Biochemical Pharmacology 141 (2017) 143–155

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Chinese herbal medicine for Alzheimer's disease: Clinical evidence and possible mechanism of neurogenesis

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ARTICLE INFO

Article history:
Received 31 March 2017
Accepted 5 July 2017
Available online 8 July 2017

Chemical compounds studied in this article:
Catalpol (PubChem CID: 91520)
Liquiritin (PubChem CID: 503737)
Glabridin (PubChem CID: 124052)
Astragaloside IV (PubChem CID: 13943297)
Tanshinone I (PubChem CID: 114917)
Salvianolic acid A (PubChem CID: 5281793)
Ginsenoside Rg1 (PubChem CID: 441923)
Ginsenoside Rb1 (PubChem CID: 9898279)
Icariin (PubChem CID: 5318997)
Tetramethylpyrazine (PubChem CID: 14296)

Keywords:
Dementia
Traditional Chinese medicine
Neurogenesis
Mini-Mental State Examination
Systematic review

ABSTRACT

Currently, there is lack of cure or disease-modifying treatment for Alzheimer's disease (AD). Chinese herbal medicine (CHM) is purported to ameliorate AD progression, perhaps by promoting hippocampal neurogenesis. Here, we conducted an updated systematic review to investigate the efficacy and safety of CHM for AD based on high-quality randomized controlled trials (RCTs) and reviewed its possible mechanisms of neurogenesis according to animal-based researches. Twenty eligible studies with 1767 subjects were identified in eight database searches from inception to February 2017. The studies investigated the CHM versus placebo (n = 3), CHM versus donepezil (n = 9 with 10 comparisons), CHM plus donepezil versus donepezil (n = 3), CHM versus a basic treatment (n = 3), and CHM plus basic treatment versus basic treatment (n = 2). Adverse events were reported in 11 studies, analyzed but not observed in 3 studies, and not analyzed in 6 studies. The main findings of present study are that CHM as adjuvant therapy exerted an additive anti-AD benefit, whereas the efficacy of CHM as a monotherapy was inconclusive. Additionally, CHMs were generally safe and well tolerated in AD patients. Active molecules in frequent constituents of CHMs can alter multiple critical signaling pathways regulating neurogenesis. Thus, the present evidence supports, to a limited extent, the conclusion that CHM can be recommended for routine use in AD patients and its possible mechanism enhances adult hippocampal neurogenesis through activating the multi-signal pathways.

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive; ADL, Activities of Daily; Aβ, β-amyloid protein; bid, bis in die; BDNF, brain derived neurotrophic factor; ChEIs, cholinesterase inhibitors; CHM, Chinese herbal medicine; CI, confidence intervals; CREB, cAMP response element-binding protein; DSM, Diagnostic and Statistical Manual of Mental Disorder; eIF2α, eukaryotic initiation factor α; EMBASE, Excerpta Medica database; ERK, Extracellular signal regulated kinase; FEM, fixed-effects model; Fig., figure; g, gram; GRb1, Ginsenosides Rb1; GRg1, Ginsenosides Rg1; GSH-Px, glutathione peroxidase; GSK3, Glycogen Synthase Kinase-3; HO-1, heme oxygenase-1; ICD, International Classification of Disease; ICR, Institute of Cancer Research; ITT, intent-to-treatment; MD, mean difference; MDA, malondialdehyde; MEK, Methyl Ethyl Ketone; mg, milligram; ml, milliliter; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrah ydropyridine; NPI, Neuropsychiatric Inventory Patient-assessment Rating; NPCs, neural progenitor cells; NPI-Q, Neuropsychiatric Inventory Brief Questionnaire Form; Nrf 2, nuclear factor erythroid 2-related factor 2; NSCs, neural stem cells; n_T/n_C, $n_{Treatment}/n_{Control}$; PERK, protein kinase R-like ER kinase; PI3K, phosphatidylinositol 3-kinase; p.o., per os; qd, quaque die; qn, quaque nocte; PPARg, peroxisome proliferator-activated receptor-g; qd, quaque die; RCT, randomized clinical trial; REM, random-effects model; RoB, risk of bias; SMD, standard mean difference; SOD, super oxide dismutase; TCM, Traditional Chinese medicine; TrkB, Tyrosine kinase B; tid, ter in die; vs., versus; w, week (s).

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http://dx.doi.org/10.1016/j.bcp.2017.07.002
0006-2952/

1. Introduction

According to the 2016 World Alzheimer Report produced by Alzheimer's Disease International, there were about 47 million people living with memory loss globally as of 2015, and this figure is expected to rapidly to 131.5 million by 2050 due to increasing life expectancy [1]. Alzheimer's disease (AD) is a major cause of dementia, accounting for up to 70% of all cases of dementia [2]. It is associated with substantial healthcare challenges, creating an economic burden for both societies and healthcare providers [3].

The diagnosis of AD, for which there is no definitive diagnostic test or reliable biomarker, is based on a combination of clinical examinations and biomarker information [4]. Meanwhile, the conventional medicine for AD, namely cholinergic enhancing cholinesterase inhibitors (ChEIs; e.g., donepezil, galantamine, and rivastigmine) and non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., memantine) provide only symptomatic relief [5]. Thus far, these drugs slow the symptomatic progression of AD, without reducing or halting the underlying pathology [6]. Thus, novel treatments that can prevent or delay the onset of the clinical symptoms of AD, or that can slow, or even halt, the progression of AD are urgently needed [7].

Traditional Chinese medicine (TCM) is an ancient and holistic approach to health and healing [8]. It was the commonly available mode of healthcare throughout eastern Asia before modern Western medicine was introduced to these regions [9]. TCM, including Chinese herbal medicine (CHM), acupuncture, and other non-pharmacological therapies, is still used widely in China and elsewhere in the world [10]. CHM has been used to treat memory impairment for thousands of years and has a long, rich history [11]. There are a number of traditional herbs that continue to be used contemporarily for AD and have been reported to have biological activities that improve learning and memory; the suggested mechanisms of benefit are manifold, including protecting neurons from damage by β-amyloidprotein (Aβ), inhibiting secretion of Aβ, decreasing tau hyperphosphorylation, increasing synthesis of acetylcholine, antioxidant functions, anti-inflammatory actions, and suppression of apoptosis [12,13]. Several systematic reviews have supported the view that CHM can improve dementia [14–18]. However, there is not yet sufficient evidence to support routine use of CHMs for AD due to the poor methodological quality of the primary studies, as indicated by the Cochrane group guidelines for clinical reviews, which calls for the strict exclusion of "not-so-good" studies [19]. Thus, based on our previous meta-analysis study design [20], we conducted an updated systematic review to evaluate the efficacy and safety of CHM for AD, including only high-quality studies that met the requirements of at least 4 of the 7 domains of the Cochrane risk of bias (RoB) tool.

Adult neurogenesis occurs selectively in certain parts of human body, including the olfactory system, dentate gyrus of the hippocampus, and subventricular zone. The hippocampus is critical for learning and memory and is especially vulnerable to damage in early-stage AD [21]. Recent findings suggest that adult hippocampal neurogenesis is important for cognitive functions affected in both animal models of AD and patients with AD [22]. Alterations in adult hippocampal neurogenesis are considered to be an integral part of AD. Neuronal stem/progenitor cells (NSCs/NPCs) in the hippocampus can be regulated by intrinsic and extrinsic agents, such as dietary components and herbal supplements [23,24]. Because CHMs, and/or their active ingredients can activate multiple signaling pathways involved in neurogenesis, there is great interest in examining their neurogenic potential in the hippocampus and whether they represent a novel biochemical AD treatment [25]. Thus, another objective of present study was to explore the mechanism of neurogenesis in AD after a CHM intervention.

2. Methods

2.1. Search strategy and study selection

To identify studies of CHM for AD, electronic searches were performed in four English databases (PubMed, EMBASE, Web of Science, and Cochrane Library) and four Chinese databases (VIP information database, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Data Information Site) from the inception up to February 2017. The search terms were as follows: (traditional Chinese medicine OR herb* OR herbal medicine OR decoction OR integrative medicine) AND (Alzheimer's disease OR Alzheimer's dementia OR senile dementia OR dementia OR cognitive disorder OR cognitive impairment) AND (randomized controlled trial OR controlled clinical trial OR clinical trial OR clinical study OR control* study OR random* trial OR random* study OR clinical observ*). All search terms were used in both the English and Chinese database searches. Conference proceedings, dissertations, and reference lists of retrieved articles were also searched manually for additional relevant studies.

According to the prespecified inclusion and exclusion criteria, two authors (WTY and XWZ) identified the eligible studies independently by reading each study title, abstract, and full text. A discussion with the corresponding author (GQZ) was conducted to solve any discrepancies.

2.2. Inclusion and exclusion criteria

2.2.1. Type of study

Randomized controlled trials (RCTs) that assessed the efficacy and safety of CHM for AD were included, regardless of language. If the study had a three-arm design, we extracted data only for the group(s) involving CHM and the control group(s). Quasi-randomized trials, such as those in which patients were allocated according to date of birth and order of admission number were excluded.

2.2.2. Participants

All participants were patients with a diagnosis of AD based on one of the following criteria: (i) The Diagnostic and Statistical Manual of Mental Disorder (DSM) III, III-R, IV or IV-R; (ii) The International Classification of Disease (ICD) (9th or 10th edition); (iii) The National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS/ADRDA); (iv) Chinese Classification of Mental Disorders (CCMD-3). Diagnostic criteria made by other authors with comparable definitions were also used. Studies containing participants suffering from other types of dementia were excluded.

2.2.3. Interventions

Analyzed interventions included CHMs used as monotherapies or in combination with conventional medicine or basic treatment (i.e., supportive treatment other than non-conventional medicine). Comparator interventions were restricted to no intervention, placebo, conventional medicine (i.e., ChEI and/or NMDA receptor antagonist), and basic treatment. Studies comparing a CHM agent with another TCM agent were excluded. Co-intervention applied in all arms was allowed.