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Review article:

NAVIGATING NEUROLOGICAL DISORDERS: HARNESSING THE POWER OF NATURAL COMPOUNDS FOR INNOVATIVE THERAPEUTIC BREAKTHROUGHS

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ABSTRACT

Novel treatments are needed as neurological issues become more frequent worldwide. According to the report, plants, oceans, microorganisms, and animals contain interesting drug discovery compounds. Alzheimer's, Parkinson's, and stroke reviews emphasize neurological disorders' complexity and natural substances' safety. Learn about marine-derived and herbal substances' neuroprotective characteristics and applications. Molecular pathways show these substances' neurological healing effects. This article discusses clinical usage of Bryostatin-1, Fucoidan, Icariin, Salvianolic acid, Curcumin, Resveratrol, etc. Their potential benefits for asthma and Alzheimer's disease are complex. Although limited, the study promotes rigorous scientific research and collaboration between traditional and alternative medical practitioners. Unexplored natural compounds, quality control, well-structured clinical trials, and interdisciplinary collaboration should guide future study. Developing and employing natural chemicals to treat neurological illnesses requires ethical sourcing, sustainability, and public awareness. This detailed analysis covers natural chemicals' current state, challenges, and opportunities in neurological disorder treatment.

Keywords: Neuroprotection, natural compounds, animal sources, marine sources, neurological disorders

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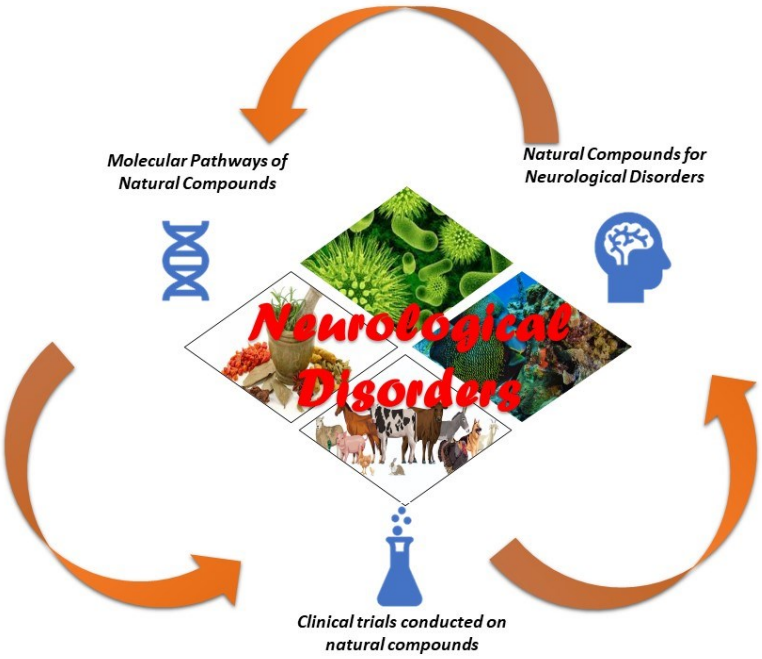

Figure 1: Graphical abstract

INTRODUCTION

Neurological disorders constitute a broad and complex category of medical conditions that afflict millions of individuals worldwide, transcending age, gender, and geography. These disorders, which encompass a multitude of ailments affecting the central and peripheral nervous systems, carry profound implications for both the individuals' living with them and whole society (Patel et al., 2016). Characterized by a wide range of symptoms, neurological disorders can manifest as cognitive, motor, sensory, or autonomic dysfunction, and their impacts can extend well beyond physical and mental health. Neurological disorders have a profound global impact, affecting hundreds of millions of individuals. Each year, over 6 million lives are lost to strokes, with more than 80 % of these fatalities occurring in low- and middle-income countries. Worldwide, more than 50 million people grapple with epilepsy. Dementia afflicts approximately 47.5 million people globally, with an additional 7.7 million new cases arising annually. Alzheimer's disease stands as the predominant cause of dementia, contributing to 60-70 % of these cases (Hussain et al., 2023). Migraine is prevalent in over 10 % of the world's population. As the global population ages, the prevalence of neurological disorders is on the rise, adding urgency to the need for innovative treatments and interventions that can alleviate suffering, enhance the quality of life, and reduce the economic burden associated with these conditions. The prevalence of neurological disorders varies significantly depending on the specific disorder, geographic region, and demographic factors. Neurological disorders encompass various conditions affecting the nervous system, including the brain, spinal cord, and peripheral nerves. Tension-type headaches and migraines are among the most prevalent neurological disorders worldwide. Migraines alone affect more than 1 billion people globally, making them the third most prevalent illness globally. Epilepsy is one of the most common severe neurological disorders, with an estimated 50 million people affected worldwide (Rushendran et al., 2023). Alzheimer's disease, a progressive neurodegenerative disorder, affects over 50 million people globally. This number is expected to rise significantly as the population ages. Parkinson's disease is estimated to affect more than 6 million people worldwide. Its prevalence increases with age.

Multiple sclerosis affects approximately 2.8 million people globally (Singh et al., 2022, 2023; Suresh et al., 2022). Its prevalence varies by region, with higher rates in North America and Europe.

The intricate and bidirectional connection between depression, anxiety, and neurological disorders is characterized by a complexity that extends beyond the conventional boundaries of mental health (Krishnan and Nestler, 2008; Maj et al., 2020). Although depression and anxiety are typically classified as mental health disorders, there is compelling evidence supporting a substantial interplay with neurological elements. Shared characteristics include imbalances in neurotransmitters, changes in the structure and function of brain, and involvement of inflammatory processes and immune system dysregulation (Giannakopoulou et al., 2021; Remes et al., 2021). The confluence of chronic stress, common risk factors, and genetic susceptibilities further contributes to the overlapping nature of these conditions. Additionally, medications prescribed for neurological disorders may exert an impact on mood. Managing chronic health conditions, particularly neurological disorders, poses challenges that can exacerbate or play a role in the onset of depression and anxiety (Mariotti, 2015; McEwen, 2017). Recognizing this intricate connection emphasizes the need for a comprehensive and holistic approach to comprehend and address health's mental and neurological facets. This underscores the crucial role of healthcare professionals in conducting thorough assessments to ensure accurate diagnosis and effective treatment.

Stroke stands as a major contributor to global mortality and disability, with millions of new cases reported annually. The prevalence varies by region and is influenced by lifestyle and risk factors. Amyotrophic lateral sclerosis is a neurodegenerative condition primarily impacting the motor system, yet it is increasingly acknowledged for its additional non-motor manifestations. Progressive muscle weakness and atrophy result from the loss of both upper and lower motor neurons in the motor cortex, brain stem nuclei, and the anterior horn of the spinal cord. While ALS typically begins focally, it subsequently extends to various body regions, and respiratory muscle failure commonly limits survival to 2–5 years post-onset. Extra-motor manifestations, observed in up to 50 % of cases, encompass alterations in executive dysfunction, behavior, and language difficulties. Notably, 10-15 % of patients exhibit such pronounced issues that they meet the clinical criteria for frontotemporal dementia (Masrori and Van Damme, 2020). Autism is a genetic, developmental neurological disorder, and its prevalence varies by region and diagnostic criteria. In some areas, it affects as many as 1 in 54 children. Peripheral neuropathy, a condition affecting the nerves outside the central nervous system, has a broad range of causes (Masrori and Van Damme, 2020). Its prevalence depends on the underlying condition but can be substantial. It's important to note that these statistics provide a general overview of the prevalence of common neurological disorders. The actual numbers may vary over time and across different populations. Additionally, as the global population ages and diagnostic capabilities improve, the prevalence of many neurological disorders is expected to increase, making them a significant public health concern (Pan et al., 2021; Vaquerizo-Serrano et al., 2021; Wang et al., 2023). In this article, we delve into the world of neurological disorders, exploring their prevalence, challenges, and the pressing need for novel treatments, with a particular focus on the potential of natural compounds in revolutionizing neurological disorder drug discovery. Neurological disorders represent a critical public health challenge, given their prevalence, impact, and the limitations of existing treatments. Novel approaches, such as exploring the potential of natural compounds, offer hope for addressing these disorders by providing innovative, safe, and effective treatments to improve the quality of life for those affected.

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UNMET NEEDS AND THE POTENTIAL OF NATURAL COMPOUNDS FOR NEUROLOGICAL DISORDERS

Neurological disorders encompass various conditions affecting the nervous system, including the brain, spinal cord, and peripheral nerves. They are a significant global health concern due to their prevalence and profound impact on individuals, families, and society. Conditions such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, and stroke affect millions of people worldwide and are significant causes of disability and mortality. Many neurological disorders remain without effective cures or even disease-modifying treatments. Existing therapies often focus on managing symptoms rather than addressing the underlying causes of the disorders. Patients and their caregivers face a significant burden in managing these chronic and debilitating conditions. Neurological disorders impose substantial economic and social burdens. Healthcare costs for treatment and long-term care are substantial. The cognitive and physical impairments associated with these disorders often limit individuals' ability to work and participate in daily life, resulting in reduced quality of life and social isolation. As the global population ages, the prevalence of neurological disorders is expected to rise significantly. This demographic shift adds urgency to the need for innovative treatments and interventions that can slow disease progression or alleviate symptoms. Traditional drug discovery and development processes for neurological disorders have proven challenging. Identifying safe and effective compounds, especially for complex conditions like Alzheimer's or Parkinson's, has been formidable. Natural compounds, derived from plants, animals, microorganisms, or marine organisms, have gained attention as potential sources for novel neurological disorder treatments. Frequently, these compounds boast a rich tradition in traditional medicine and may present distinctive bioactive characteristics. Natural compounds can provide a holistic approach to addressing neurological disorders, potentially targeting multiple aspects of the disease pathology. This approach aligns with the growing recognition that neurological disorders often have multifactorial origins, illustrated in Figure 2. Many natural compounds are well-tolerated and have a favorable safety profile, making them attractive options for long-term use. Additionally, their renewable and sustainable sources align with the need for environmentally responsible drug development.

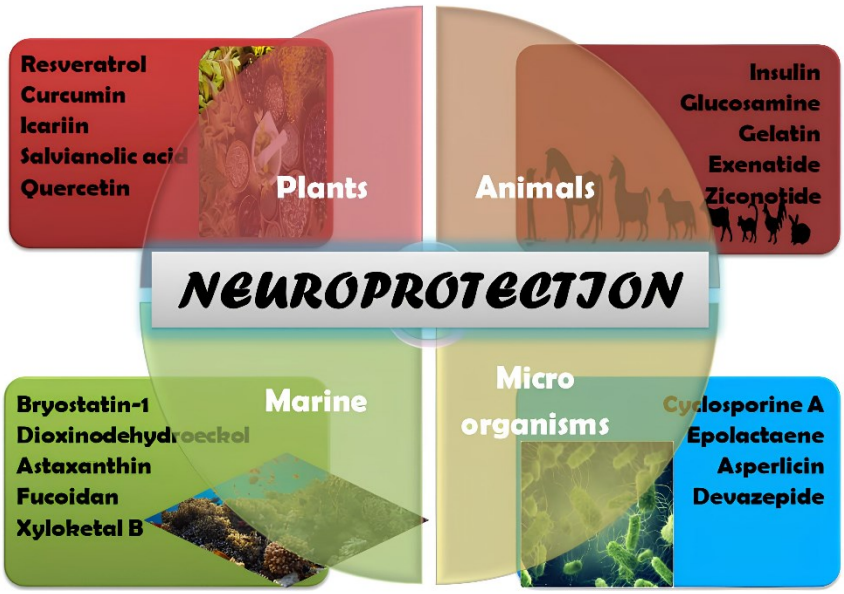

Figure 2: Natural compounds from diverse origins for neurological disorders

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NATURAL COMPOUNDS AS POTENTIAL SOURCES FOR DRUG DISCOVERY

Natural compounds have long been recognized as valuable sources for drug discovery due to their diverse chemical structures and potential therapeutic properties. Natural compounds represent a valuable and fertile ground for drug discovery due to their chemical diversity, historical use, bioactivity, and potential for creating effective and safe pharmaceuticals. The exploration of natural compounds continues to be a promising strategy in the search for novel treatments across a wide range of diseases and conditions. Natural compounds are derived from various sources, including plants, microorganisms, marine organisms, etc. This diversity provides a vast library of chemical structures to explore for potential drug candidates. Natural compounds often have complex and unique chemical compositions, which can lead to novel therapeutic properties. Many natural compounds have been used in traditional medicine for centuries, providing rich empirical evidence regarding their safety and efficacy. This historical knowledge can guide modern drug development efforts. Natural compounds often have specific biological activities. For example, plants produce secondary metabolites as a defense mechanism against predators and environmental stressors. Some of these compounds exhibit biological activities that can be harnessed for therapeutic purposes. Natural compounds frequently serve as a starting point for the development of pharmaceutical drugs. Scientists often isolate and modify these compounds to enhance their efficacy, safety, and bioavailability, leading to the creation of new drug candidates. Some natural compounds are highly selective in their actions, which can benefit drug development. They can target specific molecular pathways or receptors involved in disease processes with minimal off-target effects. Natural compounds can be used as building blocks for combinatorial chemistry, enabling the creation of large libraries of potential drug candidates with varying structures and properties. In an era of increasing environmental awareness, the sustainable and renewable nature of natural compound sources aligns with the demand for more environmentally responsible drug development practices. Many natural compounds have a long history of human consumption, making them more likely to be well-tolerated and safe for pharmaceutical use. The pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics (effect on the body) of some natural compounds are well-understood, which can expedite the drug development process. Some natural compounds work synergetic with other compounds, potentially enhancing their therapeutic effects while reducing side effects. The complexity and diversity of natural compounds can help address the issue of drug resistance, particularly in infectious diseases, by offering multiple mechanisms of action. The study of natural compounds has the potential to rejuvenate drug discovery by providing new avenues for drug development, especially in areas where traditional approaches have had limited success.

EXPLORE EMERGING TRENDS IN THE USE OF NATURAL COMPOUNDS FOR NEUROLOGICAL DISORDER TREATMENTS

At the time of our last knowledge update in November 2023, significant progress and notable developments had occurred in utilizing natural compounds to treat neurological disorders. It's important to acknowledge that subsequent developments may have transpired. Marine-derived compounds display diverse activities encompassing anti-inflammatory, anti-apoptotic, anti-oxidant, anti-cancer, and neuroprotective effects. Promisingly, certain compounds demonstrate potential in addressing neurological disorders like Alzheimer's disease, Parkinson's disease, stroke, and traumatic brain injury. The mechanisms of action often involve specific processes such as inhibiting protein aggregation, modulating oxidative stress, and regulating pathways associated with neuroinflammation. These compounds hail from various marine

organisms, including bryozoans, sea cucumbers, mollusks, and sponges, underscoring the rich biodiversity of marine ecosystems. Herbal compounds sourced from Punica granatum, Cannabis sativa, and Centella asiatica showcase neuroprotective effects. Many of these compounds act as anti-oxidants, providing a defense against oxidative stress, a prevalent factor in neurodegenerative disorders. The compounds originate from a diverse array of herbs, emphasizing the potential inherent in natural sources for neuroprotection. Compounds sourced from animals exhibit neuroprotective effects (Table 1) through diverse mechanisms, including the regulation of signaling pathways, the inhibition of inflammation, and the enhancement of neuronal survival. Experimental studies commonly employ animal models such as rats and mice to assess the neuroprotective potential of these compounds. Notably, several compounds in this category focus on alleviating neuroinflammation, a shared contributor to various neurological conditions. A recurring theme across all tables is the focus on compounds with neuroprotective properties, indicating a shared interest in developing therapies for protecting and preserving neuronal function. Compounds are derived from various sources, including marine organisms, herbs, and animal tissues, showcasing the exploration of biodiversity for potential neurological treatments. The compounds often target multiple pathways, suggesting a multifaceted approach to addressing neurological disorders by modulating inflammation, oxidative stress, and protein aggregation. Several compounds emerge as potential candidates for further research and development due to their efficacy in preclinical studies. The varied and optimistic terrain of natural compounds has been a beacon of hope in the exploration of new therapeutic possibilities for neurological disorders.

MOLECULAR PATHWAYS OF NATURAL COMPOUNDS IN NEUROLOGICAL DISORDERS

Natural compounds often work at a molecular level to address neurological disorders by influencing various biological pathways and processes within the nervous system. Some natural compounds exhibit neuroprotective properties by shielding nerve cells from damage and promoting survival. This process can be crucial in conditions such as neurodegenerative diseases where neurons are progressively lost. Chronic neuroinflammation is a common feature of many neurological disorders. Natural compounds like curcumin and resveratrol have anti-inflammatory properties and can reduce inflammation in the nervous system. Research suggests that curcumin and resveratrol may help reduce inflammation in the nervous system by targeting specific inflammatory markers and pathways. For example, they may inhibit the activity of nuclear factor kappa B (Gonzales and Orlando, 2008; Mazzanti and Di Giacomo, 2016; Salehi et al., 2018). Oxidative stress plays a role in various neurological disorders. Oxidative stress is intricately linked to the pathogenesis of numerous neurological disorders, playing a pivotal role in the progression of these conditions. The heightened metabolic activity of neurons, coupled with their relatively low anti-oxidant capacity, renders them particularly susceptible to the damaging effects of reactive oxygen species (Kim et al., 2015a; Li et al., 2015; Pizzino et al., 2017). This imbalance leads to cellular damage, including lipid peroxidation, protein misfolding, and DNA modifications, contributing to the dysfunction and demise of neurons. Mitochondrial dysfunction, another consequence of oxidative stress, not only disrupts cellular energy production but also amplifies ROS generation, creating a self-reinforcing cycle. Moreover, oxidative stress is intimately associated with inflammatory processes in the central nervous system, further accelerating neuronal injury and impairing overall neurological function. Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's

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Table 1: Compounds sourced from animals with potential neurological applications

Compound/ Substance	Source	Activity	Findings	Reference
Insulin	Cattle and pigs	Neuroprotection, oxidative stress, Parkinson's disease	Insulin shields neuronal viability from oxidative stress, mitigating both necrotic and apoptotic cell death. Additionally, insulin thwarts lipid and protein oxidation induced by ascorbate/Fe2+, reducing overall neuronal oxidative stress. Insulin's intervention prevents the heightened 4-hydroxynonenal (4-HNE) adducts on GLUT3 glucose transporters induced by exposure to ascorbate/$Fe2^{+}$, suggesting a potential interference with glucose metabolism. The impact of insulin on anti-oxidant defense mechanisms in cortical neurons was also assessed. This highlights insulin's potential utility in averting oxidative stress-related injuries seen in various neurodegenerative disorders. Furthermore, insulin enhances tyrosine hydroxylase (TH) and insulin signaling pathways in dopaminergic neurons by activating PI3K/Akt/GSK-3 survival pathways. This, in turn, inhibits MPP+-induced iNOS and ERK activation, along with modulating the Bax to Bcl-2 ratio. These findings propose a protective role for insulin against MPP+-induced neurotoxicity in SH-SY5Y+RA cells.	Duarte et al., 2005; Ramalingam and Kim, 2016
Premarin, conjugated estrogen	Pregnant mare	Neuroprotection, spinal cord injury (SCI), Alzheimer's disease, Amnesia	Blinded grading using the Basso–Beattie–Bresnahan locomotor scale assessed the impact of PRM, an E2 receptor antagonist, on locomotor function. Over a 7-day treatment period, PRM demonstrated a reduction in post-spinal cord injury (SCI) lesion volume, mitigating neuronal cell death, inflammation, and axonal damage. PRM also influenced the balance of pro- and anti-apoptotic proteins in favor of cell survival, enhanced angiogenesis, and promoted microvascular growth. Increased expression of estrogen receptors (ERs), specifically ERα and ERβ, following PRM treatment, coupled with their inhibition by an ER inhibitor, suggested that the neuroprotection associated with PRM might be E2-receptor mediated. By alleviating glial activation, reducing inflammation and cell death, and enhancing angiogenesis, PRM contributed to an improved functional outcome, as evidenced by the BBB locomotor scale. These findings underscore the therapeutic potential of PRM for enhancing post-SCI outcomes.	Acosta et al., 2009; Haque et al., 2022; Zhao and Brinton, 2006
Glucosamine	Chitin from shell fish	Neuroprotective, anti-neuroinflammatory, stroke, pro-neurogenic effects, brain	"GlcN demonstrates effective stroke suppression in acute animal models with low or negligible toxicity, making it a safe oral option for human administration. Our study suggests that GlcN holds potential in	Hwang et al., 2010; Jamialahmadi et

		injury including cerebral ischemia and hypoxic brain damage	combating strokes and other inflammatory-related diseases. It inhibits postischemic microglial activation and the upregulation of proinflammatory mediators induced by lipopolysaccharide (LPS), both *in vivo* and in culture systems using microglial or macrophage cells. The anti-inflammatory effects are primarily attributed to GlcN's ability to inhibit nuclear factor kappa B (NF-κB) activation. In the middle cerebral artery occlusion (MCAO) model, GlcN significantly reduces infarct volume, motor impairment, and neurological deficits. Hwang et al. (2010) demonstrated the anti-inflammatory effects of GlcN in the MCAO model. Additionally, in an *in vivo* serum/glucose deprivation model of neuronal ischemia, GlcN pretreatment of PC12 cells enhances cell viability, suppresses apoptosis, and reduces intracellular production of reactive oxygen species. In another study using an *in vitro* ischemic stroke model of oxygen-glucose deprivation in SH-SY5Y cells, GlcN promotes neuronal viability, cellular proliferation, neurite outgrowth, and downregulates mRNA levels of proinflammatory genes."	al., 2013; Jhelum et al., 2022; Nasr et al., 2019; Shin et al., 2013
Gelatin	Pig/beef skin, bone and tissue	Neuroprotective, anti-oxidant, ischemic stroke	The study aimed to assess the anti-oxidative and neuroprotective impact of extracts from pig skin (PS) and gelatin hydrolysates from pig skin (LPS) using the human neuroblastoma cell line (SH-SY5Y). PS exhibited a threefold higher extraction yield compared to LPS, and its protein content was approximately tenfold higher than that of LPS.	Joachim et al., 2014; Kim et al., 2013
Exenatide	Saliva of Gila monster	Neuroprotective effect, cognitive function, Parkinson's disease (PD)	The compound demonstrated comparable inhibitory effects on the JNK pathway and expression of ERS-related proteins (Cyt-t, Caspase-3, p-JNK, and p-c-JUN). These findings suggest that exenatide enhances cognitive function in diabetic rats, potentially by suppressing apoptosis through the inhibition of JNK/c-JUN activation. In rats induced with Parkinson's disease by rotenone, levels of malondialdehyde and tumor necrosis factor-alpha increased. However, in rats treated with exenatide, these levels significantly decreased. These results indicate that exenatide exhibits neuroprotective, anti-inflammatory, and anti-oxidant effects in a rotenone-induced rat model of Parkinson's disease.	Aksoy et al., 2017; Wang et al., 2022a
Ziconotide	Cone snail venom	Anti-convulsant, anxiolytic, anti-depressant, sedative effect	Ziconotide significantly reduced seizure frequency and prolonged latency compared to the control. Chronic administration led to decreased sleep latency and increased sleep duration, while a single dose had no effect on these parameters. Rats treated with ziconotide showed significantly lower amygdala corticosterone levels than the control group. Ziconotide exhibits favorable neurobehavioral effects in an	Bozorgi et al., 2020; Zamani et al., 2020

			epilepsy model with comorbid anxiety, potentially linked to reduced brain corticosterone levels. Notably, ziconotide lacks the tolerance, dependency, and addiction issues associated with benzodiazepines, highlighting the need for improved drug delivery protocols and the mitigation of adverse effects in ziconotide-based therapies.	
Eptifibatide	venom of the southern pygmy rattlesnake	Neuroprotective, ischemic stroke, anti-platelet	Eptifibatide, a GPIIb/IIIa inhibitor, enhances embolus dissolution efficiency, reduces infarct volume, and improves microvascular patency when compared to a standalone fibrinolytic agent. Combining rt-PA with a GPIIb/IIIa antagonist not only diminishes perfusion deficits but also significantly augments cortical perfusion.	Kaur et al., 2013
Batroxobin	South American pit vipers	Neuroprotective, spinal cord injury (SCI), traumatic brain injury (TBI)	Batroxobin markedly elevated VEGF expression from day 3 to 2 weeks post spinal cord injury (SCI) in SD rats ($P<0.05$). Long-term behavioral studies demonstrated motor function improvement in injured mice treated with batroxobin. Additionally, batroxobin reduced neuronal apoptosis and inflammation during the acute stage. Furthermore, administration of batroxobin mitigated scar formation and diminished lesion size at 4 and 14 days post-brain injury. These findings indicate the favorable effects of batroxobin on nigrostriatal pathway injury, suggesting its potential clinical application.	Kang et al., 2007; Li et al., 2016; Yu et al., 2015

disease, and amyotrophic lateral sclerosis (ALS), showcase the cumulative impact of oxidative stress, where chronic exposure to ROS contributes to the aggregation of abnormal proteins and the progressive loss of neurons. Recognizing the central role of oxidative stress provides a foundation for exploring therapeutic strategies aimed at mitigating its effects and preserving neurological health (Singh et al., 2019; Uttara et al., 2009; Zhang et al., 2021a). Several pathways are involved in the impact of oxidative stress on neurological health. For instance, genetic damage can impair the function of tumor suppressor genes like P53, CDK4, and CDK6 (Fan et al., 2023). Alternatively, oxidative stress may reduce the activity of PP2A while increasing GSK3β, leading to Tau hyperphosphorylation (Bartolome et al., 2022). It can also promote matrix metalloproteinase (MMP) activity, which damages the blood-brain barrier (Hu et al., 2022). Furthermore, oxidative stress can disrupt proteasomal function and cause protein misfolding, leading to the accumulation of amyloid beta proteins (Lévy et al., 2019). Oxidative stress can activate the caspase pathway by reducing ATP levels, resulting in apoptosis (Zhuang et al., 2020). Additionally, it can enhance the NFκB pathway, leading to the production of inflammatory molecules such as TNF alpha, IL1 beta, and MCP-1, which further stimulate the inducible nitric oxide synthase (iNOS) to produce nitric oxide, contributing to neuroinflammation (Chen et al., 2023). Other factors like interferon-gamma (INF gamma), damage-associated molecular patterns (DAMPs), and lipopolysaccharides (LPS) can also activate the MAPK and NFκB pathways, exacerbating neuroinflammation (Zhang et al., 2021b). Natural compounds with anti-oxidant properties, such as vitamin E, vitamin C, and flavonoids, can neutralize harmful free radicals and reduce oxidative damage to nerve cells. Some natural compounds can influence the production, release, or function of neurotransmitters, the chemical messengers that transmit signals in the brain. This can help regulate mood, cognition, and other neurological functions. Figure 5 illustrates the pathways involved in oxidative stress-mediated neurological health impairment. Natural compounds like ginkgo biloba can improve blood circulation in the brain, which may benefit conditions associated with reduced cerebral blood flow, such as vascular dementia (Arulselvan et al., 2016; Kurutas, 2016; Teleanu et al., 2019). Natural compounds facilitate neuroplasticity, the brain's ability to reorganize and adapt. This can be vital for recovery after brain injuries or for learning and memory. Some natural compounds can stimulate the production of neurotrophic factors, such as brain-derived neurotrophic factor. These factors promote the growth and maintenance of neurons. Figure 3 provides a visual representation of the diverse pathways investigated by neuroprotective agents derived from both plant and animal sources and Figure 4 provides a visual representation of the diverse pathways investigated by neuroprotective agents derived from both microbial and marine sources. This illustration highlights the complexity and versatility of these agents in promoting neuroprotection across various pathways.

In Alzheimer's disease, the accumulation of beta-amyloid plaques is a hallmark. Natural compounds like curcumin have been investigated for their ability to reduce the formation and accumulation of these plaques (Mishra and Palanivelu, 2008). Certain natural compounds can influence the activity of ion channels in nerve cells, affecting their excitability and signal transmission. Some natural compounds act as enzyme inhibitors, impacting the breakdown or production of specific molecules relevant to neurological disorders. For instance, acetylcholinesterase inhibitors are used to treat Alzheimer's disease (McGleenon et al., 1999; Saxena and Dubey, 2019; Subramanian et al., 2022). Natural compounds can affect gene expression in neurons, influencing various processes related to neurological health and function. It's essential to note that the mechanisms of action can vary widely among different natural compounds, and their effectiveness may differ from one neurological disorder to another. Moreover,

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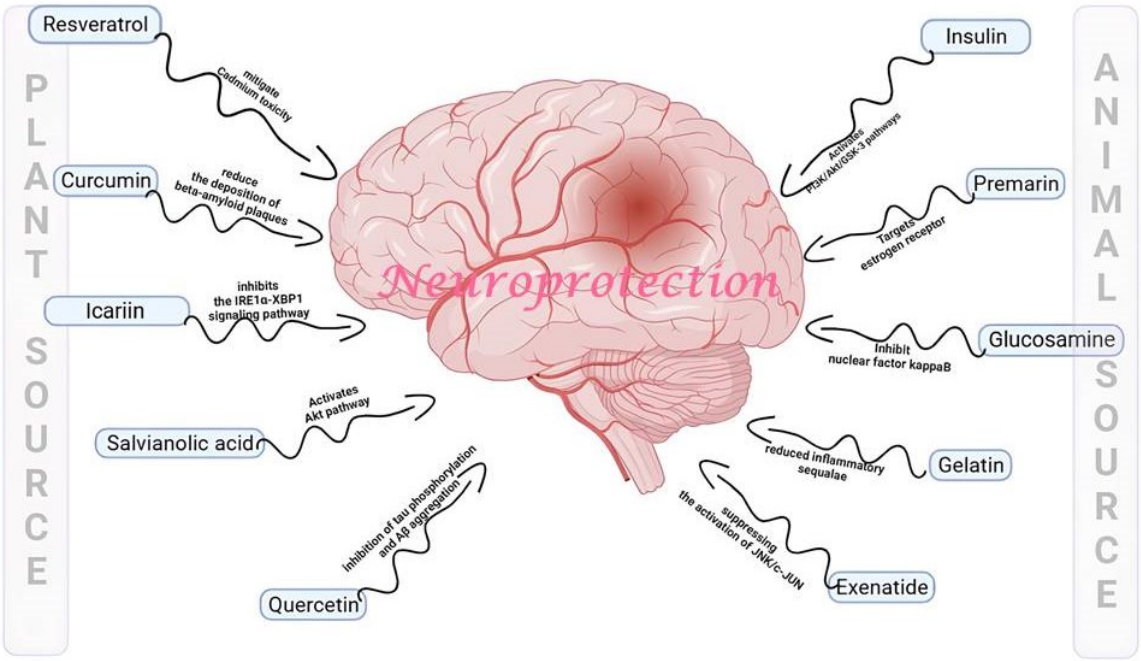

Figure 3: Illustration depicting the diverse pathways explored by neuroprotective agents derived from both plant and animal sources. Insulin activates PI3K pathway; Premarin targets estrogen receptors; Glucosamine inhibits NFκB pathway; Gelatin reduces inflammatory sequelae; Exenatide suppresses JNK activation; Quercitin inhibits tau phosphorylation and amyloid beta aggregation; Salvianolic acid activates AKT pathway; Icariin inhibits IRE1α-XBP1 pathway; Curcumin reduces deposition of beta-amyloid plaques; Resveratrol mitigates cadmium toxicity which collectively is involved in neuroprotection.

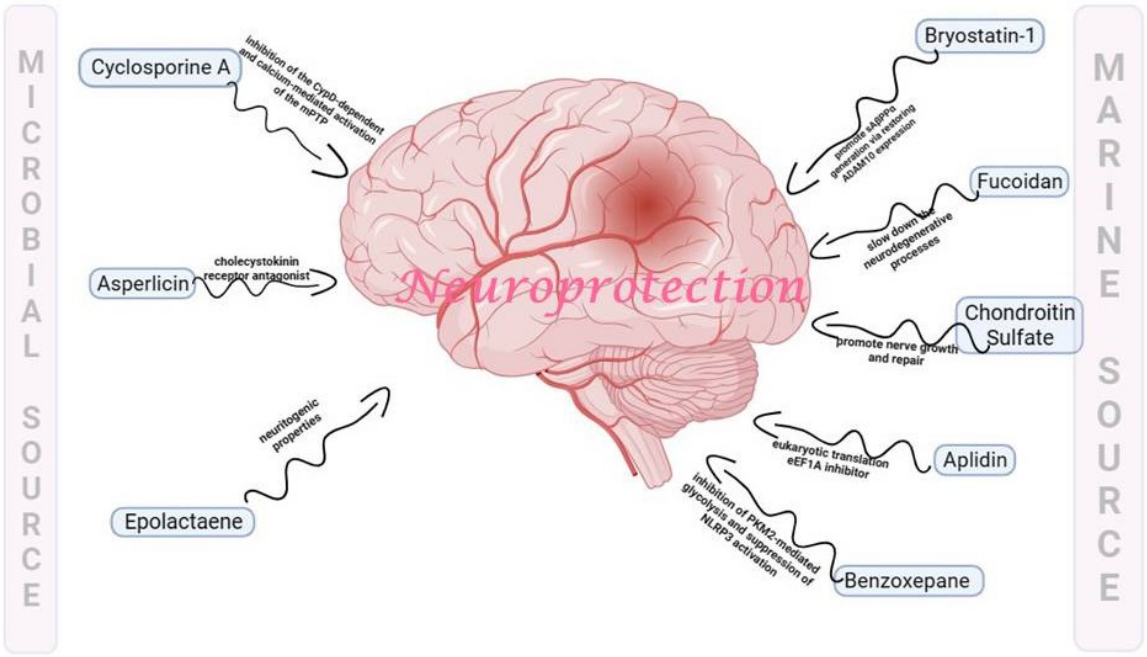

Figure 4: Schematic representation of the diverse pathways explored by neuroprotective agents derived from microbial and marine sources. Bryostatin 1 restores ADAM10 expression; Fucoidan slows down the neurodegenerative process; Chondroitin sulfate promotes nerve growth and repair; Aplidin acts as EF1A inhibitor; Benzoxepane inhibits PKM2N and suppresses the activation of NLRP3; Epolactaene acts as neuritogenic; Asperlicin acts as cholecystokinin antagonist; Cyclosporine A inhibits CYPD-dependent and activation of mPTP which collectively leads to neuroprotection.

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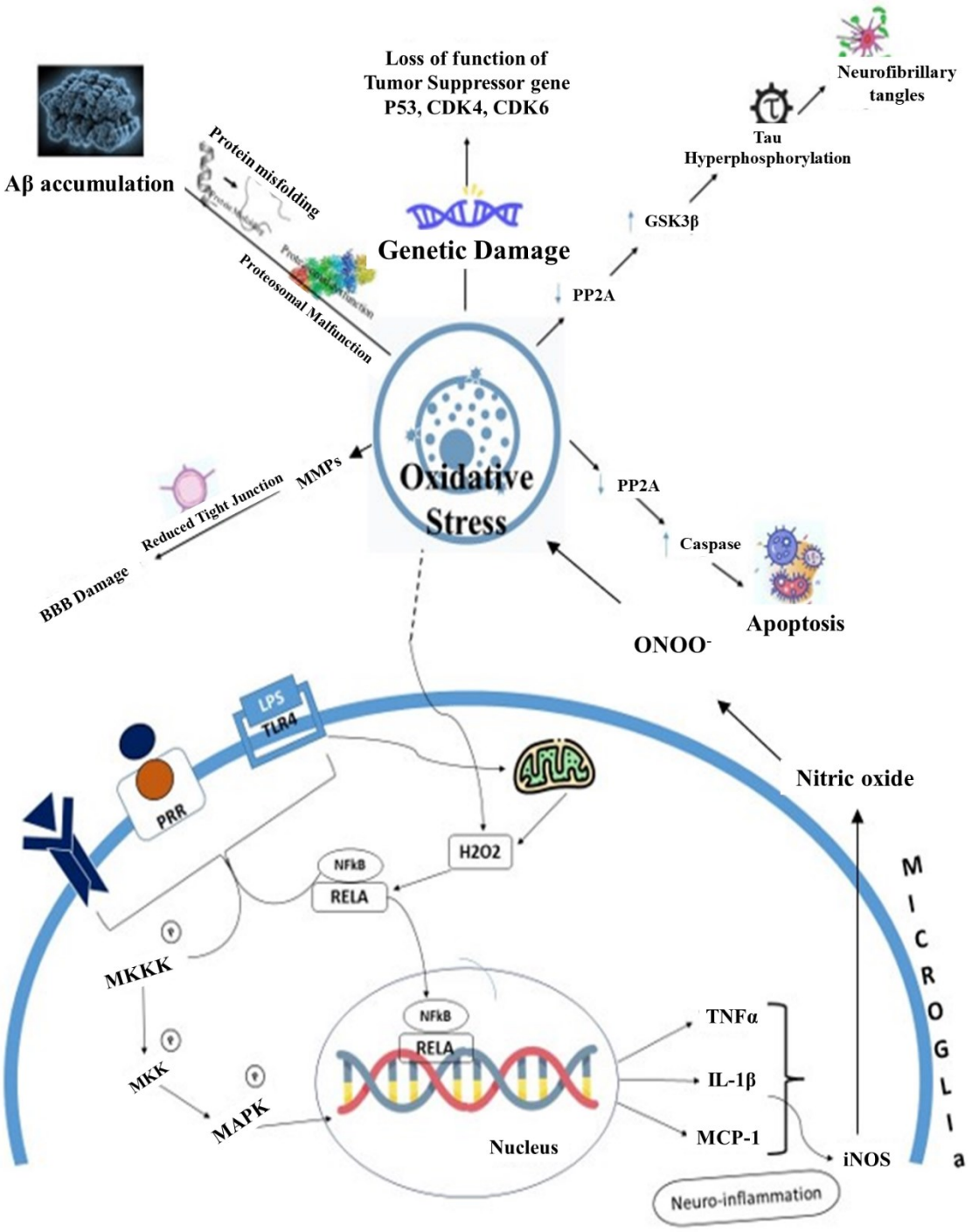

Figure 5: Pathways involved in oxidative stress-mediated neurological health impairment

ongoing research continuously reveals new insights into how these compounds work at a molecular level, providing potential avenues for drug discovery and therapy development

CLINICAL TRIALS CONDUCTED ON NATURAL COMPOUNDS

As per the information available until our last update in November 2023, Bryostatin-1 had been studied in various preclinical investigations and clinical trials, primarily focusing on its potential therapeutic applications in

neurological disorders and cancer. Bryostatin-1 has shown promise in preclinical studies for conditions such as Alzheimer's disease, multiple sclerosis, fragile X syndrome, stroke, traumatic brain injury, and depression. It demonstrated potential in addressing various neurological disorders. It is a potential inhibitor of protein aggregation, modulation of oxidative stress, and regulation of neuroinflammatory pathways. Bryostatin-1 possesses anti-inflammatory, anti-oxidant, MMPs inhibitory, and neurogenesis stimulatory properties, along with the added advantages of crossing the blood-brain barrier and being orally available, appears to be a suitable option for treating multiple sclerosis (Safaeinejad et al., 2018). The impacts of bryostatin-1 likely encompass two aspects: acute safeguarding of the blood-brain barrier and chronic preservation of neuronal stability. Precision in timing and dosage is imperative to discern the most suitable protective treatment intervals. Modulation of protein kinase C presents a promising therapeutic avenue for averting the enduring consequences linked with neurotrauma (Lucke-Wold et al., 2015). The neuro-pharmacological activity of other natural compounds derived from marine source were listed in Table 2.

Fucoidan has demonstrated various therapeutic potentials, including anti-inflammatory, neuroprotective, anti-oxidant, and anti-tumor effects. Clinical trials or medical applications may be exploring its efficacy. The administration of oligo-fucoidan has the potential to decrease the lymphocyte proportion and lower inflammatory factor concentrations in individuals with asthma. This may contribute to the suppression of respiratory tract inflammation and an improvement in pulmonary function (Yeh et al., 2022). A solitary administration of fucoidans can potentially impact the expression of genes associated with essential cellular processes. Furthermore, it substantiates earlier findings that fucoidans have an effect on immunity, cancer cells, inflammation, and neurological function (Gueven et al., 2020). Additionally, the administration of fucoidan twice daily over a 90-day span did not significantly impact insulin resistance or other assessed parameters of cardiometabolic health in a group of obese, non-diabetic individuals. This lack of effect might stem from inherent inefficacy, adherence levels lower than recorded, or the possibility that a more extended therapy duration and higher baseline insulin resistance are necessary to achieve a notable impact (Wright et al., 2019). Wheat peptides and fuconoids have brought fresh insights into dietary strategies for chronic gastritis. They have offered clinical and theoretical evidence supporting the development and commercialization of health foods tailored for this condition (Kan et al., 2020). Fucoidan derived from Okinawa mozuku is deemed safe for consumption as a food product and has been shown to boost NK cell activity, particularly among males. Over a 12-week period, ingesting fucoidan at a dosage of 3 grams daily did not lead to troublesome adverse effects. Furthermore, no abnormalities were observed in blood or biochemical tests (Tomori et al., 2021).

Icariin derived from Epimedium brevicornu Maxim, icariin has been investigated for its neuroprotective, anti-apoptotic, and anti-inflammatory effects and may be a subject of clinical interest. Icariin holds potential as an effective drug for treating patients with ankylosing spondylitis. However, additional follow-up studies involving larger group sizes are necessary to validate its efficacy (Wang et al., 2017). Icariin and p-icariin exhibit anti-oxidant properties and provide hepatoprotection, as evidenced by decreases in serum liver injury markers and elevated levels of anti-oxidative enzymes. These alterations can potentially alleviate liver injury and are, to some extent, associated with the anti-oxidant properties of both compounds. While both components demonstrate similar free radical scavenging effects, p-icariin demonstrates superior hepatoprotective effects compared to icariin (Xiong et al., 2014). There was a notable reduction in mortality, and 6-phosphate icariin exhibited a more pronounced effect than icariin. The likely mechanism behind the *in vitro* anti-viral activity of 6-phosphate icariin and

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Table 2: Marine derived compounds for neurological disorders

Compound	Marine source	Activity	Findings	Reference
Bryostatin-1	Bryozoan *Bugula neritina*	Alzheimer's disease, multiple sclerosis, fragile X syndrome, stroke, traumatic brain injury, and depression	It indicates that Bryostatin-1 could be a promising contender for addressing neurological disorders.	Tian et al., 2023
Dioxinode-hydroeckol	*Ecklonia Cava*	Neuroprotective Anti-adipogenic effect Hepatotprotective	It is a potential inhibitor from the pool of screened compounds that could be efficacious in targeting multiple proteins associated with neurological disorders.	Ahmad et al., 2022; Alves et al., 2018; Kim and Kong, 2010
Benzoxepane derivatives	*Rhizophora annamaloyana* *Ulocladium botrytis*	Anti-inflammatory Anti-ischemic stroke	Through its inhibition of PKM2-mediated glycolysis and suppression of NLRP3 activation, this compound highlights PKM2 as a fresh target in addressing neuroinflammation and associated brain conditions. Notably, this particular compound exhibits a more favorable safety profile in comparison to shikonin, a known PKM2 inhibitor, positioning it as a lead compound for targeting PKM2 in the treatment of diseases linked to inflammation.	Gao et al., 2020
Dehydrosinulariolide	Sea cucumber	Anti-Parkinson's disease	It alleviates Parkinson's disease by inhibiting α-synuclein aggregation.	Diao et al., 2023
Inosine	Marine Sponges	Anti-oxidant	By prolonged usage, it elevates uric acid levels in both serum and cerebrospinal fluid, effectively restraining oxidative stress.	
Astaxanthin	*Haematococcus pluvialis*, *Chlorella zofingiensis*, *Chlorococcum*, and *Phaffia rhodozyma*	Anti-inflammatory	Suppressing the activation of microglia and the secretion of pro-inflammatory cytokines within the brain	Ambati et al., 2014; Diao et al., 2023
Pramipexole	Marine yeast	Anti-Parkinson's disease	Enhancing mood-related symptoms resulting from disrupted dopamine function in individuals with Parkinson's disease	Diao et al., 2023
Xyloketal B	*Xylaria* species	Anti-inflammatory Anti-apoptosis Stroke	It was proposed as a potential therapeutic approach for ischemic stroke by mitigating blood-brain barrier disruption, addressing mitochondrial dysfunction induced by excessive reactive oxygen species, and leveraging its anti-inflammatory and anti-apoptotic properties.	Diao et al., 2023; Gong et al., 2018

Fucoidan	*Ecklonia cava, Cladosiphon okamuranus, Ascophyllum nodosum, Saccharina longicruris, Undaria pinnatifida, Sargassum polycystum, Saccharina latissima, Fucus vesiculosus, Laminaria japonica, and Fucus serratus*	Anti-inflammatory Neuroprotective Anti-oxidant Anti-tumor Anti-coagulant Anti-thrombatic	Therapeutically, fucoidan may be useful for intervening in brain damage and neurodegenerative illnesses because of its potential to slow down the neurodegenerative processes and show protective benefits against brain injury.	Anisha et al., 2022; Wang et al., 2022b; Wang et al., 2021
Kahalalide F	Molluscs	Anti-cancer Anti-leishmanial Neuroprotective	kahalalide F has shown potential in the treatment of brain tumors and may have applications in addressing brain-related disorders.	Cruz et al., 2009; Wyer et al., 2022
Aplidin or Plitidepsin	sea squirt	Neuroprotective anti-inflammatory Anti-viral Anti-malarial Anti-oxidant	Aplidin reduces the vitality of osteoblasts and osteoclasts and prevents the differentiation and function of MM cells. As a result of inhibiting many proliferative genes, aplidin slows the growth of MM cells.	Delgado-Calle et al., 2019; Negi et al., 2017; Şimşek-Yavuz and Komsuoğlu Çelikyurt, 2021
Chondroitin Sulfate	*Salmo salar* *Raja hyperborean* *Galeus melastomus*	Neuroprotective anti-inflammatory	Potential to promote nerve growth and repair in neurological injuries	Abdallah et al., 2020; Egea et al., 2010; Miyata and Kitagawa, 2016
Halichondrin B	*Halichondria okadai*	Anti-cancer Neuroprotective	Its microtubule-stabilizing properties may have implications in neurological disorders as well.	Ortega and Cortés, 2012; Ruiz-Torres et al., 2017
Conotoxins	cone snails	Neuroprotective Cardioprotective Analgesic	Pharmaceutical techniques for researching pain signaling that inhibit several nervous system pathways and show promise as novel analgesics.	Di Cesare Mannelli et al., 2014; Oliveira et al., 2018; Twede et al., 2009

icariin involves interference with virus replication and release. This suggests that the unique structure deserves further investigation for potential applications (Xiong et al., 2015). Icariin exhibits various positive effects in the treatment of Alzheimer's disease. By combining pharmacological and molecular biological research, Icariin has the potential to be a promising candidate for accelerating the progress of traditional Chinese medicine in the clinical management of Alzheimer's disease (Zheng et al., 2023). Icariin has the ability to control the expression of miR-144-3p and ATP1B2, while also promoting the phosphorylation of PI3K, Akt, and mTOR (Pan et al., 2022). In conjunction with high-dose methylprednisolone, Icariin demonstrates synergistic effects in alleviating experimental autoimmune encephalomyelitis. This is achieved by modulating hypothalamic-pituitary-adrenal function and promoting anti-inflammatory and anti-apoptotic effects (Wei et al., 2016).

Salvianolic acid obtained from Salvia miltiorrhiza has been studied for its neuroprotective and anti-ischemic properties and may be used in medical applications. Yimin has examining how food influences the pharmacokinetics of Salvianolic Acid A in healthy subjects, with the compound currently undergoing Phase I clinical trials (Yimin, 2019). Salvianolic acid B demonstrates effective reversal of liver fibrosis in chronic hepatitis B. Compared to IFN-gamma, Salvianolic acid B exhibits superior results in reducing serum hyaluronic acid content, decreasing four serum fibrotic markers, and reducing ultrasound imaging scores. Salvianolic acid B is particularly suitable for anti-fibrotic treatment in cases of chronic hepatitis B with mild liver injury. Importantly, Salvianolic acid B shows no apparent side effects (Liu et al., 2002). Additionally, Salvianolic acid B intralesional injections improved mouth opening and burning sensations in these oral submucous fibrosis patients (Jiang et al., 2013). Salvianolic acid B exhibits neuroprotective effects against cerebral injury which was induced by ischemia or reperfusion (I/R) and holds promise as a valuable candidate for further advancement in clinical therapy development (Fan et al., 2018). Salvianolic acid B has the capability to stimulate autophagy and facilitate the elimination of NLRP3, leading to neuroprotective and anti-depressant effects (Jiang et al., 2017). It additionally mitigates neurological apoptosis in ischemic stroke by enhancing Stanniocalcin 1 (Bi et al., 2022). The dose-dependent administration of Salvianolic acid B significantly inhibited the mRNA and protein overexpression of pro-inflammatory mediators, including ICAM-1, IL-1β, IL-6, IL-8, and MCP-1, in the penumbra cortex induced by ischemia/reperfusion (Xu et al., 2017). Table 3 and Table 4 enumerate the neuro-pharmacological effects of additional natural compounds sourced from plant and microorganism origins.

Compounds from Cannabis sativa, especially phytocannabinoids, are reported to have potential neuroprotective effects. Cannabidiol (CBD) is a well-known cannabinoid that has been studied for its medicinal properties. Administration of oral medicinal cannabinoids may alleviate symptom burden in the palliative care of advanced cancer such as glioblastoma multiforme (Doherty and de Paula, 2021, Good et al., 2019). CBD's can be utilized as a therapeutic potential in addressing neurological conditions such as Alzheimer's disease, Parkinson's disease, and epilepsy (Tambe et al., 2023). Cannabidiol demonstrated a notable decrease in seizures associated with tuberous sclerosis complex when compared to a placebo. The safety profile of the 25 mg/kg/day dosage was superior to that of the 50 mg/kg/day dosage (Thiele et al., 2021). Both transdermal cannabidiol doses (195 mg and 390 mg) were well tolerated and deemed safe in drug-resistant epilepsy adults. No significant difference in effectiveness was observed between cannabidiol and the placebo during the double-blind treatment phase. The open-label extension confirmed the enduring safety, tolerability, and acceptance of transdermal cannabidiol delivery (O'Brien et al., 2022). Clinical reports suggest that cannabidiol may have the ability to reduce stress

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Table 3: Herbal compounds and their neuroprotective activities

Compound	Herb	Activity	Findings	Reference
Ellagitannins	*Punica granatum*	Neuroprotection	Ellagitannis, particularly found in pomegranates, plays a significant role in enhancing human brain health.	García-Villalba et al., 2023
Phytocannabinoids	*Cannabis sativa*	Alzheimer's disease	The elements present in Cannabis sativa, notably phytocannabinoids, terpenes, and specific flavonoids, are documented to exhibit potential neuroprotective effects. Various cannabinoids have been identified for their anti-oxidant properties and anti-aggregatory actions against the toxic hallmark protein associated with Alzheimer's disease.	Laws and Smid, 2022
Terpenoids Flavanoids	*Lindera glauca Blume*	Alzheimer's, Anti-fungal, Anti-tumor, Pain reliever, anti-oxidant	*L. glauca* induces neuroprotection by activating CREB, improving behavioral abnormalities induced by Aβ1-42. Additionally, it inhibits degenerative changes associated with both Aβ and tau.	Kim and Cho, 2021
Resveratrol	Grapes, berries, peanuts, red wine, veratrum*, Polygonum cuspidatum*	Neuroprotection	Resveratrol is noted for its ability to mitigate cadmium toxicity, a primary contributor to neurodegenerative disorders, thereby offering neuroprotection.	Liu et al., 2022
Sesquiterpenoid-enriched extract	*Inula britannica*	Anti-oxidant, Anti-neuroinflammatory, and microglial polarization capabilities	Various forms of sesquiterpenoids have been identified to play a crucial role in providing neuroprotection.	Tang et al., 2021
Ginsenoside	*Caenorhabditis elegans*	Alzheimer's, Neuroprotection	Decreasing the accumulation of tau aggregates and averting tau proteotoxicity.	Zhang et al., 2022
Triterpene	*Centella asiatica*	Enhancement of neurogenesis and neuroprotection	*Centella asiatica* exhibits a neurogenesis-promoting effect. Furthermore, it safeguards brain cells from oxidative stress-induced damage by regulating proteins associated with the cell cycle and apoptosis. Consequently, *Centella asiatica* leaf extracts have the potential to boost neurogenesis, neuroregeneration, and neuroprotection, particularly in the context of neurodegenerative disorders.	Kim et al., 2015b
Lycibarbarines	*Lycium barbarum*	Neuroprotection	The neuroprotective effect of the alkaline-rich fraction of *Lycium barbarum* is achieved through the inhibition of pro-apoptotic signaling pathways.	Ho et al., 2007

Astragaloside IV	*Astragalus membranaceus*	Neuroprotection, brain ischemia	Astragaloside shields against neuronal apoptosis and parthanatos, diminishes reactive oxygen species production, and impedes calcium flow. It also fosters M2 polarization of microglia/macrophages. Astragaloside treatment correlates with reduced infarct volume and neurological deficits. Furthermore, it safeguards cerebral-cortical neurons exposed to oxygen glucose deprivation by regulating the PKA or CREB signaling pathway and preserving mitochondrial function.	Zhu et al., 2022
Baicalin	*Scutellaria baicalensis*	Neuroprotective, Anti-oxidant, Anti-apoptotic, anti-inflammatory	Baicalin enhances mitochondrial membrane potential, promotes mitophagy, and markedly decreases infarct volume and neurological deficits by suppressing reactive oxygen species production.	Li et al., 2017
Harmine and Harmaline	*Banisteriopsis caapi*	Anti-oxidant, Management of Parkinson's disease and other neurodegenerative diseases	Harmine and harmaline function as potent inhibitors of Monoamine Oxidase (MAO)-A and -B enzymes, contributing to the release of dopamine. *Banisteriopsis caapi* exhibits moderate inhibitory activity against MAO-B and possesses anti-oxidant properties, primarily attributed to the proanthocyanidins (−)-epicatechin and (−)-procyanidin. These compounds serve to protect neuronal cells from oxidative free radical damage.	Krishnapriya et al., 2022
Polysaccharides	*Lycium barbarum*	Anti-oxidants, Anti-aging and neuroprotection	The polysaccharides found in *Lycium barbarum* are pivotal in conferring anti-aging properties and exerting neuroprotective effects. *Lycium barbarum* promotes neurogenesis and additionally influences the enhancement of learning and memory.	Chang and So, 2008
Curcumin	*Curcuma longa*	Alzheimer's disease, Neurogenesis and Anti-inflammatory	Curcumin has the capability to reduce the deposition of beta-amyloid plaques, which serves as a crucial factor in Alzheimer's disease.	Begum et al., 2008
Fruit mycelium	*Hericium erinaceus*	Anti-dementia, Alzheimer's	*Hericium erinaceus* reduces the cerebral burden of Aβ plaques, contributing to the management of Alzheimer's disease.	Tsai-Teng et al., 2016
Icariin	*Epimedium brevicornu Maxim*	Neuroprotective, Anti-apoptotic, Cerebral ischemia, Anti-inflammatory	Icariin inhibits the IRE1α-XBP1 signaling pathway, protecting neurons from apoptosis induced by endoplasmic reticulum stress following OGD/R injury.	Dai et al., 2021
Catalpol	*Rehmannia glutinosa*	Anti-cardiovascular, cerebrovascular diseases, anti-	Catalpol promotes angiogenesis and protects the vascular structure. It has demonstrated the ability to enhance	Dong et al., 2016

		diabetics, anti-ischemic and immune enhancement	stroke-induced STAT3 activation and cerebral blood flow. Additionally, Catalpol aids in the restoration of STAT3 activity by re-establishing STAT3 binding to VEGF. Furthermore, Catalpol treatment has been observed to increase the expression of p-S6 and GAP-43, contributing to its neurorestorative effects through pro-axonal regeneration.	
Salvianolic acid	*Salvia miltiorrhiza*	Neuroprotective, anti-ischemic	Salvianolic acid participates in the augmentation of Akt phosphorylation and activation of the Akt pathway. This contributes to the prevention of brain damage and reduces the risk of cerebrovascular diseases.	Zhuang et al., 2012
Carnosol	*Rosmarinus officinalis*	Anti-oxidant and anti-inflammatory effects	Carnosol exerts a neuroprotective effect by inhibiting cell death in dopamine neuron cells and elevating tyrosine hydroxylase expression. This is accomplished through the Raf-MEK-ERK1/2 pathway, which pertains to the Raf-mitogen-activated protein kinase (MEK)-extracellular signal-regulated kinase (ERK)1/2 signaling pathway. Potent antioxidants such as carnosol may have potential utility in alleviating Parkinson's disease symptoms and enhancing the function of the dopamine system.	Faridzadeh et al., 2022
Bacosides	*Bacopa monnieri*	Anti-oxidants, suppression of neuronal oxidative stress, Alzheimer's, Parkinson's, Ischemic stroke, epilepsy, Schizophrenia, Huntington's disease and Memory booster	Bacosides facilitate the elimination of free radicals, prevent lipid peroxidation, and stimulate anti-oxidant enzymes, collectively contributing to a decreased state of oxidative stress. This enhancement is reflected in increased caspase-3 and tyrosine hydroxylase activity, as well as elevated expression of neurogenic genes in the substantia nigra of the brain.	Shalini et al., 2021
Berberine	*Berberis sibirica*	Neuroprotective	Berberine exhibits neuroprotective properties, promoting the augmentation of nerve fibers and parvalbumin-immunoreactive neurons in the CA1–CA3 regions of the hippocampus. Additionally, it has the potential to modulate the effects of Ca^{2+} in neurons.	Angeloni and Vauzour, 2023
Quercetin	*Allium cepa, Malus pumila, Vitis vinifera*	Anti-oxidant, Anti-Alzheimer's and Neuroprotective	Quercetin plays a crucial role in mitigating oxidative stress. Its anti-Alzheimer's disease properties encompass the inhibition of tau phosphorylation and Aβ aggregation. Additionally, it elevates acetylcholine levels by impeding the hydrolysis of acetylcholine by the AChE enzyme.	Khan et al., 2019

Catechin	*Camellia sinensis*	Anti-inflammatory, Anti-cancer, Anti-diabetic and neuroprotective	Catechins play a pivotal role in diminishing the accumulation of fibrous materials and alleviating oxidative stress.	Pervin et al., 2018
Astaxanthin (Marine)	*Haematococcus pluvialis*	Alzheimer's disease, Reduction in aging of skin	The aging process gradually diminishes the body's antioxidant defense system. Astaxanthin exhibits anti-aging properties by preserving the effectiveness of anti-oxidant enzymes. Additionally, it aids in preventing the formation of amyloid plaques, thereby enhancing neuroprotection.	Balendra and Singh, 2021
Lycopene	*Solanum lycopersicum, Carica papaya, Citrullus lanatus*	Anti-oxidant, Anti-Inflammatory, Anti-proliferative, Treatment of Alzheimer's, Parkinson's, Huntington's diseases	Lycopene's neuroprotective effects have been shown to involve mechanisms such as the restoration of mitochondrial function, suppression of oxidative stress and neuro-inflammation, and inhibition of neuronal apoptosis. Furthermore, lycopene's neuroprotective impact might also be attributed to other mechanisms, including the inhibition of c-Jun N-terminal kinase (JNK) signaling and the restoration of intracellular Ca^{2+} homeostasis.	Chen et al., 2019
Cerebrosides and ceramides	*Holothuroidea*	Neuroprotection, treats memory loss	It functions to prevent brain atrophy and memory loss, reducing the accumulation of plaques and oxidative stress.	Che et al., 2017
Gallic acid	*Juglans regia*	Neuroprotection, Anti-oxidant, Anti-diabetic	Gallic acid plays a crucial role in alleviating motor dysfunctions and inhibiting plaque formation.	Hosseini Adarmanabadi et al., 2023
Stigmasterol	*Arachis hypogaea, Helianthus annuus*	Treat memory impairment, Alzheimer's disease	Stigmasterol aids in addressing Alzheimer's disease symptoms by mitigating memory impairment, tau phosphorylation, and plaque formation.	Park et al., 2012
Withanone	*Withania somnifera*	Anti-Alzheimer's	Ashwagandha serves as a potential antagonist for the NMDA receptor. The primary mechanism underlying its neuroprotective effects is its anti-oxidant activity. By elevating glutathione levels, an endogenous component of the anti-oxidant defense system, ashwagandha also modulates non-enzymatic anti-oxidant levels. Glutathione acts as a substrate to regulate enzymes and reacts with oxygen free radicals and organic peroxides.	Zahiruddin et al., 2020
α-Spinasterol	*Spinacia oleracea*	Anti-diabetic, anti-inflammatory, anti-tumor, neuroprotection	α-Spinasterol exhibits various pharmacological activities, contributing to memory enhancement and serving as a neuroprotective agent by mitigating oxidative stress.	Majeed et al., 2022

Rutin	*Abelmoschus esculentus*	Anti-inflammatory, protection of myocardial ischemia, neuro-protective	The Abelmoschus esculentus extract was found to enhance learning abilities, displaying anti-oxidant properties that contribute to its neuroprotective effects. Additionally, it exhibited antagonistic activity against NMDA receptors.	Tongjaroenbuangam et al., 2011

Table 4: Neuroactive Compounds from Microbial Sources

Microorganism	Source	Compound	Activity	Findings	Reference
Cyanobacteria	Blue-green algae	Spirulina plantensis	Anti-oxidant, anti-Parkinson's, anti-Alzheimer's	The polysaccharide derived from Spirulina platensis demonstrates protective effects against MPTP-induced dopaminergic neuron loss in C57BL/6J mice. Its neuroprotective impact is likely attributed to its anti-oxidative properties. Spirulina-derived polysaccharide, abbreviated as SPI, partially reverses reductions in immunoreactivity and mRNA expressions of tyrosine hydroxylase and dopamine transporter in the substantia nigra. Moreover, it mitigates the decrease in dopamine levels and the increase in dopamine metabolism rate, along with alleviating behavioral and neurochemical alterations in hemiparkinsonian rats. These findings highlight Spirulina's neuroprotective potential and warrant further translational studies, suggesting its potential as an alternative treatment for Parkinson's disease.	Bermejo-Bescós et al., 2008; Lima et al., 2017; Zhang et al., 2015
Aspergillus alliaceus	Fungal metabolite	Devazepide/ Asperlicin	Neuropathic pain, Cholecystokinin antagonist	The potent and specific interaction of asperlicin with cholecystokinin receptors was shown using *in vitro* biochemical assays. The discovery of the panicogenic effect of CCK-4 in man raised the hypothesis of the involvement of CCK2 receptors in the pathogenesis of panic disorders, consequently CCK2 antagonists were considered potential anxiolytic agents. In fact, most of the potent CCK2 antagonists have shown anxiolytic-like effects in diverse animal models, without the side effects of the classic benzodiazepine anxiolytics, such as sedation, development of tolerance, and withdrawal anxiogenesis after termination of the treatment. However, these anxiolytic effects have not been confirmed in clinical trials neither in patients with generalized anxiety and panic disorders neither against CCK-4-induced panic symptoms in healthy volunteers.	Goetz et al., 1985; Herranz, 2003

CEP-1347 (KT-8138) staurosporine	semi-synthetic derivative of K-252a	Nocardiopsis	Parkinson's disease	A potent inhibitor of members of the mixed lineage kinase (MLK), which have a key role in the activation of c-Jun N-terminal kinase (JNK), involved into govern neuronal dysfunction and subsequent death. It didn't show immediate impact on Parkinson's symptoms or levodopa's pharmacokinetics, making it ideal for extensive, prolonged studies to assess its potential in altering the progression of PD.	Falsig et al., 2004; Murata, 2008; Parkinson Study Group, 2004
Trichoderma polysporum	Aerobic fungi	Cyclosporine A	Stroke, trauma, neurodegeneration, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis	Neuro-protective properties in stroke, trauma and neuro-degeneration reducing the neuron cell death by the inhibition of critical enzymes and free radicals, and protecting the mitochondria. Strong immunosuppression would present as a side-effect during CsA use as a neuroprotectant. The results of this study will help to discriminate between the CsA immunosuppressive effect and the neuroprotective effect at the molecular level and may lead to the development of new conceptual and pharmacological tools.	Kalantari-Dehaghi et al., 2013; Kawakami et al., 2011; Zhang et al., 2019
***Penicillium* sp.**	marine fungus	Epolactaene	Neuritogenic properties	It displayed neuritogenic properties by arresting the cell cycle at the G_0/G_1 phase and inducing the outgrowth of neurites in human neuroblastoma SH-SY5Y cells.	Kakeya et al., 1995

and anxiety (Spinella et al., 2021). The safety and potential therapeutic use of hemp-derived cannabidiol is thus beneficial for alleviating pain associated with arthritis (Verrico et al., 2020). The phytocannabinoid CBD exhibits anti-seizure and neuroprotective properties. Similar to endocannabinoids, CBD can modulate various aspects of neuronal function, including excitability, pain, inflammation, feeding regulation, learning and memory, and emotion regulation. Recent research indicates that CBD reduces inflammation, safeguards against neuronal loss, normalizes neurogenesis, and is an anti-oxidant. Cannabinoids exert diverse pharmacological effects through the activation of CB1 and CB2 receptors. While the psychoactive effects of THC are attributed to the activation of CB1, the mechanisms underlying the neuroprotective effects of CBD are still under investigation (Reddy, 2023). CBD has been identified as generally safe and efficacious for treating seizures that resist conventional therapies in children experiencing severe early-onset epilepsy (Golub and Reddy, 2021). CBD demonstrates anti-neuroinflammatory activity by suppressing NADPH oxidase-mediated reactive oxygen species, as well as downregulating the TLR4-NFκB and IFN-β-JAK-STAT pathways (Yousaf et al., 2022). The findings from scientific studies conducted thus far on the clinical application of CBD could offer hope for patients who do not respond to conventional anti-epileptic medications (Silvestro et al., 2019). To ascertain the effectiveness of CBD as a neuroprotective agent, extensive and well-designed randomized clinical trials will be required to obtain conclusive results regarding its potential as a therapeutic approach for diseases like Parkinson's and Alzheimer's (Viana et al., 2022).

Resveratrol, present in grapes, berries, peanuts, red wine, and *Polygonum cuspidatum*, has garnered attention in medical research due to its studied neuroprotective effects. It is also considered promising in the treatment of colorectal cancer (CRC) by influencing crucial molecules and signaling pathways associated with cancer, including SIRT1, P53, P21, ROS, COX-2, AMPK, BMP7, Wnt, caspases, NO, NF-κB, TNFs, EMT, and the pentose phosphate pathway (Vernousfaderani et al., 2021). Human clinical trials exhibit significant variations in the administered doses of resveratrol and the duration of treatment. In general, the notable impacts of resveratrol include a decrease in body weight among obese individuals and a partial decline in systolic blood pressure, fasting blood glucose, and HbA1c levels in some clinical trials involving patients with diabetes mellitus (Breuss et al., 2019). The trajectory suggests that we are entering an era where approaches to treatments and strategies, especially nutritional interventions like resveratrol supplementation, aimed at addressing obesity and metabolic syndrome, will require a personalized approach tailored to each individual to maximize effectiveness (Chaplin et al., 2018). Using nano-formulations of resveratrol might be the preferable strategy, considering their potential ability to target specific sites and minimize toxicity. It appears prudent to initiate new trials involving resveratrol nano-formulations or to further develop and refine previously validated innovative formulations. Considering the existing gaps, a substantial amount of work still needs to be undertaken before resveratrol can be regarded as a viable therapeutic agent for cancer treatment (Ren et al., 2021). Resveratrol safeguards dopaminergic neurons from apoptosis, a hallmark of Parkinson's disease, by enhancing mitochondrial health through the upregulation of mitophagy and mitochondrial biogenesis (Kung et al., 2021). Resveratrol hinders the activation of NF-κB and NLRP3 inflammasomes while diminishing the production of inflammatory cytokines. Its impact on reducing reactive oxygen species and oxidative stress is likely mediated through Nrf2 and its downstream anti-oxidant genes. The neuroprotective effects of resveratrol are impeded by the AMPK inhibitor (Chiang et al., 2022).

Curcumin found in Curcuma longa has been extensively studied for its anti-inflammatory and neuroprotective properties. It is used in various medical applications (Zia et

al., 2021). Extensive research has been conducted on the neuroprotective effects of curcumin, with clinical trials aimed at substantiating these claims. However, the trials revealed that despite being a well-tolerated natural compound, curcumin did not demonstrate efficacy in improving the quality of life or clinical symptoms for patients with Parkinson's disease (Ghodsi et al., 2022). Curcumin, a naturally occurring polyphenolic phytochemical renowned for its potent anti-inflammatory and anti-oxidant characteristics, in conjunction with IFN β-1a treatment, may boost the efficacy of IFN β-1a in managing radiological signs of inflammation in multiple sclerosis. However, despite a notable dropout rate, curcumin does not seem to provide neuroprotective effects, as indicated by clinical and MRI parameters (Petracca et al., 2021). The nano-curcumin and coenzyme Q10 may collaborate to exert neuroprotective effects by modulating inflammation and oxidative stress. This suggests a potential synergistic impact of nano-curcumin and Co-Q10 on the clinical features of migraines (Parohan et al., 2021). The examination of curcumin's efficacy as a supplementary agent alongside standard anti-psychotic medications in individuals with chronic schizophrenia uncovered that incorporating curcumin as an add-on to anti-psychotics for addressing negative symptoms could present a novel and safe therapeutic avenue in schizophrenia management. Nonetheless, it is crucial for these findings to be validated through additional studies (Miodownik et al., 2019). Studies on both human subjects and experimental models of migraine have highlighted the involvement of COX-2/iNOS in the neuroinflammatory pathogenesis of migraines. Omega-3 fatty acids and curcumin, an active polyphenol found in turmeric, exhibit anti-inflammatory and neuroprotective effects by suppressing the expression of iNOS and COX-2 genes and their serum levels. These results suggest that a combination therapy involving ω-3 fatty acids and nano-curcumin holds promise as a novel and practical approach for preventing migraines (Abdolahi et al., 2019). Nano-curcumin and ω-3 fatty acids have shown neuroprotective effects through modulation of IL-6 gene expression and CRP levels and can be considered as a promising target in migraine prevention. Indications suggest that tumor necrosis factor (TNF)-α contributes to the neuroimmune pathogenesis of migraines (Abdolahi et al., 2017, 2018). The nano-curcumin appears to be a safe addition to treatment and may enhance the likelihood of survival in ALS patients, particularly those with pre-existing bulbar symptoms. However, to validate these observations, further studies with larger sample sizes and extended durations are essential (Ahmadi et al., 2018). Research on curcumin has been explored due to its robust neuroprotective properties in mitigating damage resulting from spinal cord injury. Although the mechanism by which it preserves the function of the blood-spinal cord barrier remains unclear, the observed enhancement in motor function post-spinal cord injury raises intriguing possibilities for its potential role in improving the integrity of the blood-spinal cord barrier (Mokhber et al., 2014). The research investigation of alterations in NF-κB DNA binding activity when subjected to TNF-α treatment both before and after intervention showed that the pre-intervention samples rose significantly in mean NF-κB DNA binding activity in response to TNF-α. Interestingly, there was an absence of NF-κB induction by TNF-α in the post-intervention samples. These results imply a potential protective function against human oxidative stress, achieved through administering a compound comprising four essential natural agents. Further exploration and research on this compound can potentially contribute to developing strategies aimed at shielding individuals from the adverse impacts of oxidative stress (Dominiak et al., 2010).

Quercetin, a flavonoid compound, is abundant in various plant-based foods, including fruits, vegetables, leaves, and grains. Dietary sources rich in quercetin encompass apples, onions, berries, citrus fruits, red grapes, cherries, broccoli, leafy greens, tea, and red wine. Moreover, quercetin can be

acquired through the use of dietary supplements (Anand David et al., 2016). The association between quercetin and cognitive performance in Alzheimer's disease thus exerts its potential as a key compound in clinical applications (Khan et al., 2019). Quercetin collaborates with agents to enhance therapeutic efficacy by modulating signal molecules and interrupting the cell cycle. Synergistic therapy allows for a reduction in agent doses, minimizing the risk of potential toxicity and side effects during treatment. While quercetin treatment may carry some possible side effects, it remains safe within anticipated usage conditions. Consequently, quercetin holds application value and promising potential as a clinical drug. Additionally, as the principal effective therapeutic component in traditional Chinese medicine, quercetin may be efficacious in treating and preventing (Zou et al., 2021). Quercetin provides effective protection against seizure induced neuron death both *in vitro* and *in vivo* studies. It also mitigates impairment in cognitive function through modulation of the Nrf2/SIRT1/GPX4/SLC7A11 pathway (Xie et al., 2022). Quercetin has demonstrated robust bioactivity in the fields of wound healing, neuroprotection, and anti-aging research (McKay et al., 2023). High doses or extended administration of quercetin-conjugated superparamagnetic iron oxide nanoparticles can enhance cognitive function and stimulate neurogenesis without inducing toxicity. This can be attributed to QC's ability to impede protein aggregation and counteract iron overload through activities such as iron chelation, regulation of iron homeostasis genes, radical scavenging, and mitigation of the Fenton/Haber-Weiss reaction (Bardestani et al., 2021). Quercetin regulates neurotransmitter levels, enhances the regeneration of hippocampal neurons, ameliorates hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and diminishes inflammatory states and oxidative stress (Chen et al., 2022).

HIGHLIGHTS

- ✓ Numerous natural compounds exhibit excellent tolerability and boast a favorable safety profile, making them appealing choices for the prolonged management of chronic neurological conditions.
- ✓ Natural compounds frequently serve as starting points for developing pharmaceutical drugs. Isolation and modification enhance efficacy, safety, and bioavailability.
- ✓ Marine-derived compounds show promise in addressing neurological disorders, including Alzheimer's, Parkinson's, stroke, and traumatic brain injury. Mechanisms often involve inhibiting protein aggregation, modulating oxidative stress, and regulating neuroinflammatory pathways.
- ✓ Bryostatin-1 showed promising results in preclinical studies for Alzheimer's, multiple sclerosis, fragile X syndrome, stroke, traumatic brain injury, and depression.
- ✓ Fucoidan exhibits therapeutic potentials including anti-inflammatory, neuroprotective, anti-oxidant, and anti-tumor effects.
- ✓ Icariin shows potential effective treatment for ankylosing spondylitis and exhibits anti-oxidant properties, providing hepatoprotection.
- ✓ Salvianolic acid B is effective in reversing liver fibrosis in chronic hepatitis B and exhibits neuroprotective effects against cerebral injury induced by ischemia or reperfusion.
- ✓ CBD considered safe and efficacious for treating seizures in severe early-onset epilepsy.
- ✓ Resveratrol inhibits NFκB and NLRP3 inflammasomes, reducing inflammatory cytokines and oxidative stress.
- ✓ Quercetin collaborates with other agents for enhanced therapeutic efficacy.
- ✓ Nano-curcumin and coenzyme Q10 collaboration shows potential neuroprotective effects.

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CHALLENGES AND LIMITATIONS

The use of natural compounds from plants and herbs introduces variability, leading to inconsistent treatment outcomes. Scientific evidence supporting their efficacy, compared to pharmaceutical drugs, is often limited, necessitating further research for validation in neurological conditions. Challenges include potential interactions with medications, difficulty determining dosages, and limited bioavailability. Natural compounds may induce side effects, have slower therapeutic onset, and face varying regulatory oversight, potentially resulting in subpar products. Costly and limited availability can hinder access for neurological patients, and adherence challenges arise from taste, odor, and dosing requirements. Patients' beliefs and ethical/environmental concerns also impact their effectiveness. As they are not suitable for all neurological conditions, natural products may be limited to certain condi-tions, while conventional drugs are often the primary treatment option.

FUTURE DIRECTIONS

Unearthing novel natural compounds holds the key to innovative therapies for neurological disorders. This involves investigating uncharted territories like unexplored plant species, marine life, and microorganisms for bioactive substances. Standardizing and ensuring the quality of these compounds are paramount, requiring stringent testing methodologies for uniformity. Understanding their mechanisms of action is crucial for comprehending their interactions with neurological pathways. To enhance efficacy, efforts focus on improving bioavailability through advanced delivery methods and dedicated clinical trials. Personalized medicine is explored, considering individual responses based on genetic factors. Investigating synergies with conventional pharmaceuticals and examining potential interactions are avenues for improved therapeutic outcomes. Long-term studies are vital for assessing prolonged safety, addressing concerns associated with extended use. Regulatory measures and standardized guidelines ensure quality and safety, promoting ethical sourcing and sustainability. Collaboration among researchers, pharmacologists, chemists, and clinicians accelerates the translation of findings into effective treatments. Public awareness and education play a crucial role in ensuring safe and informed adoption of natural compounds. Addressing issues related to intellectual property, safeguarding traditional knowledge, and ensuring equitable access are of significant importance. Exploring the preventive potential of natural compounds and utilizing digital health technologies for real-world effectiveness are promising avenues for future research in neurological disorders.

SUMMARY AND CONCLUSION

In conclusion, neurological disorders present a significant global health challenge, affecting millions of lives and posing complex medical, societal, and economic burdens. The prevalence of conditions such as Alzheimer's disease, Parkinson's disease, epilepsy, and migraines underscores the urgent need for innovative treatments. The impact of these disorders extends beyond physical and mental health, influencing the overall quality of life for individuals and their communities. The current landscape of neurological disorder treatments faces limitations, with many existing therapies focusing on symptom management rather than addressing underlying causes. Additionally, the aging global population contributes to the escalating prevalence of these disorders, emphasizing the necessity for novel interventions. Natural compounds, derived from diverse sources such as plants, marine, microorganisms, and animal, emerge as promising candidates for revolutionizing neurological disorder drug discovery. The multifaceted properties of natural compounds, including neuroprotection, anti-inflammation, and anti-oxidant effects, offer a holistic approach to address the complex nature of neurological disorders. Exploring the potential of marine-derived compounds, herbal compounds, and other natural sources unveils a rich diversity of bioactive substances

with neuroprotective effects. These compounds hold promise for conditions like Alzheimer's, Parkinson's, stroke, and traumatic brain injury, offering novel avenues for therapeutic development. The molecular pathways through which natural compounds operate in neurological disorders, influencing inflammation, oxidative stress, neurotransmission, and gene expression, provide a comprehensive understanding of their mechanisms of action. These compounds exhibit potential in modulating various aspects of neurological health and function. While embracing natural compounds as potential treatments, it is crucial to recognize the challenges and limitations associated with their use. Standardization, evidence-based support, and addressing issues of quality control are essential for their integration into mainstream medical practice. Moreover, considerations such as potential interactions, dosage determination, and adherence must be carefully navigated. Looking ahead, future directions in natural compound research for neurological disorders involve ongoing exploration of uncharted compounds, enhancing quality control measures, understanding mechanisms of action, and conducting well-structured clinical trials. Embracing personalized medicine, investigating combinatory approaches, and ensuring ethical sourcing practices are pivotal for advancing the field. In this dynamic landscape, collaboration among researchers, pharmacologists, clinicians, and traditional medicine practitioners is essential for translating research findings into effective treatments. Public awareness and education play a crucial role in fostering safe and informed utilization of natural compounds.

Credit author statement

RR, RFB, AS, PL: Writing - original draft, writing - review and editing. CV, BP, PP: Conceptualization, data curation, formal analysis, writing - review and editing. All the authors critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript for publication.

Conflict of interest

The authors declare that they have no conflict of interest.

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