The Use of Traditional Chinese Herbs, Danggui-Shaoyao-San to Prevent the Development of Vascular Dementia (VD) and Alzheimer's Disease (AD) in the Elderly

Zahrah Hisanah Rifdah[a], Sanchia Callista Raihanah Wiryawan[a], Riska Ayu Eliana[a], Yuani Setiawati[b*], Mariza Fitriati[c]

[*]yuani-s@fk.unair.ac.id
[a]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, Indonesia
[b*]Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, Indonesia
[c]Department of Anesthesiology and Reanimation, Dr. Soetomo General Academic Hospital, Surabaya 60132, Indonesia

Abstract

Dementia causes cognitive decline that is chronic and progressive. People with dementia in the world in 2015 reached 50 million and is estimated to continue to grow. Dementia mostly affects the elderly (5% of the elderly over 60 years). The most common dementias are Alzheimer's disease and Vascular dementia. The current treatment for dementia has not been effective, so alternative treatments are needed, one of which is traditional Chinese medicine, namely Danggui-Shaoyao-San (DSS). This literature study aims to determine the effectiveness of Danggui-Shaoyao-San in preventing and treating cognitive decline in dementia. Literature searches using search engines such as Google Scholar, PubMed, and Science Direct. In dementia, there is a neurotoxic beta amyloid deposition in the brain. Dementia treatment of acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) provides only marginal therapeutic benefit and does not halt disease progression. DSS extract, namely JD-30, can reduce the escape latency time in experimental rats injected with Senescence-accelerated mouse prone 8 (SAMP8) in the Morris water maze test. Mice were injected with SAMP8 to determine the effect of DSS in preventing cognitive decline with age. In addition to treating Alzheimer's disease, DSS also reduced Nissl body damage in the CA1 hippocampus and oxidative stress in experimental rats with Vascular Cognitive Impairment (VCI). DSS research is still focused on the oral administration of DSS. However, many people with dementia have difficulty swallowing, so non-oral administration of DSS should be considered. From the various literature, DSS has been proven to be an alternative therapy for dementia, but research on non-oral DSS administration is still very little so further research is needed.

Keywords: Alzheimer disease; Danggui-shaoyao-san; Dementia, Vascular dementia; Traditional chinese medicine

1. Introduction

Dementia is a group of various symptoms characterized by a decrease in brain function that is more often chronic and progressive. Symptoms that often occur are such as memory loss and cognitive decline, so that sufferers experience disturbances in their daily activities. In 2015, people with dementia reached 50 million people worldwide (roughly 5% of the elderly population over the age of 60). The number of people with dementia is expected to increase to 82 million people in 2030 and 152 million in 2050 with an estimated population aged 60 years and over with dementia 5-8%. [1]

There are many causes and types of dementia. Dementia is divided into primary dementia and secondary dementia. Primary dementia consists of Alzheimer's disease (AD), Vascular dementia (VD), dementia with Lewy bodies, and Frontotemporal dementia (decreased cognitive abilities caused by neurodegenerative processes). The most common dementia in patients with Alzheimer's disease is followed by vascular dementia and dementia with Lewy bodies. Secondary dementia is caused or associated with other diseases such as HIV, head injury, multiple sclerosis, thyroid disorders, or vitamin B12 deficiency. In secondary dementia, cognitive decline is followed by symptoms in other organ systems. [2]

The current treatment for dementia is acetylcholinesterase inhibitors, one of which is carbamate class rivastigmine which is used for the treatment of Alzheimer's disease, as well as galantamine and donepezil. In addition to acetylcholinesterase inhibitors, there is also memantine. Memantine acts as an antagonist of NMDA (N-methyl-D-aspartate). [3] Many pharmaceutical companies are competing in developing anti-dementia treatments, but these companies have to face various challenges from mechanisms such as nerve damage caused by acetylcholine synthesis, beta amyloid protein deposition, and Tau protein hyperphosphorylation. [4]

Therefore, many drug candidates have been successful in animal trials, but not effective in human clinical trials. Due to the large number of drugs that do not completely cure dementia, we recommend dementia therapy with an herbal plant, Danggui-Shaoyao-San (DSS). DSS is a formula consisting of Angelica gigas, Paeonia lactiflora, Ligusticum chuanxiong, Poria cocos, Atractylodes macrocephala, and Alisma orientalis. This DSS can be used for prevention or as a therapeutic agent in the reduction of cognitive impairment. In addition, DSS can work on the cognitive function of Alzheimer's disease and Vascular disease as described in the MMSE and HDS Scores. [4] Therefore, this literature study was made to determine the effectiveness of Danggui-Shaoyao-San to prevent and treat cognitive decline in people with dementia.

2. Methods

This literature study was made by searching, collecting, analyzing, and citing various journals and studies related to herbal medicine for dementia. The search for various journals and studies was carried out using search engines such as Google Scholar, PubMed, and Science Direct which were published in the last 10 years. The keywords used were "dementia", "Danggui-Shaoyao-San", "Alzheimer disease", "vascular dementia", and "vascular cognitive impairment".

3. Results and Discussion

3.1. Pathogenesis of dementia

The most common dementia is Alzheimer's disease. One of the hallmarks of Alzheimer's disease is atrophy and gliosis of the temporal lobes and hippocampus. On histopathological preparations, extracellular amyloid eosinophilic deposits were found consisting of Aβ peptide or amyloid plaques and intraneuronal aggregates of protein-associated microtubules (Neurofibrillary tangles). In histopathological abnormalities, two formations were found, namely extracellular aggregation of neuritic plaques (senile plaques), which are deposits of beta amyloid derived from amyloid precursor protein (APP) and neurofibrillary tangles (NFTs), which are intracellular accumulations of hyperphosphorylated Tau protein in certain brain regions. [5]

The increase in Alzheimer's disease can occur through slow onset and rapid onset. Late onset is associated with apolipoprotein E variant 4 (ApoE), whereas early onset is associated with polymorphisms in amyloid precursor protein (APP) namely presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2). Aβ deposition in the brain is one of the pathogenesis of Alzheimer's disease. This accumulation of Aβ can lead to neuronal dysfunction,

neurodegeneration, and dementia. An increase in Aβ42, which is a major component of amyloid deposited in the brain can also cause aggregation, fibril formation, and neurotoxic effects. [6]

Treatments that can be given to people with dementia include non-pharmacological therapy and pharmacological therapy. Non-pharmacological therapies include behavioral management, cognitive stimulation, reality orientalist therapy, and so on. While pharmacological therapy includes Acetylcholinesterase inhibitor drugs (donepezil, galantamine, and rivastigmine) and NMDA receptor antagonists (memantine). Although these drugs have been recommended, they are not fully able to treat dementia. [7]

3.2. Pharmaceutical treatment for dementia

Currently, there are only two groups of drugs approved to treat dementia, namely Acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) antagonists. Acetylcholinesterase inhibitors (AChEIs), such as donepezil, galantamine, and rivastigmine, as well as N-methyl-D-aspartate (NMDA) antagonists, such as memantine, are currently used to stop or delay the development of Alzheimer's disease and vascular dementia, but these drugs do not completely treat all forms of the disease itself.[8] The symptomatic therapeutic effect of these drugs used for memory impairment in Alzheimer's disease patients is transient and somewhat limited, so the disease can progress to cognitive impairment. [9]

Acetylcholinesterase inhibitors (AChEIs)

Three drugs in the AChEIs group (donepezil, rivastigmine, and galantamine) that are currently available have shown similar treatment effects for Alzheimer's disease in randomized controlled studies. This effect is associated with decreased destruction of acetylcholine, a neurotransmitter associated with memory function, by blockage of the enzyme acetylcholinesterase. The side effects caused by this group of drugs mainly affect the gastrointestinal system. However, vagotonic side effects may also be associated with CVD risk. [10]

Galantamine and donepezil selectively inhibit acetylcholinesterase, which is the main mechanism for the hydrolysis of acetylcholine in the brain, while rivastigmine also inhibits butyrylcholinesterase. In addition to its effect on acetylcholinesterase, galantamine also acts as an allosterically potent nicotinic receptor ligand and increases the strength of residual acetylcholinergic synapses. [11]

AChEI cannot eliminate AD or prevent its natural progression, but, in return, AChEI can relieve symptoms. With the use of donepezil, galantamine, and rivastigmine, improvement in the severity of the disease persists for about 6 months, but the effect rarely restores lost function. Clinical trial data for each of the three available oral AChEIs suggest that they can reduce the rate of decline in cognitive function and the severity of dementia, and improve performance in activities of daily living in people with mild to moderate AD. However, lost functional capacity (eg. the ability to manage finances or drive) is rarely recovered. [12]

N-Methyl-D-Aspartate (NMDA)

Memantine is indicated for the treatment of patients with moderate to severe Alzheimer's disease. Some evidence also shows that memantine is effective in delaying the course of the disease in dementia, as well as reducing the appearance of symptoms of behavioral disorders including agitation and aggression.

Memantine is characterized as a noncompetitive, voltage-dependent NMDA receptor antagonist, with moderate binding affinity, and rapid receptor-blocking kinetics. The uniqueness of this binding allows memantine to integrate into the glutamatergic signaling system and influences the activation of NMDA receptors that do not function properly in Alzheimer's disease.

In AD, memantine can reduce pathological 'background noise' of dysfunctional glutamate signaling, allowing it to be better differentiated from physiological signals. The mechanism acting on memantine may also serve to protect neurons from excitotoxicity from excessive glutamate stimulation caused by direct or indirect activation of NMDA receptors. Memantine has been shown to protect against pathological changes and learning retardation caused by intrahippocampal beta amyloid injection. Memantine also specifically demonstrated protection against synaptic damage induced by beta amyloid and Reactive Oxygen Species. [13]

Like other neurodegenerative diseases, AD is characterized by persistent over-activation of the glutamate N-methyl-D-aspartate receptor, where this activation can impair synaptic plasticity, and possibly due to increased intracellular calcium accumulation, which will eventually lead to neuronal degeneration. This concept has stimulated the development and use of drugs that block these receptors. However, the clinical utility of conventional NMDA antagonists is severely limited due to side effects caused by disturbances in the physiological role of glutamate signaling. In contrast, memantine appears to reduce sustained low-level activation without interfering with the physiological function of the NMDA receptor, thanks to its voltage-dependent action. It has been shown to have a positive effect on cognitive and behavioral symptoms in patients with moderate to severe AD. [4]

Galantamine, donepezil, rivastigmine, and memantine have been found to reduce behavioral disturbances that occur in moderate AD, thanks to their effects on general cognitive function and on cholinergic afferents and reciprocal serotonergic connections of the limbic system. To date, there are no specific medications available for the treatment of behavioral symptoms of AD. Physician often prescribe antianxiety drugs, anticonvulsants, antipsychotics, and antidepressants in small doses. Moderate atypical antipsychotics are also used, but their efficacy is debated, especially in mild to moderate AD because the considerable risk of side effects such as Parkinson's symptoms and tardive dyskinesia may outweigh the potential benefits of the drugs themselves. [4]

Treatment of dementia using AChEIs and NMDAs does not halt disease progression and provides only marginal therapeutic benefit. Therefore, it is necessary to develop new effective drugs for AD that can surpass AChEIs and NMDA antagonists. Many alternative strategies are being developed by researchers around the world for the treatment of dementia, including the use of natural products of plant origin. The therapeutic use of using natural products must be proven and explained by researchers through the mechanisms involved in the treatment before it can finally be released into a medicinal product as a therapeutic agent. [14]

3.3. Traditional chinese herbal alternative medicine, Danggui-Shaoyao-San

Treatment of Alzheimer's disease (AD) and Vascular Dementia (VD) with Danggui–Shaoyao–San

The deposition of beta amyloid or Aβ in the brain is a major marker of Alzheimer's disease. [6] From studies in patients with mild to moderate Alzheimer's, beta amyloid especially Aβ42 can be found in the saliva by ELISA examination, and there is a significant increase in Aβ42 levels in the saliva of patients with mild to moderate Alzheimer's. [15] Although the exact cause of dementia is not known, from various studies, beta amyloid is suspected as a strong cause of dementia. Therefore, research for the treatment of dementia targeting beta amyloid with minimal side effects is being carried out. One of them is with traditional herbal medicine from China, namely Danggui-Shaoyao-San (DSS).

Danggui-Shaoyao-San is a mixture of various traditional Chinese plants, namely Angelica gigas, Paeonia lactiflora, Ligusticum chuanxiong, Poria cocos, Atractylodes macrocephala, and Alisma orientalis. According to various studies, Danggui-Shaoyao-San can improve cognitive abilities in Alzheimer's sufferers. According to the research of Hu, Zheng-Yao et al., (2010) that the extract of DSS, namely JD-30 which was administered orally in experimental mice that had been injected with aggregates of Aβ25-35 intracerebroventricularly (ICV)

reduced the escape latency of mice in the Morris water maze tasks. The decrease in escape latency of the model mice that had been administered orally DSS proved that there was an improvement in spatial and memory abilities. In addition, JD-30 extract from DSS was also shown to inhibit and even destroy the aggregation of beta amyloid in vitro. [16]

In a follow-up study by Hu, Zheng-Yao, et al., (2011), Senescence-accelerated mouse prone 8 (SAMP8) was used. There has been a development of research focus from previous research, namely to find out that DSS is preventive in preventing cognitive impairment as people get older. Therefore, SAMP8 was used to determine the relationship between increasing age with deficits in memory and cognitive abilities. From this study, it is evident that the use of DSS can reduce the deposition of beta amyloid in the brain SAMP8, especially on CA3 and CA4 in the hippocampus. These results indicate that long-term consumption of the DSS extract, namely JD-30, can reduce the amount and deposition of beta amyloid in the brain, so it can be concluded that the administration of JD-30 which is an extract of DSS can improve cognitive impairment with age. [17]

In patients with Vascular dementia (VD) or Vascular Cognitive Impairment (VCI) administration of DSS can also improve learning and memory abilities. From the study, it was proven that there was a cognitive improvement in experimental rats with permanent common carotid artery occlusion who were given DSS. In the Morris water maze task, namely the positioning navigation test, there was a decrease in escape latency from model mice that experienced VCI which was administered by DSS. In VCI mice given DSS there was also a neuroprotective effect by preventing neuronal apoptosis, it was proven that in VCI mice there was a decrease in nissl body in the CA1 part of the hippocampus, and with high doses of DSS in VCI mice, neurons in CA1 experienced minimal damage and The morphology of the neurons appeared normal. In addition, in VCI rats there was a decrease in oxidative stress after being given DSS due to a decrease in Malondialdehyde (MDA) and Reactive Oxygen Species (ROS) in VCI rats. [18] Therefore, in addition to DSS can be used to treat Alzheimer's disease (AD), DSS can also be used to treat Vascular dementia (VD).

Danggui-Shaoyao-san Oral Administration

According to various studies on rats, the administration of Danggui-Shaoyao-San is carried out orally. [16], [19] The research focused on DSS absorption proves that one of the DSS ingredients, namely Paeoniflorin, is more effectively absorbed if it is in the form of DSS, not consumed alone without other DSS content. This proves that the bioavailability of DSS is high in the body with oral consumption. [19] In addition to the oral administration of DSS, intragastric administration was also performed on mice. [17] However, according to the authors, it is not possible to do this in humans, especially people with dementia who are routinely treated, and it was only done for experiments with rats.

Danggui-Shaoyao-San is a traditional Chinese herbal medicine. Many traditional Chinese medicines are administered orally. [20],[21] However, there have also been administrations in experimental rats by nebulizer or by inhalation. The experiment was conducted to treat asthma with Complex Traditional Chinese Medicine (CTCM). [22] However, research on DSS is still focused on the oral administration of DSS.

Taking Danggui-Shaoyao-San orally is not easy for people with dementia. Especially, in patients with moderate to severe dementia. Cognitive decline in people with dementia makes it difficult for people with dementia to swallow. In a study conducted on patients with dementia in the CDR2 (moderate dementia) and CDR3 (severe/severe dementia) groups, swallowing difficulties occurred. In the CDR2 group, there were variations in results, some had difficulty and some had no difficulty swallowing. However, in the CDR3 group as the disease progressed, swallowing difficulties occurred in many patients. [23] From the search conducted by the author, research on non-oral consumption of DSS is still minimal. Research is needed to make it easier for people with dementia who have difficulty swallowing to take DSS.

4. Conclusion

Alzheimer's disease and Vascular dementia are two types of dementia that are common in the world. One of the strong causes of dementia is the deposition of beta amyloid protein, even in patients with dementia beta amyloid can be detected in saliva. The current pharmacological treatment for dementia is the use of Acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) antagonists, which until now have not been able to stop the progression of the disease, providing only a marginal therapeutic effect. Research on effective dementia treatment is intensively carried out, one of which is traditional Chinese medicine, namely Danggui-Shaoyao-San (DSS).

Danggui-Shaoyao-San is quite effective in reducing beta amyloid deposition and triggering cognitive development. According to research, the fraction of Danggui-Shaoyao-San, namely JD-30, has been shown to be effective in increasing cognitive abilities in experimental rats who experience cognitive decline with age on the Morris water maze task with a decrease in escape latency. In addition to treating Alzheimer's disease, DSS has also been shown to improve cognitive abilities in mice with Vascular Cognitive Impairment (VCI). Therefore, DSS can be a strong candidate for alternative treatment of dementia that can prevent disease progression in people with dementia.

The administration of DSS is still done orally like most other traditional Chinese herbal remedies. However, some people with moderate to severe dementia have difficulty swallowing, so an easier and more effective way of administering DSS is needed for people with dementia.

5. Suggestion

The authors suggest further research on the administration of Danggui-Shaoyao-San other than orally, as research on the non-oral administration of DSS is scanty. Several studies conducted Intragastric non-oral administration in rats which is not possible in humans. Therefore, further research should be conducted on the administration of DSS that is more appropriate for the condition of people with dementia, especially in patients with moderate and severe dementia.

References

Prince, MpB., Guerchet, M., Prina, M., 2013. The Global Impact of Dementia 2013 – 2050. Alzheimer's Dis Int [Internet]. 1–8. Available from: https://www.alz.co.uk/research/GlobalImpactDementia2013.pdf

Dua, T., Seeher, KM., Sivananthan, S., Chowdhary, N., Pot, AM., Saxena, S., 2017. Risk reduction of cognitive decline and dementia. Vol. 13, Alzheimer's & Dementia. 1450–1451 p.

Katzung, T., 2015. Pharmacology Examination & Board Review. Mc Graw Hill Educarion. 359 p.

Kim, Y., Cho, SH., 2020. Danggui-Shaoyao-San for dementia: A PRISMA-compliant systematic review and meta-analysis. Medicine. Jan;99(4).

Nisa, KM., Lisiswanti, R., 2016. Faktor Risiko Demensia Alzheimer. Majority [Internet]. 5(4):86. Available from: http://juke.kedokteran.unila.ac.id/index.php

Pattni, KAM., 2014. Beta-Amyloid As Pathogenesis of Alzheimer Disease. Beta-Amyloid As Pathog Alzheimer Dis. 2(8):1306–17.

Harahap, HS., Rianawati, SB., 2015. Infection-Associated Dementia. Jurnal MNJ. 1(01)

Kim, Y., Cho, S., 2020. Danggui-Shaoyao-San for dementia. Med [Internet]. 4 (November 2019):2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004764/

Kimura, T., Takamatsu, J., 2015. Ferulic Acid and Angelica archangelica Extract in Dementia: Effects on Cognitive Functions and Behavioral and Psychological Symptoms of Dementia [Internet]. Diet and Nutrition in Dementia and Cognitive Decline. Elsevier Inc.; 993–1001 p. Available from: http://dx.doi.org/10.1016/B978-0-12-407824-6.00092-6

Nordström, P., Religa, D., Wimo, A., Winblad, B., Eriksdotter, M., 2013. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: A nationwide cohort study in subjects with Alzheimer's disease. Eur Heart J [Internet]. 34(33):2585–91. Available from: https://academic.oup.com/eurheartj/article/34/33/2585/408582

Giannopoulos, PF., Praticò, D., 2015. Alzheimer's Disease [Internet]. Diet and Nutrition in Dementia and Cognitive Decline. Elsevier Inc. 13–21 p. Available from: https://www.sciencedirect.com/science/article/pii/B9780124078246000021

Brady, R., Weinman, J., 2013. Adherence to cholinesterase inhibitors in Alzheimer's Disease: A review. Dement Geriatr Cogn Disord [Internet]. 35(5–6):351–63. Available from: https://www.karger.com/Article/FullText/347140

Parsons, CG., Danysz, W., Dekundy, A., Pulte, I., 2013. Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. Neurotox Res [Internet]. 24(3):358–69. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3753463/

Mani, V., Ahmad, A., Ramasamy, K., Lim, SM., Majeed, ABA., 2015. Murraya koenigii Leaves and Their Use in Dementia [Internet]. Diet and Nutrition in Dementia and Cognitive Decline. Elsevier Inc. 1039–1048 p. Available from: http://dx.doi.org/10.1016/B978-0-12-407824-6.00097-5

Sabbagh, MN., Shi, J., Lee, M., Arnold, L., Al-Hasan, Y., Heim, J., et al. 2018. Salivary beta amyloid protein levels are detectable and differentiate patients with Alzheimer's disease dementia from normal controls: preliminary findings. BMC Neurol. 18(1):155.

Hu, ZY., Liu, G., Yuan, H., Yang, S., Zhou, WX., Zhang, YX., et al., 2010. Danggui-Shaoyao-San and its active fraction JD-30 improve Aβ-induced spatial recognition deficits in mice. J Ethnopharmacol [Internet]. 128(2):365–72. Available from: http://dx.doi.org/10.1016/j.jep.2010.01.046

Hu, ZY., Liu, G., Cheng, XR., Huang, Y., Yang, S., Qiao, SY., et al., 2012. JD-30, an active fraction extracted from Danggui-Shaoyao-San, decreases β-amyloid content and deposition, improves LTP reduction and prevents spatial cognition impairment in SAMP8 mice. Exp Gerontol [Internet]. 47(1):14–22. Available from: http://dx.doi.org/10.1016/j.exger.2011.09.009

Cai, H., Cai, T., Zheng, H., Liu, L., Zhou, L., Pang, X., et al., 2020. The Neuroprotective Effects of Danggui-Shaoyao San on Vascular Cognitive Impairment: Involvement of the Role of the Low-Density Lipoprotein Receptor-Related Protein. Rejuvenation Res. 23(5):420–33.

Liu, J., Wang, JS., Kong, LY., 2011. Comparative pharmacokinetics of paeoniflorin in plasma of vascular dementia and normal rats orally administrated with Danggui-Shaoyao-San or pure paeoniflorin. Fitoterapia [Internet]. 82(3):466–73. Available from: http://dx.doi.org/10.1016/j.fitote.2010.12.004

Wang, X., Sun, H., Zhang, A., Jiao, G., Sun, W., and Yuan, Y., 2011. Pharmacokinetics screening for multi-components absorbed in the rat plasma after oral administration traditional Chinese medicine formula Yin-Chen-Hao-Tang by ultra performance liquid chromatography-electrospray ionization/quadrupole-time-of-flight mass spectrometry combined with pattern recognition methods. Analyst. 136:5068 –5076.

He, MY., Deng, YX., Shi, QZ., Zhang, XJ., Lv, Y., 2014. Comparative pharmacokinetic investigation on baicalin and wogonoside in type 2 diabetic and normal rats after oral administration of traditional Chinese medicine Huanglian Jiedu decoction. J Ethnopharmacol. 155:334–342.

Chang, HC., Gong, CC., Chen, JL., Mak, OT., 2011. Inhibitory effects of inhaled complex traditional Chinese medicine on early and late asthmatic responses induced by ovalbumin in sensitized guinea pigs. BMC Complement Altern Med. p11.

Correia, SM., Morillo, LS., Jacob, FW., Mansur, LL., 2010. Swallowing in moderate and severe phases of Alzheimer's disease. Arq Neuropsiquiatr. 68(6):855–61.