SUPPLEMENTARY MATERIAL

Oral Chinese herbal medicine combined with donepezil for mild cognitive impairment: A systematic review and meta-analysis

Lingling Liu[1,2,#] PhD, Claire Shuiqing Zhang[1,#] PhD, Anthony Lin Zhang[1] PhD, Yefeng Cai[2,*] MD, Charlie Changli Xue[1,2,] PhD**

SUPPLEMENTARY MATERIAL

Supplementary Table S1. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3–4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5–6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6–7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8

Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8–9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8–9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8–9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8–9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8–9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8–9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8–9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 10, Supplementary Table S3, S4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11, Supplementary Figure S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 12–15, Figure 2, 3, Supplementary Figure S13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 12–15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the	Page 12–15,

		summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 2–3, Supplementary Figure S2, S6, S13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 12–14
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 14
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 14–15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 15–16
	23b	Discuss any limitations of the evidence included in the review.	Page 21–22
	23c	Discuss any limitations of the review processes used.	Page 21–22
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16–21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 32
Competing interests	26	Declare any competing interests of review authors.	Page 32
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 34–35

SUPPLEMENTARY MATERIAL

Supplementary Table S2. Search strategy.

Database/ Registry platform/website	Search strategy
PubMed	**#1** (Cognitive Dysfunction[MeSH Terms]) OR (Cognitive Dysfunctions[All Fields]) OR (Dysfunction, Cognitive[All Fields]) OR (Cognitive Impairments[All Fields]) OR (Cognitive Impairment[All Fields]) OR (Mild Cognitive Impairment[All Fields]) OR (Mild Cognitive Impairments[All Fields]) OR (Mild Neurocognitive Disorder[All Fields]) OR (Mild Neurocognitive Disorders[All Fields]) OR (Neurocognitive Disorder, Mild[All Fields]) OR (Neurocognitive Disorders, Mild[All Fields]) OR (Cognitive Decline[All Fields]) OR (Cognitive Declines[All Fields]) OR (Mental Deterioration[All Fields]) OR (Mental Deteriorations[All Fields]) OR (mild cognitive disorder[All Fields]) OR (mild neurocognitive impairment[All Fields]) OR (mild neurocognitive dysfunction[All Fields]) OR (minor cognitive disorder[All Fields]) OR (minor neurocognitive impairment[All Fields]) OR (minor neurocognitive decline[All Fields]) OR (minor neurocognitive disorder[All Fields]) **#2** (Medicine, Chinese Traditional[All Fields]) OR (Drugs, Chinese Herbal[All Fields]) OR (Herbal Medicine[All Fields]) OR (Medicine, Traditional[All Fields]) OR (Medicine, Kampo[All Fields]) OR (Plant Preparations[All Fields]) OR (Plants, Medicinal[All Fields]) OR (Plant Extracts[All Fields]) OR (Ethnopharmacology[All Fields]) OR (Ethnobotany[All Fields]) OR (Phytotherapy[All Fields]) OR (Materia Medica[All Fields]) OR (TCM[All Fields]) OR (Chinese AND (agent OR drug OR extract OR formula OR herb* medici* OR preparation OR prescription OR plant OR remedy OR therapy)) OR ((herb* OR botanical OR phyto) AND (agent OR drug OR extract OR materia* OR medici* OR mixture OR preparation OR product OR prescription OR plant OR remedy OR substance OR therapy)) OR (herb or herbs or herbal) **#3** (Randomized Controlled Trial[Publication Type]) OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR (Controlled Clinical Trial[Publication Type]) OR (Clinical Trial[Publication Type]) OR (Clinical Trials as Topic[MeSH Terms]) OR ((clinical[Title/Abstract] AND trial[Title/Abstract])) OR (Drug Therapy[MeSH Terms]) OR (Therapeutic use[MeSH Subheading]) OR (Random Allocation[MeSH Terms]) OR (Random*[Title/Abstract]) OR (Placebos[MeSH Terms]) OR (Placebo[Title/Abstract])

SUPPLEMENTARY MATERIAL

Database/ Registry platform/website	Search strategy
	#4 #1 AND #2 AND #3 **#5** Animals [MeSH Terms] NOT (Humans[MeSH Terms] AND Animals[MeSH Terms]) **#6** #4 NOT #5
Embase	**#1** 'mild cognitive impairment'/exp OR 'mild neurocognitive disorder'/exp OR 'mild cognitive defect'/exp OR (mild:ti,ab,kw OR minor:ti,ab,kw) AND (cognitive:ti,ab,kw OR neurocognitive:ti,ab,kw) AND (impair*:ti,ab,kw OR disorde*:ti,ab,kw OR dysfuncti*:ti,ab,kw OR declin*:ti,ab,kw OR defic*:ti,ab,kw OR defec*:ti,ab,kw) OR nmci:ti,ab,kw OR amci:ti,ab,kw OR mmci:ti,ab,kw OR cognitive deficit:ti,ab,kw OR cognitive decline:ti,ab,kw OR mental deterioration:ti,ab,kw **#2** 'traditional medicine'/exp OR 'Chinese herb'/exp OR 'Chinese medicine'/exp OR 'Chinese drug'/exp OR 'Chinese medicinal formula'/exp OR 'herbal medicine'/exp OR 'herbaceous agent'/exp OR 'medicinal plant'/exp OR 'plant medicinal product'/exp OR 'plant extract'/exp OR 'ethnopharmacology'/exp OR 'ethnobotany'/exp OR 'phytotherapy'/exp OR 'materia medica'/exp OR 'Kampo medicine'/exp OR '(Chinese AND (agent OR drug OR extract OR formula OR herb* medici* OR preparation OR prescription OR plant OR remedy OR therapy)):ti,ab,kw OR ((herb* OR botanical OR phyto) AND (agent OR drug OR extract OR materia* OR medici* OR mixture OR preparation OR product OR prescription OR plant OR remedy OR substance OR therapy)):ti,ab,kw OR (herb or herbs or herbal):ti,ab,kw **#3** 'randomized controlled trial'/exp OR 'random*' OR placebo* OR ((singl* or doubl* or treb* or trip*) AND (blind* or mask* or dummy)) **#4** #1 AND #2 AND #3

SUPPLEMENTARY MATERIAL

Database/ Registry platform/website	Search strategy
	#5 [animals]/lim NOT ([humans]/lim AND [animals]/lim) **#6** #4 NOT #5
CENTRAL	**#1** MeSH descriptor: [Cognitive Dysfunction] explode all trees OR MeSH descriptor: [Neurocognitive Disorders] explode all trees OR MeSH descriptor: [Cognition Disorders] explode all trees OR (Mild Cognitive Impairment):ti,ab,kw OR (Mild Cognitive Disorder):ti,ab,kw OR (Mild Neurocognitive Impairment):ti,ab,kw OR (Mild Neurocognitive Disorder):ti,ab,kw OR (Mild Neurocognitive Dysfunction):ti,ab,kw OR (Minor Neurocognitive Impairment):ti,ab,kw OR (Minor Cognitive Disorder):ti,ab,kw OR (Minor Neurocognitive Decline):ti,ab,kw OR (Minor Neurocognitive Disorder):ti,ab,kw OR (Cognitive Decline):ti,ab,kw OR (Cognitive deficit):ti,ab,kw OR (Cognitive defect):ti,ab,kw OR (Mental Deterioration):ti,ab,kw **#2** Medicine, Chinese Traditional OR Drugs, Chinese Herbal OR Herbal Medicine OR Medicine, Traditional OR Medicine, Kampo OR Plant Preparations OR Plants, Medicinal OR Plant Extracts OR Ethnopharmacology OR Ethnobotany OR Phytotherapy OR Materia Medica OR (TCM):ti,ab,kw OR (Chinese AND (agent OR drug OR extract OR formula OR herb* medici* OR preparation OR prescription OR plant OR remedy OR therapy)):ti,ab,kw OR ((herb* OR botanical OR phyto) AND (agent OR drug OR extract OR materia* OR medici* OR mixture OR preparation OR product OR prescription OR plant OR remedy OR substance OR therapy)):ti,ab,kw OR (herb or herbs or herbal):ti,ab,kw **#3** (Randomized Controlled Trial):pt OR (Random*):ti,ab,kw OR (placebo*):ti,ab,kw OR ((singl* or doubl* or treb* or trip*) AND (blind* or mask* or dummy)):ti,ab,kw **#4** #1 AND #2 AND #3 [Filter:Trials]
CINAHL	**#1** Cognitive Dysfunction OR Cognitive Impairment OR Cognitive Decline OR Cognitive deficit OR Cognitive defect OR Mental Deterioration OR Mild Cognitive Impairment OR Mild Cognitive Disorder OR Mild Neurocognitive Impairment OR Mild

SUPPLEMENTARY MATERIAL

Database/ Registry platform/website	Search strategy
	Neurocognitive Disorder OR Mild Neurocognitive Dysfunction OR Minor Cognitive Disorder OR Minor Neurocognitive Impairment OR Minor Neurocognitive Decline OR Minor Neurocognitive Disorder **#2** Medicine, Chinese Traditional OR Drugs, Chinese Herbal OR Herbal Medicine OR Medicine, Traditional OR Medicine, Kampo OR Plant Preparations OR Plants, Medicinal OR Plant Extracts OR Ethnopharmacology OR Ethnobotany OR Phytotherapy OR Materia Medica OR TCM OR (Chinese AND (agent OR drug OR extract OR formula OR herb* medici* OR preparation OR prescription OR plant OR remedy OR therapy)) OR ((herb* OR botanical OR phyto) AND (agent OR drug OR extract OR materia* OR medici* OR mixture OR preparation OR product OR prescription OR plant OR remedy OR substance OR therapy)) OR (herb OR herbs OR herbal) **#3** Limiters: Randomized Controlled Trials **#4** #1 AND #2 AND #3
AMED	**#1** Cognitive Dysfunction OR Cognitive Impairment OR Cognitive Decline OR Cognitive deficit OR Cognitive defect OR Mental Deterioration OR Mild Cognitive Impairment OR Mild Cognitive Disorder OR Mild Neurocognitive Impairment OR Mild Neurocognitive Disorder OR Mild Neurocognitive Dysfunction OR Minor Cognitive Disorder OR Minor Neurocognitive Impairment OR Minor Neurocognitive Decline OR Minor Neurocognitive Disorder **#2** Medicine, Chinese Traditional OR Drugs, Chinese Herbal OR Herbal Medicine OR Medicine, Traditional OR Medicine, Kampo OR Plant Preparations OR Plants, Medicinal OR Plant Extracts OR Ethnopharmacology OR Ethnobotany OR Phytotherapy OR Materia Medica OR TCM OR (Chinese AND (agent OR drug OR extract OR formula OR herb* medici* OR preparation OR prescription OR plant OR remedy OR therapy)) OR ((herb* OR botanical OR phyto) AND (agent OR drug OR extract OR materia* OR medici* OR mixture OR preparation OR product OR prescription OR plant OR remedy OR substance OR therapy)) OR (herb OR herbs OR herbal)

SUPPLEMENTARY MATERIAL

Database/ Registry platform/website	Search strategy
	#3 Randomized Controlled Trial OR Random* OR placebo* OR (singl* or doubl* or treb* or trip*) AND (blind* or mask* or dummy) **#4** #1 AND #2 AND #3
CBM	**#1** 认知功能障碍 OR 轻度认知障碍 OR 轻度神经认知障碍 OR 认知减退 OR 认知损害 **#2** 中医 OR 中西医 OR 中医疗法 OR 辨病论治 OR 辨证 OR 辨证论治 OR 辨症施治 OR 汉方 OR 祖国医学 OR 传统医学 OR 传统治疗 OR 替代医学 OR 替代治疗 OR 中国传统医学 OR 民族医药 OR 草药 OR 中草药 OR 中药 OR 中药疗法 OR 中西药 OR 传统医药 OR 中成药 OR 植物药 OR 中医治法 **#3** #1 AND #2 [Filter: 随机对照试验]
CNKI Wanfang CQVIP	**#1** 认知功能障碍 OR 轻度认知障碍 OR 轻度神经认知障碍 OR 认知减退 OR 认知损害 **#2** 中医 OR 中西医 OR 中医疗法 OR 辨病论治 OR 辨证 OR 辨证论治 OR 辨症施治 OR 汉方 OR 祖国医学 OR 传统医学 OR 传统治疗 OR 替代医学 OR 替代治疗 OR 中国传统医学 OR 民族医药 OR 草药 OR 中草药 OR 中药 OR 中药疗法 OR 中西药 OR 传统医药 OR 中成药 OR 植物药 OR 中医治法 **#3** 随机 **#4** #1 AND #2 AND #3

SUPPLEMENTARY MATERIAL

Database/ Registry platform/website	**Search strategy**
ICTRP	mild cognitive impairment OR MCI OR mild cognitive decline OR CIND OR 'not demented' OR 'no dementia' (in title; Recruitment status: ALL)
ClinicalTrials.gov	Condition or disease: mild cognitive impairment; Study Status: all study; Study Type: interventional
ChiCTR	研究疾病名称: 轻度认知障碍; 研究类型: 干预性研究
Google Scholar	**# 1** mild cognitive impairment, Chinese herbal medicine, donepezil, random [with all of the words] **# 2** 轻度认知障碍 中药 多奈派齐 随机 [with all of the words] **# 3** #1 OR #2

Abbreviations: AMED, Allied and Complementary Medicine Database; CBM, China Biomedical Literature; CENTRAL, Cochrane Central Register of Controlled Trials; ChiCTR, Chinese Clinical Trial Registry; CINAHL, Cumulative Index of Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure Database; CQVIP, Chongqing VIP Database; Embase, Excerpta Medica Database; ICTRP, International Clinical Trials Registry Platform.

SUPPLEMENTARY MATERIAL

Supplementary Table S3. Characteristics of included studies.

Study	Sample size randomised (dropouts)		Main inclusion criteria of the study population	Treatment		Treatment duration/ Follow-up duration	Outcome measures
	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil		
Gan PP 2020	26 (0)	26 (0)	• MCI with type 2 diabetes mellitus • MoCA < 26, CDR = 0.5 • Age: 45–75 years • Education level: primary school and above	*Bu shen qing nao* ultrafine granular powder + Donepezil + usual care (control of diabetes, hypertension, hyperlipoidemia, exercise, diet control, psychological guidance and health education)	Donepezil + usual care (control of diabetes, hypertension, hyperlipoidemia, exercise, diet control, psychological guidance and health education)	12 weeks/No	MoCA, HCY, blood glucose, vascular endothelial growth factor, hs-CRP, lipoprotein, AEs
Gao FQ 2017	60 (0)	60 (0)	• Vascular MCI with diabetes mellitus • HIS ≥ 4 • Age: 50–75 years	CHM for nourishing kidney, eliminating phlegm and damp + Donepezil	Donepezil	6 months/No	MMSE, MoCA, TCM syndrome scores, SDSVD, ADL, MDA, SOD, AChE, AEs
Gao HR 2017	99 (0)	99 (0)	• VCIND • Age ⩾ 60 years	*Shu yu* pill + Donepezil + usual care (control of hypertension, diabetes, hyperlipoidemia, antiplatelet agents, neuroprotective agents, tobacco cessation, decreased alcohol consumption)	Donepezil + usual care (control of hypertension, diabetes, hyperlipoidemia, antiplatelet agents, neuroprotective agents, tobacco cessation, decreased alcohol consumption)	8 weeks/No	MMSE, MoCA, mean flow velocity of the cerebral arteries, P300
Gu LL 2018	35 (0)	35 (0)	Vascular MCI	*Yi zhi wen dan* decoction + Donepezil	Donepezil	12 weeks/No	MMSE, DSR, ADL, TCM syndrome scores, AEs
Guo DW 2019	48 (0)	47 (0)	• VCIND due to CSVD • MoCA < 26	*Yang xue qing nao* granule + Donepezil + usual care (control of hypertension, diabetes,	Donepezil + usual care (control of hypertension, diabetes, hyperlipoidemia, antiplatelet agents,	8 weeks/No	MoCA, hs-CRP, HCY, cerebral perfusion indicators,

SUPPLEMENTARY MATERIAL

Study	Sample size randomised (dropouts)		Main inclusion criteria of the study population	Treatment		Treatment duration/ Follow-up duration	Outcome measures
	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil		
				hyperlipoidemia, antiplatelet agents, neurotrophic agents, treatment for improving cerebral circulation)	neurotrophic agents, treatment for improving cerebral circulation)		EEG, P300, SF-36
Han LX 2020	44 (3)	44 (1)	• Vascular MCI • HIS > 7 • MMSE: 21–26 • ADL > 60 • Age: 40–80 years	*Bu shen yi zhi* decoction + Donepezil + usual care (control of hypertension, diabetes, hyperlipoidemia)	Donepezil + usual care (control of hypertension, diabetes, hyperlipoidemia)	12 weeks/No	MMSE, ADL, TCM syndrome scores, AEs
He JH 2017	40 (0)	40 (0)	• MCI • MMSE < 27	*Huan nao yi cong* decoction + Donepezil	Donepezil	8 weeks/No	MMSE, TCM syndrome scores, hemodynamic indexes, AEs
Li Q 2022	32 (0)	32 (0)	• MCI with type 2 diabetes mellitus • MoCA < 26 • Age: 45–75 years	*Di huang yin zi* decoction + Donepezil+ usual care (control of diabetes, health education, diet and exercise)	Donepezil+ usual care (control of diabetes, health education, diet and exercise)	8 weeks/No	MMSE, MoCA, glucose, HbA1C, TCM syndrome scores, AEs
Li QW 2014	34 (0)	34 (0)	• MCI • MMSE ≥ 24 • ADL < 26 • HIS ≤ 4 • Disease duration > 3 months	*Di huang yin zi* capsule + Donepezil	Donepezil	180 days/No	MMSE, MoCA
Li XQ	30 (0)	30 (0)	• MCI due to AD	*Xi xin* decoction + Donepezil	Donepezil	4 weeks/No	MMSE, AVLT

SUPPLEMENTARY MATERIAL

Study	Sample size randomised (dropouts)		Main inclusion criteria of the study population	Treatment		Treatment duration/ Follow-up duration	Outcome measures
	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil		
2020			• Age: 65–80 years				
Liu XR 2020	43 (0)	43 (0)	• MCI	*Bu yang huan wu* decoction + Donepezil	Donepezil	2 months/No	MMSE, MoCA, SDSVD, BI
Ma CY 2022	32 (2)	32 (2)	• Vascular MCI due to CSVD • MoCA < 26 • Age: 35–80 years	*Bu shen jian pi huo xue* decoction + Donepezil + usual care (Aspirin, Atorvastatin)	Donepezil + usual care (Aspirin, Atorvastatin)	60 days/No	MoCA, TCM syndrome scores, Fazekas scale, ADL, AEs
Qian DD 2019	32 (1)	34 (2)	• MCI due to degenerative aetiology • CDR = 0.5 • SAS < 50 • Age: 55–75 years	*Tai yuan* decoction + Donepezil + usual care (control of hypertension, diabetes, coronary heart disease)	Donepezil + usual care (control of hypertension, diabetes, coronary heart disease)	12 weeks/No	MMSE, MoCA, TCM syndrome scores, AEs
Shen LH 2014	38 (0)	38 (0)	• MCI	*Huang lian wen dan* decoction + Donepezil	Donepezil	3 months/No	MMSE, AEs
Shou FY 2022	41 (0)	41 (0)	• MCI • CDR = 1 • Age: 60–75 years	*Sheng hui* decoction + Donepezil	Donepezil	12 weeks/No	MoCA, BI, DVR
Wang LL 2018	45 (0)	45 (0)	• MCI	*Yang xue qing nao granule* + Donepezil	Donepezil	3 months/No	MMSE, ADL

SUPPLEMENTARY MATERIAL

Study	Sample size randomised (dropouts)		Main inclusion criteria of the study population	Treatment		Treatment duration/ Follow-up duration	Outcome measures
	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil		
Wang XJ 2021	30 (0)	30 (0)	• Amnestic MCI • MMSE: 18–27 • MoCA: 19–25 • CDR = 0.5 • ADL: 14–22 • GDS: stages 2 to 3 • WMS-IV < 1.5 SDs • Ages: 60–85 years	*San bu* recipe + Donepezil	Donepezil	3 months/No	MMSE, MoCA, ADL, TCM syndrome scores, MDA, SOD, GSH-Px, AEs
Xie LY 2015	30 (0)	30 (0)	• MCI	*Bu yang huan wu* decoction + Donepezil	Donepezil	60 days/No	MMSE, MoCA, BI
Xie S 2020	32 (0)	32 (0)	• Vascular MCI due to CSVD • MoCA: 18–25	*Yang xue qing nao* pill + Donepezil + usual care (control of hypertension, dyslipidemia)	Donepezil + usual care (control of hypertension, dyslipidemia)	3 months/No	MoCA, ADL, NSE, AChE, MDA
Yang JJ 2011	34 (2)	34 (1)	• MCI • MMSE ≥ 24 • CDR = 0.5	*Wu ling* capsule + Donepezil + usual care (control of hypertension, diabetes and cardiovascular disease)	Donepezil + usual care (control of hypertension, diabetes and cardiovascular disease)	60 days/No	MMSE, MoCA, CDR, GDS, HAMD, AEs,

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; ADL, Activities of Daily Living; AEs, Adverse events; AVLT, Auditory Verbal Learning Test; BI, Barthel Index; CDR, Clinical Dementia Rating; CHM, Chinese herbal medicine; CSVD, cerebral small vessel disease; DSR, Delayed Story Recall Test; DVR, Delayed Verbal Recall Test; EEG, electroencephalography; GDS, Global Deterioration Scale; GSH-Px, glutathione peroxidase; HAMD, Hamilton Depression Rating Scale; HbA1C, hemoglobin A1C; HCY, homocysteine; HIS, Hachinski ischemic score; hs-CRP, high-sensitivity C-reactive protein; MCI, mild

cognitive impairment; MDA, malondialdehyde; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; NSE, Neuron-specific enolase; P300, 300 is an event-related potential used as an tool to assess cognitive function; SAS, Self-Rating Anxiety Scale; SDs, standard deviations; SDSVD, scale for the differentiation of syndromes of vascular dementia; SF-36, 36-Item Short Form Health Survey; SOD, superoxide dismutase; TCM, traditional Chinese medicine; VCIND, vascular cognitive impairment, no dementia; WMS-IV, Wechsler memory scale-fourth edition.

SUPPLEMENTARY MATERIAL

Supplementary Table S4. Participants characteristics of included studies.

Study	Age (mean ± SD), years		Gender (male/female)		Education (mean ± SD), years		Disease duration (mean ± SD)		Baseline assessment	Baseline cognitive score (mean ± SD)/median (IQR)	
	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil
Gan PP 2020	57.0 ± 3.40	58.0 ± 2.60	15/11	16/10	8.90 ± 2.60	9.30 ± 4.20	NS	NS	MoCA	21.62 ± 2.97	21.54 ± 3.23
Gao FQ 2017	62.4 ± 5.95	62.08 ± 5.92	36/24	34/27	10.47 ± 1.30	10.52 ± 1.33	NS	NS	MMSE	15.79 ± 2.95	15.84 ± 2.98
									MoCA	15.82 ± 2.27	15.96 ± 2.35
Gao HR 2017	60–65 y (n = 15) 65–70 y (n = 34) 70–75 y (n = 31) ≥ 75 y (n = 19)	60–65 y (n = 18) 65–70 y (n = 32) 70–75 y (n = 33) ≥ 75 y (n = 16)	48/51	54/45	Illiteracy (*n* = 13), primary school (*n* = 23), secondary school (*n* = 22), senior secondary school (*n* = 33), tertiary education (*n* = 8)	Illiteracy (*n* = 11), primary school (*n* = 24), secondary school (*n* = 19), senior secondary school (*n* = 34), tertiary education (*n* = 11)	2.05 ± 2.01 m	1.93 ± 1.82 m	MMSE	24.08 ± 2.01	24.25 ± 1.85
									MoCA	20.46 ± 2.17	20.32 ± 2.38
Gu LL 2018	68.40 ± 3.50	69.2 ± 3.7	19/16	20/15	NS	NS	2.40 ± 0.70 y	2.0 ± 0.6 y	MMSE	23.60 ± 3.81	23.72 ± 3.66
Guo DW 2019	62.29 ± 9.30	63.73 ± 10.81	27/21	28/19	Secondary school and below (*n* = 18), senior secondary school (*n* = 20), tertiary education (*n* = 10)	Secondary school and below (*n* = 20), senior secondary school (*n* = 18), tertiary education (*n* = 9)	6.94 ± 3.12 y	7.20 ± 3.80 y	MoCA	16.29 ± 2.74	16.12 ± 2.84
Han LX	56.77 ± 4.67	67.63 ± 3.86	20/21	19/24	Primary school	Primary school	3.59 ± 1.48	3.23 ± 1.27	MMSE	23.20 ± 1.42	23.47 ± 1.28

SUPPLEMENTARY MATERIAL

Study	Age (mean ± SD), years		Gender (male/female)		Education (mean ± SD), years		Disease duration (mean ± SD)		Baseline assessment	Baseline cognitive score (mean ± SD)/median (IQR)	
	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil
2020					and below (n = 5), secondary school (n = 18), senior secondary school (n = 14), tertiary education (n = 4)	and below (n = 6), secondary school (n = 19), senior secondary school (n = 12), tertiary education (n = 6)	m	m			
He JH 2017	72.32 ± 5.30	71.05 ± 6.83	22/18	23/17	10.42 ± 3.01	11.02 ± 3.12	6.32 ± 2.41 m	6.22 ± 2.38 m	MMSE	21.30 ± 3.20	21.40 ± 3.80
Li Q 2022	59.03 ± 7.15	60.06 ± 6.58	21/11	22/10	Primary school and below (n = 11), secondary school and above (n = 21)	Primary school and below (n = 13), secondary school and above (n = 19)	2.46 ± 0.68 y	2.65 ± 0.88 y	MMSE MoCA	22.75 ± 1.39 21.53 ± 1.92	22.94 ± 1.48 21.44 ± 1.78
Li QW 2014	57.36 ± 9.48	58.46 ± 9.18	20/14	19/15	NS	NS	97.56 ± 9.25 d	96.85 ± 8.79 d	MMSE MoCA	21.78 ± 1.61 12.88 ± 2.13	21.62 ± 1.56 13.65 ± 1.76
Li XQ 2020	61.5 ± 11.5	62.3 ± 7.8	18/12	16/14	Secondary school and above		NS	NS	MMSE	24.73 ± 0.87	24.83 ± 0.87
Liu XR 2020	69.01 ± 3.35	68.36 ± 3.54	21/22	22/21	NS	NS	1.36 ± 0.31 y	1.35 ± 0.30 y	MMSE MoCA	19.68 ± 2.21 20.36 ± 2.35	20.01 ± 2.15 20.98 ± 2.75
Ma CY	61.4 ± 11.93	64.20 ± 10.48	15/15	16/14	Illiteracy (n = 1),	NS	40.5 ± 14.1	42.4 ± 12.32	MoCA	21.47 ± 2.18	21.03 ± 1.94

SUPPLEMENTARY MATERIAL

Study	Age (mean ± SD), years		Gender (male/female)		Education (mean ± SD), years		Disease duration (mean ± SD)		Baseline assessment	Baseline cognitive score (mean ± SD)/median (IQR)	
	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil
2022					primary school (*n* = 8), secondary school (*n* = 7), senior secondary school (*n* = 11), tertiary education (*n* = 3)		d	d			
Qian DD 2019	66.13 ± 5.51	67.59 ± 5.3	19/12	18/14	Illiteracy (*n* = 0), primary school (*n* = 21), secondary school and above (*n* = 10)	Illiteracy (*n* = 0), primary school (*n* = 23), secondary school and above (*n* = 9)	NS	NS	MoCA	20.58 ± 1.67	20.28 ± 1.44
Shen LH 2014	70.32 ± 4.57		50/26		Illiteracy (*n* = 7), primary school (*n* = 16), secondary school (*n* = 24), senior secondary school (*n* = 21), tertiary education (*n* = 8)		NS	NS	MMSE	22.92 ± 1.80	22.86 ± 1.79
Shou FY 2022	67.9 ± 7.61	68.03 ± 7.77	28/13	26/15	Secondary school (*n* = 7), senior secondary school and above (*n* = 34)	Secondary school (*n* = 9), senior secondary school and above (*n* = 32)	5.25 ± 0.67 y	5.11 ± 0.61y	MoCA	22.85 ± 3.01	22.94 ± 3.04
Wang LL 2018	71.2 ± 4.6	70.2 ± 4.2	23/22	22/23	NS	NS	7.60 ± 0.30 y	7.30 ± 0.50 y	MMSE	23.42 ± 3.14	23.58 ± 3.08

SUPPLEMENTARY MATERIAL

Study	Age (mean ± SD), years		Gender (male/female)		Education (mean ± SD), years		Disease duration (mean ± SD)		Baseline assessment	Baseline cognitive score (mean ± SD)/median (IQR)	
	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil		CHM + Donepezil	Donepezil
Wang XJ 2021	68.83 ± 5.5	68.53 ± 5.29	17/13	16/14	Illiteracy (*n* = 3), primary school (*n* = 11), senior secondary school and above (*n* = 19)	Illiteracy (*n* = 2), primary school (*n* = 13), senior secondary school and above (*n* = 15)	27.40 ± 2.13 m	27.20 ± 2.11 m	MMSE	25(18, 27)	25(19, 27)
									MoCA	22(20, 24)	22(20, 24)
Xie LY 2015	59.12 ± 16.76	60.15 ± 14.68	18/12	17/13	NS	NS	0.50–2.00 y	0.50–2.00 y	MMSE	22.72 ± 3.09	18.26 ± 2.99
									MoCA	21.03 ± 2.25	20.55 ± 2.78
Xie S 2020	68.23 ± 2.15	67.82 ± 1.97	19/13	17/15	NS	NS	NS	NS	MoCA	21.69 ± 0.87	21.74 ± 0.83
Yang JJ 2011	65.5 ± 10.9	63.5 ± 8.9	19/15	22/12	NS	NS	NS	NS	MMSE	25.89 ± 1.93	25.02 ± 1.59
									MoCA	22.55 ± 1.28	22.06 ± 2.17

Abbreviations: CHM, Chinese herbal medicine; d, days; IQR, interquartile range; m, months; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NS, not stated; SD, standard deviation. y: years.

SUPPLEMENTARY MATERIAL

Supplementary Table S5. Ingredients of Chinese herbal medicine preparations of included studies.

Study	CHM formulae/products	CHM ingredients (***Pin yin*** **names & plant names[a])**
Gan PP 2020	*Bu shen qing nao* ultrafine granular powder	***Pin yin*** **names:** *Tai zi shen, Dan shen, Tian ma, Wu wei zi, Nv zhen zi* **Plant names:** *Pseudostellaria heterophylla* (Miq.) Pax, *Salvia miltiorrhiza* Bunge, *Gastrodia elata* Blume, *Schisandra chinensis* (Turcz.) Baill., *Ligustrum lucidum* W.T.Aiton
Gao FQ 2017	CHM for nourishing kidney, eliminating phlegm and damp	***Pin yin*** **names:** *Ren shen, Shan yao, Fu ling, Dan shen, Rou cong rong, Ban xia, Sha ren, Shi chang pu, Gan Cao* **Plant names:** *Panax ginseng* C.A.Mey., *Dioscorea oppositifolia* L., *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Salvia miltiorrhiza* Bunge, *Cistanche deserticola* Ma, *Pinellia ternata* (Thunb.) Makino, *Wurfbainia villosa* (Lour.) Škorničk. & A.D.Poulsen, *Acorus calamus var. angustatus* Besser, *Glycyrrhiza uralensis* Fisch.
Gao HR 2017	*Shu yu* pill	***Pin yin*** **names:** *Shan yao, Dang Gui, Gui Zhi, Shen qu, Di huang, Dou huang juan, Gan cao, Ren shen, Chuan xiong, Shao yao, Bai zhu, Mai men dong, Xing ren, Chai hu, Jie geng, Fu ling, E jiao, Gan jiang, Bai lian, Fang feng, Da zao, Feng mi* **Plant names:** *Dioscorea oppositifolia* L., *Angelica sinensis* (Oliv.) Diels, *Cinnamomum cassia* (L.) J. Presl, stir-fried Medicated leaven, *Rehmannia glutinosa* (Gaertn.) DC., *Glycine max* (L.) Merr., *Glycyrrhiza uralensis* Fisch., *Panax ginseng* C.A.Mey., *Ligusticum striatum* DC., *Dioscorea oppositifolia* L., *Atractylodes macrocephala* Koidz., *Ophiopogon japonicus* (Thunb.) Ker Gawl., *Prunus armeniaca* L., *Bupleurum chinense* DC., *Platycodon grandiflorus* (Jacq.) A.DC., *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., Donkey-hide gelatin, *Zingiber officinale* Roscoe, *Ampelopsis japonica* (Thunb.) Makino, *Saposhnikovia divaricata* (Turcz.) Schischk., Ziziphus jujuba Mill., Honey

SUPPLEMENTARY MATERIAL

Study	CHM formulae/products	CHM ingredients (***Pin yin*** **names & plant names[a])**
Gu LL 2018	*Yi zhi wen dan* decoction	***Pin yin*** **names:** *Ren shen, Chuan xiong, Shu di huang, Shi chang pu, Zhi shi, Fu ling, Yi zhi, Yuan zhi* **Plant names:** *Panax ginseng* C.A.Mey., *Ligusticum striatum* DC., *Rehmannia glutinosa* (Gaertn.) DC., *Acorus calamus var. angustatus* Besser, *Citrus aurantium* L., *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Alpinia oxyphylla* Miq., *Polygala tenuifolia* Willd.
Guo DW 2019	*Yang xue qing nao* granule	***Pin yin*** **names:** *Shu di huang, Dang gui, Chuan xiong, Bai shao, Xia ku cao, Ji xue teng, Yan hu suo, Zhen zhu mu, Xi xing, Gou teng, Jue ming zi* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Angelica sinensis* (Oliv.) Diels, *Ligusticum striatum* DC., *Paeonia lactiflora* Pall., *Prunella vulgaris* L., *Spatholobus suberectus* Dunn, *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu, Nacre, *Asarum heterotropoides* F.Schmidt, *Uncaria rhynchophylla* (Miq.) Miq., Senna tora (L.) Roxb.
Han LX 2020	*Bu shen yi zhi* decoction	***Pin yin*** **names:** *Shu di huang, Yi zhi, Sheng gui ban, Shan yao, Shan zhu yu, Huang jing, Mu dan pi, Ze xie, Fu ling, Gan cao* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Alpinia oxyphylla* Miq., tortoise plastron, *Dioscorea oppositifolia* L., *Cornus officinalis* Siebold & Zucc., *Polygonatum kingianum* Collett & Hemsl., *Paeonia suffruticosa* Andrews, *Lycopus lucidus* Turcz. ex Benth., *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Glycyrrhiza uralensis* Fisch.
He JH 2017	*Huan nao yi cong* decoction	***Pin yin*** **names:** *He shou wu, Shi chang pu, Ren shen, Huang lian, Hu lu ba, Chuan xiong* **Plant names:** *Polygonum multiflorum* Thunb., *Acorus calamus var. angustatus* Besser, *Panax ginseng* C.A.Mey., *Coptis chinensis* Franch., *Trigonella foenum-*

SUPPLEMENTARY MATERIAL

Study	CHM formulae/products	CHM ingredients (***Pin yin*** **names & plant names[a])**
		graecum L., *Ligusticum striatum* DC.
Li Q 2022	*Di huang yin zi decoction*	***Pin yin*** **names:** *Shu di huang, Ba ji tian, Shan zhu yu, Shi hu, Rou cong rong, Fu zi, Yuan zhi, Rou gui, Wu wei zi, Fu ling, Mai dong, Shi chang pu, Bo he, Sheng jiang, Da zao* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Morinda officinalis* F.C.How, *Cornus officinalis* Siebold & Zucc., *Dendrobium nobile* Lindl., *Cistanche deserticola* Ma, *Aconitum carmichaelii* Debeaux, *Polygala tenuifolia* Willd., *Cinnamomum verum* J.Presl, *Schisandra chinensis* (Turcz.) Baill., *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Ophiopogon japonicus* (Thunb.) Ker Gawl., *Acorus calamus var. angustatus* Besser, *Mentha canadensis* L., *Zingiber officinale* Roscoe, *Ziziphus jujuba* Mill.
Li QW 2014	*Di huang yin zi* capsule	***Pin yin*** **names:** *Shu di huang, Shan zhu yu, Ba ji tian, Rou cong rong, Shi hu, Mai dong, Wu wei zi, Fu zi, Rou gui, Fu ling, Yuan zhi, Shi chang pu, Bo he, Zi he che, San qi* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Cornus officinalis* Siebold & Zucc., *Morinda officinalis* F.C.How, *Cistanche deserticola* Ma, *Dendrobium nobile* Lindl., *Ophiopogon japonicus* (Thunb.) Ker Gawl., *Schisandra chinensis* (Turcz.) Baill., *Aconitum carmichaelii* Debeaux, *Ci*nnamomum v*erum* J. Presl, *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Polygala tenuifolia* Willd., *Acorus calamus var. angustatus* Besser, *Mentha canadensis* L., *Panax notoginseng* (Burkill) F.H.Chen
Li XQ 2020	*Xi xin* decoction	***Pin yin*** **names:** *Dang shen, Fu shen, Suan zao ren, Ban xia, Chen pi, Shen qu, Gan cao, Fu zi, Shi chang pu* **Plant names:** *Salvia miltiorrhiza* Bunge, *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Ziziphus jujuba var. spinosa* (Bunge) Hu ex H.F.Chow., *Pinellia ternata* (Thunb.) Makino, *Citrus reticulata* Blanco, stir-fried Medicated leaven, *Glycyrrhiza uralensis*

SUPPLEMENTARY MATERIAL

Study	CHM formulae/products	CHM ingredients (***Pin yin*** **names & plant names[a])**
		Fisch., *Aconitum carmichaelii* Debeaux, *Acorus calamus var. angustatus* Besser
Liu XR 2020	*Bu yang huan wu* decoction	***Pin yin*** **names:** *Huang qi, Dang shen, Dang gui, Chi shao, Tao ren, Hong hua, Di long, Ji xue teng, Zhi gan cao, Dan shen* **Plant names:** *Astragalus mongholicus* Bunge, *Salvia miltiorrhiza* Bunge, *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Prunus persica* (L.) Batsch, *Carthamus tinctorius* L., *Pheretima aspergillum* (E.Perrier), *Spatholobus suberectus* Dunn, *Glycyrrhiza uralensis* Fisch., *Salvia miltiorrhiza* Bunge
Ma CY 2022	*Jian pi bu shen huo xue* decotion	***Pin yin*** **names:** *Huang qi, Dang shen, Chao bai zhu, Sang ji sheng, Du zhong, Huai niu xi, Rou cong rong, Dan shen, Chuan xiong, Shi chang pu, Zhi gan cao* **Plant names:** *Astragalus mongholicus* Bunge, *Salvia miltiorrhiza* Bunge, *Atractylodes macrocephala* Koidz., *Taxillus chinensis* (DC.) Danser, *Eucommia ulmoides* Oliv., *Achyranthes bidentata* Blume, *Cistanche deserticola* Ma, *Salvia miltiorrhiza* Bunge, *Ligusticum striatum* DC., *Acorus calamus var. angustatus* Besser, *Glycyrrhiza uralensis* Fisch.
Qian DD 2019	*Tai yuan* decoction	***Pin yin*** **names:** *Shan yao, Huang qi, Bai zhu, Bai shao, Ze lan, He ye, Sheng ma, Ba ji tain, Huang qin, Bei sha shen, Sha ren, Shui hong hua zi, Gan cao* **Plant names:** *Dioscorea oppositifolia* L., *Astragalus mongholicus* Bunge, *Atractylodes macrocephala* Koidz., *Paeonia lactiflora* Pall., *Lycopus lucidus* Turcz. ex Benth., *Nelumbo nucifera* Gaertn., *Actaea cimicifuga* L., *Morinda officinalis* F.C.How, *Scutellaria baicalensis* Georgi, *Glehnia littoralis* F.Schmidt, *Wurfbainia villosa* (Lour.) Škorničk. & A.D.Poulsen, *Persicaria orientalis* (L.) Spach, *Glycyrrhiza uralensis* Fisch.
Shen LH	*Huang lian wen dan*	***Pin yin*** **names:** *Huang lian, Zhu ru, Zhi shi, Qing ban xia, Chen pi, Fu ling, Gan cao,*

SUPPLEMENTARY MATERIAL

Study	CHM formulae/products	CHM ingredients (*Pin yin* names & plant names[a])
2014	decoction	*Sheng jiang* **Plant names:** *Coptis chinensis* Franch., *Citrus aurantium* L., *Citrus aurantium* L., *Pinellia ternata* (Thunb.) Makino, *Citrus reticulata* Blanco, *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Roscoe
Shou FY 2022	*Sheng hui* decoction	***Pin yin* names:** *Shu di huang, Shan zhu yu, Rou cong rong, Ba ji tian, Lu jiao jiao, Gui ban jiao, Fu shen, Ren shen, Gan cao, Yuan zhi, Bai jie zi, Suan zao ren, Bai zi ren, Shi chang pu* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Cornus officinalis* Siebold & Zucc., *Cistanche deserticola* Ma, *Morinda officinalis* F.C.How, Deer antler glue, Glue of tortoise plastron, *Wolfiporia cocos* (Schw.) Ryv. & Cilbn., *Panax ginseng* C.A.Mey., *Glycyrrhiza uralensis* Fisch., *Polygala tenuifolia* Willd., Sinapis alba L. , *Ziziphus jujuba var. spinosa* (Bunge) Hu ex H.F.Chow., *Platycladus orientalis* (L.) Franco, *Acorus calamus var. angustatus* Besser
Wang LL 2018	*Yang xue qing nao* granule	***Pin yin* names:** *Shu di huang, Dang gui, Chuan xiong, Bai shao, Xia ku cao, Ji xue teng, Yan hu suo, Zhen zhu mu, Xi xing, Gou teng, Jue ming zi* **Plant names:** *Rehmannia glutinosa* (Gaertn.) DC., *Angelica sinensis* (Oliv.) Diels, *Ligusticum striatum* DC., *Paeonia lactiflora* Pall., *Prunella vulgaris* L., *Spatholobus suberectus* Dunn, *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu, Nacre, *Asarum heterotropoides* F.Schmidt, *Uncaria rhynchophylla* (Miq.) Miq., *Senna tora* (L.) Roxb.
Wang XJ 2021	*San bu* recipe	***Pin yin* names:** *Gou qi zi, Huang qi, Fu ling* **Plant names:** *Lycium barbarum* L., *Astragalus mongholicus* Bunge, *Wolfiporia cocos*

SUPPLEMENTARY MATERIAL

Study	CHM formulae/products	CHM ingredients (***Pin yin*** **names & plant names[a])**
		(Schw.) Ryv. & Cilbn.
Xie LY 2015	*Bu yang hua wu* decotion	***Pin yin*** **names:** *Huang qi, Dang gui, Chuan xiong, Tao ren, Chi shao, Di long, Hong hua* **Plant names:** *Astragalus mongholicus* Bunge, *Angelica sinensis* (Oliv.) Diels, *Ligusticum striatum* DC., *Prunus persica* (L.) Batsch, *Paeonia lactiflora* Pall., *Pheretima aspergillum* (E.Perrier), *Carthamus tinctorius* L.
Xie S 2020	*Yang xue qing nao* pill	***Pin yin*** **names:** *Dang gui, Chuan xiong, Bai shao, Shu di huang, Gou teng, Ji xue teng, Xia ku cao, Jue ming zi, Zhen zhu mu, Yan hu suo, Xi xin* **Plant names:** *Angelica sinensis* (Oliv.) Diels, *Ligusticum striatum* DC., *Paeonia lactiflora* Pall., *Rehmannia glutinosa* (Gaertn.) DC., *Uncaria rhynchophylla* (Miq.) Miq., *Spatholobus suberectus* Dunn, *Prunella vulgaris* L., *Senna tora* (L.) Roxb. , Nacre, *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu, *Asarum heterotropoides* F.Schmidt
Yang JJ 2011	*Wu ling* capsule	***Pin yin*** **names:** *Wu ling jun* **Plant names:** *Xylaria nigripes* (Kl.) Sacc.

Abbreviation: CHM, Chinese herbal medicine.

[a]Plant names are sourced from the 'World Flora Online' (www.worldfloraonline.org, accessed 20 December 2023).

SUPPLEMENTARY MATERIAL

Supplementary Table S6. Most frequently used herbs in included studies.

Herb name in *Pin yin*[a]	**Number of studies**	**Plant names[b]**
Fu ling	10	*Wolfiporia cocos* (Schw.) Ryv. & Cilbn.
Chuan xiong	8	*Ligusticum striatum* DC.
Shi chang pu	8	*Acorus calamus* var. angustatus Besser
Shu di huang	8	*Rehmannia glutinosa* (Gaertn.) DC.
Dang gui	6	*Angelica sinensis* (Oliv.) Diels
Bai shao	5	*Paeonia lactiflora* Pall.
Huang qi	5	*Astragalus propinquus* Schischkin
Ren shen	5	*Panax ginseng* C.A.Mey.
Rou cong rong	5	*Cistanche deserticola* Y.C.Ma
Yuan zhi	4	*Polygala tenuifolia* Willd.

[a]Herb names in *Pin yin* were standardised based on the 2020 Pharmacopoeia of the People's Republic of China (Chinese Pharmacopoeia Commission, 2020). Herbs from the same part of a plant that were processed in different ways or were named different over time, were identified as one herb during frequency analysis.

[b]Plant names are sourced from the 'World Flora Online' (www.worldfloraonline.org, accessed 20 December 2023).

SUPPLEMENTARY MATERIAL

Supplementary Table S7. MMSE and MoCA: Baseline, End-of-Treatment, and Change scores.

Study	Cognitive assessment tool	Baseline scores (mean ± SD)/median (IQR)		EoT scores (mean ± SD)/median (IQR)		Change scores[a] (mean ± SD)	
		CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil
Gan PP 2020	MoCA	21.62 ± 2.97	21.54 ± 3.23	25.93 ± 3.25	23.76 ± 3.18	4.31 ± 3.12	2.22 ± 3.21
Gao FQ 2017	MMSE	15.79 ± 2.95	15.84 ± 2.98	24.67 ± 5.86	19.21 ± 3.62	8.88 ± 5.07	3.37 ± 3.35
	MoCA	15.82 ± 2.27	15.96 ± 2.35	27.56 ± 4.16	21.03 ± 3.28	11.74 ± 3.61	5.07 ± 2.93
Gao HR 2017	MMSE	24.08 ± 2.01	24.25 ± 1.85	28.02 ± 1.83	26.26 ± 2.01	3.94 ± 1.93	2.01 ± 1.93
	MoCA	20.46 ± 2.17	20.32 ± 2.38	26.48 ± 1.15	24.65 ± 1.36	6.02 ± 1.88	4.33 ± 2.07
Gu LL 2018	MMSE	23.60 ± 3.81	23.72 ± 3.66	27.10 ± 3.77	24.33 ± 4.02	3.50 ± 3.79	0.61 ± 3.85
Guo DW 2019	MoCA	16.29 ± 2.74	16.12 ± 2.84	24.25 ± 2.10	20.73 ± 2.57	7.96 ± 2.48	4.61 ± 2.72
Han LX 2020	MMSE	23.20 ± 1.42	23.47 ± 1.28	26.46 ± 1.34	25.16 ± 0.92	3.26 ± 1.38	1.69 ± 1.14
He JH 2017	MMSE	21.30 ± 3.20	21.40 ± 3.80	26.50 ± 3.60	23.80 ± 4.30	5.20 ± 3.42	2.40 ± 4.07
Li Q 2022	MMSE	22.75 ± 1.39	22.94 ± 1.48	27.03 ± 2.45	25.44 ± 2.51	4.28 ± 2.13	2.50 ± 2.19
	MoCA	21.53 ± 1.92	21.44 ± 1.78	25.78 ± 3.15	24.19 ± 2.9	4.25 ± 2.75	2.75 ± 2.53
Li QW 2014	MMSE	21.78 ± 1.61	21.62 ± 1.56	28.27 ± 1.63	26.47 ± 1.93	6.49 ± 1.62	4.85 ± 1.77
	MoCA	12.88 ± 2.13	13.65 ± 1.76	22.66 ± 3.68	19.19 ± 2.54	9.78 ± 3.20	5.54 ± 2.25
Li XQ 2020	MMSE	24.73 ± 0.87	24.83 ± 0.87	29.83 ± 0.46	27.77 ± 1.07	5.10 ± 0.75	2.94 ± 0.99
Liu XR 2020	MMSE	19.68 ± 2.21	20.01 ± 2.15	25.36 ± 3.56	22.56 ± 2.96	5.68 ± 3.11	2.55 ± 2.65
	MoCA	20.36 ± 2.35	20.98 ± 2.75	25.32 ± 3.89	22.35 ± 2.68	4.96 ± 3.39	1.37 ± 2.72
Ma CY 2022	MoCA	21.47 ± 2.18	21.03 ± 1.94	26.77 ± 1.14	23.27 ± 1.93	5.30 ± 1.89	2.24 ± 1.94
Qian DD 2019	MoCA	20.58 ± 1.67	20.28 ± 1.44	24.10 ± 1.74	22.47 ± 2.05	3.52 ± 1.71	2.19 ± 1.82
Shen LH 2014	MMSE	22.92 ± 1.8	22.86 ± 1.79	28.65 ± 1.78	26.73 ± 1.83	5.73 ± 1.79	3.87 ± 1.81
Shou FY 2022	MoCA	22.85 ± 3.01	22.94 ± 3.04	25.29 ± 3.44	24.03 ± 3.37	2.44 ± 3.25	1.09 ± 3.22
Wang LL 2018	MMSE	23.42 ± 3.14	23.58 ± 3.08	26.63 ± 4.05	24.53 ± 3.58	3.21 ± 3.68	0.95 ± 3.36

SUPPLEMENTARY MATERIAL

Study	Cognitive assessment tool	Baseline scores (mean ± SD)/median (IQR)		EoT scores (mean ± SD)/median (IQR)		Change scores[a] (mean ± SD)	
		CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil	CHM + Donepezil	Donepezil
Wang XJ 2021	MMSE	25(18, 27)	25(19, 27)	27(21,28)	26(21,28)	1.85 ± 5.06	1.27 ± 4.97
		[a]22.79 ± 5.19	[a]23.04 ± 5.02	[a]24.64 ± 4.92	[a]24.31 ± 4.91		
	MoCA	22(20, 24)	22(20, 24)	25(23,28)	25(22,27)		
		[a]21.95 ± 3.22	[a]21.95 ± 3.22	[a]25.52 ± 4.06	[a]24.2 ± 4.08	3.57 ± 3.71	2.25 ± 3.73
Xie LY 2015	MMSE	22.72 ± 3.09	18.26 ± 2.99	24.15 ± 3.87	20.29 ± 2.77	1.43 ± 3.54	2.03 ± 2.89
	MoCA	21.03 ± 2.25	20.55 ± 2.78	24.17 ± 3.54	21.87 ± 2.57	3.14 ± 3.10	1.32 ± 2.68
Xie S 2020	MoCA	21.69 ± 0.87	21.74 ± 0.83	26.09 ± 0.87	24.47 ± 1.26	4.40 ± 0.87	2.73 ± 1.11
Yang JJ 2011	MMSE	25.89 ± 1.93	25.02 ± 1.59	27.12 ± 2.13	26.02 ± 2.23	1.23 ± 2.04	1.00 ± 1.99
	MoCA	22.55 ± 1.28	22.06 ± 2.17	24.82 ± 2.13	23.28 ± 2.68	2.27 ± 1.86	1.22 ± 2.46

Abbreviations: CHM, Chinese herbal medicine; EoT, end of treatment; IQR, interquartile range; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SD, standard deviation.

[a]Change scores: None of the included studies provided direct information on the change scores in MMSE and MoCA. Consequently, we computed the mean and SD of the change scores utilising their baseline and EoT scores, employing the methodology outlined in the Cochrane handbook (https://training.cochrane.org/handbook/current/chapter-06#section-6-5-2-3).

SUPPLEMENTARY MATERIAL

Supplementary Table S8. Grade assessment for MMSE and MoCA.

Outcomes	No. RCTs	No. participants	MD [95%CI], I^2	Certainty of the evidence (GRADE)
MMSE	12	993	1.88 [1.52, 2.24], 41%	Moderate[a]
MoCA	11	854	2.01 [1.57, 2.44], 52%	Low[a, b]

Abbreviations: CI: confidence interval; I^2: index of heterogeneity; MD, mean difference; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RCT: randomised controlled trial.

[a] Downgraded 1 level due to the presence of risk of bias.

[b] Downgraded 1 level due to inconsistency.

SUPPLEMENTARY MATERIAL

Supplementary Table S9. Summary of adverse events.

Study	CHM + Donepezil	Donepezil
Gan PP 2020	0	2 participants reported gastrointestinal discomfort 1 participant reported headache, dizziness
Gao FQ 2017	3 participants reported dizziness 2 participants reported headache 1 participant reported flushed face 2 participants reported vomit	2 participants reported dizziness 1 participant reported headache 1 participant reported hypotension 1 participant reported vomit
Gao HR 2017	No information	No information
Gu LL 2018	1 participant reported abnormal complete blood count	2 participants reported severe insomnia 1 participant reported abnormal liver function
Guo DW 2019	No information	No information
Han LX 2020	0	0
He JH 2017	2 participants reported muscle spasms 3 participants reported insomnia 2 participants reported gastrointestinal discomfort	1 participant reported muscle spasm 2 participants reported insomnia 1 participant reported gastrointestinal discomfort
Li QW 2014	No information	No information
Li XQ 2020	No information	No information
Li Q 2022	2 participants reported dizziness	2 participants reported tinnitus 1 participant reported mild insomnia 2 participants reported constipation

SUPPLEMENTARY MATERIAL

Study	CHM + Donepezil	Donepezil
Liu XR 2020	No information	No information
Ma CY 2022	0	0
Qian DD 2019	0	3 participants reported gastrointestinal discomfort with diarrhea
Shen LH 2014	4 participants reported nausea 8 participants reported diarrhea 2 participants reported insomnia	5 participants reported nausea 7 participants reported diarrhea 3 participants reported insomnia
Shou FY 2022	No information	No information
Wang LL 2018	No information	No information
Wang XJ 2021	2 participants reported fatigue	1 participant reported nausea 3 participants reported fatigue
Xie LY 2015	No information	No information
Xie S 2020	No information	No information
Yang JJ 2011	2 participants reported insomnia	1 participant reported insomnia

Abbreviation: CHM, Chinese herbal medicine.

SUPPLEMENTARY MATERIAL

Supplementary Table S10. Frequency distribution of different adverse events.

AEs	No. of studies	No. of participants reported AEs	
		CHM + Donepezil	Donepezil
Gastrointestinal symptoms (vomiting/nausea/diarrhea/constipation)	7	16	22
Insomnia	5	7	9
Headache/dizziness	4	8	4
Fatigue	1	2	3
Muscle spasms	1	2	1
Tinnitus	1	0	2
Flushed face	1	1	0
Hypotension	1	0	1
Abnormal complete blood count	1	1	0
Abnormal liver function	1	0	1

Notes: AEs, adverse events; CHM, Chinese herbal medicine.

SUPPLEMENTARY MATERIAL

Supplementary Table S11. Pharmacological mechanisms of *Kai xin san* and *Si wu* decoction

Formula	Composition	Pharmacological mechanisms [1-16]
Kai xin san	*Panax ginseng* C.A.Mey. (*Ren shen*) *Polygala tenuifolia* Willd. (*Yuan zhi*) *Acorus calamus* var. angustatus Besser (*Shi chang pu*) *Wolfiporia cocos* (Schw.) Ryv. & Cilbn. (*Fu ling*)	• Modulates the cholinergic system • Mitigates damage to synaptic plasticity • Attenuates tau hyperphosphorylation and neuroinflammation • Suppresses neuronal apoptosis and oxidative stress • Increases the expressions of nerve growth factor and brain-derived neurotrophic factor.
Si wu decoction	*Ligusticum striatum* DC. (*Chuan xiong*) *Rehmannia glutinosa* (Gaertn.) DC. (*Shu di huang*) *Angelica sinensis* (Oliv.) Diels (*Dang gui*) *Paeonia lactiflora* Pall. (*Bai shao*)	• Reduces β amyloid deposition, tau phosphorylation and neuroinflammation • Modulates the cholinergic system and restores cholinergic neuron function • Inhibits neuronal apoptosis and enhances synaptic plasticity • Provides neuroprotective, anti-inflammatory and antioxidant effects • Suppresses microglial activation and neurotoxicity • Mitigates mitochondrial dysfunction, regulates autophagy and balances intestinal flora.

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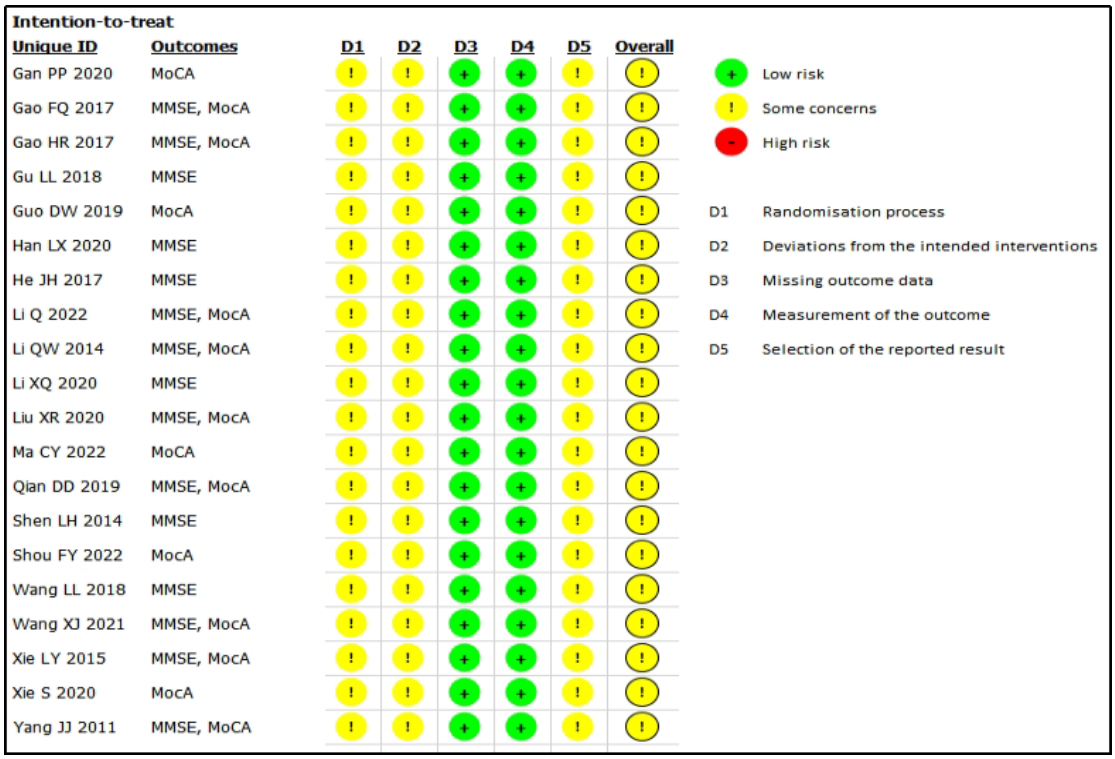
SUPPLEMENTARY MATERIAL

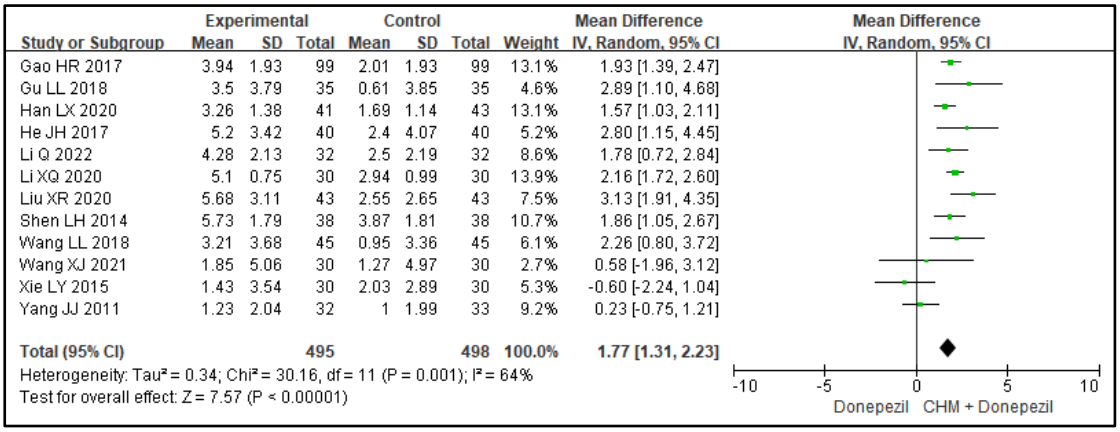
Supplementary Figure S1.



Supplementary Figure S1. Risk of bias in included studies.

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

Supplementary Figure S2.

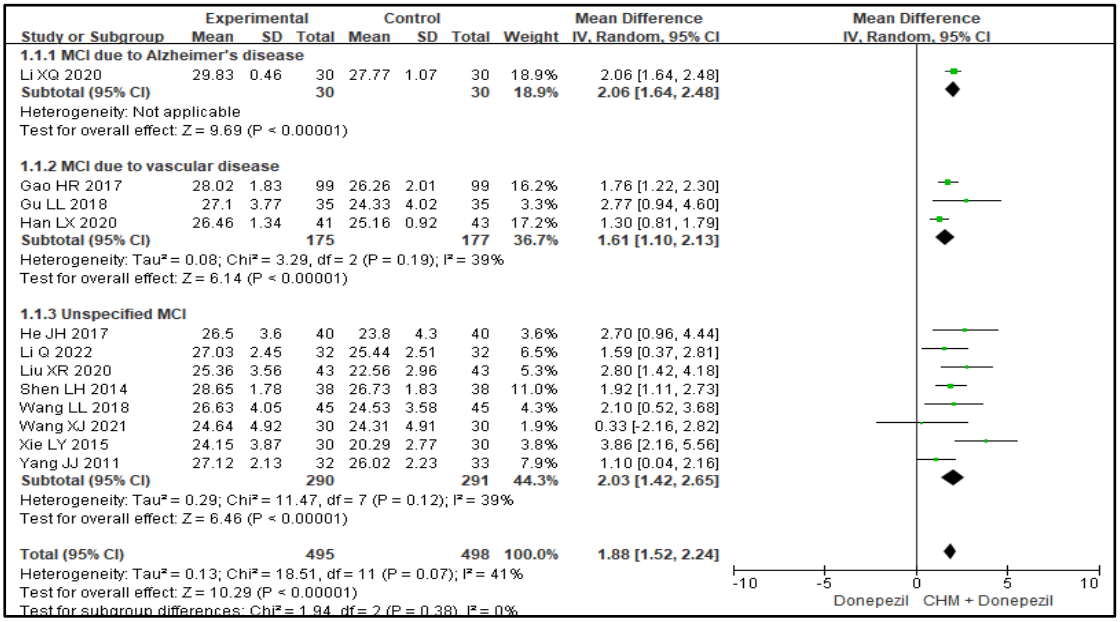


Supplementary Figure S2. Overall meta-analysis on change scores of MMSE.

Abbreviation: CHM, Chinese herbal medicine.

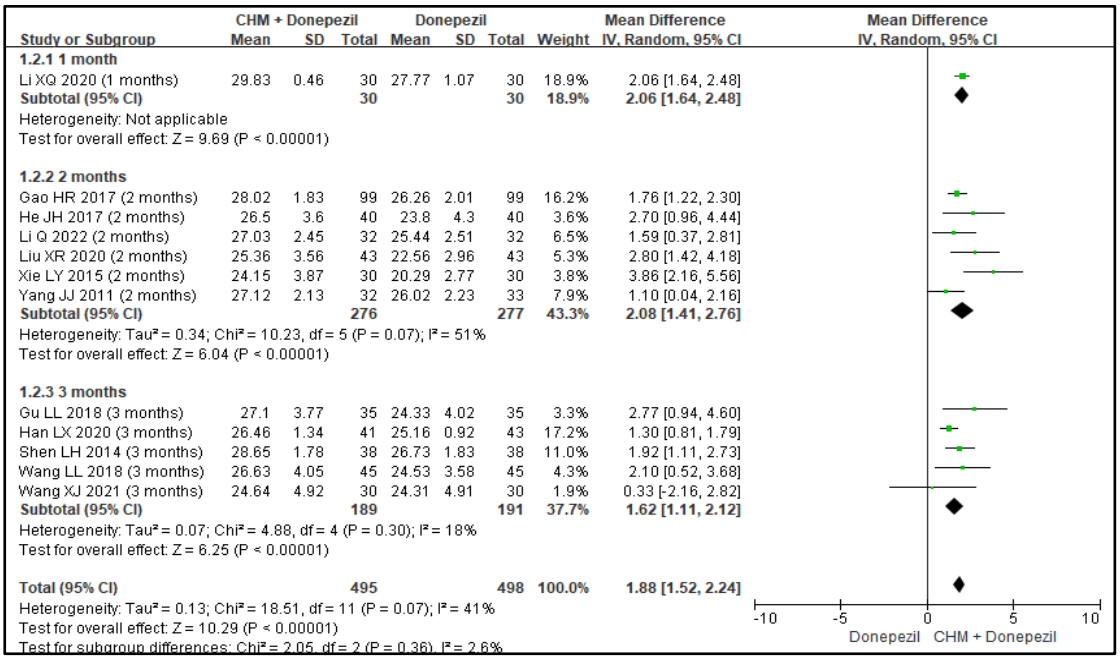
SUPPLEMENTARY MATERIAL

Supplementary Figure S3.



Supplementary Figure S3. Subgroup analysis on MMSE at the end of treatment (based on the MCI subtypes).

Supplementary Figure S4.



Supplementary Figure S4. Subgroup analysis on MMSE at the end of treatment (based on the treatment duration).

SUPPLEMENTARY MATERIAL

Supplementary Figure S5.

Meta-regression — Number of obs = 12
REML estimate of between-study variance — tau2 = .1617
% residual variation due to heterogeneity — I-squared_res = 45.54%
Proportion of between-study variance explained — Adj R-squared = -71.62%
With Knapp-Hartung modification

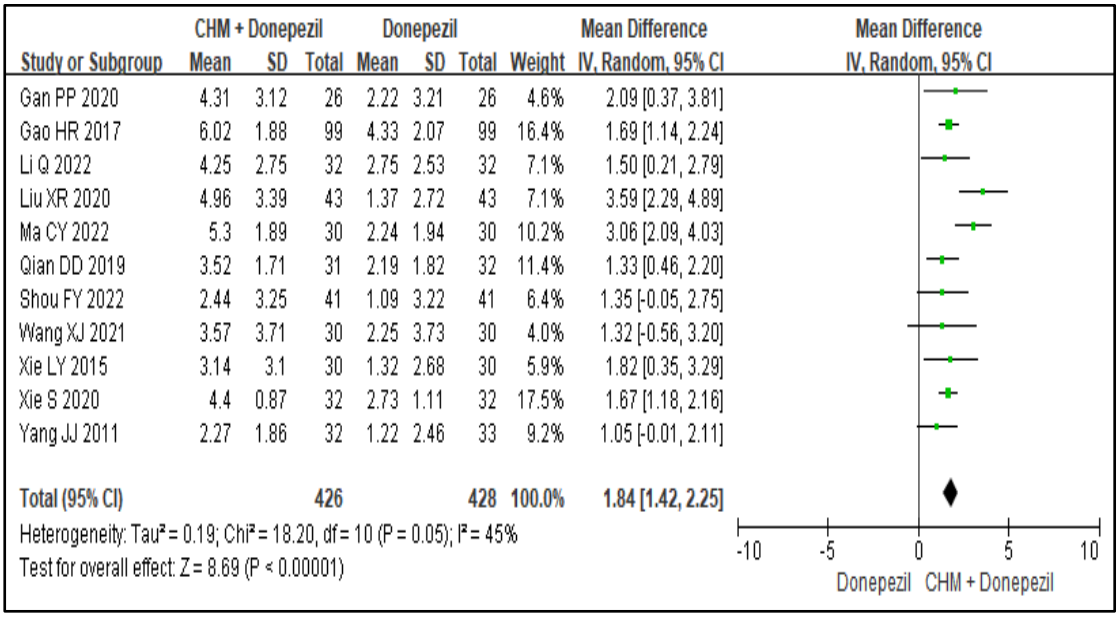
_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
subtype	.0475947	.2770052	0.17	0.867	-.5696113	.6648007
_cons	1.783822	.6658779	2.68	0.023	.3001537	3.26749

Meta-regression — Number of obs = 12
REML estimate of between-study variance — tau2 = .0581
% residual variation due to heterogeneity — I-squared_res = 34.53%
Proportion of between-study variance explained — Adj R-squared = 38.35%
With Knapp-Hartung modification

_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
duration	-.237533	.2321549	-1.02	0.330	-.7548063	.2797403
_cons	2.359516	.5277984	4.47	0.001	1.183508	3.535524

Supplementary Figure S5. Univariate meta-regression analyses for the end-of-treatment effects on MMSE.

Supplementary Figure S6.

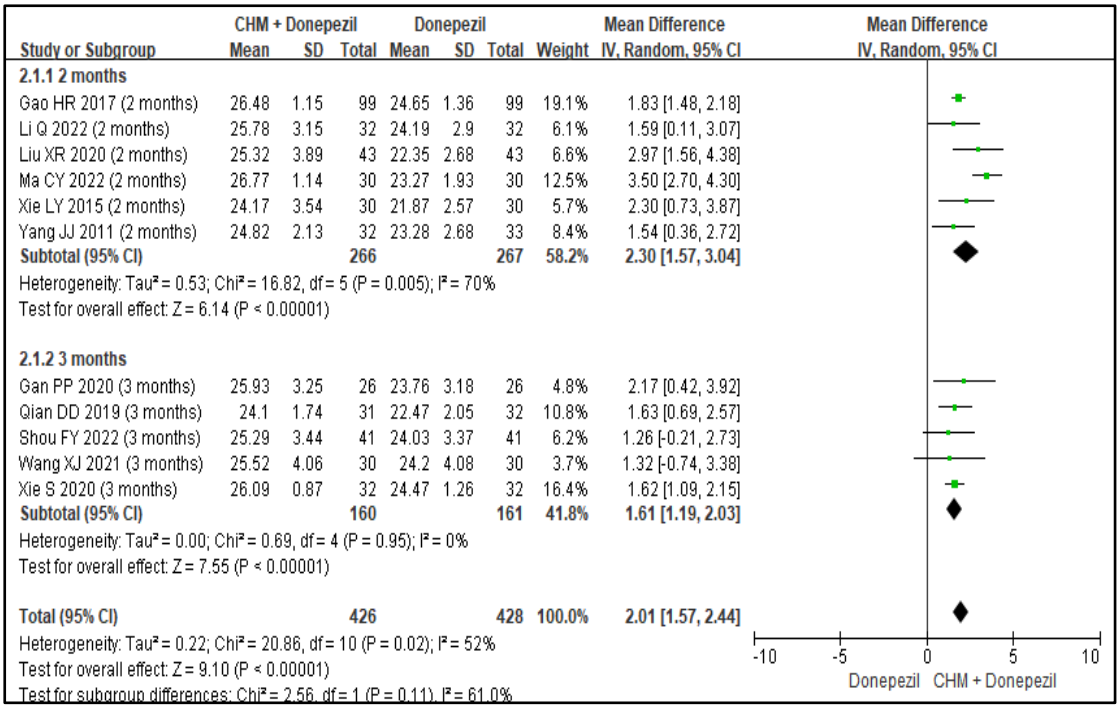


Supplementary Figure S6. Overall meta-analysis on change scores of MoCA.

Abbreviation: CHM, Chinese herbal medicine.

SUPPLEMENTARY MATERIAL

Supplementary Figure S7.



Supplementary Figure S7. Subgroup analysis on MoCA at the end of treatment (based on the treatment duration).

Supplementary Figure S8.

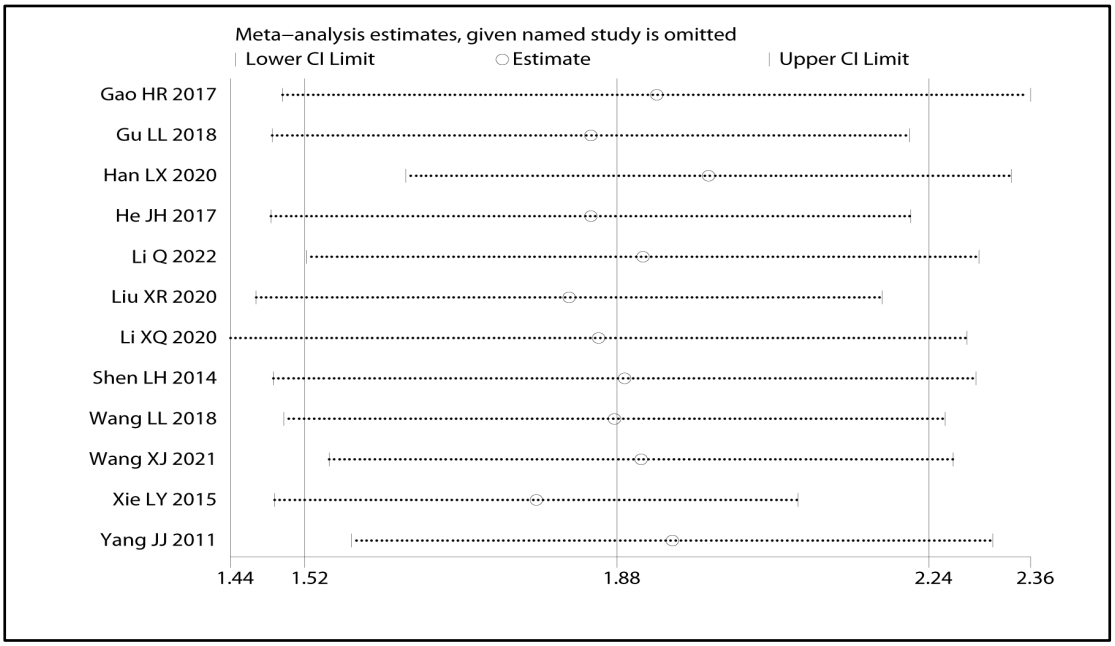
Meta-regression — Number of obs = 11
REML estimate of between-study variance — tau2 = .2413
% residual variation due to heterogeneity — I-squared_res = 48.60%
Proportion of between-study variance explained — Adj R-squared = 17.44%
With Knapp-Hartung modification

_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
duration	-.6907204	.4566105	-1.51	0.165	-1.723645	.3422042
_cons	3.677963	1.127212	3.26	0.010	1.128032	6.227893

Supplementary Figure S8. Univariate meta-regression analysis for the end-of-treatment effects on MoCA.

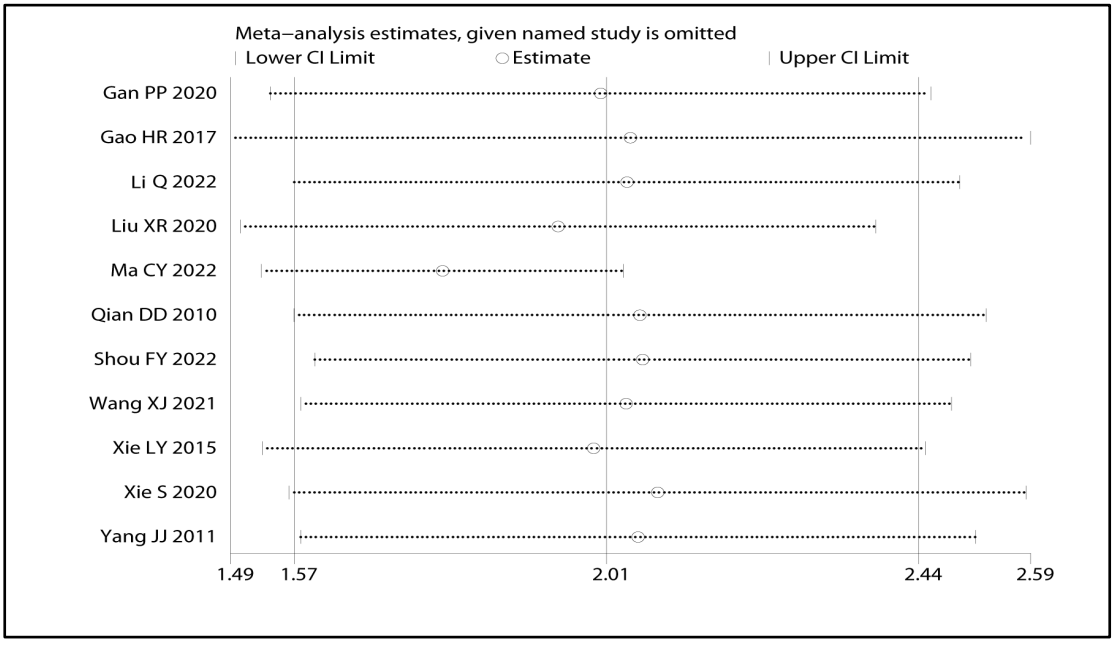
SUPPLEMENTARY MATERIAL

Supplementary Figure S9.



Supplementary Figure S9. Sensitivity analysis based on MMSE (one-by-one exclusion method).

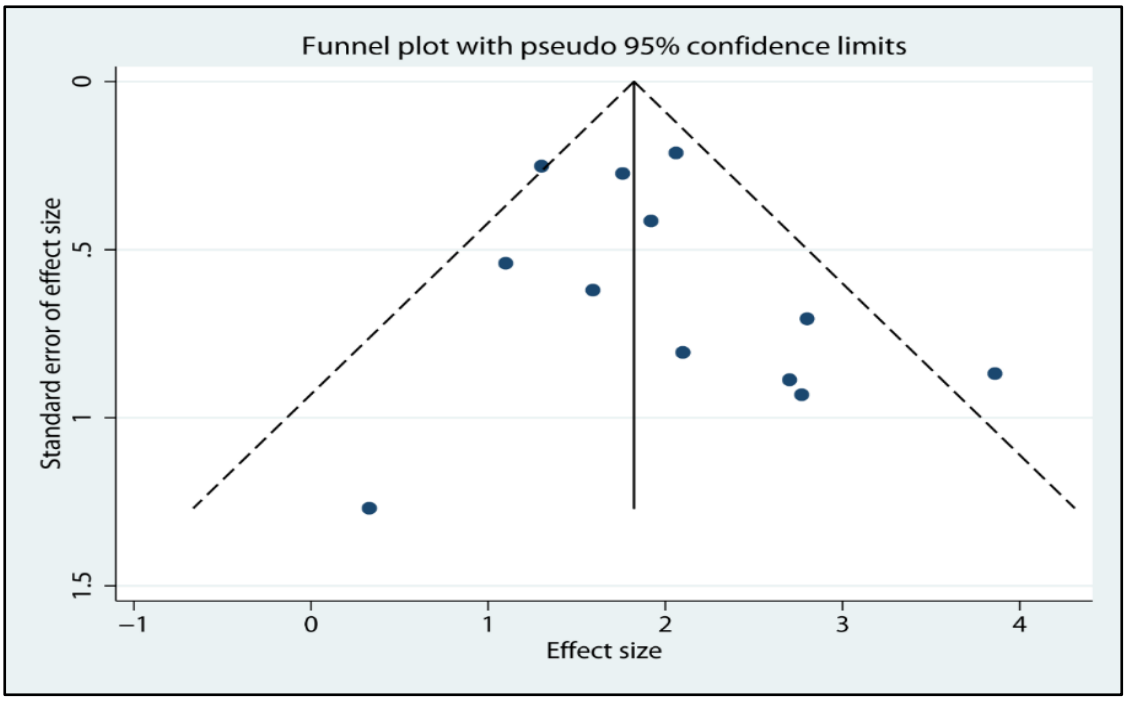
Supplementary Figure S10.



Supplementary Figure S10. Sensitivity analysis based on MoCA (one-by-one exclusion method).

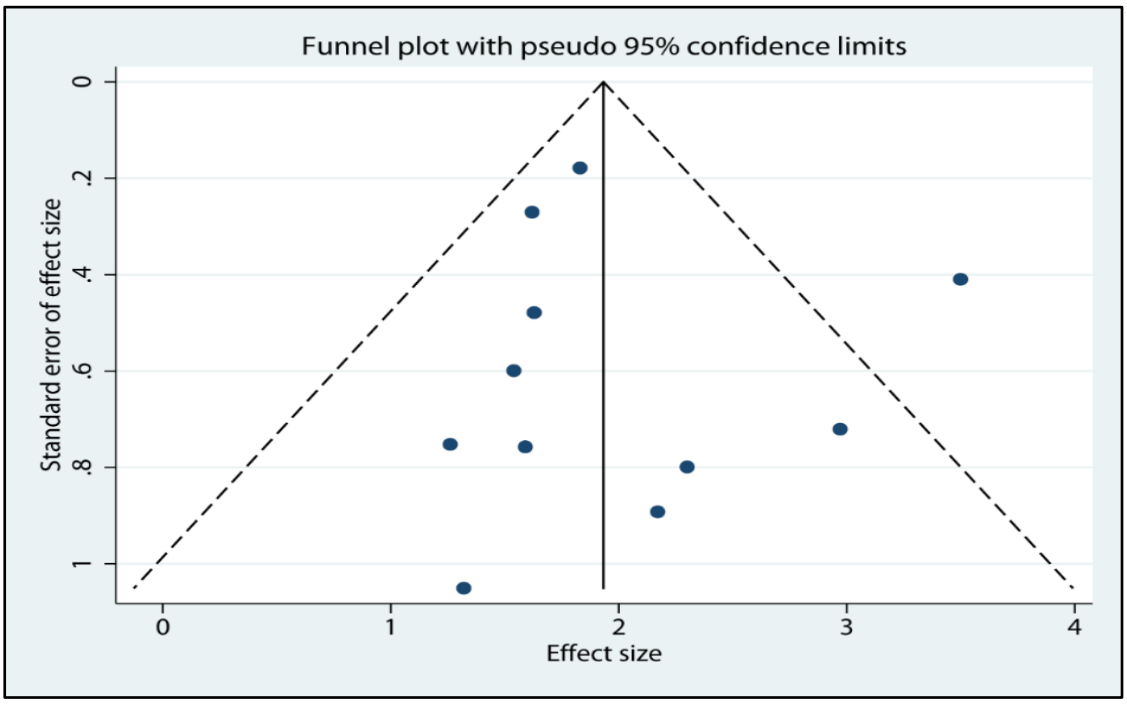
SUPPLEMENTARY MATERIAL

Supplementary Figure S11.



Supplementary Figure S11. Funnel plot of studies reporting MMSE at the end of treatment.

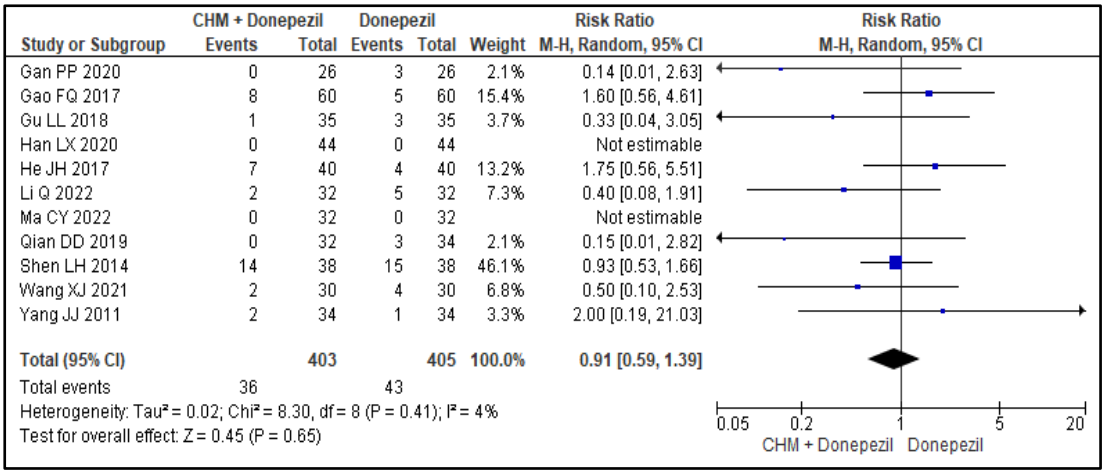
Supplementary Figure S12.



Supplementary Figure S12. Funnel plot of studies reporting MoCA at the end of treatment.

SUPPLEMENTARY MATERIAL

Supplementary Figure S13.



Supplementary Figure S13. Meta-analysis on adverse events at the end of treatment.