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Neuroprotective Properties of Aqueous Extracts from Natural Sources

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Abstract: Neurodegenerative diseases results in slow neuronal death that accompanied with losing cognitive functions and sensory dysfunction. In efforts to discover new strategies for neurodegenerative therapy, natural herbal sources products have aroused interest in the research community and in the pharmaceutical industry for their neuroprotective activity. Mixtures or extracts of natural products might have advantages compared to individual natural compounds, as they have multiple simultaneous target approaches, which could be a novel treatment option for neurodegenerative, considering the complexity of its pathophysiology. This review mainly focuses in vitro and in vivo trials of natural aqueous extract and compiles information on their mechanism of actions.

Keywords: aqueous extracts, medicinal plants, neuroprotection, oxidative stress, secondary plant metabolites.

Introduction

Central nervous system diseases, especially neurodegenerative diseases such as Parkinson's and Alzheimer's, are major public health concerns around the world, as their prevalence is increasing, and they are associated with social and financial issues. There has recently been an increase in interest in medicinal plants whose phytochemical components can improve health or provide medications with long-term effects. In response, a number of medicinal plants work as specific medications and can be utilized to address specific health effects over short or extended periods of time (Amir Rawa, Mazlan, Ahmad, Nogawa, & Wahab, 2022; Dey, Nandy, Mukherjee and Pandey, 2020).

Plant extracts, isolated phytochemicals, and herbal formulations are known to mitigate radical induced cell damage. In various preclinical and clinical studies, the underlying molecular mechanism of action of such products and their therapeutic applications were found to be promising (Cui, Lin and Liang, 2020).

The literature related to the topic indicates the proven efficacy of herbs and natural products in the treatment of several neurological and psychological disorders (Chiavaroli et al., 2021; Cui et al., 2020; Leclerc, Dudonne and Calon, 2021).

Medicinal plants have been extensively studied for the presence of natural antioxidants, but essential oils or hexane, acetone, ethanol, methanol, and carbon dioxide extracts have received the most attention (Jha and Sit, 2022).

In recent years, new extraction technologies need to be more environmentally friendly. Also, the Eco-Friendly extraction must to reduce synthetic chemicals, shorter operational time, and improved yield and quality of the extract (Jha et al., 2022).

Aqueous extracts obtained from herbal have a protective effect against lipid oxidation. This is due to a high content of phenols that may also be active in eradicating active oxygen species and suppressing their effects, which is believed to be the case in tea phenols (Plaza, Amigo-Benavent, del Castillo, Ibáñez and Herrero, 2010; Triantaphyllou, Blekas and Boskou, 2001).

Neurodegenerative disorders are closely linked to the aging of individuals. Moreover, is it closely linked to pathological changes in nerve cells that manifest and persist throughout the human lifespan. Such neuronal changes or lesions are characterized by tangles of nerve fibres and increased presence of β-amyloid and tau hyperphosphorylate in the brain, ultimately leading to a decline in nervous system function (Cui et al., 2020). The antioxidants found in extracts plants can successfully scavenge free radicals, protect cells, postpone aging, and fend off diseases linked to aging. Therefore, the function of plant antioxidants applies not only to protecting nerve cells, but also to protecting the body's entire nervous system.

This review will highlight the therapeutic potential of natural extracts herbs and their bioactive compounds that exert neuroprotective effects on the pathologies of neurodegenerative diseases.

Various Neurodegenerative Disorders

Neurodegenerative diseases are a group of disorders characterized by the breakdown and subsequent loss of neurons. These changes in the human brain can cause the patient's cognitive or functional deterioration over time. Many neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis, are characterized by its pathological condition (MS) (Eddin, Jha, Meeran, Kesari, Beiram and Ojha, 2021). As seen with the various neuropathologies, neuronal deterioration accelerates with age and is especially severe in old age. Most neurodegenerative diseases are still incurable today. As previously stated, current treatment only relieves symptoms and does not slow disease progression, emphasizing the need for more effective treatment strategies. According to estimates, neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias will account for 38% of global disability by 2030, as measured by years of life lost due to disability (Afzal et al., 2022).

As shown in figure 1, the molecular factors involved in neurodegenerative diseases are (1) specific protein dynamics coupled to degradation and aggregation of the impaired protein, (2) formation of free radicals and oxidative stress, (3) mitochondrial dysfunction and deficient bioenergetics, and (4) pesticide and metal toxicity (Afzal et al., 2022).

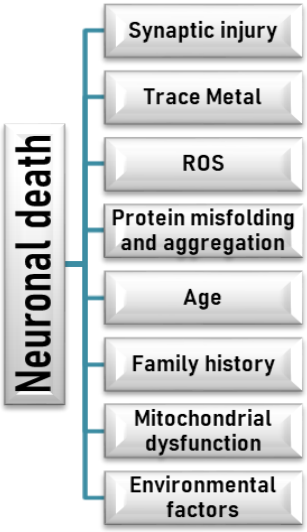

Figure 1. Physiopathological factors that may contribute to neurodegeneration (Afzal et al., 2022).

Parkinson’s Disease. Parkinson's disease is a neurological disorder of the motor system that slowly worsens with age and typically affects people over 50. But individuals under 50 can also be impacted. A-synuclein is a protein with 140 amino acids that was found to be present in the brain. It is primarily expressed in the pre-synaptic cleft of nerve cells and is involved in neuronal differentiation, dopamine synthesis regulation, and neuronal apoptosis suppression. The balance between α-synuclein's monomeric and oligomeric forms prevents it from forming a fibrillary structure under normal physiological circumstances (Afzal et al., 2022).

Alzheimer’s Disease. On the molecular mechanism of catechins, numerous in vivo, in vitro, and in silico studies have been carried out. Catechins' antioxidant properties might aid in preventing neurodegeneration. As already mentioned, late-onset neurodegenerative diseases are associated with increased oxidative stress. Patients with Alzheimer's disease have been found to have higher levels of peroxidised lipids, proteins, and DNA. Rats were given green tea catechins (0.5 percent in water) for 26 weeks, and it was discovered that this prevented amyloid-induced cognitive impairment. In comparison to controls, lipid peroxide and ROS levels in the hippocampal and plasma were both 20% lower (Afzal et al., 2022).

Down syndrome is a genetic condition associated with intellectual disabilities that are brought on by a third copy of chromosome 21. It is characterised by a number of recognisable facial characteristics, including epicanthus, a flattened face, upturned eyes, and hypotonia. Because of an imbalance between massive synaptic suppression in the hippocampus and excessive cerebral cortex activation, the cognitive abnormalities in Down syndrome range in intensity (Dierssen, 2012).

Neuroprotective Effects of Herbal Products

Natural products have been shown to play neuroprotective roles in almost all of the above-mentioned molecular models (table 1). When focusing on natural product mixtures and extracts, the observed neuroprotective effects have typically been recognized as being obtained through anti-oxidative or anti-neuroinflammatory activities, preventing A and tau protein aggregation, and enhancing cholinergic signalling (Chen, Drew, Berney and Lei, 2021).

The cholinergic system is linked to a variety of cognitive processes, including memory and learning. The brain and hippocampus

receive most of their innervation from cholinergic neurons. By facilitating the transfer of the acetyl group from the coenzyme acetyl-CoA to choline, they release choline O-acetyltransferase (ChAT), which contributes to the creation of acetylcholine (ACh). ACh is hydrolyzed back to choline by the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are expressed at lower levels than AChE. According to the cholinergic hypothesis, cognitive problems in AD patients are brought on by a reduction in cholinergic neurotransmission and the death of these neurons. Researchers discovered that, in addition to ChAT's mRNA expression level declining in the AD brain; its activity is also declining, occurring independently of synaptic loss (Wojtunik-Kulesza, Oniszczuk, Moldoch, Kowalska, Szponar, & Oniszczuk, 2022). An in vitro study of aqueous extracts from 80 traditional Chinese medicinal plants (from the Berberidaceae, Ranunculaceae, and Rutaceae families) revealed that extracts high in isoquinoline alkaloids effectively inhibit AChE activity (Chen et al., 2021).

To prevent tau aggregation, an aqueous extract of *Glycyrrhiza inflata* can improve the growth of the repeat domain and axons in mutant tau protein in vitro. This extract can also increase the expression of unfolded protein response-mediated chaperones, which helps to prevent tau misfolding. The main compound extracted from *Cornus officinalis* is cornel iridoid glycoside (Chang et al., 2016).

The oral administration of the aqueous *Benincasa hispida* L. pulp extract to AD mice prior to the bilateral intracerebroventricular colchicine infusion prevented senile plaques development. The chemical components that contain the antioxidant-active flavanols, flavonoids, and vitamins A, C, and E may be responsible for this neuroprotective action. The prevention of dentate granule cell death in the hippocampus and the prevention of the extracellular deposition of senile plaques in a colchicine-induced Alzheimer's Disease rat modelled researchers to the conclusion that *B. hispida*, with its preventive potential for Alzheimer's Disease through antioxidant scavenging actions, protected rat neurons from the damage caused by colchicine-induced oxidative stress (Chen et al., 2021).

Other research has shown that the aqueous extract of P. lentiscus leaves and the ethanolic extract of its oleoresin have AChE inhibitory activity, with IC50 values of 13.67 0.69 g/mL and 6.5 g/mL, respectively (Moeini, Memariani, Asadi, Bozorgi and Gorji, 2019).

G. inflata (*Fabaceae*) aqueous extract can further upregulate unfolded protein response-mediated chaperones to reduce tau misfolding (Chang et al., 2016).

Berberis bealei Fortune (*Berberidaceae)*, *Coptis chinensis Franch* (*Ranunculaceae*), and *Phellodendron chinensis* (*Rutaceae*) were shown to effectively inhibit AChE function in vitro in a study using aqueous extracts from 80 traditional Chinese medicinal plants. Berberine, coptisine, and palmatine alkaloid combinations have been found to have synergistically enhanced inhibitory activity (Kaufmann, Kaur Dogra, Tahrani, Herrmann and Wink, 2016).

Table 1

Plant metabolites and aqueous extracts with neuroprotective potential

Scientific name	Country	Type of extract	Model	Target	Discution	Source
Ocimum sanctum Linn.	India	aqueous extract, refluxed at 75–80 ◦C	Wistar rats; male; maximal electroshock-, atropine-, and cyclosporine-induced dementia	AChE	cognitive behavioral performance improvement	(Giridharan, Thandavarayan, Mani, Ashok Dundapa, Watanabe, & Konishi, 2011)
Coffea arabica L.	UK	boiled water extraction	in vitro enzymatic assay	AChE	AChE inhibition, IC50: 0.41 ± 0.004 mg/mL	(Okello, Savelev, & Perry, 2004)
Glycyrrhiza inflata	China	Aqueous extract	in vitro		Reduction in ROS and tau misfolding, potent anti-Aβ aggregation and radical-scavenging activities. Suppressed the production of NO, TNFα, IL-1β, PGE2, and/or Iba1	(Chang et al., 2016)
Benincasa hispida L.	China	Aqueous extract	rats		Prevented SP formation; antioxidant scavenging actions; Aqueous extract prevention of dentate	(Chang et al., 2016)

					granule cell destruction in the hippocampus and by preventing the extracellular SP deposition	
Camellia sinensis	USA	aqueous extract of green tea	in vitro enzymatic assay	AChE, BuChE, and BACE-1	AChE inhibition, IC50: 7.2 µg/mL	(Qosa et al., 2015)
Camellia sinensis, WTE		aqueous extract of white tea	in vitro enzymatic assay	AChE	AChE inhibition, IC50: 8.06 µg/mL	(Okello, Leylabi, & McDougall, 2012)
Camellia sinensis, GTE-PG		aqueous extract of green tea processed through simulated gastrointestinal digestion to obtain post-gastric digested extract	in vitro enzymatic assay	AChE	AChE inhibition, IC50: 17.84 µg/mL	(Okello et al., 2012)
Camellia sinensis, GTE-CA	UK	aqueous extract of green tea processed through simulated gastrointestinal digestion to obtain colon-available digested extract	in vitro enzymatic assay	AChE	AChE inhibition, IC50: 9.59 µg/mL	(Okello et al., 2012)
Camellia sinensis, WTE-PG	UK	aqueous extract of white tea processed through simulated gastrointestinal digestion to obtain post-gastric digested extract	in vitro enzymatic assay	AChE	AChE inhibition, IC50: 16.1 µg/mL	(Okello et al., 2012)
Camellia	UK	aqueous	in vitro	AChE	AChE	(Okello et

sinensis, WTE-CA		extract of white tea processed through simulated gastrointestinal digestion to obtain colon-available digested extract	enzymatic assay		inhibition, IC50: 4.22 µg/mL	al., 2012)
Camellia sinensis	Chine	aqueous extract of black tea	in vitro enzymatic assay	AChE and BuChE	AChE inhibition, IC50: 0.06 ± 0.005 mg/mL; BuChE inhibition, IC50: 0.05 ± 0.007 mg/mL	(Okello et al., 2004)
Camellia sinensis	Serbia	aqueous extract of green tea	Wistar rats; male; injection with green tea extract, saline, or $AlCl_3$ into the left-brain hemisphere cornu ammonis region 1 of the hippocampus	AChE	↑COX and AChE activities with GTE injection, ↓$AlCl_3$ neurotoxicity, 3-epigallocatechin gallate and epicatechin in extract improves cholinergic synaptic functions	(Jelenkovic et al., 2014)
Camellia sinensis	India	brewed at 85 ◦C	Wistar rats, male, $AlCl_3$ (100 mg/kg, i.p. 60 days) induced AD	AChE, APP, β and γ secretases, Aβ	memory-enhancing effect ↓TBARS, ↑GSH, ↑SOD, ↑catalase, ↑GPx	(Mathiyazahan, Justin Thenmozhi, & Manivasagam, 2015)
Pistacia atlantica		aqueous extract	In vitro	AChE inhibitory activity		(Moeini et al., 2019)

Note: AchE, acetylcholinesterase; BuChE, butyrylcholinesterase; BACE-1, β-secretase; COX, cyclooxygenase; TBARS, thiobarbituric acid reactive substances; GSH, glutathione; SOD, superoxide dismutase; GPx, glutathione peroxidase;

CONCLUSIONS

Mounting evidence has demonstrated the great neuroprotective potentials of natural products and natural bioactive compounds in neurodegenerative disorders treatment with few harmful side effects.

Among the many mechanisms are activity targeting cholinergic neurotransmission and neuroinflammation; generating an imbalance of iron in the organism; inhibiting α-synuclein, as well as BACE and MAO; affecting Aβ accumulation and aggregation; and reducing tau phosphorylation, as well as inducing anti-inflammatory and antioxidant effects.

The plant metabolites and their combinations are a valuable collection of natural products that should be tested to prevent and effective treat AD. These naturally based drugs will surely have fewer side effects than the currently available pharmacological treatments.

REFERENCES

Afzal O., Dalhat M.H., Altamimi A.S.A., Rasool R., Alzarea S.I., Almalki W.H., Murtaza B.N., Iftikhar S., Nadeem S., Nadeem M.S. and Kazmi, I., 2022, Green Tea Catechins Attenuate Neurodegenerative Diseases and Cognitive Deficits. Molecules, 27(21).

Amir Rawa M. S., Mazlan M.K.N., Ahmad R., Nogawa T. and Wahab H.A., 2022, Roles of Syzygium in Anti-Cholinesterase, Anti-Diabetic, Anti-Inflammatory, and Antioxidant: From Alzheimer's Perspective. Plants (Basel), 11(11).

Chang K.H., Chen I.C., Lin H.Y., Chen H.C., Lin C.H., Lin T.H., Weng Y.T., Chao C.Y., Wu Y.R., Lin J.Y., Lee-Chen G.J., & Chen C.M., 2016, The aqueous extract of *Glycyrrhiza inflata* can upregulate unfolded protein response-mediated chaperones to reduce tau misfolding in cell models of Alzheimer's disease. Drug Des Devel Ther, 10:885-896.

Chen X., Drew J., Berney W. and Lei W., 2021, Neuroprotective Natural Products for Alzheimer's Disease. Cells, 10(6).

Chiavaroli A., Balaha M., Acquaviva A., Ferrante C., Cataldi A., Menghini L., Rapino M., Orlando G., Brunetti L., Leone S., Recinella L. and di Giacomo V., 2021, Phenolic Characterization and Neuroprotective Properties of Grape Pomace Extracts. Molecules, 26(20).

Cui X., Lin Q. and Liang Y.,2020, Plant-Derived Antioxidants Protect the Nervous System from Aging by Inhibiting Oxidative Stress. Front Aging Neurosci, 12, 209.

Dey A., Nandy S., Mukherjee A. and Pandey D.K., 2020, Plant Natural Products as Neuroprotective Nutraceuticals: Preclinical and Clinical Studies and Future Implications. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences, 90(5):929-943.

Dierssen M., 2012, Down syndrome: the brain in trisomic mode. Nat Rev Neurosci, 13(12):844-858.

Eddin L.B., Jha N.K., Meeran M.F.N., Kesari K.K., Beiram R. and Ojha S., 2021, Neuroprotective Potential of Limonene and Limonene Containing Natural Products. Molecules, 26(15).

Giridharan V.V., Thandavarayan R.A., Mani V., Ashok Dundapa T., Watanabe K. and Konishi T., 2011, *Ocimum sanctum* Linn. leaf extracts inhibit acetylcholinesterase and improve cognition in rats with experimentally induced dementia. J Med Food, 14(9):912-919.

Jelenkovic A., Jovanovic M.D., Stevanovic I., Petronijevic N., Bokonjic D., Zivkovic J. and Igic R., 2014, Influence of the green tea leaf extract on neurotoxicity of aluminium chloride in rats. Phytother Res, 28(1):82-87.

Jha A.K. and Sit N., 2022, Extraction of bioactive compounds from plant materials using combination of various novel methods: A review. Trends in Food Science & Technology, 119:579-591.

Kaufmann D., Kaur Dogra A., Tahrani A., Herrmann F. and Wink M., 2016, Extracts from Traditional Chinese Medicinal Plants Inhibit Acetylcholinesterase, a Known Alzheimer's Disease Target. Molecules, 21(9).

Leclerc M., Dudonne S. and Calon F., 2021, Can Natural Products Exert Neuroprotection without Crossing the Blood-Brain Barrier? Int J Mol Sci, 22(7).

Mathiyazahan D.B., Justin Thenmozhi A. and Manivasagam T., 2015, Protective effect of black tea extract against aluminium chloride-induced Alzheimer's disease in rats: A behavioural, biochemical and molecular approach. Journal of Functional Foods, 16:423-435.

Moeini R., Memariani Z., Asadi F., Bozorgi M. and Gorji N., 2019, Pistacia Genus as a Potential Source of Neuroprotective Natural Products. Planta Med, 85(17), 1326-1350.

Okello E.J., Leylabi R. and McDougall G.J, 2012, Inhibition of acetylcholinesterase by green and white tea and their simulated intestinal metabolites. Food Funct, 3(6):651-661.

Okello E.J., Savelev S.U. and Perry E.K., 2004, In vitro anti-beta-secretase and dual anti-cholinesterase activities of *Camellia sinensis* L. (tea) relevant to treatment of dementia. Phytother Res, 18(8), 624-627.

Plaza M., Amigo-Benavent M., del Castillo M.D., Ibáñez E. and Herrero M., 2010, Facts about the formation of new antioxidants in natural samples after subcritical water extraction. Food Research International, 43(10):2341-2348.

Qosa H., Mohamed L.A., Batarseh Y.S., Alqahtani S., Ibrahim B., LeVine H. 3rd, Keller J.N. and Kaddoumi A., 2015, Extra-virgin olive oil attenuates amyloid-beta and tau pathologies in the brains of TgSwDI mice. J Nutr Biochem, 26(12):1479-1490.

Triantaphyllou K., Blekas G. and Boskou D., 2001, Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. Int J Food Sci Nutr, 52(4): 313-317.

Wojtunik-Kulesza K., Oniszczuk T., Moldoch J., Kowalska I., Szponar J. and Oniszczuk A., 2022, Selected Natural Products in Neuroprotective Strategies for Alzheimer's Disease-A Non-Systematic Review. Int J Mol Sci, 23(3).