Medicinal plants: A promising breakthrough in the management of Alzheimer's disease progression compared to than NSAID: A systematic review

Paulus Sugianto
Department of Neurology, General and Academic Hospital of Dr. Soetomo and Medical Faculty of Universitas Airlangga
Corresponding author email: paulus.sugianto@fk.unair.ac.id

Widiana Ferriastuti
Department of Radiology, General and Academic Hospital of Dr. Soeotmo and Medical Faculty of Universitas Airlangga

Kiking Ritarwan
Department of Neurology, Medical Faculty of Universitas Sumatra Utara

Dwi Putri Rahayu Tampubolon
Department of Midwifery, Medical Faculty of Universitas Airlangga

Abstract---Treatment of Alzheimer's Disease is currently limited only to slowing the severity of the symptoms felt by patients, not curing Alzheimer's itself. Current FDA-approved therapies such as Donepezil, Tacrine, Galantamine, Rivastigmine, and Memantine have quite disturbing side effects for Alzheimer's sufferers, 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 the Non-Steroid Anti-Inflammatory Drugs (NSAIDs) can be given to people with Alzheimer's, this is pro and cons because in one study NSAIDs can reduce the risk of Alzheimer's progression through inhibiting inflammatory process on AD pathogenesis; on the contrary, other studies have argued that giving NSAIDs to Alzheimer's sufferers is not necessary. Despite administering Alzheimer's drugs and NSAIDs which have adverse side effects on long-term use as well as 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. This review
found that some medicinal plants had better/similar outcome compared to NSAID in the long term management of Alzheimer's disease progression.

**Keywords**---Alzheimer disease, herbal medicine, NSAID, medicinal plant.

**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). This AD’s symptoms 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 disease 8 to 10 years (Bird, 2018).

Overproduction and impaired clearance of β-amyloid is thought to be the cause of 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 (Apostolova, 2018). 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. It is hypothesized that NSAID had multiple mechanisms in AD pathogenesis (Zhang, 2018). Major process of AD is in forming of fibrillary Aβ. It consist of inflammatory mechanism in forming amyloidogenic plaque and tau phosphorylation which was found can be reduce through NSAID in mice (Sastre, 2010; Szekely, 2007; Zhang, 2018). It activates the Peroxisome Proliferator G-Nuclear Transcription Factor (PPARα) on microglia. It can which can subside the inflammatory process of AD by inhibiting cyclooxygenase-1 and cyclooxygenase-2. Study in mice showed NSAID reduced clearance and phagocytosis of Aβ before plaques formation (Sáez-Orellan, 2020). 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) (Kinney, 2018).

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 (Kinney, 2018). 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 (Roy,
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 (Potshangbam, 2022).

Various bioactive compounds such as tannins, lignans, polyphenols, flavonoids, sterols, triterpenes and alkaloids in traditional medicinal plants have the potential to overcome problems related to anti-amyloidogenic, anti-inflammatory, anticholinesterase, hypolipidemic and antioxidant effects (Roy, 2018). Antioxidant derivatives that function as neuroprotection protect various components of the nervous system in various ways and have a positive impact on the prevention of Alzheimer’s disease (Cui, 2020).

Many studies have shown that the anti-inflammatory activity of herbal extracts and herbal-derived compounds are mainly due to the induced inhibition of the metabolism of arachidonic acid (AA), cyclo-oxygenase (COX), lipo-oxygenase (LOX), pro-inflammatory cytokines. nitric oxide, and transcription activation factor (NF-kB). 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 (Debnath, 2013). This study aims to find whether medicinal plant can replace NSAID in reduce AD disease progression in long term.

**Method**

The data based used in this review are ProQuest, JSTOR, PubMed and ScienceDirect. 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, Alzheimer’s Disease, while the exclusion criteria in this review were if there was discontinuity/irrelevant topic between the abstract and the review material, the literature was incomplete (not open access), animal samples, non-research literature and other reviews.

**Results**

From the 4 data bases used, a total of 49 literatures were obtained which were then reviewed and screened based on inclusion and exclusion criteria resulting in 13 literatures to be reviewed which can be seen in figure 1. In the literature obtained several reviews, experimental in vivo, in vitro and in silico. The ability of natural products to produce anti-amyloid effects is attributed to inflammation of the nerves by natural products as well. The natural anti-inflammatory product Apigenin exhibits effects on APP processing and prevention of Aβ load through
downregulation of BACE1 levels, reduction deposition of Aβ, and decrease in insoluble Aβ levels (Olajide, 2020).

<table>
<thead>
<tr>
<th>Research identified through databases ProQuest, JSTOR, PubMed, and ScienceDirect (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclude (n=35)</td>
</tr>
<tr>
<td>• Participants Animal samples (n=2)</td>
</tr>
<tr>
<td>• Intervention Irrelevant with topic discussed (n=2)</td>
</tr>
<tr>
<td>• Outcome Does not discuss about the correlation between NSAIDs, Alzheimer and Herbal (n=31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Records after duplicated removed (n= 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened and title identified (n=13)</td>
</tr>
<tr>
<td>Articles which have been considered and eligible to be analyzed and have been read full text (n=13)</td>
</tr>
</tbody>
</table>

Fig.1: PRISMA diagram flow which illustrates the process of selection of the literature in this review

**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 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 proinflammatory cytokines, and mitochondrial cascade hypothesis which discusses amyloid beta accumulation, formation of NFT and degeneration of synapse in AD (Mahdi, 2019).

Apart from the complex cause of AD, there is no single medication which can cure the disease but only to temporally reduce the progression.(Drugbank, 2021) Major medication which has been approved for AD are Donepezil, Rivastigmine, Galantamine, Memantine and Tacrine. These drugs mostly works as AchE inhibitors, immunomodulator, and glutamate antagonist (Alzheimer’s Society United Against Dementia, 2022; Drugbank, 2021). Despite the five Alzheimer's drugs in circulation that have been mentioned above, there were several new supportive treatments which emerge such as gingko biloba, omega-3, and vitamin B. The administration of NSAIDs is also currently known to have an impact on Alzheimer’s disease. Current evidence suggests that there is a significantly reduced risk of AD with exposure to NSAIDs, particularly in cohort studies with prospective populations, whereas 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 (Zhang, 2018).

Notwithstanding the Alzheimer’s drugs and NSAIDs therapy which have been given, in patients with cognitive impairment as well as patients 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 of time and a larger sample size to clarify the role of NSAIDs in the administration of NSAIDs for the treatment of Alzheimer’s (Ali, 2019). Furthermore, in several research from which was cited by Sharma, Due to the long term side effects such as nausea, vomiting, loss of appetite, diarrhea and clumsiness, Tacrine as an Alzheimer’s therapy is no longer used (Farlow, 1992; Watkins, 1994). In patients on Tacrine treatment blood monitoring is necessary because of the side effects of hepatotoxicity given by this drug. 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 (Sharma, 2019).

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, whereas in Memantine it can result in blurred vision, dizziness, rapid weight gain, headache and many more. other unexpected symptoms (Mayo Clinic, 2021; Sharma, 2019).

There are several mechanisms which possibly happen regarding the Alzheimer’s causative hypothesis likewise 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, whilst the NSAIDs therapy only focus on the inflammation causative (Paudel, 2018). From the review of the literature that has been collected, it is found that various medical and traditional plants have ingredients that have a function against the hypothesis of the cause of Alzheimer’s disease.

These medicinal plants’ function have a mechanism of action against the Alzheimer’s Disease, such as 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 inhibit cytokine-mediated events during inflammation (Cui, 2020). Majority mechanism using the antioxidant pathway to reduce the inflammatory process which modulates beta amyloid plaque formation (Machin, 2022).
Table 1
Summary of the Literature Search which included in this study with the medical plantation which were used in the study and the result.

<table>
<thead>
<tr>
<th>No.</th>
<th>Author; Year</th>
<th>Study Design</th>
<th>Participant/ Sample</th>
<th>Summary of Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B. Chen, W. Li, G. Wang, et.al.; 2018</td>
<td>In Silico</td>
<td>Traditional Chinese Medicine, especially <em>Panax</em> and <em>Morus</em> Genera</td>
<td>Anti-AD compounds were found in 17 candidates with structurally identical to 14 existing approved drugs and most of them have been reported to have positive effect in AD. There were 11 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 1 compound has immunoregulatory Activity (Chen, 2018).</td>
</tr>
<tr>
<td>2</td>
<td>Syad,A.N Devi, K.P.; 2015</td>
<td>Review</td>
<td>The botanical pharmacology with special reference to anti-Alzheimer activity of plants and plant-derived compounds</td>
<td>There are several functions which have been found by the botanical pharmacology such as plants as a source of antioxidant, ChE inhibitors, anti-amyloidogenic activities, anti-inflammatory activities, as β-secretases inhibitors, protective effect of natural compounds against BBB breakdown and as γ-secretase inhibitors (Devi, 2014).</td>
</tr>
<tr>
<td>3</td>
<td>H. Li, X. Sun, F. Yu, et.al.; 2018</td>
<td>In Silico</td>
<td><em>Ginkgo biloba</em> L.</td>
<td>The beneficial effects of G. biloba on AD may be contributed by the regulation of hormone sensitivity, improvements in endocrine homeostatic, maintenance of endothelial microvascular integrity, and proteolysis of tau protein, particularly prior to amyloid β-protein (Aβ) plaque formation (Li, 2018).</td>
</tr>
<tr>
<td>4</td>
<td>M. Sharman, G. Verdile, S. Kirubakaran, et.al., 2019</td>
<td>Review</td>
<td>natural anti-inflammatory and oxidative stress-related</td>
<td>Natural compounds and phytomedicines represent antioxidant, anti-inflammatory, anti-amyloidogenic and neuro protective 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-term treatments at the pre-symptomatic/clinical stages of the disease (Sharman, 2019).</td>
</tr>
<tr>
<td>Page</td>
<td>Authors/Reference</td>
<td>Type</td>
<td>Plants Used</td>
<td>Key Findings</td>
</tr>
<tr>
<td>------</td>
<td>------------------</td>
<td>------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>5</td>
<td>M. Kamran, R. Kousar, S. Ullah, et al.; 2020</td>
<td>Review</td>
<td>31 medicinal plants used for Alzheimer’s Disease treatment</td>
<td>The alkaloids, flavonoids, and phenolic acids which are the secondary metabolites of plants play a crucial role in regeneration improvement and/or neurodegenerative inhibitor. Moreover, the plants which same taxonomically share common pharmacological features (Kamran, 2020).</td>
</tr>
<tr>
<td>6</td>
<td>Habtemariam, S., 2018</td>
<td>Review</td>
<td>Rosmarinic and Salvianolic acids</td>
<td>The Salvianolic acid and Rosmarinic have been proven to target not only AD’s biochemical mechanism; yet, it also effects the CVD which related to stroke (Habtemariam, 2018).</td>
</tr>
<tr>
<td>7</td>
<td>I. Mendonça, M. Aurelio, D. Freire, et al.; 2019</td>
<td>Review article</td>
<td>Curcuma longa</td>
<td>Neurotoxic and behavioral damages of in vivo, in vitro, and in vivo-in vitro models of AD were reversed by the curcumin supplementation (Da Costa, 2019).</td>
</tr>
<tr>
<td>8</td>
<td>P. Paudel, S. Seong, Y. Zhou, et al.; 2018</td>
<td>In Silico</td>
<td>Kangen-Karyu and its constituents</td>
<td>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. Root of S. miltiorrhiza and its constituents likewise Rosmarinus acid, magnesium lithospermate β, and salvionalic acids A, B and C are KK’s active component to inhibit the GSK-3β (Paudel, 2018).</td>
</tr>
<tr>
<td>9</td>
<td>Ramirez-Serrano, Cristina; Jimenez-Ferrer, Enrique; Herrera-Ruiz, Maribel; et al.; 2019</td>
<td>In Vitro</td>
<td>Malva parviflora’s fraction</td>
<td>MpF10 fraction could fix the spatial learning and memory impairment, decrease the astroglisis production in a neuroinflammation of 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 (Ramírez-Serrano, 2019).</td>
</tr>
<tr>
<td>10</td>
<td>B. Ahamd, N. Hafeez, A. Rauf, et al.; 2021</td>
<td>Review</td>
<td>Phyllanthus emblica</td>
<td>This plant has application in memory enhancing, respiratory, skin and ophthalmic disorders, and detoxification; furthermore, the biomolecular level study also has function in disease management and control (Ahmad, 2021).</td>
</tr>
<tr>
<td>11</td>
<td>K. Jamir, R. Ganguly, K.</td>
<td>In Vitro</td>
<td>Zingiber monotanum</td>
<td>The production of Nitric Oxide, Reactive Oxygen Species and Pro-Inflammatory</td>
</tr>
</tbody>
</table>
Conclusion

Traditional medicine and medicinal plants can be one of the solutions in Alzheimer’s therapy, it has been proven in both in vivo, in vitro and in silico studies. The content that is owned is very 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 be a replacement therapy for NSAIDs in the future, which have fewer side effects and risks because they are obtained from natural ingredients from traditional plants and medicinal plants (Kamran, 2020).

Acknowledgments

We would like to thank all supervisor and staff who is contribute in this article Department of Neurology, Radiology, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital and Medical Faculty of Universitas Sumatra Utara.

Author Contribution

All authors contributed equally to this work including conception, design, acquisition, analysis, or interpretation of data for the work. All substantial intellectual content had been agreed and discussed by the four authors.

Conflict of interest

The authors did not receive support from any organization for the submitted work.
Funding

The authors have no relevant financial or non-financial interests to disclose.

References


Drugbank. Tacrine. Published 2021. go.drugbank.com/drugs/DB00382


3017


