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Letter of Acceptance
25 October 2022

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I am very excited to accept your paper entitled:
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Your paper will be published in the issue of Vol. 11 Number 3, 2022.
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REVIEW

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Medicinal Plants - A Promising Breakthrough in the Management of Alzheimer's Disease Progression Compared to NSAID: A Systematic Review

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ABSTRACT

Treatment of Alzheimer's Disease is currently limited only to slowing the progression of the symptoms, not curing the disease. Current FDA-approved therapies such as Donepezil, Tacrine, Galantamine, Rivastigmine, and Memantine have quite disturbing side effects, as well as the mechanism of action of these drugs, which is dominated by working as AChE inhibitors. On the other hand, the hypothesis for Alzheimer's causes is varied. Another study also states that Non-Steroid Anti-Inflammatory Drugs (NSAIDs) can be given to people with Alzheimer's. However, the reports were conflicting as one study stated that NSAIDs can help reduce the risk of Alzheimer's; on the contrary, other studies have argued that giving NSAIDs to people with Alzheimer's is not necessary. Despite administering Alzheimer's drugs and NSAIDs, which have adverse side effects on long-term use and high doses, the administration of traditional medicines and medicinal plants can be a good solution due to lower side effects than common drugs, less risk, easy access and affordable. These medicinal plants have several mechanisms to counter the hypothesis that causes Alzheimer's disease.

Keywords: Alzheimer disease, Herbal medicine, NSAID, Medicinal plant.
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INTRODUCTION

Mild to severe dementia and challenging to recognize, memory failure or Mild Cognitive Impairment (MCI), which slowly becomes severe, and disabling the sufferer, are signs of Alzheimer's Disease (AD).[1] This AD's symptoms are followed by several supporting findings, such as confusion and associated complications, language disturbances, visual complaints, agitation, withdrawal and hallucinations. Symptoms such as Parkinson's disease, increased muscle tone, myoclonus, incontinence and mutism can also occur. In conditions of initiation, malnutrition and pneumonia can result in general death. The AD range lasts from one to 25 years, with the typical clinical duration of the disease 8 to 10 years.[2]

Overproduction and impaired clearance of β-amyloid is thought to cause AD. Tau hyperphosphorylation and neuronal toxicity are end events that can be seen. In the blood vessels in the brain, β-amyloid deposits are also found.[3] In addition, regarding the presence of Aβ plaque and NFT, evidence of sustained inflammatory response was also found in the brains of patients with AD. Observational and epidemiological studies in the 1990s demonstrated a protective quality against AD's development with the use of anti-inflammatory drugs in patients with diseases such as rheumatoid arthritis, with a 50% reduced risk of developing AD in patients treated with long term Non-Steroid Anti-Inflammatory Drugs (NSAIDs).[4]

Activation of microglia increases the number of pro-and anti-inflammatory cytokines that regulate the body's immune response due to the TREM2 mutation and other changes in microglial receptors. These cytokine-related changes have been a significant part of evaluating the presence of AD. The specific cytokines signaling in AD are TNF-α, IL-1β, IL-6, NFkB, IL-10 dan TGF-β1.[4]

The current Alzheimer's therapy process focuses on cholinesterase inhibition which limits the enzyme acetylcholinesterase (AChE), which increases acetylcholine in the brain. This cholinesterase inhibition process can be found in the drugs donepezil, tacrine, galantamine, rivastigmine, and memantine.[5] The drugs used are known to have side effects that are quite uncomfortable; hence it provides potential in alternative medicine using traditional plants. It is known that many traditional plants can improve brain function, but this still needs to be proven empirically due to limited time and sufficient resources.[6]

In traditional medicinal plants, bioactive compounds such as tannins, lignans, polyphenols, flavonoids, sterols, triterpenes, and alkaloids have

the potential to overcome problems related to anti-amyloidogenic, anti-inflammatory, anticholinesterase, hypolipidemic and antioxidant effects.[5] Antioxidant derivatives that function as neuroprotection protect various components of the nervous system in various ways and positively impact the prevention of Alzheimer's disease.[7]

Many studies have shown that the anti-inflammatory activity of herbal extracts and herbal-derived compounds is mainly due to the inhibition of the metabolism of arachidonic acid (AA), cyclo-oxygenase (COX), lipo-oxygenase (LOX), pro-inflammatory cytokines, nitric oxide, and transcription activation factor (NF-κB). Several anti-inflammatory medicinal plants are reported to stabilize the lysosomal membrane, and some cause the release of oxidative phosphorylation from intracellular signaling molecules. Many have also been shown to have strong anti-oxygen radical activity.[8]

MATERIALS AND METHODS

ProQuest, JSTOR, PubMed and ScienceDirect are used in this review. The material collection was carried out from February to March 2021 using keywords adjusted to the Medical Subject Heading (MeSH) and Boolean operators (AND, OR NOT or AND NOT) to expand or specify the search. The research method used was PRISMA guidelines followed by literature exclusions. Due to the lack of sources from the literature searched, the keywords specified were "HERBAL" AND "NSAIDs" AND "ANTIOXIDANT" AND "ALZHEIMER".

The inclusion criteria in this literature search were medicinal/traditional plants, human samples, literature from 2015-2021, and Alzheimer's Disease, while the exclusion criteria in this review were if there was discontinuity/irrelevant topic between the abstract and the review material, incomplete literature (not open access), animal samples, non-research literature and other reviews.

RESULT

From the 4 databases, a total of 49 pieces of literature were obtained, which were then reviewed and screened based on inclusion and exclusion criteria resulting in 13 papers to be reviewed which can be seen in **Figure 1**.

The literature search yielded several papers, including reviews, experimental in vivo, vitro and in-silico (**Table 1**). Particularly, interesting findings were obtained from the in-silico studies. Anti-AD compounds were reported to be the major compound in medicinal plants, with some harboring anti-inflammatory properties. Specific studies in *G. biloba* also yielded promising anti-AD substances which involve the effect toward hormone sensitivity, improvements in endocrine homeostasis, maintenance of endothelial microvascular integrity, and proteolysis of tau protein. Also, a study in *S. miltiorrhiza* yielded potential components such as rosmarinus acid, magnesium lithospermate β, salvianolic acids A, B, and C, and KK's.

Two in-vitro study provided a glimpse of the mechanistic effects of medicinal plant extract in AD. Malva parviflora's extract was capable of inhibiting NFkB activity in neuroinflammation induced by LPS. In depth analysis reveal that daucosterol was found within the extract which could explain the NFkB inhibiting effect of the extract. Another study using Zingiber monotanum cystein glycoprotein (ZCPG) extract also yielded a positive effect in terms of AD treatment. ZCPG was proven to be a potent inhibitor of NOx, ROS, and pro-inflammatory cytokines production in lipopolysaccharide-stimulated THP-1 macrophages. Since neuro-inflammation mediated by macrophages or microglia is one of the central pathogenesis in AD, the properties provided by both plant extracts could be potential anti-inflammatory alternatives for AD treatment.

Overall, the ability of natural products to provide anti-amyloid effects is mainly attributed to the inhibition of inflammation of the nerves by natural products. The natural anti-inflammatory product Apigenin affects APP processing and prevention of Aβ load through downregulation of BACE1 levels, reduced deposition of Aβ, and decreased insoluble Aβ levels.[9]

DISCUSSION

The exact cause of Alzheimer's disease is still unclear, but from several studies, it can be concluded that the hypothesis which has been known to trigger

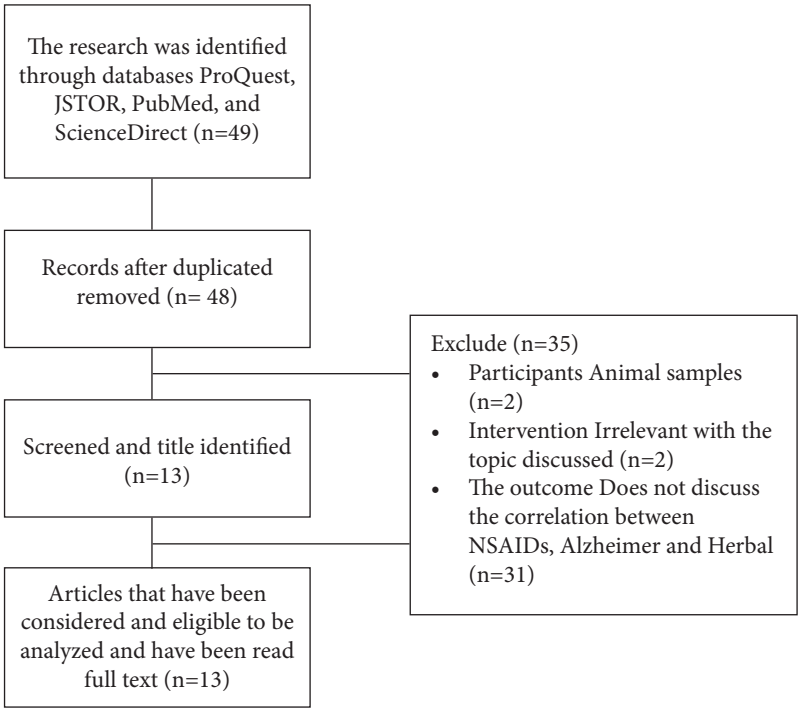

Figure 1. PRISMA diagram flow which illustrates the literature selection process in this review.

Table 1. Summary of the Literature Search included in this study.

No	Authors and Years	Study design	Participant/sample	Summary of Result
1	B. Chen, W. Li, G. Wang, et.al.; 2018	In silico	Traditional Chinese medicine, especially *Panax* and *Morus Genera*	Anti-AD compounds were found in 17 candidates structurally identical to 14 existing approved drugs, and most have been reported to affect AD positively. There were11 Anti-AD compounds with favorable properties; 7 of which are found in anti-AD Chinese plants, moreover, 4 compounds left have anti-inflammatory activity, and 1compound has immunoregulatory Activity.[20]
2	Syad,A.N Devi, K.P.; 2015	review	The botanical pharmacology with special reference to anti-Alzheimer's activity of plants and plant-derived compounds.	Several functions have been found by the botanical pharmacology, such as plants as a source of antioxidants, ChE inhibitors, anti-amyloidogenic activities, anti-inflammatory activities, as β-secretase inhibitors, the protective effect ofnatural compoundsagainst BBB breakdown and asγ-secretase inhibitors.[21]
3	H. Li, X. Sun, F. Yu, et.al.; 2018	in silico	*Ginkgo biloba L.*	The beneficial effects of *G. biloba* on AD may be contributed by the regulation of hormone sensitivity, improvements in endocrine homeostasis, maintenance of endothelial microvascular integrity, and proteolysis of tau protein, particularly before amyloid β-protein (Aβ) plaque Formation.[22]
4	(M. Sharman, G. Verdile, S. Kirubakaran, et.al., 2019)	review	natural anti-inflammatory and oxidative stress-related	Natural compounds and phytomedicines represent antioxidant, anti-inflammatory, anti-amyloidogenic and neuroprotective effects. Phytonutrients in spices, fruits and vegetables may represent the ideal candidates as they attenuate plaque and tangle formation; decrease neuroinflammation, oxidative and carbonyl stress;and are likely to be safe for long-termtreatments at thepresymptomatic/ clinical stages ofthe disease.[23]
5	M. Kamran, R. Kousar, S. Ullah, et.al.; 2020	review article	There were 31 medicinal plants used forAlzheimer's Disease treatment	The alkaloids, flavonoids, and phenolic acids, plants' secondary metabolites, play a crucial role in regeneration improvement and/or neurodegenerative inhibitors. Moreover, the plants which belong to the same taxon share common pharmacologicalfeatures.[24]
6	(Habtemariam, S., 2018)	review	*Rosmarinic* and *Salvianolic acids*	*Salvianolic acid* and *Rosmarinic* have been proven to target not only AD's biochemical mechanism but also affect the CVD related to stroke.[25]
7	I. Mendonça, M. Aurelio, D. Freire, et.al.; 2019	review article	*Curcumalonga*	Neurotoxic and behavioral damages of in vivo, in vitro, and in vivo-in vitro models of AD were reversed by the curcumin supplementation.[26]
8	P. Paudel, S.Seong,Y. Zhou, et.al.;2018	*in silico*	*Kangen-Karyu* and its constituents	proposed a system of activity by which the hydrophobic, π-activity, and hydrophilic associations of salvianolic corrosive B at ATP and substrate destinations are basic for the noticed GSK-3β restraint. The root of *S. miltiorrhiza* and its constituents, likewise Rosmarinus acid, magnesium lithospermate β, and salvianolic acids A, B, and C, are KK's active components to inhibit the GSK-3β.[27]
9	Ramirez-Serrano,Cristina; Jimenez-Ferrer, Enrique; Herrera-Ruiz, Maribel; et.al.; 2019	*in vitro*	*Malva parviflora's* fraction	MpF10 fraction could fix the spatial learning and memory impairment and decrease the astrogliosis production in neuroinflammation of the murine model, which is mediated by LPS. Moreover, the *daucosterol* (MpDau), which prevented LPS- induced neuroinflammation, was found in MpF10; surprisingly, the NFkB activity in macrophages exposed to LPS was inhibited by both MpF10 and MpDau; hence, the MpF10 is suggested as the new alternative in neuroinflammation treatment such as AD. [28]
10.	B. Ahamd, N. Hafeez, A. Rauf, et.al.; 2021	review	*Phyllanthus emblica*	This plant has memory-enhancing, respiratory, skin and ophthalmic effects and detoxification; furthermore, the biomolecular level study also revealed the potential use of this plant in disease management and control.[29]
11	K. Jamir, R. Ganguly, K. Seshagirirao;2020	in vitro	*Zingiber monotanum cystein glycoprotein* (ZCPG)	The production of Nitric Oxide, Reactive Oxygen Species and Pro-Inflammatory cytokines in lipopolysaccharide-stimulated THP-1 macrophages was inhibited by the ZCPG, while the production of IL-10 and anti-inflammatory cytokines rose.[30]
12	E. Shayganni, M.Bahmani, S.Asgary, et.al; 2016	*review*	anti-inflammatory plants and their action mechanism and its treatment	Medical plants' active Ingredients could inhibit several inflammatory disease symptoms. The free radicals tend to increase along with age and worsen the age-related metabolic disorders.[31]
13	S. Ahilya, R. Ritesh, M. Gerald; 2021	*review*	Australian plants' anti-inflammatory compounds	There were cytokines-suppressive anti-inflammatory (CSAIDs) components found in a group of anti-inflammatory which inhibit many pro-inflammatory cytokines expressions like IL-1, TNF-α, and NO; moreover, it targets the pro-inflammatory AP1.[32]

Alzheimer's disease is the AD Causative hypothesis related to the Tau hypothesis, the Amyloid Cascade hypothesis, which consists of the formation of Amyloid Beta, processing of APP, and Biochemistry of Senile plaques, Cholinergic hypothesis, Oxidative stress hypothesis related to mitochondrial respiration and aggregation of amyloid beta, inflammation hypothesis which also discusses microglia-related pathways, amyloid plaques that produce pro-inflammatory cytokines, and mitochondrial cascade hypothesis which discusses amyloid beta accumulation, formation of NFT and degeneration of synapse in AD.[10]

Apart from the unclear cause of Al[11]zheimer's, there is no therapy to cure it. Current therapies are only for slowing down the severity of symptoms of Alzheimer's, some of the drugs that the FDA has approved are Donepezil, Rivastigmine, Galantamine, Memantine and Tacrine. These FDA- approved drugs mostly work as AChE inhibitors for Donepezil, Rivastigmine, Galantamine and Tacrine, while memantine works as a Glutamate overproduce's effects blocker.[11,12]

Despite the five Alzheimer's drugs in circulation mentioned above, the administration of NSAIDs is also currently known to impact Alzheimer's disease. Current evidence suggests a significantly reduced risk of AD with exposure to NSAIDs, particularly in cohort studies with prospective populations. In contrast, aspirin, acetaminophen or NSAIDs instead of aspirin have not been found. Yet, regarding the weakness of the association, caution is needed to interpret it; hence, larger prospective studies are needed to confirm or refute these findings.[13]

Notwithstanding the Alzheimer's drugs and NSAIDs therapy that have beengiven, patients with cognitive impairment and those diagnosed with AD should not be given NSAIDs because there is no benefit based on existing clinical evidence. Further research is needed with a longer period and a larger sample size to clarify the role of NSAIDs in the administration of NSAIDs for the treatment of Alzheimer's.[14]

Furthermore, in several studies cited by Sharma, dueto the many side effects such as nausea, vomiting, loss of appetite, diarrhea and clumsiness, tacrine is no longer used as an Alzheimer's therapy.[15,16] In patients on Tacrine treatment, blood monitoring is necessary because of this drug's side effects of hepatotoxicity. Moreover, the short half-life of tacrine, as well as the adverse side effects of high doses, makes it necessary to provide a double dose regimen to maintain prolonged therapeutic activity.[17]

Insomnia, nausea, loss of appetite, diarrhea, muscle cramps and muscle weakness are side effects of giving donepezil. When given in high doses, low blood pressure, severe vomiting, muscle weakness, severe nausea, breathing problems, and bradycardia can be experienced by patients receiving donepezil therapy. The main side effects of rivastigmine are stomach upset, weight loss, diarrhea, loss of appetite, nausea and vomiting. Irregular breathing, fast or slow chest pain and slow or irregular heartbeat may occur if the patient has overdosed on rivastigmine. The main side effects of galantamine are seizures, severe nausea, stomach cramps, vomiting, irregular breathing, confusion, muscle weakness and watery eyes. In contrast, memantine can result in blurred vision, dizziness, rapid weight gain, headache and other unexpected symptoms.[17,18]

There are several mechanisms that possibly happen regarding the Alzheimer's causative hypothesis, such as AD causative, Amyloid cascade, cholinergic, oxidative stress, inflammation, and mitochondrial cascade. The Alzheimer's commercial drugs which are sold publicly mostly focus on the AChE inhibitors, while the NSAIDs therapy only focuses on the inflammation causative. From the review of the literature collected, it is found that various medical and traditional plants have ingredients that function against the hypothesis of the cause of Alzheimer's disease.

The plants' function has a mechanism of action against the Alzheimer's Disease, such as the source of antioxidant, AchE inhibitors, anti-amyloidogenic activities, anti-inflammatory activities, β-secretase inhibitors, BBB breakdown natural protector, γ-secretase inhibitors, and the newest invention is by inhibiting cytokine-mediated events during inflammation.[19]

CONCLUSION

Traditional medicine and medicinal plants can be one of the solutions in Alzheimer's therapy, and it has been proven in both in vivo, in vitro and silico studies. The owned content is multifunctional with the hypothesis of the cause of Alzheimer's. Recent studies even mention that Cytokine-Suppressive-Anti-Inflammation Drugs (CSAIDs) are obtained from natural plants, which may bea replacement therapy for NSAIDs in the future, which have fewer side effects and risks because they are obtained from natural ingredients from traditionalplants and medicinal plants.

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