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Centella asiatica: Alzheimer's Neuroprotective

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ABSTRACT

Centella asiatica (CA) in Indonesia is known as gotu kola plant which is known to have many compounds contained in it, such as Asiatic acid, madecassic acid (6-hydroxyacetic acid), asiaticoside, madecassoside, betulinic acid, thankunic acid, and isothankunic acid. This study is to determine the benefits of CA triterpenoid bioactive content and the mechanism of CA as a neuropretective against alzheimer's disease. This research used the literature study method by searching online data on various types of article publications and selected according to the PRISMA method. From the literature collected, it was found that CA has the ability as a neoroprotective against Alzheimer's disease. This is because triterpenoid compounds with the bioactive content of asiaticoside, madecid acid, and asiatic acid play a role in inhibiting the enzyme acetylcholinesterase which can act as a neuroprotective in the brain by reducing ROS production which can then restore mitochondrial dysfunction and can improve nerve function in Alzheimer's disease.

Keyword: *Centella asiatica*, neuroprotective, Alzheimer

ABSTRAK

Centella asiatica (CA) di Indonesia dikenal dengan tanaman pegagan diketahui memiliki banyak senyawa yang terkandung di dalamnya, seperti Asiatic acid, madecassic acid (6-hydroxyacetic acid), asiaticoside, madecassoside, betulinic acid, thankunic acid, dan isothankunic acid. Penelitian ini bertujuan untuk mengetahui manfaat kandungan bioaktif triterpenoid CA dan mekanisme CA sebagai neuropretektif terhadap penyakit alzheimer. Penelitian ini menggunakan metode studi literatur dengan melakukan pencarian data secara online pada berbagai jenis publikasi artikel dan diseleksi sesuai dengan metode PRISMA. Dari hasil literatur yang dikumpulkan, diperoleh hasil bahwa CA memiliki kemampuan sebagai neoroprotektif terhadap Alzheimer. Hal ini dikarenakan senyawa triterpenoid dengan kandungan bioaktif asiatikosida, asam madekasid, dan asam asiatik berperan dalam penghambatan terhadap enzim asetilkolinesterase yang dapat berperan sebagai neuroprotektif pada otak dengan menurunkan produksi ROS yang kemudian dapat memulihkan disfungsi mitokondria dan dapat meningkatkan fungsi saraf pada penyakit alzheimer.

Keyword: *Centella asiatica, neuroprotective, Alzheimer*

1. Introduction

Centella asiatica, called "ji xue cao" or "luei gong gen" in traditional chines medicine (TCM), has been utilized since more than three thousand years ago in countries throughout Asia, including India, Sri Langka, China, Indonesia as a major producer of *Centella asiatica* due to its extensive cultivation. It is known as a cold, bitter, and non-toxic herb, healing wounds, circulatory support, anti-inflammatory and skin rejuvenation [1]. *Centella asiatica* (CA), also known as Asian pennywort or Gotu kola, is a plant with a rich history of use in

Ayurvedic and traditional Chinese medicine. It contains several biologically active compounds, including alkaloids, favonoids, phenols, tannins, and terpenoids. Te triterpene saponins found in CA, such as asiatic acid, asiaticoside, madecassic acid, and madecassoside, are particularly noteworthy for their therapeutic potential. Tese compounds possess various biological activities, including anticancer, wound-healing, antibacterial, antidiabetic, anti-infammatory, and antioxidant properties. Additionally, CA has been valued for its cognitive-enhancing effects [2-4].

Studies conducted with various plant-derived *Centella asiatica* (asiaticoside, madecassoside, Asiatic acid, and madasiatic acid) showed that the compounds were able to inhibit or stop cell death-amyloid, block H^2O^2 -induced cell death, and lower the concerntration of free radicals. These results suggest that C. asiatica may play an important role in the prevention and treatment of Alzheimer's desease [1]. The reported histopathological characteristics of Alzheimer's are extracellular aggregates of Aβ (β-Amiloid) plaques and intracellular aggregations of neurofibrillary tangles (NFTs), composed of τ associated with hyperphosphorylated microtubules. Aβ plaques initially develop in the basal, temporal, and orbitofrontal neocortex regions of the brain and in later stages expand throughout the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In sritical cases, Aβ is found throughout the mesencephalon, lower brainstem, and also the cerebellar cortex. This concentration of Aβ triggers the formation of τ-tangles, which are found in the locus coeruleus and the transentorhinal and entorhinal areas of the brain. At a critical stage, the disease spreads to the hippocampus and neocortex. Aβ and NFTs are considered to be the major players in disease progression [5,6].

Further explained by Tiwari S, et.al., 2019, that the pathogenesis of amyloid begins with changes in the cleavage of amyloid percusor protein (APP), an integral protein at the plasma membrane, by β-secretase (BACET) and γ-sekretase to produce insoluble Aβ (β-Amiloid) fibrils. Aβ then oligomerizes, diffuses into the sypnatic eleft, and disrupts synaptic signals. As a result, Aβ polymerizes into insolable amyloid fibrils and aggregates into plaques. This polymerization leads to kinase activation, which causes hyperphodphorylation of microtubule-associated τ proteinds, and their polymerization into insoluble NFTs. Plaque aggregation and tangllng is followed by recruitment of microglial around the plaque. This promotes microglial activation and local inflammatory response, and contributes to neurotoxicity [5].

According to Decintya Jaya Maysha et. al., 2023, inflammatory cytokines produced by neuro inflammation are closely related to the occurrence of neurodegenerative lesions, which are manifested in Alzheimer by affecting the expression and metabolism of amyloid precursor proteins. The pathological changes caused by Alzheimer are recognized by the accumulation of neuritic plaques containing beta amyloid (Aβ). Chronic elevation of proinflammatory mediators induced neurotoxic Aβ, the formation of plaques in alzheimer. These pro-inflammatory mediators will further exacerbate neuron inflammatory by taking immune cells into the brain. Neuroinflammatory will also affect cell proliferation and maturation through proinflammatory cytokines, leading to synaptic dysfunction and neuronal death [7].

There are several factors that can increase the risk of Alzheimer's desease, namely: 1. Being>65 years old, 2. Having a family history of alzheimer's desease, 3. Having an unhealthy lifestyle, 4. Having a certain medical history, such as having had a head injury, cognitive impairment, or having hypertension and high cholesterol.The cause of Alzheimer's is not yet understood with certainly and there is no truly effective treatment for this disease [8,9]. The purpose of writing this article is to determine the benefits of CA triterpenoid bioactive content and the mechanism of CA as a neuroprotective against Alzheimer's disease.

2. Methods

This research uses the literature study method by searching data on various types of article publications. Article searches were conducted on Sciencedirect, PubMed, and Google Schoolar data base published until 2024. The keywords used were "Centella assiatica", "neuroprotective", and "Alzheimer". The inclusion criteris were the role of *Centella asiatica* bioactive activity against alzheimwe's or neuroprotective Alzheime's on *Centella asiatica*. The literature search resulted in 81 articles. Then the article was selected according to the PRISMA method, as in figure 1.

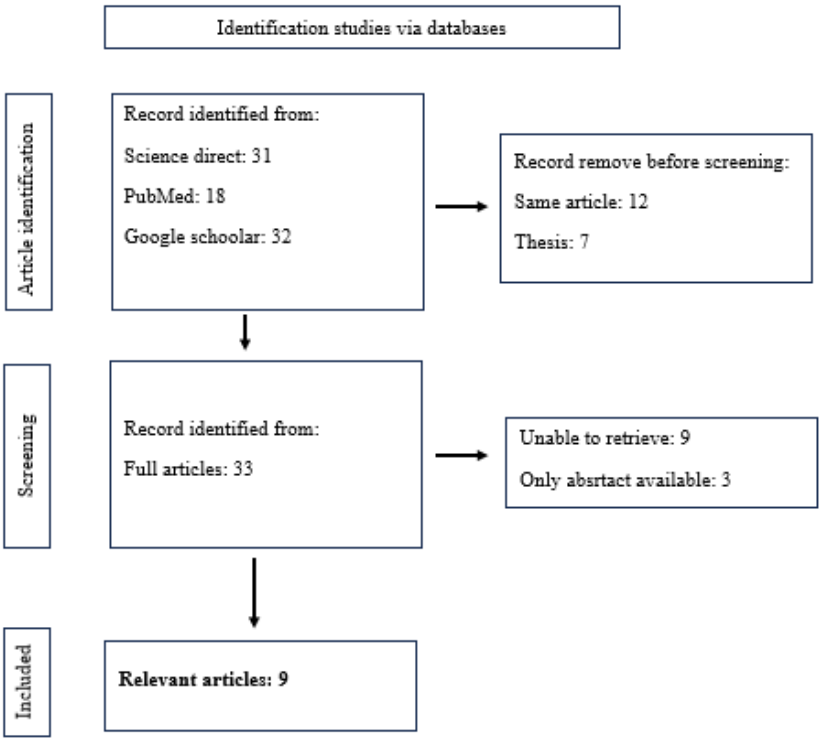

Figure 1. Flowchart with PRISMA method

3. Result and discussion

3.1 Alzheimer's Desease

Alzheimer's desease is a progressive and degenerative neurological disorder characterized by cognitive loss of thingking and memory. The pathogenesis of Alzheimer's disease remains unclear, but it is thought that the disease is caused by a combination of genetic, environmental/lifestyle, and aging factors. Initially, patients have diffculty recalling recent avents, followed by forgetfulness and confusion. As the disease progresses, the ability to read, write, speak and eat is lost. The brains of deseased Alzheimer patients show three structural abnormalities such as (1) Loss of neurons that release basal acetylcholine (Ach release centers) serulting in damage to the nucleus; (2) Accumulation of beta-amyloid plaque protein outside neurons; (3) Neurofubrillary tangles of filament bundles inside neurons (consisting of hyperphosphorylated "tau" protein). Several potential hypotheses have been established to examine the methanistic process of alzheimer's disease.

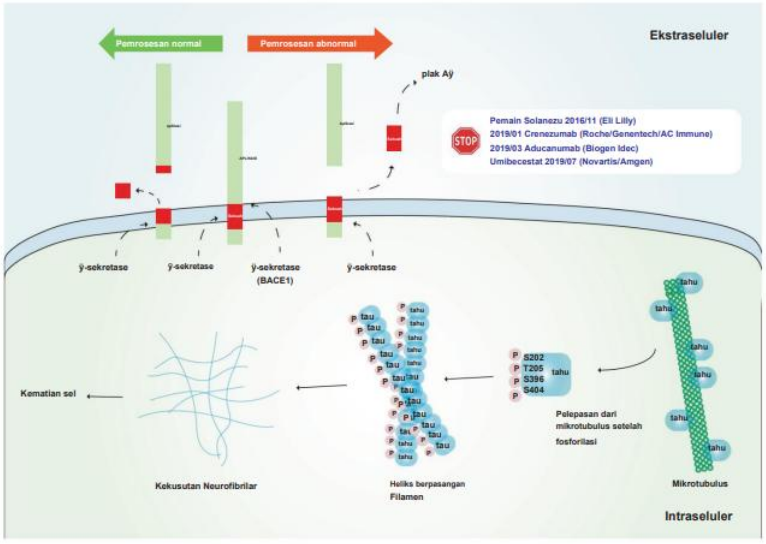

Figure 2. Schematic of the amyloid hypothesis and tau hypothesis

Figure 2 shows that the trans membrane APP protein canbe cleaved throuht teo pathways. In normal processing, APP is hydrolyzed by γ-sekretase and then by γ-sekretase, which does not produce insoluble Aγ; in abnormal processing, APP is hydrolyzed by γ-sekretase (BACE1) and then by γ-sekretase, which produces insoluble Aγ. Where as in the bottom image tau protein can be hyperphosphorylated at amino residues Ser202, Thr205, Ser396, and Ser404 (Which are responsible for tubulin binding), leading to tau release from microtubules and microtubule destabilization. Hyperphosphorylated tau monomers will aggregate to foem complex oligomers and eventually form a tanle of neurofibrils, which can lead ti cell death [10]. Then Alzheimer's disease can also be caused by influence of the mitochondrial cascade as shown in figure 3.

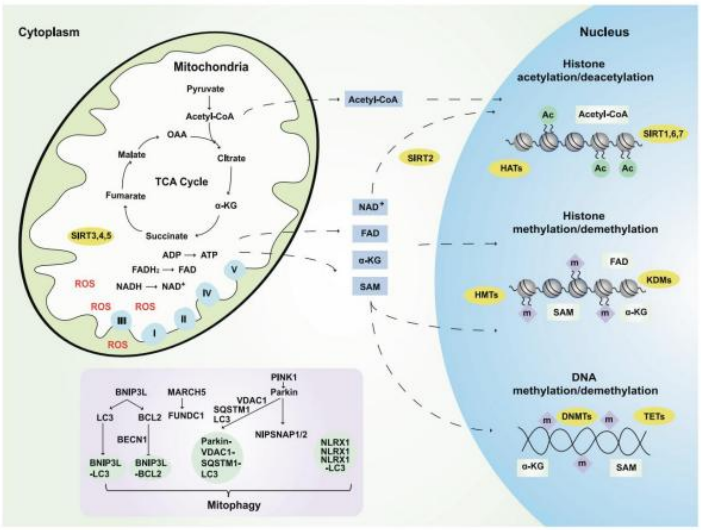

Figure 3. Mitochondrial cascade

One of the causes of alzheimer's disease is in the mitochondria are a major contributor to the production of Reactive Oxygen Speciess (ROS), shich is significantly increased in alzheimer's desease. Mitocondrial TCA metabolites, such as pyruvate, fumarate, malate, OAA, and γ-KG, not only directly regulate production but also play an important role in epigenic regulation of neurons and longevity [10]. Alzheimer's disease, can also be caused by the influence of the mitochondrial cascade as shown in figure 4.

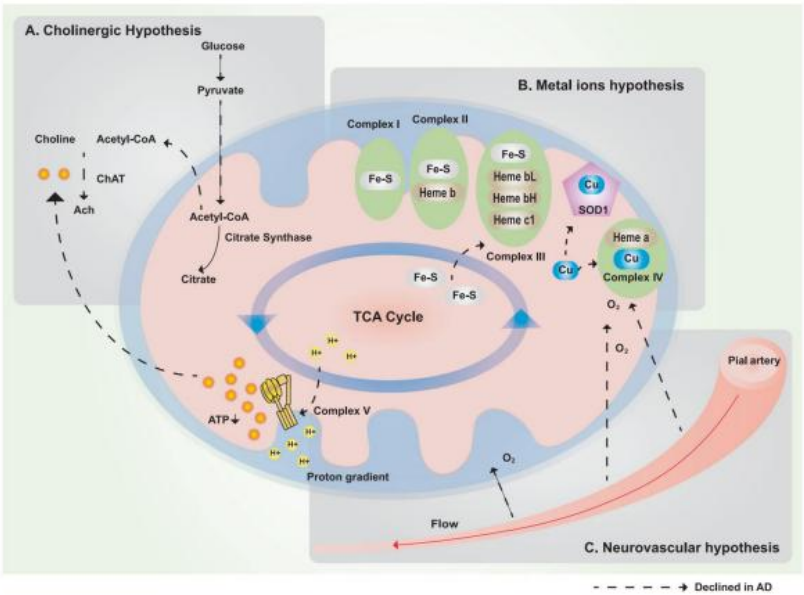

Figure 4. Hypomethabolism my underline the cholinergic hypothesis, metal ion hypothesis, and neurovascular hypothesis

Based on figure 4, it can be seen that in part 9A glucose is enzimaticallycatalyzed to produce pyruvate. Pyruvate is then converted into acetyl-CoA and then enters TCA cycle or is used in the cytoplasm to synthesize

acetylcoline. However, in patients with alzheimer's disease, due to hypometabolism, there is insufficient production of acetyl-CoA and ATP, leading to decreased acetylcholine stnthesis. In part (B) mitochondrial complexes I-III require Fe/S groups, and complexes II-IV require hemoproteins for electron transfer and oxidative phosphorylation off the respiratory chain [10]. When iron deficiency occurs, Fe/S and hemiprotein production decreases, affecting mitochondrial function and resulting in hypometabolism. In addition, copper is essential for complex IV function. Clearly, Cu-Zn superoxide dismutase (SODI) requires copper and sinc. In part (C) hypoperfusion and hypoxia in vascular desease lead to insufficient oxygen supply, which in turn leads to insufficient ATPsynthesis, resulting in hypometabolism in patients with alzheimer's disease. This explanation explains the mechanism of alszheimer's disease.Where alzheimer's disease has several factors that can increase the risk of alzheimer's disease, namely; (1) Being >65 years old, (2) Having family wirh a history of alzheimer's disease, (3) Unhealthy lifestyle, (4) Having a certain medical history, such as having had a head injury, cognitive impairment, or having hypertension anh high cholesterol.

Typical symptoms of alzheimer's disease are progressive memory loss, poor managerial tasks, and difficulty completing daily tasks. In addition, 20-30% of patients with early alzheimer's experience poor mood and depressive symptom irregularities. Significant memory loss,hallucinations, confusion, and lack of independence are common in people with advanced alsheimer's disease [11]. The clinical symptoms of alzheimer's are mainly based on the severity of cognitive decline and hidtopathological changes according to Cplabro (2020), namely alzheimer's is divided into four different phases including: preclinical, midl, moderate, and advanced stages. Preclinical, this phase is often overlooked due to the absence of severe symptoms but the earliest pathological changes begin and attack the enthorhinal cortex (first) and hippocampus (later). Mild alzheimer's, in the phase cognitive symptoms begin to appear, pathological changes reach the cerebral cortex along with memory loss and inability to recall new information, problem solving and personality changes (confusion) [12]. Moderate alzheimer's, in this phase the severity of simptoms indrease, the pathological damage spreads further to the areas responsible for language, reasoning and sensory processing (cerebral cortex) and along with behavioral problems and q tendency to withdraw from social life due to impaired language, visuospatial skills and difficulty recognizing those slosest ti them. Severe alzheimer's this phase the patient loses complete independence to perform daily activities, the pathology damage at this stage covers all areas of the cortex and coincides with inability to perform learned motor tasks, olfactory dysfuntion, sleep disturbances and parkinson's symptoms.

3.2 Alzheimer's Healing Therapy

Several drug therapies to cure alzheimer's disease were mentioned by Gail A. Stonebarger et. Al., (2021) including the administration of memantine as an NMDA receptor (N-methyl-D-aspartate receptor) antagonist therapy. It is known that NMDA receptors are a very important type of receptor in the central nervous system. These receptors play a crucial role in learning, memory, and synaptic pasticity (the brain's ability to chabge). However, overactivity of NMDA receptors can lead to nerve cell damage, especially in neurodegenerative conditions such as alzheimer's disease. Memantine works by partially blocking excessive NMDA receptor activity [13].

Cholinesterase inhibitors are a type of medication used manage yhe symptoms of alzheimer's disease. These drugs work by inhibiting the cholinesterase enzyme, which breaks down the neurotransmitter acetylcholine. Acetylcholine is an important barain chemical that palys a role in memory and learning. Even approving the combined administration of memantine and cholinesterase inhibitors[14,15]. Administration of aduacanub, an antibody shoen to reduce beta amyloid accumulation. However this approval is based solely on the surrogate endpoint of plaque reduction, so the therapeutic potential of aduacanub is unknown especially in the context of symptom relief. This is because Aβ plaques do not reliably correlate with cognitive decline. As no single drug has been identified to control alzheimer's symptoms, its management is considered difficult. The majority of existing alzheimer's treatments address neurogical and behavioral issues that can inhibit disease progression. The drugs approved by the FDA (Food and drug administration) mentioned drugs only alleviate the sumptoms of alzheimer's disease [16]. Reserch on the effectiveness of these drugs was applied to several mammalian animals such as mice and apes [17].

Previous studies have described the efficacy of *Centella asiatica* against neurodegradative diseases such as alzheimer's disease. The focus of the research is to explain how the bioactive content of CA, especially in triterpenoids, plays a role as a neuroprotective for alzheimer's disease. The folloeing are some research results from the database of articles that have been sollected can be seen in table 1.

Table 1. The role of *Centella asiatica* in alzheimer's disease.

Reference	Research result
[18]	Gotu kola (CA) with bioactive cobtents of asiaticoside, asiatic acid, madecassoside, and madecasic acid showed that these compounds were able to block H_2O_2 induced cell death, decrease free radical concentration, and inhibit γ-amiloid cell death, suggesting a potential role for in the treatment and prevention of alzheimer's disease.
[19]	The *Centella asiatica* crude extract enchanced neuroregenerative effects and exhibited antioxidant properties, suggesting synergistic activity of its phytochemical content, making the C. asiatica extract usable in preventing or treathing oxidatives stress related alzheimer's disease.
[2]	Whole plan extracts of *Centella asiatica* namely triterpenoid glycosides and saponins can be used drugs by increasing Ach levels through AChE inhibition and also reducing Aγ plaque formation.
[20]	Phytochemical studies of C. asiatica contain many bioactive compounds, the most identified of which are triterpenoid. Triterpenoid have been shoen to have neuroprotective effects due to their anti-inflammatory, antioxidant, amelioration of mitochondrial dysfuction, and enchancement of brain-derived neurotrophic factors. C. asiatica may have potential as alternative medicine for neurological conditions, such as stroke, epilepsy, Alzheimer's and Parkinson's disease.
[21]	C.asiatica can improve cognitive function because it contains triterpenoids and flavonoids that have potential as neuroprotectors, antioxidants, anti-inflammatory and antiapoptotic. C.asiatiaca containing flavonoids and polyphenols inhibits ROS by involving antioxidant mechanisms in the prevention of cognitive deficits.
[22]	The results of the study, especially on the content of active substance compounds asiaticoside, madekasid acid, and asiatic acid, play a role in inhibiting the enzyme acetylcholinesterase so that it can act as a neuroprotective in the brain. In the use of ethanol extract of gotu kola herb, it was found that the inhibition concentration value of acetylcholinesterase enzyme.
[23]	The results showed that CA could increase the mRNA expression of Bcl-2 and CA could also prevent morphological aberrations in the connus ammonis 3 sub-region of the rat hippocampus. CA can alleviate d-gal/AlCl3 induced AD-like pathology in mice through inhibition of phosphorylated bio-synthetic protein tau (P-tau), anti-apoptosis and maintenance of cytoarchitecture.
[24]	The results showed that C. asiatica and its triterpenoids had extensive beneficial effects on neurological and skin diseases, which were confirmed through clinical studies. C. asiatica exhibits anti-inflammatory effects, antioxidant stress, anti-apoptotic effects, and improved mitochondrial function.
[25]	The results showed that the role of asiatic acid as an anti-AChE inhibitor was investigated in hippocampal cell lines where asiatic acid was applied to the cell lines followed by analysis of AChE activity and possible toxicity of asiatic acid. This study reports asiatic acid as an

	effective AChE inhibitor with no toxic side effects in hippocampal cell lines.

Based on table 1, it can be seen that *Centella asiatica* can provide neuroprotective effects due to its anti-inflammatory effects, reduction of oxidative stress, improvement of mitochondrial dysfunction, and increase of brain-derived neurotropic factors.

3.3 *Centella asiatica*: Bioactive Triterpenoids

Centella asiatica is a herbaceous annual, aromatic and has single leaflets shich are arranged in a root rosette and consist of 2 to 10 leaflets. Triterpenoids are the important compounds in gotu cola plant. Tritepenoids function to improve mental function and give a calming effect. Triterpenoids contain several bioactive ingeredients such as asiaticoside, madekasoside, Asiatic acid and madekasic acid. Other chemical contents found in *Centella asiatica* are brahmosida, oxiasiaticosida, thankunicide, isothankunicide, inositol, carotenoids, as well as salts of potassium, sodium, magnesium, calcium, iron, vellarin, and tannins. Here are the molecular formulas of *Centella asiatica* bio active compounds.

Asiaticosides derived from CA have good activity where are effectiveness of this active substance can increase antioxidants. Since antioxidants have played an important role in the healing process, the effect of asiaticosides as antioxidants is certainly in the treatment of alzheimer's disease. Extracts from herb CA as antioxidants have the effect of improving cognitive function. Derivates of Asiatic acid, triterpenoid extracted from C.asiatica herb play a role in protecting neurons from oxidative damagr caused by overexposure. So in the study, the cytopritective and antioxidant prpperties of CA herb may br responsible for neuroprotection against cell death. The content of active substance compounds asiaticoside, madekasid acid, and Asiatic acid play a role in inhibiting the enzyme acetylcholinesterase so that it can play a neuroprotective role in the brain.

CA can also decrease amyloid-B1-40, 1-42 and also reduce fibrillar amyloid plaques significantly, and the extract acts as an antioxidant and prevents DNA damage [26]. The potential mechanism of CA extract in neuroblastoma cells expressing Aβ peptide is involved in phosphorylation of CREB and modulation of ribosomal protein S6 kinase (RSK) ERK/40S signaling pathway (Xu et. Al., 2008). The anti-alzheimer's potential of CA extract is through the ability of CA extract to increase Aβ-mediated reactive oxygen species production in neuronal cells [27].

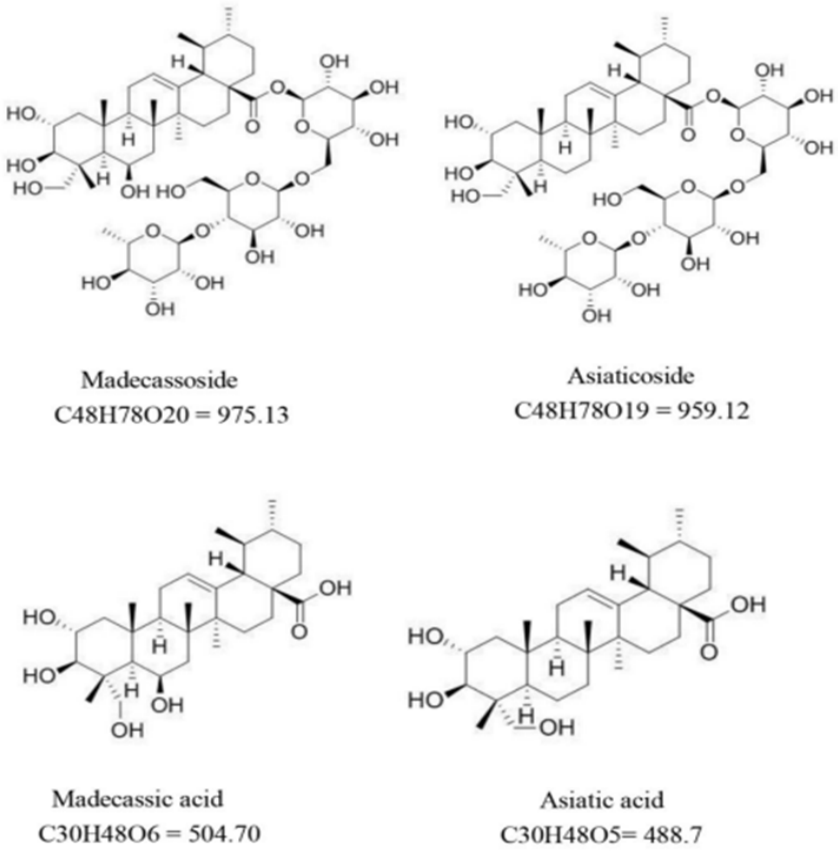

Figure 5. Molecular formulas of some of the main compounds of CA (Sun et.all. 2020).

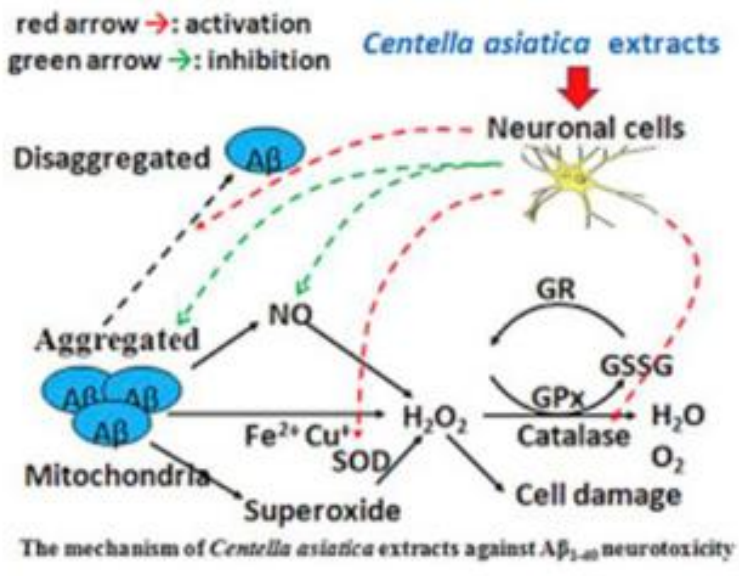

Figure 6. Mechanism of CA extract in reducing neurotixixty by amyloid beta pathway

Based on Figure 6, it can be seen that CA can function in reducing ROS production (Christov 2004). Mitochondria are the main place where cells perform aerobic respiration. When mitochondrial dysfunction occurs, it will be associated with AD [27]. Cell death signalling pathways can be activated by mitochondrial ROS. So restoring mitochondrial dysfunction will improve neuronal function in alzheimer's disease. CA exerts neuroprotective effects against beta-amyloid toxicity through attenuation of oxidative stress and possible mitigation of neuritic dystrophy around plaques. Neurite formation is considered one of the important steps in nerve regeneration, especially for memory enhancement. CA may increase hippocampal and cortical mitochondrial gene expression and increased mitochondrial activity. Memory improvement with CA treatment may be associated with increased expression of ARE genes, especially in the hippocampus. C.asiatica treatment enhances the antioxidant response following increased oxidative stress due to beta-amyloid pathology which reduces neuritic dystrophy around neuronal amyloid plaques, ultimately preserving cognitive function. Therefore, triterpenoids in this plant can reduce ROS production. CA extract has a positive effect on diseases of the nervous system. CA and its extracts ameliorate neurological diseases by reducing inflammatory factors, balancing oxidative stress, correcting abnormal expression of mitochondria-related proteins, and increasing BDNF content. In addition, CA reduces apoptosis of nerve-related cells, increases synaptic density, and improves the survival rate of nerve cells.

4. Conclusion

That *Centella asiatica* has the ability as a neoroprotective against alzheimer's , and can restore mitochondrial dysfuction so as to improve nerve in Alzheimer's patients. This study is expected to provide scientific data regarding the potential of *Centella asiatica* as a theraupeutic agent in alzheimer's therapy. The result can contribute to the development of phytopharmaceuticals based on natural ingredients to improve the quality of life of alzheimer's patients.

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