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REVIEW ARTICLE

Exploring the multifaceted neuroprotective actions of *Emblica officinalis* (Amla): a review

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Abstract

Today, neurological disorders such as epilepsy, depression, tardive dyskinesia, and stress, and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, dementia, and Huntington's disease affect millions of people all over the world. Existing pharmacological interventions do not meet the desired therapeutic benefits for a significant number of patients, and hence, numerous research studies are in progress to find novel therapies for these disorders. Herbal drugs, which have been used in traditional medicine for centuries, are also being explored and scientifically evaluated for the treatment of these neurological disorders. While substantial evidence exists for the antioxidant, anti-inflammatory, anti-hyperlipidemic, and anti-hyperglycemic effects of *Emblica officinalis*, in vivo and in vitro studies, have also revealed its beneficial therapeutic activities in numerous neurological disorders. These diverse neuroprotective pharmacodynamic actions of *E. officinalis* corroborated by accumulating evidence in pre-clinical research studies deserve the attention of the scientific community to develop viable pharmacotherapeutic strategies. The present review elaborates upon the latest scientific evidence pertaining to the pharmacological effects of *E. officinalis* in numerous neurological and neurodegenerative disorders and also gives way for future research in this area.

Keywords *Emblica officinalis* · Epilepsy · Depression · Alzheimer's disease · Stress · Memory

Introduction

In traditional systems of medicine, a large number of different plant species have been used because of their therapeutic uses in the management of a multitude of ailments. These natural, plant-derived drugs, which have been used extensively in complementary and alternative medicine (CAM) for centuries, have attracted the attention of researchers as these substances offer potential opportunities for the development of novel drugs that may confer a positive effect on human health with relatively less or no side effects as compared to existing synthetic compounds (Parvez 2017). Medicines of natural origin have continuously been demonstrated as beneficial remedies for several disorders in both pre-clinical as well as clinical studies (Edwards et al. 2018). Various health authorities such as WHO have approved such medicines as a part of therapeutic intervention for the treatment of various disease conditions ranging from malaria to cancer (Patel and Goyal 2012; Zameer et al. 2017). With the emerging interest of scientists across the globe to adopt and exploit the potential therapeutic properties of plants in traditional systems of medicine, their disinterested, scientific evaluation is imperative.

Emblica officinalis genus Phyllanthus (Euphorbiaceae) also termed as *Phyllanthus emblica* or Indian gooseberry is widely distributed in tropical and subtropical parts of countries such as India, China, Indonesia (article amla pharmacology). *E. officinalis* commonly referred to as '*amla*' in India, is a small or moderate-sized tree with greenish-gray bark and greenish-yellow flowers which have been cited to possess vital amino acids and vitamins and therefore widely used as medicine and nutritious tonic (Dias et al. 2018). It consists of a high proportion of vitamin C and minerals as compared to

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other citrus fruits. In addition, Amla also contains chemical constituents of therapeutic value such as tannins, epigallocatechin-3-gallat and polyphenols (Khan 2009; Variya et al. 2016) (Table 1). All parts of *E. officinalis* and mainly the fruits have been used as part of Ayurvedic *Rasayana* either alone or in combination with other traditional medicines for the treatment of multiple infectious and non-infectious diseases (Akhtar et al. 2011). There is substantial evidence that reveals the potential features of *E. officinalis* including anti-oxidative, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, anti-cancer and antiproliferative, anti-mutagenic, cardioprotective, hepatoprotective, etc. (Yokozawa et al. 2007; Muthuraman et al. 2011; Nain et al. 2012). Additionally, several pre-clinical studies by Singh et al. have revealed the extraordinary efficacy of the fruit extract of Amla in ameliorating heavy metal-induced toxicity such as arsenic-induced oxidative damage and apoptosis in murine splenocytes, thymocytes, and hepatocytes (Singh et al. 2013, 2014a, b). Amla has also been found effective in improving inflammation and immunotoxicity caused as a result of arsenic-exposure (Singh et al. 2015) (Table 2).

Furthermore, *E. officinalis* is also being assessed for its therapeutic role in the treatment of several neurodegenerative diseases such as dementia, Alzheimer's disease, Parkinson's disease, since these are associated with altered pathophysiological conditions like oxidative stress, inflammation, hyperlipidemia, etc. which, as mentioned previously, *E. officinalis* has shown to ameliorate (Obulesu and Rao 2011; Husain et al. 2018a, b). Research in *E. officinalis* has added an additional focus due to unsolicited adverse effects of the other medicinal systems which may lead to severe complications. The goal of this review is to discuss the comprehensive role of *E. officinalis* in improving neurobehavioral parameters such as memory and learning as well as disorders such as Alzheimer's disease, tardive dyskinesia, brain aging and cerebral-protection (Table 3). With this paper, we intend to encourage future research towards the development of *E. officinalis* as therapy and prophylactic supplement for neurodegenerative conditions.

Table 1 Phytoelements persent in fruits of *E. officinalis*

S. no.	Chemical constituents	Per 100 gm *E. officinalis* fruit
1	Carbohydrates	82.91 gm
2	Protein	6.04 gm
3	Fibers	2.78 gm
4	Fat	0.51 gm
5	Phosphors	159 mg
6	Calcium	129 mg
7	Magnesium	46 mg
8	Iron	11 mg
9	Potassium	2.54 gm
10	Chromium	0.82 mg
11	Zinc	0.23 mg
12	Copper	0.22 mg
13	Nicotinic acid	0.20 mg

Methodology An exhaustive literature search was performed in the following databases viz. Google Scholar, PubMed, ISI Web of Science, Science Direct, and Scopus with the search strings "*Emblica officinalis*", "*Phyllanthus emblica*", "Amla", "Neuro", "Brain" alone as well as in combination with each other. No date restriction was imposed in order to get comprehensive results of the studies done in this area so far. Studies involving the use of Amla in neurological disorders were included while studies involving non-neurological disorders were excluded. We found a total of 31 publications that fit this criteria (Fig. 1).

E. officinalis in Alzheimer's disease

Dementia is a conjoint symptom of neurodegenerative disorders associated with aging. Alzheimer's disease (AD) is one of the principal attributes of dementia which is an emerging health problem affecting millions of people around the world. AD is a progressive neurodegenerative disorder characterized by decline in cognitive functions which is a consequence of extracellular deposition of amyloid beta peptide (senile plaques) and intracellular neurofibrillary tangles (Albert et al. 2011; Hussain et al. 2018). Though the etiopathology of AD remains unclear, various reports have cited that the oxidative stress, inflammation, hyperlipidemia, impaired energy metabolism, and reduced cholinergic neurotransmission are the contributing factors for AD (Husain et al. 2017). Some therapeutic interventions such as AChE inhibitors (donepezil) and NMDA receptor antagonist (memantine) have been employed for the treatment of AD, but these drugs work by providing symptomatic relief, in turn leaving this progressive neurodegenerative disorder with unmet therapeutic needs (Zameer et al. 2017). Researchers have continuously been targeting new compounds that prove to be fruitful in this emerging global health problem.

E. officinalis has been considered to exert potential therapeutic effects in neurodegenerative disorders due to its complementary antioxidant, cholesterol-lowering and anti-inflammatory properties. Cholinergic dysfunction is also supposed to be one of the crucial aspects of the pathophysiology of AD (Hampel et al. 2017). In vitro studies have demonstrated that methanolic extract of *E. officinalis* fruit has the potential to inhibit AChE enzyme ($IC_{50} < 100$ μg/mL) which is primarily responsible for cholinergic dysfunction associated with AD as well as confer 2,2-diphenyl-1-picrylhydrazyl (DDPH) scavenging activity ($IC_{50} < 10$ μg/mL) (Mathew

Table 2 Major phytoconstituents present in fruits of *E. officinalis*

S. no.	Chemical constituents	Per 100 gm *E. officinalis* fruit
1	Emblicanin-A, -B	Antioxidant
2	Punigluconin	Antioxidant
3	Pedunculagin	Antioxidant
4	vitamin-C (Ascorbic acid)	Antioxidant, Anti-diabetic
5	Chlorogenic acid	Antioxidant, Anti-inflammatory, Anti-hypertensive
6	Chebulagic acid	Antioxidant, Anti-inflammatory, Anti-diabetic, Anti- proliferative
7	Coumaric acid	Antioxidant, Antihyperlipidemic
8	Myricetin	Antioxidant
9	Caffeic acid	Antioxidant, Anticancer, anti-hyperlipidemic, Anti- inflammatory
10	Gallic acid	Antioxidant, Anti-inflammatory, Anti-proliferative, Anti- cancer, Anti-diabetic, Cardio-protective, Neuroprotective, Antibacterial
11	Ellagic acid	Antioxidant, Anti-proliferative, Anti-cancer, Anti- diabetic,
12	Quercetin	Antioxidant, Protein kinase inhibitor
13	Phyllaemblicin-A, B and C	Anti-bacteial, Anti-viral
14	L-malic acid 2-O-gallate	Anti-proliferative
15	Trihydroxysitosterol	Cytotoxic
16	Glucogallin	Aldose reductase inhibitor
17	3,6-di-O-galloyl-d-glucose	Antioxidant, Neuroprotective,

and Subramanian 2014). An in vitro study by Biswas et al. to assess the AChE and butyrylcholinesterase (BuChE) inhibitory activities of the dry fruit extract of *E. officinalis* concluded that the crude methanolic extract of the dry fruit of *E. officinalis* inhibited AChE at an IC_{50} of 53.88 μg/mL while BuChE at an IC_{50} of 65.12 μg/mL (Biswas et al. 2017). Similarly, *E. officinalis* has also proved to be protective in chemical-induced AD in rodents. In a study by Thenmozhi et al., tannoid principles of *E. officinalis* also reversed alterations in the concentration of aluminum, acetylcholine esterase activity, and amyloid beta synthesis related molecules in the chosen brain regions (Justin Thenmozhi et al. 2016b). Furthermore, it has also been determined that both ripe, as well as unripe fruits of *E. officinalis*, were useful in increasing levels of antioxidant enzymes in the brain, however, extract from unripe fruits were more efficient. A decline in the AChE activity and better performance in neurobehavioral tests were observed in rodents treated with *E. officinalis* indicating a promising role of *E. officinalis* in the treatment of Alzheimer's disease (Uddin et al. 2016).

Besides Aβ deposition, intracellular accumulation of hyperphosphorylated tau is also a critical pathological factor in the pathogenesis of AD (LaFerla et al. 2007). Furthermore, it was revealed that various signaling pathways at molecular level such as Akt/GSK-3β play a vital role in AD (Jimenez et al. 2011). Recently it was elucidated that *E. officinalis* at a dose of 100 mg/kg (b.w. orally) for 60 days countered the aluminum chloride-induced toxicity and cognitive deficit in rats. The above therapy led to a fall in the oxidative stress along with reduced expression of apoptosis markers Bax, caspases-3, −9, cytosolic cytochrome c, and pTau. Additionally, in the same study, it was also demonstrated that GSK-3β and pAkt were also altered by *E. officinalis* (Justin Thenmozhi et al. 2016a; Bharathi and Thenmozhi 2018). In our laboratory, we evaluated the effect of tannins enriched fractions of *E. officinalis* on high salt and cholesterol diet (HSCD)-induced cognitive impairment in rats. It was observed that HSCD led to the activation of Nrf2-ARE pathway as well as increased expression of NF-κB, indicating the presence of both oxidative stresses as well as inflammation, thereby causing cognitive impairment which was corroborated by various neurobehavioral tests (Husain et al. 2018a). Further, it was observed that the administration of tannins enriched fractions of *E. officinalis* led to significant amelioration of cognitive deficits, which was confirmed by the substantial improvement in the performance of rats in tests of neurobehavioral parameters as well as by numerous in vitro and in vivo studies (Husain et al. 2018b). Further studies of this valuable plant in diverse experimental models of AD hold a lot of potentials.

E. officinalis in epilepsy

Epilepsy is a chronic disorder of brain manifested by recurrent seizures that are brief episodes of involuntary movement that may affect a part of the body (partial) or the entire body (generalized) (Fabene et al. 2010). It is reported that this disorder affects 50 million people across the world and thus the use of anti-epileptic medications is widespread (LaPenna and Tormoehlen 2017). Different generations of anti-epileptic

Table 3 Role of *E. officinalis* (Amla) in varied range of neurological disorders

S. no.	Type of study	Treatment	Dose and duration	Mechanism of action	Reference
In Alzheimer's disease					
1	In vitro	Methanolic extract of EO		Inhibition of AChE and DPPH scavenging action	Mathew and Subramanian 2014
2	In vivo ($AlCl_3$ induced AD in rats)	EOT	200 mg/kg bw for 2 months	Inhibition of AChE enzyme, reduction of amyloid precursor protein (APP), amyloid beta ($A\beta_{42}$) and gamma secretase activity as well as improvement in locomotor activity and learning and memory	Justin Thenmozhi et al. 2016b
3	In vivo ($AlCl_3$ induced AD in rats)	EOT	100 mg/kg bw for 2 months	Reduced expression of GSK-3β, pAKT and apoptotic markers	Justin Thenmozhi et al. 2016a
In epilepsy					
4	In vivo (PTZ- and Kainic acid-induced epilepsy in rats)	Pretreatment of Hydroalcoholic extract of EO	300, 500 and 700 mg/kg i.p. for 7 days	Alleviation of generalized tonic seizure and status epilepticus	Golechha et al. 2010, 2011
5	In vivo (Kainic acid-induced epilepsy in rats)	Pretreatment of Hydroalcoholic extract of EO	500 and 700 mg/kg i.p. for 7 days	Reduction of kainic acid induced increase in TNF-α level	Golechha et al. 2011
6	In vivo (PTZ-induced epilepsy in rats)	Epigallocatechin-3-gallat and polyphenol component of EO	25 and 50 mg/kg i.p. each day	Dose-dependent suppression of PTZ-induced kindling and oxidative stress as well as improved cognitive functions	Xie et al. 2012
In depression and tardive dyskinesia (TD)					
7	In vivo (Depression; Forced swim and tail suspension)	Aqueous extract of EO	200 mg/kg and 400 mg/kg for 14 days	Antidepressant-like activity; Reduced MAO-A enzyme levels	Dhingra et al. 2012
8	In vivo (Haloperidol-induced TD)	Tannoid principles of EO	10, 20, and 50 mg/kg, po, for 28 days	Reduction in TD parameters viz. chewing movements, buccal tremors, and tongue protrusion	Bhattacharya et al. 2000a, b
Learning and memory					
9	In vivo (Scopolamine-induced amnesia)	Anwalachurna (An Ayurvedic Preparation of *Emblica officinalis*)	50, 100, 200 mg/kg p.o. for 15 days	Dose-dependent improvement in memory scores. Reversed scopolamine-induced amnesia.	Vasudevan and Parle 2007a, b
10	In vivo (Scopolamine and sodium nitrite-induced memory deficits)	Methanolic extract of *Emblica officinalis*	75 and 150 mg/kg p.o. for 7 days	Improved performance in neurobehavioral parameters.	Ashwlayan and Singh 2011
Stress and neuroprotection					
11	In vivo (Footshock-induced stress-induced perturbations)	EOT	10 and 20 mg, p.o.	Tendency towards normalization of catalase, superoxide dismutase, glutathione peroxidase enzymes, with reduction in lipid peroxidation.	Bhattacharya et al. 2000b
12	In vivo (Acute stress induced by restraint stress method)	Alcoholic extract of *Emblica officinalis* fruits	100, 250, and 500 mg/kg, p.o.	Improved performance in elevated plus maze and reversal in the elevated plasma glucose and cortisol levels.	Kumar et al. 2013
13	In vivo (Stress induced by noise)	Crude powder of *Emblica officinalis* fruit mixed with 0.9% saline	333 mg/kg b.w., p.o.	Improved immobilization, fecal bolus, rearing, and performance in elevated plus maze.	Wankhar et al. 2014.
14	In vivo (Alcohol-induced mitochondrial dysfunction)	*Emblica officinalis* fruit extract	250 mg/kg b.w., p.o.	Reduction in NO levels, lipid peroxidation, and carbonyl levels. Increased activity of NADH dehydrogenase, SDH, and cytochrome c oxidase.	Reddy et al. 2011.
15	In vivo (Fluoride-induced neurotoxicity)	*Emblica officinalis*	100 mg/kg b.w., p.o.	Increased memory retention was observed in treatment groups as compared to control group. Elevation in protein content and ChE activity in the brains was also observed in the treatment group.	Shalini and Sharma 2015

Abbreviations: *AD* Alzheimer's disease, *AChE* Acetylcholinesterase, *Amyloid beta* $A\beta_{42}$, *APP* Amyloid precursor protein, *$AlCl_3$* Aluminium chloride, *b.w* Body weight, *DDPH* 2,2-diphenyl-1-picrylhydrazyl, *EO Emblica officinalis*, *EOT* Tannoid principles of *Emblica officinalis*, *i.p.* Intraperitoneally, *NO* Nitric oxide, *GSK-3β* Glycogen synthase kinase 3 beta, *MAO-A* Monoamine oxidase A, *NAD* Nicotinamide adenine dinucleotide, *pAkt* Phosphorylated protein kinase B, *p.o.* Per os, *PTZ* Pentylenetetrazole, *SDH* Succinate dehydrogenase, *TD* Tardive dyskinesia, *TNF- α* Tumor necrosis factor α

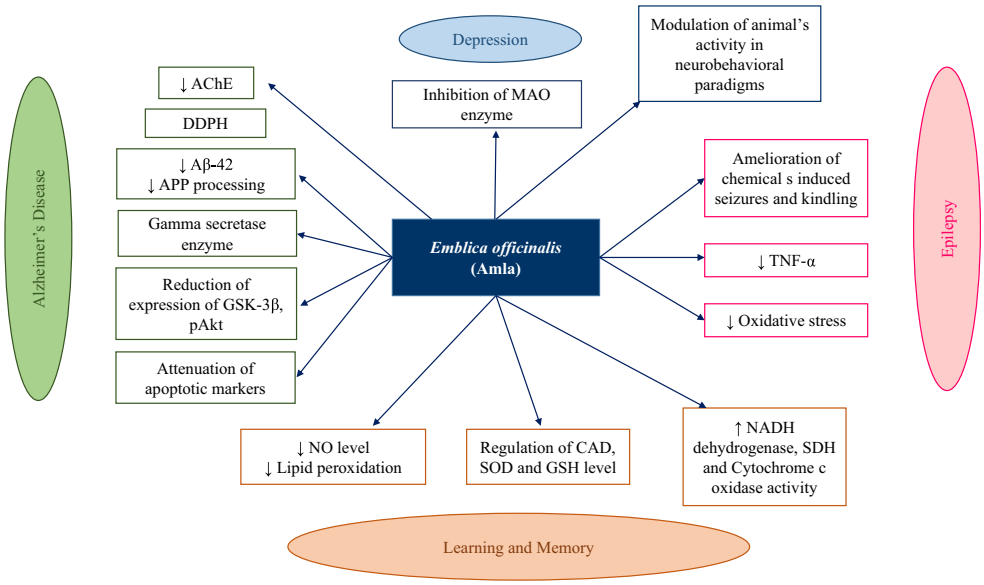

Fig. 1 Pharmacological actions of Emblica officinalis AChE: Acetyl cholinesterase; Aβ: Beta-amyloid; Akt: Protein Kinase B; APP: Amyloid precursor protein; CAD

drugs have been developed, but these impose several adverse effects on human health. To counteract these problems, the current line of research is targeting new therapeutic molecules with fewer associated side effects. Several medicinal plants have been investigated to fulfill the need of proper drug therapy controlling epilepsy (Noor et al. 2012; Arafa et al. 2013). The hydroalcoholic extract of *E. officinalis* given for 7 days in different doses viz. 300, 500, and 700 mg/kg i.p. in rats were evaluated in pentylenetetrazole (PTZ) and kainic acid-induced epilepsy, where it was found that pretreatment of *E. officinalis* alleviated generalized tonic seizure and status epilepticus respectively (Golechha et al. 2010, 2011). In addition to this finding, cognitive deficit associated with epilepsy was also observed to be upgraded following *E. officinalis* treatment. Similarly, it was cited to have potential to attenuate the kainic acid-induced increase in TNF-α in rats brain in a dose-dependent manner which is supposed to be its natural antioxidant and anti-inflammatory activity (Golechha et al. 2011). Since *E. officinalis* is a rich source of numerous therapeutically useful chemical constituents, Xie and co-workers evaluated the antiepileptic potential of epigallocatechin-3-gallat and polyphenol component present in *E. officinalis* in PTZ-induced epilepsy in male Sprague Dawley rats. Suppressed progression of PTZ-induced kindling as recorded in ECG in conjunction with improved activity in Morris water maze task indicating enhanced cognitive functions were observed, therefore confirming the potential ability of *E. officinalis* in the treatment of epilepsy (Xie et al. 2012).

E. officinalis in tardive dyskinesia

Depression is a pervasive, debilitating psychological disorder with significant sociological and clinical relevance. Some common symptoms of depression include altered mood, anhedonia, sleep, and psychomotor disturbances, etc. (Brigitta 2002). Pathologically, depression involves a decrease in dopamine, 5-hydroxytryptamine (5-HT), norepinephrine and thus, several antidepressants have been developed to ameliorate these underlying causes (Krishnan and Nestler 2008). Although synthetic drugs impart benefits in depressed patients, about one-third of the patients are not successfully treated even after several sequential monotherapies and combined treatments (McGrath et al. 2014).

In a study by Dhingra et al., aqueous extract *of E. officinalis* at a dose of 200 and 400 mg/kg was administered to Swiss albino mice for 14 days, after which the mice were subjected to tail suspension test and forced swim test to induce depression. Significant antidepressant-like activity was observed in mice treated with *E. officinalis*, and its efficacy was found to be comparable to established antidepressants such as imipramine, fluoxetine, etc. However, significant effect on locomotor activity was not observed. Additionally, a diminution in monoamine oxidase-A (MAO-A) enzyme in the brain was also noted, and administration of antagonists of α_1 adrenoceptors, serotonin receptors, dopaminergic D_2-receptor, and GABA-B receptors led to the cessation of antidepressant activity, reflecting interaction of *E. officinalis* with these receptors (Dhingra et al. 2012).

Clinical studies have reported that a decrease in neurotransmission in the synapse of patients with depression turns receptors to be super-sensitive which leads to a collective appearance of tardive dyskinesia in patients with depression (Davis et al. 1976; Kosel et al. 2007). Tardive dyskinesia is a disorder that encompasses involuntary, repeated body movements either rapid jerking movement or slow writing movement and also includes sticking out of tongue and smacking of the lips. It has been considered as a long-term complication of

neuroleptics (antipsychotics) or centrally acting dopamine receptor blocking drugs that are meant for mental illness (Kosel et al. 2007; Aquino and Lang 2014). To treat this disorder of abnormal movements, check on neuroleptic use or use in lower dose and medications such as valbenazine, tetrabenazine, or botulinum toxin have been recommended (Muller 2015). In addition to these synthetic drugs, administration of active tannoid principles of *E. officinalis* have also shown to improve haloperidol-induced tardive dyskinesia in rodents and henceforth, established the prophylactic effect of these phytoconstituents of *E. officinalis* against tardive dyskinesia (Bhattacharya et al. 2000a, b).

E. officinalis in learning and memory

Learning, the process of acquiring information, skill, and memory are psychological processes, which constitute major components of cognition. Learning indicates the process of acquiring new information and skill, while memory, the second important contributing factor of cognitive function, is the subsequent retention of information. Cognition encompasses different processes including knowledge, evaluation, attention, and memory (Dehaene and Naccache 2001). Elderly people are more prone to learning and memory impairment. In addition to this, cognitive impairment is also accompanied with, or a precursor to, several other neurological disorders. A varying number of mechanisms such as cholinergic dysfunction, oxidative stress, neuroinflammation, etc. are cited to be involved in cognitive impairment. Several researchers are working to provide therapeutic intervention leading to improvement of learning and memory. AChE inhibitors (donepezil, rivastigmine), NMDA receptor antagonist (memantine) and nootropics are prescribed to patients with dementia and Alzheimer's disease for improvement of cognition (learning and memory), but as mentioned before, there are several reports of adverse events, and therefore, new studies have been performed targeting the implementation of herbal medicines (Zameer et al. 2017). Nootropic (memory enhancing) effect of the wide range of herbal drugs has already been reported (Akram and Nawaz 2017).

A study on a traditional Ayurvedic preparation of *E. officinalis* called *Anwalachurna* was performed by employing exteroceptive (elevated plus-maze and Hebb-Williams maze) and interoceptive behavioral models and it was concluded that treatment with *Anwalachurna* led to significant improvement in memory and reversal of amnesia induced by scopolamine and diazepam in rats (Vasudevan and Parle 2007a, b). Later, a similar study investigating the therapeutic efficacy of the hydroalcoholic extract of *E. officinalis* in scopolamine-induced amnesia model in mice also gave promising results and indicated the potential use of *E. officinalis* in cognitive deficits caused as a result of cholinergic dysfunction (Golechha et al. 2012). These reported outcomes show that the nootropic potential of *E. officinalis* is due to its inhibitory potential against AChE enzyme leading to improved cholinergic flow. Its nootropic effects due to its potential influence on the cognitive pathway provides a compelling case for conducting further studies of this drug, consisting of either solitary administration or as an adjunct/combination therapy in the management of Alzheimer's disease and other neurodegenerative conditions (Vasudevan and Parle 2007a, b; Ashwlayan and Singh 2011; Golechha et al. 2012)

E. officinalis in stress and neuroprotection

Stress is a condition that highlights the adaptive response of our body to external demands and puts advantages of enhanced gene expression for neuroprotection and neurogenesis associated genes in brain parts (hippocampus). Although it is a beneficial response in a short period, it can impose significant adverse health effects in the long-term (Prokai and Berga 2016; Sannino et al. 2016). Since it is challenging to identify the chronic stress state clinically, some objective measures define chronic stress. The oxidative burden is contemplated as the chief contributing factor to stress, and other ailments arise with increasing age (Suomalainen and Battersby 2017).

E. officinalis has a particularly high antioxidant activity, and administration of *E. officinalis* tannins (emblicanin A, emblicanin B, punigluconin, and pedunculagin) in unpredictable footshock-induced alterations in oxidative free radical scavenging activity resulted in a reversal of changes in biochemical markers of oxidative stress. Furthermore, enhanced activity of antioxidant enzymes was observed in the frontal cortex and striatum of rat brain, which corroborated the previous observations (Bhattacharya et al. 2000a, b).

Stress has been granted as a critical factor for altered behavior and psychological state. Altered glucose and hormonal level mainly corticosteroids have also been found to be responsible for such stress-induced changes in psychological state. In a study by Kumar on restraint stress model in mice, it was observed that alcoholic extract of *E. officinalis* significantly controlled the increase in glucose and cortisol levels induced by stress and also led to improved performance in neurobehavioral parameters such as the elevated plus maze test. These findings which reflect the capability of *E. officinalis* to regulate altered behavioral and biochemical parameters depicts the positive effect of *E. officinalis* on anxiety and stress-induced physical and mental disorders (Kumar et al. 2013).

Noise exceeding 90 dB is regarded as a major stressor as it significantly influences mental health negatively. Wistar albino rats treated with *E. officinalis* preceding exposure to 100 dB noise for 4 h each day for 15 days were examined and a reversal of noise-induced behavioral changes in open

field and elevated plus maze, increased immobilization, rearing and fecal bolus were observed which in turn outlined the anti-stressor activity of *E. officinalis* against noise-induced stress (Wankhar et al. 2014).

Neuroprotection is a crucial aspect of recovering, regenerating or salvaging any drastic change in the nervous system. Currently available drugs imposing neuroprotection in human disease are based on the evidence of their neuroprotective potential in distinct animal models. (Vajda 2002). Neuroprotection has a vital role to play in numerous brain disorders including neurodegeneration. *E. officinalis* has been widely used in ancient Indian system of medicine for neurodegeneration. Akin to this, in vitro studies were performed on human neuroblastoma cells (SK N SH) and the prior treatment of these cells with aqueous or methanolic extract of *E. officinalis* (0.1–1.0 mg/ml) for 24 h was found with significant neuroprotection against H_2O_2-induced neuronal oxidative DNA damage appeared due to its antioxidant potential (Ramakrishna et al. 2014). Reddy and co-workers have reported the protective effect of *E. officinalis* fruit extract interpreted by reversal of the altered levels of NO, protein carbonyls and improved activity of endogenous antioxidant system and cytochrome C oxidase which resulted in attenuation of alcohol (20%) induced brain mitochondrial dysfunction in male Wistar rats (Reddy et al. 2011). In a study by Shalini and Sharma, fluoride-induced neurotoxicity model of rats was significantly attenuated in rats administered dried powder of *E. officinalis* (Shalini and Sharma 2015).

Conclusion and future perspective

Researchers are increasingly focusing on drugs of natural origin and ethnopharmacological research to find viable drug candidates for the treatment of numerous disorders. There is substantial evidence that supports the ability of *E. officinalis* in the therapy of various neurological disorders. Various formulations of *E. officinalis* ranging from tannins enriched fractions to ethanolic extracts to dried powder have been found efficacious in a multitude of animal studies of neurological ailments. Moreover, *E. officinalis* has been hypothesized to act through multiple neuroprotective pathways, which could be the reason behind its comprehensive pharmacodynamic effects. However, most of the studies on this plant has done so far have employed extracts, and little or no research has been on molecules behind the pharmacological activity of this multifaceted plant. We believe that further research is required to identify specific phytoconstituents in *E. officinalis* behind its pharmacological activity as well as to perform exhaustive preclinical studies on them in order to translate them into a viable clinical therapy. Semi-synthetic analogs of these molecules could also be developed to improve their activity. It is also important to evaluate the efficacy of *E. officinalis* in exhaustive clinical studies in order to uphold its use in traditional systems of medicine, which has been carried out for centuries as well as to develop it as a clinical therapy for the aforementioned neurological disorders.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests or any other conflicts of interest.

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