Efficacy and Safety of Nootropic Herbal Medicines in Increasing Cognitive Function in Alzheimer Patients

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Abstract

Background: Alzheimer's disease is the most common type of dementia found in society and it is estimated that the number of dementia sufferers will increase. Declining cognitive function is a hallmark symptom and the treatment that has been used to combat the symptom is still unsatisfactory and has side effects. This review explores other herbal and nootropic alternative treatments.

Methods: Published Randomized Clinical Trials (RCT) and meta-analyses regarding the efficacy and safety of herbal medicine in increasing cognitive function in Alzheimer patients are searched in PubMed and Google Scholar while applying several inclusion and exclusion criteria.

Results: 14 articles are retrieved, which are 3 RCTs and 11 meta-analyses, and are analyzed further. Several interventions are examined, which include Ginkgo biloba, Curcuma longa, Crocus sativus, Huperzine A, Panax ginseng, and Chinese herbal medicine. Each of these interventions exert different levels of efficacy and safety, and differ in their price range.

Conclusion: Out of all the analyzed interventions, Crocus sativus could be used as a potential treatment for Alzheimer patients due to its comparable level of efficacy and safety to that of standard therapy and cost effective, but there needs to be a standardized extract for the Indonesian population to easily obtain.

Keywords: herbal medicine, nootropics, cognitive function, Alzheimer's disease

Abstrak

Latar belakang: Penyakit Alzheimer merupakan jenis demensia yang paling sering ditemukan dalam masyarakat dan diperkirakan angka penderita akan terus meningkat beberapa tahun kedepannya. Salah satu gejala khas dari penyakit Alzheimer adalah gejala menurunnya fungsi kognitif, dan obatan-obatan yang sekarang dipakai untuk melawan gejala tersebut belum memuaskan dan terdapat beberapa efek samping. Berdasarkan hal tersebut dibuat tinjauan untuk menelusuri terapi alternatif yang bersifat herbal dan nootropik.

Metode: Dilakukan penelusuran artikel publikasi Randomized Controlled Trial (RCT) dan meta-analisis mengenai khasiat dan keamanan tanaman obat untuk meningkatkan fungsi kognitif pada pasien Alzheimer dalam database PubMed dan Google Scholar dengan menerapkan beberapa kriteria inklusi dan kriteria eksklusi.

Hasil: Terdapat 14 artikel berupa 3 RCT dan 11 meta-analisis yang dianalisa lebih lanjut. Beberapa intervensi yang ditelusuri adalah Ginkgo biloba, Curcuma longa, Crocus sativus, Huperzine A, Panax ginseng, dan Obat herbal Cina. Masing-masing intervensi memiliki khasiat untuk meningkatkan fungsi kognitif, tingkat keamanan, dan rentang harga yang berbeda.

Kesimpulan: Dari semua intervensi yang dianalisa, Crocus sativus dapat menjadi terapi alternatif untuk pasien Alzheimer dikarenakan intervensi ini dapat meningkatkan fungsi kognitif, memiliki tingkat keamanan yang setara dengan terapi standar dengan harga terjangkau, namun perlu adanya sediaan ekstrak terstandard yang dapat dijangkau masyarakat Indonesia.

Kata kunci: pengobatan herbal, zat nootropik, fungsi kognitif, penyakit Alzheimer

INTRODUCTION

Dementia is a disease mostly found in the aging population. In the year 2010, it was estimated that 35.6 million people lived with dementia. The number of dementia cases are rising and it is predicted that 115.4 million people will be suffering from dementia in 2050. Alzheimer's disease is the most common form of dementia where 60 - 80% of dementia cases are attributed to it.[1] Alzheimer's disease is characterized by a declining cognitive function of which no available medicine has been able to fully treat the disease and instead aims to decelerate the progression of cognitive function loss. Acetylcholinesterase (AChE) inhibitors, such as donepezil, rivastigmine, galantamine, work by increasing the number of acetylcholine within the brain and thus impedes on the declining cognitive function brought upon by Alzheimer's disease. The standard therapy currently accessible does not come without downsides however as said medications provide less than satisfactory results and may cause side effects.[2-3] A meta-analysis by Blanco-silvente et al (2019) reported that donepezil, galantamine, and rivastigmine showed no clinical relevance in improving cognitive function. The study also described the increase in discontinuation of donepezil use as a result of unintended side effects.[4] Therefore, the research of new dementia treatments are still ongoing, including natural-based drugs that exert nootropic effects.

Nootropics are a substance purported to improve mental functions such as memory, cognition, and concentration. A number of plants have been the subject of focus in the research of nootropics for Alzheimer's disease, for instance, *Ginkgo biloba,* *Crocus sativus*, and other medicinal herbs which contain similar medicinal properties.[5] Research and meta-analyses available to date generally focus on a single herb or a group of herbal blends with inconsistent results. This review aims to look at and compare the efficacy and safety of various medicinal plants as a nootropic on the cognitive function of Alzheimer's patients based on previous studies. In addition, the novelty of this review also includes the identification of interventions based on whether it is indigenous Indonesian herbs or not and their possible application to the Indonesian population.

METHODS

A literature review was conducted pertaining to the efficacy and safety of herbal medicines to increase the cognitive function of Alzheimer's patents. Scientific articles were searched for in PubMed and Google Scholar. The search terms used were (("herbal medicine" OR "complementary medicine" OR "traditional medicine") AND "Alzheimer's disease" AND "increased cognitive function"). Articles were then screened using several inclusion and exclusion criteria. The inclusion criteria were randomized clinical trials and meta-analyses published from 2011 - 2021 in Indonesian and English language. Incomplete, inaccessible, or articles unrelated to the topic were excluded. After screening, clinical trials were then evaluated for quality. At the end of the search, 14 articles were extracted by the first author, assessed further by second author and were presented in the form of text and tables. Critical appraisal of randomized clinical trials was assessed based on Oxford University's Center for Evidence-based Medicine (CEBM).
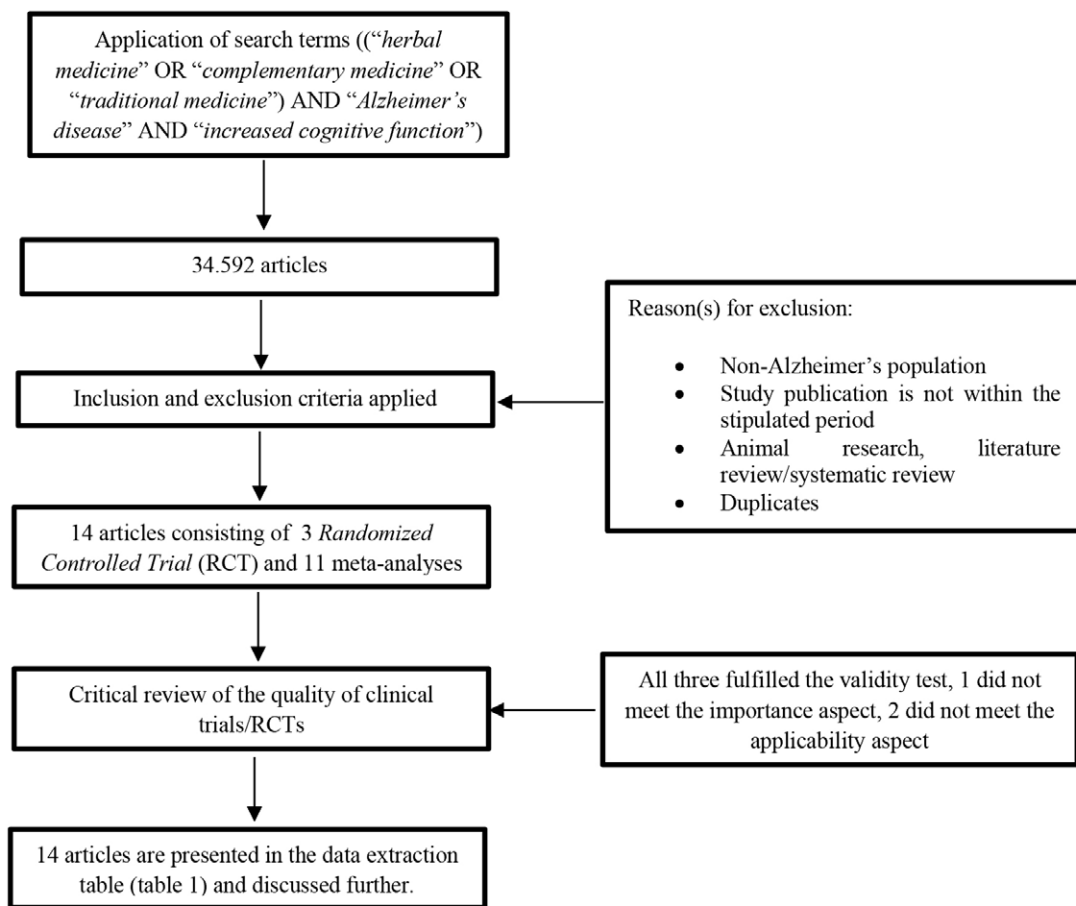
Figure 1. Flow Diagram of Article Selection.

Table 1. Data Extraction Table of Research Articles

No.	Title and Author (Year)	Population	Study Design	Intervention	Comparison	Findings	Conclusion	Research Article Strengths and Weaknesses
Randomized Controlled Trials								
1.	*Efficacy and Tolerability of a Once Daily Formulation of Ginkgo biloba Extract EGb 761® in Alzheimer's Disease and Vascular Dementia: Results from A Randomized Controlled Trial*: Ihl R, *et al* (2011).	Male and female subjects aged 50 and above with mild to moderate dementia caused by Alzheimer's disease, (n = 333).	Subjects are randomly assigned into 2 groups. The first group received EGb 761 and the second group received placebo. *Syndrom-Kurztest* (SKT) was used to assess cognitive function.	240 mg per day of *Ginkgo biloba* extract (EGb 761) for 24 weeks.	Placebo once per day for 24 weeks.	EGb 761 group experienced a 1.7 points decrease measured in the SKT cognitive test after 24 weeks in comparison to the placebo group (p<0.001) and experience the same frequency of side effects as placebo.	EGb 761 is superior in regards to efficacy to improve the cognitive function of Alzheimer patients and has a level of safety comparable to that of placebo.	Based on the critical review of randomized controlled trials, it was found that this study was valid, important and applicable. *Ginkgo biloba* is not a plant native to Indonesia and therefore needs to be sourced from abroad. It is accessible to the Indonesian population at a relatively high price.

| 2. | *Oral Curcumin for Alzheimer's Disease: Tolerability and Efficacy in A 24-week Randomized, Double Blind, Placebo-Controlled Study*: Ringman J, *et al* (2012). | Male and female subjects aged 50 and above with mild to moderate Alzheimer's disease (n = 36). | Subjects are randomly assigned into 3 groups. The first group received 2 g of *Curcuma longa* extract per day, the second group received 4g of the same extract per day, the third group received placebo. Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) were used to measure cognitive changes. (ADAS-cog). | 2 g or 4 g of *Curcuma longa* extract per day for 24 weeks. | Placebo once per day for 24 weeks. | Both intervention groups suffered a decline in cognitive function indicated by worse scores measured in MMSE (p = 0.08) and ADAS-cog (p = 0.26) in comparison to the placebo group. 1 subject dropped out of the intervention group and 5 subjects dropped out of intervention group however when accounted for, the occurrence of side effects is still statistically insignificant (p = 0.33). | *Curcuma longa* extract exerts an inferior efficacy in comparison to placebo in enhancing cognitive function with a level of safety comparable to placebo. | Based on the critical review of randomized controlled trials, it was found that this study was valid, not important and applicable.

Curcumin is a plant native to Indonesia and is readily accessible at a low cost. However some of them are not a standardized extract.

Moreover, this study was limited by a small sample size as well as a short study period. |
| 3. | *Comparing The Efficacy and Safety of Crocus sativus L. With Memantine in Patients with Moderate to Severe Alzheimer's Disease: A Double-Blind Randomized Clinical Trial*: Farokhnia M, *et al* (2014). | Male and female subjects aged 60 and above with moderate to severe Alzheimer's disease (n = 68). | Subjects are randomly assigned into 2 groups. The first group received *Crocus sativus* and the second group received memantine. A cognitive evaluation for each individual groups was conducted every month for 1 year. Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST) were used to measure cognitive changes. | 30 mg of dry extract of *Crocus sativus* per day for 1 year. | 20 mg of memantine per day for 1 year. | Both groups experienced a comparable level of efficacy (SCIRS: p = 0.38, FAST: p = 0.87) and safety (4 subjects from each group withdrew during the trial). | *Crocus sativus* exerts a level of efficacy and safety comparable to memantine in increasing cognitive function. | Based on the critical review of randomized controlled trials, it was found that this study was valid, important and not applicable. *Crocus sativus* is a plant not native to Indonesia and therefore needs to be sourced internationally but is easily accessible after import.

This study however was limited but a small sample size and a short study period and so long term effects of *Crocus sativus* cannot be established. |

Meta-Analysis of Clinical Trials

| 4. | *Huperzine A for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trial*: Yang G, *et al* (2013). | 3 (n = 1823) of 20 studies are used to assess the efficacy of Huperzine A in comparison to placebo on cognitive function. Measurement was taken using MMSE, Hasegawa Dementia Scale (HDS), and Wechsler Memory Scale (WMS) after 8 weeks. 3 different studies of 20 were used to assess the effects of the intervention after 12 weeks. Another 3 studies of 20 were used to assess the efficacy of Huperzine A in comparison to piracetam after 8 weeks using MMSE. | A systematic review and meta-analysis were conducted to review the efficacy of Huperzine A on cognitive function in Alzheimer's patients. | *Huperzia serrata* extract (Huperzine A). | Placebo or piracetam | Huperzine A was found to have a significant effect on improving cognitive function after 8 weeks in MMSE (Mean Difference = 3.75, p<0.05), HDS (MD = 3.18, p<0.05), and WMS (MD = 16.77, p<0.05). A same signifcant results was also found after 12 weeks (MMSE: MD = 2.89, P<0.05) and if Huperzine A is compared to piracetam (MMSE: MD = 4.83, p<0.05). | Huperzine A exerts a level of efficacy superior to placebo and piracetam on increasing cognitive function in Alzheimer's patients. | This study groups the efficacy of the intervention into a specific number of weeks, allowing for more detail and clarity as to how the intervention acts in the cognitive function of subjects.

However, the number of studies used in the calculation of the meta-analysis was minimal and was found to have a high risk of bias due to the poor quality of the studies. A funnel plot done was shown to indicate publication bias was present. |

5.	*A Systematic Review on Natural Medicines for the Prevention and Treatment of Alzheimer's Disease with Meta-Analyses of Intervention Effect of Ginkgo*: Yang M, *et al* (2014).	6 RCTs (n = 1294) were included in a meta-analysis to asses the efficacy of *Ginkgo biloba* on cognitive function. 3 studies utilized ADAS-cog and the remaining 3 used SKT.	A systematic review was done to review the effect of herbal medicines on Alzheimer's disease and a meta-analysis was conducted to assess the efficacy of *Ginkgo biloba* on cognitive function in Alzheimer's patients.	*Ginkgo biloba* extract.	Placebo.	*Ginkgo biloba* was found to have a significant effect on improving cognitive function (Standardized Mean Difference = -1.61, p = 0.003).	*Ginkgo biloba* exerts a level of efficacy superior to placebo on improving the cognitive function of Alzheimer's patients.	The small number of studies used did not allow for a publication bias test. A high degree of heterogeneity was also found in the meta-analysis.
6.	*Efficacy and Adverse Effects of Ginkgo Biloba for Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis*: Tan MS, *et al* (2015).	9 RCTs (n = 2561) involving subjects with Alzheimer's disease or vascular dementia. An Alzheimer's disease meta-analysis subgroup was formed. ADAS-cog measurements was used.	A systematic review and meta-analysis was conducted to assess the efficacy and safety of EGb 761 on cognitive function in Alzheimer's patients.	*Ginkgo biloba* extract (EGb 761).	Placebo.	EGb 761 was found to have a significant effect on improving cognitive function (total MD = -2.54, p<0.00001) and is superior in regards to safety when compared to placebo (Odds Ratio = 0.74, p = 0.01).	EGb 761 exerts a level of efficacy and safety superior to placebo in increasing cognitive function.	This study formed a subgroup specifically for Alzheimer's disease, permitting the efficacy of the intervention has on Alzheimer's disease to be more clearly illustrated. However, this study did not present the article selection flow and risk of bias assessment for each study used in detail. The number of studies used was also insufficient for a publication bias test. In addition, a high level of heterogeneity was also found in the meta-analysis.
7.	*Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Controlled Trials*: Yang G, *et al* (2016).	21 RCTs (n = 2608) involving subjects with Alzheimer's disease or Mild Cognitive Impairment (MCI). 2 of 20 studies involving Alzheimer patients were calculated into a meta-analysis to assess the efficacy of *Ginkgo biloba* with donepezil in comparison to donepezil alone on cognitive function using the measurement taken from MMSE. Some studies were calculated into a subgroup meta-analysis to assess the safety of *Ginkgo biloba* in comparison to placebo.	A systematic review and meta-analysis were conducted to assess the efficacy safety of *Ginkgo biloba* on cognitive function in Alzheimer's patients.	*Ginkgo biloba* and donepezil for cognitive function. *Ginkgo biloba* only for safety.\	Donepezil for cognitive function. Placebo for safety.	*Ginkgo biloba* with donepezil was found to have a significant effect on improving cognitive function (MD = 2.39, p<0.0001) when compared to donepezil alone. No significant difference was found between *Ginkgo biloba* and placebo in regards to safety (OR = 0.82, p = 0.13 for adverse events and OR = 0.82, p = 0.60 for severe adverse events).	*Ginkgo biloba* with donepezil exerts a level of efficacy superior to donepezil alone on improving cognitive function in Alzheimer's patients shows a level of safety comparable to placebo.	This study identified that different forms of *Ginkgo biloba* preparations may have an effect on the efficacy of the intervention. Although a large number of studies was used, only 2 of 20 research articles were included in the meta-analysis therefore a precise conclusion cannot be drawn. This is consistent with previous Cochrane meta-analyses and reinforces the possibility that the effect of *Ginkgo biloba* on improving cognitive function has been yet to be confirmed. In addition, this study does not depict a combined result in a forest plot. A publication bias test was not able to be conducted due to the insufficient number of studies used.

No.								
8.	*Ginseng for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*: Wang Y, *et al* (2014).	4 RCTs (n = 259 were included in a meta-analysis. Results after 12 and 24 weeks of intervention measured using MMSE and ADAS-cog were used.	A systematic review and meta-analysis were conducted to assess the efficacy of ginseng with conventional medication on the cognitive function of Alzheimer's disease.	Ginseng with conventional medication.	Conventional medication.	The meta-analysis showed inconsistent and varying outcomes. Some meta-analyses showed a significant effect while some showed no significant effect was found.	The efficacy of ginseng with conventional medicine in comparison to conventional medicine alone is inconclusive.	This study groups the efficacy of the intervention into a specific number of weeks, allowing for more detail and clarity as to how the intervention affects the cognitive function of subjects. However, no large amount and poor quality studies were included in the meta-analysis. No publication bias test was able to be conducted to the minimal amount of studies. In addition, this study does not depict a combined result in a forest plot, making the overall effect of the intervention more difficult to infer. The level of heterogeneity in the meta-analysis is also unknown which may affect the results of the meta-analysis.
9.	*Acupuncture plus Herbal Medicine for Alzheimer's Disease: A Systematic Review and Meta-Analysis*: Zhou S, *et al* (2017).	15 RCTs (n = 1217) were included. 11 of 15 were analyzed in a subgroup to assess the efficacy of Chinese herbal medicine with acupuncture in comparison to conventional medicine. MMSE was used in the calculation.	A systematic review and meta-analysis were conducted to assess the efficacy of Chinese herbal medicine with acupuncture in comparison to conventional medicine on the cognitive function in Alzheimer's patients.	Chinese herbal medicine such as *Yizhi Jiannao Pellet* with acupuncture	Conventional medication such as donepezil and piracetam.	Chinese herbal medicine with acupuncture was found to have a statistically significant effect on improving cognitive function in comparison to conventional medicine (MD = 2.10, p = 0.004).	Chinese herbal medicine with acupuncture exerts a level of efficacy superior to conventional medicine on improving cognitive function in Alzheimer's patients.	The number of studies included were large and a publication bias test was able to be conducted. However publication bias was found to a high degree which may have an influence on the outcome. Poor quality studies may also contribute to the outcome of the meta-analysis.
10.	*Comparisons Between Traditional Medicines and Pharmacotherapies for Alzheimer Disease: A Systematic Review and Meta-analysis Of Cognitive Outcomes*: May B, *et al* (2017).	30 RCTs (n = 2660) were included. Results from MMSE and ADAS-cog were used. Subgroups were formed based on different time points at weeks 12, 24, and 48-52.	A systematic review and meta-analyses were conducted to assess different Chinese herbal medicine in comparison to donepezil on improving cognitive function in Alzheimer's patients.	Various types of Chinese herbal medicine such as *Fufanghaisheji-aonang*.	Donepezil.	Chinese herbal medicine was found to have a level of efficacy comparable to donepezil.	Chinese herbal medicine exerts the same level of efficacy on improving cognitive function as donepezil.	A large number of studies was included and no statistically significant publication bias was detected. The efficacy of the intervention were also categorized based on a certain number of weeks, allowing for more clear and detailed effects of the intervention. However a high level of heterogeneity was detected and the studies included did not utilize intention-to-treat analysis. No pooled outcome was also available. As a result, an overall effect of the intervention was difficult to conclude.

11.	*Danggui-Shaoyao-San for Dementia A PRISMA-compliant Systematic Review and Meta-analysis*: Kim Y, *et al* (2019).	9 RCTs (n = 567) were included where 2 subgroups were formed. The first subgroup involved Danggui-Shaoyan-San (DSS) in comparison to vitamin E and the second subgroup involved DSS and acupuncture in comparison to acupuncture alone. Results used were measured from MMSE.	A systematic review and meta-analysis were conducted to assess the efficacy of DSS on the cognitive function in Alzheimer's patients.	DSS with or without acupuncture.	Vitamin E or acupuncture.	DSS with vitamin E was shown to have a statistically significant effect on improving cognitive function (MD = 4.60, p<0.001) and in DSS alone (MD = 1.69, p<0.001).	DSS exerts a level of efficacy superior to the interventions in combination with acupuncture or without.	A more objective assessment was able to be provided by the authors as they are from Korea, of which the studies included in the meta-analysis were from China. However, a high risk of bias was present due to the minimal amount, poor quality, and short time frame of research of studies included. No publication bias test was able to be conducted.
12.	*Chinese Herbal Medicines on Cognitive Function and Activity of Daily Living in Senior Adults with Alzheimer's Disease: A Systematic Review and Meta-analysis*: Zhang Y, *et al* (2019).	24 RCTs (n = 1711) were included. 23 of 24 were added to a subgroup to assess the efficacy of Chinese herbal medicine in comparison to conventional medicine on cognitive function using the results of MMSE.	A systematic review and meta-analysis were conducted to assess the efficacy of Chinese herbal medicine on the cognitive function and Activity of Daily Living in the elderly with Alzheimer's disease.	Various types of Chinese herbal medicine such as DSS and *Yizhi Jiannao Granule*.	Conventional medication such as (donepezil).	Chinese herbal medicine was found to have a significant effect on improving cognitive function in comparison to conventional medicine (SDM = 0.66, p <0.05)	Chinese herbal medicine exerts a level of efficacy superior to conventional medicine on improving cognitive function the elderly with Alzheimer's disease.	A large number of studies were included and no publication bias of statistical significance was detected, allowing for a more conclusive result of the efficacy of the intervention. However the studies included showed a high risk of bias and a high degree of heterogeneity was found in the meta-analysis.
13.	*Saffron for Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-analysis of Randomized Clinical Trial*: Ayati Z, *et al* (2020).	4 RCTs (n = 203) involving subjects with Alzheimer's disease or MCI were included. A subgroup comprised of only Alzheimer's patients were formed to assess the level of safety of *Crocus sativus*, where 3 of 4 studies were included.	A systematic review was done to review the efficacy of *Crocus sativus* on the cognitive function in patients with Alzheimer's disease or Mild Cognitive Impairment. A meta-analysis was conducted to assess the level of safety.	Standardized extract of *Crocus sativus*.	Placebo, donepezil, or memantine.	*Crocus sativus* is statistically insignificant in regards to safety compared to the controls (p>0.05).	*Crocus sativus* exerts a level of safety comparable to the controls.	No meta-analysis on the efficacy of *Crocus sativus* on cognitive function was available. No publication bias test was also conducted due to the minimal amount of studies involved.
14.	*Meta-analysis of Ginkgo biloba Preparation for the Treatment of Alzheimer's Disease*: Liao Z, et al (2020).	4 (n = 939) of 7 studies were included in a meta-analysis on the efficacy of EGb 761 in comparison to placebo on cognitive function in Alzheimer's patients. Results from ADAS-cog and SKT were used. 4 studies were included in a meta-analysis to assess the level of safety of EGb 761.	A systematic review and meta-analysis were conducted to assess the efficacy and safety of *Ginkgo biloba* on the cognitive function in Alzheimer's patients.	*Ginkgo biloba* extract (EGb 761) with or without donepezil.	Placebo or donepezil.	EGb 761 was found to have a significant effect on improving cognitive function (Relative Risk = 1.983, p<0.001) and has a superior level of safety (RR = 0.916, p = 0.046).	EGb 761 exerts a level of efficacy and safety superior to placebo or donepezil in Alzheimer's patients.	The results of the meta-analysis on the efficacy of *Ginkgo biloba* are reliable due to the statistically insignificant level of heterogeneity. The studies used were also of high quality due to the low risk of bias. However only a small number of studies were included in this study there no publication bias test was able to be conducted.

DISCUSSIONS

Alzheimer's Disease

Alzheimer's disease is a progressive and irreversible disorder which slowly impairs memory and other cognitive functions. The onset of cognitive function decline in Alzheimer's disease begins with an impaired episodic memory and anterograde amnesia which then progresses into disturbing other aspects of the brain controlling different functions such as language, attention, and problem solving. Donepezil, rivastigmine, and galantamine are common cholinesterase inhibitors used in Alzheimer's disease, targeting presynaptic cholinergic deterioration. Cholinesterase inhibitors bind and inhibit acetylcholinesterase and butyrylcholinesterase, enzymes responsible for the hydrolysis of synaptic acetylcholinesterase. The amount of acetylcholine within the synapses increase due to the inhibition of the enzymes, which allows the neurotransmitter to bind to cholinergic receptors in postsynaptic cells. The use of cholinesterase inhibitors is expected to improve cognitive and behavioral symptoms found in an Alzheimer's patient.[6]

The pathophysiology of Alzheimer's disease is highly complex and is not fully understood, but it is believed a number of various processes take place. The formation of β-amyloid plaques and neurofibrillary tangles (NFTs) are seen as hallmark characteristics in Alzheimer's disease. β-amyloid plaques are deposits of extracellular β-amyloid oligomers found throughout cerebral vessels and is induced by the truncation of amyloid precursor protein (APP) by β-secretase and leads to the formation and subsequently the aggregation of β-amyloid into insoluble β-amyloids . This is known as the amyloidogenic pathway. The most common forms of β-amyloid are β-40 and β-42, of which β-42 is more highly neurotoxic and more abundant than β-40 and induces oxidative stress and promotes the hyper phosphorylation of the τ protein. The formation of β-amyloid plaques will lead to the formation of NFTs as well, which can interfere with the communication and signaling process between neurons and can cause apoptosis.[7-8] As a result of the formation of plaques and NFTs, microglia cells release pro-inflammatory cytokines, contributing to the neurotoxicity already present within the brain. Mitochondrial function impairment brought upon by inflammation will lead to the formation of reactive oxygen species (ROS), disturbing the function of neurons and the loss of cholinergic neurons as well as a reduction of acetylcholine.[9]

Ginkgo biloba

A randomized controlled trial by Ihl R et al (2011) reported 240 mg of EGb 761 has a superior effect in increasing cognitive function in comparison to placebo. This was supported by a meta-analysis by Yang M et al (2014), Tan MS et al (2016), and Liao Z et al (2020), mentioning the same outcome. If given with donepezil, it was reported to have a better effect than donepezil alone according to Yang G et al (2016). The studies also corroborated that a greater level of safety was also achieved with *Ginkgo biloba* with or without donepezil than placebo or donepezil alone (table 2). In Indonesia, EGb 761 is available in the form of tablets. Based on online searches, 120 mg of EGb 761 is priced from IDR 500,000 to IDR 800,000.

Ginkgo biloba is a plant originating from East China and belongs in the family *Ginkgoceae*. This specific medicinal plant dates back to 5000 ago years to treat various cardiovascular or respiratory ailments such as bronchitis and asthma in China. In general, the leaves of the plant are used as medicine and is available as a standardized extract, EGb 761. [10-11] Flavonoids and terpenes are active compounds contained within *Ginkgo biloba*, and offers neuroprotection while acting as antioxidants, anti-inflammatory, mitochondrial dysfunction protectors, τ protein phosphorylation modulators, β-amyloid inhibitors, and other mechanisms of action.[11]

Curcuma longa

Ringman J et al (2012) reported *Curcuma longa* extract has an inferior effect on increasing cognitive function but with a comparable level of safety when compared to placebo in Alzheimer's patients (table 1). *Curcuma longa*, or often referred to as turmeric, is a plant belonging to the Zingiberaceae family and has been widely used in Asia as a coloring agent and a medicinal ingredient in Ayuverdic medicine and traditional Chinese medicine. Turmeric is able to relieve inflammation and was used to combat diabetes, hepatic diseases, rheumatism, and other ailments in Indian medicine.[12] Turmeric is a plant indigenous to Indonesia and is easily obtained whole of which the rhizome is used. *Curcumin C3 Complex®* is also available as an extract of turmeric. Based on online searches, every 250 gr of whole turmeric is priced at IDR 5,000 to IDR 10,000 and 120 capsules of *Curcumin C3 Complex®* with a dose of 500 mg is priced at IDR 500,000 to IDR 700,000.

Curcumin, the active compound in turmeric, acts as a neuroprotector in Alzheimer's disease by preventing the formation and reducing the toxicity of β-42 oligomers, preventing β-amyloid aggregation, protecting PC-12 cells and endothelial cells from oxidative stress induced by β-amyloid, and reducing the expression of enzymes playing a role in β-amyloid formation such as β-secretase and BACE.[13]

Crocus sativus

Farokhnia M et al (2014) reported that dry extract of *Crocus sativus* is comparable to memantine in regards to efficacy and safety in increasing cognitive function. Ayati Z et al (2020) reported *Crocus sativus* has a comparable level of safety to placebo, donepezil, and memantine (table 1). Based on online searches, 1 gr of saffron is priced from IDR 40,000 to IDR 150,000, depending on the type of saffron. Memantine is not a drug covered by the Indonesian National Health Insurance while donepezil is, according to the 2019 National Formulary of Indonesia. 5 mg of Donepezil is priced from IDR 170,000 to IDR 255,000 for every 30 tablets while 10 mg of memantine has a price range of IDR 932,000 to IDR 1,370,000 based on online searches.

Crocus sativus or saffron is a part of Iridaceae family and has been used as a medicine in various medical systems such as traditional Chinese medicine, Ayuverda, and in Greece. The stigma, the part of the saffron that is derived for use, can act as a treatment from asthma and arthritis or other chronic disease to a fever or a cough. In addition, saffron is purported to have properties as an expectorant and an antidyslipidemic. However saffron is not cultivated in Indonesia and sourcing from countries that do is required.[15-16] Crocin and safranal are the active compounds of saffron. It is suspected to aid in Alzheimer's disease treatment by increasing long-term potentiation, heightening anti-amyloidogenic activity, and acting as an acetylcholinesterase inhibitor and an antioxidant.[17]

Huperzine A

A meta-analysis by Yang G et al (2013) reported Huperzine A has a superior effect when compared to placebo in increasing cognitive function in Alzheimer's disease (table 1). Huperzine A is an extract from the plant *Huperzia serrata,* belonging to the Lycopodiaceae family. It has been used for

treating Alzheimer's disease as the compounds act as a selective, reversible, and potent acetylcholinesterase inhibitor. In China it has been used as a treatment for fever, inflammation, and hematological disorders.[18-19] However *Huperzia serrata* is not native to Indonesia. Based on online searches, 15 capsules of 200 μg Huperzine A is priced from IDR 80,000 to IDR 120,000.

Huperzine A works in the cholinergic system as an acetylcholinesterase inhibitor. Other neuroprotective effects of Huperzine A include preventing mitochondrial dysfunction from β-amyloid toxicity, increasing the secretion and signaling of Nerve Growth Factor (NGF), working as an NMDA receptor antagonist, and inhibiting neuronal apoptosis. Potentially, Huperzine A reduces iron levels in the brain, leading to reduced β-amyloid production, aggregation, and toxicity.[20]

Panax ginseng

Wang Y et al (2016) reported that due to the inconsistency found in the meta-analyses done, the efficacy of ginseng with conventional medicine in comparison to conventional medicine alone cannot be determined (table 1). *Panax ginseng* is a part of the Araliaceae family and is often referred to as ginseng. The root of this plant has been used in Korea, China, and Japan as a way to increase physical strength, revitalize physical and mental health, slow aging, and increase energy.[21] Ginseng is not native to Indonesia and based on online searches, 50 gr of *Panax ginseng* is purchasable for IDR 25,000 to IDR 90,000.

The active compounds within ginseng are ginsenoside and gintonin, each of them having different properties. Ginsenoside decreases β-amyloid formation, inhibits the activity of acetylcholinesterase and toxicity of β-amyloid, and decreases neuronal inflammation and reactive oxygen species. Gintonin also inhibits β-amyloid toxicity and formation, as well as increasing acetylcholine expression and choline acetyltransferase.[22]

Chinese Herbal Medicine

Yizhi Jiannao pellet, DSS, and *Fufanghaishejiaonang* have been included in the 4 meta-analyses in this study. May B et al (2017) reported that Chinese herbal medicine has a comparable level of efficacy with donepezil. While Zhang Y et al (2019) described when compared to conventional medicine, Chinese herbal medicine has a superior efficacy. A meta-analysis

conducted by Kim Y et al (2019) reported DSS is superior to vitamin E alone in regards to efficacy, as well as DSS in combination with acupuncture in comparison to acupuncture alone. Finally, Zhou S et al (2017) noted the superior efficacy of Chinese herbal medicine in tandem with acupuncture when compared to conventional medicine.

Chinese herbal medicine is a part of traditional Chinese medicine, which has been used to treat diabetes, infections, allergies, inflammation, and cancer. Various medicinal plants in Chinese medicine are also thought to improve physical health and blood flow.[23] Based on online searches, Chinese herbal medicine vary in price, dosage, and the types for sale.

Chinese herbal medicine is believed to have several mechanisms in treating Alzheimer's disease. In general, Chinese herbal medicine regulates the inflammation process by inhibiting pro-inflammatory cytokines, inhibiting oxidative stress, inhibiting τ protein phosphorylation, reducing abnormal β-amyloid deposits, regulating nuclear transcription factor NF-κB, and increasing the cholinergic system. *Yizhi Jiannao* pellets specifically strongly inhibits PC12 cell apoptosis induced by β-amyloid.[24] DSS is reported to protect neurons and restore impaired long-term potentiation as a result of β-amyloid neurotoxicity, as well as containing antioxidant and anti-inflammatory properties, and increasing the amount and the release of acetylcholine, dopamine, and norepinephrine. Finally, *Fufanghaishejianang*, otherwise known as Reinhartdt and sea cucumber capsule, is reported to exert it effects on a cellular and molecular level by increasing acetycholine and superoxide dismutase in the brain, in addition to decreasing glutamic acid and lipid peroxidation.[25]

CONCLUSION

The clinical trials and meta-analyses data available to date show a potential of several herbal plants as a nootropic in Alzheimer's disease due to positive effect of improving cognitive status or function. *Ginkgo biloba* with or without the administration of donepezil has a superior efficacy and safety in comparison to placebo or donepezil alone at a fairly expensive price. *Curcuma longa* has an inferior efficacy in comparison to placebo but with a level of safety equivalent to placebo. *Crocus sativus* has a superior efficacy and safety comparable to memantine or any other conventional Alzheimer's medication

and is affordable. Huperzine A has a superior efficacy in comparison to place but not enough data are available to ascertain it's safety. The efficacy and safety of *Panax ginseng* cannot be confirmed yet. Chinese herbal medicine with or without acupuncture has a superior efficacy in comparison to conventional medication, vitamin E, or acupuncture alone, but is not applicable in Indonesia. Based on the scientific evidence available, it can be concluded that *Crocus sativus* can be made as an alternative therapy to increase cognitive function in patients with Alzheimer's. However a standardized extract needs to be available for common Indonesians to use. *Crocus sativus* works as an acetylcholinesterase inhibitor, anti-amyloidogenic, and might has other mechanisms of action.

Conflict of Interest

All authors have no conflict of interest to disclose.

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