Targeting LPS-Mediated Neurodegeneration in Alzheimer's Disease: Insights into the Phyto-pharmacological Properties of *Madhuca longifolia*

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Abstract

Progressive cognitive decline and memory loss are main symptoms of Alzheimer's disease (AD). Lipopolysaccharide (LPS) is commonly used in experiments to reproduce the inflammation seen in Alzheimer's disease. These studies have demonstrated what role medicinal plants have in managing inflammation. The traditional medicine plant Madhuca longifolia has been found to be anti-inflammatory and protective for the brain. We wish to explore the plant-based properties of Madhuca longifolia and its capacity to deal with neuro-inflammation associated with Alzheimer's disease.

Keywords: *Alzheimer's disease, LPS, neuro-inflammation, Madhuca longifolia, neuroprotection.*

1. Introduction

Alzheimer's disease is a type of neurodegenerative disorder that is very commonly mentioned. In 1906 Dr. Alzheimer was the first person to discover Alzheimer disease, a neurodegenerative illness. Around the globe, there are 44 million people with AD. The main symptom is a gradual loss of memory which is then followed by difficulties with how we perceive space, our ability to navigate, alternative thinking processes, speaking and writing, with the appearance of senile plaques and neurofibrillary tangles as well as reduced acetylcholine and certain other neurotransmitters. It gradually starts impacting normal everyday actions. Problems like oxidative stress, obesity, diabetes, hypertension, air pollution, smoking, increased cholesterol also help cause AD. Now, the Food and Drug Administration (FDA) has approved two types of drugs for treating Alzheimer's: Tacrine, Galantamine, Donepezil, Memantine, and Rivastigmine (1).

Alzheimer has caused over 36.5 million cases to this point and it is predicted to reach 65.7 million in 2030 and 115.4 million in 2050. World Health Organization has found out that more than half of the people affected by AD live in developing nations. As soon as 2025, the percentage of elderly people may reach 70% (2).

1.1 Role of neuro-inflammation in AD progression

AD arises because of a mix of genes and multiple factors and its pathology is not easy to understand. The three major areas of the brain which are changed by Alzheimer's disease are seen in figure 1 (3). In Alzheimer disease, Aβ accumulates around the neurons outside the cells and within the cells, the over-phosphorylation of Tau proteins contributes to the formation of tangles, reducing the Ach chemical signal (4). Among brain neurons, cholinergic neurons play an important role by helping to synthesize acetylcholine which

handles signal transmission and messaging. It helps our brains with learning and remembering things. Plaques and neurofibrillary tangles are deposits in the brain that cause cholinergic neurons in the hippocampus and cortical regions to degrade and acetylcholine levels to drop (5). Reduced acetylcholine levels cause the cholinergic pathway's uncontrolled signal transmission, which is linked to AD. AD is associated with cholinergic dysfunction, which is responsible for the cholinergic pathway's uncontrolled signal transmission. Cognitive impairment results from cholinergic regulatory malfunction that starts in the basal forebrain and interacts with pathogenic features of AD, such as Aβ plaque, NFTs, inflammation, and oxidative stress (6).

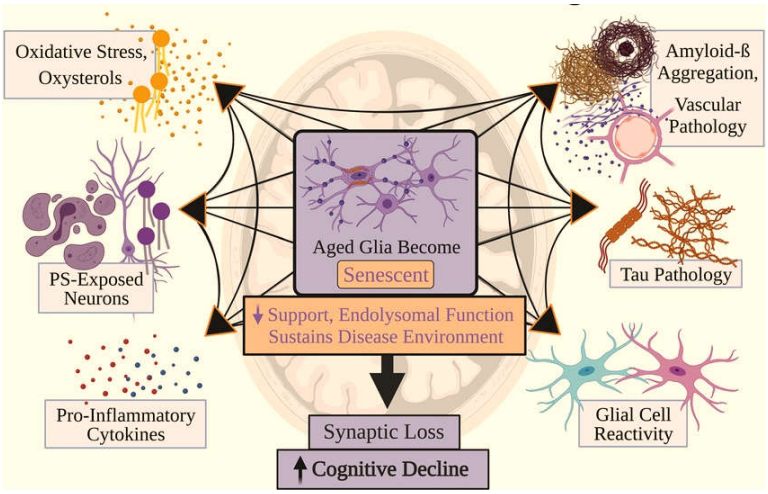

Figure no. 1 Pathology of Alzheimer's disease (PS-phosphatidylserine)

In addition to AD progression, neuronal circuit degradation causes neurotransmitters such as dopamine, serotonin, glutamine, and noradrenergic neurotransmitters to dysregulate by changing the activity of some other serotonergic, dopaminergic, glutamatergic, and adrenergic neurons. Neuronal tissues express the type-I transmembrane protein known as amyloid precursor protein (APP).

1.2 Lack of curative treatments and the need for alternative therapies

Tacrine was the first acetylcholinesterase inhibitor introduced for AD in 1993. Following the acceptance of the amyloid theory in 1990, research was directed at antioxidants, hormone agents, and anti-inflammatory drugs. The first NMDA antagonist, memantine, was authorized in 2003 for the treatment of Alzheimer's disease. Research on NMDA (N-methyl-D-aspartate) antagonists began in the early 1980s (7). However, none of them worked to treat the illness, therefore more cholinesterase inhibitors including donepezil, galantamine, and rivastigmine were created.

2. Pathophysiology of LPS-Mediated Neuro-inflammation

Endotoxin-induced neuro-inflammation is a model of neurodegenerative illnesses that is solely driven by inflammation. It suggests that neuroprotection will occur when microglial synthesis of neurotoxic mediators is suppressed. This increases interest in the quick development of treatments that target neuro-inflammation. Efforts include the discovery of new synthetic compounds that specifically downregulate neuro-inflammatory responses, the screening of licensed CNS medications for additional purposes, and the separation of natural products and their active ingredients. Additionally,

NFκB is a crucial regulator of the production of cytokine genes, such as TNF-α and IL-1β, which suggests that blocking NFκB may be a therapeutic target in AD (8). Curcumin, a naturally occurring food pigment with well-known anti-inflammatory and antioxidant qualities, was then chosen to assess its effectiveness in an AD model produced by LPS.

The pathophysiology of certain neurodegenerative illnesses, including as Alzheimer's disease, Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), frequently includes endotoxin (LPS)-induced inflammation and microglial activation (9). Studies conducted on animal models over the past 20 years have shown that inflammation brought on by lipopolysaccharide (LPS) can mimic some of the features of AD, such as the nigrostriatal system's selective loss of dopaminergic neurons and widespread activation of microglia. An essential tool for defining the precise role of several pro-inflammatory and neurotoxic variables in dopaminergic neurodegeneration is the LPS-induced AD model.

Furthermore, according to current research, people are frequently exposed to LPS because it is prevalent in the air as a part of PM2.5, an air pollutant, or as part of household dust and aerosols produced from tainted water (10). Particulate matter smaller than 2.5 μm, or PM2.5, comes from a variety of sources, including power plants, oil refineries, metal processing facilities, tailpipe and brake emissions, household fuel combustion, and wildfires.

Additionally, other research has indicated that occupational exposure to LPS is widespread among those working in textile mills or agricultural settings (11). Additionally, endotoxins can be exposed through bacterial translocation from the stomach or systemic or localized gram-negative bacterial infections from exogenous sources, which can expose people to LPS. By activating microglial cells, the endotoxin triggers an overwhelming inflammatory host response once it enters the bloodstream. These cells then release a variety of pro-inflammatory cytokines, such as TNF-α and IL-1β, and they also produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) by activating NADPH oxidase (12).

Additionally, there is interest in creating antioxidant medicines to counteract the harmful effects of oxidative shocks because of the connection between oxidative stress and neuro-inflammatory responses. Through the action of microglial NADPH oxidase, activated microglia are the primary mediators of ROS generation and inflammation produced by LPS. Thus, pharmacological inhibition of NADPH oxidase provides neuroprotection against LPS-induced loss of SNpc DA-nergic neurons, as evidenced by the presence of NADPH oxidase and its protein components in astrocytes and microglia cells as well as evidence of its involvement in inflammatory responses linked to neurodegenerative diseases (13).

3. Pharmacological Profile of *Madhuca longifolia*

It is well recognized that *Madhuca longifolia* has ethno medical use. It is a member of the Sapotaceae family and is frequently referred to as Mahua. Known to possess antimicrobial, anti-ulcer, hepato-protective, anti-diabetic, anti-inflammatory, and analgesic properties, this deciduous tree can reach a height of 60 feet (14).

- Botanical names include Vidoricum longifolium (J. Koenig ex L.) Kuntze, Bassia longifolia (J. Koenig ex L.), and *Madhuca longifolia* (J.F. Macbr).
- Colloquial names: Iluppai in Tamil, Mahua in Hindi, Ippe in Kannad, and Mowra butter tree in English; and Ippa in Telugu.

Table no. 3 Taxonomical Classification

Kingdom	Plantae
Phylum	Tracheophyta
Class	Equisetopsida C. Agardh
Order	EricalesBercht. & J. Presl
Family	Sapotaceae
Subfamily	Caesalpinioideae
Genus	Madhuca
Species	*Madhuca longifolia* (J.Koenig ex L.) J.F.Macbr.

The fast-growing *Madhuca longifolia* tree is typically found in southern Asia, where it is grown in a warm, humid climate. It has evergreen and semi-evergreen foliage and can reach a height of about 20 meters. It is a member of the Ericales order and the Sapotaceae family. For the Central Indian tribal people, it serves as a vital lifeline. It is well-known for its tasty fruit and flowers, the latter of which are used to make vinegar and alcohol (15). Stout trunk with white sap and spreading branches.

Broad, dense, and packed leaves at the apex of the shoot. Soft brown hair covers fruits, flowers, and shoot tops. Clusters of flowers on stems without leaves. Its leaves are 10 to 30 cm long, lanceolate, narrowed at both ends, leathery, thick, and glabrous with noticeable nerves. *Madhuca longifolia* is a huge deciduous tree that grows in the wild and provides shade. The tree needs an elevation of 1200 meters, an annual temperature between 28°C and 50°C, and 550 to 1500 mm of precipitation to grow.

3.1 Chemical Constituents

Total lipids (TL) make up roughly 50–60% of M. longifolia seeds, along with 22% carbs, 16.9% protein, 3.2% fiber, 3.4% ash, 2.5% saponins, and 0.5% tannins. Barks contain oleanic acids, α-spinasterol, erythrodiolmonocaprylatebetulinic acid, α-terpeniol, and sesquiterene alcohol, whereas fruits consist of quercetin, dihydroquecertin, β-sitosterol, and α and β amyrin acetates. Sesquiterene alcohol, a-terpeneol, 3ß-capryloxyoleanolic acid, 3B monocaprylic ester of eythrodiol, and ethylcinnamate. Amyrin acetates ß- and α- (16).

3.2 Known pharmacological activities

Mahua butter is the edible fruit that *Madhuca longifolia* produces, and it is said to have therapeutic qualities. *Madhuca longifolia* has long been used to treat arthritis, headaches, piles, snake bites, and skin allergies. *Madhuca longifolia* seed cake has been used as organic manure with insecticidal and pesticidal qualities. Due to its high fatty acid content, *Madhuca longifolia* seed oil is used as fuel oil and for cooking and skin care. The high fat content of *Madhuca longifolia*'s fruit and seed is used to cure rheumatism, headaches, skin conditions, and piles. The plant's fat-rich portion is used to make soap, and the seed cake is used as an insecticide and pesticide as well as for fishing (17).

Madhuca longifolia bark is used to cure fever, leprosy, and diarrhea. Dihydroquericetine, palmitic acid, β-sitosterol, β-D-glucoside, β-carotene, oleanolic acid, quercetine, stigmasterol, triterpenoids, amyrin acetate, myricetine, and saponins A and B are among the chemical components of *Madhuca longifolia*. It is well known that the bark's ethanolic extract possesses antibacterial, wound-healing, anti-inflammatory, and hypoglycemic properties. The stem's ethanolic extract is reported to possess antibacterial properties. *Madhuca longifolia* bark is known to have anti-ulcer properties.

By doing biochemical and histological investigation, studies on *Madhuca longifolia*'s ethanolic leaf extract have demonstrated its protective effect against acetaminophen-induced toxicity. *Madhuca longifolia* leaf ethanolic extract is said to possess anti-inflammatory, anti-cancer, and antioxidant properties. *Madhuca longifolia* aqueous leaf extract has been shown to have antiulcer and antidiabetic properties. *Madhuca longifolia* leaves are used to make ghee and to cure intestinal worms, eczema, respiratory infections, emaciation, and debility.

It is well known that methanolic extracts of flowers, leaves, stems, and bark have antibacterial properties. The bark's methanolic extract is recognized to have anti-diabetic and anti-hyperglycemic properties. *Madhuca longifolia* flower extract in ethanol is reported to have anti-ulcer properties (18).

4. Mechanism of Neuroprotection of *Madhuca longifolia* in LPS Models

The primary cause of age-related cognitive decline, which may be linked to the development of Alzheimer's disease in older adults, is reactive oxygen species (ROS). Additionally, *Madhuca longifolia* possesses antioxidant qualities. The antioxidant properties of *Madhuca longifolia* extract contribute to its neuroprotective action by reducing oxidative stress on vulnerable neurons, which in turn improves neuronal function and minimizes neuronal damage. According to this investigation, *Madhuca longifolia* ethanolic extracts at a dosage of 200 mg/kg have nootropic activity equivalent to that of the prescription drug piracetam. Ethanolic leaf extract from *Madhuca longifolia* raised GSH levels while lowering NO. Consequently, the ethanolic leaf extract of *Madhuca longifolia* has significant nootropic action (19).

4.1 Experimental studies supporting neuroprotection

By measuring the biochemical changes in the mice's brain, Khare et al. assessed the preventive effect of *Madhuca longifolia* ethanolic leaf extract flavonoid fraction against colchicine-induced cognitive impairment and oxidative damage in Swiss albino mice. The study also included estimations of total flavonoids, total phenols, and HPTLC. For 28 days, the analysis was carried out on a model that was caused by colchicine. Biochemical markers including glutathione and nitric oxide were assessed, while behavioral experiments were conducted using the Morris water maze and passive avoidance paradigm. The 48 Swiss albino mice were divided into eight groups of six mice each. The first group received 1 percent w/v carboxymethyl cellulose. The second cohort received 200 mg/kg of piracetami.p. Group III was administered 1 mg/kg intracranially of colchicine. 100 and 200 mg/kg of ethanolic *Madhuca longifolia* leaf extract were administered to the fourth and fifth groups, respectively. Colchicine 1 mg/kg, i.p., was administered 60 minutes after the 28th day of piracetam injection, while Group VI received piracetam (200 mg/kg, i.p.) for 28 days. Groups VII and VIII received oral extracts of *Madhuca longifolia* leaves at doses of 100 and 200 mg/kg for 28 days. On the 28th day, they received an intracellular injection of colchicine (1 mg/kg) 90 minutes after the extract was administered. One-way ANOVA was used, followed by the Dunnett's test

and, lastly, an analysis of the results. Leaf extract from *Madhuca longifolia* significantly decreased transfer latency and showed signs of morris water maze. The passive avoidance model's transfer delay significantly increased. The leaf extract from *Madhuca longifolia* showed a significant decrease in total protein and NO and a significant increase in GSH concentrations. The aforementioned discovery led to the conclusion that *Madhuca longifolia* has a neuroprotective effect against colchicine-induced memory loss (19).

Khare et al. previously described how the leaves of *Madhuca longifolia* (Sapotaceae) can improve cognition. In their investigation, intracerebrovascular colchicine treatment for 28 days triggered dementia. Using an actophotometer, elevated plus maze (EPM), and biochemical assessment of brain AChE and MDA levels, the cognitive-enhancing potential of an ethanolic extract of *Madhuca longifolia* leaves was assessed in mice with colchicine-induced dementia. The typical medication was piracetam (200 mg/kg p.o.). Colchicine-induced mice employing EPM exhibited transfer latency (TL), which was significantly higher ($p<0.01$) than in the normal control group. There was no discernible impact on the mice's locomotor activity. Compared to normal control, mice given colchicine showed a significant ($p<0.01$) increase in AChE and a drop in MDA levels. The traditional argument was based on these findings, and *Madhuca longifolia*'s flavonoid content suggests that it may improve memory (20).

4.2 Effects on inflammatory mediators (TNF-α, IL-1β, IL-6)

According to a recent analysis by Gupta and Roy (21) the natural compounds in *Madhuca longifolia* have demonstrated multifarious medicinal potential and have showed promising effects in numerous animal models of neurological problems. Through a variety of methods, these chemicals demonstrate anti-inflammatory, antioxidant, and mucosal healing effects. They successfully decrease the activity of 5-lipoxygenase (5-LOX), a crucial enzyme in the inflammatory cascade, and pro-inflammatory cytokines such as Interleukin-1 beta (IL1β) and Tumour Necrosis Factor-alpha (TNF-α). These compounds have also been shown to alter antioxidant factors like glutathione (GSH) and superoxide dismutase (SOD) and lower intestinal oxidative stress markers like malondialdehyde (MDA).

In a different investigation, Tanget et al. discovered that the phytoconstituent, a pentahydroxy flavone, isolated from M. longifolia, reduces the hyperalgesia caused by FCA by inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), inflammatory mediators (NF-kβ, Ikβα, COX-2, and P2X7), and elevated oxido-nitrosative stress in experimental rats. Treatment with 10 and 20 mg/kg demonstrated a significant ($p < 0.05$) reduction in the symptoms of neuronal arthritis caused by FCA. Flavone considerably ($p < 0.05$) decreased the high synovial oxido-nitrosative stress and protein levels of TNF-α, IL-1β, and IL-6. Flavone significantly reduced ($p < 0.05$) the up-regulated levels of NF-kβ, Ikβα, COX-2, and P2X7 proteins, according to Western blot examination (22).

4.3 Role in oxidative stress and mitochondrial function

Simon and Prince's study assessed the protective effect of M. longifolia's aqueous leaf extract against diclofenac-induced toxicity, which resulted in excessive oxidative stress in the experimental animals' cellular mitochondria. Five groups of six rats each were formed from the rats. Group I served as the standard control. Diclofenac (50 mg/kg b.w./day, i.p.) was given to Group-II on the fourth and fifth days. Aqueous leaf extract of M. longifolia (500 mg/kg b.w./day, oral) was administered to Group-III rats for five days in a row, and on the fourth and fifth days, diclofenac (50 mg/kg b.w./day, i.p.) was administered. The conventional medication, silymarin (25 mg/kg b.w./day, oral), was

administered to the rats in group IV on days four and five in addition to diclofenac. Group-V received only an oral 500 mg/kg b.w./day dose of M. longifolia leaf extract. Following the study period, the rats' levels of cytokines, antioxidant parameters, histopathological alterations, and liver enzyme markers were assessed. ELISA was used to assess the hepatic pro-inflammatory mediator cytokines, such as TNF-α, IL-6, and IL-1β. Caspase-3, COX-2, and NF-κB protein expression was examined using Western blotting methods. The alterations brought on by diclofenac were able to be restored by an aqueous leaf extract of M. longifolia. The current investigation shows that the aqueous leaf extract of M. longifolia protects against toxicity caused by diclofenac (23).

5. Mechanistic Insights Possible molecular pathways modulated by *Madhuca longifolia*

Alzheimer's disease (AD) has been connected to key targets such AKT1, JUN, and STAT3. JUN is engaged in oxidative stress responses and neuro-inflammation, MAPK and STAT3 are implicated in neuroprotection, while AKT1 reduces neurotoxicity and promotes neuronal survival (24). Other genes, such as CSNK2A1, CHRM3, PIK3CA, MAP2K1, and GRM5, have also been connected to AD. MAP2K1 regulates cell signaling, GRM5 is linked to synaptic plasticity, CSNK2A1 influences tau phosphorylation, CHRM3 is engaged in cholinergic neurotransmission, and PIK3CA is implicated in the PI3K/Akt pathway (25).

The *Madhuca longifolia*-AD PPI network's top ten targets (AKT1, TNF, EGFR, HSP90AA1, JUN, STAT3, CASP3, MTOR, PTGS2, PPARG) were ranked by degree. The serine/threonine protein kinase AKT1, which is crucial for regulating both apoptosis and cell survival, was the most prominent of these targets. Zeng highlighted the importance of brain AKT phosphorylation in insulin and growth factor regulation and linked it to the neuropathology and cognitive impairment of Alzheimer's disease (26). Through ROS-mediated oxidative modification, which can result in synaptic dysfunction and the loss of activity-dependent protein translation—which is crucial for preserving and adjusting synaptic plasticity—AKT1 may also play a part in AD, according to research. The crucial role that AKT1 plays in AD is highlighted by a number of studies on network pharmacology in the disease (27). It has been demonstrated that AKT1 activation reduces neurotoxicity brought on by amyloid-beta peptides, which are a defining feature of AD pathology. AKT1 also controls neuronal activity and synaptic plasticity, which affects cognitive processes in AD. Its potential as a therapeutic target is highlighted by the possibility that dysregulation of AKT1 signaling pathways in the brain contributes to the neurodegeneration and cognitive loss seen in Alzheimer's disease (28). Although pro-inflammatory markers like TNF and EGFR are frequently employed in AD, the other key targets are essential to the development of the illness.

Key pathways linked to the pathophysiology of AD are highlighted by KEGG pathway analysis, such as the PI3K-Akt signaling pathway, metabolic pathways, and neuroactive ligand-receptor interactions. These results offer important new information on the possible processes behind *Madhuca longifolia*'s therapeutic benefits in AD (29).

6. Conclusion and Future Prospects

To sum up, this study methodically examined *Madhuca longifolia*'s therapeutic methods for Alzheimer's disease (AD). We have identified the primary targets and pathways linked to *Madhuca longifolia*'s possible effectiveness against AD by thoroughly examining its active ingredients, molecular targets, and related pathways. The results of this study demonstrate the potential of *Madhuca longifolia* as a natural treatment for AD and provide insightful information that merits more experimental validation. Compared

to existing treatments, these substances may be more effective and cause fewer adverse effects, which would improve patient outcomes and reduce the progression of the disease. The identification of these pathways' aids in the group's search for efficient AD treatments. The findings reported here have the potential to strengthen the scientific basis for clinical judgments in the field of AD treatments in the future. Future research should concentrate on using cellular and animal models of Alzheimer's disease to experimentally validate the chemicals found in *Madhuca longifolia*. Examine their toxicity profiles, bioavailability, and pharmacokinetics. Additionally, investigate synergistic effects with current AD medications and carry out clinical trials to evaluate the safety and effectiveness of the treatment in humans.

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