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BIOACTIVE NATURAL COMPOUNDS TARGETING CENTRAL NERVOUS SYSTEM DISORDERS AND NEUROPROTECTION STRATEGIES INSIGHTS

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ABSTRACT

Disorders that affect the central nervous system (CNS), including neurodegenerative diseases like dementia, stroke, epilepsy, various forms of depression, and neuroinflammatory conditions, represent a significant global healthcare challenge. They have complex pathophysiology (i.e., how these diseases affect brain and central nervous system function) and current clinical treatments are limited. New classes of bioactive natural compounds are considered to be very good

candidates for use as prevention and treatment of CNS disorders because they have been found to have many different types of pharmacological activities, are relatively safe, and can act on multiple targets at once. Bioactive compounds from natural sources (e.g., plants) include polyphenols, flavonoids, alkaloids, terpenoids, and many other phytochemicals. They have shown effectiveness in promoting the survival of neurons by acting through multiple mechanisms, including the following: 1) Antioxidant activity; 2) Anti-inflammatory activity; 3) Anti-apoptotic activity; and 4) Neuroregeneration. In animals, dietary intake of high levels of bioactive compounds has been associated with reduced risk of developing neurodegenerative diseases and reduced risk of comorbidity with other chronic diseases. Major bioactive natural compounds are therapeutically beneficial for CNS disorders, and this review will highlight common bioactive compounds and mechanisms of action with respect to the treatment of different popular CNS disorders. Additionally, new strategies for neuroprotection will be presented. These strategies involve the modulation of different signaling pathways, enhancement of neurotrophic factors, regulation of neurotransmitter systems and ontologies, and improvement of BBB integrity. Furthermore, new drug delivery technologies and methods to improve bioavailability and specificity will also be presented as viable options for overcoming the challenges associated with using bioactive natural compounds for treating CNS disorders.

Keywords: *Central nervous system disorders; Neuroprotection; Bioactive natural compounds; Neurodegenerative diseases; Oxidative stress; Neuroinflammation; Phytochemicals; Flavonoids; Polyphenols; Blood–brain barrier; Mitochondrial dysfunction; Drug delivery systems.*

Introduction

The CNS (Central Nervous System), which includes the brain and spinal cord, is a very complex network that coordinates and regulates all physiological functions, cognitive processes, sensory experiences and motor activity, allowing humans to live. CNS disorders include a broad range of both neurological and psychiatric disorders. Some common CNS disorders are Alzheimer's, Parkinson's, stroke, epilepsy, multiple sclerosis, anxiety and depression. The high prevalence of these types of disorders relative to the general population, make them among the primary contributors to disability and mortality worldwide; therefore creating significant social and economic burdens on affected individuals, their families and on healthcare systems. Also, the increase in number of individuals diagnosed with these disorders is directly related to the increase in the number of older people in the population, to a variety of environmental factors, genetic predisposition to develop these disorders, as well as lifestyle-related risk factors (e.g., smoking and obesity). Despite considerable progress in CNS related research and drug creation, most currently available compounds treat only symptoms instead of stopping the disease from progressing. The inherent complexity of CNS pathology, along with the limitations of the blood-brain barrier for the majority of drug types currently available, prevent conventional treatments from providing satisfactory levels of improvement. As a result, researchers are actively investigating alternative medication/combinations of medical modalities that will treat both the multiple paths by which each of the disorders can progress and that will provide improved neuroprotective effects. Bioactive natural substances are of particular interest due to their broad range of available pharmacological actions and relative safety. (Kumar et al., 2023)

Medicinal plants, marine and micro-organisms have been utilized as traditional treatments for a wide variety of neurological disorders for thousands of years throughout history. Through modern scientific evaluation of these traditional uses, we have been able to identify both the traditional uses and the bioactive components present within these natural treatments that provide significant neuroprotection. The bioactive compounds in these natural products (e.g., flavonoids, polyphenols, alkaloids, terpenoids, carotenoids, and glycosides) exhibit potent antioxidant and anti-inflammatory properties, both of which contribute to neuronal protection. Oxidative stress and chronic neuroinflammation are recognized as two of the primary pathological processes that lead to the initiation and progression of several different CNS disorders

(including Alzheimer's, Huntington's, Parkinson's, and multiple sclerosis). Excessive production of reactive oxygen species can induce damage to proteins, lipids, and nucleic acids within cells, ultimately resulting in neuronal dysfunction and cell death. Through neutralizing free radicals, increasing the activity of endogenous antioxidant defence systems, and modulating the signalling pathways involved in inflammation, natural compounds reduce the amount of injury incurred by neurons. In addition, many bioactive compounds have demonstrated the ability to effect neurotransmitter systems and enhance synaptic plasticity, which is what healthcare practitioners are looking for to prevent or delay the onset of neurodegenerative disease. (Patel et al., 2022)

Numerous studies have discussed the use of bioactive compounds from plants and other natural sources for improving health—the term "bioactive" refers to any component of food that can have beneficial effects on one or more physiological functions in the body. The benefits of these compounds, however, extend beyond their role as antioxidants, and there are several different ways that bioactive molecules can impact various pathways that promote the health of your central nervous system (CNS). Multiple studies have found that a wide variety of natural compounds inhibited the misfolding and aggregation of proteins, which are two processes that have strong connections with neurodegenerative diseases. Natural compounds can also support mitochondrial function; improve neuronal survival; and stimulate the development of new neurons through activation of neurotrophic signaling pathways. Some examples of natural compounds that are considered to have great potential to modulate these signaling/molecular pathways are: curcumin, resveratrol, quercetin, epigallocatechingallate, and ginsenosides. All of these bioactive compounds are thought to affect cellular signaling cascades such as NF-κB, Nrf2, MAPK, and PI3K/Akt pathways. These signaling cascades ultimately lead to a reduction in apoptosis rates (death of cells), increasing cellular resilience (the ability to survive stress), and increasing the rate of neuronal repair. The ability of these compounds to affect multiple disease mechanisms makes them particularly advantageous for treatment because CNS disorders are often the result of interactions among genetics, biochemistry, and environmental factors that occur over time. Consequently, interventions that target multiple disease mechanisms at once are likely to result in more effective treatment outcomes than synthetic drugs which typically have a single target.(Zhou et al., 2023)

Neuroprotection is now one of the main areas of interest in today's neuroscience research because it is felt that preventing injury to the neurons is far better than trying to restore large areas of neurodegeneration. Neuroprotective techniques aim to maintain the cellular and functional integrity of nerve cells by reducing cellular damage due to oxidative stress, reducing neuroinflammation, controlling excitotoxicity, and preserving the integrity of mitochondria. In addition to pharmaceutical approaches, emerging approaches to neuroprotection are through enhancing the body's own antioxidant systems, increasing the expression of neurotrophic factors, improving cerebral blood flow and enhancing the integrity of the blood-brain barrier. Natural bioactive compounds are being included in these approaches due to their ability to affect several neuroprotective biochemical pathways simultaneously. Evidence from experimental animal studies has shown that natural products can decrease neuronal damage in animal models of stroke, traumatic brain injury, Alzheimer's disease, and Parkinson's disease. There is also evidence that dietary changes that include neuroprotective phytochemicals have the potential to minimize the risk of cognitive decline due to age. These findings demonstrate the increasing importance of natural compounds as adjunctive and preventative treatment options for CNS diseases. (Martinez et al., 2022)

While promising, there have been numerous obstacles that delay the conversion of bioactive natural products into viable clinical therapies. Bioactive natural products can demonstrate poor bioavailability; low stability; an accelerated rate of metabolism; limited ability to cross the blood–brain barrier; and low therapeutic efficacy. To overcome these limitations, investigators are

developing advanced drug delivery systems for the controlled release and targeted delivery of bioactive natural products to the CNS, such as nanoparticles; liposomes, polymeric drug carriers; and nano-emulsions. In addition, combination therapies combining bioactive natural products with conventional drugs will be explored to improve therapeutic outcomes and reduce adverse drug reactions. There will be a need for additional research to create standard formulations; optimize the drug dosing regimens; and conduct well-controlled clinical trials to study the long-term safety of these products. It will also be necessary to establish how bioactive natural products are neuroprotective; this knowledge will lay the foundation for developing new therapeutic approaches for the treatment of the increasing incidence of CNS disorders, which will ultimately improve patients' quality of life. (Brown et al., 2023)

CNS disorders affect brain and spinal cord function

CNS, which means central nervous system, is made up of many different things that stop the brain and spinal cord from working properly. The central nervous system is basically the body's command center. It makes sure everything happens together, such as seeing, hearing, moving, thinking, remembering, feeling, and doing things that you need to live. When CNS is damaged or does not work well, the patient will have a variety of different symptoms like difficulty moving, loss of ability to think clearly, difficulty with seeing, hearing or feeling, personality changes, and inability to care for himself/herself. There are many reasons for the development of CNS disorders, including genetic mutations, infections, trauma, autoimmune disease, blood vessel problems, and aging. Examples of CNS disorders include: Alzheimer's disease, Parkinson's disease, stroke, epilepsy, and multiple sclerosis, which all have a high number of cases worldwide. Because of the current trends of population aging and increasing life expectancy, CNS diseases will continue to be a burden. These diseases not only affect the actual patient physically and mentally, they also create a lot of emotional and financial burden for the patients' family and the health care system. Timely diagnosis and treatment are very important for slowing the disease process, and improving the quality of life. (Anderson et al., 2024)

The higher cognitive functions of the Brain include learning, memory, reasoning, language and emotional regulation. Disorders of the brain and central nervous system (CNS) are very likely to severely affect these vital cognitive functions and therefore reduce an individual's productivity and quality of life. Neurodegenerative diseases, which are caused by the progressive death of neurons and synapses, lead to both mental and physical decline over time. For example, Alzheimer's disease mainly affects memory and cognitive abilities, and Parkinson's disease mainly disrupts movement and motor function/coordination. Other causes of brain injury include trauma, ischemia and infection and can lead to permanent neurologic deficits. In addition, psychiatric disorders including depression and anxiety have been increasingly recognized as having an underlying basis of altered brain structure and function. Common pathologic processes that are involved with many CNS disorders include neuroinflammation, oxidative stress, mitochondrial dysfunction, and abnormal aggregation of proteins – all of which contribute to neuronal damage and impaired communication between neurons. Therefore, understanding the biological pathways that contribute to these mechanisms and disease progression is extremely important for the purpose of developing appropriate treatment modalities. There are both pharmacological and non-pharmacological approaches being explored by researchers aimed at preserving the integrity of neurons, enhancing cognitive function, and preventing additional decline in neurologic function. (Thompson et al., 2023)

The spinal cord is critical to relaying information from the brain to the body so that movement, sensation and other autonomic functions occur normally. Disorders of the spinal cord can interrupt pathways for communicating information between the brain and body leading to substantial neurological deficits. Individuals with traumatic spinal cord injury often suffer partial or complete paralysis depending upon the location and severity

of the injury. Other diseases such as multiple sclerosis, which cause inflammation and autoimmune damage, will damage the protective myelin sheaths that wrap around nerve fibres, leading to demyelination, which interferes with the relay of nerve signals from one neuron to another resulting in symptoms such as weakness in muscles, fatigue, numbness or tingling sensations, impaired coordination and other major physical disabilities. Similarly, individuals who suffer from degenerative spinal conditions, spinal cord tumors or spinal cord infections may also have their neurologic function compromised by damage to the spinal cord. The recovery from severe spinal cord injuries is a significant clinical problem because spinal cord neurons have very limited ability to regenerate after injury. In recent years many scientific advancements in the area of neuroregeneration, stem cells, neuroprotective treatments, and rehabilitation strategies have focused on improving functional outcomes after severe spinal cord injury. Furthermore, through improved understanding of the pathology of the spinal cord, treatment strategies have been developed that focus on preserving neural tissue and minimizing inflammation while promoting the repair of the injured neurons. Innovative treatment strategies designed to improve the health and function of the nervous system have provided significant hope for people experiencing debilitating conditions associated with spinal-cord disorders. (Nguyen et al., 2022)

One major challenge in CNS disorder management is the complexity of disease mechanisms. Various biological pathways frequently interact, complicating treatment development directed at multiple contributing factors. Neuron injury and disease progression from oxidative stress, chronic inflammation, mitochondrial dysfunction, excitotoxicity, and impaired protein clearance. The blood-brain barrier limits delivering therapeutic agents while protecting the brain and restricting entry of harmful substances. Alternative drug delivery systems using nanotechnology, targeted molecular therapies, and gene therapy are being researched to help overcome these barriers. Lifestyle behaviors (regular exercise, balanced nutrition, cognitive stimulation, and stress management) also provide neuroprotective effects & benefits to brain function. Utilizing preventive strategies in conjunction with cutting-edge therapeutic approaches may lower incidence & severity of CNS disorders. In addition, furthering multidisciplined research remains necessary to identify more effective treatments and long-term outcomes for people with neurological disorders. (Roberts et al., 2023)

There is an increasing number of people suffering from central nervous system disorders, which have led to an urgent need for new and effective prevention and treatment strategies. As people around the world continue to age, it is projected that they will also experience an even larger increase in the number of people diagnosed with neurodegenerative and neurological diseases over the next decade. With the advent of specific molecular biology techniques, neuroimaging methods, the genetics of different types of central nervous system disorders, and advancement in computational neuroscience, the understanding of the pathophysiology of central nervous system disorders has improved significantly. These technologies/resources have allowed researchers to use established biomarkers to help in the early diagnosis of CNS disorders. It has been suggested that drugs that act as neuroprotectants (by reducing inflammation, oxidative injury, and cell death) can be important in the preservation of neurological function. There is also increasing interest in the use of natural products, stem cells, and regenerative medicine in the restoration of normal neural networks. Public health efforts to promote a healthy lifestyle, prevent cardiovascular diseases, and screen for early stages of neurodegenerative and neurological disease may help to reduce the burden of neurological diseases. To effectively address the multifactorial challenges related to CNS disorders will require coordination and collaboration among scientists, clinicians, decision-makers, and healthcare providers. With continued research and advances in technology, it may be possible to develop more effective interventions to improve neurological and spinal function for patients and improve their overall quality of life. (Hernandez et al., 2024)

Natural compounds show neuroprotective potential

Recently, natural products have been given considerable interest due to their possible role in protecting against neurodegeneration in the CNS. Neuroprotection is defined as the preservation of neuronal structure and function, as well as the slowing or prevention of the progression of neurodegeneration. The loss of neurons and the loss of function that are common to many CNS diseases, including Alzheimer's Disease, Parkinson's Disease, stroke, and multiple sclerosis, is characterized by a progressive loss of neurons and a progressive loss of function. One of the primary benefits of natural products is that they may act on multiple targets at once, while many synthetic drugs usually only work on one pathway. Natural compounds, which are often derived from plants, fruits, vegetables, and herbs, include flavonoids, polyphenols, alkaloids, and terpenoids. The neuroprotective effects of these compounds may be largely due to their ability to exert antioxidant effects, reduce inflammation, and block apoptosis. They may also help to reduce oxidative damage to neurons. Additionally, natural products may modulate the signaling pathways required for neuron survival and those involved in neuroinflammation. Because of the multi-targeted nature of their mechanisms and low toxicity, natural products are an attractive option for the long-term management and prevention of CNS diseases. Ongoing research efforts are directed toward further understanding their mechanisms of action and improving their application in clinical practice. (Li et al., 2024)

Oxidative stress is a major factor in the onset and progression of various CNS conditions, so it is an important target for neuroprotective measures. Natural agents that have distinctive antioxidant abilities can neutralize ROS and RNS, which are toxic to nerve cells. Excessive amounts of ROS can lead to lipid peroxidation, damage DNA and proteins and result in nerve cell death by apoptosis. Compounds with bioactive properties, including quercetin, curcumin, resveratrol and catechins, possess significant ability to enhance the body's own antioxidant defence mechanisms of superoxide dismutase, catalase and glutathione peroxidase. Many of these compounds also activate the Nrf2 signalling pathway, which is responsible for regulating the cellular antioxidant response(s). By reducing oxidative damage, natural compounds can therefore facilitate the maintenance of mitochondrial health and increase the survival of nerve cells. In addition, they support the functionality of synapses and promote proper communication between nerve cells, which is critical to cognitive processes such as learning and memory. Likewise, their antioxidant ability makes these compounds particularly helpful in the prevention of neurodegeneration due to the ageing process. Research is ongoing to test the efficacy of these compounds in clinical trials, particularly in relation to diseases such as Alzheimer's disease and Parkinson's disease. (Garcia et al., 2023)

Neuroinflammation is another key factor to the pathology of central nervous system (CNS) disorders. Natural products have been shown to provide an anti-inflammatory effect in several experimental models. Chronic microglial and astrocyte activation results in the increased release of inflammatory cytokines, including TNF-α, IL-1β and IL-6, which can cause cell death. Many natural products prevent the production of these inflammatory mediators by modulating important signaling pathways such as nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK). For example, curcumin or berberine have been found to inhibit microglial activation and decrease inflammatory cytokine production, thus helping to establish an appropriate immune response in the CNS than ultimately lead to having significant levels of cell death. Furthermore, many natural products have also been shown to improve blood-brain barrier function to limit the amount of neurotoxic substances from entering the CNS. By decreasing neuroinflammation, these natural products can help to slow down the progression of CNS diseases and promote the survival of neurons. Because they have both antioxidant and anti-inflammatory capabilities, they are very effective neuroprotective agents. Researchers are currently looking at the potential of combining these natural products with standard therapies to improve treatment responses in patients with CNS disorders. (Zhang et al., 2022)

Programmed cell death, or apoptosis, is one of the major causes of neuronal loss in the central nervous system (CNS) disorders. Excessive activation of apoptotic pathways results in irreversible loss of neurons. Several natural compounds have demonstrated the ability to inhibit apoptosis by modulating both pro- and anti-apoptotic proteins, including Bax, Bcl-2, and caspases. They can promote neuronal survival through activation of the PI3K/Akt and ERK signaling pathways, which play an essential role in neuronal growth and protective functions. Natural compounds also enhance mitochondrial membrane stability, which in turn inhibits cytochrome c release (a critical event in the initiation of apoptosis). By maintaining mitochondrial health, natural compounds help maintain adequate energy production and cellular homeostasis within neuronal cells. This leads to improved cognitive and motor function in preclinical models of neurodegenerative disorders, further supporting their significance in neuroprotection strategies due to their ability to regulate cellular death pathways. Additionally, many natural compounds have been shown to exert synergistic effects when combined, thereby increasing their potential therapeutic effect. Ongoing research is examining natural compounds' role in clinical neuroprotection and when integrated into contemporary pharmacotherapy approaches. (Singh et al., 2023)

Regulating neurotransmitter systems and synaptic plasticity are two other important components of neuroprotection. Natural products can affect neurotransmitters such as dopamine, serotonin, acetylcholine, and glutamate, all of which play significant roles in brain function and behaviour. Imbalances in these neurotransmitters are implicated in many neurological disorders, including: depression; anxiety; schizophrenia; and Parkinson's disease. The activity of certain phytochemicals increases the amount of acetylcholine, which facilitates learning and memory, while other phytochemicals regulate dopamine activity and aid in motor control. In addition, natural compounds promote synaptic plasticity via enhanced gene expression of brain-derived neurotrophic factor (BDNF), which promotes neuronal growth and connectivity and, in turn, enhances cognitive resilience and learning ability. Finally, they help to reduce the excitotoxicity associated with excessive glutamate activity, a major contributor to neuronal death. Thus, natural products contribute to overall brain health by regulating neurotransmitter levels and synaptic function through multiple mechanisms. Their diverse neuropharmacological actions suggest that they will be an important part of both preventive and therapeutic strategies for treating central nervous system (CNS) disorders. More research is needed to bring these findings into clinical practice. (Ahmed et al., 2024)

Oxidative stress and inflammation cause neuronal damage

There are two main types of pathological processes that have a significant role in causing neuronal injury in the central nervous system (CNS): oxidative stress and inflammation. Oxidative stress happens when there is an imbalance between reactive oxygen species (ROS) generation and the body's ability to either detoxify ROS or repair the damage caused by them. Neurons are especially vulnerable to oxidative injury due to the uniqueness of their structure and function. The amount of oxygen that neurons normally consume is considerably greater than that of other cells. Neurons have a large amount of lipid (fat) in their membranes and their ability to neutralize potentially damaging ROS is less than other types of cells. When too much ROS damage different parts of cells, such as lipids, proteins and DNA, neuronal function is impaired and cells die. Neuronal cell death is a major reason for the initiation and progression of a variety of CNS disorders such as Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis. ROS accumulation disrupts the normal functioning of mitochondria (the part of our cells that provide energy), decreases the amount of energy each cell produces (ATP) and activates apoptosis (cell death). Oxidative injury can also disrupt how well neurons communicate with each other (synaptic function); thereby, affecting learning, memory and motor coordination. The lack of ability of the brain to regenerate after damage makes the effects of oxidative injury in the brain even more devastating

and normal neuronal function almost impossible. Therefore, the normalization of oxidative stress is essential for all neuroprotective approaches. Many scientists are exploring the use of antioxidants and natural products as treatment options to minimize oxidative injury and maintain neural integrity in those with CNS disorders. (Wang et al., 2024)

Neuroinflammation, or inflammation in the central nervous system (CNS), is an essential factor in causing injury to neurons. Activation of microglia and astrocytes, which are the immune cells of the CNS, primarily mediates neuroinflammation. These cells normally help maintain homeostasis and protect neurons; however, when activated inappropriately during pathological conditions, they can become over-activated and release pro-inflammatory cytokines that disrupt neuronal cells and synaptic function. Chronic neuroinflammation is commonly present in certain neurodegenerative diseases (i.e., dementia, Alzheimer's, Parkinson's), contributes to the loss of myelin in multiple sclerosis (MS), and contributes to poorer outcomes in stroke and traumatic brain injury. Continued inflammation leads to a sustained cycle of neuronal injury and inflammation, which accelerates neurodegeneration. In addition, the inflammatory mediators associated with neuroinflammation increase permeability of the blood-brain barrier, permitting potentially harmful substances to enter the CNS and contribute to neuronal injury. Consequently, neuroinflammation is a significant target for treatment in CNS pathology. Research is being conducted to find anti-inflammatory agents and/or natural bioactive compounds that can regulate the immune response and reduce neuronal injury associated with neuroinflammation. (Johnson et al., 2023)

Oxidative stress and inflammation have an interconnected and cyclical effect on neuronal health and can lead to additional damage to neurons in CNS disorders. Inflammation activates certain signaling cascades (e.g., NF-κB), which will lead to the upregulation of several proinflammatory cytokines. Similarly, inflammatory processes create more reactive oxygen species (ROS), which leads to even more oxidative stress. This mutual amplification causes progressive impairment of neuronal function, as well as neuronal death. The link between oxidative stress and inflammation is via mitochondrial dysfunction, as damaged mitochondria produce significant ROS and lead to the activation of inflammatory pathways. In addition, the cumulative impact of oxidative stress and inflammation facilitates increased occurrence of protein misfolding, loss of synaptic connections, and death of neurons in neurodegenerative disorders. For example, in Alzheimer's disease, aggregation of amyloid-beta creates oxidative stress and activates proinflammatory pathways, thereby contributing to the cognitive deficits associated with this disorder. Additionally, in Parkinson's disease, the loss of dopaminergic neurons is intimately associated with oxidative damage to mitochondria and the activation of the microglial inflammatory response. An understanding of how oxidative stress and inflammation interact is essential for developing effective strategies for neuroprotection. Treatment of oxidative stress and inflammation simultaneously may yield greater success than treating each individually. This has generated interest in multi-targeted drugs and natural substances exhibiting both antioxidant and anti-inflammatory actions. (Lee et al., 2022)

Damage to neurons as a result of oxidative stress and inflammation eventually causes impairment (both structurally and functionally) in the central nervous system. Prolonged exposure of neurons (nerve cells) to oxidative and inflammatory insults causes apoptosis (programmed cell death) or necrosis (uncontrolled cell death) leading to the loss of neural networks. Therefore, cognitive abilities, motor control, and sensory processing will all be affected. In addition, synaptic dysfunction occurs as a consequence of impaired neurotransmitter release and receptor sensitivity. Additionally, neuroplasticity (the brain's ability to adapt and reorganize) is also greatly diminished with these conditions. Consequently, patients develop a progressively deteriorating memory, decreased learning capacity, and overall neurological decline. In severe cases, there is a large scale loss of neurons resulting in irreversible brain damage and disability. These pathological changes emphasize the need for early intervention to reduce

the likelihood of disease progression. Several therapeutic strategies exist for reducing oxidative stress and inflammation such as using antioxidant or anti-inflammatory medications, dietary changes, and exercising as ways to treat oxidative stress/inflammation. There is considerable evidence that many natural compounds from plants can be an effective treatment for brain injury since they can modulate more than one pathway associated with neuronal injury based on results from preclinical research studies. In addition, there is currently ongoing research to convert these findings into effective therapeutic treatments for central nervous system disorders. (Garcia et al., 2023)

In order to prevent and manage the damage done to neurons caused by oxidative stress and inflammation, it is important to have a thorough understanding of the biological mechanisms that are involved. Molecular biology advances have proven that there are multiple signaling pathways related to oxidative stress and inflammation, such as Nrf2, NF-κB, MAPK, and PI3K/Akt. A pathway's activation is able to decrease neuronal injury and increase the survival of neurons when properly modulated. Another potential solution for treating neuronal injury caused by oxidative stress and inflammation is via the use of natural bioactive compounds, which act as polypharmacologic direct target agents and target a variety of pathways all at once. Some of the natural bioactive compounds that have strong antioxidant and anti-inflammatory properties include flavonoids, polyphenols, and alkaloids. Researchers are also focusing on developing nano-delivery, based on nanotechnology, systems to increase the absorption and penetration of natural bioactive compounds into the brain. There is a large volume of preclinical data supporting the use of natural bioactive compounds as anti-inflammatory and antioxidant agents; however, there are multiple challenges that must be addressed before they can be used clinically, such as the need for clinical validation, optimization of dosages, and long-term safety. Continued research will be necessary to find effective means of preventing or treating oxidative stress and inflammation in the central nervous system (CNS). In order to find solutions to the numerous challenges associated with the treatment of some CNS diseases, there will need to be a combination of pharmacology, neuroscience, and biotechnology readily available to treat patients post-diagnosis. (Zhang et al., 2024)

Flavonoids and polyphenols protect nerve cells

Bioactive compounds from plants include polyphenols and flavonoids, which have powerful neuroprotective properties. Numerous fruits, vegetables, tea, cocoa and medical herbs contain both plant-derived substances that exhibit anti-inflammatory and antioxidant potential. Neuronal cells are extremely vulnerable to injury because of their high rate of metabolism and low level of antioxidants available. Polyphenolics and flavonoids protect the neurons from damage by eliminating (neutralizing) reactive oxygen species (ROS) and thereby, decreasing oxidative stress, which contributes significantly to neurodegeneration. They will also enhance mitochondrial activity which is essential for generating energy in neurons. Research has indicated that polyphenols and flavonoids can help prevent loss of neurons from ailments like stroke, Alzheimer's disease and, Parkinson's disease as well as increase cognitive abilities. Additionally, they influence a number of different signal transduction pathways involved in cell survival (apoptosis) as well as a number of different pathways including the Nrf2, MAPK and PI3K/Akt pathways. These compounds can interact with multiple mechanisms at the same time, which makes them excellent candidates to be used for long-term neuroprotective therapies because both polyphenols and flavonoids are derived from natural sources and are relatively non-toxic. Therefore, research continues to identify the therapeutic potential for polyphenols and flavonoids' clinical application in CNS disorders. (Chen et al., 2024)

Flavonoids and Polyphenols Protect Nerve Cells through Reducing Oxidative Stress Oxidative stress occurs when there is an excess of reactive species in the body (such as reactive oxygen species) that causes damage to lipids, proteins and DNA, ultimately leading to cell death and dysfunction of the nerves. Some flavonoids, such as quercetin, luteolin, and kaempferol, and some polyphenols,

such as resveratrol and epigallocatechingallate, are strong free radical scavengers. They help to increase the activity of the body's own antioxidants, including superoxide dismutase, catalase and glutathione peroxidase. They also activate the Nrf2 signaling pathway, which regulates the production of the protective antioxidant enzymes. Thus, by helping to maintain the redox balance of nerve cells, these compounds help protect the cellular integrity of nerve cells and prevent these cells from dying via apoptosis.These compounds also enhance the energy produced in the mitochondria of the cells to be used by the nerves to generate ATP, which is important for cells that have a high metabolic demand, such as those in the brain. It has been established that the antioxidant properties of flavonoids or polyphenols is a major way that flavonoids or polyphenols will delay or inhibit neurodegenerative processes and improve brain function. The mechanism of action of flavonoids and polyphenols in regulating oxidative stress continues to be the focus of neurological research. (Kim et al., 2023)

Flavonoids and polyphenols possess powerful anti-inflammatory properties that aid in the prevention of neurons from being damaged by neuroinflammation, which is marked by the activation of glial cells such as astrocytes and microglia. Chronic conditions of the central nervous system are exacerbated when pro-inflammatory cytokines (i.e., TNF-alpha, IL-1 beta, IL-6) are released by the activated immune response and cause damage to neurons and disrupt communication between synapses. Flavonoids and polyphenols mitigate the pro-inflammatory response by interfering with a variety of pro-inflammatory pathways (e.g., NF-kappaB and MAPK) so the amount of pro-inflammatory mediators produced is reduced and the structural damage to neurons is reduced. Some flavonoids and polyphenols, such as curcumin and quercetin, have been shown to significantly decrease the activation of microglia and inhibit the development of chronic inflammation in various experimental models. By modulating the inflammatory response associated with neuroinflammation, flavonoids and polyphenols contribute to the maintenance of neuronal homoeostasis and slowing the progression of neurodegenerative diseases. Flavonoids and polyphenols also provide support for the integrity of the blood-brain barrier, thus reducing the risk of neurotoxic substances entering the central nervous system. The ability of these flavonoids and polyphenols to reduce oxidative stress and inflammation together makes them exemplary neuroprotective therapies. Ongoing studies at the preclinical and clinical levels are exploring the potential benefits of these compounds in the treatment of a variety of CNS disorders. (Singh et al., 2022)

In addition to their roles in promoting neuronal survival, flavonoids and polyphenols modulate apoptosis and enhance synaptic plasticity. One of the main mechanisms involved in neurodegeneration is apoptosis (programmed cell death), resulting in permanent loss of nerve cells (neurons). Apoptosis-related proteins (e.g., Bax, Bcl-2, caspases) are regulated by flavonoids and polyphenols, preventing excessive neuronal death. Survival signals such as the phosphoinositide 3-kinase (PI3K)/Akt and extracellular regulated kinase (ERK) pathways promote cell growth and repair. Furthermore, increased levels of brain-derived neurotrophicfactor (BDNF) resulting from flavonoids and polyphenols have been connected with enhancing synaptic plasticity involved with learning and memory. Improving the connection between neurons helps preserve cognitive function and slows the effects of aging. Flavonoids and polyphenols also help maintain proper balances of neurotransmitters, and this is critical for healthy brain function as well as behavioral health. Because of their ability to influence multiple cellular processes, flavonoids and polyphenols have the potential to provide a comprehensive protective mechanism to neuronal networks. Their ability to increase brain resilience also make them possible candidates for the prevention of cognitive disorders and improvement of neurological health. Continued research is underway to aid in understanding the long-term effects of flavonoids and polyphenols as well as their therapeutic applications for diseases of the central nervous system (CNS). (Patel et al., 2023)

Even though they have a lot of potential for protecting nerve cells, flavonoids and polyphenols can face restrictions on their use in clinical practice. One of the biggest barriers to using these types of natural compounds is the fact that they don't have high bioavailability because they get metabolized quickly and removed from the body by the liver. In addition to having poor availability, flavonoids and polyphenols are also unable to cross into the central nervous system (CNS) due to the blood-brain barrier. Researchers are working on creating new techniques to deliver these compounds such as liposomes, nanoparticles, and nanoemulsions to improve their ability to stay stable in the body and target the brain. Other strategies that researchers are considering to maximize the effectiveness of flavonoids and polyphenols include dietary supplementation and combinations of flavonoids and polyphenols. There are also many different varieties of flavonoids and polyphenols found in nature and the absorption rates will vary from person to person, causing a difference in effectiveness from one individual to the next. Although flavonoids and polyphenols are still being studied and not yet widely used in practice, there is a body of literature indicating that this type of compound may be neuroprotective, especially in the case of age-related degenerative diseases. More research is needed to determine the best dosing methods, formulation techniques, and conduct large clinical studies to determine the effectiveness of flavonoids and polyphenols as neuroprotective agents. Future advancements in drug delivery systems may allow flavonoids and polyphenols to become a critical part of new neuroprotective therapies, ultimately decreasing the impact of neurological disorders on society. (Garcia et al., 2024)

Neuroprotection helps prevent disease progression

Neuroprotection refers to the means used to protect the structure and function of neurons and thereby slow or halt the progression of disorders of the central nervous system (CNS). Neuroprotection is an essential consideration in modern neuroscience, as many neurological disorders are progressive and currently have no known cure (e.g., Alzheimer's Disease, Parkinson's Disease, stroke and multiple sclerosis). Typically, the progression of these diseases is characterized by the gradual loss of neurons, synaptic dysfunction and a loss of neural connectivity. Neuroprotective therapies are focused on halting these pathological processes at an early or intermediate stage in order to preserve the function of the remaining portion of the brain. Neuroprotective therapies can include reducing oxidative stress, suppressing inflammation, maintaining normal mitochondrial function or preventing apoptosis. Neuroprotection should not be limited to pharmacotherapy; it also includes non-pharmacological strategies such as exercise, dietary changes and cognitive stimulation. These non-pharmacological strategies are important to promote neuronal health and improve brain resilience and functional independence in patients with chronic neurological disorders. In addition, there is increasing interest in using natural compounds and bioactive molecules that can target multiple pathways of disease simultaneously. Ultimately, the goal of neuroprotection is to prolong the time until disease progression and to improve the quality of life of individuals affected by chronic neurological disorders. (Ahmed et al., 2024)

One avenue through which neuroprotection serves to limit disease progression is via the reduction of oxidative stress in the central nervous system. Oxidative stress is caused by the imbalance between the creation of reactive oxygen species (ROS) and a brain's ability to detoxify them. When the level of ROS exceeds a brain's ability to remove them, damage occurs to cellular substances, e.g., lipids, proteins, and DNA; this results in neuronal dysfunctions and ultimately leads to cell death. Neuroprotective agents enhance antioxidant enzymes, which detoxify ROS e.g., superoxide dismutase, catalase, and glutathione peroxidase; neuroprotective agents also work via the stimulation of transcription factors like Nrf2, which induce cellular injury response mechanisms. By restoring redox (oxidized/reduced) equilibrium, neuroprotection preserves mitochondrial (energy-producing organelles) structural integrity and prevents neurons from failing to produce enough energy. Mitochondrial dysfunction is a common feature in many neurodegenerative disorders and is

a primary contributor to the progression of these disorders. Preserving the structural integrity of synaptic function, provided by the reduction of oxidative damage, leads to a significant increase in a brain's ability to encode memories, as well as produce coordinated motor function; therefore, modulating oxidative stress is viewed as one of the most efficacious methods for decelerating central nervous system-related dysfunctions while preserving the overall health/functioning of the nervous system over time. (Khan et al., 2023)

Neuroprotective means having a positive effect on protecting the use and function of neurons and other cells in the brain from injury, inflammation, and neurodegenerative diseases. Neuroprotection can help regulate neuroinflammation, which is one of the main causes of disease progression in central nervous system (CNS) disorders and is primarily due to inflammatory signals mediated by activated microglia and astrocytes in the brain after injury and/or illness. Activated microglia and astrocytes release various pro-inflammatory mediators including TNF-α, IL-1β, and IL-6 which cause additional neuronal injury and impair neuronal signalling. Neuroprotective therapies focus on modulating these signalling pathways (NF-κB and MAPK) involved with regulating inflammation. By inhibiting the release of neuroinflammatory mediators during inflammatory processes, neuroprotectors may reduce the risks of chronic damage to the neuronal tissues of the CNS and may help maintain the integrity of the blood-brain barrier (BBB), which protects the brain from harmful substances in the circulation. Chronic neuroinflammation is associated with accelerating neurodegenerative changes, so controlling neuroinflammation is an important strategy to slow the progression of the disorder. By having effective neuroprotective strategies, neuroprotective agents may protect existing neurons as well as create a more stable or balanced neural environment that limits further injury and promotes healthy brain function over the long term. (Rehman et al., 2022)

The second primary goal of neuroprotection is to prevent cell death, known as apoptosis, which is thought to be a major cause of many CNS illnesses. The initiation of apoptosis is controlled by several intracellular signaling pathways, including the actions of several apoptosis-related proteins such as Bax, Bcl-2, and caspases. An excess of apoptosis activation due to the excessive stimulation of the apoptotic pathways is responsible for the irreversible death of neurons in many neurodegenerative diseases; thus, one of the central components of neuroprotective strategies is to inhibit these apoptotic pathways and increase cellular survival mechanisms. By stimulating signal transduction pathways such as PI3K/Akt or ERK signaling, these neuroprotective strategies have been shown to reduce apoptosis and promote neuronal survival. In addition, preserving the stability of the mitochondrial membrane helps to prevent the release of cytochrome c, which is a critical step in the initiation of apoptosis. Neuroprotection can help maintain structure and function of the brain for longer periods of time by preventing unwanted neuronal death. Neuroprotection is particularly vital for patients with chronic conditions, as the gradual loss of neurons from these conditions contributes to cognitive and motor decline. Therefore, targeting apoptosis is one method of slowing the progression of these diseases and enhancing the neurological outcomes of patients suffering from these CNS disorders. (Zafar et al., 2023)

Neuroprotection enhances neuroplasticity and repair processes in order to help prevent illness as well. Neuroplasticity is defined as an organism's ability to reorganize itself from trauma or adapt after receiving new information. In the case of CNS disorders, there is often ongoing neuronal injury/inflammation, making gaining back neuroplasticity difficult. Neuroprotective treatments enhance neuronal repair through restoration of synaptic connections and increase the production of neurotrophic factors (brain-derived neurotrophic factor [BDNF]). These neurotrophic factors promote neuronal growth, differentiation and survival. Increased neuroplasticity also enables an injured brain to use intact neurons in other areas of the brain to adapt to the loss of function from the damaged area of the brain, and allows for preservation of functional abilities despite the progression of the disease. Additionally, neuroprotection enhances the biomechanical balance of neurotransmitters in the

body, which promotes cognitive and emotional stability. Repairing the neural networks within the CNS and strengthening them through neuroprotection slows functional decline and prolongs the overall functional ability of persons with neurodegenerative disease. Therefore, neuroprotection is not only important in the treatment of CNS disorders, it will also serve as an important method of managing and preventing the development of severe functional disabilities in patients suffering from CNS disorders for many years into their lives. (Siddiqui et al., 2024)

Conclusion

Disorders of the central nervous system are a major challenge to global health because they are very complex and have a progressive nature, along with few options for available curative treatments. CNS disorders are diseases that affect the brain and spinal cord, resulting in impairment of cognitive, motor and sensory functioning as well as conduct, which decreases significantly the patient's quality of life. Evidence indicates that key pathological mechanisms that contribute to neuronal injury/disease progression include oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity and apoptosis. Neuroprotection has been described as an important therapeutic strategy for slowing or preventing progression of CNS diseases through preservation of the structure and function of neurons. Many of the naturally occurring, bioactive compounds (such as flavonoids, polyphenols, alkaloids, and terpenes) have demonstrated great potential in the treatment of CNS diseases by targeting multiple pathways simultaneously with antioxidant, anti-inflammatory and anti-apoptotic properties. In addition, the use of novel drug delivery systems employing nanotechnology-based methods could enhance the clinical utility of these compounds by providing improved stability and accessibility to the brain. There are currently several challenges (e.g., poor bioavailability, limited ability to cross the blood-brain barrier, and no large-scale clinical trials) that must be overcome before these novel therapies can be used broadly in the clinical setting, even though there is evidence from many preclinical studies showing positive results.

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