Review
Sciences of Phytochemistry

Neuromodulatory Effect of Plant Metabolites

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[The author informations are in the declarations section. This article is published by ETFLIN in Sciences of Phytochemistry, Volume 1, Issue 1, 2022, Page 41-59. https://doi.org/10.58920/sciphy01010047]

Received: 16 July 2022
Revised: 26 July 2022
Accepted: 26 July 2022
Published: 26 July 2022

Editor: James H. Zothantluanga

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Keywords: Neurons, Neuromodulation, Neuroprotection, Neurodegeneration, Phytocompounds.

Abstract: Neurological disorders (NDDs) are diseases that affect the central and peripheral nervous systems. Gradual malfunction and destruction of the neurons or the nerve cells characterize them. Every year, NDDs affect millions of people worldwide. Over the years, several neuromodulatory techniques have been introduced to improve the quality of life for those affected by NDDs. NDDs are chronic and incurable conditions, however, bioactive substances derived from medicinal plants have emerged as the greatest choice for their prevention and treatment. Literature evidences several benefits of plant metabolites as alternative medicines for the prevention and treatment of NDDs. Numerous investigations have shown plant metabolites to possess beneficial biological effects because of their qualities, which include but are not limited to anti-inflammatory, antioxidant, and neuroprotective actions. Practices of folk medicine and several studies have also guided many phytopharmacological interventions toward the treatment of NDDs. This review aims to highlight secondary metabolites (alkaloids, flavonoids, steroids, terpenoids) of plants with neuroprotective action that could potentially play an important role in the prevention and management of NDDs.

Introduction

Neuronal Network

Neurons are nerve cells that convey information to other neuron cells, muscle cells, and gland cells.Neuronscome in a variety of shapes and sizes including multipolar, bipolar, pseudo unipolar, and anaxonic with the quantity and arrangement of axons and dendrites varying the most. One neuron gets connections with other neurons in areas known as dendrites. The cell body contains the nucleus and other organelles necessary for cellular function, also known as the soma. Efferent signals are carried via axons. The axon is a component of nerve cells that transmits information from one portion of the neuron to the neuron's terminal regions. In certain human motor and sensory neurons, axons may be rather long, reaching up to a meter or so. The synapse is the axon's terminal portion, where one neuron connects to another and transmits information via synaptic transmission. Depending on the function and location of a neuron, there may be one or several dendrites connected with it. Dendrites can have a role in protein production as well as independent signaling with other neurons, in addition to afferent transmission. Axons generally terminate in an axon terminal, where neurotransmitters, neuromodulators, or neurohormones are produced during the conversion of an electrical signal to a chemical signal that can cross the synapse or neuromuscular junction. The synaptic cleft is a space that separates the postsynaptic and presynaptic cells. Thus, a chemical messenger must be released by the presynaptic neuron to interact with the postsynaptic cell. This messenger can be found in neurotransmitter-containing vesicles. When an action potential enters the presynaptic terminal, these vesicles fuse with the interior surface of the presynaptic membrane and release their contents, causing exocytosis to take place. The released transmitter binds to particular receptors on the postsynaptic side of the synapse after diffusing across the space between the pre and postsynaptic cells. The membrane's ion channel permeability changes as a result of receptor engagement, changing the postsynaptic synaptic potential, or membrane potential of the postsynaptic neuron (PSP) (1). Neurons transmit potentials across their membranes through ion movement through voltage-gated ion channels. The major contributions to the membrane potential of the common neuron are potassium, sodium, and chloride

ions (2-6). In this review, we will highlight different plant metabolites that had been reported to exhibit neuromodulatory effect.

Methodology

An extensive search for the literatures was carried out from “February 2022” to “June 2022” using key words ‘Neurological disorders’ in combination with ‘Neuromodulation’ and ‘Plant metabolites’ on search engines viz., Scopus, PubMed, Google Scholar, and Science Direct.

What is Neuromodulation?

Neuromodulation is defined as "technology affecting the neural interface". It involves controlling the central, peripheral, or autonomic nervous systems' activity through electrical or chemical means by blocking, stimulating, altering, regulating, or otherwise changing it (7). It is the study of how mechanical, pharmacological, and electrical interventions may alter how the nervous system functions. Neuromodulation is fundamentally adjustable, reversible, and non-destructive. Neuromodulation is defined by the INS (International Neuromodulation Society) as a field of science, medicine, and bioengineering that encompasses implantable and non-implantable electrical and chemical technologies to improve humans’ quality of life and functioning (8).

In biology, the process of neuromodulation is described as the excitation, inhibition, or tuning of nearby or distant neurons or neural networks to produce responses that are better suited to the requirements of an organism's environment and more ideal for guaranteeing its successful survival. Neuromodulation is a branch of science, medicine, and bioengineering to enhance the quality of life for persons with neurological disorders in the biotechnological environment. It comprises implantable and non-implantable electrical and chemical devices (9).

In the Clinical Context, Neuromodulation Can Be Defined as:

a. The study of the effects of electrical, chemical, and mechanical interventions on the central and peripheral nervous systems.

b. A type of therapy in which neurophysiological signals are generated or influenced to change the nervous system's function and performance to achieve therapeutic results.

c. The use of implanted or non-implanted devices to change activity in the central, peripheral, or autonomic nervous systems for therapeutic reasons, either electrically or pharmacologically (9).

The Field of Neuromodulation

The field of neuromodulation encompasses a diverse range of conditions such as psychiatric and neurobehavioral disorders, spasticity, stroke, traumatic brain injury, urinary frequency, urinary utopia, urinary frequency, urinary urgency, urinary and fecal incontinence, eyesight, gastric motility, epilepsy, headaches, hearing loss, limb and organ ischemia, movement disorders, occipital neuralgia, chronic pain, peripheral neuralgias, and movement disorders. Because the nervous system regulates bodily functions and disorders of those functions are common, many clinical specialists, including anaesthesiologists, cardiologists, gastroenterologists, neurologists, neurosurgeons, ophthalmologists, otolaryngologists, pain physicians, psychiatrists, physical medicine and rehabilitation specialists, and urologists, use neuromodulation therapies (8).

Neuromodulation has been defined as the treatment of specific types of chronic pain, spasticity, epilepsy, ischemia, cardiac, bowel, bladder dysfunction, nervous system injury, and movement, visual, auditory, or psychiatric disorders using reversible electrical stimulation or centrally delivered pharmaceutical agents to manipulate nervous system activity (9).

Neuromodulation for Chronic Pain

Examples of chronic pain issues include chronic pain syndrome (CRPS), headaches, occipital neuralgia, failed back pain, neck pain, extremities pain, central pain, cancer pain, visceral pain, and other disorders involving pain (8).

Brain Neuromodulation

Brain neuromodulation including cortical and subcortical neurostimulation is becoming increasingly popular, with a variety of new applications involving a wide range of diseases. A new era of brain neuromodulation implants has begun as a result of the adoption of deep brain stimulation in the treatment of Parkinson's disease and other movement disorders. The use of brain stimulation in the treatment of neurobehavioral diseases such as obsessive-compulsive disorder, depression, and epilepsy is becoming more common (8).

Neuromodulation for Spasticity

Patients with spasticity caused by multiple sclerosis, stroke, and other diseases have benefited greatly from the use of intrathecal baclofen infusion pumps (8).

Neuromodulation Therapy

According to Jan Holsheimer (2003), a therapy must include the following elements to be termed

neuromodulation:

a. A dynamic, ongoing (continuous or intermittent) intervention, as opposed to a one-time, one-time-only process, is required for the treatment.

b. Continuous electrical or neuropharmacological stimulation affects the activity of certain brain networks.

c. To meet a patient's demand, the clinical impact can be constantly controlled by adjusting one or more stimulation settings.

Using implantation technology like epidural or intrathecal delivery systems, chemical neuromodulation places chemicals directly into neural tissues; by contrast, electrical neuromodulation stimulates the brain, spinal cord, peripheral nerves, nerve plexuses, the autonomic system, and muscles through functional electrical stimulation (8). Operative neuromodulation is a field of medicine that uses implanted devices to change neuronal signal transmissions, either electrically or chemically, for therapeutic stimulation, inhibition, or modification of the activity of neurons or neural networks (9). In the rapidly expanding interdisciplinary discipline of neuromodulation, treatments are administered to the nervous system with the potential to affect every organ or system in the human body. Clinical specialists in anesthesiology, neurosurgery, neurology, neurophysiology, cardiology, and orthopedics currently practice neuromodulation, but due to the systemic effects and advantages of this therapy, this relatively new area of medicine will likely influence or encompass most medical specialties (9).

The enhancement of the nervous system and its activity by implanted devices that offer electrical stimulation, medication or chemical administration, or cell implantation to generate therapeutic benefits is known as neuroaugmentation. To generate functional activation or inhibition of certain neuronal groups, pathways, or networks, electrical currents with varying parameters are delivered through implanted electrodes. This process is known as neurostimulation. Functional Electrical Stimulation (FES) refers to the ability to control motions that have been hampered by disability. It improves the movement of paralyzed limbs and increases the activation of afferent neural pathways. FES devices are used to control motor function as neuro-orthoses or external controllers (8). Neuroprosthetics is the study, design, creation, and implantation of artificial devices that produce electrical impulses by igniting action potentials in nerve fibers to take the place of the function of damaged areas of the nervous system (9). Neural stimulators or microinfusion pumps are the current implantable neuromodulation technologies. These devices are used to treat a variety of ailments, including chronic pain, movement problems, mental health issues, epilepsy, immobility disorders, pacing disorders, spasticity, and others (8).

Neuroprotection

The term "neuroprotection" refers to methods and measures taken to protect the central nervous system (CNS) from neuronal damage brought on by short-term or long-term neurodegenerative illnesses (NDs) (10). The dysfunction and atrophy of CNS neurons cause acute and chronic illnesses. The symptoms of the onset of NDs are usually moderate in addition to progressive which includes primarily short-term memory loss, motor coordination, learning challenges, and other functional losses (11, 12). In elder age symptoms like inflammation, protein aggregation, oxidative damage, and neurotransmitter depletion are frequent (10, 13, 14).

Neurodegenerative Diseases

Neurodegenerative Disorders (NDs) are an untreatable diversified group of diseases that are distinguished by continuous degeneration of function and structure of the peripheral nervous system and central nervous system occur due to neuronal cell death (15). This causes notable functional and structural injury to a healthy brain. The deterioration is frequently related to the onset of symptoms like ataxias, dementias, person's inability to speak, move, and breathe (16).

Alzheimer’s Disease

AD is a fatal disorder of perception and behavioral deterioration that influences communal and occupational activities (10, 17). Clinically the disease is identified by irreversible and developing memory loss, personality changes, emotional collapse, and motor and sensory functions (18). The start of AD normally occurs after the age of 65, with the risk rising every 5 years after that (19). The growth of protein clumps, known as neurofibrillary tangles (NFTs) and senile plaques, is a clinical hallmark of AD. The production of oxidative damage (20), neurotoxicity (19), and inflammation (21) are processes by which AD is caused by Aβ peptide aggregation. The "cholinergic hypothesis of AD" was developed in response to reports of significant neocortical deficits in the enzyme choline acetyltransferase (ChAT), which produces acetylcholine (ACh), as well as decreased choline uptake, Ach release, and loss of cholinergic perikarya from the nucleus basalis of Meynert (17).

Parkinson’s Disease

About 1% of people over 60 have PD, an illness that primarily affects mobility and is cognitive (13). The symptoms of Parkinson's disease (PD) include bradykinesia, extrapyramidal rigidity, resting tremors, and loss of postural reflexes like walking or balancing.

Dopaminergic neurons of the substantia nigra's pars compacta and their terminals in the corpus striatum are lost in Parkinson's disease (22). PD is connected to non-motor disorders like dementia as neurodegeneration is not limited to basal ganglia. The link between PD and neuronal oxidative injury has long been known. Auto oxidation of dopamine has been connected to semi-quinone metabolism, creation of anion superoxide, hydrogen peroxide production, and expression of monoamine oxidase (19).

Other Neurodegenerative Diseases

It is believed that a mutation in the gene that codes for the enzyme superoxide dismutase is what causes Amyotrophic Lateral Sclerosis (ALS) (SOD). ALS is an incurable disease with a three-year median survival time. Slurred voice, dropping of the wrist and foot while running and sadness are all indications of this condition (23, 24). Another incurable ND is Huntington's disease (HD). It is an autosomal dominant genetic illness with adult-onset that causes rapid decline and mortality as well as gradual brain degradation. Involuntary movement, dementia, and behavioral abnormalities are all symptoms of the disorders (25). The aggregation of misfolded prion proteins causes a category of uncommon NDs known as prion disorders. Prion proteins are thought to induce spongiform encephalopathy, a kind of ND, which is a contagious disease (26, 27).

Plant Metabolites and Their Role in Neuroprotection

Traditional medicine is still a major alternative medical source across the globe, accounting for nearly 80% of basic healthcare systems in some underdeveloped nations. The rising occurrence of drug resistance, unwanted negative consequences, hefty price, and loss of effectiveness after repeated usage of currently available medications has sparked a fresh interest in the growth of novel medication candidates derived using natural means (28, 29). Amantadine, memantine, donepezil, selegiline, galantamine, and rivastigmine, for example, are only capable of providing symptomatic relief and slowing the advancement of NDs (30, 31).

Alkaloids

Galantamine

It is an alkaloid isolated from the species Galanthus woronowii (Amaryllidaceae), G. caucasicus as well as and from kindred genera Narcissus, Lycoris (Lycoris radiate), Leucojum (Leucojum aestivum) (32).

As an AChE inhibitor (AChEI), galantamine improves cholinergic neurotransmission by lowering ACh breakdown (33, 34). Evidence suggests that blocking nicotinic agonists reduces learning and memory in AD patients with functional nAChR dysfunction (especially the 7 subtype) (35, 36). Galantamine increases nicotinic neurotransmission and improves cognition and memory via allosterically modulating nAChR activation (37). It stimulates hippocampus neurogenesis via α7 nicotinic Ach receptors (38). Galantamine has been shown in several investigations to reduce Aβ build up and cytotoxicity, both of which are hallmarks of Alzheimer's disease pathogenesis (39, 40).

Berberine (BBR)

It's an isoquinoline alkaloid with a bitter taste and a yellow colour. Hydrastis canadensis (Golden seal), Berberis vulgaris (barberry), Coptis chinensis and Berberis aristata are some of the plants from which it may be separated (tree turmeric) (41).

Because of its capacity to reduce Aβ, BBR might be useful in the treatment of Alzheimer's disease (42). The APP-cleaving enzyme is called BACE-1 and this starts the Aβ synthesis process (43). It also inhibits MAO and AChE, which are both implicated in the progression of Alzheimer's disease (44, 34). BBR inhibits the formation of Aβ plaques and the development of BACE-1 (45).

BBR improves motor synchronization and stability by preventing dopaminergic neuronal degeneration. Inhibiting apoptosis and promoting neurogenesis in the hippocampus dentate gyrus enhances short-term memory (46). BBR was reported to drastically reduce substantia nigra (SN) dopaminergic neuronal loss and apoptosis in the hippocampus and prevent both balance and memory loss in people with Parkinson's disease (47).

Morphine

Morphine is an isoquinoline alkaloid that has strong narcotic and analgesic properties and is used to treat moderately severe to severe pain. Morphine's analgesic action is mediated by the μ-opioid receptor (MOR) (48, 49).

By attaching to MOR in the CNS, morphine plays a significant part in the treatment of AD by increasing GABA levels at brain synapses (50) and protecting against oxidative stress-induced neurotoxicity (51). Morphine protects rats and humans from intracellular Aβ (iAβ) venomousness present in primary neuronal cultures. It can counteract the electrophysiological alterations caused by iAβ, including capacitance and resting membrane potential (52).

Salsoline

The isoquinoline alkaloid salsoline belongs to the Chenopodiaceae family (53). About 120 species of widespread bushy plants belong to the genus Salsola (Chenopodiaceae) (53).

Three salsola species were discovered to be AChE and BuChE inhibitors for the first time in studies, which is effective in the treatment of AD (54). Salsoline has a specific activity on BuChE, making it a unique therapy option for AD (53).

Geissospermine

It is an indole alkaloid isolated from the Brazilian tree Geissospermum vellosii and belongs to the Apocynaceae family. It is a medicinally significant plant with a vast range of pharmacological properties, like anti-oxidant (55), antibacterial, and antimalarial properties (56, 57).

GSP has been shown to increase cholinergic transmission due to its ability to inhibit AChE (58). His440 and Ser200 were shown to have the catalytic triad's impact on the AChE inhibitory mechanism through GSP, which may help with the treatment of AD (59).

Physostigmine

Physostigmine, sometimes known as eserine, is a pyrroloindole alkaloid. It was isolated from mature dry seeds of Physostigma venosum and belongs to the Leguminosae family. It can pass across the blood-brain barrier (BBB) (60).

Rivastigmine (a physostigmine analog) has a dual effect, blocking both AChE and BuChE, which helps to alleviate the symptoms of AD (58, 61).

In Parkinson's disease, α-synuclein expression was shown to be higher. There is a scarcity of information about physostigmine's antiparkinson impact. Phenserine, on the other hand, is a physostigmine derivative that has been shown to reduce α-synuclein expression in brain cell lines (62).

Isorhynchophylline (IRN)

Isorhynchophylline (IRN) is a tetracyclic oxindole alkaloid that is derived from Uncaria rhynchophylla, herbal medicine from China that is often used to treat neural-related illnesses (63, 64).

IRN, a phytochemical, is said to have a neuroprotective effect against the neurotoxicity caused by Aβ, making it effective in the treatment of AD (58) via control of oxidative stress and the mitochondrial route-mediated prevention of cellular apoptosis (65, 66).

Most -synuclein clumps make up Lewy bodies, which are recognizable pathological features in the brain of people with Parkinson's disease (67). IRN destroys α-synuclein (68) and protects neuronal cells via the pathway of autophagy-lysosome (69), making it an effective treatment for Parkinson's disease (58).

Piperine (PIP)

Long pepper (Piper longum) and black pepper (Piper nigrum) contain piperine, which is the main alkaloid (Piper nigrum) and they belonged to the Piperaceae family (70).

AChE and β-secretase enzyme inhibition by PIP improve cognitive improvement. PIP has recently been shown to increase the neuroprotective impact of quercetin while also reducing cognitive impairments in Alzheimer's disease due to oxidative stress (71).

MAOs are enzymes exclusive to the mitochondria that regulate the number of neurotransmitters like dopamine, implying that they are targets for neurodegenerative diseases like Parkinson's disease (72). Piperine has been shown to block the MAO B enzyme, which metabolizes DA. PIP also has a strong antidepressant effect, which is advantageous in the case of PD (73, 72).

Lobeline

Lobeline is a piperidine alkaloid found in Lobelia inflata that has been shown to have neuroprotective properties (58). Indian tobacco has a lipophilic alkaloidal component (74).

1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), a chemical that lowers the substantia nigral DA, is protected by lobeline (74). The reverse transit of DA from synaptic vesicles and inhibits DA absorption into synaptic vesicles is encouraged through connection with the vesicular monoamine transporter 2 (75).

Nicotine

Nicotine is a pyridine alkaloid found mostly in Nicotiana tobaccum, a Solanaceae family plant. It has a wide range of pharmacological effects in both the central and peripheral nervous systems, which are mediated through nicotinic acetylcholine receptors (nAChRs) activation (76).

Nicotine significantly upregulates the nAChRs 4 and 7, demonstrating its potential effectiveness in enhancing neuroprotection in Alzheimer's disease (77). According to some theories, activating neuropeptide Y (NPY1) receptors via binding to the α-helical structure reduces the generation of Aβ-peptide and enhances memory and learning (58). Cotinine manifests its abilities as a nicotine substitute and may have protective qualities against the degenerative mechanisms of Alzheimer's disease (78).

Caffeine

Caffeine is a methyl-xanthine derivative extracted from the coffea arabica plant that has long been used as a psychoactive drug, notably in soft drinks, tea, and coffee (58). Its function as a brain stimulant principally

involves increased cortical activity, cerebral energy metabolism, and extracellular acetylcholine levels, which all contributed to greater alertness (79).

In Alzheimer's disease, mutations in the genes encoding presenilins 1 and 2 cause a change in the activity of β-secretase and the production of the Aβ42 isoform (80). Caffeine inhibits the amount of presinilin-1 (PS1), β-secretase and reduces Aβ deposition in the cortex and hippocampus (81).

Pharmacologically inhibiting the A2 receptor can reduce the amount of neuronal death brought on by excitotoxicity. In Parkinsonism, caffeine increases locomotor activity by acting as an adenosine A2 receptor antagonist (82). The neuro-inflammatory progression of Parkinson's disease has consistently been associated with an increased number of activated microglial cells. Caffeine mediates dopamine receptor-mediated behavioral responses, including those affecting cognition and movement (83).

Harmine

Harmine is an indole β-carboline belonging to Nitrariaceae family which is isolated from Peganum harmala. It portrays a neuroprotective effect due to the inhibition of AChE, MAO-A and MAO-B (84) and tyrosine- phosphorylation regulated kinase (DYRK1A) (85).

Owing its capacity to possibly permeate the BBB, the brain’s parenchyma cells, and inhibit the activity of AChE (86), a pivotal enzyme that takes part in the metabolism and breakdown of Ach which is a neurotransmitter (87).

Flavonoids

One of the most researched chemical classes for its neuroprotective qualities is flavonoids, and a few well-known instances of this structural class are discussed here.

Isoflavones

Genistein (Gen)

By inhibiting microglial inflammatory processes in response to external stimuli, Gen may be able to limit the development of neurodegeneration followed by inflammation (88).

Gen is the most abundant phytoestrogen in soybeans (89). Estrogen can prevent Aβ-induced neuronal cell death in the positive sense (90). Because estrogen receptors (ERs) drive the defense response against Aβ-induced damage, Gen has the neutral neuroprotective potential (91). It can also reduce the generation of reactive oxygen species (ROS), suggesting that it can act as an anti-oxidant (92).

Gen may protect dopaminergic neurons from lipopolysaccharide-induced neurotoxicity in a dose-dependent manner. It lessens the production of NO, TNF-, and superoxide in both microglia and mesencephalic neuron-glia cultures (93). Furthermore, when brain microglia are triggered in reaction to an infection or damage, pro-inflammatory chemicals (88) such as NO and superoxide (94) are released, which can form complexes with proteins, altering their activities and finally leading to cell death (93, 94).

Daidzein

Daidzein is a flavonoid found solely in legumes and soybeans in nature (95). It is produced through the phenyl propanoid pathway's secondary metabolism in a variety of plants, including Kudzu (Pueraria lobata) and KwaoKrua (Pueraria mirifica) (96).

In BV-2 microglial cells, daizzein suppresses the production of inflammatory mediators caused by lipopolysaccharide (97). It generates responsive nitrogen oxides (NO) and oxygen- species (ROS), which damage the body's biosystem and are linked to changes in the structure and function of brain cells. Accordingly, it has been linked to a variety of NDDs, including Alzheimer's disease and Parkinson's disease (98).

Flavones

Luteolin

Luteolin (30, 40, 5, 7-tetrahydroxyflavone) is a flavone that is prevalent in plants (99). Cabbage, chrysanthemum flowers, apple skins, broccoli, carrot, celery, onion leaves, and parsley are only a few examples of fruits and vegetables that contain it (100-102).

Lutein has been shown to prevent cognitive impairment in cerebral hypo-perfused rats (103). To investigate if luteolin could reduce Aβ generation, researchers used primary neuronal cells from SweAPP-overexpressing mice and found that it did (104).

In PD, the amount of dopamine in the SN is lowered. The aetiology of Parkinson's disease (PD) also involves inflammation in the brain, which is followed by over-stimulation of microglia (105-107).

Apigenin

Apigenin (40, 5, 7-trihydroxyflavone) is a flavone flavonoid that occurs naturally. It is obtained naturally from Hypericum perforatum blooms and buds. Onion, parsley, grapefruit, and orange are examples of common vegetables and fruits that contain them (108, 109).

Treatment with 10 M apigenin can stop copper-induced increased production of Aβ precursor protein, but not at any other concentration (110). Apigenin can also help with memory loss linked with Alzheimer's disease, minimize oxidative stress, and reduce the load

of Aβ plaques. Apigenin is said to protect neurons from inflammatory stress, limit apoptotic cell death, and diminish neuronal hyper-excitability (108). Apigenin also inhibited the activation of pro-inflammatory cytokines and NO generation, shielding AD neurons from inflammatory stress (111).

Acacetin

Acacetin (5, 7-dihydroxy-4-methoxyflavone) is another flavonoid chemical that belongs to the flavone family of flavonoids. It comes from Clerodendrum inerme (L.) Gaertn (Cl), is a plant with potential therapeutic value in the treatment of neuropsychiatric diseases (112).

Inflammation-mediated neurodegeneration necessitates the activation of microglia. Microglial activation can cause neuronal cell death and CNS diseases by releasing cytotoxic and pro-inflammatory substances such as IL-1β and TNF-α (113, 114). Nuclear factor κB (NF-κB) is a transcription factor that controls IL-1β, TNF-α, and iNOS expression (115). Microglial-induced inflammation is also linked to mitogen-activated protein kinases (MAPKs), such as JNK and p38 (116, 117). Acacetin has been shown to suppress NO release while also lowering IL-1β and TNF-α levels. Acacetin also prevents the activation of p38 MAPK and NF-κB. Acacetin appears to stop glutamate from being released, in turn, inhibits a cascade of harmful cellular activities (118).

Acacetin prevents the synthesis of inflammatory factors and thereby protects dopaminergic neurons, which are significant targets in the development of Parkinson's disease (119).

Flavanones

Hesperetin

Hesperetin (30, 5, 7-trihydroxy-4-methoxyflavanone) is a flavonoid found in citrus fruits (120). It belongs to the flavanone class of flavonoids. It's made from the aglycone hydrolysis hesperetin (7-rhammnoglucoside) (121).

Insulin signaling is inhibited in neurons, and membrane insulin receptor (IR) function is reduced, resulting in lower insulin levels and glucose transporters (GLUTs) in AD patients' brains (122). Glucose absorption is hampered by A25–35 depositions, and cellular autophagy causes neuronal injury. Hesperetin protects against A25–35 stimulated neuronal injury (123). It can also modestly improve Aβ impaired glucose absorption by slowing autophagy (124). Importantly, oxidative damage mediated by lipid peroxidation is another aspect linked to the pathogenesis of AD, similar to Aβ aggregation (123, 124).

Naringin

One of the principal active components of Chinese herbal treatments including Citrus medica L. (CM), Citrus aurantium L. (CA), and Drynaria fortunei (Kunze) J. Sm. (DF) is naringin, a flavanone glycoside derived from naringenin (a flavonoid) (125, 126).

The brain's innate immune cells, known as microglial activation, are involved in PD. Naringin oral administration reduces microglial activation by reducing glial fibrillary acidic protein synthesis (GFAP) (127). The brain injury in PD is observed because of GFAP expression change (148).

Flavanols

(−) Epigallocatechingallate

One form of catechin is (−) epigallocatechingallate (EGCG), which has three phenol ring structures. Although it is present in minor amounts in black tea as well, it is the main bioactive component of green tea leaves (129).

EGCG is an anti-oxidant that inhibits the death of hippocampal neuronal cells (130). Programmed cell death, also known as apoptosis, is thought to be a distinct method of cell eradication from necrotic cell death. In A-induced neuronal cell death, caspase may have a significant proliferative role. By decreasing ROS, EGCG can prevent apoptosis in neuronal cells by blocking the increased caspase activity caused by A25-35 (131). Above all, EGCG can pass the blood-brain barrier (BBB) and enter the brain parenchyma (132).

(−) Epicatechin

(−) Epicatechin (EC) is a flavanol that is generated from plants and is present in blueberries, coca, tea, and grapes (133). It is known to be a bioactive flavanol that may pass through the blood-brain barrier and enter the circulation after meals high in flavanols have been digested (134, 135).

Green tea polyphenols (GTP), especially EC, protected dopaminergic neurons in a rat model of Parkinson's disease by modulating NO and ROS levels, conserving free radicals and preventing an elevation in nitrate/nitrite levels (136). ROS causes lipid peroxidation, mitochondrial membrane damage, and hence impairs Ca2+ homeostasis (137). Interestingly, GTP, via regulating Ca2+ homeostasis, inhibits NO altitude (136).

Quercetin

Quercetin (3, 30, 40, 5, 7-pentahydroxylflavone) is a flavonoid that belongs to flavanol class (138) and may be discovered in red wines, berries, tea, apples, onions, and tea (139, 140). Additionally, it is present in therapeutic herbs including Ginkgo biloba, Sambucus canadensis, and Hypericum perforatum (St. John's Wort) (141).

Quercetin also inhibits accumulation and lowers the

amount of BACE-1, which facilitates APP cleavage (142). Furthermore, in the case of AD, quercetin protects neuronal cells against neurotoxicity caused by oxidative stress (143).

Kaempferol

One of the most prevalent flavonoids in the diet and a phytoestrogen is kaempferol (3, 4, 5, 7-tetrahydroxyflavone). Numerous foods, such as tea, strawberries, apples, beans, broccoli, and grapefruits, may contain it. (144, 145). It has potent neuroprotective properties against a variety of necrosis and apoptosis-inducing damage, including oxidizing low-density lipoproteins (146, 147).

In a rotenone-induced acute toxicity model, kaempferol was found to protect the brain from damage produced by ROS at a dosage of 30 μM (148). Notably, kaempferol has MAO-A inhibitory property that may be useful in the treatment of Parkinson's disease (149). Experiments also suggested that kaempferol treatment altered motor synchronization and increased striatal DA in a dose-dependent manner (150).

Anthocyanidin

Cyanidin

Cyanidin-3-glucoside (C3G) is a naturally containing anthocyanin that can be seen in a wide variety of red berries, including cranberries, blueberries, blackberries, mulberries, acai berries, and raspberries (151). Additionally, mulberry fruit-derived C3G protects neurons against glutamate-induced and oxygen-glucose-depleted neuronal cell death (152, 153).

C3G has been demonstrated to diminish the Aβ25–35-induced expression of ER stress proteins, cell viability loss, and intracellular ROS generation in SK-N-SH cells (154). It can penetrate the BBB and reduces age-related neuronal impairments (155). C3G suppresses oxidative stress-induced ROS generation at the membrane level and concentrates in various brain areas essential for learning and learning, like the hippocampus and cortex, to safeguard neurons (156). Therefore, it is conceivable that C3G inhibits oligomer-induced lipid peroxidation and neural instability. (154).

Pelargonidin (Pel)

Pelargonidin (Pel) is a flavonoid that is derived from anthocyanins and is an ER agonist with few estrogen side effects (157). It would also be one of the most effective replacements for preventing age-related memory and cognitive losses (157).

Pel suppresses the inducible nitric oxide synthase (iNOS) protein and mRNA expression, NO generation, and NF-κB expression (158). ERs are abundant in memory-related brain regions such as the frontal amygdala, cortex, and hippocampus (159) and similarly, they have neuroprotective properties in NDDs (160).

Pel reduces neuronal loss and injury by reducing free radical production and altering the antioxidant defense system (161). The reason for its capacity to reduce dopamine oxidation caused by peroxynitrite, it may have neuroprotective properties. Pel has neuromodulatory effects due to its capacity to penetrate the BBB and accumulate at nanomolar quantities in the brain (162, 163).

Steroids

Natural Neuroprotective Steroids

Natural neuroprotective hormones such as DHEA, testosterone, estradiol, and progesterone increase neuronal survival by stimulating multiple pathways in the CNS. These largely increase ion channel activity that is connected to neurotransmitter stimulation, activate antioxidant effects via steroid receptor-independent pathways, and regulate cell survival and metabolism via steroid receptor signalling that starts in the mitochondria. By preventing apoptosis, excitotoxicity, and damaging free radical production, all of these techniques extend the lifespan of neuronal cells. (164, 165-167).

C-18 Steroids

A sex hormone called estradiol is required for the development and upkeep of female reproductive tissues. In many experimental conditions, estradiol primarily modulates cholinergic neurotransmission, increases neuronal survival, and enhances synaptic transmission as well (165, 168, 169). It controls β-amyloid build up in test animals' brains to protect neuronal cells from the destruction of β-amyloid via several methods, including modulation of apoptotic protein production and suppression of excitotoxic neuronal death. Additionally, it can prevent the aberrant hyperphosphorylation of tau protein, a defining feature of AD. (170). Estradiol also has neuroprotective benefits against PD and MS (Multiple sclerosis) in experimental animal models of MS and PD (171, 172).

C-19 Steroids

The most plentiful endogenous steroid hormone in the human body, DHEA is mostly produced in the gonads and adrenal glands. Under the action of the enzyme sulfotransferase, DHEA is reversibly transformed into its sulfate ester DHEAS (173). DHEA may easily pass across the blood-brain barrier (BBB), however, its sulfated form cannot pass through the BBB from the blood into the brain. DHEA is transformed into testosterone, dihydrotestosterone, or estradiol where it exercises its neuroprotective effects via the brain's estrogen and androgen receptors (202). The result of clinical research shows that DHEA administration slows the processing of APP via a nonamyloidogenic mechanism, preventing the build up of toxic Aβ

proteins in Alzheimer's patients. DHEA therapy also increases neurite outgrowth by enhancing nonamyloidogenic production (nontoxic protein forms). DHEA and DHEAS are neurotrophic substances that protect neurons from a variety of damaging events, including excitotoxicity (164). It involves the prevention of NMDA excitotoxicity as well as the increase of NGF levels within the hippocampus and also its receptor present in the forebrain. In animal models of AD, it also decreases amyloid overexpression and inhibits tau proteins' hyperphosphorylation (174).

C-21 Steroids

While it can also be found in the testicles and adrenal glands of men, progesterone is typically a female hormone produced in the corpus luteum and placenta of the ovary. Progesterone and its derivatives, including allopregnanolone, can, however, be created from scratch inside the nervous system. In males and females, progesterone has neuroprotective benefits that consist of the prevention of neuronal edema, death, and improved functional retrieval (175). Other neuroprotective properties of progesterone include: slowing cytokine (IL-1, IL-6, TNF-α) driven responses, reducing excitotoxicity by inhibiting glutamate receptors, inhibiting glial cell initiation in the CNS, and reducing oxidative stress by upregulating antioxidant enzymes (174). Progesterone also stimulates signaling enzymes related to neuroprotection mechanisms in the brain, like serine/threonine protein kinase, extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinase (MAPK). Pregnenolone is a steroid hormone that is generated in the brain and serves as a precursor of progestogens, androgens, mineralocorticoids, glucocorticoids, as well as estrogens (177). Pregnenolone has neuroprotective properties, particularly when it comes to glutamate and amyloid protein-caused neurotoxicity (164).

Synthetic Neuroprotective Steroids

Brief biological half-lives, rapid metabolism, and restricted oral bioavailability are only a few of the problems that natural neurosteroids have. As a result, synthetic alterations of natural neurosteroids are a promising strategy for developing strong neuroprotective medicines for the treatment of a variety of neurodegenerative diseases (178).

Estrane Derivatives

Estradiol is an antioxidant with neuroprotective properties. It defends brain cells from glutamate and oxidative damage caused by peroxide. (165). The 17 - O-alkyl derivatives (1) of estradiol have shown increased neuroprotection against glutamate-induced oxidative damage in a dose-dependent manner. In vitro, greater 17 -alkyl ethers of estradiol (n = 3 to n = 8) provided stronger protection against oxidative stress in HT-22 neural cells, but substitution of lower alkyl ethers (n < 2) drastically reduced neuroprotective benefits (179). HT-22 (a mouse hippocampus cell line) neural cells were used to examine a library of estrane derivatives for their capacity to prevent cell damage brought on by glutamate and iodoacetic acid (IAA). Estratriene analogs 1-3's phenolic A-ring is necessary to prevent glutamate or IAA from inducing the death of neuronal cells (180).

Androstane Derivatives

Abdalla et al. Modified the structure of 16 arylideneandrostane. Structure-activity relationship (SAR) investigations of synthetic alterations reveal that all produced derivatives operate as proton acceptors, forming hydrogen bonds with A-42 or A-40 and their precursors, in addition to secretase enzymes, interfering with biosynthetic pathways and blocking the production of A. Additionally, the latter is better tolerated than the former and the substituents with -I (Inductive) effects boost the anti-Alzheimer activity in comparison to those with -M (Mesomeric) effects (181).

Pregnane Derivatives

The components GluN1, GluN2A-GluN2D, GluN3A, and GluN3B makes up glutamate-gated ion channels known as NMDA receptors. In the brain, overactive NMDA receptors cause the excitotoxic response, which results in the death of neuronal cells and causes AD, PD, and TBI (182).

Prednisolone Derivatives

Methylprednisolone has neuroprotective qualities that include preventing cerebral ischemia and decreasing oxygen-free radical-induced lipid peroxidation. It improves neurological recovery in individuals with spinal cord injuries following intravenous administration within 8 hours of damage. Unresolved issues with methylprednisolone therapy include the optimal time frame for treatment, the therapeutic window, and the appropriate combination with other neuroprotective medications. (183).

Cholestane Derivatives

Haiyan Hu and co-authors described cholestane-3, 5, 6-triol (Triol40), a significant cholesterol metabolite, as an endogenous neuroprotectant (184). Triol 40 along with cultured neuron treatment protects the neuronal cell from damage in both in vitro and in vivo animal models through negative modulation of NMDA receptors. The findings suggest that Triol treatment reduces the intracellular concentration of calcium ions caused by glutamate and blocks the NMDA receptors directly, perhaps resulting in neuroprotective effects (184). Diol 41 therapy increased the survival rate of cerebellar granule neurons of animals against glutamate or hypoxia-induced neuronal damage. The Diol therapy was shown to substantially reduce the amount of MCAO-induced infarction in mice. The findings imply that Diol is a potent neuroprotectant and

that synthetic techniques like this could be effective in the creation of potential candidates for stroke treatment (185).

Terpenoids

Triterpenoids

Ginsenosides

These are some of the neuroprotective triterpenoids found in the rhizomes and roots of P. ginseng and P. notoginseng (Araliaceae) (168). In SH-SY5Y human neuroblastoma cells, the aqueous extract of P. ginseng was studied for neuroprotective properties against MPP+-induced cytotoxicity (187). It was found that the extract decreased reactive oxygen species (ROS) overproduction, cytochrome c release, caspase-3 activation, and raised the Bax/Bcl-2 ratio, consequently enhancing cell survival. By inhibiting ERK1/2 (extracellular signal-regulated kinases1/2) and lowering NF-B signalling pathway activity, ginsenosideRg1 also shields cells from H2O2-induced destruction (188). In an a6-OHDA-induced nigrostriatal damage model of PD, ginsenoside Rg1 was found to have a neuroprotective effect in dopaminergic neurons via the IGF1 receptor signalling pathway (189).

Diterpenoids

Diterpenes have been found to have neuroprotective properties. Ginkgolides are a class of diterpenoids obtained from the Ginkgo biloba (Ginkgoaceae) tree, which is an ancient Chinese tree famous for its health-promoting properties (190-192). Ginkgolides guard PC12 cells against hypoxia-induced damage by upregulating HIF-1 (hypoxia-inducible factor 1) expression and HIF-1-DNA binding activity via the p42/p44MAPK pathway (193). The neuroprotective effect of ginkgolide K on glutamate-induced cytotoxicity in PC12 cells suppresses ROS production and Ca2+ influx (194). Additionally, bilobalide has been connected to several neuroprotective mechanisms, including the preservation of mitochondrial ATP synthesis, downregulation of apoptotic injury brought on by staurosporine or serum-free medium, downregulation of hypoxia-induced membrane degradation in the brain, and actions that increase mitochondrial expression (195).

Sesquiterpenes

Commiterpenes A–C, three cadinane sesquiterpenes, were discovered in the resinous exudates of Commiphora myrrha (Burseraceae) and were found to have neuroprotective properties in SH-SY5Y cells against MPP+-induced neuronal cell death (196). Furthermore, tricyclic sesquiterpene-copaene protects against H2O2-induced neurotoxicity (197). Shizukaol B has been found to decrease iNOS and COX-2 expression as well as NO, TNF-, and IL-1 production in LPS-stimulated BV2 microglia. It also suppresses LPS-mediated JNK 1/2 activation and dramatically inhibits LPS-induced AP-1 activation (198).

Monoterpenes

It has been shown that paeoniflorin, a compound produced from Paeoniae alba Radix (a member of the Paeoniaceae), preserves striatal nerve fibers and TH-positive neurons in SN, lessens bradykinesia in the MPTP model of PD, and slows the degradation of dopaminergic neurons (199). The neuroprotective and anti-inflammatory actions of Paeoniflorin can also be connected to adenosine A1receptor activation (200). It also blocked MPP+-induced upregulation of lysosome-associated membrane protein 2a, decreased Ca2+ infiltration and cytosolic content, enhanced microtubule-associated protein 1A/1B-light chain 3-phosphatidyl ethanolamine conjugate protein, and protected PC12 cells from acid and MPP+-induced damage (201, 202).

Conclusion

The nerve cells that convey information and communicate with other cells are called neurons. The process by which a neuronal network consisting of neurons are excited inhibited or tuned to adjacent or remote neurons to communicate and thus showing better adaptability hence ensuring an organism's successful survival is known as neuromodulation. Therapy by process of neuromodulation consists of different types depending on the techniques involved. Millions of people around the world are still affected by neurological disorders which effects both the central and peripheral nervous system, the actual cause of which remains a mystery in healthcare. These disorders mainly consist of AD, PD, Huntington's, ALS, and prion disorders. Aging is the leading factor among many factors contributing to the cause of these diseases. Since these are an untreatable group of diseases and can be fatal, they are becoming *a big challenge for modern societies.* It has been well known that food and health are related to each other for thousands of years. For many years, the traditional usage of herbal remedies has attracted considerable interest due to its therapeutic potential. Conclusions from various studies and research have also confirmed the benefits of a natural compound extracted from plants as a promising medicine for the prevention and management of neurological disorders and many other diseases. Their effectiveness is mainly attributed to their antioxidative, anti-inflammatory, and anticholinesterase activities. Plant metabolites like, but not limited to alkaloids, flavonoids, steroids, and terpenoids are demonstrated the therapeutic benefits by scientific investigations against neurological disorders. It can thus be concluded that plant metabolites offer an abundant source of structurally and functionally diverse molecules for potential and promising prevention and therapeutic management of neurological disorders.

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

Not applicable.

Ethics Statement

Not applicable.

Funding Information

Not applicable.

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How to cite: Barman, D., Dey, N., Sen, S., Kakoti, B.B., Vanlalhriatpuii, C.. Neuromodulatory Effect of Plant Metabolites. Sciences of Phytochemistry. 2022; 1(1):41-59