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Review Article

Antioxidant and Neuroprotective Activities of *Phyllanthus emblica* L.: A Review

Novi Ayuwardani[1], Zaenal M. Sofro[2], Nanang Fakhrudin[3,4], Zullies Ikawati[5]*

[1]*Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia*
[2]*Departement of Physiology, Faculty of Medicine, Nursing, and Public Health, Univeristas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia*
[3]*Medicinal Plants and Natural Products Research Center, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia*
[4]*Departement of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia*
[5]*Departement of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia*

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ABSTRACT

Phyllanthus emblica L., known as Indian gooseberry (Euphorbiaceae), has been used in traditional Indian medicine for its benefits in treating various diseases. Antioxidant and neuroprotective activities of *Phyllanthus emblica* L. provide great benefits in medicine. Antioxidants can help lower the risks of many diseases, including neurological conditions, by preventing reactive oxygen species (ROS) and lipid peroxidation. Research on herbal plants as alternative treatments is increasing; hence, the current research trend aims to examine new treatments for these conditions. Scientific research has extensively explored herbal medicine for neurological disorders. Both *in vitro* and *in vivo* studies have demonstrated the therapeutic potential of the antioxidant activity of *P. emblica* in addressing various neurological disorders. This article provides an overview of the roles of antioxidant and neuroprotective activities of *P. emblica* in treating various neurological and neurodegenerative disorders. It also paves the way for future research in this field by involving chemical compounds as references for understanding the mechanisms of neuroprotective action of *P. emblica*.

Keywords: *Emblica officinalis*, Reactive oxygen species (ROS), Neurodegenerative, Neurological disorders.

Introduction

Numerous plant species with therapeutic benefits have been used in traditional medicine for curing various diseases.[1,2] Researchers are increasingly interested in studying plant-derived medicines for their potential as a source of new drugs to enhance human health with fewer or no side effects compared to current available synthetic chemical compounds, as evidenced in pre-clinical and clinical trials.[3] *Phyllanthus emblica* L., known as Indian gooseberry (Euphorbiaceae family), is widely distributed across tropical and subtropical regions in Asia.[4,5] All parts of the *P. emblica* can be employed for medicinal purposes, especially its fruit, which has been used in Ayurveda as a rejuvenating agent called Rasayana, and applied in other traditional treatments, such as Chinese herbal and Tibetan medicines.[6] The *P. emblica* has a rich history in traditional medicine use for treating health problem, such as jaundice, diarrhea, and inflammation, and exhibits antibacterial, antioxidant, antidiabetic, hypolipidemic, antiulc erogenic, gastroprotective, hepatoprotective, anti-anemia, osteoporosis, chemopreventive, and neuroprotective properties.[5–11] The whole plant (fruit, leaves, roots) is rich in phytochemicals.

*Corresponding author. E mail: zullies_ikawati@ugm.ac.id
Tel: +62 815-6854-012

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Another research revealed that polyphenols, a major class of secondary metabolites, have been found in multiple components, including phenolic acids, flavonoids, tannins, phenolic compounds, and other derivatives. The ellagic and gallic acids in *P. emblica* fruit extract are associated with neuroprotective effects in several neuroinflammatory conditions. Numerous studies have explored the role of antioxidant activities of *P. emblica* fruit extract in treating neuroinflammation and neurodegeneration.[12,13]

Natural antioxidants particularly can mitigate oxidative damage and proinflammation within cells caused by oxidative stress. Oxidative stress has been associated with more than 200 diseases and contributes to the aging process.[8] Oxidative stress damages vascular endothelial cells, resulting in hippocampal injury in the brain, as the hippocampus is more vulnerable to oxidative damage than other brain regions.[14] Plant secondary metabolites with antioxidant properties, such as phenolic acids, flavonoids, and carotenoids, demonstrate various biological effects that can be used for therapeutic purposes.[15] *P. emblica* fruit, as a good source of natural antioxidants containing phenolic compounds and vitamin C, has been used in herbal beverage formulations to boost the immune system. In addition, phytochemical contents in *P. emblica* extract exhibit antioxidant activity associated with neuroprotective effects against neuroinflammatory conditions, showing pharmacological activity and playing an important role in protecting neurons.[16,17]

Furthermore, several studies show that *P. emblica* demonstrates therapeutic effects in the treatment of neurodegenerative diseases, such as dementia, Parkinson's disease, Alzheimer's disease, and Huntington's disease, as well as neurological disorders like epilepsy, depression, tardive dyskinesia, and stress. The pathophysiology of these conditions is associated with oxidative stress and inflammation, which has been scientifically assessed both *in vitro* and *in vivo*. This review aims to discuss a potential neuroprotective agent of *P. emblica* for enhancing neurobehavioral parameters. The goal of this study is to encourage future research on the development of *P. emblica* as a therapeutic supplement for neurodegenerative conditions and neurological disorders

Materials and Methods

A literature search was conducted using PubMed, ScienceDirect, Scopus, and Google Scholar with the keywords *"Emblica officinalis" OR "Phyllanthus emblica"* AND "Antioxidant" AND "Neuroprotective" OR "Neuro," with a time restriction from 2010 to 2023. This study was undertaken to acquire up-to-date and comprehensive data from an original article on *P. emblica* extract as an antioxidant and neuroprotective agent. This study excluded articles discussing non-neurological disorders and ultimately obtained 33 publications that met the specified criteria.

Isolation and Purification of Compounds

P. emblica is a deciduous tree or shrub belonging to the Euphorbiaceae family, reaching 8 meters in height. It features a slightly curved trunk and straight lateral branches measuring 10–20 cm. The leaves are pinnate, very small, and closely attached along the lateral branches up to the base. It has yellowish flowers. The fruit is round, smooth, and hard characterized by six vertical lines with a sour, bitter, and astringent taste, making it suitable for a high-fiber diet.[9,18] *P. emblica* is extensively grown in tropical and subtropical regions, originating from China, India, Pakistan, Sri Lanka, and other Asian countries. *P. emblica*, especially its fruit, containing high levels of ascorbic acid and other nutrients, has long been used for food and medicine.[9] The general description of the *P. emblica* plant can be seen in Figure 1.

Common names of the *P. emblica* plant include ganlanshu, youganzi (China); emblic myrobalan, Indian gooseberry (English); kemloko (Japanese, Indonesian); chu me, kam lam (Vietnamese); amla (Malay, Indonesian); and *balaka*, *malakah*, and *kalimoko* (Indonesian).[19,20] *Emblica officinalis*, *Phyllanthus glomeratus*, *Phyllanthus mairei*, *Phyllanthus mimosifolius*, *Phyllanthus pomiferus*, *Phyllanthus taxifolius*, and *Cicca emblica* are synonyms for *Phyllanthus emblica*. Taxonomic hierarchy of *P. emblica* as shown in Table 1.

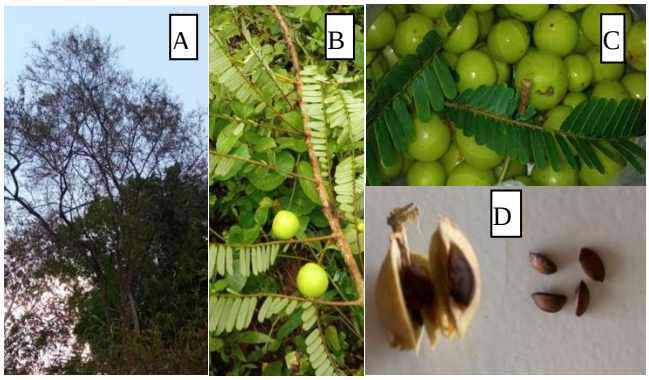

Figure 1: *Phyllanthus emblica* L. tree in forest land in the Giringan Hydropower Plant Area, Madiun Regency (A); Branches displaying the leaf and fruit arrangement (B); Fruits (C); Seed

Table 1: Taxonomic Hierarchy of *P. emblica*

Taxonomic Level	Classification
Kingdom	Plantae
Division	Flowering plants
Class	Magnoliopsida
Order	Malpighiales
Family	Euphorbiaceae/phyllanthaceae
Tribe	Phyllantheae
Subtribe	Flueggeinae
Genus	Phyllanthus
Species	*P. emblica*

Phytochemical Constituents

There are various compounds contained in *P. emblica* shown in figure 2, including chebulagic acid, gallic acid, chebulinic acid, corilagin, ellagic acid, rutin, kaempferol, wogonin, epicatechin, catechin, resveratrol, procyanidin B2, myricetin, hamamelitannin, ethyl gallate, methyl gallate, quercetin-3-*O*-rhamnoside, ascorbic acid, chlorogenic acid, and phyllantin.[21] The leaves contain secondary metabolites, including gallic acid, chebulinic acid, rutin, catechin, caffeic acid, apigenin, myricetin, quercetin, kaempferol, phyllantidine, hentriacontane, dotriacontane, tetracontane, tritetracontane, pentacosane, octadecanoic acid, methyl ester, tocopherol, sulfurous acid, heptadecyl ester, tetracontane-1,40-diol, sulfurous acid, butyl octadecyl ester, hexacosanol, acetate, gamma-sitosterol, 12-Oleanen-3-yl acetate (3 Alpha), and tetrapententacontane.[22–26] The seeds contain fixed oil, phosphatides, and essential oil,[26] whereas the roots contain phyllaemblic acid, ellagic acid, and lupeol.[26] The fruit is highly preferred for use in research investigating pharmacological activities, as it has been extensively used in traditional medicine. The compounds found in *P. emblica* fruit include phenolic acids, hydroxybenzoic acids (4-hydroxybenzoic acid, coumaric acid, gallic acid, quinic acid, ascorbic acid, protocatechuic acid, syringic acid, vanillic acid, nicotinic acid, L-pyroglutamic acid, 2-hydroxycinnamic acid, caffeic acid, 6-gingerol, corilagin, ethyl gallate, methyl gallate, chebulinic acid, neochebulic acid, ellagic acid, catechin, epicatechin, kaempferol, luteolin, pinocembrin, quercetin, glisitein, emblicanin A, emblicanin B, quercetin, myricitrin, and myricetin.[27–33] Previous studies revealed that *P. emblica* fruit contains phenolic compounds and hydrolysable tannins. There are 12 ecotypes of *P. emblica* fruit from various regions, and the total phenolic content in the water extract ranges from 72.91±2.1 to 115.2±1.9 mg gallic acid/g extract. High total phenolic content is associated with elevated antioxidant activity. The ascorbic acid content in the water extract of *P. emblica* fruit ranges from 217.7±3.1 to 400±2.4 mg/100 g fruit across the 12 ecotypes.[8] A study of the methanol extract of *P. emblica* fruit reported that the total phenolic content is 663.53 mg GAE/g, the total flavonoids content is 418.89 mg QE/g, and the total tannins content is 337.50 mg GAE/g.[21]

Antioxidant Activity

Reactive oxygen species (ROS) are spontaneously generated as byproducts of cellular metabolism. ROS is a term used to describe a molecule containing at least one oxygen atom and one or more unpaired electrons with biological functions related to signalling cell damage due to oxidants.[34,35] Mitochondria are the primary cellular organelles responsible for ROS production as a byproducts of respiration. ROS are essential for maintaining intercellular signaling and immune responses at low concentrations. Under pathological conditions, mitochondria over produce ROS.[8,36] The increased accumulation of ROS leads to oxidative stress within the cellular system, resulting in detrimental conditions. Furthermore, oxidative stress, which can be triggered by environmental stressors, such as ultraviolet radiation, heavy metals, pollutants, and xenobiotics, causes cell and tissue damage and exacerbates health complications, such as diabetes mellitus, cancer, inflammation, respiratory disorders, renal disorders, and neurodegenerative diseases.[21,37,38] Elevated levels of ROS within cells subsequently induce lipid peroxidation mediated by lipoxygenase (LOX), utilizing arachidonic acid or linoleic acid as substrates and generating hydroxides.[39]

Antioxidants are agents that neutralize free radicals and prevent chemical compounds from being oxidized. Herbal plants are abundant in antioxidants and widely used in food and drink preparation.[40] Antioxidant activity involves the process of binding products to free radicals. It can be studied using various *in vitro* methods, such as DPPH (2,2-diphenlyl-1-picrylhydrazyl) radical scavenging, FRAP (ferric reducing antioxidant power), ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), thiobarbituric acid reactive species (TBARS), or measured as malondialdehyde (MDA) concentration *in vivo*, which serves as a marker for lipid peroxidation and products contributing to oxidative damage to DNA. The metal-catalyzed formation of ROS results in damage not only to DNA and proteins but also to other cellular components involving unsaturated fatty acid residues of phospholipids, which are sensitive to oxidation.[16,41,42] Antioxidants have been proven to be effective in rodent

models with epilepsy, stroke, and Alzheimer's disease. Some studies have also investigated the role of free radicals in epilepsy, as indicated by decreased brain malondialdehyde (MDA) levels and reduced seizures in animal models, as well as increased free radical levels during seizures. Administration of antioxidants to animal models with cognitive impairment showed decreased levels of oxidative stress. Thus, it is hoped that antioxidant compounds can be an alternative curative treatment for epilepsy or cognitive impairment (neurodegenerative) due to the involvement of oxidative stress mechanisms.[43–45]

In a study by Sharif et al (2023), methanol extract of *P. emblica* at 400 mcg/ml gave an IC_{50} of 311.31 mcg/ml in the DPPH radical, compared to the standard ascorbic acid with an IC_{50} of 130.53 µg/Ml.[21] The IC_{50} values for antioxidant assessment with DPPH in methanol extracts of fruit flesh, fruit, and seeds showed significant differences compared to the ascorbic, acid standard, with values of 6 µg/mL, 11.2 µg/mL, 13 µg/mL, and 5.3 µg/mL, respectively.[33] LOX was used to evaluate *in vitro* anti-inflammatory activity, and *P. emblica* fruit extract, particularly the methanol extract, demonstrated inhibition of 15-LOX (an inflammatory mediator) and protease enzymes. This indicates the presence of bioactive compounds in the extract with anti-inflammatory properties against inflammation mediated by 15-LOX.[21] *P. emblica* fruit contains metabolite compounds serving as antioxidants to counteract free radicals, as evidenced through different methods of testing. The inhibition of ROS and lipid peroxidation is associated with its application in treating several diseases, including brain disorders. Information on the antioxidant activity of *P. emblica* extract is shown in Table 2.

Neuroprotective Activity

The brain controls all organ systems and functions in the human body. Any disturbance pathological disorder or condition characterized by dysfunction, progressive loss of nerve structure and function in the brain will cause disease, affecting a person's daily activities. Two critical variables contributing to the disease's growth are genetic abnormalities and poor environmental circumstances. Unhealthy lifestyle choices exacerbate the condition. Millions of people worldwide are affected by neurological conditions, such as epilepsy, anxiety, stress, and depression, as well as neurodegenerative conditions like dementia, Parkinson's disease, Huntington's disease, and Alzheimer's disease.[46–48] Increasing age contributes to a higher risk of neurological disorders, so it is essential to maintain brain health with the ability to learn and judge, use language, and have a good memory in daily activities.[49] Common characteristics and pathways of neurodegenerative illnesses include aberrant protein misfolding and aggregation, inflammation, oxidative stress, defective Ca^{2+} homeostasis, mitochondrial dysfunction, excitotoxicity, and apoptosis. People who can still perform most routine tasks may experience mild cognitive impairment of memory loss or other cognitive impairment in the early stages.[47,49–52]

Neuroprotective agents shield the central nervous system (CNS) from neurodegenerative diseases by preventing cell death and restoring damaged neuron function. These diseases can be acute (e.g., head injury, stroke, traumatic brain injury, brain hemorrhage, and ischemic brain damage) or chronic (e.g., dementia, Parkinson's, Alzheimer's, epilepsy, etc.).[53,54] Neuroprotective agents are also applied in the treatment of neuropsychiatric disorders (depression, anxiety) due to damage to the nerve cells and decreased neurogenesis. Therefore, neuroprotective agents can increase neurogenesis in the hippocampus, making it essential in treatment options to improve mood, emotions, and cognitive function and achieve therapeutic targets in someone with neurological disorders.[47,55] Neurological disease models that mimic many experimental studies using animals to test and evaluate the presence of neuroprotective effects can show neurological diseases in humans. The goal of disease modeling in experimental animals is to use molecular tracing, either with cells *in vitro* or organs or tissues *in vivo*, to explain the behavior activities, targets, and effects of pharmacological action. Behavior is essential in determining the quality of life of someone with neurological disorders. In neuroscience, rodents are the most used mammalian models in behavioral studies. Rodent models of neurological disorders are critical for preclinical testing of treatments and more profound knowledge of the common underlying causes of brain disorders, such as neurodevelopmental, neuropsychiatric, and neurodegenerative diseases.[56,57]

Mechanisms involved in the pharmacological action of Phyllanthus emblica L.

Stress is a biological factors proven to influence synaptic plasticity and memory function in the brain.[58] The pharmacological effects and methods of utilization of *P. emblica* as a neuroprotective agent are shown in Table 3.

Neuroprotective Action

The neuroprotective action of *P. emblica* has been tested *in vitro* on pheochromocytoma (PC12) cells, which was shown by increased percentages of protection from PC12 cell damage.[6] Neurological disorders are associated with neuroinflammation, a patho logical condition in neurodegenerative conditions. Disturbances in the blood-brain barrier (BBB) also contribute to neuroinflammation.[59] The anti-inflammatory activity of ellagic acid and gallic acid, which are the main compound component in *P. emblica* fruit involves the inhibition of nitric oxide production (NO), prostaglandin E-2 (PGE-2), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), while increasing the levels of inducible nitric oxide synthase (iNOS) and mitogen-activated protein kinases (MAPK).[14,60,61] Prophylaxis and treatment with *P. emblica* extract provide a significant improvement in functional outcomes with a reduction in infarct size in the brain. The expression of brain-derived neurotrophic factor (BDNF), phosphatidylin-ositol-3-kinase (PI3K), stromal cell-derived factor-1 (SDF1), and vascular endothelial growth (VEGF) increases, while Rho-associated kinase 2 (ROCK2) decreases after administering *P. emblica* extract at a dose of 100 mg/kg, thus regulating the BDNF/PI3K pathway to modulate glutathione in ischemic stroke for mitoprotection and neuroprotection.[62]

Cognitive Disorders

Cognitive decline is a crucial factor influencing lifestyle in older age. Cognitive disorders, including dementia, amnesia, and delirium, represent an individual's inability to recognize spatial and temporal orientation. Cognitive disorders are associated with neurodegenerative diseases caused by neuroinflammation, characterized by temporary (delirium) and progressive condition (dementia/Alzheimer's).[63,64] Human metabolic diseases are closely related to an increased risk of cardiovascular disorders and cognitive decline. Chronic metabolic disturbances lead to atherosclerosis and hyalinosis in small blood vessels in the brain, resulting in cognitive dysfunction.[65] NF-κB (nuclear factor kappa B) is a cytokine transcription factor playing a crucial role in neurodegenerative diseases caused by neural inflammation. The presence of pro-inflammatory substances increases the expression of NF-κB protein. Therefore, treatments for cognitive disorders aims to reduce pro-inflammatory agents, leading to the inhibition of NF-κB protein expression.[66,67] Additionally, neural inflammation causes an increase in TNF-α (Th1) cytokines and a decrease in IL-10 (Th2).[66,68,69] Cognitive disorders resulting from acute sleep disturbances are also associated with increased ROS, pro-inflammatory factors, and brain damage.[70] Previous studies have observed the effects of *P. emblica* fruit on cognitive impairment and anxiety caused by acute paradoxical sleep deprivation (SD), showing a reduction in total time and distance to reach the platform at a dose of 80 mg/kg in the morris water maze (MWM) test, enhanced nuclear factor erythroid 2-related factor 2 (Nrf2), hemeoxygenase-1 (HO-1), and superoxide dismutase (SOD1) cell counts, and reduced relative expression of IL-6, TNF-α, and IL-1β in the hippocampus.[29] The Nrf2 plays a role in enhancing cell survival and protecting against oxidative stress or inflammatory responses. Increased ROS stimulates Nrf2 signaling.[71,72] Lipopolysaccharide induces neuroinflammation, as evidenced by increased production of IL-6 and TNF-α as inflammatory cytokines and nitric oxide (NO).[73]

Table 2: Antioxidant Activity of *P. emblica* Extract

Part of Plant	Type of Extract	Measurement Method	Result	Reference
Fruits	Methanol extract	DPPH	The fruit flesh extract in the DPPH test has an IC_{50} value of 311.31 µg/mL, while the standard ascorbic acid has an IC_{50} value of 130.53 µg/mL.	21
	Ethanol extract	DPPH	The IC_{50} value of the extract is 7.626 ± 0.41 µg/dL.	32
	Methanol extract. Hexane fraction, dichloromethane.	DPPH	The best IC_{50} value in the DPPH test is in the ethyl acetate fraction (11.98±0.36 µg/mL), followed by the water fraction at 22.34±2.71 µg/mL. The IC_{50} for the quercetin control group is 2.86±0.51 µg/mL.	87
	Methanol extract, methanol, and distilled water	FRAP, H_2O_2, and DPPH	The water extract has the highest concentration in the FRAP test (1.1533±0.00416), with the ascorbic acid standard (1.4647±0.00306 µl). In the H_2O_2 test, the water extract shows the highest hydrogen peroxide (H_2O_2) capture activity (80.8667 µg). The DPPH free radical scavenging capacity test indicates that water extract has a higher potential (83.0200± 0.24021) than the standard ascorbic acid (83.9100±0.35000).	88
	Water extract, 50% and 95% ethanol	DPPH, lowering power activity and inhibiting lipid peroxidation activity	The 95% ethanol extract shows potential in the DPPH radical scavenging activity, has the highest reduction potential, and has higher inhibitory activity in lipid peroxidation inhibition activity.	6
	Methanol extract (1:3), chloroform fraction, ethyl acetate fraction, and butanol fraction	DPPH, ABTS, FRAP, NO-scavenging, and CAA	The ethyl acetate fraction has the highest potential for free radical scavenging in the DPPH test (IC_{50} 12.14 ± 0.11 µg/mL) and ABTS test (IC_{50} 16.93 ± 0.08 µg/mL). The FRAP assay still indicates that the ethyl acetate fraction has the highest antioxidant potential by reducing Fe (275.61 ± 0.06 mg FeSO4/g), exhibited the highest potential for nitric oxide (NO) scavenging (IC_{50} 57.65 ± 0.04 µg/mL), and inhibits intracellular ROS formation (IC_{50} 14.04 ± 1.08 µg/mL) with the highest antioxidant capacity.	89
	95% methanol extract	DPPH, OH radical scavenging and lipid peroxidation activity	Free radical inhibition in the DPPH test is 73.21 µg/ml. The highest hydroxyl radical scavenging activity is 85.16% with an IC_{50} value of 0.426 mg/mL. Lipid peroxidation activity shows that the extract has activity equivalent to ascorbic acid.	90
	Water/ethyl acetate extract	MDA and RBC-GSH	In *P. emblica* extract (150 and 200 lg/mL), RBC-MDA levels are significantly reduced, while RBC-GSH levels are significantly enhanced.	91
	Water extract	DPPH	The DPPH radical scavenging activity of the extract is 21.18 ± 0.30 µmol TE/g.	92
	Ether extract, ethyl acetate extract, butanol extract, aqueous extract	DPPH and ABTS	The ethyl acetate extract has the highest antioxidant potential with an SC50 value of 1.33 ± 0.77 µg/mL for the DPPH assay and 4.13 ± 0.99 µg/mL for the ABTS assay.	4
	Water extract	TBARS, DPPH, and total antioxidant	The water extract exhibits inhibition against TBARS, as indicated by a decrease in TBARS concentration (nmol/gram tissue). The antioxidant activity measured by DPPH shows an increase in % free radical scavenging. Total antioxidants assessed using the phosphomolybdenum test are expressed in terms of ascorbic acid equivalents.	8
	Methanol extract	DPPH, radical inhibition activity, and total antioxidant	The antioxidant activity with DPPH results in an IC_{50} of 11.2 µg/mL for extract and 5.3 µg/mL for Vit C. The radical inhibition activity by nitrite yields an IC_{50} of 65 µg/mL for extract and 25 µg/mL for Vit C. The total antioxidant content is 172,378 (µg Vit. C equivalent per mg dry weight).	33
	Methanol extract	DPPH, superoxide radical and hydrogen peroxide scavenging assays	The extract exhibits values for DPPH free radical reduction power (IC_{50} 15.5 µg/mL), superoxide radical (IC_{50} 26 µg/mL), and hydrogen peroxide scavenging assays (IC_{50} 22 µg/mL).	93
	Water extract	MDA and TAC	A reduction in MDA levels and an increase in TCA are good in the extract at a dose of 500 mg/kg/day compared to the control group.	94
Fruits	Hydroalcoholic extract	TBARS and GSH	A dose of 700 mg/kg can reduce TBARS levels in the brain (196.56 ± 3.83 nmol/g wet tissue) compared to the epilepsy model (361.29 ± 10.79 nmol/g wet tissue). There is an increase in GSH levels compared to other doses (87.70 ± 1.42µg/g wet tissue) compared to the epilepsy model group (50.0 ± 2.54 µg/g wet tissue).	85

Part of Plant	Type of Extract	Measurement Method	Result	Reference
	Hydroalcoholic extract	MDA and GSH	The 700 mg/kg dose is best at reducing brain MDA levels (190.00 ± 13.40 nmol/g tissue) compared to the epilepsy model (282.67 ± 7.93 nmol/g tissue). Likewise, brain GSH levels decrease (89.79 ± 3.75 µg/g tissue) compared with the epilepsy model group (54.58 ± 3.71 µg/g tissue).	84
Fruit flesh	Methanol extract	DPPH, NO-scavenging and total antioxidant	The IC_{50} value for the extract is 6 µg/mL and 5.3 µg/mL for Vit C in the DPPH test. Nitrite radical inhibitory activity produces an IC_{50} of 41 µg/mL and 25 µg/mL for Vit C. The total antioxidant is 178.919 (equivalent to µg Vit. C per mg dry weight).	33
	Water extract	DPPH	DPPH radical scavenging activity of the extract is 19.56 ± 0.24 µmol TE/g.	92
Seeds	Methanol extract	DPPH, NO-scavenging and total antioxidant	The IC_{50} value for the extract is 13 µg/mL and 5.3 µg/mL for Vit C. Nitrite radical inhibitory activity produces 70 µg/mL and 25 µg/mL for Vit C. The total antioxidant is 171,351 (µg Vit. C equivalent per mg dry weight).	33
Leaves	Methanol extract	DPPH, NO-scavenging and lipid peroxidation assay	The extract shows an IC_{50} value in the DPPH test of 39.73 ± 2.12 µg/mL. Inhibition of nitric oxide results in an IC_{50} of 39.14 ± 2.31 µg/mL. Inhibition of lipid peroxidation resulted in an IC_{50} value of 84.10 ± 3.04 µg/mL.	24

DPPH = 2,2-diphenlyl-1-picrylhydrazyl); FRAP = ferric ion reducing antioxidant power; H_2O_2 = hydrogen peroxide; ABTS = 2–2′-azinobis (3-ethyl-benzothiazoline-6-sulfonic acid) di-ammonium salt; NO = nitric oxide; CAA = cellular antioxidant activity; MDA = malondialdehyde; RBC-MDA = red blood cell-malondialdehyde; RBC-GSH = red blood cell- glutathione; TBARS = thiobarbituric acid reactive species; GSH = glutathione; TAC = total antioxidant capacity;

Table 3: Neuroprotective Activity of *P. emblica* Fruit Extract

Pharmacological Activity	Method	Induction	Comparison Group	Treatment Group/ Route Administration	Duration of Intervention	Behavioral Observation	Molecular Action Mechanism	Author /Year
Neuroprotective	*In vitro*/rat adrenal pheochromocytoma cell line (PC12 Cell)	H_2O_2	-	Water extract, 50% and 95% ethanol (10, 50, 100 µg/mL) on rat cell line PC12	24 hours	-	Ethanol (50%) extract exhibits the highest protective activity on PC12 cells. Higher extract doses provide greater protection.	6
	In vitro/PC12 cell	Glutamate	-	95% methanol extract (250, 500, and 1000 µg/mL) on the human neural cell lines (PC12)	24 hours	-	MTT assay indicates cell inhibition at extract concentrations of 500 and 1000 µg/, at 74.15% and 65.03%, respectively. Increasing extract concentrations inhibits lactate dehydrogenase release, decreases ROS, and elevates glutathione levels.	90
Cognitive function	*In vivo*/ mice	Acute sleep disturbance with a multiple-platform approach for 72 hours	Normal control, negative control, positive control (modafinil of 80 mg/kg)	Powdered fruit solution (40 and 80 mg/kg). Administered orally once daily	1 day	Enhanced behavior in the MWM test compared to the control group.	Enhanced Nrf2, HO-1, and SOD1 cell counts and reduced relative expression of IL-6, TNF-α, and IL1β in the hippocampus.	29
	In vitro/ microglial	LPS	Negative control, gallic acid, ellagic acid	70% ethanol extract of *P. emblica* fruit on BV2 cells, a	2 days	-	Decreased nitric oxide, IL-6, and TNF-α production in BV2	73

	(BV2) and neuroblastoma (Neuro2a) cells			mouse microglial cell line and neuro2a cells, a mouse neuroblastoma cell line			cells. Increased neurite length in Neuro2a, is associated with elevated TuJ1 and MAP2 expression.	
	In vivo/ mice	A high-fat diet (59.28% energy from fat) for 12 weeks	Control group, induction group	Fresh juice. Administered orally once daily	6 weeks	Observing behavior with the novel object recognition test, including increased recognition index and discrimination index in the treated sick group compared to the untreated sick group.	Measurement of hippocampal IL-6 shows a significant decrease in the treated sick group compared to the untreated sick group.	[95]
	In vivo/rats	High-salt and cholesterol diet for 8 days	Normal control, negative control, positive control (piracetam of 200 mg/kg)	Extract (100 and 200 mg/kg). Administered orally once daily	7 days	Improved behavior and memory in the step-down type passive avoidance test with a significant dose increase compared to the control group.	Reduced nitrile levels in the brain and serum TNF-α (Th1), while serum IL-10 (Th2) increased. Decreased Aβ 1-42 levels in the brain and NF-κB protein expression.	[66]
Anxiety	*In vivo*/ mice	Acute sleep disturbance with a multiple-platform approach for 72 hours	Normal control, negative control, positive control (modafinil of 80 mg/kg)	Powdered fruit solution (40 and 80 mg/kg). Administered orally once daily	1 day	Increased behavior in the OFT and elevated plus maze tests.	Increased Nrf2, HO-1, SOD1 cell counts and reduced relative expression of IL-6, TNF-α, IL1β in the hippocampus.	[29]
	In vivo/ mice	A high-fat diet (59.28% energy from fat) for 12 weeks	Control group, induction group	Fresh juice. Administered orally once daily	6 weeks	Observing behavior with the OFT, including increased time spent by the animal in the center of OFT, reduced time spent on grooming behavior, and delayed grooming behavior compared to the untreated sick group.	-	[95]
Stress	*In vivo*/rats	Noise stress for 15 days (100 dB/4 hours per day)	Negative control, sick control	*P. emblica* fruit solution (333 mg/kg). Administered orally once daily	48 days, 32 days	Increased immobility, rearing, fecal output, and decreased ambulation and grooming in the OFT. Elevated plus maze indicates a significant decrease in the number of entries in open arm entries, time spent in the open arm.	-	[96]

Depression	*In vivo*/ mice	FST, TST OFT, chronic FST	Negative control, positive control (fluoxetine of 20 mg/kg)	Water extract (390, 780, 1560, and 3120 mg/kg). Administered orally once daily	7 days, 14 days	Significant decrease in immobility compared to the control group in the FST and TST.	The extract interacts with prazosin (alpha-adrenergic antagonist), and p-chlorophenylalanine (serotonin synthesis inhibitor), and is suspected to increase serotonin in the brain, as evidenced by a significant decrease in immobility in the tail suspension test.	[79]
	In vivo/ mice	-	Control, imipramine (15 mg/kg), fluoxetine (20 mg/kg), phenelzine (20 mg/kg)	Water extract (200 and 400 mg/kg) administered orally once daily	14 days	Significant decrease in immobility in the TST and FST compared to the control group.	*P. emblica* fruit water extract produces antidepressant-like effects through interaction with α1 adrenoreceptor with prazosin (α_1 adrenoreceptor antagonist), dopamine D_2 receptor with sulpiride (selective dopamine D_2 receptor antagonist), serotonergic with p-CPA (serotonin synthesis inhibitor), and $GABA_B$ receptor with baclofen ($GABA_B$ agonist). Thus, the water extract can increase norepinephrine, dopamine, and serotonin levels, reduce GABA levels, and decrease MAO activity in the brains of rats.	[80]
	In vivo/ mice	-	Negative control group, positive control group (fluoxetine of 20 mg/kg)	Methanol extract (100, 200, 400, and 600 mg/kg). Administered orally once daily	14 days	Significant decrease in immobility in the TST and FST in the dose group compared to the negative control group.	A significant increases in dopamine and norepinephrine levels is observed in the 400 mg/kg dose group compared to the negative control.	[81]
Epilepsy	*In vivo*/rats	Kainic acid of 10 mg/kg	Normal group, control group (model)	Hydroalcoholic extract (300, 500, and 700 mg/kg). Once a day in Intraperitoneal (ip)	7 days	Increased seizure latency time in the high-dose extract group is better (99.85 ± 2.64 minutes), while the model epilepsy group is 42.54 ± 3.64 minutes.	Decreased TNF-*α* levels in the brain and increased GSH in the brain at the 700 mg/kg extract dose (dose-dependent). The extract group shows significant values compared to	[85]

						the control and epilepsy model groups.	
In vivo/rats	Pentylenetetrazole (PTZ) of 60 mg/kg	Normal group, control group (model)	Hydroalcoholic extract (300, 500, and 700 mg/kg). Once a day in Intraperitoneal (ip)	7 days	Increase in latency time (s) to myoclonic jerk at a dose of 700 mg/kg (290.16±10.42), compared to the epilepsy model group (34.66±3.05). No appearance of GTS in the dose groups of 500 and 700 mg/kg. GTS latency and GTS duration increased at a dose of 300 mg/kg (51.83±6.50 seconds) compared to the epilepsy model group (43.5±3.09 seconds).	-	[84]

MWM = morris water maze; TST = tail suspension test; FST = forced swim test; OFT = open field test; LPS = lipopolysaccharide; Aβ = amyloid β-protein; MTT = 3,-4,5 dimethylthiazol-2,5 diphenyl tetrazolium bromide; HO-1 = hemeoxygenase-1; SOD = superoxide dismutase; TNF-α = tumor necrosis factor alpha; IL = Interleukins; TuJ1 = beta-III tubulin; MAP2 = microtubule-associated protein-2; p-CPA = DL-parachlorophenylalanine; GABA = gamma-aminobutyric acid; MAO = monoamine oxidases; GTS = generalized tonic seizures;

Sleep disturbances can lead to physical and mental disorders and irritability, as good sleep habits contribute to both physical and mental well-being. Sleep problems increase the risk of anxiety, as proven by several studies that have utilized sleep disturbance models in rodents to measure anxiety levels.[14,29,74,75] Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a role in the anti-oxidative response to stress and anti-inflammatory processes.[71,72] Activation of the Nrf2 pathway in the hippocampus is associated with neuroprotective actions in improving anxiety behavior in animal models of anxiety. *P. emblica* fruit extract at doses of 40 and 80 mg/kg significantly increased anxiety-like behavior in the open field test (OFT) and elevated plus maze (EPM) tests, as indicated by a significance value for the sleep disturbances model group, but was not significantly different from the positive control (modafinil). Treatment with 80 mg/kg *P. emblica* fruit extract and equivalent positive control significantly increased the protein expression of Nrf2 and hemeoxygenase-1 (HO-1) in the rat hippocampus compared to the sleep disturbances model group. Meanwhile, the protein expression of IL-6, TNF-α, and IL1β in the hippocampus of mice in the extract and positive groups decrease significantly compared with the model group.[29]

Depression

Depression is a common mental disorder with typical symptoms, namely mood disorders, inability to feel pleasure, and lack of energy or fatigue. Depression can occur from adolescence to adulthood, with very high medical costs.[76,77] During a depressive episode, individuals experience a depressed mood (feeling sad, easily irritable, or empty), loss of pleasure, and a pervasive lack of interest in activities throughout most of the day, occurring for at least two weeks. Other symptoms include decreased concentration, excessive guilt, hopelessness about the future, thoughts of death or suicide, sleep disturbances, changes in appetite or weight, and profound fatigue or low energy. Individuals with depression are at a high risk of suicide.[78] *P. emblica* fruit aqueous extract at 200 mg/kg and 400 mg/kg for 14 days reduces immobility in the tail suspension test (TST and FST compared to the negative control group.[79–81] The aqueous extract (200 mg/kg) produces antidepressant effects through interaction with α_1 adrenoreceptors, dopamine D_2 receptors, serotonergic receptors, and $GABA_B$ receptors, thereby increasing norepinephrine, dopamine, and serotonin levels, reducing GABA levels, and inhibiting MAO-A activity in the rat brain.[80] MAO inhibitors can enhance monoamine levels, making them a prescribed antidepressant treatment. The methanol extract of *P. emblica* fruit at 400 mg/kg significantly raises the levels of dopamine and norepinephrine in the brain compared to the negative control group.[81] Therefore, *P. emblica* can act as a potential natural source of psychotherapeutic agents to treat depression by increasing neurotransmitters and inhibiting MAO activity related to depression pathology.

Antibacterial Activity

Epilepsy

Epilepsy is characterized by episodic abnormal bursts of electrical activity in neurons that may spread throughout the brain. Epilepsy is generally caused by excessive stimulation or failure of the inhibitory action of acid receptors due to changes in the functional properties of $GABA_A$ receptors. Such abnormal nerve activity may significantly impact an individual's cognitive and behavioral functions.[82,83] The hydroalcoholic extract of *P. emblica* fruit increased myoclonic jerk latency and completely eliminates generalized tonic seizures (GTS) at doses of 500 and 700 mg/kg induced by pentylenetetrazole (PTZ) (i.p).[84] The group treated with the *P. emblica* fruit extract at a dose of 700 mg/kg had a better seizure latency time (99.85 ± 2.64 minutes), while the epilepsy model group induced with kainic acid at a dose of 10 mg/kg (i.p.) had a lower seizure latency time (42.54 ± 3.64 minutes).[85] In experimental seizure models, there is proven overexpression of TNF-α in the brain area where seizures occur and spread.[86] In addition, *P. emblica* fruit extract at a dose of 700 mg/kg (normal saline i.p.) reduced the levels of TNF-α as proinflammatory cytokines in the brain, compared to the control group and the kainic acid-induced epilepsy model group.[85] As a result, *P. emblica* fruit has the potential to be used as an adjuvant in antiepileptic drug treatment.

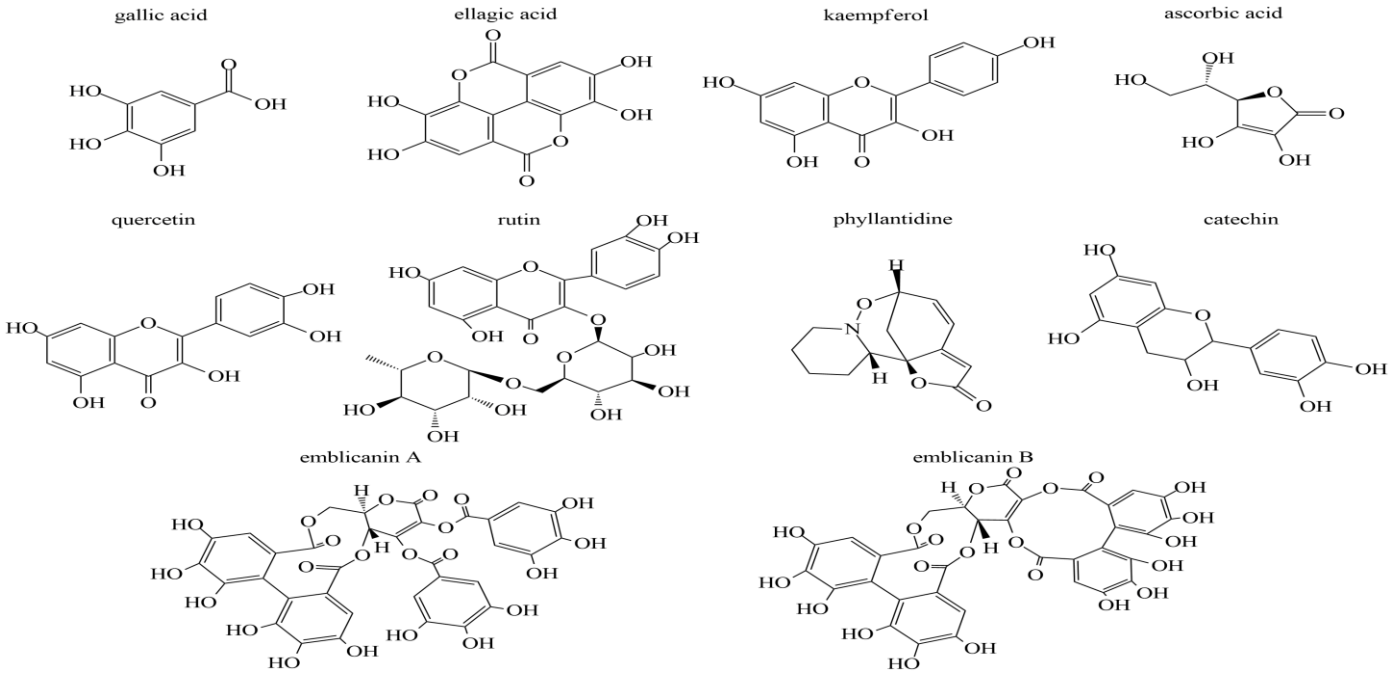

Figure 2: The Primary Phytochemical Compounds in *Phyllanthus emblica* L.

Conclusion

P. emblica contains high polyphenolic compounds associated with neuroprotective effects by reducing neuroinflammation and neurodegeneration caused by oxidative stress. Molecular neuroprotective mechanisms include reducing proinflammatory cytokines (TNF-α, interleukins), which are overexpressed in modes such as seizures, cognitive impairment, and anxiety. It can reduce GABA and increase neurotransmitter levels (dopamine, norepinephrine, and serotonin) by inhibiting MAO in rodent models that mimic depression. Behavioural observations in rodents with similar pathological condition models treated with *P. emblica* extract showed

behavioural improvements, as evidenced by MWM test, OFT, EPM test, TST, and FST.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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