Egypt. J. Chem. **Vol. 68**, No. 12 pp. 455 - 468 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

The Therapeutic Potential of *Phyllanthus* Species in Neurodegenerative Disorders: A Systematic Review

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Abstract

This review identifies, collects, and summarizes the existing literature on the relationship between *Phyllanthus* and neurodegenerative diseases, particularly Alzheimer's disease (AD), over the past 20 years. *Phyllanthus* (Phyllanthaceae) contains about 800 species distributed in various habitats in both hemispheres and of broad folk traditional uses in Indian and Brazilian culture. Research has demonstrated extensive biological activities correlated with diversity in its active constituents. In this systematic review, the software "VOS Viewer" was employed to visualize existing scientific data and identify trends and studies related to *Phyllanthus*. The review focuses on the correlation between *Phyllanthus* species and neurodegenerative diseases over the past two decades. A thorough search of databases including Web of Science, Scopus, Wiley, Taylor & Francis, and PubMed resulted in 21 articles being deemed relevant for this report. Ninety-four articles were identified as potentially relevant, and twenty-one articles were included in the systematic review. *P. acidus*, *P. amarus*, *P. emblica*, and *P. niruri* were the species among the inclusion criteria with *in vivo*, *in vitro*, and computational studies performed. This review sheds light on the mechanisms through which *Phyllanthus* species may serve as promising candidates for treating neurodegenerative disorders, particularly emphasizing their major phytoconstituents.

Keywords: *Phyllanthus*; neurodegenerative disorders; VOS Viewer; phytoconstituents; systematic review.

1. Introduction

Cognition refers to the mental processes involved in acquiring and processing information, which can be impaired by neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease [1, 2]. AD, the most common form of dementia, affects nearly 45 million people globally and is the fifth leading cause of death [2]. It is characterized by the accumulation of extracellular β-amyloid plaques and intracellular neurofibrillary tangles (NFTs) caused by the hyperphosphorylation of tau protein [3, 4]. This aggregation leads to neuronal damage, oxidative stress, and cellular dysfunction Lord [5]. Oxidative stress is an imbalance between free radicals and antioxidants, plays a significant role in AD's progression and is considered a clinical marker of the disease [6, 7]. Acetylcholinesterase (AChE) is also implicated, as its elevated activity contributes to neurodegeneration [8-11].

Neurodegenerative diseases present significant challenges due to their progressive nature and the lack of effective treatment options. The search for natural compounds with neuroprotective properties has become a key focus in research. The *Phyllanthus* genus has attracted attention for its diverse bioactive compounds and potential neuroprotective effects. Preliminary evidence suggests that *Phyllanthus* species may offer neuroprotective benefits, warranting further investigation into their therapeutic potential [11].

The genus *Phyllanthus* belongs to the family Phyllanthaceae and comprises approximately 2000 species classified into 49 genera, instead of the previously named Phyllanthoideae subfamily of Euphorbiaceae [12-14]. *Phyllanthus* species are used traditionally in South India for treating jaundice and hepatitis [15], while in South America for controlling blood glucose levels and hypertension [16], whereas in Brazil acting as diuretic and for treating jaundice, diabetes, and hepatitis [17].

Phyllanthus species are abundant in bioactive compounds, making them valuable for applications in healthcare, nutrition, and the cosmetic industry. The genus *Phyllanthus* a large source of tannins, flavonoids, lignins, triterpenoids, and alkaloids. Lignins, and tannins represent the predominant classes of this genus. The major lignans are phyllanthin and hypophyllanthin [18]. While, the most abundant tannins are corilagin and geraniin [19]. Pharmacological activities include antioxidative, antibacterial, laxative, anti-inflammatory, antipyretic, antiviral, antiatherosclerotic, antineoplastic, tonic, analgesic, immunomodulatory, and dementia were reported [20].

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Received date 25 February 2025; Revised date 07 April 2025; Accepted date 26 April 2025
DOI: 10.21608/ejchem.2025.363478.11364

This work comprehensively evaluates the current evidence on the neuroprotective effects of *Phyllanthus* species in relation to its phytoconstituents, elucidating their mechanisms of action, through anti-inflammatory, antioxidant, and anti-apoptotic pathways, as well as their role in modulating the signaling pathways associated with neurodegeneration. VOSviewer software, was used to generate comprehensive visual maps that illustrate the relationships and trends in the research on *Phyllanthus* and its biological activities. This visualization aids in identifying key research areas and how the focus on different activities of *Phyllanthus* has evolved and predicts future directions.

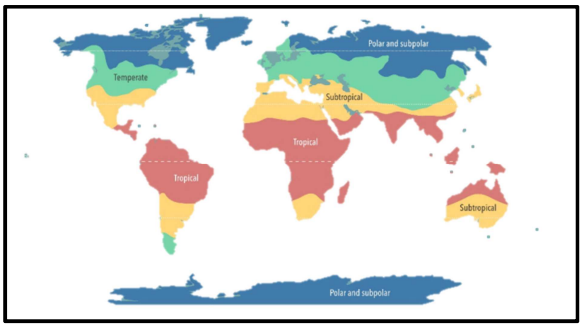

Figure 1: Schematic representation of *Phyllanthus* distribution in tropical and subtropical regions.

2. Results and Discussion

2.1. Bibliometric analysis

A bibliometric network of the publications dealing with "*Phyllanthus*" was implemented using the software VOS viewer version 1.6.17. This tool exhibits large bibliometric maps in an understandable manner consisting of nodes and edges that are weighted based on the incidence of the terms and the depth of the relationships between them. For our visualization, we used data from 1475 papers published between 2000 and 2024, extracted from the Web of Science database. We selected all publications dealing with *Phyllanthus* species. Figure 2 illustrates the major research themes and their interconnections within the scientific literature. In the network visualization, each node represents a keyword, and the size of the node indicates its occurrence frequency in the literature. The edges (lines) between nodes represent the co-occurrence of keywords within the same publications, with thicker lines indicating stronger associations. Different colours represent clusters of closely related keywords, identified through the VOS viewer's clustering algorithm. Clusters highlight several biological activities, including cytotoxic, anticancer, hepatoprotective, and antioxidant activity. Overlay visualization shows the published years highlighted in different colours ranging from dark (blue) representing the older to the most recent publications coloured light (yellow); the size of circles and font is affected by frequency of occurrence; while distance of keywords visualizes relatedness of keywords. The largest cluster (Figure 3), correlates research related to the antioxidant potential, lipid peroxidation, oxidative stress, and blood glucose levels besides catalase and malondialdehyde. Correlation between Alzheimer's, diabetes, inflammation, and antioxidants has been the focus of recent research [21, 22].

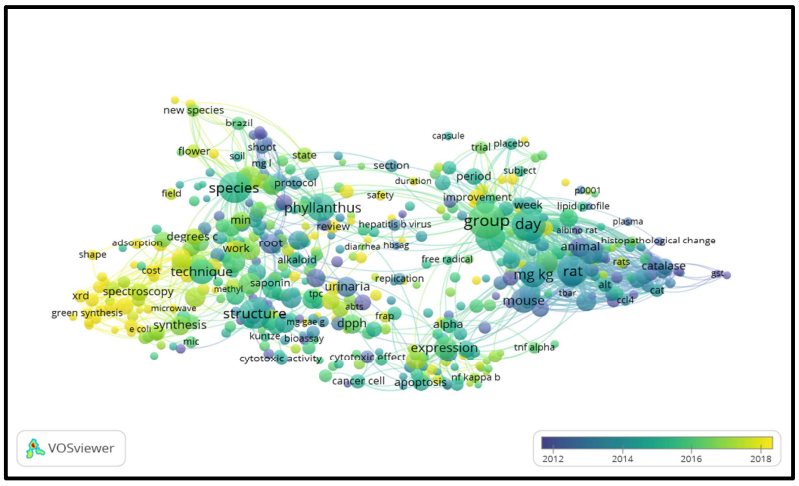

Figure 2: Overview of keyword links mentioned in literature dealing with *Phyllanthus.*

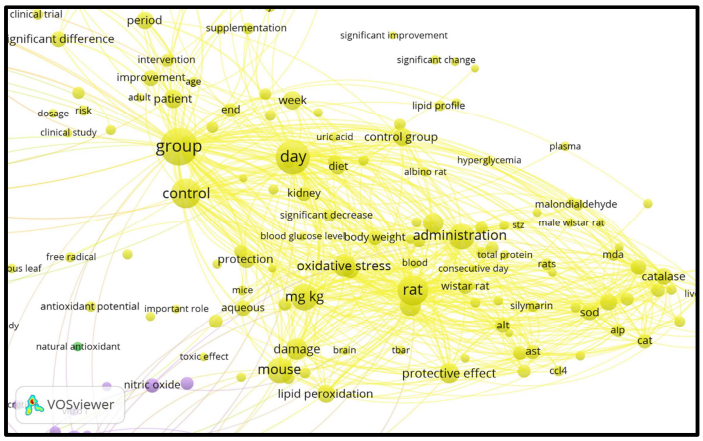

Figure 3: *Phyllanthus* and antioxidant effects.

2.2. Eligibility criteria

Preliminary searches of the selected databases identified 49 records with the terms "*Phyllanthus*" in the title and "*Alzheimer's*" and "*Neuroprotective*" (in all fields) using the four databases. After screening the titles and abstracts of these records, 28 articles were excluded. 14 articles were excluded by title (Five of them were review articles), six by the abstract, one excluded by the language as its original language was Chinese, and one was excluded after reading the whole article. Also, four duplicates were detected and two weren't available.

Figure 4 shows the flowchart diagram of the reports that were finally identified after the duplicate removal and finally screened and included in the review.

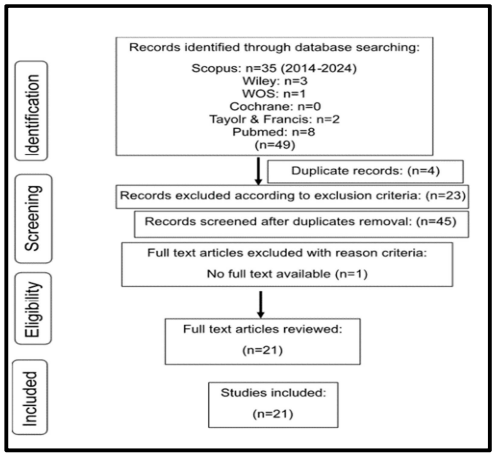

Figure 4: PRISMA flowchart showing the number of selected articles.

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2.3. *Phyllanthus* species in the treatment of neurodegenerative disorders

Phyllanthus species, widely recognized for their diverse medicinal properties, have gathered substantial attention as a source for treating neurodegenerative disorders. They contain a rich variety of bioactive compounds, including polyphenols, flavonoids, tannins, lignans, and alkaloids, which contribute to their therapeutic effects.

Research has shown that these compounds exhibit powerful antioxidant, anti-inflammatory, and cholinesterase-inhibiting activities, all of which are critical for helping in the treatment of conditions like Parkinson's disease, AD, and other cognitive disorders. The following tables (1, 2, 3, 4 and 5) provide a detailed overview of four *Phyllanthus* species (*P. acidus, P. amarus, P. emblica, and P. niruri*) and their key constituents based on the available *in vitro*, *in vivo*, and computational studies, showcasing their potential in the management of neurodegenerative diseases. Figure 5 offered a collective presentation of the underlying mechanisms of *Phyllanthus* species as a powerful agent in neurodegenerative disorders.

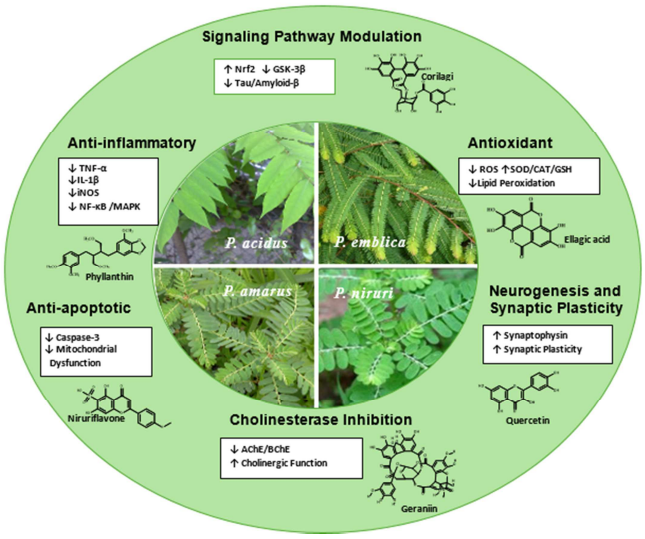


Figure 5: The potential mechanisms of action of *Phyllanthus* species in neurodegeneration.

Table 1: *P. acidus* and/or their isolated constituents in the treatment of neurodegenerative disorders

P. acidus		
In vitro		
Tested sample	**Study design**	**Main findings**
Fruits's methanolic extract (MEPA)	**Antioxidant assays:** **-** Determination of total antioxidant and reducing power capacities, DPPH radical scavenging, hydroxyl radical scavenging, metal chelating, lipid peroxidation inhibition, Acetylcholinesterase (AChE) inhibitory, and Butyrylcholinesterase (BChE) inhibitory activities.	- MEPA exhibited antioxidant activity, anti-AChE and anti-BChE activity suggesting its efficiency against AD and other neurodegenerative disorders. It exhibited strong radical scavenging, Fe^{3+} reducing power, and lipid peroxidation inhibition (IC_{50} of 471.63 µg/ml). - The polyphenols and flavonoids of *P. acidus* revealed potential antioxidants and radical scavenging actions, and effectively inhibited AChE and BChE activity [23].

Table 2: *P. amarus* and/or their isolated constituents in the treatment of neurodegenerative disorders

P. amarus		
Computational study		
Tested sample	**Study design**	**Main findings**
Leaves water extract.	Docking analysis with AChE, 5′ - nucleotidase, Angiotensin-I converting enzyme (ACE), and adenosine deaminase (ADA), proteins as the target proteins.	Docking analysis exhibited a high binding affinity of the compounds (caffeic, chlorogenic, ellagic, and gallic acids, catechin, epicatechin, rutin, isoquercitrin, kaempferol, quercetin, and quercitrin) with ADA, 5′ - nucleotidase, ACE, and AChE activities. Ellagic acid had the highest binding affinity [24].
The whole plant 80% ethanol extract. Oral administration of *P. amarus* extract (100, 200, and 400 mg/kg) for 14 and 28 days.	1 mg/kg lipopolysaccharide (LPS) i.p. **- Toxicity tests:** Subchronic neurotoxicity study **- Neurobehavioral tests:** Functional observational battery and histopathological evaluation. **- Cognitive behavioural studies:** Novel object discrimination task, locomotor activity, and measurement of cytokines. **- Nitrite levels:** Griess assay. **- Total protein concentrations**: Western blot. **- Immunohistochemistry of brain slices.**	Corilagin, geraniin, hypophyllanthin, isonirtetralin, niranthin, phyllanthin, phyltetralin, and ellagic and gallic acids were identified and quantified. *P. amarus* ethanolic extract protected the animals from LPS-induced memory impairment. It considerably diminished the release of proteins like tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, inducible nitric oxide synthase (iNOS) in the brain tissue, nitric oxide (NO) levels, CD11b/c integrin expression, and synaptophysin immunoreactivity. It alleviated neuroinflammatory responses and prevented memory impairment induced by LPS [25].

Table 2: ***Cont.***

P. amarus		
In vivo		
Hydroethanolic extract of the aerial parts and esculetin (6,7-dihydroxycoumarin) 400 mg/kg bwt/ml/day p.o, for 21 days.	Streptozotocin 60 mg/kg bwt, i.p, **Behavioural tests:** Motor coordination and maze learning tests, **Biochemical estimation of** glycosylated Hb (HbA1c), and nitrite/*in vivo* antioxidant activity. **Myeloperoxidase (MPO)/Anti-inflammatory activity:** protein, calcium Na^+-K^+ ATPase, acetylcholine (Ach), and nerve conduction velocity (NCV) measurements. **Histological:** Stained using haematoxylin and eosin (H&E) stains and transmission electron microscopy (TEM).	The administration of the extract on diabetic neuropathy in STZ-induced diabetic rats revealed an increase in the levels of $Na^{+/}K^+$-ATPase, NCV, Ach, protein, motor coordination, and maze learning ability, while decreased levels of calcium, HbA1c, nitric oxide (NO), and myeloperoxidase after its [26].
Leaves alkaloid extract 1 mg/ml for 14 days	Flies were exposed to a diet containing 40 mM $AlCl_3$, and *P. amarus* alkaloidal extracts (0.1 and 1 mg/ml) for 14 days. - Survival test, measurement of locomotor performance by negative geotaxis, aversive phototaxic suppression assay for learning and memory. **Biochemical assays:** catalase, monoamine oxidase (MAO), acetylcholinesterase (AChE) activity, determination of tissue malondialdehyde (MDA) content, and total protein.	Alkaloid extract ameliorated $AlCl_3$ induced behaviourally and biochemically impaired flies. HPLC analysis of the extract showed plenty of Amaryllidaceae alkaloids, where carpaine and 6-hydroxybuphanidrine are the most abundant, and thought to be responsible for treating neurodegenerative disease [27].
Leaves water extract. 200 and 400 mg/kg bwt of *P. amarus* orally for 14 days.	15 mg/kg (bwt) of doxorubicin (DOX) i.p. **- Cognitive evaluation using Y-maze and Morris water maze tests** Neuronal arginase activity **- Assay of enzymes associated with cognitive dysfunction:** 5′ -nucleotidase, acetylcholinesterase, butyrylcholinesterase, arginase activities, Angiotensin-converting enzyme (ACE), and Adenosine deaminase (ADA). **- Assessment of oxidative stress biomarkers:** Catalase, non-protein thiol (NPSH), and thiobarbituric reactive species (TBARs) activities. **- Total protein determination**	The extract exhibited a high mitigating effect against memory dysfunction and a major reduction in the latency of escape, AChE, ACE, 5′-nucleotidase, arginase activity, and the production of TBARS levels. This reduction might be credited to the phenolic constituents of the plants' extracts, leading to a reverse in the *β*-amyloid production, cognitive impairment, and immunosuppression [24].
Alkaloid extract of *P. amarus* leaves. *P. amarus* and *A. paniculata* (50 mg/kg/bwt/d) for 21 days.	**Streptozotocin** (STZ)-induced diabetic male rats. Injection of STZ (50mg/kg/bwt, i.p) **Determination of:** blood glucose level, cholinesterase (AChE and BChE), intestinal *α*-glucosidase and pancreatic *α*-amylase activities. - **Purinergic enzymes:** 5′ nucleotidase, ATPDase, and ADA activities. **- Oxidative stress markers:** reactive oxygen species (ROS) and thiobarbituric acid reactive species (TBARS) content levels. **- Neuronal antioxidant enzyme activities:** Catalase (CAT) and superoxide dismutase (SOD) activities.	The alkaloid extract decreased high blood glucose and can be considered as a source of ameliorative agent for managing and treating the cognitive impairment associated with diabetes via decreasing the AChE, *α*-amylase, *α*-glucosidase, BChE, ATPDase, ADA activities, while increasing the antioxidant enzyme activities [28].

Table 3: *P. emblica* and/or their isolated constituents in the treatment of neurodegenerative disorders

P. emblica		
Computational study		
Tested sample	**Study design**	**Main findings**
P. emblica Linn. MS/MS screened components of fruit polyphenols PEFPs (corilagin, chebulinic acid, and ellagic acid) were docked with nuclear factor erythroid 2-related factor 2 (Nrf2).	**Molecular docking to the active Nrf2 pathway.** (MS/MS screened components of fruit polyphenol PEFPs corilagin, chebulinic acid, and ellagic acid)	PEFPs active components; corilagin, chebulinic acid, and ellagic acid activate the Nrf2 pathway, with binding energies of 10, 8, and 8 kcal/mol, respectively. That leads to the improvement of the cognitive impairment and anxiety induced by sleep deprivation [29].
P. emblica		
In vitro		
Tested sample	**Study design**	**Main findings**
Juice	**Antioxidant assays:** bovine serum albumin (BSA), fructose and BSA, free radical scavenging activity (DPPH), ferric reducing antioxidant power (FRAP), methylglyoxal (MGO), thioflavin-T, beta amyloid 1-42 ($A\beta_{1-42}$) advanced glycation end-products (AGEs), and acetylcholinesterase (AChE) inhibition assays. - Inhibition of cytotoxicity of murine BV-2 microglia and differentiated human SH-SY5Y neuronal cells induced by hydrogen peroxide (H_2O_2). - Quantification of total tau protein levels in differentiated human SH-SY5Y neuronal cells. - Cell culture conditions and Cell viability - Quantification of nitric oxide species (NOS) by Griess assay. - *In vivo Caenorhabditis elegans* assay.	*P. emblica* extract demonstrated strong antioxidant activity in both the DPPH and FRAP assays. It exhibited potent anti-glycation activity, with 85.3% inhibition of AGE formation, primarily due to its antioxidant properties. It also showed significant inhibition of MGO-induced AGE formation (74.1% scavenging activity) and reduced Aβ1-42 fibril formation by 47.9% and inhibited AChE effects by 43.1%. The extract suppressed NOS production by 19.0%. In cells exposed to H_2O_2, the extract increased cell viability by 76.9% [30].
Methanolic fruit extract of *P. emblica* (MFEPE)	**Radical scavenging action:** DPPH radical-scavenging assays, hydroxyl radical scavenging activity and lipid peroxidase inhibition (using a ferric thiocyanate assay). **Cell line study:** 3, -4,5 dimethylthiazol-2,5 diphenyl tetrazolium bromide (MTT) assay using PC12 neural cell lines, LDH assay, measurement of intracellular reactive oxygen species (ROS), and glutathione (GSH) measurement.	MFEPE demonstrated concentration-dependent radical scavenging and lipid peroxidation activity comparable to ascorbic acids. DPPH and hydroxyl radical scavenging assays revealed IC_{50} levels of 73.21 µg/ml and 0.426 mg/mL respectively with a lipid peroxidation activity of 73.21 µg/ml. MFEPE enhanced intracellular GSH levels and reduced glutamate-induced toxicity, showing protective effects against ROS-triggered cell death in PC12 cells. The neuroprotective effects were confirmed by cell viability assays, attributed to the high flavonoid, polyphenol, and tannin content of MFEPE [31].
Polyphenols extracted from the 45% ethanol–water mixture of fruit. Against *Caenorhabditis elegans* (nematode)	***In Vitro* Antioxidant Assays:** DPPH, $ABTS^+$ 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid), and OH radical scavenging assays and FRAP Assay. **Anti-aging ability:** Thermal resistance and lifespan, the activity of AChE and BuChE, and antioxidant enzymes of SOD, CAT, and MDA levels.	*P. emblica* fruit polyphenols (chlorogenic, gallic and ellagic acids, myricetin, and quercetin) were found to slow aging marks in *C. elegans*, improving the thermal resistance, prolonging the lifespan, and inhibition of AChE and BuChE activity. This was accompanied by the increase in antioxidant enzymes activity of SOD by 30.74% and CAT by 8.42%, while decrease in MDA level by 36.25% [32].
In vivo		
Oral administrations of	Amnesia induced by scopolamine (0.4	Dose-dependent improvement in memory

Commercially Ayurvedic preparation of ***E. officinalis*** **(*P. emblica*)** Dose:50, 100 and 200 mg/kg, p.o. for 15successive days.	mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). Elevated plus-maze, brain cholinesterase activity and total cholesterol levels.	scores of young and aged mice was observed. Amnesia was reversed, brain cholinesterase activity and total cholesterol levels were reduced [33].
Tannoid principles of *E. officinalis* (EoT), **standard** emblicanin A, emblicanin B, punigluconin, and pedunculagin EoT dose is200 mg/kg bwt Duration: administered orally for 60 days.	Intraperitonial injection of $AlCl_3$, $AlCl_3$ and EoT (50, 100, and 200 mg/kg bwt), and EoT (200 mg/kg bwt) alone groups. **Behavioral studies:** Morris water maze and open field tests. Estimation of aluminum concentration and acetylcholinesterase activity. **Immunohistochemical studies:** Immunostaining of A-beta1 **Protein expression studies:** Western blot analysis	Coadministration of EoT orally with $AlCl_3$ rats for 60 days considerably returned the $AlCl_3$ concentration, AChE activity, and A-beta1 synthesis-related molecules in the studied brain regions. The spatial learning, locomotor and memory impairments detected in $AlCl_3$ treated rats were significantly reduced by EoT. [34].
Tannoids principles from the fruits of *P. emblica* (100 mg/kg., bwt*i.p.*). Duration: 60 days.	**Behavioral analysis:** Passive avoidance task, elevated plus-maze, and radial arm maze tests. **Biochemical Estimation:** TBARS, SOD, glutathione peroxidase (GPx), catalase activity, GSH, and protein expression studies.	It had a neuroprotective effect against memory loss produced by $AlCl_3$ intoxication by diminishing acetylcholine esterase activity and the expression of amyloid β protein biosynthesis related markers [35].

P. emblica		
In vivo		
Tested sample	**Study design**	**Main findings**
Ethanolic extract of ripe *P.emblica* (EEPEr) and unripe (EEPEu) fruit 100 and 200 mg/kg bwt orally for 12 days	**-Acute Toxicity Study:** **-Behavioral Study:** Passive avoidance (PA) and rewarded alternation (RA) tests. **Biochemical Study:** acetylcholinesterase (AChE), catalase (CAT), glutathione (GSH), glutathione reductase (GSR), glutathione peroxidase (GSH-Px), glutathione-S transferase (GST), lipid peroxidation, and thiobarbituric acid reactive substances (TBARS) superoxide dismutase (SOD) assays were performed.	EEPE significantly improved learning, and memory in rats and was safe for oral administration up to 2,000 mg/kg bwt. Both EEPEr and EEPEu improved cognitive performance, shown by increased step-through latency, memory retention, and correct responses in behavioral tests. The administration of EEPE increased levels of CAT, GST, GSR, SOD, GSH, and GSH-Px, while reducing TBARS level and AChE activity indicating strong antioxidant potential [36].
Polyphenols of the fruits 45%, ethanol-water mixture. - *C. elegans* nematodes	*C. elegans* model - *C. elegans* Strains and Maintenance. - Thermal stress resistance assay. - Lifespan Assay. - Determination of antioxidant enzyme, cholinesterase activities, and MDA Levels.	The fruit polyphenols exhibited significant protective effects against aging in *C. elegans* model, improving thermal resistance, extending lifespan, and decreasing the activity of AChE and BuChE. EoT prevented tau hyperphosphorylation by aiming the GSK-3β/Akt signaling pathway. These potentials were attributed to the potent antioxidant properties of fruit polyphenols, including scavenging of free radicals, increasing antioxidant enzymes SOD and CAT, and decreasing MDA level [32].
Water extract of fruit (250 & 500 mg/kg/bwt /daily) **and gallic acid** (pure GA, 100 mg/ kg/bwt /daily). Rats were fed a high-fat diet (HFD) for 112 consecutive days' and treatments were administered daily by oral gavage.	**Morris Water Maze Test** **Analysis of Biochemical Parameters:** Total cholesterol (CHOL), triglyceride (TG), low-density lipoprotein (LDL), and glucose levels. **Methylglyoxal (MG) Analysis.** **Brain Tissue Homogenization and Protein Analysis:** β -actin antibody**,** amyloid precursor protein (APP), amyloid beta1-42 (Aβ 1-42), TAU-5, and receptor for advanced glycation end products	In rats with HFD-induced, the extract significantly improved body weight and steatosis by enhancing adiponectin and peroxisome proliferator-activated receptor alpha (PPAR-α) production, while reducing adipose tissues. The glyoxalase system enzymes and the coenzyme GSH were increased. While levels of AD biomarkers (Aβ 1-42, APP, and TAU-5) were decreased. Additionally, insulin resistance, inflammatory cytokines, MDA production, RAGE, MAPK,

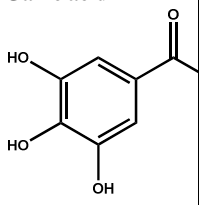
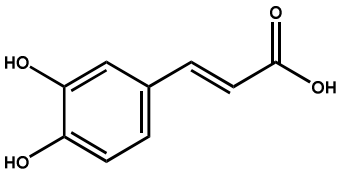
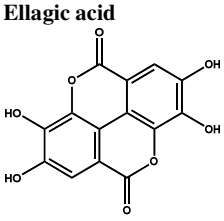
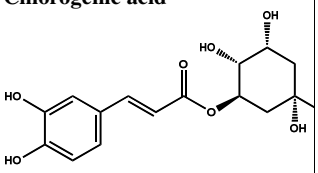
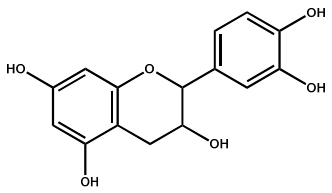
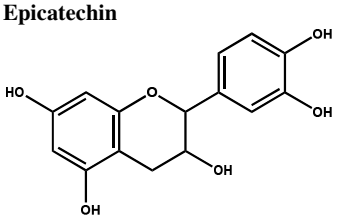
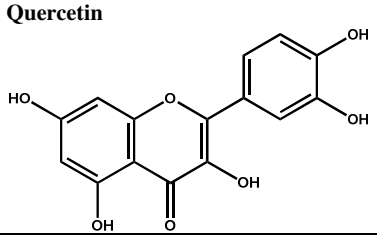
	(RAGE) antibodies p38, JNK, and ERK1/2 antibodies. - Antibodies against the phosphorylated inhibitory subunit of NF-kappa- B alpha (pIκ Bα), phospho-NF-kappa-B p65 subunit (pP65), and Iκ B kinase (IKK). **Analyses of Antioxidant Enzyme Activities and Malondialdehyde Level:** Glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), and thiobarbituric acid reactive substance (TBARS). **Glyoxalase System Enzymes and Gene Analysis:** Glyoxalase I (Glo-1) and Glo-2 activity assays. **Analysis of Advanced Glycation End Product (AGE) Contents.** **Determination of Immune-Related Cytokine Levels:** Interleukin(IL)-1β , IL-4, IL-6, TNF-α , and IL-10 ELISA. **Microbiota Analysis.**	NF-κB levels, and AD-related proteins were reduced. While both antioxidant enzyme activities and anti-inflammatory cytokine were increased. These activities were attributed to the high contents of ellagic acid and β -glucogallin, the major phenolic components in the extract. [37]**.**
P. emblica Linn. fruit polyphenols (PEFPs) (***PEFPs, 40* and *mg/kg, i.g.*)** for Four consecutive days	**Evaluation of the extract potential** against cognitive impairment and anxiety induced by acute paradoxical sleep deprivation (SD). Morris water maze, Open field test and elevated plus maze test. Haematoxylin-eosin staining. Nissl staining and golgi-Cox staining immunohistochemistry. Western blot analysis. Oxidative stress parameter (SOD1) and pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) in the hippocampus of the brain area.	PEFPs reduced the antioxidant enzyme SOD1 activities and increased the content of IL-1β, TNF-α, and IL-6. PEFPs markedly counteracted oxidative stress damage, neuroinflammation and protected against cognitive impairment and anxiety induced by paradoxical SD [29].

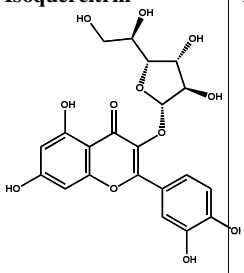
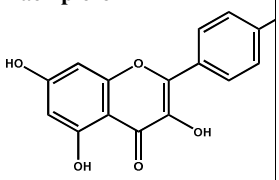
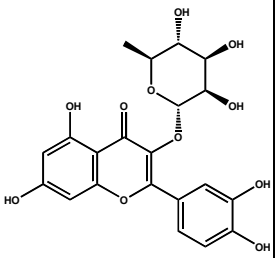
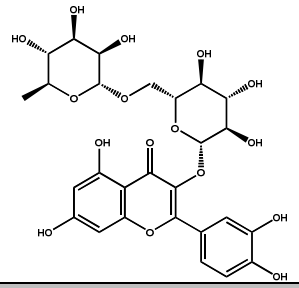
Table 4: *P. niruri* and/or their isolated constituents in the treatment of neurodegenerative disorders

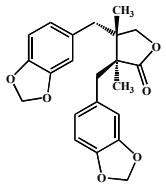
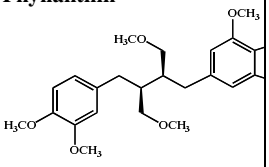
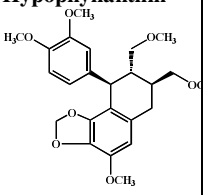
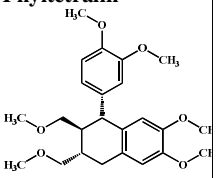
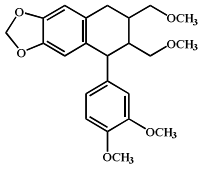
P. niruri		
Computational study		
Tested sample	**Study design**	**Main findings**
Quercitrin and Niruriflavone	Molecular docking on the active site of 5-LOX and AChE targets.	The isolated compounds showed good binding affinity with the active sites of 5-LOX and AChE [5].
In vitro		
Tested sample	**Study design**	**Main findings**
Quercitrin and Niruriflavone (whole plant)	Free radical scavenging activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Hydroxyl radical scavenging activity, using the Fe^{3+}-Ascorbate–EDTA–H_2O_2 system (Fenton reaction). -AChE inhibition using Ellman's method using rivastigmine as a positive control. -LOX assay to measure 5-Lipoxygenase inhibition activity.	Both isolated niruriflavone and quercitrin decreased oxidative damage 5-LOX, and AChE. Playing a crucial role in the treatment and prevention of AD. Niruriflavone responds better to AChE enzyme, oxidative stimuli, and inflammation. Suggesting it as a potent neuroprotective agent. [5].
In vivo		
Tested sample	**Study design**	**Main findings**
Quercitrin and Niruriflavone (whole plant) (dose: 0.125 mg/kg/bwt, duration: 24 days)	($AlCl_3$)-induced Alzheimer's disease model. **Neurobehavioral assessment:** -Morris water maze and elevated plus	Rats treated with niruriflavone had a protected spatial learning abilities and high recovery of anxiety. As the oral administration of niruriflavone

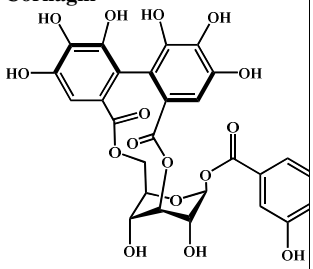
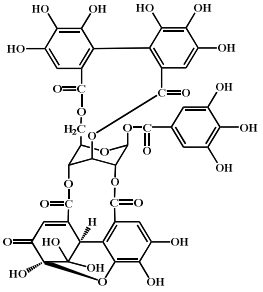
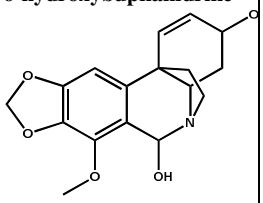
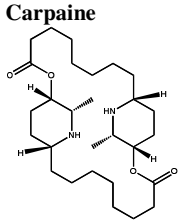
	maze test **Biochemical assessments:** Catalase (CAT), lipid peroxidation malondialdehyde (MDA) and superoxide dismutase (SOD) activities	reversed the neurobehavioral changes triggered by $AlCl_3$ [5].
Aqueous extract of aerial parts (AEPN) (dose: 75 and 150 mg/kg/day via intragastric gavage, (7^{th} day of gestation) to the end of lactation (21 days of lactation).	To investigate the effects of administration of AEPN during pregnancy and lactation, the following tests were performed on the pregnant rats and their offspring: **- Maternal toxicity:** Food consumption and weight evolution and maternal reproductive performance. **- Reflex ontogeny:** Palmar grasp, righting reflex, vibrissa placing, cliff avoidance, negative geotaxis, auditory startle response, and free-fall righting. **- Behavioral tests:** Open field habituation and object recognition tests.	AEPN accelerated the maturation reflex, influenced reflex parameters in neonates, and improved offspring memory while inducing no maternal or neonatal toxicity. Also improved short- and long-term memory parameters in the adult life of the offspring [38].
Niruriflavone-loaded chitosan nanoparticles (NFLC) (dose:0.5 ml/100 g bwt of aluminum chloride, duration: orally for 42 days. (dose:2.5 mg/kg bwt of rivastigmine, duration:42^{nd} to 60^{th} day)	***In-vitro* cell viability studies:** The neuroblastoma cell line (SHSY5Y) was treated with NFLC, and the viability of neurons was determined using the MTT test. ***In-vivo* evaluation of oxidative stress markers:** **Antioxidative enzymes:** - Superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), malondialdehyde (MDA), and thiobarbituric acid (TBARS) activities.	The 25 and 250 µg/ml concentrations of NF and NFLC caused no harm to the cells at 24 hours, with a cell viability of 85%, proving the safety of NFLC to be applied *in vivo*. Oral administration of NFLC significantly enhanced CAT, GSH, and SOD, while decreased MDA and nitrite levels. Encapsulating NF into CS nanoparticles significantly enhanced the antioxidant of free NF [39].

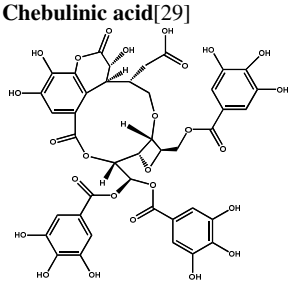
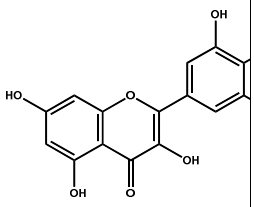
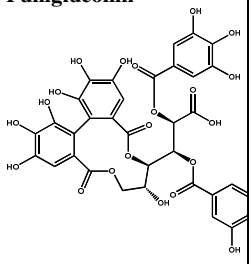
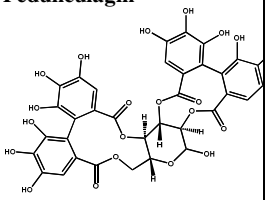
Table 5: Compounds from genus *Phyllanthus* with anticholinesterase activity

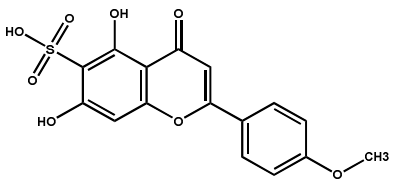
P. amarus [24]**Leaves water extract**			
Phenolic acids			
Gallic acid	**Caffeic acid**	**Ellagic acid**	**Chlorogenic acid**
			
Flavonoids			
Catechin	**Epicatechin**	**Quercetin**	
			

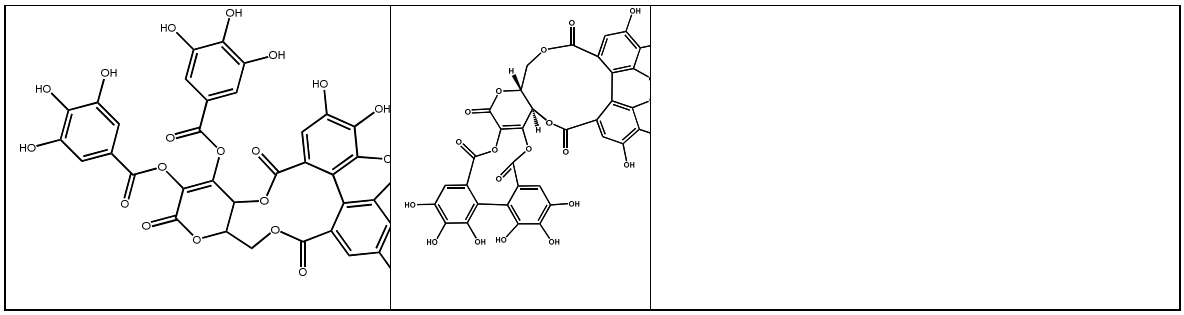
Isoquercitrin	Kaempferol	Quercitrin	Rutin
			

P. amarus [25]**Whole plant 80% ethanol extract**				
Lignans				
Niranthin	**Phyllanthin**	**Hypophyllanthin**	**Phyltetralin**	**Isonirtetralin**
				

Tannins		**Leaves alkaloids extract** [27]**Alkaloids**	
Corilagin	**Geraniin**	**6-hydroxybuphanidrine**	**Carpaine**
			

P. emblica			
Fruit polyphenols [29]		**Tannoid principles** [34]	
Ellagitannin	**Flavonoid**	**Ellagitannins**	
Chebulinic acid[29]	**Myricetin**[32]	**Punigluconin**	**Pedunculagin**
			

Tannoid principles [34] **Hydrolyzable tannins**		***P. niruri* whole plant** [5]
		Flavone sulfonic acid
Emblicanin A	**Emblicanin B**	**Niruriflavone**
		



Abbreviations

ABTS$^+$	2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)	**LDH**	Lactate dehydrogenase
ACE	Angiotensin-I converting enzyme	**LDL**	Low-density lipoprotein
Ach	Acetylcholine	**LOX**	5- lipoxygenase
AChE	Acetylcholinesterase	**LPS**	Lipopolysaccharide
AD	Alzheimer's disease	**MDA**	Malondialdehyde
ADA	Adenosine deaminase	**MEPA**	Methanolic extract of *Phyllanthus acidus*
AGEs	Advanced glycation end-products	**MFEPE**	Methanolic fruit extract of *P. emblica*
AGEs	Glycation end products	**MG**	Methylglyoxal
Akt	Ak strain transforming	**MGO**	Methylglyoxal
APP	Amyloid precursor protein	**mol**	Mole
ATPase	Adenosine triphosphatase	**MPO**	Myeloperoxidase
A$\beta_{1\text{-}42}$	Beta amyloid 1-42	**MS/MS**	Tandem mass spectrometry
Aβ 1-42	Amyloid beta1-42	**MTT**	3, -4,5 dimethylthiazol-2,5 diphenyl tetrazolium bromide
BChE	Butyrylcholinesterase	**NFLC**	Niruriflavone-loaded chitosan Nanoparticles
BSA	Bovine serum albumin	**NFT**	Neurofibrillary tangles
BuChE	Butyrylcholinesterase	**NO**	Nitric oxide
Bwtt	Body weight	**Nrf2**	Nuclear factor erythroid 2-related factor 2
CAT	Catalase	***P.***	*Phyllanthus*
CHOL	Total cholesterol	**p.o**	Taken by mouth, or orally
DOX	Doxorubicin	**p38**	Mitogen-activated protein kinases
DPPH	2,2-Diphenyl-1-picrylhydrazyl	**PA**	Passive avoidance
EDTA	Ethylenediaminetetraacetic acid	**PEFPs**	*P. emblica* fruit polyphenols
EEPEr	Ethanolic extract of ripe *P.emblica* fruit	**pIκ Bα**	Phosphorylated inhibitory subunit of NF-kappa- B alpha
EEPEu	Ethanolic extract of unripe *P.emblica* fruit	**pP65**	Phospho-NF-kappa-B p65 subunit
ELISA	Enzyme-linked immunoassay	**RA**	Rewarded alternation
EoT	Tannoid principles of *E. officinalis*	**RAGE**	Receptor for advanced glycation end products
ERK1/2	Extracellular signal-regulated kinase 1	**ROS**	Reactive oxygen species
FRAP	Ferric reducing antioxidant power	**SD**	Sleep deprivation
Glo-1	Glyoxalase I	**SOD**	Superoxide dismutase
GPx	Glutathione peroxidase	**SOD1**	Superoxide dismutase type 1
GSH	Glutathione	**STZ**	Streptozotocin
GSK-3β	Glycogen Synthase Kinase-3β	**TAU-5**	Tubulin associated unit-5
GSR	Glutathione reductase	**TBARS**	Thiobarbituric acid reactive species
GST	Glutathione-S transferase	**TEM**	Transmission electron microscopy
H&E	Stained using haematoxylin and eosin	**TG**	Triglyceride
HbA1c	Glycosylated Hb	**TNF-α**	Tumour necrosis factor-α
HNE	4-hydroxy-2-nonenal	**IL-1β**	Interleukin
i.p.	Intraperitoneal	**iNOS**	Inducible nitric oxide
IC_{50}	Half-maximal inhibitory concentration	**JNK**	Jun N-terminal kinase
IKK	Iκ B kinase	**kcal**	Kilocalorie

3. Experimental

VOS viewer visualization of scientific data concerned with *Phyllanthus* species

"VOS Viewer (Nees Jan van Eck and Ludo Waltman; Leiden; The Netherlands, version 1.6.17—© 2021) was used to generate a keyword map based on the analyzed literature using Web of Science, where the search included only *Phyllanthus.*

VOS viewer facilitates the identification and analysis of research clusters, highlighting key focus areas in *Phyllanthus* studies, particularly its biological activities.

3.1. Database search and initial screening

Two independent investigators (***Salma K. Gabr*** **and** ***Reham O. Bakr***) screened the literature by evaluating titles, abstracts, and full texts. In case of dissimilarity, another reviewer was consulted (***Mona M. Okba***). All documents were included in the primary search, then the list was refined by eliminating duplicates, and only one was kept. PubMed, Scopus, Taylor & Francis, Web of Science, and Wiley databases were searched in the period from 2000-2024 for the following terms: "*Phyllanthus*" in the title and "*Alzheimer*" and "*Neuroprotective*" in all fields except for Scopus, where the search begins in 2014.

3.2. Inclusion and exclusion criteria

The peer-reviewed articles, *in-vivo* and *in-vitro* studies, clinical trials, observational studies, studies involving animal models, or human participants diagnosed with neurodegenerative disorders were included in the inclusion criteria. **Interventions** include the use of *Phyllanthus* species extracts or isolated phytochemicals. O**utcomes** involving neuroprotective effects, reduction in neurodegeneration markers, improved behavioural outcomes, and enhanced neurogenesis have been investigated.

Exclusion criteria include review articles, non-English articles, book chapters, letters, conference papers, notes, manuscripts without full text available, short reports, and short surveys, studies with incomplete results or without IC_{50}, and any publications where the term "*Phyllanthus*" was only mentioned in the references.

3.3. Full review process and data Extraction

All included articles were cautiously scanned to confirm their relevance and adherence to the inclusion criteria, and related data from the included studies were extracted. Extracted data included study design, sample size, species and part of *Phyllanthus* used, dosage, duration of intervention, methods of neuroprotection assessment, and key findings related to *Phyllanthus* neuroprotective effects, antioxidant, anticholinesterase, anti-inflammatory, and active metabolites if available in the published paper.

4. Conclusions

In this systematic review, we comprehensively analyzed the current evidence on the neuroprotective potential of *Phyllanthus* species in the context of neurodegenerative disorders. The findings consistently highlight the genus's ability to mitigate oxidative stress, suppress neuroinflammation, and regulate apoptotic and cholinergic pathways. These effects were linked to key bioactive compounds, notably flavonoids and ellagitannins, which demonstrated antioxidant properties and inhibitory activity against enzymes such as acetylcholinesterase and butyrylcholinesterase.

Both in-vitro and in-vivo models supported the therapeutic promise of *Phyllanthus* extracts and isolated constituents, showing improvements in memory, motor function, and neuroinflammatory markers. Computational studies further supported these results by identifying potential molecular targets and strong binding affinities of several compounds with key enzymes implicated in neurodegeneration.

Overall, the evidence underscores the potential of *Phyllanthus* species as a valuable source for developing novel interventions against neurodegenerative diseases. However, further clinical studies are warranted to validate these preclinical findings and explore their translational applicability.

5. Conflicts of interest

In accordance with our policy on Conflict of interest please ensure that a conflicts of interest statement is included in your manuscript here. Please note that this statement is required for all submitted manuscripts. If no conflicts exist, please state that "There are no conflicts to declare".

6. Formatting of funding sources

This study did not receive any funding from any sector.

7. Acknowledgments

Not applicable.

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