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REVIEW

Exploring the neuroprotective benefits of phytochemicals extracted from indigenous edible fruits in Bangladesh

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Abstract

The increasing incidence of neurodegenerative diseases (NDs) and the constraints of existing treatment methods have spurred a keen interest in investigating alternative therapies. Medicinal plants, renowned for their long-standing use in traditional medicine, offer a hopeful avenue for discovering new neuroprotective agents. This study emphasizes the potential neuroprotective characteristics of edible fruit plants in Bangladesh, specifically focusing on their traditional folk medicine uses for neurological disorders. This study provides an in-depth overview of the different types of edible fruit trees in Bangladesh and their phytochemicals, including flavonoids, terpenoids, and phenolic acids. This work examines the scientific data supporting the neuroprotective properties of bioactive chemicals from plants. It further explores

ABBREVIATIONS: SCZ, Schizophrenia; cAMP, Cyclic adenosine monophosphate; iNOS, Inducible nitric oxide synthase; MAO-A, Monoamine oxidase A; FRAP, Ferric reducing antioxidant power; LOX, Lipoxygenase; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; SNL, Spinal nerve ligation; KET, Ketamine; Iba1, Ionized calcium-binding adapter molecule 1; AHP, After hyperpolarization potential; CPZ, Chlorpromazine; cGMP, Cyclic guanosine monophosphate; FST, Forced swim test; RSV-LPC, Retinyl stearate-lysophosphatidylcholine; NF-κB, Nuclear factor kappa B; TST, Tail suspension test.

Sumon Roy and Mehrukh Zehravi have contributed equally to this study.

the mechanisms by which these compounds work to counteract oxidative stress, decrease inflammation, and stimulate neurogenesis. Moreover, the study investigates toxicological characteristics and bioactive components of some fruits, emphasizing the importance of further investigation to measure their safety profile comprehensively. This thorough study highlights the potential benefits of Bangladesh's edible fruit trees as a rich source of neuroprotective chemicals. It also shows that additional research might lead to novel approaches for improving brain functioning and preventing NDs.

KEYWORDS
Bangladesh, edible fruit plants, neuroprotection, phytochemicals, traditional medicine

1 | INTRODUCTION

The term "neuroprotection" refers to the protection of the central nervous system (CNS) from neuronal damage caused by various neuropsychiatric and neurodegenerative diseases (NDs), including Parkinson's disease (PD), Alzheimer's disease (AD), anxiety, cerebrovascular impairment, meningitis, encephalitis, stroke, dementias, idiopathic epilepsy, schizophrenia, and multiple sclerosis (MS).[1,2] Emerging data suggest a global rise in the morbidity and mortality associated with neurological disorders, prompting growing recognition as a significant public health challenge in the coming decades.[3] Although communicable neurological illnesses have decreased over the past 30 years, the absolute number of fatalities has increased by 30%, and disability-adjusted life-years (DALYs), which are the total years of death and years spent with impairment, have increased by 15%. Low-income and middle-income nations (LMICs) bear the heaviest cost.[4] By the year 2040, it is predicted that NDs will rank as the second leading cause of mortality among older people.[5] The CNS and peripheral nervous system (PNS) are both affected by NDs, which are irreversible abnormalities of the CNS that may result from the continuous and cumulative loss of brain cells. Although several variables are known to contribute to the beginning of neurodegeneration, the key causative element is the production of free radicals by reactive oxygen and nitrogen species (ROS and RNS).[2] However, aging is regarded as one of the critical concerns in NDs. Other contributors to NDs include protein breakdown, numerous environmental triggers, mitochondrial anomalies, family history, and aberrant protein buildup in neurons.[1,6–8] In several animal models of stroke, brain injury, and spinal cord injury, the capacity of pharmacological medicines to reduce subsequent biochemical impairment and cell death has been well documented; nevertheless, the outcomes of similar neuroprotective therapy approaches in human disease have been dismal.[9]

Humans have traditionally employed goods derived from nature as an essential supplier of therapeutic substances to treat various diseases, sicknesses, and frailty. The adverse effects and dangerous nature of some natural compounds are also unknown to those taking these medications.[10] The Sumerian and Akkadian civilizations are known for using plants that have these medicinal compounds therapeutically. Fruits are known and regarded as endowed with magical power among all parts of the plant. The first food source recognized by humans is fruits. Fruits are frequently mentioned in classical literature. They are a great supplier of vitamins, enzymes, and nutrients. They have a cleaning impact on the blood and digestive system and are simple to digest. Moreover, fruits can treat illnesses caused by consuming unnatural meals. Thus, fresh and dried fruits are not only a healthy food but also a healthy remedy.[11]

South Asian countries, including Bangladesh, have various fruit-bearing plants. These evergreen trees grow all year-round. Many of these trees produce fruit that may be consumed by animals living in the scrub, and the locals also use some of these fruits for folk medicine.[12] Phenols, alkaloids, terpenoids, saponins, fatty acids, or polyunsaturated fatty acids are phytochemicals frequently present in various fruits. These phytochemicals can play a vital role in neuroprotection. Polyphenols present in fruit juice offer more neuroprotection than antioxidant vitamins. The phenolic compounds, such as catechins and epicatechins, are capable of safeguarding neurons against various oxidative and metabolic insults, including preventing dopaminergic neurons from being damaged by 6-hydroxydopamine (6-OHDA) in a rat model of PD and preventing retinal neurons from suffering from ischemia–reperfusion injury.[13] These phenolic compounds additionally have neuroprotective activities that are partially mediated by activating protein kinase C (PKC) and have been put forth as potential inhibitors of the etiology of AD and neuroprotectants.[14] By inhibiting age-related neurodegeneration, flavonoids regulate neuronal activity. Flavonoid-rich foods may help with learning and memory by shielding susceptible neurons, increasing current activity, or encouraging neuronal regeneration.[15] A large class of naturally occurring substances called alkaloids typically comprise oxygen, nitrogen, carbon, and hydrogen. Alkaloids may have an impact on the CNS, including the brain and spinal cord nerve cells, which regulate several direct bodily processes and behavior. They may also impact the autonomic nervous system.[16] Terpenoids, saponins, and fatty acids have a role in neuroprotection.[15] Wild edible fruits (WEFs) are often the only food source for rural populations of Bangladesh, who rely on

them to meet their nutritional needs. They rely on WEFs for both their daily dietary requirements and food security, as well as for their daily medical treatments and other therapeutic uses. These untamed food fruits significantly impact their quality of life and access to food. By providing a crucial safety net to the rural poor via nutritional supplements, WEFs perform a pivotal role.[17] In this review, different fruits that have a role in neuroprotection, and their phytochemicals responsible for neuroprotection, are available in the various regions of Bangladesh, generally used as edible food or traditional medicine.

2 | TRADITIONAL HERBAL PLANTS IN NEUROPROTECTION

Many fruit plants in Bangladesh possess neuroprotective properties. Here is a summary list of edible fruit plants and their conventional uses (Table 1).

3 | PHYTOCHEMICALS IN FRUIT PLANTS

Most of the fruit phytochemicals are polyphenols that are shown to have neuroprotective functions. Polyphenols are a class of chemicals that are widely distributed and very plentiful in the kingdom of plants.[62] The broad shikimate pathway and photosynthesis are both necessary for the synthesis of polyphenols in plants. Three essential amino acids, L-tryptophan, L-phenylalanine, and L-tyrosine are produced by this route. These amino acids contribute to the general growth and development of plants by acting as building blocks for vital proteins, hormones, pigments, complex aromatic compounds (such as phenylpropanoids and alkaloids), and the production of cell wall components.[63] Polyphenols come in many forms, from basic molecules like phenolic acids to more complex and highly polymerized substances like tannins. Usually found in conjugated forms, they frequently have one or more sugar residues attached to hydroxyl groups. On the contrary, there are also direct connections between the sugar unit and an aromatic carbon atom.[62]

3.1 | Phenolic acids

One of the major groups of polyphenols is phenolic acids.[64] Aromatic acid compounds with an organic carboxylic acid function and a phenolic ring are known as phenolic acids, often referred to as phenol carboxylic acids (Figure 1). Hydroxycinnamic and hydroxybenzoic acids are the two primary groups that comprise this particular class of polyphenols.[65] Therefore, hydroxylated benzoic or cinnamic acid derivatives are the source of all phenolic acids. Phenolic acids are biosynthesized by methylation, hydroxylation, and deamination. Let's sum up by saying that the amino acids phenylalanine and tyrosine can be deaminated to produce p-coumaric acid and cinnamic acid, which are not phenolic acids. Benzoic acid (C_6–C_1) is produced when cinnamic acid (C_6–C_3) loses its ethyl side chain.[66] Phenolic acids have been shown to have a variety of biological actions, such as being an antioxidant,[67] anti-inflammatory, anticancer, antidiabetic, antimicrobial, antimutagenic, antihypertensive, anticholesterolemic, and antineurodegenerative.[64–66,68–70] Phenolic acids exhibit an unexpected dose-dependent neuroprotective effect, contradicting the conventional assumption of higher dosage leading to increased efficacy. Studies have observed that lower concentrations (15–50 μmol/L) of caffeine acid dimethyl ether and ferulic acid ethyl ester are more effective in promoting neuroprotection compared to higher dosages (50–100 and 15 μmol/L, respectively).[64] A natural phenolic antioxidant, ellagic acid may be found in a wide variety of fruits and vegetables. Clinical investigations showed this compound's limited bioavailability. More specifically, plasma concentrations in human patients ranged between 30 and 200 ng m/L for both low and high oral administration.[71]

3.2 | Flavonoids

Flavonoids are the largest class of polyphenols; more than 2000 specific flavonoids have been identified.[72] Flavonoids are chemicals with a benzo-γ-pyrone structure that are widely dispersed. The route known as phenylpropanoid mediates their synthesis.[73] The core component of flavonoids is the flavan nucleus, derived from a 15-carbon skeleton with the configuration C_6-C_3-C_6. Two aromatic rings joined by a three-carbon chain define the structure of this flavonoid skeleton (Figure 1).[74] Flavonoids can be divided into several groups based on their molecular structure, such as anthocyanins and anthoxanthins.[72] Citrus flavonoids can cross the blood–brain barrier (BBB) and prevent neuronal degeneration. Examples of these chemicals are naringenin and hesperidin. Citrus flavonoid nobiletin reduces inflammatory responses and shows antineuroinflammatory properties. These results point to the therapeutic potential of flavonoids in the fight against cellular stress, making them attractive options for developing targeted drugs for managing NDs.[75] Brain-penetrant flavonoids that elevate cAMP levels might offer pleiotropic benefits by suppressing proinflammatory mediator production and inducing mitochondrial biogenesis by activating relevant transcription factors.[76] Research results suggest that flavonoids may prevent the emergence of NDs by inhibiting cellular stress responses.[75]

3.3 | Stilbene

Stilbenes are a class of metabolites produced from phenols ($C_{14}H_{12}$) (Figure 1). Stilbenes are chemical compounds having a compact structure, one phenyl group, and a central ethylene portion. The phenyl group is found at the extremities of the carbon

TABLE 1 List of edible fruit plants with potential source of neurotherapeutics and their conventional uses.

Sl. No.	Plant name	Family	Local name with the region	Traditional uses	References
1.	*Citrus maxima*	Rutaceae	Jambura	Epilepsy, leprosy, convulsive spasmodic cough, hemorrhage, hiccough, mental disorientation, nausea, chorea, headaches	[18]
2.	*Musa balbisiana*	Musaceae	Bichi kola	Bladder blocks, bronchitis, severe dysentery and diarrhea, ulcers, diabetes, hysteria, epilepsy, leprosy, and hemorrhages	[18]
3.	*Rosa centifolia*	Rosaceae	Golap	Diabetes, AIDS, AD (dementia), inflammatory diseases, and cardiovascular disorders	[18]
4.	*Morinda citrifolia* Linn.	Rubiaceae	Holdi Kachu, Noni	Instances of psychosis resembling schizophrenia	[19]
5.	*Ananas comosus* (L.)	Bromeliaceae	Pineapple	Used as antidepressant	[20]
6.	*Cassia fistula* L.	Fabaceae	Shonalu, Banor lathi	Nervous weakness, constipation	[21]
7.	*Lagenaria vulgaris*	Cucurbitaceae	Lau	To cure nerve illnesses, such as epilepsy, sleeplessness, and a high body temperature eliminates cardiac, gastrointestinal, and urologic issues	[18]
8.	*Nerium indicum*	Apocynaceae	Korobi	Asthma, cancer, epilepsy, skin conditions, inflammatory conditions, high body temperature, migraines, and high blood pressure and to heal a wound	[18]
9.	*Phyllanthus emblica*	Phyllanthaceae	Amloki	Jaundice, biliousness, colic, hyperacidity, inflammations, anemia, dysentery, hemorrhages, heart problems, headache, dizziness, and scorpion and snake bites	[18,22]
10.	*Crescentia cujete* L.	Bignoniaceae	Jummu makal	Brain disease	[23]
11.	*Hyptis suaveolens* (L.)	Lamiaceae	Tukma (pignut)	Physical weakness, sense of hotness in the head or head issues	[22]
12.	*Terminalia bellirica*	Combretaceae	Bohera	Loss of appetite, headache	[22]
13.	*Terminalia chebula*	Combretaceae	Horitoki	Loss of appetite, headache	[22]
14.	*Achyranthes aspera* L.	Amaranthaceae	Apang	Epilepsy, paralysis, anticonvulsant	
15.	*Carissa carandas* L.	Apocynaceae	Karamcha	Fruit insanity, headache, anticonvulsant, and epilepsy, serve as an aphrodisiac to soothe the nervous disorder	[22,24]
16.	*Colocasia esculenta* L.	Araceae	Mukhikachu	Nervous system disease, nerve tonic	[25]
17.	*Typhonium trilobatum* L.	Araceae	Ghetkaachu	Nervous debility and mental disorder	[26]
18.	*Areca catechu* L.	Arecaceae	Shupari	Stroke (Sa), AD, depression	[27,28]
19.	*Borassus fabellifer* L.	Arecaceae	Tal	Epilepsy	[22]
20.	*Phoenix sylvestris* L.	Arecaceae	Khejur	Nervous debility	[29]
21.	*Litchi chinensis*	Sapindaceae	Lychee	Neurodegenerative disease, diabetes, inflammation	[30]
22.	*Punica granatum* L.	Punicaceae	Anar (pomegranate)	Brain ischemia in newborns, impotency in males, AD, rheumatoid arthritis	[31]
23.	*Tamarindus indica*	Fabaceae	Tamarind	Sleep, epilepsy	[32]
24.	*Amomum aromaticum* Roxb.	Zingiberaceae	Elach	Mental and nervous system disorders, epilepsy	[33]
25.	*Withania somnifera* (L.) Dunal	Solanaceae	Aswagandha	Mental problem, AD, PD	[34]
26.	*Citrus grandis Osbeck*	Rutaceae	Jambura	Epilepsy	[35]
27.	*Aegle marmelos* (L.) Correa	Rutaceae	Bel	Dementia, SCZ, paralysis	[19]
28.	*Nigella sativa* L.	Ranunculaceae	Kalojira	Epilepsy, AD, PD, schizophrenia	[36]

TABLE 1 (Continued)

Sl. No.	Plant name	Family	Local name with the region	Traditional uses	References
29.	*Persicaria hydropiper* (L.)	Polygonaceae	Bishkatal	Epilepsy, acetylcholinesterase inhibitor	[37]
30.	*Benincasa hispida*	Cucurbitaceae	Chalkumra	Epilepsy, nervous system disorder Management of depressive illness	[38]
31.	*Citrullus lanatus*	Cucurbitaceae	Tarmuj	Neurodegenerative diseases, brain tonic (nervous debility)	[39]
32.	*Averrhoa carambola*	Oxalidaceae	Kamranga	AD, antitumor, analgesic, anthelmintic, antimicrobial, anti-inflammatory, antioxidant	[40]
33.	*Syzygium samarangense*	Myrtaceae	Zamrul	Analgesic, antidepressant, and anti-inflammatory	[41]
34.	*Syzygium cumini* (L.) Skeels.	Myrtaceae	Jam	Multiple sclerosis, anticonvulsant action, CNS action, anti-inflammatory action	[42]
35.	*Fragaria ananassa*	Rosacea	Strawberry	Reversing the neurodegenerative disease, PD, AD, antioxidant	[43]
36.	*Musa sapientum*	Musaceae	Kola (banana)	Anxiety, depression, and memory impairment	[44,45]
37.	*Ziziphus mauritiana*	Rhamnaceae	Boroi	Epilepsy, AD, PD	[46]
38.	*Cocos nucifera* L.	Arecaceae	Coconut (narikel)	Depressant and anticonvulsant action, antioxidant	[47]
39.	*Artocarpus heterophyllus*	Moraceae	Jack fruit (kathal)	Anxiety, antioxidant, anti-inflammatory effect	[48]
40.	*Spondias mombin*	Anacardiaceae	Amra	Neurological dysfunction, antioxidant	[49]
41.	*Carica papaya* L.	Caricaceae	Papaya	Memory enhancement, AD, antioxidant	[50]
42.	*Citrus aurantium* L.	Rutaceae	Orange (kamala)	Minimize CNS disorder, multiple sclerosis	[51]
43.	*Citrus limon*	Rutaceae	Lemon	Multiple sclerosis, PD, AD, memory problem	[52]
44.	*Cucumis sativus* L.	Cucurbitaceae	Shosha (cucumber)	AD, antiaging, hypertension	[53]
45.	*Vitis vinifera* L.	Vitaceae	Grpaes(angur)	AD, PD, prevent neuron death, antioxidant	[54]
46.	*Citrus paradisi*	Rutaceae	Grapefruit	Antidepressant, anxiolytic, antioxidant	[55]
47.	*Tamarindus indica*	Fabaceae	Tentul	Epilepsy	[32]
48.	*Malus domestica*	Rosaceae	Apple	AD, enhance memory	[56]
49.	*Mangifera indica*	Anacardiaceae	Mango (aam)	AD, PD, depression, anxiety	[57]
50.	*Elaeocarpus floribundus* Blume	Elaeocarpaceae	Jalpai (olive)	Dementia and schizophrenia, PD, AD	[58]
51.	*Diospyros malabarica*	Ebenaceae	Gaab	Anxiolytic, antidepressant, antibacterial	[59]
52.	*Cucumis melo* L.	Cucurbitaceae	Bangi (muskmelon)	AD, amentia, leprosy, dyspepsia	[60]
53.	*Phoenix dactylifera*	Arecaceae	Date palm	Huntington's disease	[61]

Abbreviations: AD, Alzheimer's disease; CNS, central nervous system; PD, Parkinson's disease.

double bonds. Stilbenes are sometimes known as Tran's stilbenes.[70] Although the human diet contains very little stilbenes, resveratrol is the most represented and researched polyphenol, as it is thought to be the primary source of health benefits. More specifically, several recent studies have shown that resveratrol has many health advantages for people, including antibacterial, antioxidant, anti-inflammatory, and anticancer properties. Resveratrol is found in high concentrations in red wine and grape juice, as it has been found in many different plants, especially in red grapes.[71] Potent antioxidants and resveratrols play a vital role in building stronger muscular tissue. They treat cancer, diabetes, heart disease, NDs, and inflammation. They are also used to regulate body metabolism.[77]

3.4 | Tannins

Tannins, classified as phenolic compounds with a high molecular weight between 500 and more than 3000 Da, are primarily present in the tissues inside the vacuoles of plants' leaves, bark, fruit, and roots. The two primary categories of tannins are hydrolyzable (HT) and condensed tannins (CT), based on their chemical makeup and

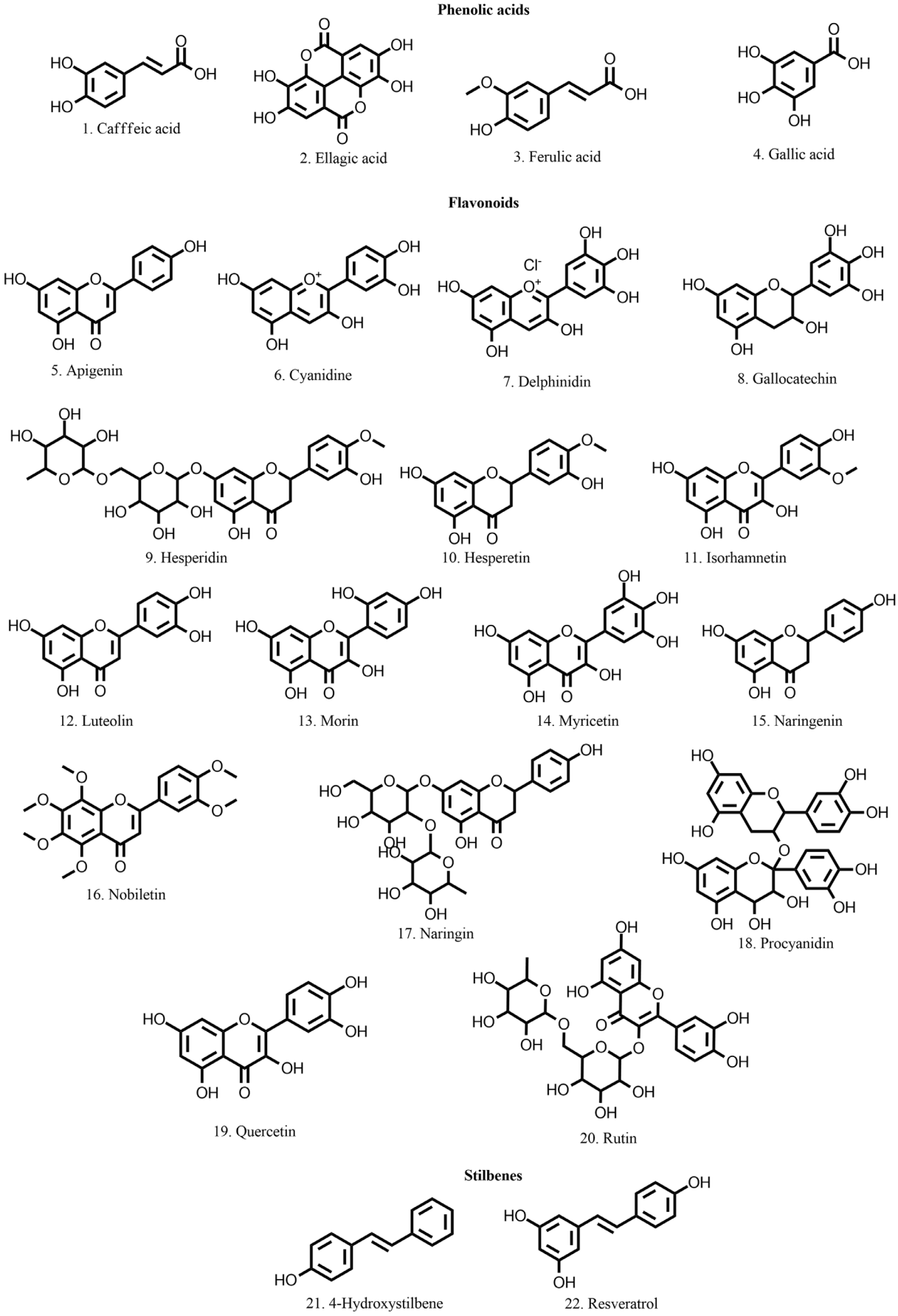

FIGURE 1 Chemical structures of phytochemicals present in edible fruit plants in Bangladesh.

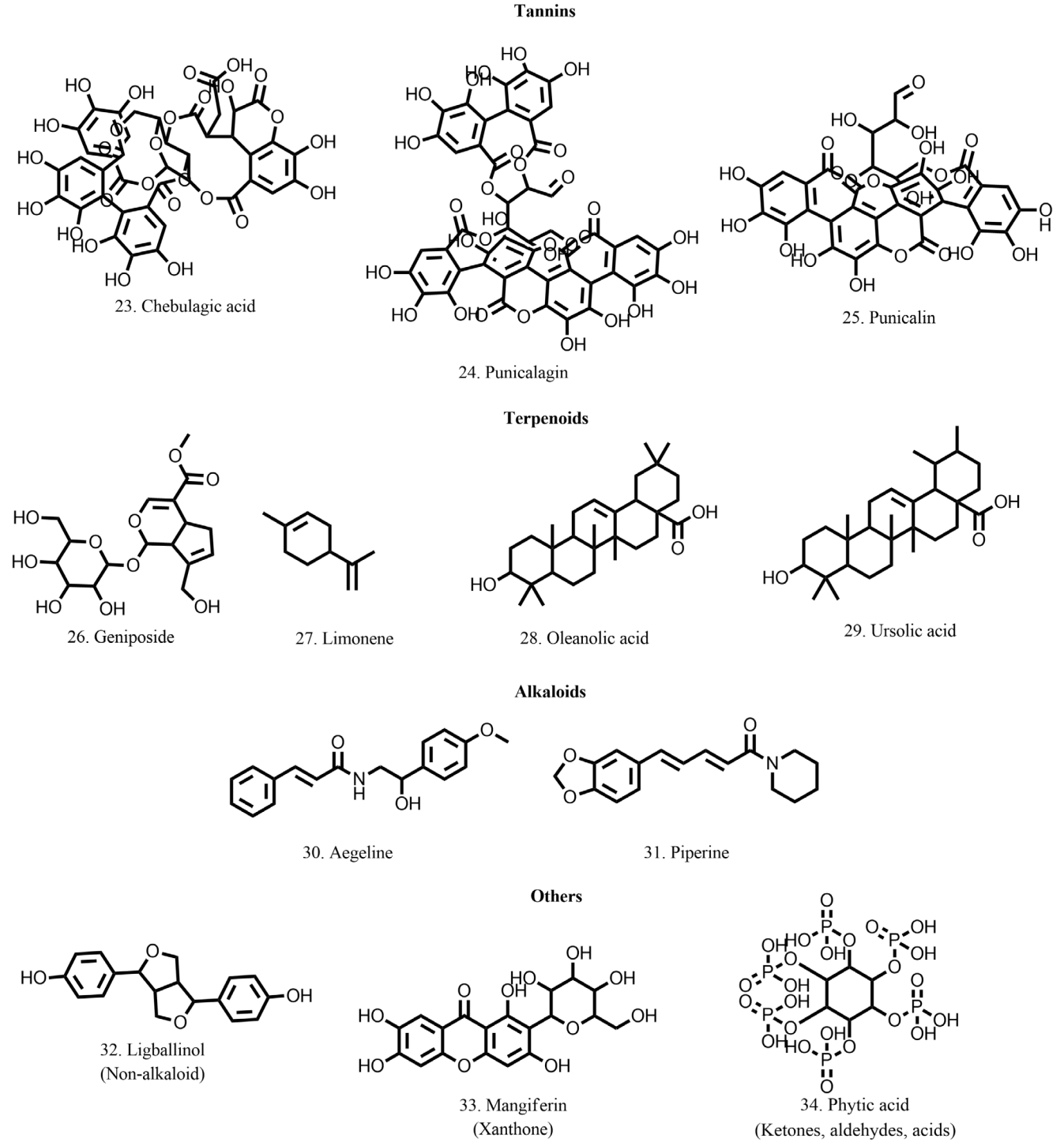

FIGURE 1 (Continued)

characteristics (Figure 1).[78] Regarding controlling health-related factors in every living creature, including humans, tannins are potent biological substances. Because of their many positive effects, they may be used to treat a wide range of illnesses. These characteristics include, among many others, anticancer, anti-inflammatory, antioxidative, and anticonvulsant effects. Significantly, research has shown their efficacy in the pathophysiology of numerous non-degenerative diseases (NDs), including AD, PD, and MS.[79]

3.5 | Terpenoids

In the past, the hydrocarbon $C_{10}H_{16}$, frequently included in essential oils such as turpentine, was referred to as "terpene." Likewise, compounds that had been oxygenated were called "camphor." Terpenoids are found in most plant portions, although they are more concentrated in flowers and fruits, where they help to produce the volatile oils that give plants their distinctive fragrances.

Terpenoids are an essential family of naturally occurring chemicals produced by cyclizing squalene epoxide. This process creates a framework of isoprene units with five carbons that are connected head-to-tail. "Triterpenoid" refers to a class of naturally occurring chemicals with 30 carbon atoms based on 6 isoprene units.[80] By preventing amyloid beta (Aβ) from binding to microglia, ursolic acid (UA) reduces the production of proinflammatory cytokines and neurotoxic ROS. This leads to an effect that is neuroprotective against Aβ.[81] As a triterpene, oleanolic acid (OA) has been shown to possess neuroprotective qualities because of its anti-inflammatory and antioxidant characteristics.[81] Therefore, triterpenoids may be used to treat or prevent NDs, such as AD, PD, MS, and Huntington's disease (HD).[80]

3.6 | Alkaloids

Alkaloids are a broad class of around 12 000 naturally occurring substances.[82] The paramount need for being categorized as an alkaloid is having a basic nitrogen atom (Figure 1)[83] in any position within the molecule; this excludes nitrogen found in amide or peptide bonds. This in-depth description indicates that alkaloids are a group of structurally diverse and biogenically unrelated compounds.[82] Alkaloids are well known for being a reliable source of therapeutic chemicals that may be used to treat long-term illnesses, including cancer, diabetes, and NDs.[84] Plant-derived alkaloids have been recognized as possible preventive agents against mental diseases, a variety of other maladies, and neurodegenerative disorders, including AD and PD. These substances provide unique lead compounds for pharmaceutical research. Because of their diverse mechanisms of action, alkaloids can be used as starting materials to make novel medications or, to a lesser extent, to treat problems related to NDs.[85] Neuroprotection, neurogenesis, neuroinflammation, tau hyperphosphorylation, and Aβ aggregation are among the pathways that alkaloids affect.[84] Piperine treatment has shown promise in mitigating behavioral aberrations and neurological deficiencies in preclinical experiments using animal disease models. Examples include its ability to prevent maximal electroshock seizures (MES), increase sucrose consumption, raise plasma corticosterone levels in response to mild chronic stress, and improve cognitive deficits caused by streptozotocin (STZ).[86] Computational modeling (in silico docking) suggests aegeline, a molecule from *Aegle marmelos* fruit, readily binds to the active sites of iNOS and MAO-A enzymes. This was further supported by in vivo studies where both *A. marmelos* fruit extract (AMFE) and purified aegeline were significantly reduced. Furthermore, there was an increase in decreased glutathione levels compared to the group that received reserpine treatment. Additionally, the iNOS expression increase generated by reserpine was offset by AMFE and aegeline, based on immunofluorescence tests. These results indicate that AMFE and aegeline may have a protective impact by reducing oxidative and nitrosative stress, interleukin-6 (IL-6) levels, and MAO-A hyperactivity.[87]

3.7 | Others

There are more categories for other chemical components as well. A few examples (32–34) include the nonalkaloid ligballinol, the xanthone mangiferin, and the phytic acid (PA) (which belongs to the ketones, aldehydes, and acids) (Figure 1). These substances show neuroprotective qualities against several NDs, including PD and AD.

4 | PHARMACOLOGICAL ACTIVITY IN VITRO AND IN VIVO

4.1 | Alzheimer's disease

AD, a common and untreatable condition affecting older people, damages brain cells. Two hallmarks define it: sticky clumps of protein outside brain cells (amyloid plaques) and tangled protein fibers inside cells (neurofibrillary tangles). Most AD cases (sporadic AD) involve both environmental and genetic factors. The first identified gene linked to AD, called APOE, influences susceptibility. In contrast, rare cases of familial AD are caused by specific gene mutations inherited from parents. These mutations affect genes involved in making or disposing of amyloid proteins, like APP, PSEN1, and PSEN2. Studying these gene mutations led to the "amyloidogenic cascade" theory, suggesting that AD starts with too much amyloid building up in the brain. This theory is still actively researched and debated.[88] AD is the prevailing type of dementia, accounting for 60%–80% of all dementia cases.[89] According to Alzheimer's Disease International, approximately 44 million individuals worldwide are currently affected by AD or a related form of dementia. This global figure is projected to rise to 65.7 million by the year 2030. AD is recognized as a significant economic challenge in many developed nations. Research indicates that by 2030, the cost associated with AD, including caregiving expenses, will reach $7 billion in the United States alone. Currently, the prevalence of this condition is higher in developed countries, in line with their larger elderly populations. In contrast, Bangladesh, with its predominantly rural population and high population density, demonstrates relatively little awareness or concern about AD among the general population.[90]

Terminalia chebula fruit extracts were found to block enzymes linked to AD, namely acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). By analyzing the plant's natural chemicals, researchers discovered a substance called 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose. This compound potently inhibited AChE and BChE, with half-maximal IC_{50} of around 29.9- and 27.6 μM, respectively. The compound 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose holds promise as a potential natural source for combating AD due to its noteworthy AChE and BChE inhibitory properties. Additionally, it displayed strong antioxidant activity, as determined by the FRAP assay, with an IC_{50} value of about 4.6 ± 0.2 μM.[91] A study demonstrated that the ethyl acetate fraction, administered at doses of 1, 5, 15, and 25 mg/mL, exhibited inhibitory effects on AChE at rates of 29.36%, 32.44%, 45.82%, and 62.32%, respectively. In a

comparable in vitro investigation, Vinutha et al. employed methanolic and aqueous extracts from *T. chebula* fruit, and their findings revealed that the IC_{50} values for the aqueous extract of *T. chebula*, which showed a minimum inhibition rate of 12.45%, exhibited greater potency than the methanolic extract, where the minimum inhibition rate was 1.21%.[92] Reports indicate that gallic acid and ellagic acid, extracted from *T. chebula*, have demonstrated the ability to inhibit AChE. These findings also propose that tannins might be the active constituents within *T. chebula* responsible for its potential impact on neurodegenerative conditions.[93] An in vitro study found that the fresh juice obtained from *Citrus hystrix* and *Citrus maxima* fruits exhibited potent anticholinesterase activity, with values ranging from 75.71% to 79.74%. Among these fruit juices, *C. hystrix* displayed the most robust activity, followed by *C. maxima* (red) and *C. maxima* (white).[94] Researchers discovered that the best way to extract valuable compounds from the white inner layer (albedo) of pomelo (*C. maxima*) was to use a 50% alcohol–water solution at room temperature for 4 h. This method yielded extracts rich in antioxidants and other beneficial plant chemicals, especially hesperidin and naringenin. Notably, the extract showed the strongest ability to inhibit an enzyme linked to AD, suggesting potential therapeutic applications.[95] In an experiment, rats subjected to a high-fat diet (HFD) for 9 weeks exhibited cognitive deficits when tested using the Y-maze, NORT, and EPM tasks. Specifically, the HFD-fed rats displayed reduced correct alternation in the Y-maze test and a lower discrimination index in the NORT. As assessed by the NORT, it is well documented that high-fat diets have previously been linked to impaired spatial learning in the Y-maze paradigm and deficits in nonspatial memory. However, when the rats were administered the peel extract of *Ananas comosus* fruit (PEAC) for 4 weeks, the memory impairment induced by the HFD was reversed. It's worth noting that a prior study had reported the cognitive-enhancing effects of pineapple juice in a model of amnesia induced by scopolamine.[96] In an in vivo study, it was observed that both pineapple juice and an ethanolic pineapple extract, administered intraperitoneally at doses of 50, 75, and 100 mg/kg, effectively re-established the mice's capability to recognize objects. This outcome was particularly notable in mice previously receiving scopolamine treatment at 100 µL, 1 mg/kg intraperitoneally. These results strongly indicate that pineapple possesses a protective function against amnesia induced by scopolamine, pointing to its potential in addressing cognitive disorders.[97] Amla fruit extract, packed with powerful compounds, called emblicanin A and B, shielded mice brains from aluminum chloride's damaging effects. When given daily for 60 days at a dose of 100 mg/kg, the extract countered cell death mechanisms linked to AD. This protection regulated key proteins like Bax, cytosolic cytochrome c, and caspase enzymes. Interestingly, the extract also lowered the activity of an enzyme linked to memory loss in the cerebellum. Similar findings were observed in another experiment, where amla extract again modulated protein expression and reduced harmful changes in a protein associated with AD. Moreover, researchers discovered that the extract protected brains by influencing a specific signaling pathway crucial for brain health.[98] In vitro investigations have revealed that methanol extracts from *Phyllanthus emblica* fruits effectively inhibit the AChE enzyme, with an IC_{50} value of less than 100 µg/mL. This inhibition is significant because it addresses one of the primary factors contributing to cholinergic dysfunction seen in AD. Furthermore, Biswas and colleagues have reported that the crude methanol extract from *P. emblica* (FPE) demonstrates inhibitory effects against both AChE (IC_{50} 53.88 µg/mL) and BChE (IC_{50} 65.12 µg/mL). A separate study by Thenmozhi and associates highlighted that tannin compounds derived from *P. emblica* effectively reversed disruptions in the brain associated with alterations in aluminum concentration, AChE activity, and Aβ synthesis-related molecules. This, in turn, led to decreased AChE activity and improved performance in neurobehavioral tests among rodents treated with *P. emblica*. These results indicate the promising potential of *P. emblica* in treating AD.[99] A study observed that extracts from *P. emblica* L. (Indian gooseberry) fruit effectively shielded the retinas of mice from the harmful effects induced by Aβ. The primary components within this extract, namely hydrolyzable tannins and their glycoside derivatives, are believed to be potential active agents. This is attributed to their strong antioxidative capabilities, neutralizing free radicals and augmenting protein levels in genes like SIRT1.[93] In an experiment, mice afflicted with AD were given diets enriched with 2% and 4% acetone-extracted date palm fruit over 14 months. The outcomes were then compared to those of mice receiving a standard control diet. Notably, when mice were fed date palm fruit at these 2% and 4% levels, there was a significant reduction in oxidative stress (OS) markers, such as protein carbonyl levels and lipid peroxidation. Additionally, there was an observable restoration of anti-OS enzymes.[100] In a research investigation, green fruits of *Momordica charantia* were employed for extracting various compounds, and their anticholinesterase potential was assessed. Among the identified plant compounds, ligballinol exhibited the most noteworthy inhibitory effect against BChE, with an IC_{50} value of 32.20 µM. Importantly, this inhibition was observed to be both reversible and noncompetitive.[101] Piperine is a nitrogen-based alkaloid found in the fruits of black pepper (*Piper nigrum*) and long pepper (*Piper longum*), belonging to the Piperaceae family. Experimental trials conducted with animal models have confirmed the neuroprotective properties of this potent alkaloid. In these experiments, male Wistar rats were orally given varying doses of piperine, both 2 weeks before and 1 week after the bilateral intracerebroventricular administration of ethylcholine aziridinium (AF64A) ion. It's worth noting that ethylcholine aziridinium can induce cholinergic effects, which are relevant to AD patients.[102] The fruit known as *Carica papaya* is widely recognized for its medicinal properties. In SH-SY5Y cells subjected to amyloid-induced conditions, copper can induce neurotoxic effects. However, treatment with fermented papaya preparation (FPP) has been observed to reduce the generation of ROS, decrease nitric oxide (NO) production, and enhance cell viability in these cells. Although the precise mechanism of action remains unclear, it is

believed that FPP mitigates cell apoptosis by influencing the bax/bcl-2-sensitive pathway.[102] *Artocarpus* genus is rich in the antioxidant hydroxyl stilbene, specifically 2,4,30,50-transtrihydroxystilbene, abbreviated as OXY. OXY bears similarities to resveratrol but distinguishes itself by having an additional hydroxyl group, which functions as a hydrogen donor. OXY has demonstrated neuroprotective properties in cortical neurons subjected to Aβ-induced neurotoxicity. Furthermore, when SH-SY5Y cells were pretreated with OXY, it mitigated neurotoxicity induced by 6-OHDA. The toxic effects of Aβ-induced damage are attributed to OS and increased intracellular calcium levels. OXY has been reported to modulate Aβ-induced neurotoxicity by reducing cytosolic calcium levels, curtailing the generation of ROS and limiting glutamate release.[102]

In a study to explore the potential treatment of AD, researchers administered geniposide, a compound found in Gardenia fruits, to mice with the disease. Chronic treatment significantly improved synaptic function and restored mitochondrial transport in nerve cells, with increasing benefits at higher doses. This improvement was linked to increased levels of proteins crucial for memory and communication between brain cells. Further investigation revealed geniposide's protective effects on brain cells by reducing inflammation, clearing harmful protein deposits, and enhancing brain activity. Additionally, geniposide was shown to improve cognitive function in treated mice, possibly by regulating other proteins involved in memory formation and reducing harmful protein buildup. These findings suggest that geniposide may hold promise as a potential therapeutic agent for AD. However, further research is needed to fully understand its mechanisms and confirm its effectiveness in humans.[103] In a study involving dementia model mice induced by scopolamine, an extract known as GJ-4, enriched with crocin and derived from *Gardenia jasminoides* fruits, demonstrated that the most effective dosage range was between 25- and 100 mg/kg. The administration of GJ-4 significantly and dose-dependently improved the memory and cognitive abilities of mice injected with Aβ25-35.[104] In an in vitro investigation, it was observed that *Cocos nucifera*, when administered at doses of 250–500 μg/mL, significantly inhibited the activity of brain AChE. However, there were no notable differences in AChE activity between the control group and those treated with *Cymbopogon citratus* and *Nauclea latifolia*. These findings suggest that *C. nucifera* might elevate acetylcholine levels in the brain, potentially countering deficits in acetylcholine associated with brain conditions induced by OS.[105] A preclinical study investigated the neuroprotective potential of mangiferin, a xanthone compound, against neurodegeneration. Mangiferin demonstrated significant protective effects on neuronal cells (Neuro 2A) with a potent level of protection (59.79%). Furthermore, it exhibited inhibitory activity against enzymes implicated in AD pathology: AChE and LOX, with IC_{50} values of 55.42- and 42.28 μg/mL, respectively. Additionally, mangiferin displayed robust antioxidant properties (IC_{50} values: 18.50 μg/mL by DPPH, 17.76 μg/mL by FRAP, and 11.70 μg/mL by phosphomolybdenum complex method). In a scopolamine-induced memory impairment model (pole climbing and Morris water maze), oral administration of mangiferin (100 mg/kg) significantly reversed scopolamine-induced memory deficits. These findings suggest that mangiferin, potentially due to its polyphenolic structure, might offer multifaceted benefits in mitigating AD progression.[106] Morin is a compound found in guava fruits (*Psidium guajava* L.) and has shown promise in benefiting various human diseases. Morin shows promise in combating AD. This natural compound inhibits an enzyme (glycogen synthase kinase 3) linked to the disease, even at low doses. Laboratory studies confirmed its effectiveness in reducing harmful protein changes, with similar results in animal models. Morin also targets another key enzyme (β-secretase 1) involved in AD's development, potentially slowing disease progression. Morin effectively inhibits β-secretase 1, with an IC_{50} value of approximately 20 μM.[107]

Resveratrol, a polyphenolic compound known as 3,5,4′-trihydroxystilbene, is commonly found in various fruit plants, with grapes and grape derivatives being notable sources. Recent efforts have focused on developing nanostructures loaded with resveratrol to target the brain. This interest arises from resveratrol's pharmacological potential as an anti-inflammatory and antioxidant agent. One approach involved creating lipid-core nanocapsules, measuring around 249 ± 5 nm, and loading them with resveratrol (RSV-LPCs) using interfacial polymer deposition. These RSV-LPCs were then tested on an AD animal model. The outcomes established that RSV-LPCs effectively mitigate neuronal impairments induced by Aβ1–42 treatment, leading to improved memory function and reduced synaptic damage.[108] In a research study, the optimized nanoemulsion formulation achieved a resveratrol concentration of 2.6442 mg/mL. Both in vitro drug release experiments conducted in pH 6.8 phosphate buffer and in vitro permeation studies using goat nasal mucosa demonstrated the superior performance of this nanoemulsion formulation. When administered intranasally to rats at a resveratrol dosage of 2 mg/kg, the nanoemulsion formulation effectively targeted the brain. In summary, this study highlights the advantages of consuming resveratrol-rich fruits, and incorporating it into a nanoemulsion system holds promise as a potential alternative for AD management.[109] Quercetin therapy, particularly in aluminum chloride–induced conditions, has displayed a protective role. This protection is achieved through reducing oxidative stress, inhibiting AChE, and enhancing cognitive and behavioral functions, as evidenced in a zebrafish model of AD. In an AD rat model induced by aluminum chloride, the utilization of quercetin nanoparticles (QNPs) effectively prevented the formation of neurofibrillary tangles (NFTs) and amyloid plaques, increasing the activity of tyrosine hydroxylase (TH), thereby improving neuronal function. This suggests that QNPs hold the potential for delaying or preventing the onset of AD. Furthermore, in transgenic AD model mice, quercetin reduced Aβ-mediated cytotoxicity (Figure 2), mitigated tauopathy and histopathological symptoms, and enhanced cognitive and emotional functions without causing adverse effects.[110] Naringin (40- and 80 mg/kg, p.o.) exhibited

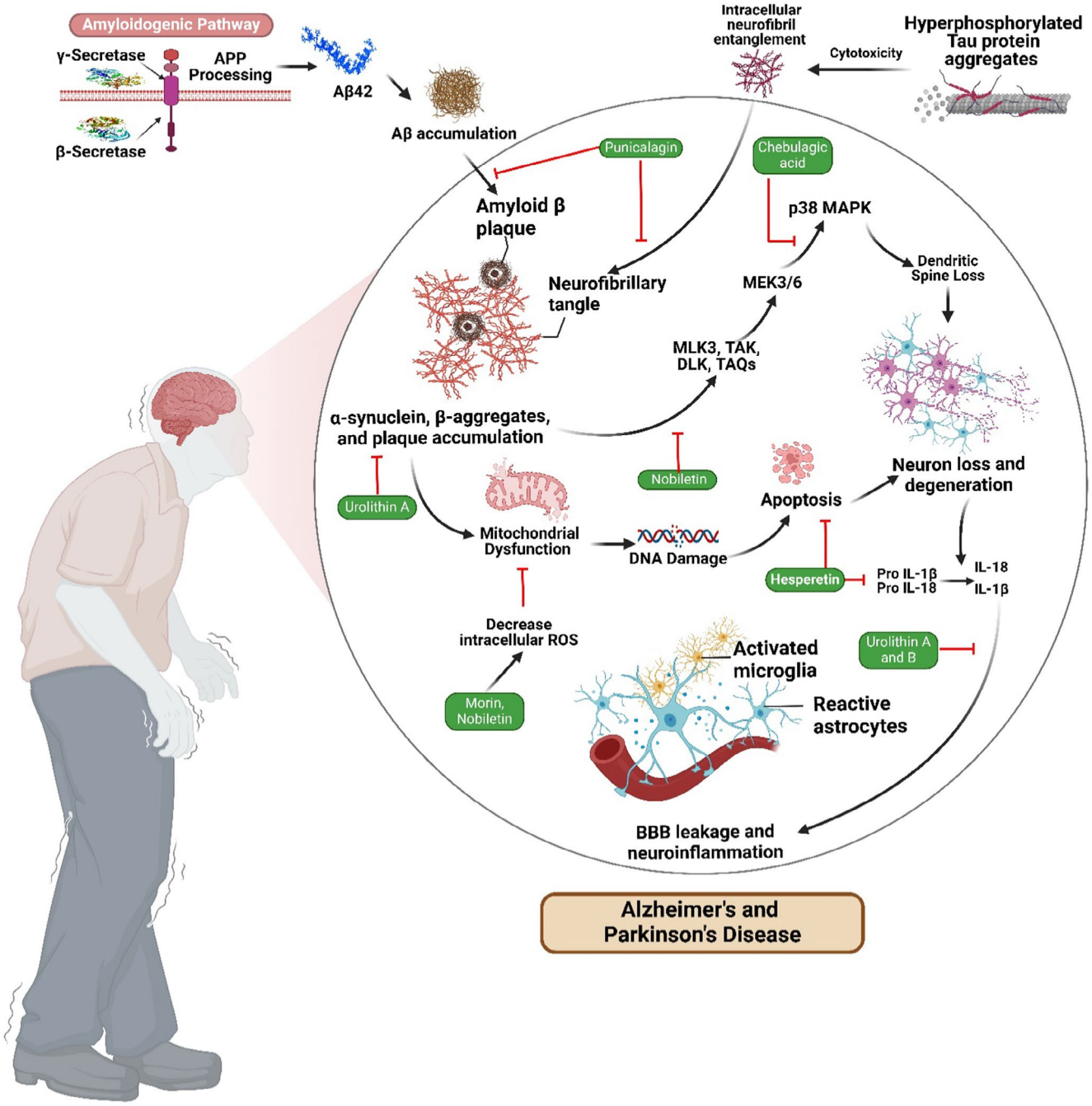

FIGURE 2 Illustration representing the role of edible fruit bioactive compounds in Alzheimer's and Parkinson's disease.

anti-Alzheimer's effects in rats with colchicine-induced cognitive impairments. Colchicine, administered intracerebroventricularly at a dose of 15 μg/5 mL, was responsible for inducing poor memory retention and reducing AChE activity in both models.[111] In the AD model, it was observed that limonene exhibited antioxidant and anti-inflammatory properties and demonstrated a neuroprotective impact against Aβ-induced cytotoxicity. However, the exact mechanism of its action remains unclear.[110] Another study showed in vitro and in vivo information indicating that anthocyanins and secondary metabolites have the potential to function as antioxidants by stimulating antioxidant pathways. As a result, these compounds could be advantageous in preventing age-related neurological conditions, such as AD.[112] Anekonda et al. investigated the protective potential of PA in countering Aβ pathology, both in MC65 cells and a Tg2576 mouse model. Their results revealed that a concentration of 100 mM of PA exhibited a neuroprotective impact in the cell culture model (MC65). Moreover, at the same concentration, PA treatment offered complete protection against Aβ-induced cytotoxicity by diminishing hydrogen peroxide levels (Table 2).[121]

TABLE 2 Experimental evidence regarding the use of edible fruit plants in neuroprotection.

Disease name	Plant name	Solvent extract	Phytochemicals	Dose	Model	Outcome	References
Memory loss	*Cuminum cyminum*	Aqueous	Fruit essential oil (FEO)	100, 200, and 300 mg/kg body weight	Wistar rats	Attenuate scopolamine-induced memory loss	[113]
Depression	*Citrus* sp.	–	Apigenin (4′,5,7-trihydroxyflavone)	(20 mg/kg, intragastrically)	Adult male Sprague–Dawley (SD) rats	Apigenin reduces inflammation by boosting a protective molecule (PPARγ) and blocking an inflammatory trigger (NLRP3), leading to less inflammatory protein	[114]
Memory problem	*Citrus limon and Puncia granatum*	Juice	Flavonoids (flavones, flavanols, and anthocyanins)	0.4 mL/kg *C. limon* + 5 mL/kg pomegranate and 0.2 mL/kg *C. limon* + 8 mL/kg pomegranate	Adult albino mice	Associated with improved cognitive function, including short-term memory	[115]
Parkinson's disease	*Citrus* sp.	–	Hesperetin	50 mg/kg for 1 week	6-OHDA-induced PD rats	Promoted brain health by regulating Nrf2, lowering inflammation, and stopping cell death, leading to better movement	[52]
Parkinson's disease	Nuts, banana, and mango	–	Phytic acid (IP6)	30 and 100 μmol/L	Cell line (1RB3AN27)	Pretreatment with IP6 effectively mitigates 6-OHDA-induced cellular apoptosis, regardless of normal or iron-excess conditions	[116–118]
Parkinson's disease	*Morus alba*, *Psidium guajava*	–	Morin	5–50 μmol/L and 5, 20, 40, or 100 mg/kg body weight	Male B57/BL mice	Protects against cell death, brain damage, and movement problems caused by MPP+	[119,120]
Alzheimer's disease	Nuts, banana, and mango	–	Phytic acid (IP6)	100 μM	MC65 cells	Demonstrated protective effects by reducing ROS, β-amyloid aggregates, and activating autophagy through beclin-1 upregulation	[121]
Parkinson's disease	*Terminalia chebula* and *Phyllanthus emblica*	–	Chebulagic acid	1.56, 3.13, 6.25, 12.5, and 25 μM	SH-SY5Y cell lines	Activates autophagy in brain cells (SH-SY5Y), potentially protecting them from damage caused by MPP+	[122]
Parkinson's disease	*P. granatum*	Juice	Ellagitannins (urolithin A)	500 mg/kg body weight/day	Male albino Wistar rats	Exhibits postural stability improvement, enhanced neuronal survival, protection against oxidative damage, and α-synuclein aggregation	[123]
Alzheimer's disease	*P. granatum*	Pomegranate juice extract (PJE)	Polyphenols	4% pomegranate fruit diet	APPsw/Tg2576 mice	Shows notable memory, learning, and locomotor function improvement, along with reduced anxiety	[124]

TABLE 2 (Continued)

Disease name	Plant name	Solvent extract	Phytochemicals	Dose	Model	Outcome	References
Alzheimer's disease	*P. granatum*	Pomegranate extract (POMELLA)	Ellagitannins (urolithin A and B)	100 or 200 mg/kg/day for 3 weeks	SH-SY5Y cell, transgenic (R1.40) mice	Attenuate neuroinflammation	[125]
Alzheimer's disease	*P. granatum*	–	Punicalagin (PUN)	1.5 mg/kg; administered in drinking water every day for 4 weeks	Male ICR mice	Inhibits lipopolysaccharide-induced memory impairment via anti-inflammatory and anti-amylogenic mechanisms through inhibition of NF-kB activation	[126]
Alzheimer's disease	*Citrus* sp.	–	Nobiletin	30 mg/kg	3XTg-AD	Improves short-term and recognition memory, reduces Aβ1-40 levels, and lessens free radical generation in the hippocampus	[127]
Multiple sclerosis	*Citrus* sp. (lemon and orange)	–	Hesperidin (HP)	50 or 100 mg/kg/day	C57BL/J6 female mice	Antiapoptotic effect via downregulating caspase3-like immunoreactivity	[128]
Depression	*Citrus* sp.	–	Naringenin	2, 5, 10, 20, and 50 mg/kg	Male ICR mice (24 ± 2 g)	Potent antidepressant-like property via serotonergic and noradrenergic systems	[129]
Multiple sclerosis	Lemon, *T. chebula*	–	Luteolin	1–100 μm	Jurkat cells, clone E6-1	Inhibit myelin basic protein-induced human mast cell activation	[130,131]
Alzheimer's disease	Banana and papaya	Ethanol	Delphinidin, rutin, quercetin, gallocatechin and cyanidin, gallic acid, caffeic acid, isorhamnetin, and ferulic acid	200 and 400 mg/kg, p.o	Alzheimer's-induced rats	Antioxidant activity, spatial long-term memory enhancement	[132]
Neuropathic pain	*P. guajava*, *Syzygium cumini*	–	Myricetin	0.1–10 mg/kg intraperitoneal, 0.1–5 μM (low), 10–100 μM (high)—in vitro	Adult male Wistar rats	Reduces SNL-induced mechanical allodynia and thermal hyperalgesia	[133,134]
Neuropathic pain	*Citrus* sp.	–	Hesperetin	20, 50 mg/kg	Wistar rats	Reduces pain sensitivity and inflammatory markers in a nerve injury model	[135]
Neuropathic pain	*Citrus* sp., apples, strawberries	–	Quercetin	0.1, 1%	Male SD rats	Inhibition of satellite glial cells	[136]
Neuropathic pain	*Citrus* sp., apples, strawberries	–	Quercetin	10–100 mg/kg	SD rats	Alleviate SNL-induced thermal and cold hyperalgesia	[137]

(Continues)

TABLE 2 (Continued)

Disease name	Plant name	Solvent extract	Phytochemicals	Dose	Model	Outcome	References
Multiple sclerosis	*Syzygium cumini*, *Artocarpus heterophyllus*, *Morus rubra*	–	Resveratrol	100 mg/kg/day per 30 days	C57BL/6 mice	Inducing apoptosis in spinal cord T cells reduces inflammatory symptoms and proinflammatory markers	[138,139]
Anxiety and depression	*Musa sapientum*	Fruit pulp and peel extract	Flavonoids, polyphenols	400 mg/kg	Male Albino Wistar mice	Reduces immobility time and strengthens memory, possibly through antioxidants, and lessens anxiety/fear, improving short- and long-term memory	[45]
Anxiety	*Citrus* sp.	Fruit peel extract	Naringenin	50 mg/kg/day	Male rats of the Wistar strain	Naringenin regulates ectonucleotidase activity and expression, including enzymes like ATP diphosphohydrolase and 5′-nucleotidase	[140,141]
Alzheimer's disease	*Averrhoa carambola*	–	2-Dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione. Proteins	5, 10, and 20 μmol/L	SH-SY5Y cells	Cell viability loss and apoptosis ↓; Bax, caspase-3, caspase-8 and caspase-9 protein expression levels ↓; Bcl-2 protein expression ↑	[142]
Epilepsy	*Citrus* sp.	–	Naringenin 4′,7- dimethyl ether		Zebrafish and mice model	Antiepileptic effects by suppressing seizures	[10]
Huntington's disease	*P. granatum*	Seed oil	6,9-octadecadiynoic acid	40 μM	PC12 cells	Neutralize ROS; antioxidant gene expression↑	[61,143]
Impaired motor coordination	*Flacourtia jangomas* (Lour.) Raeusch	Seed and fruit extracts of	–	200, 400, and 600 mg/kg	Rodents	Modulate the GABAergic system without causing excessive sedation or motor impairment	[144]
Schizophrenia	Citrus fruits, tomatoes	–	Ascorbic acid	–	Amphetamine-induced mice model	Decrease in serum MDA; decrease ROS formation; upregulation of NMDAR	[145–147]
Schizophrenia	Mulberry, guava, almond	–	Morin	–	KET-induced mice model	Increase BDNF expression and GABAergic neurotransmission; downregulates Nox-2-induced oxidative damage and NF-κB expression	[148,149]

Abbreviations: ATP, adenosine triphosphate; PPARγ, proliferator-activated receptor γ; ROS, reactive oxygen species.

4.2 | Parkinson's disease

PD is a neurological condition that worsens over time and is characterized by motor dysfunctions such as tremor, stiffness, bradykinesia, and postural instability.[150] In most populations, around 3%–5% of cases of PD can be attributed to specific genetic factors associated with known PD genes, which falls under the category of monogenic PD. On the contrary, a group of 90 genetic risk variations collectively accounts for 16%–36% of the inherited risk for non-monogenic PD. Furthermore, additional factors that can increase the risk of PD include having a family member with the condition or experiencing symptoms like tremors and constipation.[151] The second leading neurodegenerative condition, PD affects 1% of people over 60 globally.[152]

A recent study used highly concentrated pomegranate juice (500 mg/kg body weight per day) to treat rotenone-induced PD models. The juice treatment began 11 days before the rotenone administration, and the results showed significant decreases in α-synuclein clustering and neural cell apoptosis. Additionally, this intervention produced substantial enhancements in postural stability.[108] Mulberry, the fruit of *Morus alba* from the Moraceae family, showed promising effects in mitigating neurotoxicity induced by 6-OHDA in SH-SY5Y cells. A 70% ethanol extract of mulberry at a 100 μg/mL concentration exhibited its neuroprotective properties by combating OS and apoptosis. It achieved this by inhibiting the generation of ROS and NO, preserving mitochondrial membrane potential, and reducing caspase-3 activity. Additionally, it played a role in regulating the expression of Bcl and Bax proteins. Furthermore, researchers created an in vitro model of 1-methyl-4-phenyl-1,2,3 ,6-tetrahydropyridine (MPTP)-induced PD in mice. In this experimental setup, the administration of mulberry extract at a dosage of 500 mg/kg demonstrated the ability to prevent the loss of dopaminergic neurons and alleviate bradykinesia. These findings suggest that mulberry extract holds promise as a potential therapeutic agent for PD treatment.[153] Neuroinflammation significantly influences PD progression, which is also a potential therapeutic target. Various kinds of fruit contain UA, a naturally occurring pentacyclic triterpenoid carboxylic acid that has been shown to have anti-inflammatory and antioxidant effects. Orally administered UA at a dosage of 25 mg/kg body weight significantly decreased inflammatory markers (Iba1 and tumor necrosis factor-α [TNF-α]), as well as the transcription factor NF-κB, which controls these inflammatory indicators, in an in vivo study using a PD rat model induced by intraperitoneal injections of MPTP (Figure 2). This inhibition successfully prevented neuroinflammation driven by MPTP. The immunoreactivity of tyrosine hydroxylase (TH) in the substantia nigra pars compacta (SNpc) of mice with PD was also noticeably elevated by UA treatment. The neuroinflammation, neurodegeneration, and related deficits in both biochemical and behavioral measures induced by MPTP were seen to be brought back by UA. As a result, UA exhibits a potent anti-inflammatory effect by preventing dopaminergic neurons in PD-induced rats from degenerating.[154] In a related experiment, rotenone (12 g/L) was stereotaxically injected bilaterally into the substantia nigra (SN) of rats. They then received oral UA therapy for 30 days at dosages of 5- and 10 mg/kg. Different neurobehavioral evaluations were conducted during the investigation, including the Rota-rod, Open field, and Barnes maze (BM) tests. At the end of the 30 days, a variety of tests were carried out, including immunohistochemical analysis (detection of TH-positive neurons and glial fibrillary acidic protein [GFAP]), antioxidant markers (reduced glutathione, superoxide dismutase, catalase, and lipid peroxidation), the inflammatory parameter TNF-α, mitochondrial complex I function, mitochondrial biogenesis (MB), and mitochondrial function. The results revealed that UA greatly reduced motor impairments, indicating that TH-positive neurons were protected from deterioration. Additionally, UA significantly improved cognitive performance, which was tested using the BM. Biochemically, UA successfully reduced the OS and inflammation that is rotenone induced. Additionally, it significantly reduced complex I inhibition in the mitochondria and promoted mitochondrial biogenesis. These preliminary findings provide compelling evidence that UA can protect against rotenone-induced neurotoxicity in rats.[155] OA, a bioactive pentacyclic triterpenoid molecule, has several therapeutic benefits, such as anti-inflammatory and antioxidant effects. In research using PC12 cell culture treated with 6-OHDA, OA was used before and after the treatment at 100 mg/kg, demonstrating the substance's neuroprotective properties. The decrease in striatal microglial activation, which is involved in the neuroinflammatory processes linked to PD, clearly indicated these effects.[156] Ferulic acid, a typical phenolic acid found in many plants, protected dopamine neurons in the SNpc region and nerve terminals in the striatum from the rotenone insult in a rotenone-induced PD rat model. Ferulic acid also prevented glutathione depletion, restored antioxidant enzymes (SOD and CAT), and inhibited lipid peroxidation (MDA level). Proinflammatory cytokines and inflammatory mediators decreased. Phenolic acid's antioxidant and anti-inflammatory properties are hypothesized to mediate the favorable benefits seen.[112] In a cell culture model subjected to 6-OHDA-induced apoptosis, Xu et al. investigated the protective effects of PA under both normal iron levels and conditions with excess iron. According to their research, PA protects cells from 6-OHDA-induced apoptosis when excess iron is found. It is still unknown if iron buildup in the brain contributes to or results from the onset of PD. Iron chelators, however, have been demonstrated to delay the disease's development when used in PD treatment.[116] The peroxisome proliferator-activated receptor γ (PPARγ) is activated by resveratrol administration, which reduces α-synuclein oligomers in human H4 neuroglioma cells transfected with S1/S2. PD pathogenesis is influenced by PPARγ, which also controls mitochondrial biogenesis and energy metabolism. Resveratrol accomplished this on a molecular level by decreasing the expression of the protein α-synuclein through the miR214 pathway in both the MPTP-induced mice model of PD and the neuroblastoma cells subjected to MPP+-induced neurotoxicity. Cuminaldehyde demonstrated the ability to prevent α-synuclein fibrillation, even in the presence of seeds, and had a minimal disaggregating impact on preformed α-synuclein fibrils. Remarkably, it outperformed baicalein, a known

α-synuclein fibrillation inhibitor, and hindered protein assembly into β-structural fibrils, attributed to its interaction with the amine and aldehyde groups in its chemical structure.[157] Morin, a naturally occurring flavonoid found in the Moraceae family's fruits, wine, and herbs, was investigated in an in vivo mouse model induced by MPTP by Zhang et al. Their research confirmed that morin, administered at doses ranging from 20 to 100 mg/kg, can mitigate behavioral impairments, prevent striatal dopamine depletion, and inhibit the death of dopaminergic neurons (Table 2).[119] The administration of nobiletin at a dose of 10 mg/kg body weight had a noteworthy protective effect on damaged dopaminergic (DA) neurons located in the SN of rats that had received unilateral MPP+ injections. Additionally, nobiletin treatment effectively inhibited the activation of microglial cells. These findings indicate that nobiletin might safeguard against MPP+ toxicity by reducing neuroinflammation.[127]

4.3 | Epilepsy

Epilepsy is a neurological condition characterized by a lasting susceptibility to produce epileptic seizures and the resultant cognitive and societal implications. An epileptic seizure is a transitory alteration in behavior that may manifest as observable signs or subjective sensations (such as loss of consciousness, muscle rigidity, convulsions, a sensation originating from the abdomen and extending to the chest, a burnt rubber smell, or déjà vu). These seizures are triggered by abnormal excessive or synchronous neuronal activity in the brain. Seizures can originate in a specific localized area or hemisphere of the brain (referred to as focal onset), diffuse across both hemispheres (referred to as generalized onset), or have an unidentified origin (if clinical and laboratory data cannot pinpoint whether it's focal or generalized).[158] Several environmental and genetic factors might be blamed for the development of epilepsy. However, acquired epilepsy—which accounts for around half of all cases of epilepsy—is connected to earlier brain damage. Traumatic brain injury (TBI), newly developing status epilepticus (SE), exposure to nerve toxins, brain infections, brain tumors, and strokes are the primary triggers that might result in permanent epilepsy.[159] The World Health Organization (WHO) estimates that 50 million people globally suffer from epilepsy, a widespread, chronic neurological condition that has a significant negative impact on sufferers' quality of life.[160]

In a study, rats were administered varying doses of a hydroalcoholic extract from *P. emblica* fruit for 7 days, ranging from 300 to 700 mg/kg via intraperitoneal injection. This treatment effectively mitigated generalized tonic seizures induced by pentylenetetrazole (PTZ) (Figure 3) and status epilepticus induced by kainic acid in the rats.[99] In a study, mice received oral doses of bael extract at both 100 and 200 mg/kg. The administration of this extract demonstrated preventive effects on hind limb tonic extensions (HLTE) triggered by PTZ-induced seizures. Moreover, treatment with ethanolic bael extract delayed the onset of maximal electroshock seizures (MES) and PTZ-induced convulsions, suggesting interference with the gabaminergic mechanism and resulting in an anticonvulsant effect. These beneficial effects were attributed to the presence of flavonoids in bael. Another study also indicated that bael extract could reduce post-traumatic seizures (PTS) and MES-induced convulsions.[161] Research on coconut oil's effect on epilepsy in animals is mixed. Although a ketogenic diet using coconut oil showed no benefit in rats with pilocarpine-induced seizures, virgin coconut oil reduced seizure duration in rats with electroshock-induced seizures. Though these findings are inconclusive for its standalone use, coconut oil might be helpful in combination therapy. It interacts with antiepileptic drugs like sodium valproate and phenobarbital, boosting their anticonvulsant effects.[162] Using intracellular methods, the impacts of *Cuminum cyminum* fruit essential oil on PTZ-induced epileptiform activity was evaluated. The results showed that external application of *C. cyminum* essential oil (at concentrations of 1% and 3%) considerably decreased the incidence of spontaneous activity produced by PTZ. It was shown that both time and attention affected this decrease. Additionally, the essential oil demonstrated a protective effect against PTZ-induced epileptic activity by extending the time between action potentials, lowering the amplitude of the AHP that follows the action potential, dropping the peak of action potentials and inhibiting firing rates.[163] The 6-Hz model, the maximal electroshock test (MEST), PTZ, and the second hit PTZ test during the chronic stage of the pilocarpine model were the four different mouse seizure models that Shaikh et al. used to evaluate the effects of acute and chronic intraperitoneal injections of luteolin. According to the study's conclusions, luteolin had no particularly notable pro- or anticonvulsant effects in the 6-Hz, MEST, or PTZ tests when given as a single dosage or repeatedly each day. TLR4 mRNA levels remained stable throughout the model's chronic phase despite an initial rise 3 days following pilocarpine-induced status epilepticus. After receiving several luteolin injections, no noticeable effects were shown in the second hit PTZ test. This shows that TLR4 signaling may not be a factor in seizure threshold.[130]

4.4 | Multiple sclerosis

MS, an autoimmune disease targeting young adults, is the leading cause of nontraumatic neurological disability.[164] It's characterized by distinct features: inflammatory demyelination (nerve sheath damage) and proliferation of astroglial cells (gliosis) alongside neurodegeneration. This damage is confined to the CNS, not affecting the peripheral nerves. Clinically, MS presents as either relapsing or progressive. Typically, early stages involve relapsing–remitting MS with distinct neurological episodes followed by partial or complete recovery, but sometimes no recovery. Although relapse frequency often decreases over time, gradual deterioration can occur, leading to the continuous progression of secondary progressive MS.[165]

An in vivo experiment involving *Nigella sativa* seeds (fruit part) administered orally at a dosage of 2.8 g/kg in rats showed a reduction in the β1 expression. This treatment led to an increase in remyelination within the cerebellum in an autoimmune

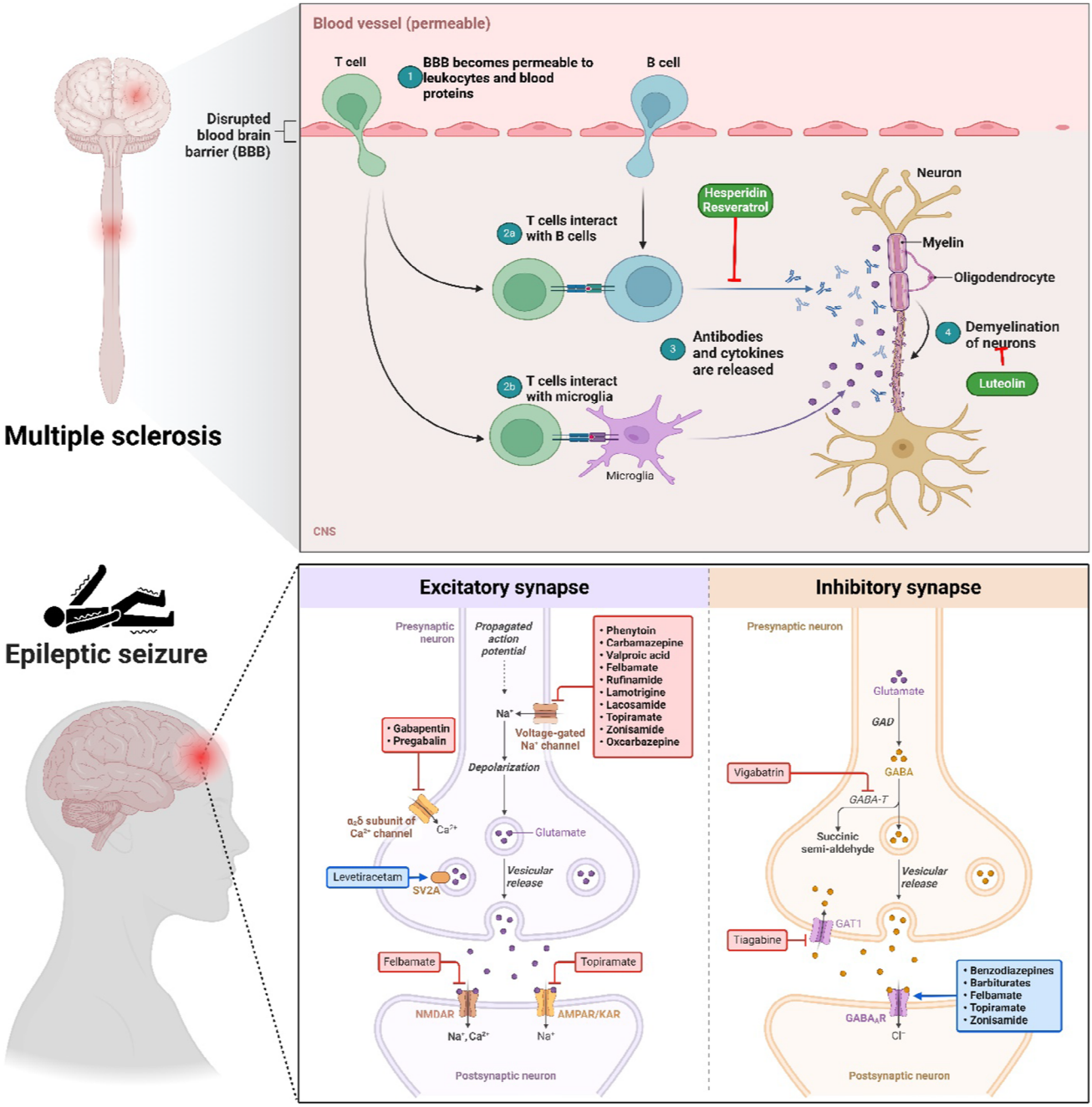

FIGURE 3 Illustration representing the role of edible fruit bioactive compounds in epilepsy and multiple sclerosis.

encephalomyelitis model, ultimately decreasing the severity of MS. Similarly, in a study involving Quercetin, administered orally at doses of 50 and 100 mg/kg in rats, a decrease in the migration of monocytes and activation of T cells was noted within the autoimmune encephalomyelitis model. Also, this resulted in a reduction in the severity of MS.[166] The survival of neurons in conditions like MS and other demyelinating ailments hinges on preserving myelin and the remyelination of axons. The primary objective is to safeguard myelin in the CNS. UA, a natural compound, has been proposed as a protective agent for neural cells. In a study, mice were administered UA daily through their drinking water at a concentration of 1 mg/mL for 6 weeks to prevent myelin damage caused by CPZ pellets, which induces axonal demyelination in the corpus callosum. The results revealed that UA effectively reduced the extent of demyelination and enhanced the intensity of myelin staining within the corpus callosum while shielding oligodendrocyte lineage cells from the harmful effects of cuprizone toxin. UA demonstrated the potential to safeguard myelinated structures in the corpus callosum, providing promising evidence for its potential application in treating demyelinating diseases and traumatic injuries.[167] In a study using a mouse model of MS, the extended oral administration of UA at a dose of 25 mg/kg demonstrated positive effects, which included an increase in MBP+ levels, a rise in myelinated axons, and the activation of the PPARγ pathway.[168]

4.5 | Ischemic stroke

Ischemic stroke is known as acute neurological impairment caused by the interruption of blood flow to a specific area of the brain. This impaired cerebral blood flow causes a severe lack of oxygen and glucose at the molecular level, reducing the generation of adenosine triphosphate (ATP). This is followed by the occurrence of lactate acidosis and the disruption of cellular balance.[169] The majority of stroke cases—between 60% and 80%—are ischemic strokes.[170] Acute ischemic stroke (AIS) is a prevalent condition, with nearly 700 000 new or recurrent cases annually in the United States. AIS rates are higher among women, starting with an elevated risk in the perimenopausal stage and continuing into older age groups. An increased risk is seen in the perimenopausal stage and persists into older age groups, contributing to the higher AIS incidence among women.[171]

A study investigated the potential of malvidin, an anthocyanin from red grape skins, to protect the heart from ischemia/reperfusion (I/R) injury. Using isolated and Langendorff-perfused rat hearts, the researchers found that malvidin activated the PI3K/NO/cGMP/PKG pathway, leading to increased intracellular cGMP and phosphorylation of essential proteins like eNOS, PI3K-AKT, ERK1/2, and GSK-3β. This activation protected the heart from I/R damage and mitigated the associated OS, potentially benefiting both the heart and brain.[172] A meta-analysis conducted by Wang et al. confirmed that individuals who consume diets high in flavonols (with a daily intake of 20 mg) experienced a 14% reduction in their risk of developing strokes, particularly in the case of men.[173] Wan et al. demonstrated that resveratrol offers neuroprotection by inhibiting phosphodiesterase and controlling the cAMP, AMPK, and SIRT1 pathways. This regulation helps to decrease ATP energy consumption during ischemia.[174] In a study in vitro using an OGD/Rep model and in vivo with an MCAO model, Naringenin's (NAR's) potential antiapoptotic and antioxidant properties in the context of ischemic stroke were investigated. The researchers measured the impact of NAR on the apoptosis of cortical neuron cells through the TUNEL assay. The results from reverse transcription–polymerase chain reaction (RT-PCR) analysis suggested that NAR at concentrations of 40 and 80 μM could significantly reduce apoptosis induced by OGD/Rep ($p < 0.05$). These findings indicate that NAR may have a protective effect against neuronal cell apoptosis in vivo.[175] Consuming 28 g of nuts every 4 weeks is linked to a 24% decrease in the risk of ischemic heart disease (IHD) and a 22% reduction in the risk of nonfatal IHD. Similarly, having one serving of nuts daily is associated with a 27% lower risk of all-cause mortality, and a daily serving of nuts is linked to a 39% decrease in cardiovascular disease (CVD) mortality.[176] Quercetin can downregulate the expression levels of caspase-3 and poly ADP-ribose polymerase (PARP), reducing the volume of cerebral infarction in animal models of focal cerebral ischemia (CI). It also diminishes neuronal apoptosis, inhibits myeloperoxidase (MPO) activity within ischemic brain tissue, and lessens nerve injury from OS.[177] In a comparative study, morin has demonstrated superior effectiveness to conventional drugs like protocatechuic acid. This improvement has been experimentally observed through enhancements in histochemical and psychomotor abnormalities in rodent CI models. Furthermore, the administration of morin in CI animals resulted in the downregulation of apoptotic genes, providing additional evidence for its neuroprotective effects in CI pathology[178] Jasminoidin was investigated for its benefits in rat models of focal CI. When CI caused the development of inflammatory markers such as TNF-α, IL-1β, and von Willebrand factor, jasminoidin successfully inhibited it. As a result, it showed that reducing inflammation might reduce vascular endothelial cell damage and prevent the progression of CI-related damage.[179] Hesperidin, a flavonoid present in citrus fruits, has been shown to significantly enhance the levels of antioxidant enzymes like CAT, SOD, and GSH in ischemic stroke models involving rats or mice. This improvement is accompanied by the alleviation of cerebral damage and the normalization of abnormal behavior.[180]

4.6 | Anxiety

Anxiety is a mood state that looks ahead to the future and is linked to getting ready for potential adverse events that may occur.[181] The most common mental illness, anxiety disorders influence 7.3% of the world's population today. Women are about 1.5–2 times more likely than men to experience anxiety problems throughout adolescence, making them more vulnerable to developing anxiety-related disorders. The complexity of treatment for nonspecialists is heightened by the extensive overlap between anxiety disorders and depressive disorders, particularly generalized anxiety and panic disorders. As a result, primary healthcare frequently fails to recognize and adequately treat anxiety disorders.[182]

The elevated plus maze (EPM), a commonly employed model for studying animal anxiety, relies on the premise that rats tend to avoid open elevated paths due to fear. A study found that an HFD heightened anxiety levels in the subjects. However, when the rats were orally given PEAC, their tendency to avoid open arms was notably reduced. It increased the proportion of time spent exploring these open arms. This outcome indicated that PEAC had an anxiolytic, or anxiety-reducing, effect.[96] An in vivo study investigated the effects of *Citrus limon* (lemon) on rat behavior using three doses: low, moderate, and high. The mild dose (0.4 mL/kg) was found to have anxiolytic-like effects, as evidenced by increased distance traveled, central entries, rearing actions, and open-arm entries in behavioral tests. The moderate dose also reduced immobility and increased climbing duration in the forced swimming test, suggesting an antidepressant-like effect. These findings suggest that moderate doses of lemon may have potential benefits for reducing anxiety and depression.[183] Quercetin, a potent natural compound found in various herbal products, including coconut oil, exhibited remarkable effects on lowering anxiety-like behaviors in rats. This was evident when rats were subjected to the elevated plus-maze and open field tests after receiving daily doses of quercetin (10, 50, and 100 mg/kg) for 21 days.[184] Sloley

et al. studied that apigenin inhibits rat-brain monoamine oxidases (MAOs) in vitro. MAOs belong to a family of flavin-containing amine oxidoreductase enzymes present in human neurons and astroglia. Irregular MAO activity has been linked to various psychiatric and neurological disorders. Inhibitors such as apigenin have demonstrated their efficacy not only as antidepressants and anti-anxiety agents but also as potential treatments for AD and PD.[185] Luteolin has been shown to have anxiolytic-like effects when administered orally or intraperitoneally in mice, indicating its ability to penetrate the BBB.[130]

4.7 | Depression

Depression is a prevalent chronic health problem that can have an impact on one's thoughts, mood, and physical well-being. Low mood, fatigue, sadness, sleeplessness, and a loss of enjoyment of life are some of its hallmarks. Clinical investigations have so far indicated that the therapy outcomes for depression patients are not sufficient.[186] Among adults in the United States, 8.3% experienced a major depressive episode in 12 months, and 19.2% encountered depression at some point in their lives. Typically, depression begins in early adulthood, with an average age of onset at 26 years. Although the distribution of lifetime depression is relatively uniform among age groups in early and middle adulthood, it becomes less common in individuals over the age of 65. Across all age groups, women are significantly more likely to experience depression compared to men.[187] Internationally, the WHO has established that depressive disorders rank among the foremost contributors to global illness. WHO's findings indicate that depression stands as the fourth most significant contributor to the worldwide burden of disease, accounting for 4.4% of total DALY. A research study revealed varying depression prevalence rates, ranging from 6.6% to 97%, in diverse populations within Bangladesh, alongside a notable incidence of sleep disorders and anxiety.[188]

Human consumption of bananas causes the release of serotonin, which can be detected in the pulp and ranges in concentration from 8 to 50 μg/g and is responsible for emotions of pleasure and well-being. Significant levels of dopamine and norepinephrine are also present in bananas. Serotonin, norepinephrine, and dopamine concentrations in banana pulp were listed in the first study at 28, 1.9, and 7.9 μg/g, respectively. The amount of dopamine in the pulp varies depending on the kind of banana, with the yellow banana (*Musa acuminata*) having 42 μg/g, the red banana (*Musa sapientum*) having 54 μg/g, and the plantain having 5.5 μg/g. The importance of dopamine as a neurotransmitter with a significant influence on mood and emotional stability was highlighted by researchers.[189] Hesperidin and naringin were assessed for their antidepressant activity through the FST and TST models, and both demonstrated noteworthy antidepressant effects. These positive outcomes in *C. maxima* plant extracts are likely attributed to their interaction with serotonergic 5-HT1A and κ-opioid receptors. *C. maxima* extracts have been reported to have favorable motor-stimulating propertie.[111] Although research by Dhingra et al. suggests amla polyphenols hold potential antidepressant properties, their study in rat's hints at specific mechanisms involved. When they administered amla extract alongside inhibitors targeting certain brain chemicals (GABA, alpha-1 adrenergic receptors, D2 dopamine receptors, and tryptophan hydroxylase), the extract's antidepressant effects were partially reduced.[98] Antidepressant effects of bael have been observed in mice when compared to anxiolytic medications through the tail suspension test and elevated plus maze test. Parameters assessed include the number of entries, stretches attended posture, head dips in the arms of the elevated plus maze, and the time spent on and duration of immobility in the tail suspension test. There is a decrease in monoamine levels at the postsynaptic site, and the antidepressant effects of imipramine and fluoxetine are enhanced. Bael's antidepressant activity is primarily attributed to its agonistic action on serotonin receptors.[161]

Researchers extracted aegeline from *A. marmelos* fruit extract and tested its effects on reserpine-induced pain and depression in mice. Both the extract and isolated aegeline significantly alleviated pain and depression symptoms compared to mice given reserpine only. Docking studies and further analysis suggest that aegeline's protective effects may be due to its interaction with specific enzymes and reduction of inflammatory markers. These findings indicate the potential of both *A. marmelos* extract and aegeline for alleviating pain and depression.[87] In an investigation, male rats were given either distilled water, a hydroalcoholic extract of *C. nucifera* husk fiber (HECN) (50, 100, or 200 mg/kg), or 400 mg/kg of vitamin E intraperitoneally for 7 days. The findings revealed that HECN100 had an antidepressant-like effect by reducing the immobility duration throughout the FST and TST examinations.[190]

5 | TOXICITY STUDY

Recent studies have identified potential health concerns associated with litchi fruit consumption. Profilin, a plant allergen, can trigger severe allergic reactions in sensitive individuals. Additionally, litchi, along with longan and dried longan, has been shown to stimulate the production of prostaglandin E2 (PGE2), a molecule linked to inflammation, in immune cells. Interestingly, litchi exhibited the most substantial PGE2-inducing effect, requiring a lower dosage than longan varieties. Furthermore, research suggests that litchi may possess diverse chemical properties beyond PGE2 induction. Extracts made with different solvents revealed the presence of additional compounds like benzyl alcohol, which can significantly increase PGE2 and NO production. Although other identified compounds showed a milder stimulatory effect, their presence highlights the potential for litchi to induce inflammatory responses. In severe cases, litchi consumption has been linked to toxic hypoglycemia, especially in malnourished infants with depleted glucose reserves. Additionally, unexplained acute neurological illnesses have been reported in litchi-producing regions like India, Bangladesh, and Vietnam. These illnesses, primarily affecting young children,

present with symptoms like seizures, low blood sugar, and encephalopathy. Although the exact cause remains unclear, potential culprits include exposure to methylenecyclopropylglycine (MCPG) from litchi seeds or pesticides used in orchards. Further research is ongoing to elucidate the definitive causes of these health concerns associated with litchi consumption.[191]

The study examined the acute toxicity of extracts derived from *Citrullus lanatus* in animal models. The assessment of the acute toxicity classification of the *n*-hexane extract of *C. lanatus* seed oil (CLSO) was performed following the guidelines specified in OECD number. The safety of CLSO was deemed satisfactory at a dosage of up to 2000 mg/kg body weight. A toxicity evaluation was also performed on mice using the aqueous extract from the roots and leaves. Throughout the observation period, there were no instances of mouse mortality. Therefore, a maximal tolerance experiment was conducted following the Good Laboratory Practice (GLP) guidelines of 2003, as mandated by the State Food and Drug Administration. Twenty mice were administered a single maximum oral dosage of 43.5 g/kg at two distinct time intervals. However, no mortality was seen among the mice over the 7-day observation period. The oral ingestion of the ethanolic extract derived from *C. lanatus* did not result in any mortality at the highest dosage level of 2000 mg/kg body weight.[192]

An evaluation of the safety profile of the 70% ethanolic extract of *Benincasa hispida* fruit pulp was undertaken by acute toxicity and sub-chronic toxicity study lasting for 90 days in experimental animals. The research used a hydroalcoholic extract (composed of ethanol and water in a ratio of 70:30) that was chemically characterized. This choice was based on the fact that traditional medicinal practices often employ methanol/ethanol or aqueous solutions for extracting plant compounds. Additionally, hydroalcoholic extraction enhances both the extractive value and the storage stability of the extract. The lethal dose of 50% of the extract was determined to exceed 2000 mg/kg when administered orally. The botanical extract may be categorized as a class 5 pharmaceutical agent, qualifying as a nontoxic compound.[193] It might be hypothesized that administering hydroalcoholic extract of *Punica granatum* at doses lower than 0.1 mg/embryo does not demonstrate any detrimental effects. The LD_{50} value of 731.1 mg/kg was obtained from the intraperitoneal injection of its extracts to mice. The calculated confidence interval for the observed variable is from 565 to 945 mg/kg. No gender-based inequalities in acute toxicity were detected. The most notable hazardous indication seen in mice was piloerection. The primary latter provides evidence supporting the alteration of the PNS. The examination demonstrated the existence of saponins, alkaloids, and flavonoids within the extract. These compounds' presence may provide insights into the mechanisms behind both antiviral and embryotoxic effects. Developing an entire link between the structure and toxicity of the extract is a substantial barrier.[194]

The current investigation demonstrates the notable acute anti-inflammatory efficacy of *Carissa carandas* fruit extracts in an experimental model of induced acute inflammation in Wistar rats. The inflammatory reaction may be caused by irritants or phlogistic substances, resulting in paw edema. Agents such as formalin, carrageenan, bradykinin, serotonin, histamine, and others, when administered through injection into the dorsum of the foot of rats, elicit the rapid onset of acute paw edema within a few minutes. The induction of rat PE by carrageenan has emerged as a widely used and well-regarded experimental animal model for studying acute inflammation. The induction of acute inflammatory edema by carrageenan is well understood to have a biphasic response pattern. The carrageenan model's first period (1–2 h) primarily involves the mediation of serotonin and histamine (5-HT). The subsequent stage (2–4 h) is facilitated by bradykinin, polymorphonuclear cells, leukotrienes, and prostaglandins generated by tissue macrophages. The current investigation showed that both test extracts exhibited substantial suppression of rat paw edema generated by carrageenan following a 3-h time frame. The current study examined the effectiveness of reducing inflammation in Wistar rats using the carrageenan-induced paw edema model and the cotton pellets–induced granuloma. There was a steady rise in the level of inhibition observed at doses of 100 and 200 mg/kg throughout the 3 h. The ripe fruits exhibited the maximum activity level after 3 h when given a 200-mg/kg dosage. In the context of carrageenan-induced rat paw edema, it was reported that the percentage of inhibition at a dosage of 100 mg was higher in unripe fruits (68%) compared to the percentage of inhibition observed in ripe or mature fruits after 3 h. After 5 h, it was noticed that the extract derived from ripe fruits exhibited an increase in percentage inhibition, but the extract obtained from immature fruits showed a fall in percentage inhibition.[195]

Upon macroscopic inspection, it was observed that there were no discernible alterations indicative of toxicity in the important organs of rats that were treated with aqueous acetone extract of *Terminalia bellirica* (AATB). Due to their crucial roles in toxin processing, the liver and kidneys are very susceptible to pathological alterations. Consequently, these organs were chosen for comprehensive histological assessment. The present state of toxicology research emphasizes using female rats to assess safety considerations related to plant-based treatments. This preference stems from the fact that female rats exhibit heightened vulnerability to toxic circumstances, resulting in more dramatic and well-defined pathological alterations. According to the findings of the toxicity research, it is expected that the LD_{50} value of AATB will exceed 2000 mg/kg body weight. According to the rules set out by the OECD, AATB may be categorized as a class 5 chemical with a fatal dosage (LD_{50}) above 2000 mg/kg of body weight.[196] At dosages of 1250 mg/kg, the enteral acute toxicity investigation was carried out on *A. marmelos* (L.) *Correa* did not reveal any toxic manifestations, behavioral abnormalities, or death. Under the LD_{50}, the extract had no observable physiologically relevant harmful effects. This research offers an overview and first data on the toxicity profile of this plant's ethanolic extract[197] for future preclinical research.

Rats given a 5000-mg/kg dosage of *P. emblica* extract, both male and female, did not exhibit any toxicity during the trial. Rats of both sexes showed no discernible difference in body weight increase between treatment and control groups. Brain and lung

weights were marginally but substantially decreased in the administered male group compared to the untreated group. Acute exposure to 5000 mg/kg in rats is considered nontoxic. A study conducted in 1971 by Mokkhasmit et al. showed that mice given a 50% ethanol fruit extract at a level of 10 g/kg body weight did not show acute toxicity. Because of this, *P. emblica* fruit extract is thought to be nontoxic after acute exposure in rats, with an $LD_{50} > 5000$ mg/kg. *P. emblica* extract was administered at 300, 600, and 1200 mg/kg/day to evaluate chronic toxicity. These doses correspond to 1.5–12 times the typical human dose of 100–200 mg/kg. Throughout the trial period, there were no toxic symptoms or behavioral changes due to the continuous oral administration of *P. emblica* water extract (300, 600, and 1200 mg/kg). The body weight and its increase in male and female rats in the treatment groups were considerably lower in the test group compared to the control group. Although the average body weight of the satellite groups remained normal until the conclusion of the trial, the body weight of the male treatment group in instances of 600- and 1200-mg/kg dosages dramatically reduced on day 180. Furthermore, on day 270, the body weight and weight increase in the group receiving all treatments dramatically reduced. The female treatment rats showed a considerable rise in platelet counts for the 600-mg/kg/day dosage in hematological examinations. Still, the masculine treatment rats showed no alteration in the number of platelets. In the male and female treatment groups, respectively, a substantial rise in neutrophils and eosinophils was seen at 300 mg/kg/day. In addition, the female satellite group saw a noteworthy reduction in neutrophils and an increase in lymphocytes. Nevertheless, these results were within the normal range, suggesting that the aqueous extract of *P. emblica* did not affect hematopoiesis or leukopoiesis in rats.[198] A study assessed the toxicity of *Mangifera indica* L (MSBE) in mice and rats. The test substance was administered orally to the animals at a single dose of 2000 mg/kg body weight using gastric intubation. MSBE was suspended in 0.5% carboxymethyl cellulose for administration and given at 10 mg/kg body weight for mice and 5 mg/kg body weight for rats. Following OECD Protocol 434 (2004), MSBE was also applied dermally to the animals as a single dose of 2000 mg/kg body weight.[199]

6 | CONCLUSION AND FUTURE SCOPE

In conclusion, the comprehensive evaluation of frequently found fruit plants in Bangladesh as possible neuroprotective agents against NDs emphasizes their enormous therapeutic perspective. This study supports the high pharmacological value of these natural resources by conducting a thorough analysis of previously done in vitro and in vivo studies. Understanding how these resources provide neuroprotective benefits involves investigating probable phytochemical substances and carefully exploring their mechanistic activities. Prospects in this area look promising as the boundary between conventional thinking and cutting-edge scientific inquiry merge. In addition to supporting their traditional use, clarifying potential phytochemicals and their stated modes of action fills the gap between folklore and scientific verification. The next steps in turning these insights into useful therapeutic applications include more investigation into improving dosing regimens, assessing extended safety profiles, and identifying potential synergistic correlations. The complicated nature of NDs and the varied genetic makeup of patient groups necessitate a more thorough investigation to translate preclinical results into significant clinical applications. Harnessing the full therapeutic potential of these fruit plants requires a multidisciplinary strategy that integrates the knowledge of botanists, pharmacologists, clinicians, and geneticists to address the challenges of NDs. By supporting these teamwork initiatives and adopting technological advances, we may open the door for creative, successful approaches that might revolutionize the treatment of NDs.

AUTHOR CONTRIBUTIONS

Sumon Roy: Conceptualization; data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **Sajib Chandra Roy:** Formal analysis; investigation; resources; visualization; writing – original draft; writing – review and editing. **Mehrukh Zehravi:** Conceptualization; data curation; formal analysis; resources; supervision; visualization; writing – original draft; writing – review and editing. **Sherouk Hussein Sweilam:** Data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **Rajib Das:** Data curation; formal analysis; investigation; resources; writing – original draft; writing – review and editing. **Mylsamy Palanisamy:** Data curation; resources; validation; visualization; writing – review and editing. **Venkata Lakshamana Sagar Dantinapalli:** Data curation; formal analysis; validation; visualization; writing – review and editing. **Selvaraja Elumalai:** Formal analysis; investigation; resources; validation; writing – review and editing. **Jeetendra Kumar Gupta:** Formal analysis; investigation; validation; visualization; writing – review and editing. **Mohammed Ali Alshehri:** Data curation; investigation; validation; visualization; writing – review and editing. **Mohammed Asiri:** Resources; validation; visualization; writing – review and editing. **Irfan Ahmad:** Funding acquisition; validation; visualization; writing – review and editing. **Mohamed H. Nafady:** Data curation; formal analysis; investigation; resources; visualization; writing – review and editing. **Talha Bin Emran:** Conceptualization; investigation; project administration; supervision; validation; visualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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