REVIEW ARTICLE

Impact of Phytochemicals on Managing Chronic Brain Disorders: Exploring Therapeutic Potential

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Abstract

Numerous neuropsychiatric such as anxiety and depression as well as neurodegenerative conditions such as dementia and Alzheimer's disease (AD) are primarily emerging in contemporary times as a result of stressful lifestyles. Presently approved pharmacological interventions for the majority of chronic brain disorders appear to address symptoms only, lacking significant disease-modifying effects. The use of synthetic drugs in the treatment is also associated with serious and life-threatening side effects. At present, there has been a notable surge in research investigating phytochemicals as substitutes for primary conventional antipsychotic and memory-enhancing medications. Phytochemicals sourced from herbal plants take part in a crucial role in conserving the chemical equilibrium of the brain further they are effective in protecting from neurodegeneration, preventing the progress of neurological disorders as well as improving the condition of depression and anxiety. In this study, we mainly focus on highlighting the therapeutic potential of phytochemicals in neuroprotection, dementia, AD, and depression. In addition, an attempt to list out the phytochemicals used in the management of chronic brain disorders has been made.

Key words: Alzheimer, dementia, depression, phytochemicals, phytocompounds neuroprotection

INTRODUCTION

The human brain is often characterized as the most intricate component of the body, comprising neurons and neuroglia. Neurons are tasked with transmitting and getting nerve impulses or signals. Microglia as well as astrocytes become vital for promising the effective operation of neurons, swiftly stepping toward assist after neurons encounter injury/stress. As protectors of neuron well-being, any malfunction in the functioning of microglia or astrocytes could result in significant repercussions for brain functionality. When neurons experience acute injury, they produce signals that communicate their status to the neuroglia. Depending on the extent of damage to neurons, the neuroglia work in two ways first supports the indignant neurons in their regeneration process and second, eradicates them if the neurons are deemed non-viable.[1,2]

Neurodegeneration is a phenomenon present in both neuropathological disorders and the aging of the brain. It is recognized that brain disorders such as cerebrovascular and neurodegenerative diseases are a primary cause of mortality globally. Inflammation and oxidative stress play roles in the natural aging process as well as in acute and chronic age-related brain conditions. Phytochemicals are naturally occurring active compounds found in medicinal plants, edible fruits, as well as vegetables. As compared to vitamins and minerals, they are not necessary for maintaining cell function. However, they are crucial for safeguarding neural cells against inflammation and oxidative stress linked to neurological disorders such as Alzheimer's disease (AD), anxiety, depression, and neuroprotection.[2-4]

Consumer consciousness regarding healthy living, aiming for maximum health and a longer lifespan, has shifted focus

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primarily to nutrition that provides health benefits beyond basic sustenance. Indeed, diets rich in bioactive compounds, consumed in appropriate quantities, are essential for sustaining good health, highlighting the critical importance of a well-balanced diet. Herbal medicine, also known as botanical medicine, involves utilizing plants for medicinal purposes. The historical practice of herbal medicine in treating and preventing various illnesses predates modern conventional medicine. Herbal products play a vital role in traditional medicine, with numerous plants and plant-derived items having been employed since ancient eras. Various traditional medical systems such as Ayurveda, Unani, as well as Chinese, further, Korean and Kampo utilize herbal remedies that have been employed globally for centuries if not millennia. Herbal products offer unparalleled advantages, including extensive clinical usage and a distinctive array of chemical compositions and biological properties. They have emerged as crucial resources for the development of novel lead compounds and frameworks, continuously contributing to addressing the pressing demand for effective medications. In addition, they are poised to assume a pivotal role in drug discovery efforts aimed at treating human ailments, particularly those of a critical nature. While plants are clearly valuable for providing food and shelter, their importance as a medicinal asset is frequently overlooked. Human civilization has depended on plants for sustenance, shelter, and medicinal needs for a comparable length of time.[4,5]

Phytochemicals encompass a wide range of compounds derived from plants, thought to play a substantial role in preventing numerous diseases often linked with diets abundant in fruits, vegetables, and plant-derived beverages such as tea and wine. These substances appear to operate individually as well as in conjunction with each other, potentially alongside vitamins and other nutrients, to hinder, disrupt, or reduce the advancement of diseases. Hence, it is essential to prioritize the intake of whole foods rather than depending solely on supplements.[4,6]

The phytochemicals found in medicinal plants as secondary metabolites have various therapeutic advantages as reported by many researchers. The presence of these phytochemicals in natural herbs possesses a wide variety of medicinal properties at cellular and molecular levels. These phytochemicals have proved beneficial in a wide array of disorders as well as in central nervous system (CNS) disorders and neuroprotection as shown in Figure 1. The present study aimed to provide the role of different phytochemicals in some CNS disorders and neuroprotection.[7,8]

Neuroprotection

The term "nootropic" originates from Greek and signifies influencing the mind. Medications designed to enhance neurofunction typically function by adjusting the equilibrium of specific brain chemicals known as neurotransmitters.

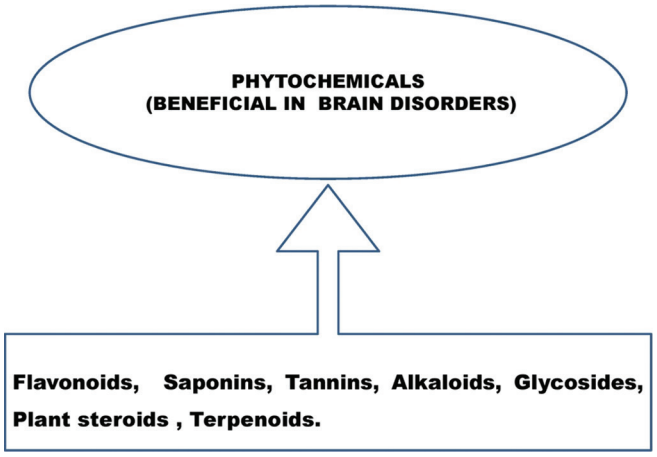

Figure 1: Phytochemicals advantageous in brain disorders[7,8]

Several medications are sourced from medicinal plants and have demonstrated memory-boosting effects due to their active phytochemical components. Reduced cholinergic activity in the brain is one proposed mechanism underlying dementia. In traditional medicinal practices, a plethora of plants have been utilized for addressing cognitive disorders, which encompass neurodegenerative ailments. Supporters of herbal medication argue that the ability of plants to heal come from the collective impact of its various components, as opposed to the isolated chemicals typically identified by pharmacologists in conventional medications. As a result, traditional medicines are thought to be effective with little to no negative side effects. More than 100 traditional medicines are currently employed in Asian countries for treating CNS disorders.[7,8]

The brain possesses significant oxidative capacity potential, yet it has a restricted capability to mitigate stress related to oxidation. Stress produced by oxidation reaction has been associated with processes that result in neuronal cell damage across a range of brain-related pathological conditions, such as neurodegenerative disorders. Although the brain makes up below 2% of the weight of the body, it consumes about 20% oxygen gained all the way during respiration. This high demand for oxygen renders the brain particularly vulnerable to oxidative harm. Phytopharmaceuticals are increasingly recognized for their therapeutic benefits, both within modern medical practices and traditional medicinal systems, highlighting their growing significance. New types of antioxidants could provide a reliable and secure method for enhancing the body's ability to combat free radicals. Cells in the CNS have the ability to counteract oxidative stress utilizing various limited resources such as vitamins, bioactive compounds, lipoic acid, oxidation-reduction enzymes, and redox-sensitive protein transcription factors. Nevertheless, nutritional antioxidants such as polyphenols, flavonoids, terpenoids, and fatty acids have the capability to trigger or adjust this defense mechanism. Abundant scientific and empirical evidence substantiates the utilization of antioxidants for managing neurodegenerative disorders. Antioxidants

derived from phytochemicals may play a neuroprotective role, inhibiting apoptosis, and promoting neuroregeneration. This is achieved by mitigating or reversing cellular damage and slowing the progression of neuronal cell loss.[8,9]

Numerous phytochemicals have demonstrated neuroprotective effects in animal as well as cell culture models. Research conducted on human populations through epidemiological studies, as well as experiments involving animal models for evaluation of neurodegenerative disorders, demonstrates that isolated phytochemicals found in edible fruits and vegetables are able to protect the neuronal network from diseases. Neuroprotective effects of different phytochemicals are linked to decreased levels of oxidative stress. Several key phytochemicals play a significant role in neuroprotection as shown in Figure 2.[10-12]

Anxiety

Anxiety serves as a vital adaptive mechanism crucial for an organism's survival. However, when anxiety becomes excessive, it can result in anxiety disorders, often co-occurring with other psychiatric conditions. The increasing prevalence of individuals experiencing anxiety disorders is a worrying trend, affecting approximately 25% of the population in developed nations with an estimated global total of more than 250 million affected individuals. The interplay among stress, susceptibility of genes, and adversity during childhood as well as distress contributes to neurobiological and neuropsychological dysfunctions. These dysfunctions are marked by changes in cognition, emotion, and behavior. Various anxiolytic medicines are used for anxiety disorders. While anxiolytic medications prove to be therapeutically beneficial, various adverse effects have been documented. These include memory impairment, insomnia, dependency, susceptibility to abuse, and sexual dysfunction.[12,13]

On the contrary, recent studies have noted both the efficacy of herbal treatments for anxiety and their increasing acceptance among patients. Researchers propose that herbal products offer more advantages than disadvantages when used short term by individuals with anxiety.[14,15] Numerous studies indicate that certain plant-based foods and herbs possess pharmacological properties that can effectively regulate anxiety. Over 40% of individuals with anxiety seek complementary and alternative therapies, with herbal medicines being the preferred option due to their purported ability to deliver more favorable outcomes with lower toxicity. Phytochemicals derived from diverse plants exhibit a range of theoretical biological activities on the CNS, potentially yielding anxiolytic effects. Bioactive phytochemicals typically operate through the neurotransmission systems within the brain. Some of the examples of anxiolytic phytochemicals are given in Figure 3.[15-17]

Dementia

Dementia refers to a decline in cognitive abilities across various domains to a degree that significantly impacts one's social as well as occupational performance. Dementia is an irreversible condition typically associated with aging, characterized by a gradual decline in cognitive function that impairs an individual's capacity to carry out daily tasks.[18] Even though significant advancements have been achieved in understanding dementia over the past few decades, the exact underlying mechanisms causing the condition remain inadequately comprehended. Dementia impacts more than 55 million individuals globally, and its occurrence is anticipated to rise substantially in the coming decades due to the aging population. Dementia stems from various illnesses and traumas impacting the brain.[19,20] AD stands as the prevalent type of dementia, potentially accounting for more than 60% of occurrences. At present, dementia ranks as the 7th primary cause of death and represents a significant source of disability and reliance among elderly populations worldwide. The primary pathological features of AD, such as senile plaques, emerge from the buildup of amyloid beta (Aβ) protein outside cells as well as neurofibrillary tangles form due to accelerated phosphorylation and aggregation of Tau protein.[19] The accumulation of Aβ initiates a series of processes, such as oxidative stress and inflammation. Moreover, microglia, triggered by Aβ, discharges various substances such as pro-inflammatory cytokines highly

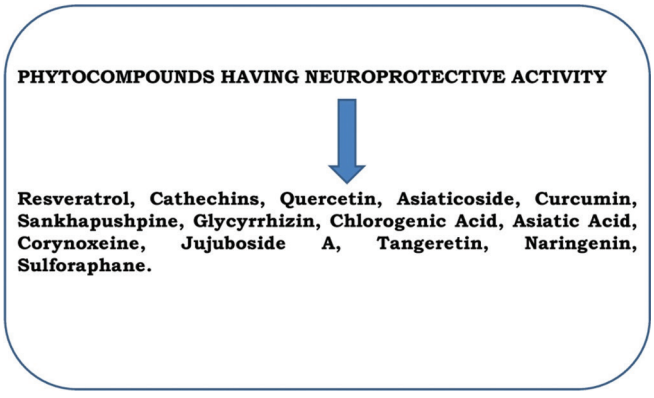

Figure 2: Phytocompounds having neuroprotective activity[9,10,12]

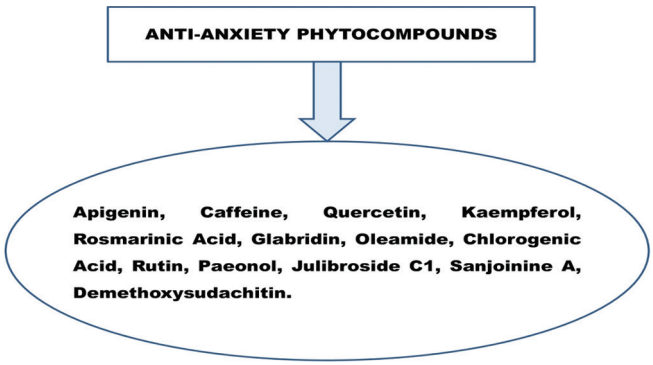

Figure 3: Phytocompounds having anti-anxiety effect[14,15]

reactive oxygen species and nitrogen species, inducing dysfunction of mitochondrial. This dysfunction results in the release of glutamate and subsequent excite-toxic neuronal demise.[20,21] The National Institute of Health categorizes numerous variations of dementia as given below in Table 1.

At present, synthetic medications on the market provide effectiveness for only 1–4 years in cases of mild-to-moderate AD. Synthetic medication displays numerous adverse side effects. Scientific research on the effectiveness of phytochemicals in preventing and treating AD has been steadily growing. This research indicates that they are both safe and economically efficient. Oxidative stress has been established as one of the confirmed factors contributing to AD. Yet, plants contain antioxidants that can alleviate the impact of AD. It is recommended to incorporate fruits, vegetables, grains, and nuts into your diet regularly to support general well-being, encourage healthy aging, and lower the likelihood of age-related conditions like AD.[22,23]

Phytochemicals have been widely used as treatments for various medical conditions, and consuming a balanced diet abundant in phytochemicals can lower the likelihood of developing AD.[22] Research conducted in laboratory settings and living organisms have demonstrated that phytochemicals hold promise for the treatment of AD, leading to some of them progressing into clinical trial phases.[23] Research suggests that phytochemicals have the potential to enhance the activity of the α-secretase enzyme, further they decrease the formation of the protein β-amyloid, diminish hyperphosphorylation of tau as well as boost antioxidant enzymes, and augment learning and memory. Phytochemicals have the potential to treat AD through multifaceted mechanisms.[24,25] The beneficial phytochemicals are shown in Figure 4.

DEPRESSION

Depression is a condition marked by profound feelings of sadness and a reduction in mental functions, often accompanied by disturbances in physical functions, with anxiety symptoms frequently co-occurring.[26] The illness causes changes in numerous neural networks as well as neurotransmitter systems; also it causes dysfunction in the hypothalamus-pituitary-adrenal axis, resulting in concurrent changes in the immune response. Typically, there is a simultaneous rise in pro-inflammatory agents alongside oxidative and nitrosative harm due to a decrease in antioxidant defenses.[27] As per the World Health Organization, there is a global rise in the prevalence of depression and other mental health conditions, particularly in nations with low incomes, attributable to the expanding life expectancy and the greater number of individuals reaching the age range when these mental disorders typically manifest. Moreover, these countries exhibit a higher prevalence of risk factors, such as shortage, joblessness, bereavement, relationship breakdowns, critical illness, psychological stress, and substance abuse involving alcohol and drugs.[28] Worldwide, approximately three hundred million individuals, constituting 4.4% of the population, are affected by depression. Depression is more prevalent among elderly individuals and women compared to other demographics. The prevalence of depression in women ranges from 10% to 25%, while in men, it ranges from 5% to 12%. Depression leads to alterations in mood, cognitive challenges, and diminished interest, along with physical issues, such as headaches, sleep disturbances, fatigue, and sexual dysfunction. These conditions are categorized as major depressive disorder and dysthymia. The first one involves feelings of sadness, diminished interest, and reduced energy and can range from mild to severe. The second one, dysthymia presents with similar symptoms that are less severe but persist over a longer duration. Symptoms of anxiety disorders encompass sensations of anxiety and fear. Symptoms can vary in intensity, ranging from mild to moderate or severe.[29]

Table 1: Different categories of dementia[20]

S. No.	Types of dementia	Total percent cases found (%)
1.	Alzheimer's disease	More than 60
2.	Vascular dementia	20
3.	Dementia with lewy bodies	10
4.	Fronto-temporal dementia	2
5.	Mixed dementias	1

Pharmacological treatment for depressive disorders involves the use of tricyclic antidepressants, inhibitors of monoamine oxidase, and selective serotonin reuptake inhibitors and for anxiety disorders use of pregabalin, benzodiazepines, buspirone, and tricyclic antidepressants are used. All the given drugs are synthetic category. However, patients frequently fail to adhere to these conventional antidepressants or anxiolytic treatments due to adverse effects or the characteristic delay in effectiveness.[30] These drugs are also associated with serious side effects such as sexual problems and addiction. The origins of the condition encompass genetic predispositions, biochemical alterations in the brain, psychosocial stressors, psychodynamic influences, fluctuations in hormone levels, diverse physical ailments, medications, malnutrition, and even dietary factors.[31,32] The main focus of pathophysiological theories concerning depression revolves around abnormalities in brain monoamine receptors, secretion of monoamines, overall dysfunction of the monoamine system, and impairment of the second messenger system.[32]

Some individuals achieve partial or indirect improvement, while others demonstrate resistance to pharmacological interventions. Therefore, there is a strong emphasis on the importance of exploring novel classes of antidepressants. Because of the negative side effects associated with synthetic and chemical medications, employing medicinal plants and their phytocompounds as an alternative therapy may

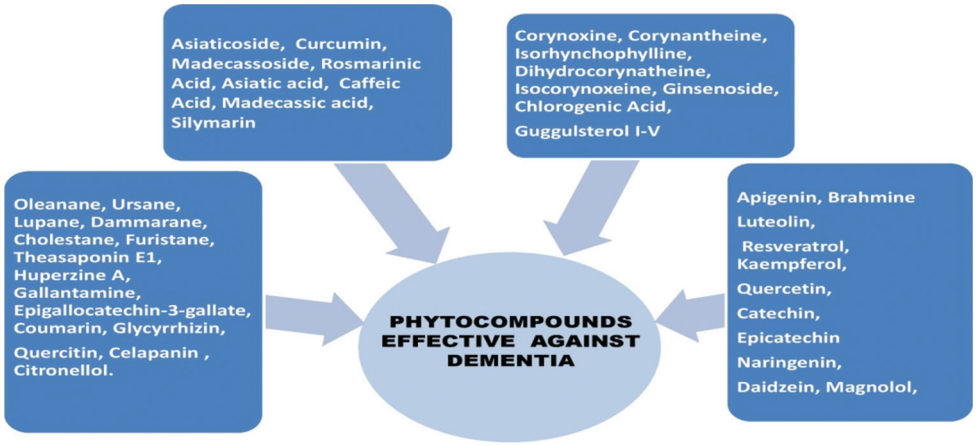

Figure 4: Phytocompounds effective against dementia[20-22]

Table 2: Phytocompounds having anti-depression effect

S. No.	Phytochemical name	References
1.	Icariin	[34]
2.	Coumaric acid	[35]
3.	Ferulic acid	[35]
4.	Caffeic acid	[36]
5.	Apigenin	[36]
6.	Quercetin	[37]
7.	Luteolin	[37]
8	Hypericin and hyperforin	[38]
9.	Linalool	[39]
10.	Ursolic acid, Glycyrrhizin, and Rosavin	[40,41]

offer a comparatively superior option. Numerous studies utilizing various models have documented the beneficial pharmacological effects of plants and phytocompounds in managing depression.[33] Phytocompounds have the capacity to influence neurotransmission either by directly impacting receptors or by modulating the synthesis, distribution as well as function of neurotransmitters. They can also regulate immunological processes. The phytocompounds possess antidepressant action and produce effects through a mechanism such as an effect on serotonin and γ–aminobutyric acid receptors; they also inhibit the enzyme monoamine oxidase and reuptake of monoamines.[32] The phytocompounds having anti-depressant effects are showed in Table 2.

CONCLUSION

Several lifestyle factors support the well-being of the nervous system by subjecting neural cells to mild stress. Plants generate a wide array of organic compounds, with a significant portion seemingly unrelated to their primary growth functions. These substances, known as secondary metabolites, vary in prevalence across distinct groups within the plant realm. Plants harbor numerous chemical compounds renowned for their medicinal attributes, such as alkaloids, terpenoids, flavonoids, glycosides, saponins, and others. Phytochemicals found in dietary supplements, herbs, and spices represent an abundant reservoir of molecules that can enhance human health. Phytochemicals, the non-nutritive elements found in plants, offer a range of therapeutic effects including neuroprotective, antioxidant, anticancer, antidepressant, anti-inflammatory, antianxiety, anti-stress, and CNS receptor modulating properties.[42] Recent research in the field of evaluating phytochemicals proved that the phytochemicals are beneficial in memory enhancing as well as protecting neurons from further damage. These effects make the phytochemicals to be used in dementia and AD. Various studies also suggest that the isolated phytoconstituents from medicinal plants had an advantageous effect on anxiety and related disorders. In addition, these phytochemicals are also involved in regulating several neurotransmitters responsible for the pathophysiology of anxiety and depressive disorders.[25,32,43]

This review aims to gather and condense the existing knowledge on the uses of plants and their derived components in treating chronic disorders of the CNS, specifically targeting different pathways within the human body. Due to their demonstrated safety, efficacy, and extensive historical utilization in diverse traditional medical practices, phytochemicals are regarded as safe. While the demand for phytochemicals is increasing, validation requisite is essential before they become more widely accepted and utilized. Therefore, phytochemicals could offer a fresh avenue for beneficial neuropsychotropic drugs.

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