

# Analysis of Secondary Metabolite Compounds of Papaya Leaf Extract (*Carica papaya* L.) and Noni Leaf Extract (*Morinda citrifolia* L.) as Neuroprotective Agents in Alzheimer's Disease

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**Abstract:** Alzheimer's disease is a neurological disorder associated with the accumulation of amyloid proteins in the brain. Papaya (*Carica papaya* L.) and noni (*Morinda citrifolia* L.) are known as natural sources with high antioxidant activity, which have the potential to function as neuroprotective agents. This study aims to identify secondary metabolites and evaluate the antioxidant activity of ethanol extracts from papaya and noni leaves. Extraction was performed using the maceration method with 40% ethanol. Phytochemical testing was performed qualitatively with several reagents appropriate for testing each compound. Phytochemical screening revealed that papaya and noni leaf extracts contain similar secondary metabolite compounds, namely alkaloids, flavonoids, phenolics, tannins, saponins, and triterpenoids. However, only papaya leaf extract showed the presence of steroid compounds, indicating a difference in the composition of secondary metabolites that could potentially affect the activity of each extract as a neuroprotective agent in Alzheimer's disease.

## 1 INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder characterized by a decline in cognitive function, memory impairment, and behavioral changes resulting from the deterioration of brain nerve cells (Chandany, 2025). The main pathogenic factors involved are the accumulation of  $\beta$ -amyloid protein, hyperphosphorylation of tau protein, and increased oxidative stress due to excessive free radical production. The combination of these factors accelerates oxidative damage, chronic inflammation, and neuronal apoptosis, ultimately

leading to impaired brain function (Kaur & Prakash, 2021).

Current efforts to prevent Alzheimer's disease are not solely reliant on synthetic therapies but are also directed toward the search for natural neuroprotective agents capable of working through multi-target mechanisms. Several literature reviews have emphasized that bioactive compounds derived from plants, particularly secondary metabolites such as flavonoids, alkaloids, saponins, tannins, phenols, and terpenoids, play an important role in antioxidant activity, anti-inflammatory responses, and modulation of cellular signaling pathways that

support neural protection (Safutra *et al.*, 2023; Singh *et al.*, 2020). These natural compounds have been reported to reduce free radical accumulation, suppress neuroinflammation, and maintain neuronal homeostasis.

Papaya (*Carica papaya* L.) is a tropical plant that has long been used in traditional medicine and is known to contain important secondary metabolites. Papaya leaves have been reported to contain flavonoids, alkaloids, saponins, and tannins, each of which contributes to various biological effects. Flavonoids, for instance, are known for their antioxidant activity that scavenges free radicals, thereby protecting neurons from oxidative damage (Kharaeva *et al.*, 2022). Several studies have shown that papaya extract consumption can enhance the body's antioxidant capacity and reduce the risk of neuronal damage caused by oxidative stress (Prabhu *et al.*, 2021).

Noni (*Morinda citrifolia* L.) is another tropical plant rich in phytochemicals such as flavonoids, iridoids, phenols, and terpenoids. Iridoid compounds are known to inhibit the production of pro-inflammatory cytokines, thereby playing a crucial role in reducing neuroinflammation. Animal studies have demonstrated that noni extract at certain doses can enhance spatial memory and improve cognitive function, indicating neuroprotective effects (Zhang *et al.*, 2022). In addition, the traditional use of noni has been associated with increased vitality and brain health (Chan-Blanco *et al.*, 2006).

Qualitative phytochemical analysis is an important preliminary step to identify the presence of secondary metabolites in medicinal plants. Although descriptive in nature, the results of phytochemical screening can provide an initial insight into the

potential biological activity of these plants. The identification of metabolites such as flavonoids, alkaloids, saponins, tannins, phenols, and terpenoids in papaya and noni is expected to explain the scientific basis of why these plants may serve as potential neuroprotective agents (Wang *et al.*, 2021).

However, research data indicate certain limitations. As of 2022, more than 70% of studies on papaya have focused on antimicrobial, anticancer, and antiparasitic activities, while fewer than 10% have explored its neuroprotective potential (Santiago & Mayor, 2024). Similarly, studies on noni have been largely directed toward immunomodulatory and hepatoprotective effects, whereas specific investigations on the role of its secondary metabolites in Alzheimer's disease prevention remain scarce (Palu & West, 2023). Furthermore, most existing studies have employed pure extracts or isolated compounds, rather than basic phytochemical analyses of papaya and noni leaves directly. This research gap highlights the need for an initial qualitative phytochemical screening to map the secondary metabolite content of these plants that may support neuroprotective activity.

This study focuses on the phytochemical screening of papaya and noni leaves. The screening was carried out as an initial step to identify the secondary metabolites contained in both plants. Secondary metabolites are known to have potential biological activities, including as neuroprotective agents. Therefore, this research seeks to explore the role of phytochemical constituents in preventing neuronal damage. The findings are expected to provide a scientific basis for the development of tropical plant-based phytotherapy for the prevention of Alzheimer's disease.

## 2 METHOD

### Tools and Materials

This research was conducted at the Basic Chemistry Laboratory of Sunan Ampel State Islamic University in Surabaya. Some of the equipment used in this research included a UV-Vis spectrophotometer, cuvettes, measuring pipettes, measuring cups, reaction tubes, Erlenmeyer flasks, Falcon tubes, beaker glasses, vortexes, centrifuges, drying ovens, analytical scales, rotary evaporators, as well as *Fourier Transform Infrared (FTIR)* and *High Performance Liquid Chromatography (HPLC)* devices. Meanwhile, the materials used included papaya leaf powder, noni leaves, p.a methanol solution, 70% ethanol, distilled water, hydrochloric acid (HCl), sulfuric acid (H<sub>2</sub>SO<sub>4</sub>), acetic acid, chloroform (CHCl<sub>3</sub>), sodium carbonate (NaCO<sub>3</sub>), Folin Ciocalteu reagent, Dragendorff reagent, Liebermann Burchard reagent, magnesium, FeCl<sub>3</sub>, Mayer Wagner, NaOH, DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (3-ethylbenzothiazoline-6-sulfonic acid), TPTZ (2,4,6-tripyridyl-s-triazine), ferrous sulfate, as well as gallic acid, quercetin, and Trolox standards.

### Research Procedure

- **Leaf Extraction Process**

Extraction of papaya leaves (*Carica papaya* L.) and noni leaves (*Morinda citrifolia* L.) was carried out using the maceration method with 70% ethanol solvent. The extraction process began with separating the leaves from the stems, then washing them with running

water until clean. The leaves were cut into small pieces to speed up the drying process, either under the sun or using a drying oven. Once dry, the leaves were ground into a fine powder. A total of 250 grams of leaf powder was weighed and placed in a sealed glass container.

Next, 1,250 ml of distilled water was added, stirred until homogeneous, then left to stand for 2×24 hours with periodic stirring. The resulting maserate is filtered and squeezed using filter paper to obtain a liquid extract. The extraction process continues with the decoction of the leaf residue, which involves boiling the remaining extract solids using 70% ethanol solvent until boiling, with the aim of extracting any remaining compounds. The maserate is evaporated until only the pure leaf extract remains, which can then be used for phytochemical testing.

- **Phytochemical Test**

Phytochemical tests on papaya and mangosteen leaf extracts were conducted using various reagents to determine the presence of secondary metabolites, such as alkaloids, flavonoids, phenolics, tannins, saponins, steroids, and triterpenoids.

- a. Alkaloid

Identification of alkaloid compounds was carried out by adding 1% HCl and Dragendorff's reagent to 0.5 grams of extract, where the formation of a precipitate indicated a positive result.

b. Flavonoid

Flavonoid testing was conducted by dissolving 0.2 grams of extract in ethanol, then heating it for 5 minutes, adding concentrated HCl and magnesium powder. The appearance of a blackish red color indicated the presence of flavonoids.

c. Phenolic

Phenolic compounds were tested by dissolving 0.5 grams of extract in 70% ethanol, then adding a 5% FeCl<sub>3</sub> solution, and positive results were indicated by the appearance of a blackish green color.

d. Tannin

Tannin was tested by reacting 0.5 grams of extract solution in 70% ethanol solvent, then adding 5% FeCl<sub>3</sub> solution, and a positive result was indicated by a blue-green color change.

e. Saponin

The presence of saponin compounds is determined through a foam test, which involves dissolving the extract in hot distilled water, then adding 2N HCl, and stirring until a stable foam forms.

f. Steroid and Triterpenoid

The second test for steroids and triterpenoids was conducted by reacting the extract with CHCl<sub>3</sub>, acetic acid, and concentrated H<sub>2</sub>SO<sub>4</sub>, where a reddish-brown color change indicated the presence of steroids. Meanwhile, the formation of a red ring indicated the presence of triterpenoid compounds.

### 3 RESULT

The results of phytochemical screening of papaya and noni leaf extracts are shown in the table below (Table 1).

Table 1: Phytochemical Test Result

| Compounds    | Phytochemical Test Result |          |
|--------------|---------------------------|----------|
|              | Papaya                    | Noni     |
| Alkaloid     | Positive                  | Positive |
| Flavonoid    | Positive                  | Positive |
| Phenolic     | Positive                  | Positive |
| Tanin        | Positive                  | Positive |
| Saponin      | Positive                  | Positive |
| Steroid      | Positive                  | Negative |
| Triterpenoid | Positive                  | Positive |

(Source: Personal Data, 2025)

### 4 DISCUSSION

Sudarma's (2024) research shows that Alzheimer's disease involves progressive neuron death associated with the accumulation of  $\beta$ -amyloid (A $\beta$ ) plaques and the formation of neurofibrillary tangles (NFTs) from hyperphosphorylated tau protein. This damage causes disruption of communication between neurons, disruption of nerve cell metabolism, and loss of neuronal cellular repair capabilities (Amin *et al.*, 2025). The neurodegenerative process triggers oxidative stress, neural inflammation, and mitochondrial dysfunction, which cause nerve cell death through apoptosis and necrosis mechanisms. These disorders can result in cognitive and memory impairment in Alzheimer's patients, as well as neurochemical changes such as decreased activity of the cholinergic system, which is vital in the learning and memory processes (Safutra *et al.*, 2023). Neuroprotective agents play a crucial role

as compounds or substances capable of protecting neurons from damage triggered by the pathological processes of Alzheimer's disease. Neuroprotection is achieved through antioxidant mechanisms that inhibit neurotoxic oxidative stress, anti-inflammatory mechanisms that suppress excessive inflammatory responses from microglia, and apoptosis inhibition to prevent neuronal cell death. Additionally, neuroprotective agents can stimulate neuron regeneration, enhance mitochondrial function, and repair damaged synaptic communication, thereby maintaining cognitive function despite neuropathological damage (Sudarma, 2024).

Neuroprotective agents play an important role as compounds or substances that can protect neurons from damage caused by the pathological processes of Alzheimer's disease. Neuroprotective effects can be achieved through antioxidant mechanisms that inhibit neurotoxic oxidative stress, anti-inflammatory mechanisms that suppress excessive inflammatory responses from microglia, and apoptosis inhibition to prevent nerve cell death. Additionally, neuroprotective agents can stimulate neuron regeneration, enhance mitochondrial function, and repair damaged synaptic communication, thereby maintaining cognitive function despite neuropathological damage. Thus, exploring bioactive compounds from plants with neuroprotective potential is an important step in the development of Alzheimer's therapies (Sudarma, 2024).

Phytochemical testing is the first step in identifying the chemical compounds present in extract samples by observing changes in color and certain physical characteristics. This test is conducted qualitatively using reagents that produce characteristic color changes in the tested extract

(Swandono *et al.*, 2025). The screening results are greatly influenced by the type of solvent and extraction method used, as both play an important role in determining the efficiency of bioactive compound acquisition. In this study, 70% ethanol solvent was used, because the chemical compounds in papaya and mengkudu leaves are known to be easily soluble and optimally extracted with this solvent (Pasaribu *et al.*, 2025). The following are the results of phytochemical tests on papaya and noni leaf extracts (Table 1).

The phytochemical screening results showed that papaya and noni leaf extracts both contained alkaloids, flavonoids, phenolics, tannins, saponins, and triterpenoids, while steroids were only detected in papaya leaf extract. These compounds are known to have neuroprotective potential. The alkaloid test was carried out by adding Dragendorff's reagent to the sample, which was indicated by the formation of an orange precipitate as a positive result (Royani & Yuliyanti, 2025). The addition of HCl serves to increase the solubility of alkaloid compounds, where basic compounds will turn into salts in an acidic environment, making them more soluble and react optimally (Febriani *et al.*, 2025).

Flavonoid testing was carried out using the Shinoda method, which involves adding magnesium powder and concentrated HCl solution. A positive reaction is indicated by a change in the color of the solution to red, orange, or yellow, resulting from the reduction of the flavonoid nucleus by magnesium in acidic conditions (Lingga & Rosa, 2025). To detect saponin compounds, the sample was dissolved in distilled water, then shaken to form foam. Stable foam that did not disappear after the addition of 1 N HCl solution indicated the presence of saponin, a

property related to the ability of saponin compounds to reduce surface tension like surfactants (Mogi & Tia, 2025).

Tannin testing is carried out by adding  $\text{FeCl}_3$  solution to the sample. A positive reaction is indicated by the appearance of a dark blue to blackish green color resulting from the complex bond between the phenol group in tannin and  $\text{Fe}^{3+}$  ions (Oktavia & Sutoyo, 2021). Phenolic compounds can also be detected with  $\text{FeCl}_3$  reagent, which produces blue, purple, or green colors due to the formation of complexes between phenolic hydroxyl groups and metal ions (Ayuchecaria *et al.*, 2020). Steroid testing is carried out using the Liebermen-Burchard reagent, which is a mixture of anhydrous acetic acid and concentrated sulfuric acid (Azalia *et al.*, 2023). A positive reaction is indicated by the formation of a bluish-green color as a result of the condensation of the steroid nucleus with the reagent (Nasution, 2020). Meanwhile, triterpenoids were tested using the same method, but positive results were indicated by the formation of a red to purple color, which indicated the presence of double bonds in the triterpenoid structure that reacted with strong reagents (Manongko *et al.*, 2020).

Secondary metabolites play a role in inhibiting the  $\beta$ -secretase enzyme (BACE1), which is responsible for the formation of  $\beta$ -amyloid peptides, thereby reducing the accumulation of  $\beta$ -amyloid plaques. In addition, secondary metabolites can also activate antioxidant signaling pathways such as Nrf2/ARE, which increase the expression of endogenous antioxidant enzymes to counteract free radicals that cause oxidative stress (Tazuyyun, 2020). The inhibition of neurogenic inflammation occurs through a decrease in the production of pro-

inflammatory cytokines, such as  $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$ , accompanied by the prevention of neurotoxic microglia (Putri, 2024). Secondary metabolites also modulate the apoptosis pathway by decreasing the expression of pro-apoptotic proteins such as Bax and increasing the anti-apoptotic protein Bcl-2, thereby protecting neurons from cell death. Secondary metabolites can affect memory and cognitive function by inhibiting acetylcholinesterase, thereby increasing acetylcholine levels in the synapses (Pramessti, 2025).

The alkaloids in both extracts act as cholinesterase enzyme inhibitors, resulting in increased levels of acetylcholine at nerve synapses, a neurotransmitter that is very important for learning and memory processes, which are often impaired in Alzheimer's patients (Reubun *et al.*, 2025). Additionally, alkaloids have anti-inflammatory effects by inhibiting the NF- $\kappa$ B signaling pathway, which reduces the production of pro-inflammatory cytokines such as  $\text{IL-1}\beta$  and  $\text{TNF-}\alpha$ , thereby reducing chronic inflammation that can accelerate neuronal degeneration (Putri, 2024). Flavonoids and phenolics are known as powerful antioxidants that can counteract free radicals and reduce oxidative stress in neurons by donating electrons to neutralize reactive oxygen species (ROS) that damage cellular components, including membranes, proteins, and mitochondrial DNA (Widiasriani *et al.*, 2024). In addition to their antioxidant properties, flavonoids can modulate neuroprotective signaling through the activation of kinase pathways, such as protein kinase C (PKC) and mitogen-activated protein kinase (MAPK), and increase the expression of the transcription factor CREB, which stimulates the production of brain-derived neurotrophic factor

(BDNF), which is important for synaptic plasticity and neuron regeneration (Suleman, 2019).

Tannins play a role in inhibiting the aggregation of beta-amyloid (A $\beta$ ) proteins, one of the main triggers for the formation of amyloid plaques that damage nerve tissue in the brains of Alzheimer's patients (Sudarma, 2024). By inhibiting A $\beta$  oligomerization and fibrillation, tannins prevent plaque accumulation that causes synaptic dysfunction and neuronal death (Debby *et al.*, 2023). Saponins support nerve regeneration and repair tissue damage by increasing the secretion of nerve growth factor (NGF) and suppressing excessive microglia activation, thereby reducing neurodegenerative inflammation (Safutra *et al.*, 2023). Steroids from papaya leaf extract function as central nervous system modulators by maintaining nerve cell membrane stability and controlling microglia activity through the glucocorticoid receptor pathway, reducing inflammatory molecule production and preventing neuron apoptosis (Fatimah, 2019). Triterpenoids complement the neuroprotective mechanism by inhibiting pro-apoptotic proteins, such as Bax, and increasing anti-apoptotic proteins, such as Bcl-2, regulating the balance of cell death pathways, and suppressing the activation of inflammatory pathways, such as p38 MPK and NF- $\kappa$ B pathways, thereby preventing excessive neuronal death due to oxidative and inflammatory toxicity (Mustariningrum *et al.*, 2024).

Papaya leaves (*Carica papaya* L.) contain various bioactive compounds that contribute significantly to their health benefits and nutritional value. The main compounds contained therein include polyphenols, triterpenoids, and glycosides. These components are known to have antioxidant

activity that helps maintain cell membrane stability, protect lipids from peroxidation, and prevent protein and DNA damage (Amin & Maharani, 2025). The high polyphenol content in papaya leaves plays a role in reducing the amyloid burden through two mechanisms, namely suppressing  $\beta$ -secretase activity, thereby reducing the formation of A $\beta$  from APP, and binding to A $\beta$  oligomers to inhibit their aggregation and toxicity to synaptic membranes. Additionally, polyphenols stimulate the clearance of pathological proteins, including increased autophagy and proteasomal activity, thereby accelerating the degradation of A $\beta$  oligomers (Gondokesumo & Susilowati, 2021).

In addition to the protective mechanism of polyphenolic compounds against amyloid free radicals, the triterpenoid content in papaya leaves also contributes to neuroprotective effects by targeting pro-apoptotic pathways and tau hyperphosphorylation (Widiasriani *et al.*, 2024). Glycosides and saponins in papaya leaves also contribute to the improvement of cholinergic neurotransmission through the inhibition of acetylcholinesterase, and can increase neurotrophic signaling that supports synaptic plasticity and long-term potentiation (Manongko *et al.*, 2020). The three compounds polyphenols, triterpenoids, and glycosides also play a role in reducing neuroinflammation by suppressing the NF- $\kappa$ B and inflammasome pathways, altering the phenotype of microglia toward a reparative state, and decreasing the production of proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ ) (Debby *et al.*, 2023).

On the other hand, noni leaf extract is known to have neuroprotective activity as a multitarget agent against Alzheimer's through three main mechanisms,

namely antioxidant activity (flavonoids), anti-inflammatory activity (iridoid glycosides), and neurotransmission modulation (scopoletin). Flavonoids play an important role as antioxidants by neutralizing free radicals, enhancing the activity of endogenous antioxidant enzymes such as SOD, catalase, and GPx, and protecting neurons from oxidative stress, which contributes significantly to the pathogenesis of Alzheimer's disease (Sari, 2024). Meanwhile, iridoid glycosides, particularly asperuloside and deacetylasperulosidic acid (DAA), exhibit anti-inflammatory mechanisms by inhibiting the activation of the NF- $\kappa$ B pathway and NLRP3 inflammasome, thereby reducing the secretion of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6). This effect is able to reduce the hyperactivation of microglia and astrocytes, which often accelerate nerve tissue damage. In addition, the presence of scopoletin in noni leaves acts as a neurotransmitter modulator by inhibiting the acetylcholinesterase enzyme, which ultimately helps improve cholinergic transmission in the brains of Alzheimer's patients (Putri, 2024). The synergy between antioxidant, anti-inflammatory, and neurotransmission modulation activities makes noni leaves a potential multitarget agent in slowing the progression of Alzheimer's disease, although further clinical research is still needed to confirm the efficacy and bioavailability of its active compounds (Nasution *et al.*, 2025).

Overall, papaya leaf extract shows potential as a multi-target agent in the treatment of Alzheimer's disease, due to its ability to work on various key aspects of the disease's pathology, ranging from A $\beta$  formation and aggregation, tau hyperphosphorylation, mitochondrial dysfunction, to decreased cholinergic neurotransmission activity

(Manongko *et al.*, 2020). In contrast, noni leaf extract is more prominent through its anti-inflammatory and antioxidant activities, mainly due to its flavonoid and iridoid content, which effectively suppresses microglia activation and reduces oxidative stress that exacerbates neuronal damage (Sari, 2024). Thus, the two extracts complement each other, with papaya leaves providing broad protective effects on various molecular pathways, while noni leaves strengthen the defense of nerve cells against inflammation and oxidative stress. The combination of the two opens up great opportunities for development as complementary phytotherapy in slowing the progression of Alzheimer's disease (Gondokesumo & Susilowati, 2021).

## 5 CONCLUSIONS

Alzheimer's disease is a progressive neurodegenerative disorder that causes nerve cell death due to the accumulation of  $\beta$ -amyloid plaques and hyperphosphorylated tau proteins. Phytochemical testing shows that papaya and noni leaf extracts contain secondary metabolites such as alkaloids, flavonoids, phenolics, tannins, saponins, and triterpenoids, with steroids only present in papaya leaf extracts. These compounds have the potential to act as neuroprotective agents through antioxidant, anti-inflammatory, and apoptosis-inhibiting mechanisms. Papaya leaf extract excels in multi-target activity that broadly protects neurons, while noni leaf extract is effective in reducing inflammation and oxidative stress. The combination of the two has the potential to serve as a complementary therapy to slow the progression of Alzheimer's disease.

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