ORIGINAL ARTICLE

A REVIEW ON THE NEUROPROTECTIVE POTENTIAL OF *TAMARINDUS INDICA*: EVIDENCE FROM PRECLINICAL STUDIES DONE BETWEEN 2016 TO 2023

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ABSTRACT

Neurological disorders like Alzheimer's and Parkinson's disease present substantial challenges globally. Despite advancements in health sciences, effective treatments for neurodegenerative conditions remain elusive. Tamarindus indica, a tropical tree with a rich history in traditional medicine, holds promise as a potential neuroprotective agent due to its diverse phytochemical composition. This narrative review aims to evaluate Tamarindus indica's neuroprotective potential by systematically analyzing studies published in English Language retrieved from PubMed, Scopus databases, and Google Scholar. The algorithm ("Tamarindus indica" OR "tamarind") AND (Brain OR neuroprotect* OR behavioural OR neurodegenerative diseases OR Alzheimer's OR Parkinson's) was run on the two databases and search engine on the 2nd of October 2023 without any filters. Tamarindus indica, possesses phytochemicals such as flavonoids, alkaloids, and tannins, contributing to its medicinal properties. Despite its medicinal significance, caution is advised regarding the toxicity of certain components like seeds and potential allergic reactions. Nevertheless, research indicates its anti-inflammatory and antioxidant, mainly attributed to its flavonoids content, suggesting neuroprotective effects that could mitigate oxidative stress, lipid peroxidation, neuroinflammation and neuroexcitotoxicity, which are pivotal factors in neurodegeneration. While promising, a comprehensive understanding of Tamarindus indica's mechanisms, clinical applications, and safety profile is warranted. Further investigation is essential to unlock its therapeutic potential in combating neurodegenerative diseases. Tamarindus indica stands as a hopeful natural resource, necessitating continued exploration to harness its neuroprotective properties for improved neural health.

Keywords: Tamarindus Indica, Medicinal Use, Toxicology, Neuroprotective, anti-inflammatory, Phytochemical

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1.0 INTRODUCTION

Neurological disorders and Neurodegenerative disorders pose a significant challenge in healthcare systems worldwide, and impacts individuals' quality of life (1). These conditions, including Alzheimer's disease and Parkinson's disease are characterized by progressive neuronal dysfunction and cognitive decline (2). As these disorders advance, they severely compromise daily functioning, cognition, mobility, and, ultimately, autonomy (3). Moreover, they exert an emotional and financial burden on affected individuals and their caregivers (4,5). Despite ongoing scientific advancements, current regenerative therapies such as allopathic drugs, surgical procedures, tissue transplantation, and stem cell therapy primarily focus on alleviating symptoms rather than halting or reversing the underlying neurodegenerative processes (6).

In the search for effective treatments, numerous plant-derived compounds have emerged as potential candidates to combat neurodegeneration; aligning with WHO proclamation that more than 75% of the world population still depends on plant-based traditional medicines for primary health care (7). Plant-based therapies, owing to their diverse phytochemical compositions, have garnered attention for their neuroprotective properties (8–10). In this context, *Tamarindus indica*, commonly known as tamarind, stands as an intriguing botanical resource; a tropical tree with a rich history of traditional medicinal use that spans centuries (11–14). This fruit-bearing tree is native to Africa and has since disseminated to various tropical and subtropical regions worldwide. Beyond its culinary applications, *Tamarindus indica* has garnered attention for its potential medicinal properties, particularly its neuroprotective potential (6,15).

The importance of studying *Tamarindus indica* for its neuroprotective potential cannot be overstated. Finding effective and safe neuroprotective agents is crucial in mitigating the impact of these conditions (16). *Tamarindus indica*, with its long history of medicinal use, presents a promising avenue for exploration. The presence of various phytocompound in the leave, stem, pulp, back, root of *T. indica* explain its possible use in folk medicine (17). Flavonoids present in *T. indica* include apigenin, luteolin, catechins and taxifolin; and have all been reported to possess anti-inflammatory, anti-analgesic and antioxidative potentials (6).

This review aims to comprehensively analyze the existing literature to shed light on *Tamarindus indica's* potential as a possible neuroprotective agent. This research can provide valuable insights into the utilization of *Tamarindus indica* as a natural neuroprotective resource, offering hope for the prevention and treatment of neurodegenerative diseases.

2.0 METHODOLOGY

2.1 Search Strategy

For our extensive literature review on *Tamarindus indica's* neuroprotective potential, we used a structured and systematic approach. This methodology involved carefully selecting databases, search terms, and inclusion criteria to ensure we gathered relevant and up-to-date research articles.

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We systematically searched various academic databases, including PubMed and Scopus, and Google Scholar search engine. The algorithm ("Tamarindus indica" OR "tamarind") AND (Brain OR neuroprotect* OR behavioural OR neurodegenerative diseases OR Alzheimer's OR Parkinson's) was run on the two databases and search engine on the 2nd of October 2023 without any filters.

2.2 Study Selection Criteria

The search yielded one hundred and fifty-one articles from PubMed, Scopus, and Google scholar. The articles were downloaded as comma separated value (CSV) files. The documents were merges and duplicates were removed. The remaining articles were retrieval and screened for eligibility. Only peer reviewed studies which focused on the neuroprotective potential of *Tamaridus indica* and were published in English language were included. All authors, EME, JAM, DM, JI, VBA, and IMU carried out blinded and overlapping screening of titles and abstracts to determine eligibility. At the end of screening process, eleven (11) studies met the inclusion criteria for the study, hence were included (Figure 1)

2.3 Data Extraction

In unison, EME, JAM, DM, JI, VBA, and IMU extracted the following information: the names of the author, publication year, part of plant used, extract intervention/duration & dosage, study population/ model, parts of brain and possible mechanism of action (Table 1).

3.0 Results

3.1 Study Characteristics

Eleven studies made the inclusion criteria and were all published between 2016 and 2023. Tamarindus indica leaves were used in 36.4% (n=4) of the studies, 27.3% (n=3) used the pulp and 9% used the seed, seed and bark, and seed coat respectively. Ethyl acetate is the commonly used solvent 27.3% (n=3) and 45% (n= 5) of the studies used the Wistar rat as the preferred animal model. In regard to the brain part targeted; cerebral cortex was the widely targeted part of the brain in 36.4% of the studies followed by the hippocampus.

4.0 DISCUSSION

4.1 Toxicology of Tamarindus Indica

Tamarindus indica is generally considered safe for consumption, and it has a long history of use in traditional medicine and cuisine (18). However, there are some considerations related to its toxicology; Hence, it is essential to emphasize that these toxicological concerns are primarily associated with specific parts of the tamarind tree, such as the seeds, and are generally not a concern when consuming the edible pulp or using tamarind in culinary preparations. Nonetheless, as with any substance, moderation and awareness of individual sensitivities are advisable.

Various tests involving different parts of the *Tamarindus indica* (*T. indica*) plant have been conducted, including acute, sub-chronic, and chronic toxicological assessments (6,19). In an acute toxicity study on Wistar rats using the aqueous pulp extract at a dose of 4500 mg/kg, there were no observable harmful effects in the gastrointestinal tract, liver, or kidneys. Despite minor behavioral changes in the

animals, survival was 100%. The oral LD50 (lethal dose for 50% of the subjects) of the ethanolic pulp extract exceeded 5000 mg/kg with 100% survival rate. Evaluation of the ethanolic leaf extracts at 5000 mg/kg did not show any adverse changes in skin, hair, behavior, or vital organs (6). However, the ethanolic stem bark crude extract and fractions, at concentrations of 25% and 50%, increased certain blood enzymes in chicken embryos but did not reach levels indicating a disease state. High doses of the ethanolic stem bark crude extract caused significant mortality in test brine shrimp models. In a sub-chronic toxicity test with rabbits, the aqueous of *T. indica* pulp extract showed overall safety, enhancing white and red blood cell production, but resulted in mild liver and kidney pathologies (6). Nonetheless, the dosage used was below the suggested therapeutic level from a prior acute toxicity study. A chronic toxicity study indicated the safety of the pulp water extract with no significant changes in body weight, blood parameters, or clinical biochemistry at doses up to 1 g/kg daily for six months (6).

Despite these findings indicating the general safety of T. indica, further in-depth studies are warranted, specifically sub-acute, sub-chronic, and chronic toxicological investigations, to ensure long-term safety and establish a strong basis for future clinical trials.

4.2 Neuroprotective Potential of *Tamarindus Indica*

Tamarindus indica has gained attention for its potential neuroprotective properties, a reputation built on the following activities: antioxidant potential and anti-inflammatory activity.

4.2.1 Antioxidant Potential

Many neuropathological illnesses are exacerbated by oxidative stress, and a decrease in enzyme antioxidants in the brain has been linked to a variety of diseases, including Alzheimer's and Parkinson's (20). From the studies evaluated, it was observed that *Tamarindus indica* increased levels of oxidative stress biomarkers such as Glutathione (GSH), Catalase (CAT), and Superoxide Dismutase (SOD) with a corresponding elevation in Total Antioxidant Capacity (TAC) levels, implying its neuroprotective role in the brain (13,14).

In conjunction with GSH, Glutathione peroxidase (an enzymatic antioxidant) converts hydrogen peroxide (H_2O_2), hydroperoxides (R-OOH) and peroxide lipids to water (H_2O) (21). It is worth noting that the redox state of the thiol residue inside the GSH molecule is involved in important biological functions of GSH (22).

SOD works by catalyzing the dismutation of two molecules of superoxide anion (a free radical) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) with the aid of certain metal ions, therefore reducing superoxide anion's harmful effects (23) while CAT uses iron or manganese as a cofactor to catalyze the dissolution or reduction of H_2O_2 to water and molecular oxygen, completing the task of detoxification begun by SOD (24).

T. indica decreased MDA levels which is a byproduct of cellular lipid peroxidation (LPO) remarkedly seen in membrane phospholipid

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breakdown (25,26). Myelin sheath is constituted of around eighty percent lipids and lipid peroxidation is a result of increased oxidative stress (27). This implies that LPO can disrupt neurotransmission. Raised LPO is the fundamental cause of many neuropathological disorders, including Alzheimer's disease, and LPO lowering is a neuroprotective strategy (28). *Tamarindus indica"s* neuroprotective potential is demonstrated by lowering LPO and oxidative stress in the brain. *Tamarindus indica* has phytochemicals such as polyphenols and flavonoids, both of which are powerful antioxidants. (6). These compounds aid in the neutralization of free radicals and the reduction of oxidative stress, which is a major contributor to brain damage and neurodegenerative diseases, highlighting *Tamarindus indica*'s antioxidant capacity as a protective function in sustaining brain health.

4.2.2 Anti-inflammatory Potential:

Neuroinflammation and neurodegeneration are interrelated (29). Neuroinflammation (NiF) is the underlying cause of various neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD) (29). *Tamarindus indica* exhibits significant anti-inflammatory effects by inhibiting pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and Interferon-gamma (IFN-γ) (30–32) thereby highlighting its neuroprotective potential.

Interleukin 1 beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α) are pro-inflammatory cytokines involved in the body's immune response(33). In the brain, they play significant roles in neuroinflammation (34,35). IL-1β is produced by activated microglia, astrocytes, and neurons in response to infection, injury, or stress. It promotes inflammation by activating immune cells and inducing the production of other cytokines and chemokines (36). Uncontrolled elevated IL-1β levels can affect the blood-brain barrier, leading to its disruption and allowing immune cells and molecules to enter the brain, exacerbating neuroinflammation. IL-1β can modulate synaptic transmission and alter neuronal excitability, potentially affecting cognitive functions (29,37,38).

TNF-α is produced by microglia and astrocytes in response to various stimuli (39). It triggers a cascade of inflammatory responses, promoting the recruitment and activation of immune cells. TNF-α can induce neuronal death directly or indirectly by promoting the release of other neurotoxic molecules and activating cell death pathways. It can modulate synaptic plasticity and neurotransmitter release, potentially affecting neuronal communication (40).

Interferon-gamma (IFN-γ) is a cytokine primarily known for its crucial role in the immune system's response against infections and tumors (36). In the brain, microglia and astrocytes release IFN-γ (41). It helps in activating microglia, the resident immune cells of the central nervous system (CNS), to respond to infections or injuries (42). IFN-γ is involved in the regulation of neuroinflammatory processes (43). It can induce the production of other cytokines and chemokines by microglia and astrocytes, contributing to the inflammatory response in the

CNS (42,43). Prolonged or excessive IFN-γ levels may contribute to neuroinflammation-associated neuronal damage (44). IFN-γ has a dual role in the brain. While it plays a role in immune defense, excessive or chronic levels might have detrimental effects on neurons. It can induce oxidative stress and activate pathways leading to neuronal damage, contributing to neurodegenerative conditions (45). IFN-γ dysregulation is linked to various neurological conditions, including multiple sclerosis, Alzheimer's disease, and Parkinson's disease (44,46,47). It's implicated in the pathogenesis of these disorders due to its involvement in inflammation and immune responses within the CNS.

Chronic neuroinflammation is associated with various neurodegenerative diseases, and *Tamarindus indica* can reduce pivotal anti-inflammatory cytokines propagating neuroinflammation. Balancing the actions of proinflammatory cytokines is an effective way of reducing neurodegenerative changes in the brain thereby offering protection to astrocytes and surrounding cells in an unharmful manner. *Tamarindus indica* suppressed the activities and levels of key proinflammatory cytokines. This makes the anti-inflammatory properties of *Tamarindus indica* a valuable avenue of research for potential neuroprotection (48).

4.2.3 N-methyl-D-aspartate Receptor and Acetylcholinesterase Activity Inhibitory Potentials

Neuroexcitotoxicity is phenomenon which contributes to neuronal degeneration in various neurodegenerative diseases (49). NMDA (N-methyl-D-aspartate) receptors and Acetylcholinesterase (AChE) enzyme have been implicated negatively in these diseases with evidences of neuronal death. *Tamarindus indica* showed significant NMDA and AChE inhibitory potentials (50,51).

N-methyl-D-aspartate (NMDA) receptors are a subtype of glutamate receptors, playing crucial roles in various neurological functions, particularly in synaptic plasticity, learning, and memory processes in the brain (51). They are essential for synaptic plasticity, a process where synapses undergo structural or functional changes in response to experiences or stimuli. They are particularly involved in long-term potentiation (LTP) and long-term depression (LTD), mechanisms underlying learning and memory formation (50). NMDA receptors are part of the glutamatergic system and mediate excitatory neurotransmission. This implies that they respond to the neurotransmitter glutamate and are involved in regulating neuronal excitability and communication between neurons (52,53). Overactivation of NMDA receptors can lead to neuroexcitotoxicity, a process where excessive activation of these receptors results in an influx of calcium ions into neurons, causing cellular damage or death (50,54). Dysregulation or malfunction of NMDA receptors has been implicated in various neurological and psychiatric disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, and epilepsy (49,55). Abnormalities in NMDA receptor function can lead to altered synaptic plasticity, cognitive deficits, and

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neurodegeneration (56).

Acetylcholinesterase (AChE) is an enzyme responsible for breaking down the neurotransmitter acetylcholine (ACh) (57). In AD, the cholinergic hypothesis suggests that the decline in cognitive function is partly due to reduced cholinergic neurotransmission caused by the loss of cholinergic neurons and decreased ACh levels (58). AChE is not only involved in the breakdown of ACh but also plays a role in neurodevelopment, synaptic plasticity, and regulation of neurotransmission (59). Dysregulation of AChE activity can impact these processes and contribute to neurodegenerative conditions (60). Inhibitors of AChE are used as a therapeutic strategy in AD (61). AChE inhibitors aim to increase the availability of ACh in the synaptic cleft, temporarily enhancing cholinergic transmission and potentially alleviating cognitive symptoms in some individuals with AD (62). The NMDA and AChE inhibitory potentials of *Tamarindus indica* reveals important mechanism by which this plant can offer neuroprotection.

5.0 CONCLUSION

In conclusion, *Tamarindus indica* shows promise as a natural neuroprotective agent, offering a multi-faceted approach through its anti-inflammatory, antioxidant, neuroexcitotoxicity reducing, and specific flavonoid-based mechanisms. As research in this field advances, *Tamarindus indica* may find its place in the prevention and treatment of neurodegenerative diseases, providing a valuable and natural resource for improving neural health. Further investigations and clinical trials are necessary to unlock the full potential of this remarkable tropical tree in the field of neuroprotection.

While these findings are promising, several areas warrant further investigation:

1) Mechanistic Understanding: Future research should focus on elucidating the precise mechanisms by which *Tamarindus indica* exerts its neuroprotective effects. Understanding the underlying pathways and interactions will provide a more comprehensive picture of its potential.
2) Safety and Toxicology: While tamarind is generally considered safe, further studies should explore potential adverse effects and optimal dosages to ensure its safe use in therapeutic contexts.

REFERENCE

1. Ningrum DNA, Kung WM. Challenges and Perspectives of Neurological Disorders. Brain Sciences. 2023.
2. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. International Journal of Molecular Sciences. 2022.
3. Vance DE, Dodson JE, Watkins J, Kennedy BH, Keltner NL. Neurological and psychiatric diseases and their unique cognitive profiles: Implications for nursing practice and research. J Neurosci Nurs. 2013;
4. Monin JK, Schulz R. Interpersonal Effects of Suffering in Older Adult Caregiving Relationships. Psychol Aging. 2009;
5. Ransmayr G. Challenges of caregiving to neurological patients. Wiener Medizinische Wochenschrift. 2021.
6. Komakech R, Kim Y goo, Matsabisa GM, Kang Y. Anti-inflammatory and analgesic potential of Tamarindus indica Linn. (Fabaceae): a narrative review. Integr Med Res.

2019;8(3):181–6.
7. Dias DA, Urban S, Roessner U. A Historical overview of natural products in drug discovery. Metabolites. 2012.
8. Ayuba JT, Okesina AA, Usman IM, Ajenikoko MK, Pius T, Kusiima N, et al. Galinsoga parviflora restored associated motor coordination through increased linear distribution of Purkinje Cells in mercury chloride-induced toxicity of mices cerebellum. African J Cell Pathol [Internet]. 2022 Jul 31 [cited 2022 Dec 18];14(1):1–8. Available from: https://academicjournals.org/journal/AJCPath/article-abstract/F0A9D4469388
9. Mbina SA, Mada SB, Eze ED, Ajayi CO, Ifie JE, Usman IM, et al. Effect of Ethanol Leaf Extract of Khat (Catha edulis forsk) on Prefrontal Cortex Oxidative Markers and Hematological Profile of Wistar Rats. J Sci Res Reports [Internet]. 2021 Dec 15 [cited 2023 Jul 29];27(11):149–62. Available from: https://nru.uncst.go.ug/handle/123456789/9036
10. Salihu M, Batiha GES, Kasozi KI, Zouganelis GD, Sharkawi SMZ, Ahmed EI, et al. Crinum jagus (J. Thomps. Dandy): Antioxidant and protective properties as a medicinal plant on toluene-induced oxidative stress damages in liver and kidney of rats. Toxicol Reports. 2022 Jan 1;9:699–712.
11. Yusuf HR, Musa SA, Agbon AN, Eze ED, Okesina AA, Onanuga I, et al. Hepatoprotective potential of Tamarindus indica following prenatal aluminum exposure in Wistar rat pups. Toxicol Reports [Internet]. 2023 Mar 4 [cited 2023 Mar 5]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214750023000318
12. Usman IM, Agbon AN, Ivang AE, Peter AB, Afodun A, Okesina AA, et al. Ethyl Acetate Fraction of Tamarindus indica Leaf Ameliorates Aluminium Chloride Induced Neural Damage in Neonatal Wistar Rats. J Trace Elem Miner [Internet]. 2023 Jan 10 [cited 2023 Jan 12];100047. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2773050623000022
13. Usman I, Adebisi S, Musa S, Iliya I. Glial fibrillary acid protein expression and behavioral changes in hippocampus following prenatal co-administration of ethyl acetate leaf fraction of Tamarindus Indica and aluminum chloride in wistar rats. Niger J Exp Clin Biosci [Internet]. 2022;10(1):1. Available from: http://www.njecbonline.org/text.asp?2022/10/1/1/349560
14. Usman I, Buraimoh A, Ibegbu A. Histological and biochemical studies of Tamarindus indica pulp extract on the cerebral cortex in prenatal ethanol exposure in Wistar rats. J Exp Clin Anat. 2016 Jul;15(2):96–96.
15. Elmaidomy AH, Abdelmohsen UR, Alsenani F, Aly HF, Shams SGE, Younis EA, et al. The anti-Alzheimer potential of Tamarindus indica : an in vivo investigation supported by in vitro and in silico approaches. RSC Adv. 2022 Apr;12(19):11769–85.
16. Liu W, Ma H, DaSilva NA, Rose KN, Johnson SL, Zhang L, et al. Development of a neuroprotective potential algorithm for medicinal plants. Neurochem Int. 2016;100:164–77.
17. Sookying S, Duangjai A, Saokaew S, Phisalprapa P. Botanical aspects, phytochemicals, and toxicity of Tamarindus indica leaf and a systematic review of antioxidant capacities of T. indica leaf extracts. Front Nutr. 2022;9(1).
18. Usman Ibe Michael, Iliya Ibrahim Abdullahi, Ivang AndrewE, Ssempijja Fred, Ojewale Anaphato YH. Microanatomical And Biochemical Changes Of The Cerebellum Following Ethanol Gavage In Adult Wistar Rats. Vol. 8, Anatomical Journal of Africa. 2019.
19. Iskandar I, Setiawan F, Sasongko L, Adnyana I. Six-Month Chronic Toxicity Study of Tamarind Pulp (Tamarindus indica L.) Water Extract. Sci Pharm [Internet]. 2017 Mar 8;85(1):10. Available from: http://www.mdpi.com/2218-0532/85/1/10
20. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative Stress and Antioxidant Defense. World Allergy Organ J. 2012 Jan;5(1):9–19.
21. Morén C, deSouza RM, Giraldo DM, Uff C. Antioxidant Therapeutic Strategies in

Neurodegenerative Diseases. Int J Mol Sci. 2022 Aug;23(16).
22. Aoyama K. Glutathione in the Brain. Int J Mol Sci. 2021 May;22(9).
23. Islam MN, Rauf A, Fahad FI, Emran T Bin, Mitra S, Olatunde A, et al. Superoxide dismutase: an updated review on its health benefits and industrial applications. Crit Rev Food Sci Nutr. 2022;62(26):7282–300.
24. Jing M, Han G, Wan J, Zhang S, Yang J, Zong WS, et al. Catalase and superoxide dismutase response and the underlying molecular mechanism for naphthalene. Sci Total Environ. 2020 Sep;736:139567.
25. Paciorek P, Zuberek M, Grzelak A. Products of Lipid Peroxidation as a Factor in the Toxic Effect of Silver Nanoparticles. Mater 2020, Vol 13, Page 2460. 2020 May;13(11):2460.
26. Usman IM, Adebisi SS, Musa SA, Iliya IA, Ochieng JJ, Ivang AE, et al. Neurobehavioral and Immunohistochemical Studies of the Cerebral Cortex Following Treatment with Ethyl Acetate Leaf Fraction of Tamarindus indica During Prenatal Aluminum Chloride Exposure in Wistar Rats. J Exp Pharmacol [Internet]. 2022 Oct 20 [cited 2022 Oct 28];Volume 14:275–89. Available from: https://www.dovepress.com/neurobehavioral-and-immunohistochemical-studies-of-the-cerebral-cortex-peer-reviewed-fulltext-article-JEP
27. Poitelon Y, Kopec AM, Belin S. Myelin Fat Facts: An Overview of Lipids and Fatty Acid Metabolism. Cells 2020, Vol 9, Page 812. 2020 Mar;9(4):812.
28. Barnes-Vélez JA, Aksoy Yasar FB, Hu J. Myelin lipid metabolism and its role in myelination and myelin maintenance. Innov. 2023 Jan;4(1).
29. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 2020 91. 2020 Nov;9(1):1–12.
30. Sundaram MS, Hemshekhar M, Santhosh MS, Paul M, Sunitha K, Thushara RM, et al. Tamarind seed (Tamarindus indica) extract ameliorates adjuvant-induced arthritis via regulating the mediators of cartilage/bone degeneration, inflammation and oxidative stress. Sci Rep. 2015;5(November 2014):1–13.
31. Li W, Huang R, Han S, Li X, Gong H, Zhang Q, et al. Potential of Tamarind Shell Extract against Oxidative Stress In Vivo and In Vitro. Mol 2023, Vol 28, Page 1885. 2023 Feb;28(4):1885.
32. NARWANTO MI, RAHAYU M, SOEHARTO S, NURDIANA N, WIDODO MA. Neuroprotective Potency of Tamarindus indica Seed Extract for Preventing Memory Impairment in Rat Model of Alzheimer's Disease. 2020 Sep;
33. Guzman-Martinez L, Maccioni RB, Andrade V, Navarrete LP, Pastor MG, Ramos-Escobar N. Neuroinflammation as a common feature of neurodegenerative disorders. Front Pharmacol. 2019 Sep;10(SEP):452270.
34. Doğanyiğit Z, Erbakan K, Akyuz E, Polat AK, Arulsamy A, Shaikh MF. The Role of Neuroinflammatory Mediators in the Pathogenesis of Traumatic Brain Injury: A Narrative Review. ACS Chem Neurosci. 2022 Jul;13(13):1835–48.
35. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep. 2016 Apr;13(4):3391.
36. Abd-El-Basset EM, Rao MS, Alsaqobi A. Interferon-Gamma and Interleukin-1Beta Enhance the Secretion of Brain-Derived Neurotrophic Factor and Promotes the Survival of Cortical Neurons in Brain Injury. Neurosci Insights. 2020 Jul;15.
37. Kamali AN, Zian Z, Bautista JM, Hamedifar H, Hossein-Khannazer N, Hosseinzadeh R, et al. The Potential Role of Pro-Inflammatory and Anti-Inflammatory Cytokines in Epilepsy Pathogenesis. Endocrine, Metab Immune Disord - Drug Targets. 2020 Nov;21(10):1760–74.
38. Liu LR, Liu JC, Bao JS, Bai QQ, Wang GQ. Interaction of Microglia and Astrocytes in the Neurovascular Unit. Front Immunol. 2020 Jul;11:514779.
39. Szpakowski P, Ksiazek-Winiarek D, Turniak-Kusy M, Pacan I, Glabinski A. Human Primary Astrocytes Differently Respond to Pro- and Anti-Inflammatory Stimuli. Biomedicines. 2022 Aug;10(8):1769.
40. Lawrence JM, Schardien K, Wigdahl B,

Nonnemacher MR. Roles of neuropathology-associated reactive astrocytes: a systematic review. Acta Neuropathol Commun 2023 111. 2023 Mar;11(1):1–28.
41. Pang QM, Chen SY, Xu QJ, Zhang M, Liang DF, Fu SP, et al. Effects of astrocytes and microglia on neuroinflammation after spinal cord injury and related immunomodulatory strategies. Int Immunopharmacol. 2022 Jul;108:108754.
42. Kann O, Almouhanna F, Chausse B. Interferon γ: a master cytokine in microglia-mediated neural network dysfunction and neurodegeneration. Trends Neurosci. 2022 Dec;45(12):913–27.
43. Salvador AFM, Kipnis J. Immune response after central nervous system injury. Semin Immunol. 2022 Jan;59:101629.
44. Li T, Lu L, Pember E, Li X, Zhang B, Zhu Z. New Insights into Neuroinflammation Involved in Pathogenic Mechanism of Alzheimer's Disease and Its Potential for Therapeutic Intervention. Cells 2022, Vol 11, Page 1925. 2022 Jun;11(12):1925.
45. Xin Y, Tian M, Deng S, Li J, Yang M, Gao J, et al. The Key Drivers of Brain Injury by Systemic Inflammatory Responses after Sepsis: Microglia and Neuroinflammation. Mol Neurobiol 2022 603. 2022 Nov;60(3):1369–90.
46. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. Signal Transduct Target Ther 2023 81. 2023 Jul;8(1):1–32.
47. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol 2022 2211. 2022 Mar;22(11):657–73.
48. Hemshekhar M, Kemparaju K, Girish KS. Tamarind (Tamarindus indica) Seeds: An Overview on Remedial Qualities. Nuts and Seeds in Health and Disease Prevention. Elsevier Inc.; 2011. 1107–1114 p.
49. Xiong Y, Zhou D, Zheng K, Bi W, Dong Y. Extracellular ATP Binding to P2Y1 Receptors Prevents Glutamate-Induced Excitotoxicity: Involvement of Erk1/2 Signaling Pathway to Suppress Autophagy. 2022 Jan;
50. Kabir MT, Sufian MA, Uddin MS, Begum MM, Akhter S, Islam A, et al. NMDA Receptor Antagonists: Repositioning of Memantine as a Multitargeting Agent for Alzheimer's Therapy. Curr Pharm Des. 2019 Oct;25(33):3506–18.
51. Babaei P. NMDA and AMPA receptors dysregulation in Alzheimer's disease. Eur J Pharmacol. 2021 Oct;908:174310.
52. Seillier C, Lesept F, Toutirais O, Potzeha F, Blanc M, Vivien D. Targeting NMDA Receptors at the Neurovascular Unit: Past and Future Treatments for Central Nervous System Diseases. Int J Mol Sci 2022, Vol 23, Page 10336. 2022 Sep;23(18):10336.
53. Turski GN, Ikonomidou C. Glutamate as a Neurotoxin. Handb Neurotox. 2022;769–801.
54. Rodriguez-Chavez V, Moran J, Molina-Salinas G, Zepeda Ruiz WA, Rodriguez MC, Picazo O, et al. Participation of Glutamatergic Ionotropic Receptors in Excitotoxicity: The Neuroprotective Role of Prolactin. Neuroscience. 2021 May;461:180–93.
55. McGrath T, Baskerville R, Rogero M, Castell L. Emerging Evidence for the Widespread Role of Glutamatergic Dysfunction in Neuropsychiatric Diseases. Nutr 2022, Vol 14, Page 917. 2022 Feb;14(5):917.
56. Shen Z, Xiang M, Chen C, Ding F, Wang Y, Shang C, et al. Glutamate excitotoxicity: Potential therapeutic target for ischemic stroke. Biomed Pharmacother. 2022 Jul;151:113125.
57. Trang A, Khandhar PB. Physiology, Acetylcholinesterase. StatPearls. 2019 Apr;
58. Vecchio I, Sorrentino L, Paoletti A, Marra R, Arbitrio M. The State of The Art on Acetylcholinesterase Inhibitors in the Treatment of Alzheimer's Disease. J Cent Nerv Syst Dis. 2021 Jul;13.
59. Akıncıoğlu H, Gülçin İ. Potent Acetylcholinesterase Inhibitors: Potential Drugs for Alzheimer’s Disease. Akıncıoğlu, H, Gülçin, İ (2020) Potent Acetylcholinesterase Inhib Potential Drugs Alzheimer’s Dis Mini-Reviews Med Chem 20(8), 703–715 https//doi.org/10217413895575206662001031 00521Mini-Reviews Med Che. 2020 Jan;20(8):703–15.
60. Walczak-Nowicka ŁJ, Herbet M. Acetylcholinesterase Inhibitors in the Treatment of Neurodegenerative Diseases and

the Role of Acetylcholinesterase in their Pathogenesis. Int J Mol Sci 2021, Vol 22, Page 9290. 2021 Aug;22(17):9290.
61. Mitić M, Lazarević-Pašti T. Does the application of acetylcholinesterase inhibitors in the treatment of Alzheimer's disease lead to depression? Expert Opin Drug Metab Toxicol. 2021 Jul;17(7):841–56.
62. Moreira NCDS, Lima JEB de F, Marchiori MF, Carvalho I, Sakamoto-Hojo ET. Neuroprotective Effects of Cholinesterase Inhibitors: Current Scenario in Therapies for Alzheimer's Disease and Future Perspectives. J Alzheimer's Dis Reports. 2022 Jan;6(1):177–93.

Figure 1: Study Selection Flowchart

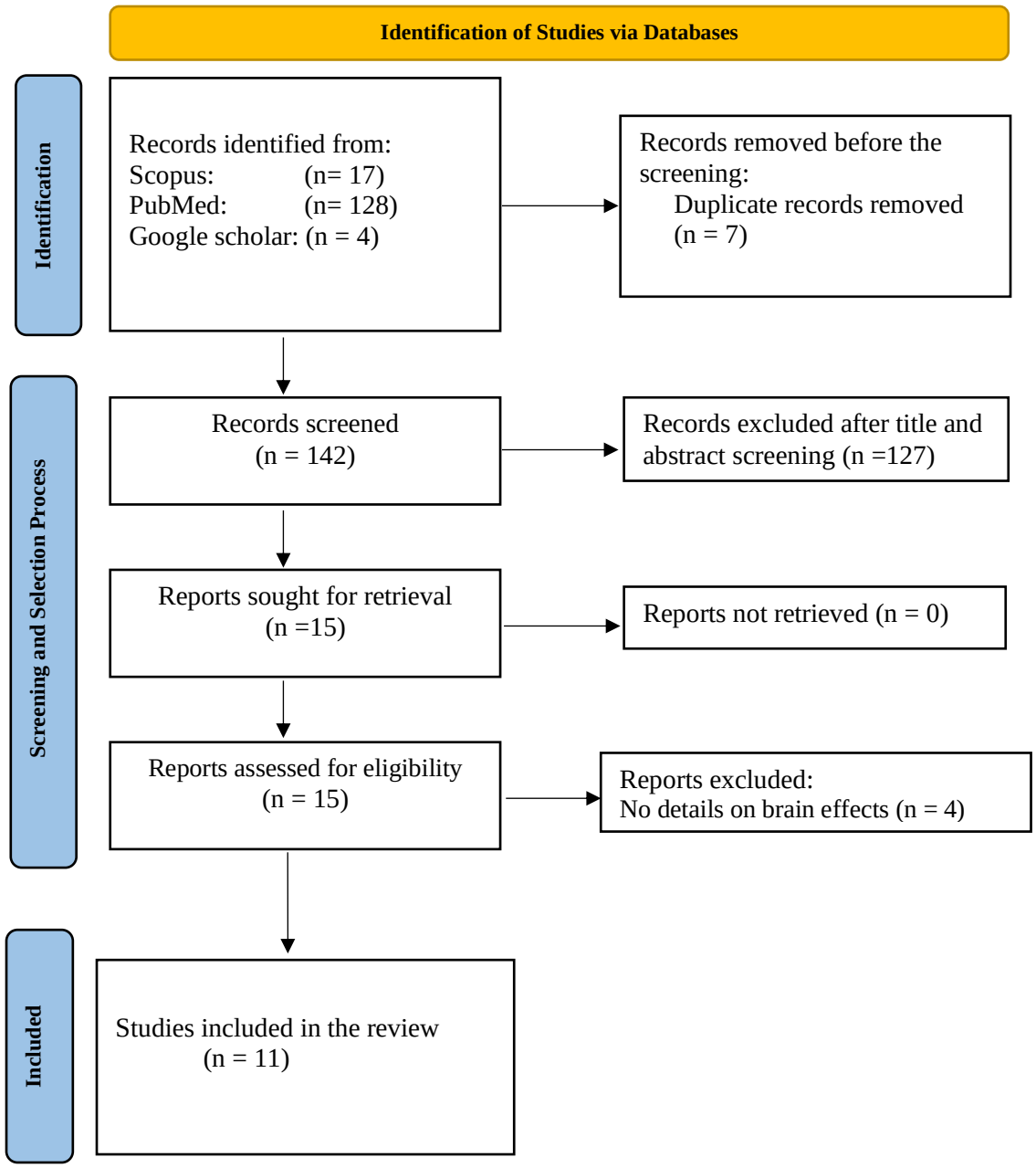

Table 1: The Various Neuroprotective Mechanisms of Extracts from Different Parts of *Tamarindus indica*

Part of Plant Used	Extract	Intervention/Duration & Dosage	Study population/ Model	Parts of Brain	Possible Mechanism	References
Seed	Methanolic	10 weeks 25-50 mg/kg/day	Wistar rat	Cerebral Cortex	Improved memory in neurobehavioral studies. Restores level of Ilβ and TNFα to normal levels. Reduced NMDA levels	[32]
Pulp	Ethanol	6 weeks 500 mg/kg/bwt	Wistar rats	Cerebral cortex and hippocampus	Improved cognitive abilities and motor coordination in neurobehavioral studies. Increased GSH, CAT, SOD and TAC levels. Reduced MDA levels. Increased Ach levels and reduced AChE, Tau and β-amyloid proteins with improved histomorphology in brain regions. Protected astrocytes and reduced GFAP reactivity.	[15]
Leaf	Ethyl acetate	14 days (7-21 PoND) 400-800 mg/kg/bw	Wistar rats	Cerebral cortex	Improved sensory-motor development, anxiety-like and motor activities in neurobehavioral tests. Increase Nissl intensity and GFAP expression.	[26]
Leaf	Ethyl acetate	14 days (7-21 PoND) 400-800 mg/kg/bw	Wistar rats	Cerebral cortex and Hippocampus	Moderate brain trace elements Cu, Zn, Fe and Calcium levels. Improved memory and increased brain sialic acid. Improved Nissl staining	[12]
Leaf	Ethyl acetate	14 days (7-21 PoND) 400-800 mg/kg/bw	Wistar rats	Hippocampus	Increased SOD and reduced MDA levels in brain. Reduced GFAP immunoreactivity scores. Improved spatial memory and learning in neurobehavioral tests.	[13]
Not specified	Phytochemical extracts from sweet tamarind	Not specified	Human neuroblastoma SH-SY5Y cells	Not applicable (in vitro cell study)	Increased cell survival	[63]
Bark and seeds	Crude methanolic extracts (CMEs)	Not specified	Not applicable (in vitro study)	Not applicable	Higher AChE inhibitory activity suggesting potential therapeutic uses of these extracts in the treatment of Alzheimer's disease and clotting disorders	[64]
Pulp	Not specified	200mg/kg bw	Prenatal ethanol-exposed Wistar rats	Cerebral cortex	Potential protective effects on the cerebral cortex during prenatal ethanol exposure. Increased CAT and Glutathione, Reduced MDA.	[14]
Seed coat	Not specified	In vitro: 0.2–200 µg/mL; In vivo: 100–500 mg/kg (B6C3F1 mice);	Murine macrophage-like cell line RAW 264.7; B6C3F1 and BALB/c mice	Not applicable	In-vitro: attenuated NO production induced by lipopolysaccharide (LPS) and interferon gamma (IFN-γ). In-vivo: suppressed TPA, LPS, and/or IFN-γ induced NO production in isolated mouse peritoneal macrophages	[31]

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pulp	Aqueous extract	21 days 200 - 800 mg/kg	Adult Wistar rats	Cerebral cortex	Preserved normal histology of the cerebral cortex	[65]
Leaf	Ethanol and hexane extracts	Not specified	In vitro study	Not applicable	Ethanolic extracts exhibited significantly higher Acetylcholinesterase inhibitory activities compared to other plants Useful against AD based on cholinergic and beta-amyloid formation hypotheses	[66]

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