies

Figures 2 and 3 (parallel studies) and Fig. 4 (cross-over study) provide a summary of each of the risk of bias domains, and an overall risk of bias assessment, for each of the twenty included studies. Green circles indicate that the domain or study has been evaluated as low risk, yellow as having some concerns, and red as high risk.

Each article was assessed in terms of randomisation, intended interventions (effect of assignment and effect of adhering to the intervention), missing outcome data, measurement of outcomes and selection in reported results. In terms of the overall risk of bias assessment, only one study was deemed as low risk (20), some concerns were found for 5/20 studies (14, 18, 21, 22, 27), and the remaining fourteen were deemed to be high risk (15–17, 19, 23–26, 28–33). Between populations, three SCI studies were assessed as having some concerns (14, 22, 27), five were deemed high risk (15, 16, 29, 31, 32), and one low risk (20). For the non-SCI studies, two were assessed as having some methodological concerns (18, 21), and the remaining nine deemed as high risk (17, 19, 23–26, 28, 30, 33).

Despite all twenty studies stating the method of intervention assignment was randomised, only fourteen sufficiently detailed the randomisation process and were deemed as low risk (15–17, 19–21, 23–26, 30–33). Intended interventions (effect of assignment to interventions) were adequately reported in five studies (low risk) (14, 20, 22, 23, 30), nine were assessed as high risk (15–17, 19, 24–26, 32, 33), and the remaining six as having some concerns (18, 21, 27–

29, 31). Twelve studies were assessed as low risk for reporting on intended interventions (effect of adhering to the intervention) (14, 16–18, 20–25, 27, 32), and eight as high risk (18, 23, 26, 28–31, 33).

In terms of missing outcome data (domain three), 16/20 studies were evaluated as low risk (14–16, 18, 20–25, 27–31, 33), and the remaining four assessed as high risk (17, 19, 26, 32). Within domain four (measurement of outcomes), 17/20 studies were deemed as low risk (14–27, 30–32) and the remaining three were as high risk (28, 29, 33). Seventeen out of twenty studies were assessed as low risk for selection in reported results (domain five) (14–16, 18–23, 25–32), with some concerns for only three studies (17, 24, 33). In terms of bias arising from period or carryover effects (domain S) in the cross-over study, this was deemed as low risk (33).

3.9 Study Results

Results for all twenty studies are outlined below including intervention efficacy on cognitive function, adverse events, and risk of bias.

3.9.1 Intervention efficacy in low risk of bias study.

Only one study was deemed to be low risk for all domains, in terms of the overall methodological assessment. This 2017 randomised, double-blind placebo-controlled trial was conducted by Cicero and colleagues (20). Participants were 30 older adults with self-perceived cognitive decline, and ingested either a *Bacopa monnieri* formulation or a placebo capsule for eight weeks; MMSE was measured at each timepoint. In terms of intervention efficacy, a significant increase in MMSE score was found from baseline to endpoint in the treatment arm. Furthermore, a significant increase in score was also found in the treatment group at endpoint, compared to placebo, demonstrating a significant improvement in cognitive function for the intervention group across time, and between groups (20). Only one adverse event was reported: an aftertaste from active product intake.

3.9.2 Intervention efficacy in remaining SCI studies.

Across time, a significant improvement on at least one cognitive outcome for participants in the intervention group (compared to placebo), was found in 6/8 of the remaining SCI studies (14, 15, 22, 27, 29, 32). Improvements were mostly found in the areas of memory (working, spatial, short-term, retention, and logical) (14, 22, 27, 29, 32), and executive functioning (14, 15, 29). Three of the eight studies utilised a capsule containing a herbal extract; one contained *Bacopa monnieri* (15), one a spearmint extract (*Mentha spicata* L.) (22), and one a standardised ginseng extract (27). One study used a combination supplement (tablet), containing 46 herbs, vitamins and minerals (mainly consisting of *Ginkgo biloba*, *Silybum marianum* Dry Fruit (St. Mary's thistle), and *Vitis vinifera* Dry Seed (grape seed)) (32). An additional study utilised a capsule containing *Tremella fuciformis* (a type of fungus) (14), and the last study did not specify an administration method but used a standardised extract of *Bacopa monnieri* (29).

Of these six studies, mild to moderate adverse events were reported in three of them (22, 29, 32). Knee pain, myalgia, headaches and heartburn, were reported in the study conducted by Herrlinger and colleagues utilising *Mentha spicata* L. as their intervention (22). These adverse events were reported for both the treatment and placebo groups, however, heartburn experienced by a participant in the 600mg/day *Mentha spicata* L. group was deemed as 'probably related', compared to all other events deemed as 'not related' (22). One participant withdrew due to maculopapular rashes in the intervention group (*Bacopa monnieri*), in the study conducted by Raghav and colleagues (29). Two participants withdrew from the study conducted by Macpherson and colleagues using a combination formula containing *Ginkgo biloba* (intervention) (32). One participant withdrew due to nausea and vomiting in the intervention group, and one in the placebo group due to a mild rash (32).

In relation to risk of methodological bias for all six SCI studies with an improvement in cognitive functioning, two of the studies utilising *Bacopa monnieri* (15, 29) and one using *Ginkgo biloba* (combination supplement) (32), were deemed as being high risk. The remaining three were assessed as having some concerns in terms of methodological reporting (14, 22, 27).

For the two studies that did not find an improvement in cognitive functioning between groups (intervention *cf.* placebo) or across time, both reported adverse events with the use of *Ginkgo biloba* alcohol/water extract (drops) (16) and a herbal/dietary supplement also containing *Ginkgo biloba* (31). Gastrointestinal upset was reported as the main adverse reaction for both studies (16, 31) with dizziness, headaches and sleep disturbance also reported in the *Ginkgo biloba* alcohol/water extract study (16). In total, Brautigam and colleagues reported adverse events for 25 participants across both the placebo and intervention groups (16). In terms of the second study, it is not known whether the two participants who reported adverse events were receiving the intervention or placebo (31). Overall, both studies were deemed as high risk in terms of the methodological risk of bias assessment.

3.9.3 Intervention efficacy in non-SCI studies.

Overall, 6/11 non-SCI studies, reported a significant improvement in cognitive functioning in the intervention group (compared to placebo), across time (17, 18, 24–26, 33). The most common improvements were in memory (long-term storage, retrieval, delayed recall, recognition) (17, 18, 25, 26), executive functioning (18, 24, 33), and language (24, 33). Two studies used a form of *Ginkgo biloba* capsule (17, 24), one a *Ginkgo biloba* tablet (25), two used a form of *Bacopa monnieri* tablet (18, 26), and one a Diosgenin-rich yam extract capsule (33). An additional study reported a significant improvement in executive functioning across time, using a combined herbal and nutritional supplement containing Ginkgo (Ginkgo Synergy® plus Choline) (23). A significant improvement in verbal fluency was also found in the secondary intervention group (across time, compared to the Ginkgo and placebo groups) using OPC Synergy®, a dietary supplement (plus Catalyn) (23). A further study using a *Ginkgo biloba* based supplement found a significant improvement in a list learning strict task in the placebo group only, across time (19).

Seven of the eight total studies were deemed as having a high methodological risk of bias (17, 19, 23–26, 33), with the remaining one (using a standardised *Bacopa monnieri* extract) as having some concerns (18). Five of the eight studies reported adverse events, in both placebo and intervention groups (Ginkgo or *Bacopa monnieri* interventions) (18, 19, 23, 25, 26). An additional study reported adverse events only occurring in the intervention group using a *Ginkgo biloba*

capsule (17). The most common events reported across the six studies were gastro-intestinal issues (including nausea, abdominal cramps, digestive problems) (18, 19, 25, 26), and sleep disturbance, with the use of *Ginkgo biloba* (17) or placebo (23).

For the three remaining non-SCI studies, all reported no significant improvements across time in cognitive functioning (for both intervention or placebo groups), nor between groups (21, 28, 30). One study used a Ginkgo tablet (30), one a sweetened cranberry juice (21), and the other a liquid solution of SRM *Salvia officinalis* L., *Rosmarinus officinalis* L. and *Melissa officinalis* L. (28).

Adverse events were monitored in two of the three studies, however, no events were reported in one (SRM solution) (28), and the other study did not report serious events or document mild/minor events (sweetened cranberry juice intervention) (21). Two of the three studies were deemed as having a high methodological risk of bias (28, 30), and the remaining one having some concerns (21).

4. Discussion

Overall, twenty studies were identified for inclusion in this review, nine with an SCI population (14–16, 20, 22, 27, 29, 31, 32), and eleven studies utilising older adults without SCI (17–19, 21, 23–26, 28, 30). Outcomes were mainly positive, with 13/20 studies overall reporting improvements in at least one area of cognitive functioning across time, in the intervention group (compared to placebo) (14, 15, 17, 18, 20, 22, 24–27, 29, 32, 33). Overall, only one study (using an SCI population) was assessed as having a low methodological risk of reporting, conduct and quality of trial design bias (20).

4.1 Extent of Literature Using Herbal and Nutritional Medicines for Older Adults with and Without SCI

Despite the growing interest in prevention and treatment of cognitive decline in older adults (4, 5), review search outcomes were not reflective of this interest, given that most of the articles eligible for this review, were conducted prior to 2018. Editorials, book chapters, reviews, and opinion articles, seem to be more common formats of evidence dissemination, compared to research using the 'gold standard' method, randomised control trials (RCTs) (34, 35) (Fig. 1).

Measurement of cognitive change was not common in the literature, rather relevant population studies focussed on biochemistry or progression to MCI or dementia. This was an unexpected outcome during the records search. Cognitive testing and assessment is generally an affordable, and accessible method of providing an insight into an individuals' current cognitive functioning, and any decline over time (36). Future research should strive to implement what is considered to be high quality research methods, in order to derive informative and translational outcomes.

4.2 Study Characteristics

In terms of participant characteristics, across the twenty studies, there were more females (61%), compared to male participants. It is difficult to ascertain the true difference in prevalence of SCI between the sexes, as a larger number of females (rather than males) are participating in these studies. Furthermore, inconsistencies in reporting prevalence between the sexes is typical in this field, again, making it hard to determine whether SCI affects more females or males (2). However, research within the area of cognitive decline suggests that females have a greater cognitive reserve, but have a faster rate of cognitive decline (particularly in the areas of global cognition and executive function) compared to males (37). This outcome has been confirmed within dementia research. Dementia is reported to be the leading cause of death in women, with twice as many females compared to males being affected by the disease (38). Further SCI prevalence research needs to be conducted to determine the true prevalence of SCI, between the sexes.

A high number of older adults reporting SCI are within the 60–64 year age range (2), compared to studies included in this review that saw an overall average age of 65 years for participants. Sex and age outcomes derived from this review highlight the importance in finding a way to address low research participation in males, and monitoring the faster rate of female decline.

In terms of participant retention and adherence to treatment, these were both surprisingly high across the studies at an average of 92% and 93% respectively, despite literature suggesting these figures are quite difficult to achieve (39). These outcomes should be considered with caution due to the subpar methodologies used to treat missing values.

4.3 Study Methodologies

Reflective of previous research, eligibility criteria for participation across the SCI and non-SCI studies, was inconsistent (4, 5), with varying scales, tests and questionnaires used, particularly for the MMSE (14–16, 19–27, 29, 30, 32). Research investigating diagnostic accuracy (sensitivity, specificity, positive and negative predictive power) of MMSE cut-off scores in detecting cognitive dysfunction, found that scores of ≤ 26 , showed optimal sensitivity and specificity balance, with a correct classification of MCI and dementia in older adults to be 90% (40). The varying MMSE cut-offs used here (≥ 20 , > 25 , and ≤ 24) may have incorrectly classified participants (with and without SCI), potentially impacting on study outcomes. This interpretation is further supported by identification of all eligible studies in this review not using a combination of self-report cognitive concerns (in line with the definition of SCI), cognitive scales (such as the MMSE), a general health questionnaire (including non-diagnosis of MCI or dementia), and screening of mental health conditions. Reliability on only one or two measures for classification of an impairment (or no impairment) is problematic, and certainly requires future attention within this area of clinical practice, and research.

An additional concern regarding the methodologies of accepted studies in this review, is the large number of those deemed as having a high risk of bias, particularly within the bias due to assignment and adherence domains (15–17, 19, 23–26, 28–33). Either intention to treat (ITT) or modified intention to treat (mITT) approaches were not employed for participants with missing outcomes or outlier data, with participants being excluded completely from analysis despite being randomised. Future studies in this field should consider using appropriate analysis to treat missing or outlier data, for post randomisation

outcomes as detailed above. Blinding of participants and other individuals involved in the trial was also identified as a concern. However, it is difficult to ascertain whether it was in fact the blinding process itself that was not conducted appropriately in these studies, or if it was simply not reported sufficiently according to the ROB assessment standards. Future studies should look to adopting greater transparency and accuracy in the process (specifically stating who was blinded and how), as this would go a long way in demonstrating non-biased outcomes.

4.4 Intervention Efficacy

Despite the majority of studies reporting positive results (14, 15, 17, 18, 20, 22, 24–27, 29, 32, 33), a large number of these were deemed as having an overall high methodological risk of bias (15, 17, 24–26, 29, 32, 33). These methodological concerns unfortunately do not assist in determining the true efficacy of herbal and nutritional medicines on cognitive functioning for older adults with and without SCI. This is particularly the case for *Ginkgo biloba* (17, 24, 25, 32) and *Bacopa monnieri* (15, 26, 29), given how common they were as interventions across the accepted studies of this review.

Efficacy of *Ginkgo biloba* has been consistently unclear across the spectrum of cognitive decline. An earlier review investigating RCTs using *Ginkgo biloba* for the treatment of dementia (41), highlighted the concerns around the low quality of studies available, namely to do with utilisation of unsatisfactory methods. However, on a positive note, adverse effects found with the use of *Ginkgo biloba* (across the accepted studies in this review), appeared to be consistent with those reported with the use of a placebo (17, 23, 25, 32), indicating that *Ginkgo biloba* may be comparable in terms of safety with placebo intake. These results are in line with what has been found previously in a dementia population (41).

4.5 Strengths and Limitations of the Review

This review had several strengths. An extensive literature search was conducted (in accordance with the aims and PICOS criteria of the review), comprehensively summarising the overall current state of the field. The lack of high-quality research has been addressed, highlighting the specific aspects which require improvement in future studies. The concerns surrounding classification of SCI, and the disparities between current research outcomes and clinical statistics has been presented. A limitation to this review was that a meta-analysis was not feasible due to the inconsistent classification of SCI and non-SCI participants, and the varying cognitive testing measures. The infancy of this area of research (despite broad interest from the general public) makes it difficult to conduct such an analysis at this time.

4.6 Recommendations for Future Research

In support of previous literature, first and foremost, an increased understanding and awareness of the features and characteristics of SCI needs to occur (4, 5). This should be considered in collaboration with the difference between the presentation of older adults without SCI, and those with MCI, in line with the cognitive decline continuum (2).

The development of a standardised measure package (including cognitive testing, medical questionnaires, self-reports, and mental health questionnaires) for the classification of SCI would be the next step in moving the field forward. Increased accuracy in the differentiation between healthy older adults (without SCI) and those with SCI, would assist in determining whether herbal and nutritional medicines have a positive effect on cognitive outcomes for this population.

4.7 Conclusions

Whilst most studies deemed eligible for inclusion in the review found positive results (particularly those that used *Ginkgo biloba* or *Bacopa monnieri*), these outcomes need to be considered with caution, due to the high risk of methodological bias found. It is hoped that future research will clarify the characteristics, classification measures, and features of SCI. Overall, by better understanding SCI, this may provide greater support for outcomes in high quality efficacy studies, utilising herbal and nutritional medicines as a means of managing self-perceived cognitive decline, and ideally, lowering dementia risk.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies, individuals, and industry. Sponsors and donors provide untied funding for work to advance the vision and mission of the Institute. The project that is the subject of this article was not undertaken as part of a contractual relationship with any organisation other than the funding declared below. It should also be noted that NICM conducts clinical trials relevant to this topic area, for which further details can be provided on request. AEC has received PhD scholarship support from FIT-BioCeuticals Pty Ltd; the funder played no role in this study. AEC, DHC, and GZS are all based at NICM Health Research Institute but have no conflicts of interest to declare.

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Author's Contributions

AEC and GZS contributed to the conceptualisation and design of the review. AEC took the lead on drafting the review paper and GZS provided guidance throughout. All authors provided critical feedback and reviewed the final manuscript.

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Not applicable.

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Figures

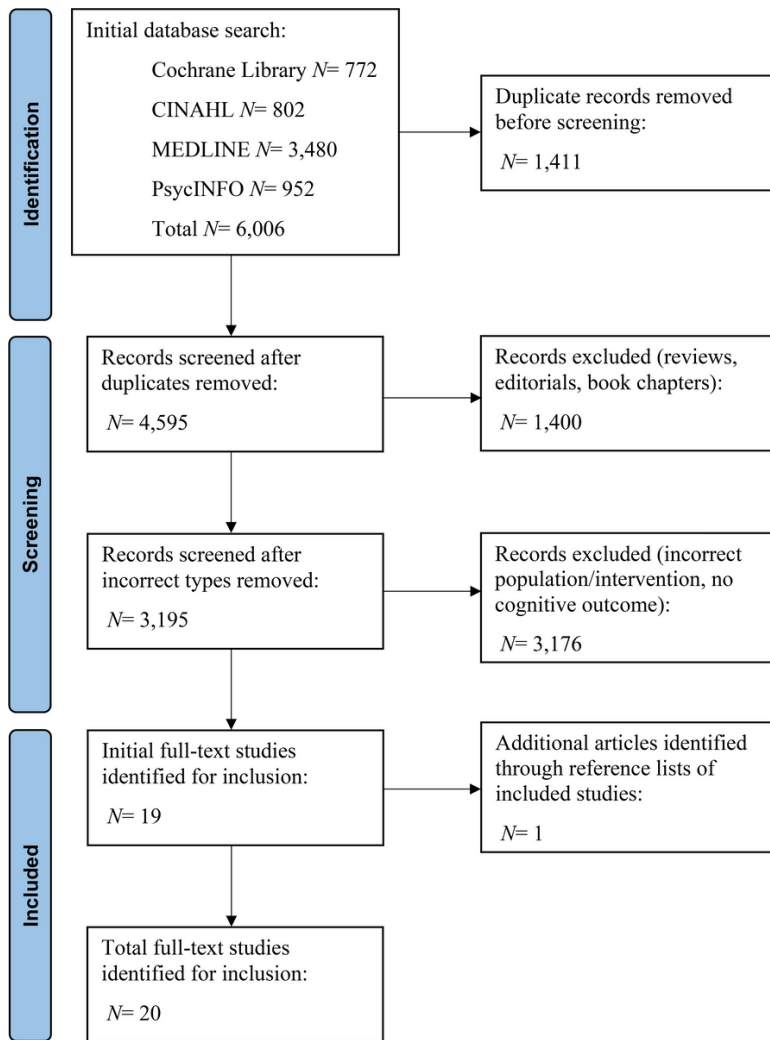


Figure 1

PRISMA flow diagram illustrating the study selection process.

	Risk of Bias Domains						
	D1	D2a	D2b	D3	D4	D5	Overall
Study	Ban et al., 2018						
	Barbhaiya et al., 2008						
	Brautigam et al., 1998						
	Cicero et al., 2017						
	Herrlinger et al., 2018						
	Macpherson et al., 2012						
	Neri et al., 1995						
	Raghav et al., 2006						
	Zhu et al., 2016						

D1= Domain 1, bias arising from randomisation; D2a= Domain 2a, bias due to deviations from intended interventions (effect of assignment); D2b= Domain 2b, bias due to deviations from intended interventions (effect of adhering to intervention); D3= Domain 3, missing outcome data; D4= Domain 4, bias in measurement of outcome; D5= Domain 5, bias in selection of reported result.

Figure 2

Risk of bias domains for older adults with SCI (parallel studies).

Study	Risk of Bias Domains						
	D1	D2a	D2b	D3	D4	D5	Overall
	Burns et al., 2006						
	Calabrese et al., 2008						
	Carlson et al., 2007						
	Crews et al., 2005						
	Lewis et al., 2014						
	Mix et al., 2000						
	Mix et al., 2002						
	Morgan et al., 2010						
	Perry et al., 2018						
	Solomon et al., 2002						

D1= Domain 1, bias arising from randomisation; D2a= Domain 2a, bias due to deviations from intended interventions (effect of assignment); D2b= Domain 2b, bias due to deviations from intended interventions (effect of adhering to intervention); D3= Domain 3, missing outcome data; D4= Domain 4, bias in measurement of outcome; D5= Domain 5, bias in selection of reported result.

Figure 3

Risk of bias domains for older adults without SCI (parallel studies).

Study	Risk of Bias Domains							
	D1	S	D2a	D2b	D3	D4	D5	Overall
Tohda et al., 2017								

D1= Domain 1, bias arising from randomisation; S= Domain S, bias arising from period and carryover effects; D2a= Domain 2a, bias due to deviations from intended interventions (effect of assignment); D2b= Domain 2b, bias due to deviations from intended interventions (effect of adhering to intervention); D3= Domain 3, missing outcome data; D4= Domain 4, bias in measurement of outcome; D5= Domain 5, bias in selection of reported result.

Figure 4

Risk of bias domains for older adults without SCI (cross-over study).

Supplementary Files

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