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The effectiveness and safety of Jihwang-eumja (Dihuang Yizi) compared to Western medications in patients with Alzheimer's disease: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: Jihwang-eumja is reported to be effective in decreasing β-amyloid expression and activating monoamine oxidase and acetylcholinesterase in rat models. This systematic review aims to evaluate the effectiveness of Jihwang-eumja in Alzheimer's disease compared to Western medications.

Methods: We searched Medline, Embase, CENTRAL, CINAHL, CNKI, ScienceON, KISS, and Kmbase. Randomized controlled trials comparing the effectiveness of Jihwang-eumja and Western medications on the cognition and the activities of daily living in Alzheimer's disease were included. The results were synthesized using meta-analysis. The risk of bias was evaluated using the Cochrane risk-of-bias tool, and the evidence level of each outcome was suggested using the GRADE system.

Results: A total of 165 studies were screened, and six were included in the systematic review and meta-analysis. A total of 245 and 240 participants were included in the intervention and comparison groups, respectively. The results showed that Mini-Mental State Examination was 3.19 (95%CI: 1.68–4.70) higher, and the standardized mean difference of activities of daily living was 1.13 (95%CI: 0.89–1.37) higher in the Jihwang-eumja group than in Western medications group. The included studies contained some concerns of the risk of bias, and the certainty of the evidence was considered moderate.

Conclusion: Despite the small number of studies and high heterogeneity, we could verify the applicability of Jihwang-eumja for Alzheimer's disease.

1. Introduction

Dementia is a complicated neurocognitive syndrome characterized by severe impairment in memory, orientation, understanding, calculation, learning, language, and judgment. Dementia is usually diagnosed when symptoms are severe enough to disturb social activities and personal relationships [1].

Over 55 million people have dementia worldwide, and it is estimated to reach 78 million by 2030 [2]. The total economic costs caused by dementia were 279.6 billion dollars in 2000 and increased by 948 billion dollars in 2016, with an annual growth rate of 15.94% [3]. Thus, dementia is considered one of the main burdens of an aging society.

In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), dementia is classified as a major neurocognitive disorder and its subtype is determined by its underlying etiology and cause. The most common subtype is Alzheimer's disease (AD), which accounts for approximately 63.6% of all dementia cases, including 42.0% of AD cases and 21.6% of cases of combined pathology of Alzheimer's disease and vascular dementia [4]. AD is characterized by progressive loss of synapses and neurons, accumulation of amyloid plaques, neurofibrillary tangles, and prominent cholinergic deficits. Additionally, the hippocampus and cerebral cortex atrophy occur at the microscopic level [5,6].

Currently, pharmacological treatment is only symptomatic and is unsatisfactory for permanently stabilizing the disease [6]. Acetylcholinesterase inhibitors are used to improve the cholinergic function, and N-methyl-D-aspartate antagonists are used to alleviate neuropsychiatric

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symptoms by decreasing glutamate-induced excitotoxicity and neurodegeneration [6]. However, side effects have been reported in 15–78% of the cases, including gastrointestinal symptoms, headache, insomnia, agitation, confusion, and cardiac arrhythmia [7].

In traditional Korean medicine, various herbal medications have been studied for AD. In 2016 and 2020, systematic reviews revealed the potential effects of herbal medicines on cognition, the activities of daily living (ADL), and the behavioral and psychological symptoms of dementia in patients with AD [8,9]. Nevertheless, these studies mainly included herbal medicines and single herb extracts, leading to difficult clinical applications in traditional Korean medicine.

Jihwang-eumja is initially found in <Seongjechongnok> [10] and introduced in the 'Wind' part of <Donguibogam, Miscellaneous disorders 1> [11] that treats disabled legs and dysarthria caused by kidney insufficiency, rendering qi incapable of reaching under the tongue. Of these, renal insufficiency is considered the main pathogenesis of dementia in Korean traditional medicine [12]. It was reported that Jihwang-eumja was more effective than donepezil in decreasing β-amyloid expression levels in rat brain tissue [13]. In addition, another study showed that Jihwang-eumja reduced the activation of monoamine oxidase and acetylcholinesterase in a rat model [14].

To date, however, no clinical studies or systematic reviews have investigated the clinical effectiveness of Jihwang-eumja in patients with AD. Based on the medical classics and experimental evidence, a systematic review and meta-analysis were conducted in this study to verify the effectiveness and safety of Jihwang-eumja compared to Western medications in cognitive function and ADL in patients with AD.

2. Methods

This study was registered in Open Science Framework (OSF Registration DOI: 10.17605/OSF.IO/HXA58), and the protocol of this systematic review was published in Medicine on May 14, 2021 (https://doi.org/10.1097/MD.0000000000025592).

2.1. Search strategies

The key clinical question was developed based on the participants, intervention, comparison, outcome, and study design (PICOS) format. P is for patients with AD, I is for Jihwang-eumja, C is for Western medications, O is for cognitive function and ADL, and S is for randomized controlled trials (RCTs). Eight electronic databases were searched on November 30, 2021, without language restriction or date limits: Medline, Embase, CENTRAL, CINAHL, CNKI, ScienceON, KISS, and Kmbase. For including grey literature, thesis papers were searched from CNKI and ScienceON. Search terms were composed using the controlled vocabulary, based on the keywords 'Alzheimer' for participants and 'Jihwang-eumja' or 'Dihuang Yinzi' for interventions (Appendix). EndNote X7.8 was used to save the search results and manage the literature throughout the study.

2.2. Eligibility criteria

Searched literature was assessed for eligibility for a systematic review and meta-analysis according to the inclusion/exclusion criteria. The eligibility criteria were organized by PICOS format. Two researchers (JYK and JYL) separately performed the selection process; they first screened the literature with the title and abstract and then cross-checked with each other. In case of disagreement, the full texts were reviewed by a third researcher (ICJ).

2.2.1. Study design

Only RCTs were included and non-randomized trials, cohort studies, case-control studies, case series, cross-sectional studies, case reports, reviews, and animal or cell research were excluded.

2.2.2. Participants

Participants with major neurocognitive disorder and diagnosed with AD according to specific diagnostic criteria were included. No restrictions were imposed on age, sex, nationality, race, inpatient or outpatient, or medical history.

2.2.3. Interventions

The form of Jihwang-eumja was unlimited; various forms such as decoction, capsules, granules, and powder were included. Modified prescriptions were included if they contained the basic components of Jihwang-eumja (*Rehmanniae Radix Preparata, Morindae Radix, Cornus officinalis Siebold et Zuccarini, Cistanche deserticola Y. C. Ma, Dendrobii Caulis, Polygalae Radix, Schisandra chinensis Baillon, Poria sclerotium, Liriope platyphylla Wang et Tang, Aconiti Lateralis Radix Preparata, Cinnamomi Cortex, Acorus gramineus Solander, Menthae Herba, Zingiberis Rhizoma Recens, and Zizyphi Fructus*) [15]. Combined interventions with Western medications, other herbal medicines, acupuncture, moxibustion, and cognitive training were excluded.

2.2.4. Comparisons

Only the studies using Western medications as comparisons were included. The studies using a placebo, herbal medicines, acupuncture, or Jihwang-eumja combined with other herbal medicine or acupuncture as comparisons were excluded.

2.2.5. Outcome measures

2.2.5.1. Primary outcomes. The Mini-Mental State Examination (MMSE), Montreal cognitive assessment (MoCA), Alzheimer's disease assessment scale–cognitive subscale (ADAS-cog), and Hasegawa dementia scale (HDS) were selected as the primary outcomes.

2.2.5.2. Secondary outcomes. The ADL scale was selected for the assessment of the functions of daily living. Adverse events (AEs) and medical examinations for safety evaluations were recorded. However, the effective ratio was excluded because of inconsistent definitions in the literature.

2.3. Data extraction

The data of the included studies were independently extracted by two researchers (JYK and JYL). Study design, intervention, comparison, treatment duration, follow-up, outcome measures, results (mean, SD, and quartiles), and AEs were recorded in Excel. Among the various reported outcomes, we extracted the data related to cognition and ADL.

2.4. Risk of bias assessment

The quality of the included RCTs was evaluated using the revised Cochrane risk-of-bias tool (ROB 2.0) [16], which consists of five items:

(1) bias arising from the randomization process
(2) bias due to deviations from intended interventions, bias due to missing outcome data
(3) bias in the measurement of the outcome
(4) bias in the selection of the reported result

Two researchers (JYK and JYL) independently assessed the risk of bias, and the third researcher (ICJ) reviewed any conflicting opinions.

2.5. Data synthesis and analysis

Meta-analysis was conducted for the outcomes measured in at least two studies, using RevMan version 5.4 provided by the Cochrane Collaboration. Continuous data were presented as mean ± standard

deviation (SD) and quartiles. For the AEs, the relative risks were estimated and synthesized. In the case of high heterogeneity between studies or synthesizing different outcome measures, the standardized mean difference (SMD) was adopted. A 95% confidence interval (CI) and p-value of less than 0.05 were considered statistically significant. The sample means and SD were estimated from the interquartile range according to the method described by Wan et al. which provides improved estimation by incorporating the information of the sample size [17]. For the meta-analysis, a random effect model was applied if the number of studies was higher than five. A fixed-effect model was used when the number was equal to or smaller than five. The heterogeneity was discussed from both clinical and statistical perspectives. Statistical heterogeneity was evaluated as follows: low heterogeneity for I^2<25%, moderate heterogeneity for I^2 25%–75%, and high heterogeneity for I^2>75%. We did not conduct a subgroup analysis due to the small number of included studies.

2.6. GRADE assessment for clinical recommendations

The evidence level across the included studies was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool [18] for clinical recommendations. The evidence was suggested in a summary of findings table, and the risk of bias was evaluated at the outcome level in terms of inconsistency, indirectness, imprecision, publication bias into 'not serious', 'serious', and 'very serious'. The certainty of the evidence was classified as follows: 'high', 'moderate', 'low', and 'very low'. Two researchers (JYK and JYL) independently performed the GRADE assessment, and the third researcher (ICJ) arranged any conflicting decisions.

3. Results

3.1. Searched literature

A total of 165 studies were identified from the eight databases.. After the duplicated records were removed (n = 163), two researchers independently screened the articles by title and abstract (n = 12). After assessing full-text articles, one RCT that studied Jihwang-eumja as an add-on therapy, one RCT that measured only depressive symptoms, three case series, and one RCT that included participants with vascular dementia were excluded. Finally, six studies were included in this systematic review and quantitative synthesis (Fig. 1).

3.2. Summary of the included studies

The six included studies were RCTs published in China (Table 1). In Zhang (2006) [19], 56 participants were diagnosed with AD according to the DSM-IV and with the deficiency of kidney syndrome complicated with phlegm and blood stasis by pattern identification. Participants were randomly divided into Jihwang-eumja and pyritinol hydrochloride groups and were treated for 60 days. After the treatment, the MMSE ($p < 0.01$), HDS ($p < 0.01$), and Functional Activities Questionnaire (FAQ) ($p < 0.01$) were more improved in the Jihwang-eumja group than the pyritinol hydrochloride group. No significant differences in ADL were detected between both groups.

In Jia et al. (2018) [20], 93 participants diagnosed with AD by imaging and clinical features were randomly administered with Jihwang-eumja decoction or donepezil for three months. Jihwang-eumja was more effective in enhancing HDS ($p < 0.05$) and MMSE ($p < 0.05$) than donepezil.

In Zhang et al. (2018) [21], 60 participants with mild to moderate dementia were identified as AD by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). Participants were also assessed in terms of pattern identification. Eventually, the deficiency of both yin and yang in kidney syndrome complicated with phlegm turbidity covering the orifices was included. To compare the effects of Jihwang-eumja granules and donepezil on cognition and daily living ability, MMSE, ADAS-cog, ADL, and the Clinician Interview-Based Impression of Change, plus caregiver interview (CIBIC-Plus) were

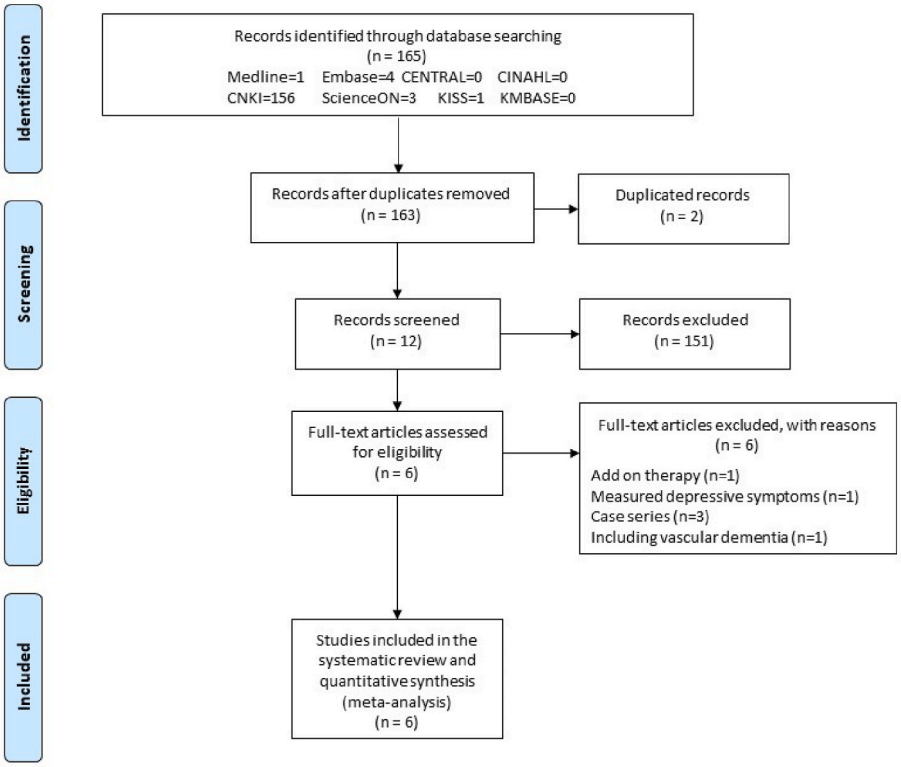

Fig. 1. PRISMA flow chart of the systematic review on Jihwang-eumja for Alzheimer's disease.

Table 1
Summary of the studies included in the systematic review of Jihwang-eumja for Alzheimer's disease.

Study	Country	Sample size	Inclusion criteria	(A) Treatment intervention (dose)	(B) Control intervention (dose)	Duration of treatment	Outcome and Results	Adverse events
Zhang (2006) [19]	China	TG:30 CG:26	(1) Aged over 50 (2) DSM-IV (3) Hachinski Scale ≤4 (4) Deficiency of kidney syndrome complicated with phlegm and blood stasis	Jihwang-eumja decoction (3 times a day)	Pyritinol Hydrochloride 0.2 g (3 times a day)	60 days	(1) MMSE: (A)>(B)** (2) HDS: (A)>(B)** (3) ADL: N.S (4) FAQ: (A)>(B)**	Not reported
Jia et al. (2018) [20]	China	TG:47 CG:46	(1) Diagnosed as Alzheimer's disease by imaging and clinical symptoms	Jihwang-eumja decoction (twice a day)	Donepezil (once a day, 5–10 mg)	3 months	(1) HDS: (A)>(B)* (2) MMSE: (A)>(B)*	TG: nausea (n = 1), fatigue (n = 1) CG: nausea (n = 3), fatigue (n = 2), skin rashes (n = 2), diarrhea (n = 2)
Zhang et al. (2018) [21]	China	TG:30 CG:30	(1) Aged 60–70, (2) NINCDS-ADRDA (3) Deficiency of both yin and yang of kidney syndrome complicated with phelgm turbidity covering orifices (4) 10≤MMSE≤24 (5) CDR 1-2 (6) Hachinski Scale <4	Jihwang-eumja granules (9am, 8pm)	Donepezil (once a day, 5 mg)	3 months	(1) MMSE: N.S (2) ADAS-cog: N.S (3) ADL: (A)>(B)* (4) CIBIC-Plus: N.S	TG: tachycardia with normal T wave (n = 1) CG: none
Wang (2017) [22]	China	TG:38 CG:38	(1) Diagnosed as Alzheimer's disease	Jihwang-eumja decoction (twice a day)	Donepezil (once a day, 5 mg)	1 month	(1) MMSE: (A)>(B)* (2) HDS: (A)>(B)* (3) ADL: (A)>(B)*	TG: nausea (n = 1), vomiting (n = 1), facial flush (n = 1) CG: nausea (n = 1), vomiting (n = 1), facial flush (n = 1)
Ma (2019) [23]	China	TG:75 CG:75	(1) WHO diagnosis criteria	Modified Jihwang-eumja decoction (twice a day) with comprehensive nursing	Donepezil (once a day, 5 mg) with usual nursing	2 months	(1) MMSE: (A)>(B)** (2) HDS: (A)>(B)** (3) ADL: (A)>(B)**	TG: fatigue (n = 1), skin rashes (n = 1), anorexia (n = 2) CG: fatigue (n = 3), diarrhea (n = 4), skin rashes (n = 4), anorexia (n = 3)
Zhang et al. (2019) [24]	China	TG:25 CG:25	(1) Aged 60–85, (2) DSM-5 (3) CDR 1, (4) Hachinski Scale ≤4	Modified Jihwang-eumja Granules (not reported)	Donepezil (once a day, 10 mg)	3 months	(1) MMSE: (A)>(B)** (2) MoCA: (A)>(B)** (3) ADL: N.S	Not reported

*: significant differences between groups by $p < 0.05$.
**: significant differences between groups by $p < 0.01$.
TG; Treatment group, CG; Control group, DSM: The Diagnostic and Statistical Manual of Mental Disorders; MMSE: Mini-Mental State Examination; HDS: Hasegawa Dementia Scale; ADL: Activities of daily living; FAQ: Functional Activities Questionnaire; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association; CDR: Clinical Dementia Rating; ADAS-cog: The Alzheimer's disease Assessment Scale–Cognitive Subscale, CIBIC-Plus: The Clinician Interview-Based Impression of Change, plus carer interview; WHO: World Health Organization; MoCA: Montreal Cognitive Assessment.
Data are presented as mean ± standard deviation, median (1st quartile, 3rd quartile).

evaluated. After three months, no differences were detected between the Jihwang-eumja and donepezil groups when comparing MMSE and ADAS-cog. In contrast, ADL improved more in the Jihwang-eumja group than in the donepezil group ($p < 0.05$).

In Wang (2017)[22]' 76 participants with AD were randomly allocated to two groups. The intervention group was prescribed Jihwang-eumja, and the comparison group was administered donepezil for one month. After treatment, Jihwang-eumja was found to be more effective in improving ADL ($p < 0.05$), MMSE ($p < 0.05$), and HDS ($p < 0.05$) than donepezil.

In Ma (2019) [23], 150 participants who satisfied the World Health Organization (WHO) diagnostic criteria for AD were selected. After a random allocation process, participants were administered Jihwang-eumja with comprehensive nursing or donepezil with usual nursing for 2 months. At the end of the treatment, ADL ($p < 0.05$), HDS ($p < 0.05$), and MMSE ($p < 0.05$) were significantly higher in the Jihwang-eumja group than in the donepezil group.

In Zhang et al. (2019) [24], 50 participants diagnosed with AD according to the DSM-5, were randomly divided into Jihwang-eumja and donepezil groups. Treatments were administered for three months. The results showed that Jihwang-eumja was more effective in improving the MMSE ($p < 0.01$) and MoCA ($p < 0.01$) than donepezil. No significant differences were detected in the ADL scores ($p > 0.05$) between both groups.

3.3. Participant characteristics

The number of participants included in the quantitative synthesis was 245 and 240 in the intervention and comparison groups, respectively. Three studies [19,21,24] limited the age, and two included severity restriction. Zhang (2006) [19] included participants over 50 years old. Zhang et al. (2018) [21] selected participants aged 60–70

years with mild to moderate dementia who scored 10 to 24 on the MMSE, 1 to 2 on the Clinical Dementia Rating (CDR), and below 4 on the Hachinski score. In Zhang et al. (2019) [24], participants were aged between 60 and 85 years and scored 1 in CDR and below 4 in the Hachinski scale. Two studies [19,21] used the pattern identification method. Zhang (2006) [19] included participants with kidney syndrome complicated with phlegm and blood stasis. Zhang et al. (2018) [21] included only the deficiency of both yin and yang of kidney syndrome complicated with phlegm turbidity covering the orifices.

3.4. Intervention

The formula, ingredients, and dose of Jihwan-eumja used in the included studies are described in Table 2. Two studies [21,24] used granules, whereas others [19,20,22,23] used decoction of Jihwang-eumja. Two studies [23,24] modified the ingredients based on the clinical symptoms of the participants and did not report the modification. One study [24] did not report the herbal ingredients in detail. The treatment period varied from one to three months. Five studies [19–22,24] used Jihwang-eumja only, whereas Ma (2019) [23] combined Jihwang-eumja with comprehensive nursing, which includes cognitive, psychological support, and patient education.

3.5. Comparisons

In all studies, the comparison group was treated with Western medications. Five RCTs [20–24] used donepezil, and one RCT [19] used pyritinol hydrochloride as the comparatives. Jia et al. (2018) [20] administered donepezil once a day to the comparison group, 5 mg during the first month, and 10 mg for the second and third months. Zhang et al. (2018) [21] provided 10 mg of donepezil per day. In studies by Wang (2017) [22], Ma (2019) [23], and Zhang et al. (2019) [24], participants were daily administered 5 mg of donepezil. In the study by Zhang (2006) [19], pyritinol hydrochloride (0.2 g) was administered three times a day to the comparison group.

3.6. Outcome measures

To evaluate cognitive function, MMSE and HDS were measured in six [19–24] and four [19,20,22,23] studies, respectively. ADAS-cog, CIBIC-Plus, and MoCA were used once. Five studies [19,21–24] assessed the level of daily activity. All studies used the ADL scale without describing the exact version, and one study [19] used the FAQ scale.

For safety evaluation, five studies [19–23] investigated AEs including specific responses, and one study [24] did not report AEs. Two studies [19,21] performed laboratory tests. One study [21] compared systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, creatinine, fasting blood glucose, glycated hemoglobin, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels before and after treatment. One study [19] described that, according to the blood and urine tests, hepatic and renal function were not significantly changed during the trial.

3.7. Risk of bias assessment

Across all the possible biases according to ROB 2.0, the included studies contained some concerns of the risk of bias (Figs. 2 and 3).

3.7.1. Bias arising from the randomization process

The six studies showed some concerns of bias arising from the randomization process because the information about allocation concealment was absent in the paper.

Table 2
The formula, ingredients, and dose of Jihwang-eumja used for Alzheimer's disease in the included studies.

First author (Year)	Formula	Ingredients	Dose
Zhang (2006) [19]	Decoction	Rehmanniae Radix Preparata 15 g, Crataegus pinnatifida 15 g, Morindae Radix 15 g, Liriope platyphylla Wang et Tang 15 g, Cistanche deserticola Y. C. Ma 15 g, Poria Sclerotium 15 g, Polygalae Radix 15 g, Dendrobii Caulis 15 g, Acorus gramineus Solander 15 g, Ostreae Concha 3 g, Draconis Resina 3 g, Menthae Herba 10 g, Schisandra chinensis Baillon 10 g, Zingiberis Rhizoma Recens 3 pieces, Zizyphi Fructus 8 pieces.	Boil to be 300 ml and take 100 ml three times a day.
Jia et al. (2018) [20]	Decoction	Schisandra chinensis Baillon 30 g, Acorus gramineus Solander 15 g, Liriope platyphylla Wang et Tang 15 g, Poria Sclerotium 15 g, Schisandra chinensis Baillon 15 g, Cistanche deserticola Y. C. Ma 15 g, Morindae Radix 15 g, Rehmanniae Radix Preparata 15 g, Atractylodes macrocephala Koidzumi 15 g, Codonopsis pilosula 15 g, Dendrobii Caulis 12 g, Polygalae Radix 12 g, Cinnamomi Cortex 10 g, Aconiti Lateralis Radix Preparata 10 g, Zizyphi Fructus 3 pieces, Zingiberis Rhizoma Recens 4 pieces	Boil and divide into two doses on a day.
Zhang et al. (2018) [21]	Granules	Rehmanniae Radix Preparata 15 g, Morindae Radix 15 g, Cornus officinalis Siebold et Zuccarini 15 g, Polygalae Radix 15 g, Acorus gramineus Solander 15 g, Liriope platyphylla Wang et Tang 15 g, Cistanche deserticola Y. C. Ma 15 g, Poria Sclerotium 15 g, Schisandra chinensis Baillon 6 g, Dendrobii Caulis 12 g, Zizyphi Fructus 10 g, Aconiti Lateralis Radix Preparata 9 g, Zingiberis Rhizoma Recens 6 g, Menthae Herba 6 g, Cinnamomi Cortex 3 g	Boil to be 400 ml and take 200 ml two times a day(at 9:00 and 20:00).
Wang (2017) [22]	Decoction	Rehmanniae Radix Siccus 15 g, Cornus officinalis Siebold et Zuccarini 15 g, Poria Sclerotium 15 g, Dendrobii Caulis 15 g, Cistanche deserticola Y. C. Ma 12 g, Liriope platyphylla Wang et Tang 10 g, Morindae Radix 10 g, Aconiti Lateralis Radix Preparata 8 g, Acorus gramineus Solander 8 g, Polygalae Radix 6 g, Schisandra chinensis Baillon 5 g, Menthae Herba 5 g, Zingiberis Rhizoma Recens 4 g, Zizyphi Fructus 4 pieces	Boil and divide into two doses on a day.
Ma (2019) [23]	Decoction	Cornus officinalis Siebold et Zuccarini 30 g, Codonopsis pilosula 15 g, Atractylodes macrocephala Koidzumi 15 g,	Boil to be 400 ml and take 200 ml two times a day.

(continued on next page)

Table 2 (*continued*)

First author (Year)	Formula	Ingredients	Dose
		Acorus gramineus Solander 15 g, Rehmanniae Radix Preparata 15 g, Liriope platyphylla Wang et Tang 15 g, Poria Sclerotium 15 g, Cistanche deserticola Y. C. Ma 15 g, Schisandra chinensis Baillon 15 g, Morindae Radix 15 g, Dendrobii Caulis 12 g, Polygalae Radix 12 g, Aconiti Lateralis Radix Preparata 10 g, Cinnamomi Cortex 10 g, Menthae Herba 6 g, Zizyphi Fructus 3 pieces, Zingiberis Rhizoma Recens 3 pieces	
Zhang et al. (2019) [24]	Granules	Not reported (Dijuang Yinzi granules produced by Beijing Tcmages Pharmaceutical Co., LTD)	Not described

3.7.2. Bias due to deviations from the intended interventions and bias due to missing outcome data

In all studies, the participants were aware of the intervention owing to the difference in dosage form between Jihwang-eumja and Western medications. In five studies [20–24], without any drop-out or missing data throughout the trials, intention-to-treat analyses could be adopted in a ratio 1:1. This rendered these studies with a low risk of bias due to deviations from the intended interventions and missing outcome data. However, in Zhang (2006) [19], the number included for analyses in the intervention and comparison groups was 30 and 26 respectively, and the information about the random sequence generation and drop-outs were unavailable. As a result, the authors agreed that Zhang (2006) [19] had a high risk of bias due to deviations from the intended interventions and some concerns of bias due to missing outcome data.

3.7.3. Bias in the measurement of the outcome

Regarding the bias in the measurement of the outcome, none of the studies stated whether assessors were blinded. However, using objective measurement tools, all studies were thought to have a low risk of bias in the measurement of the outcome.

3.7.4. Bias in the selection of the reported result

All studies contained some concerns of selection bias because neither the trials were registered nor the protocols were available.

3.8. Data synthesized by meta-analysis

A total of six RCTs were included in the meta-analysis.

3.8.1. Cognitive function

The MMSE of six RCTs was synthesized for meta-analysis, and 485 participants were included (Fig. 4). MMSE was 3.19 (95%CI: 1.68–4.70) higher in the Jihwang-eumja group than in the Western medications group. Jihwang-eumja was more effective in improving cognitive function than the comparison group. The I^2 was 92%, and the heterogeneity among the studies was considered high.

HDS was evaluated in four RCTs [19,20,22,23], and 375 participants were included in the meta-analysis (Fig. 5). Jihwang-eumja was more effective in improving the HDS by 5.90 (95%CI: 5.44–6.37) than the Western medications group. The heterogeneity across the studies was high, with a 95% I^2.

3.8.2. Activities of daily living

Four studies were selected for the meta-analysis of ADL, and a total of 110 participants were included (Fig. 6). Zhang et al. (2019) [24] also reported ADL; however, since neither the exact version of the ADL tool nor the score indicating better daily activity functions was described, it was excluded from the meta-analysis. Because none of the included studies reported the version of the ADL tool, the SMD was applied. The SMD of ADL was 1.13 (95%CI: 0.89–1.37) higher in the Jihwang-eumja group than in the Western medications group. I^2 was 95%, and the studies had high heterogeneity.

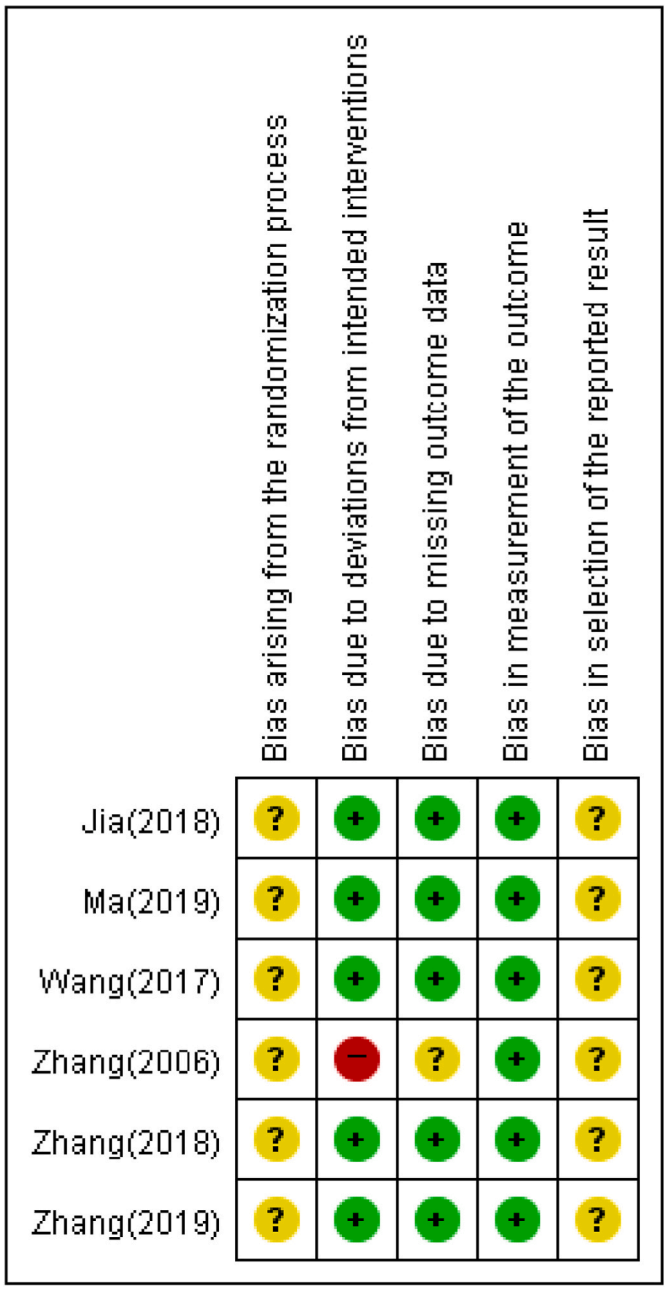

Fig. 2. Risk of bias summary of the included studies in the systematic review on Jihwang-eumja for Alzheimer's disease.

3.8.3. Safety assessment

Four studies that reported AEs were included for quantitative synthesis for safety assessment, and 379 participants were included (Fig. 7). The relative risk of AEs was 0.39-fold (95%CI: 0.20–0.78) in the Jihwang-eumja group compared to the Western medications group. The included studies showed moderate heterogeneity, with an I^2 value of 54%.

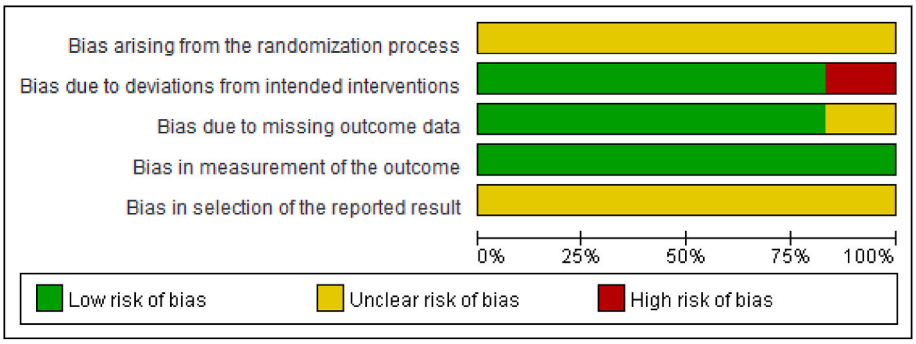

Fig. 3. Risk of bias graph of the included studies in the systematic review on Jihwang-eumja for Alzheimer's disease.

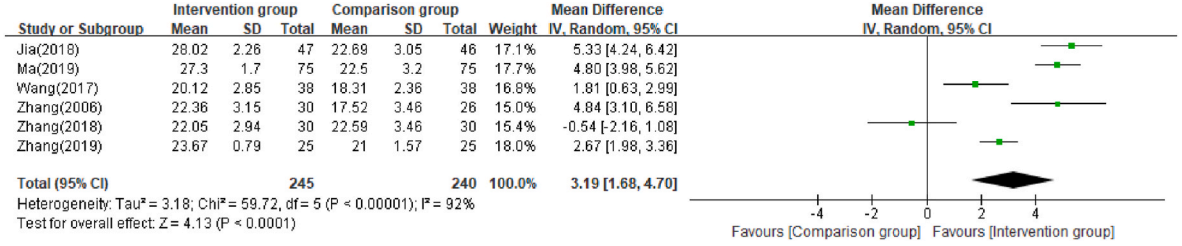

Fig. 4. Forest plot comparing the effectiveness of Jihwang-eumja and Western medications in improving the Mini-Mental State Examination (MMSE) scores of dementia patients with Alzheimer's disease.

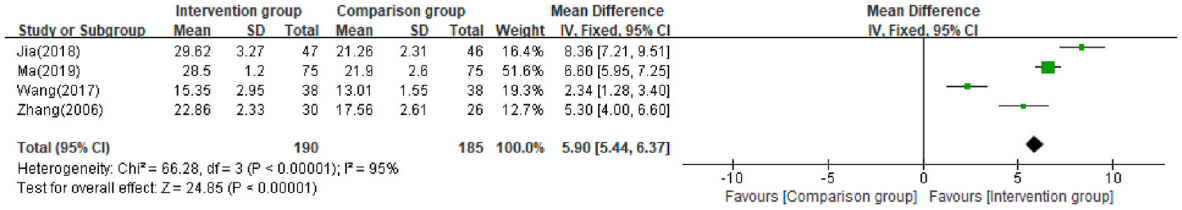

Fig. 5. Forest plot comparing the effectiveness of Jihwang-eumja and Western medications in improving the Hasegawa dementia scale (HDS) of dementia patients with Alzheimer's disease.

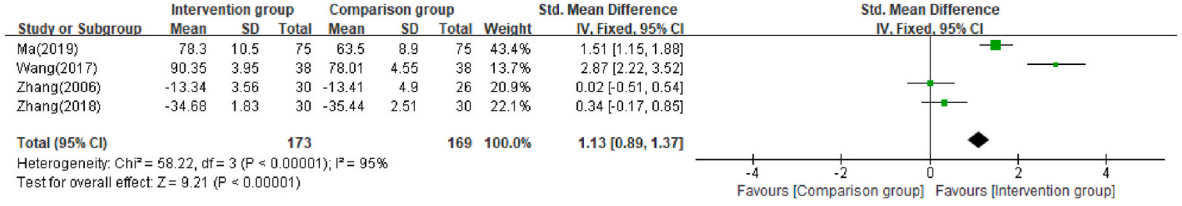

Fig. 6. Forest plot comparing the effectiveness of Jihwang-eumja and Western medications in improving the activities of daily living (ADL) of dementia patients with Alzheimer's disease.

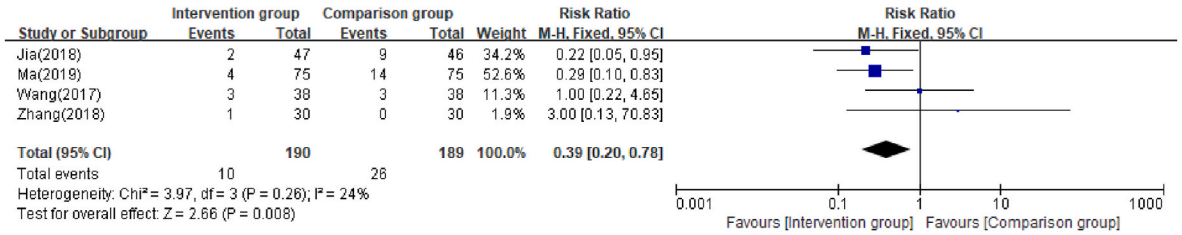

Fig. 7. Forest plot of the relative risk of adverse events during the administration of Jihwang-eumja and Western medications in dementia patients with Alzheimer's disease.

3.9. GRADE assessment for clinical recommendations

For the outcomes synthesized by meta-analysis, the certainty of the evidence was assessed using the GRADE tool (Table 3). To consider cognitive function, Jihwang-eumja was anticipated to be more effective in improving MMSE score using mean difference (MD) by 3.19 (95%CI: 1.68–4.70) and HDS score by MD 5.90 (95%CI: 5.44–6.37), compared to the Western medications. ADL was expected to raise SMD 1.13 higher in the Jihwang-eumja group compared to the Western medications group. In all of the outcomes, the level of evidence was moderate, and the benefits of Jihwang-eumja were reliable, although the relevant studies provided insufficient evidence. The authors agreed that MMSE, HDS, and ADL are critical outcome measures. In conclusion, Jihwang-eumja should be considered to improve cognitive function and ADL in patients with AD in clinical settings.

4. Discussion

In traditional Korean medicine, dementia is mentioned in various medical classics regarding its clinical features and as a symptom of aging. Dementia was first stated in <Gyeongagjeonseo> dealing with personality changes and behavioral abnormalities: dementia patients talk and behave nonsensically, suffer from depression, or wander around. It was also stated that the main causes of dementia are decreased physical strength due to aging, psychological disharmony, inappropriate ingestion, addiction, and trauma [12].

In traditional Korean medicine, the kidney produces strength and stores essentials. <Hwangjenaegyeong Somun Sanggocheonjinlon> explains the whole life cycle of birth, growth, and aging in association with the rises and declines of the essential and qi of the kidney. Essential becomes the material basis of the brain and mental operations [12]. Along with aging, the qi of the kidney and the essential declines resulting in psychological problems, where Jihwang-eumja can be beneficial.

Jihwang-eumja is composed of several components, depending on the theory for the monarch, minister, adjuvant, and dispatcher. *Rehmanniae Radix Preparata*, and *Cornus officinalis Siebold et Zuccarini* act as the monarch, adding yin to the kidney. *Cistanche deserticola Y. C. Ma*, *Cinnamomi Cortex*, *Morindae Radix*, and *Aconiti Lateralis Radix Preparata* are the ministers, heating and adding yang to the kidney. As adjuvants, *Dendrobii Caulis*, *Liriope platyphylla Wang et Tang*, and *Schisandra chinensis Baillon* supplement the yin and gather fluids in the body. *Acorus gramineus Solander*, *Polygalae Radix*, and *Poria sclerotium* act as dispatchers, circulating the body within the heart and kidney [25].

We conducted a systematic review and meta-analysis to verify the clinical effectiveness of Jihwang-eumja in cognitive function and ADL in patients with AD. In addition, we conducted a qualitative analysis to determine the limitations of current clinical trials and where further research should be conducted.

In this study, six RCTs were selected for systematic review. The included studies had some concerns about the risk of bias due to the lack of information. In common, the included studies provided insufficient information about the randomization process and assessor blinding. Although one study [19] showed a considerable imbalance in the number of participants between the groups to raise the overall possibilities of biases, only some drop-outs were detected in both groups in the remaining five studies [20–24]. The measured outcomes were concisely described reporting only the difference before and after the treatment, without subgroup or time-dependent analysis. The study protocols were not registered, and we could not determine if there were possible reporting biases.

Five of six RCTs [19,21–24] evaluated both cognitive function and ADL, and one RCT [20] studied only cognitive function. MMSE was the most frequently used outcome measure for cognitive evaluation in the included studies. The MMSE evaluates multiple domains of cognition, including orientation, memory ability, calculation, attention, and language [1]. HDS was the second outcome measure composed of questions about orientation, memory, calculation, attention, and language [26].

The versions of the ADL tool were not described in all studies. ADL is divided into physical and instrumental activities of daily living. Physical ADL is about sanitation, dining, clothing, and movement, while instrumental ADL includes phone calls, buying, cooking, using transportation, and so on. In Korea, the K-IADL, Bayer-ADL, Disability Assessment for Dementia Scale, Seoul-ADL, and Seoul-IADL have been standardized [27]. In short, the pooled data showed that the MMSE, HDS, and ADL of the Jihwang-eumja group were higher than those of the Western medications group.

In all studies, when reporting AEs, the assessment of severity or correlation with the interventions was absent. The WHO suggests some safety parameters to support phase 2 trials of herbal products. These include neurological symptoms, allergic reactions, serum creatine phosphokinase, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphate, total bilirubin, blood urea nitrogen, creatinine, albumin, total protein, uric acid, glucose, cholesterol, amylase, lipase, complete blood count, electrocardiogram, and blood pressure [28]. However, only two studies, Zhang (2006) [19] and Zhang et al. (2018) [21] reported that Jihwang-eumja did not show any significant changes in laboratory tests and no differences were recorded compared to the Western medications. On the other hand, the relative risk of AEs was significantly lower in the Jihwang-emja-treated group than that in the Western medications-treated group. Therefore, Jihwang-eumja was safe in patients with AD and induced fewer AEs than Western medications.

We adopted the GRADE system to evaluate the certainty of the

Table 3
Summary of findings table of Jihwang-eumja for dementia patients with Alzheimer's disease compared to Western medications.

Certainty assessment						Number of participants		EffectAbsolute (95% CI)	Certainty
Outcomes	Study design	Risk of bias	Inconsistency	Indirectness	Imprecesion	JHE	WM		
MMSE (Jihwang-eumja versus Western medications) 6 studies	RCT	Serious[a]	Not serious	Not serious	Not serious	245	240	MD 3.19 (1.68–4.7)	⊕⊕⊕○ Moderate
HDS (Jihwang-eumja versus Western medications) 4 studies	RCT	Serious[a]	Not serious	Not serious	Not serious	190	185	MD 5.9 (5.44–6.37)	⊕⊕⊕○ Moderate
ADL (Jihwang-eumja versus Western medications) 4 studies	RCT	Serious[a]	Not serious	Not serious	Not serious	173	169	SMD 1.13 (0.89–1.37)	⊕⊕⊕○ Moderate

CI: Confidence interval, JHE: Jihwang-eumja, WM: Western meidcations, MMSE: Mini-Mental State Examination; RCT:Randomized controlled trial; MD: mean difference; CI: confidence interval; HDS:Hasegawa Dementia Scale; ADL; Activities of daily living; SMD: standardized mean difference.

[a] All studies did not report the randomization method and protocols did not exist.

evidence at the outcome level and to draw clinical recommendations. Despite low inconsistency, indirectness, and imprecision, because of some concerns of the risk of biases, the authors agreed that the certainty of the evidence is moderate, and the true effect is probably close to the estimated effect.

To date, Jihwang-eumja has not been commonly prescribed for AD. A survey [29] showed that YukmiJihwang-Tang, Jowuiseungchung-Tang, Sibjeondaebo-Tang, and Sunghyangjunggi-San were the most frequently used prescriptions for dementia. Among these, Yukmijihwang-Tang is used for the insufficiency of kidney yin [30]. In addition, Palmihwan was investigated as a second-line prescription, which is used to treat yang deficiency of the kidney [30]. Although Jihwang-eumja was not involved in this survey, Jihwang-eumja is known to treat the same pathological phenomenon, kidney deficiency.

In China, Jihwang-eumja has been studied as an adjuvant medication for vascular dementia in several clinical trials. For example, a recent RCT conducted on vascular dementia of renal deficiency syndrome plus phlegm–stasis obstruction revealed that the curative effect of citicoline was enhanced when combined with Jihwang-eumja decoction [31]. Some studies have reported that Jihwang-eumja effectively improves the linguistic function of patients with degenerative neuropsychiatric diseases. For instance, in a case report published in Korea, Jihwang-eumja treated the voice production problem in patients with Parkinson's disease [32]. In a literature review of clinical research on the treatment of aphasia after cerebrovascular disease, the prescription frequency of Jihwang-eumja was found to be the highest among 12 prescriptions in 17 included studies [33]. Similarly, Zhang et al. (2019) [24] found that Jihwang-eumja improved the linguistic ability of patients with AD by analyzing the sub-categories of the MMSE.

Through this review, we confirmed that Jihwang-eumja could be more effective than Western medications for cognitive improvement in patients with AD. However, this study has several limitations. First, since Jihwang-eumja has not usually been applied to AD, the number of included studies was very small, and we could not assess the publication bias. Also, all included studies were published in China. Second, we tried to contact the authors of the included studies to acquire more information about ROB 2.0 and accessible data, but only one author responded. Third, the heterogeneity of the included studies was found to be high (I^2 square of 92% in MMSE, 95% in HDS, and 95% in ADL synthesis). Some factors were thought to have caused heterogeneity within the studies. Several studies have restricted the age, severity of dementia, and pattern identification type, while others did not. Regarding the interventions, different forms of Jihwang-eumja were utilized, and in two studies, Jihwang-eumja was modified. Although most of the compositions of each medication were considered similar, these differences could have caused heterogeneity. Fourth, only two studies [19,21] have used diagnostic methods for traditional herbal medicine. Zhang (2006) [19] and Zhang et al. (2018) [21] adopted the concept of pattern identification and selected participants with kidney deficiency complicated with phlegm. Fifth, although AD is a chronic degenerative disease, the treatment period was 1–3 months, and no additional follow-up was conducted to verify if the drug effect was maintained. In recent systematic reviews [8,9] for the effect of herbal medicines on AD, the treatment periods of the clinical trials ranged from 8 to 24 weeks, mostly 12 weeks, which is similar to those of the studies included in this review. In addition, in the clinical trial guidelines for AD published in Korea [34], it is recommended to conduct long-term observational research over 12-month. Lastly, although caregiver distress is also essential for managing patients with AD and closely related to the behavioral and psychological symptoms, it was not considered in the included studies [35]. The clinical trial guidelines for AD [34] also recommend assessing psychological domains for a more objective assessment of cognition since the psychological symptoms determine a large part of the severity. In one RCT [36], Jihwang-eumja was observed to more effectively improve the Hamilton Depression Rating Scale compared to sertraline ($p < 0.05$) after 60 days of treatment. In further clinical trials on Jihwang-eumja for AD, we suggest including the evaluation of pattern identification and behavioral and psychological symptoms in the form of a high-quality design and long-term follow-up study.

5. Conclusion

Jihwang-eumja was more effective than Western medications in improving cognitive function and ADL in dementia patients with AD. For safety, Jihwang-eumja appeared to have a significantly lower relative risk of AEs than Western medications. However, only six studies were included in this systematic review and contained some concerns of the risk of bias and high heterogeneity. In the future, high-quality designed RCTs are needed on Jihwang-eumja for AD, and we also suggest including the evaluation of pattern identification and behavioral and psychological symptoms to reflect the actual clinical settings.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2023.101746.

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