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The multifaceted role of bamboo in neuroprotection: Novel therapeutic insights and their mechanism of action

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Abstract

Neuroprotection is the strategy and mechanism that shields or prevents damage of the structure and function of neurons from cellular injuries induced by a variety of agents or neurodegenerative diseases. Neurodegenerative diseases affect millions of people worldwide with the main risk factor being advancing age. Various commonly used medications such as amantadine, memantine, donepezil, selegiline, galantamine and rivastigmine might have increasing incidences of resistance, undesirable side effects, high cost and lack of efficacy after prolonged use. This problem has led to renewed interest in the development of new herbal-based treatments. Bamboo and its products are well known ethnomedicine that have protective roles against neurodegenerative and central nervous system (CNS)-related disorders. Bamboo based lignoproteins, salt, extracts from *Bambusa spp*., *Phyllostachys spp.* and *Sasa spp*. have demonstrated neuroprotection *in vitro* and *in vivo* studies by suppressing apoptosis, preventing neuronal cell death, inactivating caspases, increased level of anti-apoptotic growth factors and reducing level of ROS that prevents excitatory neuron injuries. This indicates that bamboo can be a promising therapeutic agent for complementary treatment in neurological disorders and needs to be extensively investigated to be utilized and promoted as an efficient and economic therapeutics for treatment and prevention of neurodegenerative disorders.

Keywords Bamboo; Neuroprotection; Bioactive compounds; Therapeutics

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1. Introduction

Neurodegenerative disorders (NDs) are a group of conditions characterized by the progressive degeneration and dysfunction of the nervous system, primarily affecting neurons (nerve cells) in the brain and/or spinal cord affecting up to one billion people worldwide (WHO 2023). These disorders often result in the gradual decline of cognitive, motor, and sometimes even psychiatric functions. The exact causes of many NDs are not fully understood, but they are often associated with the accumulation of abnormal proteins in the nervous system. They are often chronic and progressive and cause an average annual mortality of 6.8 million people worldwide and the main risk factor being the advancing in age (WHO 2023). The most common NDs include Alzheimer's disease, Parkinson's disease, Amyotrophic disease, multiple sclerosis, Huntington's disease, frontotemporal dementia, prion disease, spinocerebellar ataxias, progressive supranuclear palsy, Wilson's disease *etc*. which share the common feature of progressive nerve cell degradation that in turn impact the life. The generation of reactive oxygen species (ROS) decreases the mitochondrial functioning by interfering the electron transport chain (ETC), reducing ATP production leading to nigrostriatal dopaminergic neuronal loss that directly contributes to the pathogenesis of NDs (Sharma et al. 2020). The diseases of the CNS often result in the deterioration of the cognitive as well as the intellectual abilities of the sufferers as includes loss of memory, difficulty in learning, motor coordination, and many other functional loses. The main causal factors of NDs are oxidative stress, neuroinflammation, apoptosis, excitotoxicity, mitochondrial dysfunction, iron accumulation, brain proteins. The formation of ROS is the first step in mitochondrial dysfunction, which could lead to the activation of endothelial cells and glial cells having a direct impact on the overproduction of proinflammatory cytokines and chemokines (Pawluk et al. 2020). Moreover, besides ageing, the other etiological factors of NDs include hypertension, genetic and/or environmental factors and infections.

2. Plant-based treatment for NDs

Neuroprotection refers to the ability of a strategy or mechanism to protect the structure and function of every neuron and especially the CNS from neural damage and injury induced by a variety of agents or NDs. Treatment of NDs is often limited, and management typically focuses on alleviating symptoms and improving overall well-being. Most neuroprotective agents are antioxidants, anti-inflammatory molecules and agents that protect neurons from cell death by attenuating the apoptotic signal transduction (Elufioye et al. 2017). Neuroprotective drugs such

as amantadine, memantine, donepezil, selegiline, edravone, galantamine and rivastigmine provides symptomatic relief and slows down the progression of diseases (Jankovic and Aguilar 2008). However, some of these standard drugs have drawbacks of poor water solubility, low stability, and bioavailability in aqueous media (Mozafari et al. 2023).

Plant based treatments are considered safe and cost effective and are in reach to almost everyone. Nature remains a great veritable source of medicines to mankind with many important drugs such as vincristine, artemisinin, gentamicin and the increasing incidence of resistance, undesirable side effects, high cost and lack of efficacy after prolonged usage has led to a renewed interest in the development of plant/natural based drug candidates that overcomes these shortcomings (Yao et al. 2017). In traditional practice of medicine, several plants have been reported effective in reducing the negative effects on nervous system associated with neurological diseases. Hence, a great deal of research focus has been given to herbs and other plant products in recent years for developing neuroprotective and memory enhancing medicines to treat age-related CNS diseases. Herbal medication, when combined with healthy lifestyle choices like eating right and getting regular exercise, can avoid diseases rather than treat them (Indira et al. 2023). Plant therapy, often known as herbal treatment, is the complementary and alternative medicine practice of making use of plant parts (leaf, branches, roots, bulbs, fruits, seeds *etc*.) for therapeutic effects.

Change in the dietary intakes by including and emphasizing fruits, vegetables, legumes whole grains, nuts, seeds *etc*. that are rich in antioxidants and healthy fats has been associated with reduced risk of cognitive decline. This plant base diet provides a variety of nutrients and bioactive compounds that health of CNS and overall health. Neuroprotection aims to either limit nerve death after CNS injury or protects the CNS from premature degeneration and other causes of nerve breakdown. Management of NDs is often disease specific. Several approaches to management are currently accepted, which either target disease pathogenesis or attempt to improve the symptoms experienced (Lamptey et al. 2022). The neuroprotective agents are free radical scavenging agents, anti-excitotoxic agents such as glutamate, apoptosis inhibitor, anti-inflammatory agents, neurotrophic factors, iron chelators and stimulants. The free radical scavenging agents are mainly the antioxidants that interact and reduce the impact of free radicals. They convert damaged and disease causing unstable free radicals into molecules that are more stable or easier for the body to manage. For example, vitamin E that have antioxidant properties

have shown to have preventive effect against Alzheimer's disease (Felman 2019). Plant-based treatments for NDs help manage symptoms, slow disease progression, or support overall brain health. The neuroprotectors available currently cannot reverse the existing damage, however, they may protect from further damage and degeneration. Extracts from plants such as *Gingko biloba*, *Curcuma longa*, *Bacopa monnieri*, *Panax ginseng*, *Salvia officinalis*, have been reported to have neuroprotective, anti-aging and memory enhancing properties (Ara et al. 2022). Green tea polyphenols have antioxidant and iron chelating properties that are used for development of neurodegenerative drug associated with oxidative stress (Nanami et al. 1998; Mira et al. 2002). Compounds such as polyphenols, quercetin, rotenone, piperine, that are extracted and isolated from plants help in prevention of neurological damage (Sharma et al. 2020).

3. Bioactive compounds in Bamboo

Bamboo has been used in traditional medicine for centuries as a seasonal delicacy and for other medicinal purposes throughout Asia. Several studies have envisioned the presence of major bioactive components, namely, phenolic compounds, polysaccharides, terpenoids, and alkaloids. The main phenolic compounds are phenolic acids and their derivatives, flavonoid and their derivatives. Ferulic acid, *p*-coumaric acid, caffeic acid, protocatechuic acid, *p*-hydroxybenzoic acid, catechin, synergic acid and chlorogenic acid are some of the major phenolic compounds and flavanols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins are the most common flavonoid whereas the terpenes in bamboo contain phytosterols mainly the β-sitosterol, campesterol, stigmasterol, cholesterol, ergosterol and stigmastanol (Tanaka et al. 2013; Lu et al. 2011; Mustaffa et al. 2022; Dadwal et al. 2022; Indira et al. 2022, 2023; Kalyan et al. 2023; Joshi et al. 2023) (Figure 1). The shoots have been proven to possess unusually high levels of acetylcholine (ACh) (Horiuchi et al. 2003). Predominant presence of monosaccharides such as galactose, glucose, arabinose, mannose, xylose, uronic acid and glucan are reported in bamboo. Dietary fiber is a type of polysaccharide that consists in higher quantity in bamboo mainly the shoot. It is non-digestible and act as roughage in the human diet thereby improving the digestive system with many health benefits (Kaur et al. 2021).

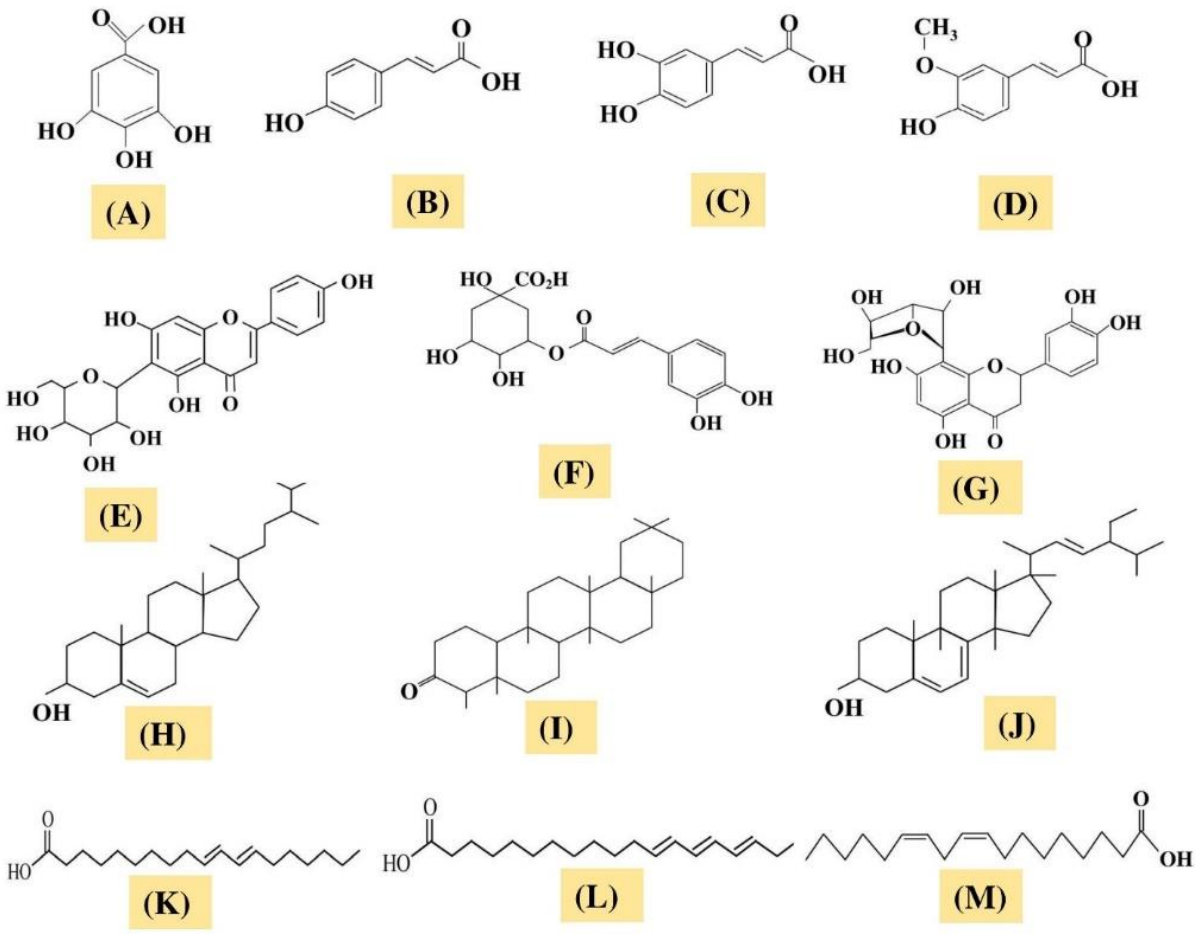

Figure 1. Major bioactive compounds in bamboo (A) Gallic acid, (B) *p*-coumaric acid, (C) Caffeic acid, (D) Ferulic acid, (E) Isovitexin, (F) Chlorogenic acid, (G) Orientin, (H) Stigmasterol, (I) Dihydrobrassicasterol, (J) Campesterol, (K) Linoleic acid, (L) Linolenic acid, (M) Linolic acid

4. Bamboo in neuroprotection

The various biologically active secondary metabolites belonging to polyphenolic groups, alkaloids and terpenoids act through diverse mechanisms of actions. The most important feature of these bioactive compounds is their potency of their antioxidant and anti-inflammatory mechanisms among others. Bamboo leaves are known to contain several phenolic compounds capable of preventing neuromelanin accumulation. Choi et al (2018) examined the inhibitory activity of an ethyl acetate fraction of 80% ethanol *P. nigra* leaf extract on tyrosinase, with melanin as a substrate. The authors reported that the bamboo leaf extract has an associated IC_{50}

value of 243.7 μg/mL. The anti-melanogenic effects of this extract have been evidenced to depend on the presence of important phenolic compounds, such as *p*-coumaric acid, caffeic acid, chlorogenic acid, luteolin, rutin, and catechin. The antioxidant capability of *P. nigra* leaves also inhibited superoxide dismutase. A scavenging potential of OH free radical with IC_{50} = 509.17 μg/mL was also reported. Khatun et al. (2013) showed that a 0.1 g/mL of an 80% methanolic *S. senanensis* leaf extract had an O_2 free radical scavenging activity of about 10%. Macwan et al. (2010) reported the NO free radical scavenging potential of *B. arundinaceae* leaf extracts with IC_{50} values of 644 μg/mL to 433 μg/mL when extracted with different solvents.

Bamboo extracts prepared from different parts were evaluated for the protection ability against various neurological disorders. Owing to high antioxidant and anti-apoptotic activity, bamboo parts and products such as leaf, rhizome, salt and bamboo derived lignophenols are reported to demonstrate the neuroprotective activity in animal models. The administration of leaves, either by infusion or direct consumption, has exerted anti-inflammatory, antioxidant, diuretic, expectorant, and anticarcinogenic properties (Jayarambabu et al. 2021; Seki et al. 2010). The influence of bamboo extracts on cholinergic, monoaminergic, glutamatergic and GABAergic systems was already assessed (Moreira et al. 2023). The polyphenols in bamboo, besides being a rich antioxidant, are attributed to numerous pharmacological roles such as anti-inflammatory effects and other biological activities related to enzyme inhibition, gene expression, and signal transduction. The protective effect against neurodegeneration by phenolic acids through inhibition of NF-κB and activator protein AP-1 and enhance expression of antioxidant protein such as HO-1 (heme oxygenase 1) and Nrf2 (nuclear factor) (Lee et al. 2005; Kim and Jang 2014). The protective effect of bamboo in protection from NDs have been illustrated in Figure 2. Terpenoids, alkaloids and polyphenols prevent the neuronal cell death through general anti-inflammatory and antioxidant mechanisms. Moreover, these compounds have shown to ameliorate the deleterious effect of protein aggregation such as Aβ and reversing the transmitter deficit associated with neurodegeneration (Elufioye et al. 2017).

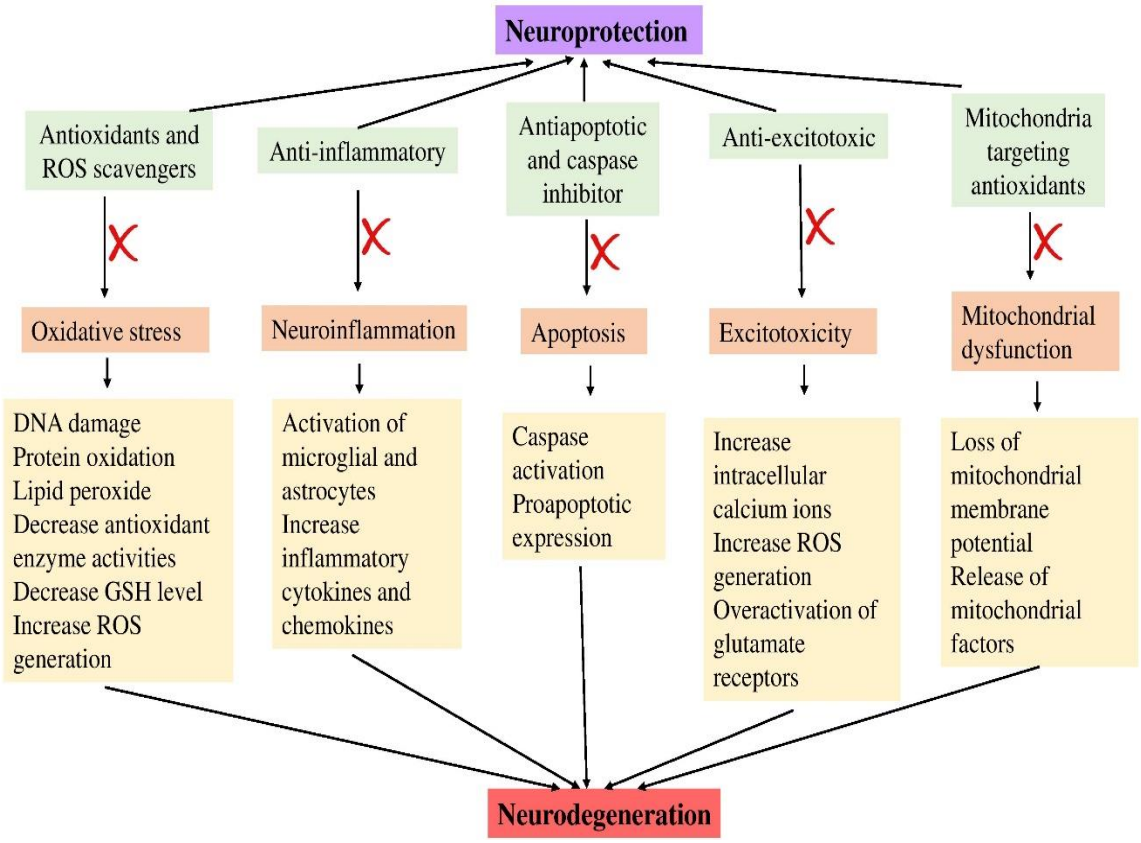

Figure 2. Mechanisms by which bamboo protects against neurodegeneration.

Neuronal toxicity is mediated and enhanced by reactive oxygen species and reactive nitrogen species by causing apoptosis and ultimately neuronal damage in NDs. This neuronal death has been reported to attenuated by antioxidants that scavenge free radical species (Nagai et al. 2022). The neuroprotective effect of bamboo has been accredited to its antioxidant mechanism and regulation of protein expression in brain. The crude ethanolic extract of *B. arundinaceae* leaf have been reported to restore the memory impairment in mice. The behavioral tests such as Morri's water maze test, pole climbing test and elevated maize test showed significant result in the dose of 200 mg/kg compared to standard drug piracetam. Moreover, AChE and MDA levels were downregulated and GSH level was upregulated in the mice of these groups. Molecular studies on gene expression further confirmed the downregulation of Bax and Bak genes and upregulation of Bcl-2. NR1, NR2B and GAP-43 proteins level was higher in the hippocampus of the mice treated with *B. arundinaceae* extract that might have reduced the cellular damage in brain (Jawaid et al. 2020).

Signal transduction to protect neuronal damage from apoptosis is a new therapeutic strategy to prevent NDs. Akao et al. (2004) reported the ameliorative effects of lignoprotein with potent antioxidant activity derived from *Phyllostachys bambusoides*, *Cryptomeria japonica*, *Fagus crenata*, and *Oryza sativa* by phase separation technique against apoptosis/cell death induced by H_2O_2 oxidative stress in human neuroblastoma SH-SY5Y cells. In their experiment, eleven kinds of lignophenols derivatives such as lignocatechol, lignoresorcinol, lignopyrogallol and lignocresol were synthesized and out of which seven exhibited protective activity. These lignophenol derivatives have the native lignin interunit with additional phenolic functionality. Among all examined lignophenol derivatives, a lignocresol derivative from *P. bambusoides* (lig-8) exhibited the most potent neuroprotective activity at 20 and 30 μM. This compound has further exhibited better anti-apoptotic properties compared to epigallocatechin gallate from green tea. The mechanism is stated as the prevention in activation of caspase-3 via either caspase-8 or caspase-9 and inhibition in dissipation of the mitochondrial membrane permeability transitions. Caspase-3 is cysteine-aspartic acid protease that is crucial mediator of programmed cell death (apoptosis) that is processed and activated by caspases 8, 9, and 10. The antiapoptotic activity was further supported as lig-8 inhibits dissipation of the mitochondrial membrane permeability transition induced by H_2O_2 or by the peripheral benzodiazepin receptor ligand PK11195. Lig-8 was also shown to have potent antioxidant activity in the H_2O_2 exposed cells, as assessed by flow cytometry using 5-(and-6)-chloromethyl-20, 70-dichlorodihydrofluorescein diacetate and *in vitro* ROS-scavenging potency. Moreover, lig-8 is highly water soluble that overcome the drawback of water insolubility nature of standard drug such as edravone. They suggested lig-8 as a promising antioxidant that affects the signaling pathway of neuronal cell death and that it would be of benefit to delay the progression of NDs. Lig-8 also reported to suppress apoptosis induced by oxygen-glucose deprivation, tunicamycin (endoplasmic reticulum [ER]–stress inducer), or proteasome inhibitor in pheochromocytoma cells (Ito et al. 2007). In addition, it reduced intravitreal N-methyl-D-aspartate–induced retinal damage (decreases in retinal ganglion cells and inner plexiform layer thickness) in mice.

Levodopa is a standard drug used for the treatment of Parkinsons disease but has some reported side effects of muscle contraction and dyskinetic movements that deteriorate motor function (Kleiner-Fisman et al. 2006). Ethanolic extract of *Bambusa vulgaris* leaf exhibited protective effects against neuronal damages and motor function deficit as indicated by the normal response

in touch, head withdrawal, foraging tests in *C. elegans*. Furthermore, the effects of L-DOPA were alleviated by the extract. Liu et al. (2015) evaluated the effect of bamboo leaf extract (B-extract) purchased from Johncan Biotechnology (Hangzhou, China) in both the behavioral and biochemical effects of dementia-induced mice through intraperitoneal injection of d-galactose and reported significant improvement in the spatial cognitive abilities. Senile dementia (SD) is a syndrome characterized by progressive neurological deterioration that causes long term deficit in memory and cognition. The behavioral assay was determined by subjecting three groups of mice (control, senile demented mice, and senile demented mice, treated with bamboo leaf extract daily for seven consecutive days) to a daily 5-D Morris water navigation test, recording the average path length and escape latency. After training for two days, average escape latency and path length of the rats in SD group were longer than control group suggesting that the rats in SD group had worse spatial memories whereas in B-extract+SD group escape latency and path length were significantly shortened compared to SD group which indicated improved spatial memory ability of dementia rats. The neurotransmitters content and activities of key enzymes in hippocampus and cerebral cortex of the rats were determined by ELISA method. The dementia model rats showed reduced levels of neurotransmitters including acetylcholine (ACh), epinephrine (E), norepinephrine (NE), and dopamine (DA), and increased activities of enzymes acetylcholine esterase (AChE) and monoamine oxidase (MAO). ACh content and AChE activity of the B-extract treated group indicated that the levels of these neurotransmitters were the highest. AChE is a hydrolase in the nervous system to degrade ACh and terminate related nerve impulse while MAO catalyzes oxidative deamination of monoamine neurotransmitters such as E, NE, and DA, and generates hydrogen peroxide to activate oxidative stress (Naaz et al. 2013; Mandel et al. 2007; Hureau et al. 2010). Treatment with B-extract (20 mg/kg/day) for 7 weeks significantly inhibited the enzyme activity compared with untreated dementia rats, and raised the levels of ACh, E, and DA in the hippocampus. Increase in synthesis and release of neurotransmitters or decrease in their degradation may improve learning and memory. In addition, treatment with B-extract elevated the level of inhibitory amino acid GABA (γ-aminobutyric acid) and reduced the level of oxidative stress producing excitatory neurotransmitter glutamate (Glu) to prevent excitatory injury of neurons.

Kang et al (2022) evaluated the neuroprotective activity of *Sasa borealis* water extract (SBW) and *S. borealis* ethanol extract (SBE) on hydrogen peroxide (H_2O_2)-induced oxidative stress by

measuring the radical scavenging activities and intracellular ROS production. HPLC analysis of extracts revealed that SBE had a high level of isoorientin than SBW which contributes to its higher antioxidative activities in 2,20-azino-bis-(3-ethylbenzothiazolin-6-sulfonic acid) diammonium salt (ABTS+) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays. Treatment of pheochromocytoma 12 (PC12) cells with SBE significantly reduced ROS generation along with increase in antioxidant enzymes and factors including heme oxygenase-1 (HO-1), superoxide dismutase 2 (SOD2), catalase (CAT), glutathione peroxidase (GPx) and NF-E2-related factor-2 (Nrf-2). Administration of black bamboo rhizome extracts (BBRE) from *P. nigra* significantly improves cognitive dysfunction neurological function score and learning and memory abilities along with reduced cerebral oedema and cerebral infarction area in Sprague-Dawley rats having cerebral ischemia-reperfusion injury (Yi et al. 2022). Rats were randomly grouped as control, middle cerebral artery occlusion (MCAO), low-dose (BBRE) drug, and high-dose (BBRE) drug groups, and each group was assessed for neurological impairment, cerebral infarction area, water content in brain tissue and changes in learning and memory abilities using the long scoring method, triphenyl tetrazolium chloride staining, Elliott formula and Morris's water maze (MWM) tests, respectively. Both black bamboo rhizome extract treatment groups reported to have lower neurological dysfunction score, significantly smaller cerebral infarction area and reduced cerebral oedema when compared with MCAO group, however the effect was more obvious in the high-dose drug group than in the low-dose drug group. In the MWM test, the incubation period was significantly reduced, the number of platform crossings was significantly increased, and the search time was prolonged in the drug groups compared with those in the MCAO group. Furthermore, increased expression cyclic adenosine phosphate response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) in the hippocampus of the BBRE drug groups compared to that in the MCAO group. BBRE improves cognitive function of rats by upregulating the expression of Bcl-2 (antiapoptotic) and downregulating the expression of apoptotic proteins (caspase 3, and Bax) in the brain in rats with cerebral ischaemia-reperfusion injury.

Hemicellulose polysaccharides from leaves of *P. pubescens* extracted with the phototungstic acid consisting of Xyl*p*, Man*p*, Glc*p*, and Ara*p* has shown protective effect has H_2O_2 induced oxidative stress in HepG2 cells by improving the enzyme activities of SOD, CAT, and GSH-Px and decreasing the production of MDA and ROS (Xiao et al. 2022).

Bamboo salt (BS) is a traditional salt of East-Asian countries, prepared by repeatedly roasting sun-dried salt within a bamboo stem to enrich it with trace elements. It is considered as healthier substitute to common salt due to its well-known therapeutic effects for diseases such as viral diseases, dental plaque, gastropathy, diabetes, circulatory organ disorders, cancer, and anti-inflammatory disorders (Kim et al. 2010; Zhao et al. 2013; Sidhu et al. 2014; Kim et al. 2016). Jeong et al. (2014) evaluated soy sauce made from bamboo salt instead of common salt, known as bamboo salt soy sauce (BSSS) for enhanced cytoprotective properties using a hydrogen peroxide (H_2O_2)-induced neuronal cell death rat model. Rat neuronal cells were pretreated with various concentrations (0.001, 0.01, 0.1, 1 and 10%) of BSSS, traditional soy sauce (TRSS) and brewed soy sauce (BRSS) and were subsequently exposed to H_2O_2 (100 μM) to examine the viability of neuronal cells and the DNA fragmentation. The result demonstrated that BSSS administration was non-toxic to rat neuronal cells up to 10% and increase cell viability with greatest increase at 0.01% concentration, whereas TRSS and BRSS pretreatment reduced neuronal cell viability in a concentration-dependent manner. Furthermore, TUNEL analysis showed that 0.1% BSSS pretreatment significantly inhibited H_2O_2-mediated neuronal cell apoptosis and DNA fragmentation. Pretreatment of neuronal cells with BSSS significantly reduced the levels of ROS generated by H_2O_2 and increased the levels of anti-apoptotic growth factors such as phosphorylated AKT and phosphorylated glycogen synthase kinase-3β. The observed effects were blocked by administration of 10 μM LY294002, a PI3K inhibitor, which indicate that neuroprotective effects of BSSS were associated with activation of PI3K/Akt pathway. Mineral contents of BSSS were also analyzed using inductively coupled plasma-atomic emission spectrometer (ICP-AES) and it was found to be enriched in K, Ca, Mg, S, Fe, P, Rb, Mo, V, Au, Pt, Ge, and Se. Among them, the levels of K, Ca, P, Rb, Mo, V, Au, and Se in BSSS were higher, as compared with those of TRSS and BRSS.

Conclusion

Plant based treatment and preventive measures for NDs are an area of growing interest. Several species of bamboo such as *B. arundinacea*, *B. vulgaris*, *P. bambusoides*, *P. nigra*, *P. pubescens*, *S. borealis*, *S. senanensis* have neuroprotective properties by various mechanism and pathways. The extracts, lignoproteins, lignocellulose, hemicellulose and salt of bamboo have also shown protective effects against Parkinson’s disease, senile dementia and other neurological disorders.

Therefore, the future prospects of bamboo in neuroprotection are promising, as researchers continue to explore the therapeutic potential of various bamboo-derived compounds for the prevention and treatment of NDs and neurological disorders. However, it is important to note that while these approaches show promise, more research is needed to fully understand their effectiveness and safety in treating NDs. Additionally, individual responses to these treatments can vary. Therefore, further research on improving the bioavailability and bioactivity of bamboo-derived compounds to ensure they can reach the brain and exert their neuroprotective effects effectively. This may involve developing novel delivery systems or formulations.

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Conflict of Interest

The authors declare there is no conflict of interest

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