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Role of phytochemicals in the pharmacological management of neurodegenerative disorders

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Abstract

Neurodegenerative diseases are a broad category of pathological illnesses characterized by the gradual deterioration of neuronal cells and the connections between the nervous system. These disorders mainly affect neuronal dysfunction and may lead to issues with movement, thinking, feeling, and strength. Molecular studies have shown that aberrant protein aggregation, neuroinflammation, mitochondrial malfunction, excessive production of reactive oxygen and nitrogen species, and other stress-related metabolic changes may cause neuronal cell death. Standard treatments for neurodegenerative diseases may only alleviate symptoms and slow the disease's course; none of these diseases are currently treatable. Because they are progressive and currently have no cure, neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's present enormous obstacles. More and more research is focusing on phytochemicals-bioactive substances sourced from plants-and their potential neuroprotective benefits, such as antioxidant, anti-inflammatory, and anti-apoptotic capabilities.

Keywords: Neurodegenerative, Phytochemicals, Neuroprotective, Diseases, Symptoms

Introduction

A major issue is neurodegenerative illnesses. Worldwide, there are an estimated 26.6 million individuals with Alzheimer's disease (AD), and the incidence of the condition is rising, according to a consensus reached using the Delphi method. In addition, projections show that this figure will rise to 106.2 million by the year 2050. An estimated 6.3 million people worldwide suffer from Parkinson's disease (PD), with 1.2 million of them people residing in Europe. Europe has a frequency of 4-8 cases per 100,000 people for Huntington's disease (HD), whereas the USA has a prevalence rate of 2-7 cases per 100,000 people for amyotrophic lateral sclerosis (ALS).

Throughout the course of many neurodegenerative disorders, patients may have a consistent pattern of symptoms. Increased oxidative and nitrosative stress, mitochondrial dysfunction, protein misfolding and aggregation, synapse loss, and reduced neuronal survival are the primary physiological signs of degenerative illnesses. Toxic protein exposure causes immune cells and neurons to expend a great deal of energy defending themselves against the environmental stress caused by nitrogen and oxygen species. This triggers apoptosis by causing mitochondria to fail and release cytochrome C and other proteins involved in mitochondrial activity. A major contributor to neuronal death is this excess of protein aggregation, which alters cellular signaling and neuronal function.

As a big societal issue, Alzheimer's disease (AD) is widely acknowledged as one of the most complex neurodegenerative illnesses. It is a long-term neurological disease that causes cognitive decline and dementia to worsen over time. The number of persons living with dementia has been increasing at a fast pace, driven by the aging populations in several nations. Dementia is not just a disease of the elderly; it may even strike youngsters who are overweight. There is no effective treatment for Alzheimer's disease at this time.

Examples of neurodegenerative illnesses are Alzheimer's

disease (AD) and Parkinson's disease (PD), which are defined by the gradual breakdown and malfunction of the neurological system. Neurons are the fundamental units of the brain and spinal cord, and these disorders mostly impact them. As a result, cognitive abilities, motor control, and general neurological function deteriorate with time. A longer life expectancy is a contributing factor to the increasing incidence of neurological diseases in recent decades. World Health Organization data shows that there are 55 million people living with dementia worldwide, and that number is rising by around 10 million cases each year (March 15, 2023).

There are serious issues with public health caused by the fast-rising incidence of neurological illnesses. A rich chemical library for the creation of new drugs against neurodegenerative illnesses may be found in traditional medicine and phytochemicals. These substances often have several targets and an abundance of chemical scaffolds. Traditional medicine and natural compounds derived from plants may help with cognitive impairment, motor dysfunction, emotional instability, and more, according to previous clinical data and pharmacological research.

Literature Review

Mishra, Akanksha *et al*. (2024) [1]. A number of neurodegenerative diseases, including Alzheimer's disease (AD), have found relief via the use of phytochemicals and medicinal plants. No medication has been licensed by the FDA to directly address the pathophysiology of AD. We still have a way to go before we can fully restore cognitive function and treat symptoms similar to psychosis. Medicinal plants have attracted a lot of attention from researchers since they are relatively harmless and have minimal adverse effects. Anticholinesterase activity, glutamate toxicity, inflammation, free radical formation, Amyloid β (Aβ) toxicity, and mitochondrial dysfunction are some of the underlying mechanisms in Alzheimer's disease (AD). There are a number of plant-based phytochemicals that have shown promise in combating these targets. These include quercitrin, andrographolide, paenol, salicornia europaea, curcuma longa, citrus junos tangaka, cassiae semen, centella asiatica, and a host of traditional medicinal plants from Iran, Turkey, China, and Europe.

Yıldırım, İlknur *et al*. (2023) [2]. Deterioration of neuronal structure or function over time is called neurodegeneration. Among the most significant neurodegenerative disorders are Alzheimer's disease (AD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), and Parkinson's disease (PD). These disorders have a complex etiopathogenesis that includes genetic variables, neurofibrillary tangles, amyloid plaque development, mitochondrial malfunction, and trauma. Some research has also linked neuroinflammation and oxidative stress to neurodegenerative disorders. A number of studies have shown the anti-inflammatory, antioxidant, and anti-apoptotic modes of action of phytochemicals contained in many fruits, vegetables, nuts, oil seeds, and whole grains. By acting on these pathways, phytochemicals may help delay the course of illness by exerting neuroprotective effects. Neurodegenerative illnesses were examined in this review in relation to phytochemicals that have antioxidant and anti-inflammatory properties.

Baranowska-Wójcik, Ewa *et al*. (2025) [3]. Dementia and other cognitive issues are hallmarks of Alzheimer's disease (AD), a neurodegenerative illness. The accumulation of amyloid β in the hippocampus, leading to the formation of so-called senile plaques, has been linked to the illness. Recent years have seen a lot of research into herbal treatments as an alternative to conventional drug regimens; this is because current AD therapies aren't enough, and synthetic drug exposure over time can cause serious side effects. For example, Ginkgo biloba and lavender are two of the many herbs that are already widely used to treat the symptoms of many neurological diseases. In view of the above, this study will focus on medicinal herbs and will attempt to explain their significance, neuroprotective characteristics, and action mechanisms. This article provides a summary of the known medicinal uses of phytomedicines with potent anti-Alzheimer's disease (AD) effects.

Trivedi, Dr. (2024) [4]. The modern period has seen a dramatic increase in the prevalence of neurodegenerative diseases like dementia and Alzheimer's disease (AD) and neuropsychiatric disorders like anxiety and depression. The majority of chronic brain illnesses do not seem to have any substantial disease-modifying benefits from the pharmaceutical therapies that are now licensed; instead, they seem to only manage symptoms. Additionally, there are major and even fatal negative effects linked to the treatment's use of synthetic medications. Researchers are now looking into phytochemicals as potential alternatives to traditional antipsychotics and memory enhancers. Herbal plant phytochemicals have an important role in maintaining the brain's chemical balance, which in turn protects against neurodegeneration, slows the progression of neurological illnesses, and alleviates symptoms of anxiety and despair. Neuroprotection, Alzheimer's disease (AD), depression, and phytochemicals as a treatment option are the primary foci of this research. Furthermore, an effort was made to compile a list of phytochemicals used in the treatment of long-term neurological conditions.

Khan, Andleeb *et al*. (2021) [5]. Degeneration of neurons causes cognitive and physical impairments in neurodegenerative illnesses, which are very complicated, multifactorial, and deadly diseases. For the time being, there are no cures that target these illnesses specifically. Commercially accessible medications alleviate symptoms and, to a lesser degree, enhance everyday functioning. Phytochemicals that work on several levels may hold great promise as medicines to combat neurodegenerative illnesses. Several plant and plant product studies have shown that they may inhibit the progression of several illnesses, including Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, Huntington's disease, and stroke. Reduced oxidative stress and increased total antioxidant load of nerve cells are two outcomes of phytochemicals' multi-property action as anti-inflammatory and antioxidant agents. Additionally, they may promote mitochondrial biogenesis and restore mitochondrial function, both of which are known to be impaired in certain disorders (e.g., resveratrol).

Research Methodology

Recent Advancements in Research

Molecular processes, bioavailability, and new delivery modalities have recently been the focus of phytochemical

study in neurodegenerative illnesses. Bypassing problems with low solubility and fast metabolism, nanotechnology has shown promise as a means to increase phytochemical bioavailability and targeted administration. For example, resveratrol and curcumin nano formulations have shown increased neuroprotective effectiveness and improved blood-brain barrier permeability Some of the phytochemicals used in recent clinical studies showed promise in improving cognitive function in those with moderate cognitive impairment and early-stage Alzheimer's disease. Recent research on the gut-brain axis has also shed insight on how phytochemicals affect neuroinflammation and cognitive processes by regulating the gut microbiota.

We tested plant extracts for their potential to target proteins associated with neuroinflammation, oxidative stress, and acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Various terms such as "plants", "phytocompounds", "phytochemicals", "phytoconstituents", "phytochemical profiling", "bioactive compounds", "dementia", "dementia-related diseases", "oxidative stress", "inflammation", "cholinesterase", "antioxidant", "neurodegenerative diseases", "anti-cholinesterase activity", "neuroprotection", "amyloid β (Aβ)", "AβO", "Alzheimer's disease", "vascular dementia", and so on were the primary search terms in authentic databases. This review article just analyzed publications published in English and omitted books, unpublished discoveries, conference abstracts, and chapters from other languages.

Data Analysis

Cholinesterase inhibitors, occupational therapy, alternative medicines, and other approaches help alleviate symptoms, but unfortunately, most dementias cannot be cured. In order to treat Alzheimer's disease, vascular dementia, Lewy body dementia, and Parkinson's disease, for instance, doctors may use donepezil, rivastigmine, and galantamine. Additionally, the remarkable health advantages of plants and their bioactive components have brought them immense attention in the last several decades. Neuroprotection, cardio protection and hepatoprotection, anti-inflammatory, anticancer, and antioxidant action, antimicrobial action, and antidiabetic and other health-beneficial actions are just a few of the many claims made by the expanding corpus of research on plants and their bioactive compounds. This study mainly aims to cover the potential uses of plants and phytocompounds in the treatment of neurological diseases. The impacts of plants are summarized in Table 1, whereas those of bioactive chemicals are summarized in Table 2.

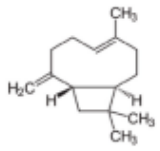
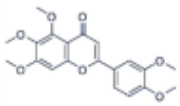
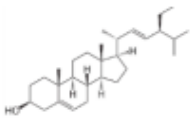
Table 1: *In vitro* and *in vivo* effects of several plant extracts in neurodegenerative disorders.

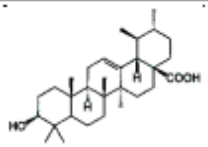
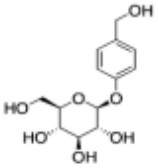
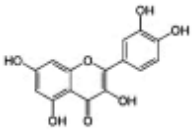
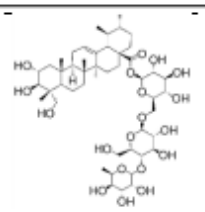
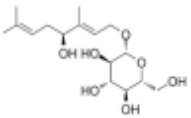
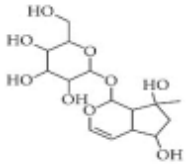
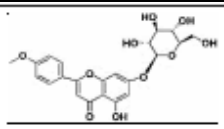
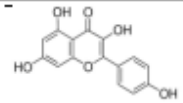
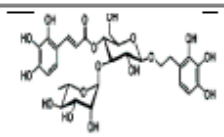
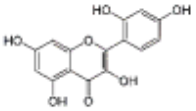
Plant	Plant Part/Extract	Type of Study	Effects
Viccinium genus (blueberries)	Fruits and leaves (methanol/water/formic acid 60:37:3 *v*/*v*/*v*)	In vivo (C57BL/6 mice)	Protected microglia cells, curtail the signs of neuroinflammation.
Acacia dealbata	Flower Ethanol/water	In vitro	Antioxidant Anti-AChE
Sophora secundiflora and *Sophora tomentosa*	Leaves Ethyl acetate and methanol	In vivo (Rats)	Antioxidant Anti-AChE
Piper divaricatum	Leaves Essential oil	In vitro	Anti-AChE
Lavandula stoechas	Aerial parts Methanol	In vivo (Swiss albino mice)	Antioxidant Anti-AChE
Elatostema papillosum	Leaves Methanol	In vivo (Wistar albino rats)	Anti-AChE Anti-BChE Antioxidant
Evolvulus alsinoides	Leaves Methanol and water	In vitro (SH-SY5Y cell-line)	Antioxidant Anti-AChE
Psychotria calocarpa	Leaves Methanol	In vitro and in vivo (Swiss albino mice)	Antioxidant
Morus alba	Leaves Water	In vivo (Swiss albino mice)	Anti-AChE, Anti-BChE Antioxidant
Bauhinia coccinea	Stems Ethanol	In vitro (HT22 neuronal cell line)	Anti-AChE Anti-BChE Antioxidant anti-amyloid-β (Aβ)
Enhydra fluctuans	Stems and leaves Chloroform	In vivo (Swiss albino mice)	Anti-AChE, Anti-BChE Antioxidant
Dillenia suffruticosa	Leaves Methanol	In vitro (Caenorhabditis elegans)	Anti-AChE Anti-BChE Antioxidant

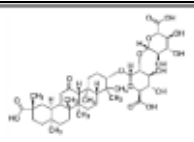
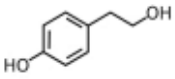
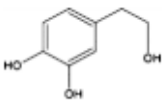
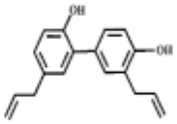
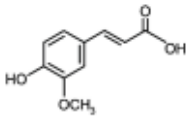
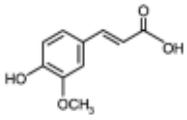
Rosmarinus officinalis	Whole plant Ethanol, ethyl acetate and water	In vitro	Anti-AChE Antioxidant
Origanum vulgare	Aerial parts Ethanol	In vitro	Antioxidant Anti-apoptotic
Bacopa floribunda	Leaves Ethanol/water	In vivo (BALB/c mice)	Suppression of oxidative stress, neuroinflammation, and microgliosis
Cyperus rotundus and Zingiber officinale	Aerial parts Ethanol/methanol	In vivo (Wistar rats)	Reduced oxidative stress and AChE levels
Typha domingensis	Whole dried plant parts Methanol and hexane	In vitro	Anti-AChE Anti-BChE Antioxidant
Annona cherimola	Fruits Methanol	In vitro	Anti-AChE
Syzygium antisepticum	Leaves Ethanol/methanol	In vitro	Anti-AChE Antioxidant
Dracaena reflexa	Aerial parts and roots Methanol, butanol, and hexane	In vitro	Anti-tyrosinase Anti-AChE, Antioxidant
Solanum macrocarpon (L.)	Leaves Methanol and ethyl acetate	In vitro	Anti-AChE Antioxidant
Bruguiera gymnorhiza (L.)	Leaves and roots Water	In vitro	Anti-tyrosinase Anti-AChE Anti-BChE Antioxidant
Artemisia scoparia, *Artemisia*	Leaves Water	In vitro	Anti-BChE
Mentha pulegium (L.)	Whole plant parts Water and methanol	In vitro	Anti-AChE, Anti-BChE Antioxidant
Lawsonia inermis	Fruits Methanol and ethyl acetate	In vitro	Anti-BChE Antioxidant
Ferula ammoniacum	Aerial parts Ethanol and methanol	In vivo (Swiss albino mice)	Anti-AChE Anti-BChE Antioxidant
Ginkgo biloba	Fruits Ethanol, butanol, and dichloromethane	In vitro	Antioxidant
Salvia eriophora	Leaves Methanol and water	In vitro	Anti-AChE Anti-BChE Antioxidant
Origanum majorana, *Origanum onites*, *Origanum syriacum*, *Origanum hirtum*	Whole plant Ethanol	In vitro	Anti-AChE Anti-BChE
Folium perseae	Leaves Ethanol	In vitro	Antioxidant

Petroselinum crispum	Leaves Water	In vivo (Wistar albino rats)	Anti-AChE Antioxidant Anti-apoptotic
Guazuma ulmifolia, *Limonium brasiliense*, *Paullinia cupana*, *Poincianella pluviosa*, *Stryphnodendron adstringens* and *Trichilia catigua*	Crude plant extract and ethyl acetate extract	In vitro (SH-SY5Y cell-line)	Anti-AChE, Antioxidant
Ocimum basilicum (L.)	Leaves Methanol and water	In vivo (mice)	Anti-AChE Antioxidant Anti-apoptotic
Stenocereus pruinosus	Aerial parts Methanol	In vitro	Anti-amyloid
Pandanus amaryllifolius	Leaves Crude alcoholic extract	In vitro (SH-SY5Y cell-line)	Anti-amyloid β
Carthamus tinctorius (L.) and *Taraxacum coreanum*	Dry seeds Water	In vivo (mice)	Inhibit β-secretase and γ-secretase activity in $A\beta_{25-35}$-infused mice.
Cirsium japonicum	Aerial parts Ethanol	In vivo (mice)	Antioxidant activity and attenuated lipid peroxidation and NO production.

Table 2: *In vitro* and *in vivo* effects of various phytochemicals against neurodegenerative disorders

Phytocompound	Structure	Plant	Study	Molecular Mechanism
β-caryophyllene		*Cannabis sativa*	In vivo (Swiss albino mice)	Neuroprotection by abrogating apoptosis through increased expression of bcl-2 and TrkB and suppression of bax and caspase-3
Sinensetin		*Citrus sinensis*	In vitro (SH-SY5Y cell-line)	In vivo and in vitro anti-inflammatory, antioxidant, and antiapoptotic activities against amyloid beta ($A\beta_{25-35}$)-induced neurotoxicity
Stigmasterol		*Calotropis gigantean*	In vitro (SH-SY5Y cell-line)	Hampered apoptosis induction by suppressing ROS production and upregulated bcl-2 and FoX3a and catalase

Rosmarinic acid and ursolic acid		*Clinopodium revolutum*	In vivo (BALB/c mice)	Improves spatial and recognition memory
Gastrodin		*Gastrodia elata*	In vivo (rats)	Prevented apoptosis induction by down-regulation of bax and alleviated autophagy by inhibiting beclin-1 and LC3-II
Quercetin		*Citrus* plants	In vivo (mice)	Inhibited cell death and degeneration by down-regulation of IL-6 and TNF-α
Asiaticoside		*Centella asiatica*	In vivo (Sprague-Dawley rats)	Elevated beclin-1 expression and decreased mTOR phosphorylation
Rosiridin		*Rhodiola rosea*	In vivo (Wistar rats)	Anti-inflammatory, antioxidant, and anti-apoptotic
Rehmannioside A		*Glutinous rehmannia*	In vivo (Sprague-Dawley rats)	Anti-inflammatory, antioxidant, and anti-apoptotic
Tilianin		*Dracocephalum moldavica*	In vivo (Sprague-Dawley rats)	Anti-neurodegenerative, antioxidant, and anti-apoptotic
Kaempferol		*Camellia sinensis*	In vivo (Wistar rats)	Anti-inflammatory, antioxidant, and anti-apoptotic
Marinoid J		*Morinda lucida*	In vivo (Sprague-Dawley rats)	Reducing MDA level and NO activity
Morin		*Moraceae family*	In vivo (Sprague-Dawley rats)	Neuroprotection by antioxidation, anti-aggregation, and anti-inflammatory mechanism

Glycyrrhizic acid		*Glycyrrhiza glabra*	In vivo (Sprague-Dawley rats)	Antioxidant activity by inhibition of ROS production and cyt-c activity
Tyrosol and hydroxytyrosol		*Olea europaea*	In vivo (APP/PS1 mice)	Anti-AβO aggregation and inhibition of caspase-3 activation
Hydroxytyrosol		*Olea europaea*	In vivo (APP/PS1 mice)	Reverse the deregulation of JAK2/STAT3, PI3K/Akt, ERK-MAPK, and JNK-p38 signalings
Honokiol		*Magnolia officinalis*	In vivo (mice)	Suppress apoptosis and neuronal damage in CA1 region of hippocampus and inhibit ROS production through attenuation of NF-κB signaling pathway
Ferrulic acid		Commelinid plants	In vivo (mice)	Anti-AβO, diminished cognitive impairment and exerted antioxidant effects by activating Nrf2
Ferrulic acid		-	In vivo (Sprague-Dawley rats)	Antioxidant and neuroprotection against $A\beta_{1-42}$-induced neurotoxicity

Resveratrol and Its Synergistic Combinations

The polyphenolic chemical resveratrol, which is present in red wine and grapes, has shown potential in reducing the symptoms of neurodegeneration. Through activation of sirtuin 1 (SIRT1), it improves mitochondrial activity and decreases amyloid-beta (Aβ) toxicity in models of Alzheimer's disease (AD). But it doesn't work well in the clinic since it's poorly soluble and metabolizes quickly. New research shows that resveratrol and other chemicals, such quercetin, pterostilbene, and epigallocatechin gallate (EGCG), may work together more effectively. By decreasing tau hyperphosphorylation and increasing synaptic plasticity, these mixtures boost neuroprotection and increase bioavailability.

Cannabidiol and Other Non-Psychoactive Cannabinoids

The putative neuroprotective effects of cannabidiol (CBD), a non-psychoactive cannabinoid extracted from the cannabis plant, have attracted interest among NDs. Though it lacks the intoxicating effects of tetrahydrocannabinol (THC), cannabidiol (CBD) modulates neuroinflammation, oxidative stress, and excitotoxicity via its interactions with cannabinoid receptors (CB1 and CB2). Evidence from animal models of Alzheimer's disease and Parkinson's disease suggests that cannabidiol (CBD) mitigates neuroinflammation by lowering levels of pro-inflammatory cytokines and microglial activation. By influencing endocannabinoid signaling and mitochondrial function, other cannabinoids, as cannibalization (CBDV) and cannabigerol (CBG), also have neuroprotective properties.

Phytochemical	Natural Source	Neuroprotective Mechanisms	Targeted Neurodegenerative Diseases	Challenges
Curcumin	*Curcuma longa* (Turmeric)	Antioxidant, Anti-inflammatory, Inhibits amyloid-beta aggregation, Mitochondrial protection	Alzheimer's (AD), Parkinson's (PD), Huntington's (HD)	Poor bioavailability, Rapid metabolism
Resveratrol	Grapes, Red Wine, Peanuts	Antioxidant, SIRT1 activator, Mitochondrial enhancer, Anti-inflammatory	AD, PD, Amyotrophic lateral sclerosis (ALS)	Low stability, Limited brain penetration
Quercetin	Onions, Apples, Berries	Antioxidant, Anti-inflammatory, Modulates	AD, PD, HD	Low water solubility,
		autophagy, Reduces oxidative stre		Rapid excretion
Epigallocatechin gallate (EGCG)	Green Tea	Antioxidant, Anti-inflammatory, Prevents amyloid-beta toxicity, Enhances synaptic plasticity	AD, PD	Gastrointestinal degradation, Low bioavailability
Ginsenosides	*Panax ginseng*	Neurogenesis stimulator, Antioxidant, Reduces neuroinflammation, Enhances cognition	AD, PD, Stroke recovery	Variable extract standardization, High metabolism

Conclusion

Conventional treatments for neurodegenerative diseases have limited efficacy due to the many serious side effects reported with currently available medications and the fact that patients' health deteriorates due to disease complexity even after receiving typical symptomatic treatments. There is currently a lack of information on the pharmacokinetics and pharmacodynamics of several bioactive chemicals obtained from plants in human clinical trials, even though numerous researchers have reported encouraging findings.

In past few decades, numerous preclinical studies showed that plant formulations and plant-derived compounds possess enormous chemo preventive and therapeutic potential against many neurodegenerative disorders.

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