Chapter 4
Pharmacological Application of *Phyllanthus emblica* as Therapeutics in Alzheimer's Disease

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Abstract Today, neurodegenerative disorders such as Alzheimer's disease and dementia are affecting millions of people around the world. Although there are treatments available, the success rate is low in achieving the desired therapeutic benefits. Hence, numerous research groups have been working on finding a novel way to treat these disorders. The traditional system of medicine has been in use for centuries. Herbal drugs comprising various plant-based products have been studied and used for treating neurological disorders including Alzheimer's disease. *Phyllanthus emblica* has been extensively studied for its therapeutic properties that include antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-diabetic, and neuroprotective actions. These pharmacological actions of *Phyllanthus emblica* are corroborated by the evidence collected from preclinical research trials. Hence, it deserves the attention of clinical researchers to develop a viable pharmacotherapeutic strategy. The present chapter elaborated the scientific evidence on the pharmacological role of *Phyllanthus emblica* in conferring protection against Alzheimer's disease.

Keywords Alzheimer's disease · Antioxidant · Oxidative stress · Neuroinflammation · Acetylcholine esterase · *Phyllanthus emblica*

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Abbreviations

AChE	Acetylcholine esterase
AD	Alzheimer's disease
APP	Amyloid precursor protein
Bax	BCL2-associated X
BuChE	Butyrylcholinesterase
CNS	Central nervous system
GABA	Gamma-aminobutyric acid
GSK-3β	Glycogen synthase kinase-3β
NMDA	N-Methyl-D-aspartic acid
pTau	Phosphorylated Tau protein

4.1 Introduction

Phyllanthus emblica Linn or *Emblica officinalis* Gaertn is commonly known as Amla or India gooseberry and is an edible fruit belonging to the family Phyllanthaceae. The plant is indigenous to the Indian subcontinent but also found in other countries like Uzbekistan, South East Asia, China, and Malaysia (Baliga and Dsouza 2011). The fruit is round-shaped, fleshy, smooth or striated, and yellowish-green in color and has a six-celled nut (Baliga and Dsouza 2011). Amla is a rich source of micronutrients and other phytochemicals. The fruit is known to be a rich source of vitamin C and also contains gallic acid, ellagic acid, kaempferol, and ellagitannin (emblicanin A, emblicanin B, punigluconin, and pedunculagin) in sufficient quantities (Baliga and Dsouza 2011; Husain et al. 2019). The fruit of this plant, commonly known as Amla, has been used in Indian cuisine to prepare pickles, murabba, chutneys, and juice concentrates (Baliga and Dsouza 2011).

Every part of *Phyllanthus emblica* is useful due to its medicinal and pharmaceutical properties. The plant has been reported to have antioxidant, antipyretic, analgesic, anti-inflammatory, antidiarrheal, anticancer, adaptogenic, antidiabetic, anti-ulcerogenic, anti-mutagenic, antiatherogenic, nootropic, antimicrobial, nephroprotective, neuroprotective, and immunomodulatory potential (Baliga and Dsouza 2011; Sancheti et al. 2005; Krishnaveni and Mirunalini 2012; Chen et al. 2011; Rajeshkumar et al. 2003; Sultana et al. 2004, 2008; Krishnaveni and Mirunalini 2010; Husain et al. 2019). Besides having beneficial actions in various disorders, *P. emblica* also prevents hyperlipidemia, osteoporosis, and several other ailments (Patel and Goyal 2012).

4.2 Nutritional Value and Phytochemical Constituents

P. emblica is rich in nutrients, and its phytochemical constituents are well characterized. Predominantly, studies indicate that the plant is rich in alkaloids, amino acids, flavonols, tannins, and phenolic compounds. Notably, the fruit is known to be the richest source of vitamin C (478.56 mg/100 mL juice) as compared to other fruits such as lime, apple, grapes, and pomegranates. The approximate composition of *P. emblica* is listed in Table 4.1 (Husain et al. 2019). There are numerous studies where the phytoconstituents present in the plant extract were identified and quantified. A list of the major phytoconstituents is given in Table 4.2 (Variya et al. 2016; Husain et al. 2019). Most notably, the plant is rich in gallic acid, glucogallin, quercetin, chebulinic acid, chebulagic acid, 3-ethylgallic acid, kaempferol, and various phenolic compounds containing mucic acid (Zhang et al. 2000, 2001b, c, 2002, 2003; Habib ur et al. 2007). Also, three norsesquiterpenoids were isolated from the roots, namely phyllaemblicin A, B, and C; phyllaemblic acid; and bisabolene-type sesquiterpenoids (phyllaemblic acid B, phyllaemblic acid C, and phyllaemblicin D with phenolic glycosides, 2-carboxylmethylphenol 1-O-D-glucopyranoside, and 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-O-D-glucopyranoside) (Zhang et al. 2000, 2001b; Gaire and Subedi 2014; Variya et al. 2016). Also, six ellagitannins, namely phyllanemblinins A–F, were isolated (Zhang et al. 2001a). Additionally, acrylated apigenin and two acrylated flavanone glycosides were isolated from the leaves (methanolic extract) of *P. emblica* (Zhang et al. 2002; El-Desouky et al. 2008). Also, two new sterols (trihydroxysitosterol and 5,6,7-acetoxysitosterol) were identified by Qi et al. (2013) from the leaves and branches. Also, 5-hydroxymethylfurfural and 5-methyl-2-furyl methyl ketone along with 1,2,3-benzenetriol (pyrogallol) exist in the methanolic extracts of leaves (Balasubramanian et al. 2014). Other phytoconstituents including polyphenols like ellagic acid, 3,5,7,3,4-penta-hydroxy flavone, and (E)-oct-4-ene-1,2,3,4,5,6,7,8-octanol were isolated from the leaves of *P. emblica* (Chugh and Bharti 2014). A

Table 4.1 Composition of *Phyllanthus emblica* L. fruit (100 g serving)

Content	Quantity
Carbohydrates	82.91 g
Protein	6.04 g
Fat	0.51 g
Dietary fiber	2.78 g
Calcium	129 mg
Iron	11 mg
Potassium	2.54 mg
Phosphorus	159 mg
Magnesium	46 mg
Chromium	0.82 mg
Zinc	0.23 mg
Copper	0.22 mg
Nicotinic acid	0.2 mg

Table 4.2 Major phytochemical constituents present in *Phyllanthus emblica* L.

Source	Chemical name
Fruit	Ascorbic acid
	Emblicanin A and B
	Glucogallin
	Chebulagic acid
	Corilagin
	Mucic acid 2-O-gallate
	Coumaric acid
	Caffeic acid
Whole plant	Gallic acid
	Ellagic acid
	Quercetin
Root	Phyllaemblicin A, B, and C
	Phyllaemblic acid
Leaves	Apigenin-7-O-(6′-butyryl-beta-glucopyranoside)
	Luteolin-4′-O-neohesperidoside
	Trihydroxysitosterol

comprehensive analysis of fruit indicates that pulp and seeds are rich in phenolic compounds and tannins, respectively. Quercetin is found only in the pulp. While coumaric acid, myricetin, caffeic acid, and synergic acid are ubiquitously present in the pulp and seed (Nambiar et al. 2015).

4.3 Pharmacological Properties

According to Ayurveda, an Indian traditional medicine system, *P. emblica* has been classified as "*Medhya Rasayana*" meaning agent for cognitive rejuvenation (Malve et al. 2014). Several phytochemicals and semi-synthetic drugs have been tested for the treatment of cerebral multifactorial disorders and neuroinflammatory ailments like Alzheimer's disease (AD) and Parkinson's disease. These are associated with altered pathophysiological conditions like oxidative stress, inflammation, etc. (Kumar 2006; Perry and Howes 2011). Several phytoconstituents are identified to act as an inhibitor of neuroinflammation associated with CNS disorders (Kulkarni et al. 2005; Vasudevan and Parle 2007a). The common risk factors and their effects on CNS are depicted in Fig. 4.1. Here, we discuss the beneficial role of *P. emblica* in ameliorating the neurodegenerative disease.

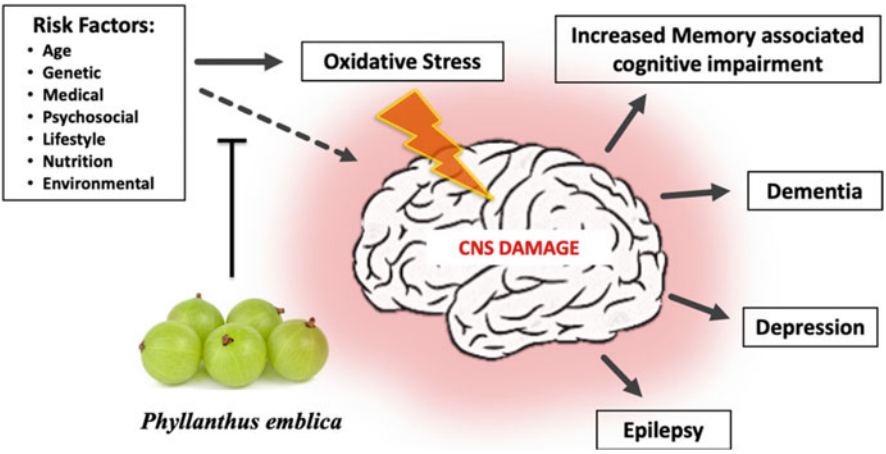

Fig. 4.1 Schematic representation of various risk factors and possible clinical manifestation of Alzheimer's disease

4.3.1 P. Emblica *as an Antioxidant*

Mechanistic studies have shown that feeding *P. emblica* extract enhanced the activity of the various antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase), the phase II detoxifying enzyme, glutathione S-transferase, and antioxidants thiol and glutathione in the blood, with a concomitant decrease in the levels of lipid peroxides (Hari Kumar et al. 2004; Jindal et al. 2009). In addition to this, studies have also shown that *P. emblica* extract was effective in preventing DNA damage caused by genotoxic agents such as radiation (Sharma et al. 2000), lead, aluminum (Dhir et al. 1990), arsenic (Biswas et al. 1999), cesium chloride (Ghosh et al. 1992), nickel (Dhir et al. 1991), chromium (Ram et al. 2003), 3,4-benzo (a)pyrene (Nandi et al. 1997), and 7,12-dimethylbenz(a)anthracene (Banu et al. 2004) and in providing protection against cyclophosphamide-induced suppression of humoral immunity (Haque et al. 2001). In addition to this, studies have also been carried out with the phytochemicals present in *P. emblica*, and research observations suggest that gallic acid (Nair and Nair 2013; Ow and Stupans 2003), geraniin (Kang et al. 2011), corilagin (Li et al. 2018), ellagic acid (Nemavarkar et al. 2004; Ahire et al. 2017; Bhosle et al. 2005; Priyadarsini et al. 2002), quercetin (Nemavarkar et al. 2004; Benkovic et al. 2008, 2009; Devipriya et al. 2008; Mashhadi Akbar Boojar 2020) also possess potent antioxidant properties and a cumulative effect that all these phytochemicals may have triggered to mediate the beneficial effects.

4.3.2 *Neuroprotective Actions of* P. Emblica

Several studies have revealed the beneficial effects of *P. emblica* as an antistress and neuroleptic agent. An earlier study utilizing the *Anwalachurna* made of *P. emblica* led to dose-dependent improvement in memory score at various age groups of both mice and rats (Vasudevan and Parle 2007a). The results using these exteroceptive behavioral models showed a reversal in scopolamine and diazepam-induced amnesia among these animals (Vasudevan and Parle 2007a, b). Other studies from various research groups have also explored the efficacy of *P. emblica* extract against scopolamine-induced amnesia. Based on the outcomes, it can be concluded that it has multifactorial benefits such as antioxidant and anticholinesterase activity that may help in improving and reversing the memory deficits and thus can be used as a remedy for the management of dementia (Perry and Howes 2011; Vasudevan and Parle 2007a, b; Golechha et al. 2012; Vinutha et al. 2007).

Studies have shown that not only did hydroalcoholic extract of *P. emblica* eliminate pentylenetetrazole and kainic acid-induced seizure and status epilepticus, but it also improved cognitive function in rats (Golechha et al. 2010, 2011). Moreover, *P. emblica* showed a dose-dependent inhibition in kainic acid-induced elevated TNF-alpha expression in the brain due to its antioxidant and anti-inflammatory properties (Golechha et al. 2010, 2011). Also, the antiepileptic potency of epigallocatechin-3-gallate and polyphenols was established by Xie et al. against the pentylenetetrazole-induced epilepsy model (Xie et al. 2012).

In addition, acetylcholinesterase (AChE) is considered a vital target in the management of Alzheimer's condition. Treatment with the methanolic extract of the *P. emblica* fruit showed a significant reduction in acetylcholinesterase activity along with improved DPPH scavenging activity with IC_{50} values of <100 μg/mL and < 10 μg/mL, respectively (Mathew and Subramanian 2014). Moreover, treatment of human neuroblastoma cells (SK-N-SH) with aqueous and methanolic extract of the fruit showed improved protection against H_2O_2-induced DNA damage and viability as seen by comet assay (Ramakrishna et al. 2014). More recently, Thenmozhi et al. showed that *P. emblica* when given in $AlCl_3$-intoxicated male Wistar rats, at a dose of 200 mg/kg for 2 months, it showed a significant reduction in acetylcholinesterase activity, amyloid precursor protein (APP), $A\beta_{42}$, β-secretase, and γ-secretase activity in the brain hippocampus and cortex area (Justin Thenmozhi et al. 2016a). Though these rats had deposition of the amyloid protein, they had recovered from the memory-learning and locomotor impairments caused by $AlCl_3$ (Justin Thenmozhi et al. 2016a).

Oxidative stress has been a vital factor in the progression of various ailments and neurological disorders. The use of *P. emblica* extract has been shown to dramatically reduce chronic unpredictable footshock-induced oxidative stress in rats (Bhattacharya et al. 2000). Also, this extract was able to protect against neuroleptic agent haloperidol-induced tardive dyskinesia, thus acting as a prophylactic neuroprotective agent (Bhattachary et al. 2000). An evaluation for its antidepressant activity by Dhingra et al. revealed that mice fed with the *P. emblica* extract had

lowered monoamine oxidase enzyme activity in the brain and inhibited affinity toward α_1- adrenoceptors, GABA-B receptors, serotonin receptors, and dopaminergic D_2-receptor (Dhingra et al. 2012). Also, the antioxidant potential of the *P. emblica* extract seems to protect rats against alcohol-induced brain mitochondrial dysfunction with lowered NO generation and protein carbonylation and improved endogenous antioxidant system and cytochrome C oxidase activity (Reddy et al. 2011). As stress is considered an aggravating factor for altered psychological state and behavior, it is worthwhile to know the key ingredients that can protect against it. Numerous studies revealed that chemical constituents such as flavonoids, tannins, and polyphenols, in particular, emblicanin-A, emblicanin-B, punigluconin, and pedunculagin, have an active pharmacological role in neuroleptic action (Bhattachary et al. 2000; Bhattacharya et al. 2000; Dhingra et al. 2012; Reddy et al. 2011). The use of a hydroalcoholic extract of *P. emblica* has been shown to reduce stress-induced elevated corticosterone levels in mice, thus likely contributing to improved mental health (Arun et al. 2018; Golechha et al. 2010). In another instance, where noise (100 dB noise for 4 h per day for 15 days) was used as an external stressor factor in albino rats, it was shown that treatment with *P. emblica* extract (333 mg/kg) can act as an anti-stressor with improved recovery from noise-induced immobilization and other behavioral alterations (Wankhar et al. 2014). Hence, several studies indicate that *P. emblica* has a nootropic potential and can be used as an adjunct therapy for the treatment of AD-like disorders (Kennedy and Scholey 2006; Hsieh et al. 2000). Also, herbal formulations containing *P. emblica* helped in correcting memory deficits induced by scopolamine and diazepam (Vasudevan and Parle 2007b). Therefore, phytoconstituents of *P. emblica* have a potential role in the management of AD-like conditions (Golechha et al. 2012; Vasudevan and Parle 2007a, b; Vinutha et al. 2007; Husain et al. 2019).

Dementia is a key symptom of neurodegenerative disorders associated with aging. AD has been one of the vital contributing factors leading to dementia, which is emerging as a health risk mainly in the older population. AD is characterized mainly by the deterioration of cognitive functions that are mostly due to the accumulation of extracellular amyloid-beta peptides (neuritic plaques) and intracellular neurofibrillary tangles (Albert et al. 2011; Hussain et al. 2018). Although the exact cause for AD is unknown, it is believed that oxidative stress due to free radicals generation, inflammation, impaired metabolic pathways, hyperlipidemia, and lowered cholinergic neurotransmission are important factors that trigger AD (Husain et al. 2017). Though there are treatments available such as the use of AChE inhibitors (donepezil) and NMDA receptor antagonist (memantine), these only provide symptomatic relief (Parsons et al. 2013; Agatonovic-Kustrin et al. 2018). Thus, there is a large gap and necessity for finding a valid solution to this emerging health problem.

Cholinergic dysfunction is found to be a vital cause of the pathophysiology of AD (Hampel et al. 2019). An in vitro study by Mathew and co-workers has shown that the methanolic extract of *P. emblica* fruit can inhibit AChE enzyme ($IC_{50} < 100$ μg/mL) and confer antioxidant activity as evident from 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity ($IC_{50} < 10$ μg/mL) (Mathew and Subramanian 2014).

Also, another study by Biswas et al., where dry fruit methanolic extract was used, found a significant inhibition in AChE (IC_{50} = 53.88 μg/mL) and butyrylcholinesterase (BuChE) (IC_{50} = 65.12 μg/mL) activities (Biswas et al. 2017). Likewise, in vivo studies in rodents with chemical-induced AD have supported a similar outcome. Thenmozhi and co-workers reported that the active principles from *P. emblica* fruit, mainly tannins, helped in a reversal in levels of AChE activity and amyloid-beta synthesis in various brain regions (Justin Thenmozhi et al. 2016a). Also, it was found that both unripe and ripe fruits of *P. emblica* were helping in increased levels of antioxidant enzymes within the brain, but unripe fruit extract had better potency than ripe fruit. Similarly, Uddin and co-workers observed that feeding *P. emblica* extract provided a concomitant decline in AChE activity followed by a better neurobehavioral performance in rodents, thus signifying a potential role as a treatment for AD (Uddin et al. 2016).

Hyperphosphorylation in the tau protein has been another factor for the pathogenesis of AD (LaFerla et al. 2007). Moreover, disruption in the signal transduction pathways such as Akt/GSK-3β is implicated to play a predominant role progression of AD (Jimenez et al. 2011). A study carried out on $AlCl_3$-induced toxicity and cognitive-deficit rats showed that feeding *P. emblica* extract given at 100 mg/kg for 60 days led to reduced oxidative stress and lower expression of apoptotic markers such as caspases 3 and 9, Bax, cytochrome c, and pTau. Also, alerted expression of glycogen synthase kinase-3β and Akt (phosphorylated) were observed (Justin Thenmozhi et al. 2016b; Singh et al. 2018). Husain and co-workers have recently shown that the increased expression of Nrf2-ARE pathway and NF-κB was a probable cause for oxidative stress and neuroinflammation, thus leading to cognitive disorder induced in rats by high-salt and cholesterol diet (Husain et al. 2018b). However, upon treatment with *P. emblica* extract containing tannin-enriched fraction, a significant improvement in the neurobehavioral parameters was observed (Husain et al. 2018a). Thus, further studies understanding the mechanistic role of *P. emblica* may hold potential in treating AD and associated neurological disorders.

4.4 Conclusion

In recent times, a lot of focus has now been given to find "natural" remedies, and therefore ethnopharmacological research has gained more attention. There is ample evidence and literature available that supports the medicinal property of *P. emblica* for various neurological disorders. Various extraction methods such as aqueous, alcoholic, and dried powder methods have been found their use in many studies. Also, molecular targets have been identified where *P. emblica* has been hypothesized to act, conferring neuroprotective action. However, the molecule/s that solely confer its pharmacological activity has not yet been deciphered. Hence, further research is required to identify specific chemical constituents that can be used for clinical therapy. Therefore, an exhaustive preclinical and clinical study is needed to

validate its use in traditional medicine and develop a sustainable clinical therapy for AD and other neurological disorders.

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Conflict of Interest The authors have no conflicts of interest to declare.

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