

Benefits of Functional Foods in the Treatment of Neurological Diseases

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ABSTRACT: Neurodegenerative diseases are chronic conditions linked to aging and are currently widespread and problematic. Their development involves both genetic and environmental factors, as well as their interactions; therefore, an intervention on lifestyle represents a strategy to counteract these diseases. In recent years, much attention has been paid to diet and nutrition as important factors for the prevention and treatment of neurological disorders. Many scientific studies report the benefits obtained by following traditional dietary patterns, such as the Mediterranean diet characterized by increased consumption of fruits, vegetables, legumes, whole grain cereals, nuts, and seeds; higher amounts of foods rich in omega-3 fatty acids; elimination of processed foods, fast food, commercial baked goods, and sweets; paying attention to probiotic intestinal bacteria. Due to conditions of suffering, pharmacological therapy is prolonged for a long time, resulting in the manifestation of undesirable effects that are poorly tolerated by patients. The purpose of this review is to highlight the need to associate pharmacological therapies with a diet rich in functional foods to improve the conditions of patients suffering from neurological diseases. It has been shown that bioactive substances present in plants can have neuroprotective effects in the treatment of mental health conditions such as depression and neurodegenerative diseases. The amount of biologically active compounds is very low in herbal medicines, and their beneficial effect becomes evident over time, as they can be taken for long periods without showing undesirable side effects. The functional foods present in them have all the characteristics for a healthy diet, being rich in fibers, vitamins, terpenes, polyphenolic compounds, and anthocyanins, which have many physiological functions and delay the onset of age-related changes, help fight infections and chronic diseases, and prevent the progression of cancer, osteoporosis, and neurological diseases.

I. INTRODUCTION

Neurological disorders are prevalent and

profoundly debilitating, particularly in light of the global population's advancing age. Consequently, there will be a growing incidence of these conditions, leading to an escalation in disability rates. These disorders encompass a wide spectrum, including tumors of the brain and nervous system, strokes, encephalitis, meningitis, tetanus, traumatic brain injuries, and spinal cord injuries. It is also critical to distinguish between non-communicable degenerative diseases that typically manifest in older adults and those that arise during youth or early adulthood.

Furthermore, aging significantly impacts national economies due to the gradual decline in workforce participation and an increase in retired individuals, driven by diminished independence among the elderly. Disabilities and, in many instances, the loss of self-sufficiency represent the primary focus for physicians and researchers aiming to enhance the quality of life for patients with neurological disorders. Lifestyle and environmental factors play a critical role in brain health: lower educational attainment is linked to an increased risk of dementia, while hearing impairment can accelerate cognitive decline and elevate dementia risk [1,2]. Numerous studies have demonstrated that unaddressed hearing loss adversely affects quality of life by contributing to social isolation, diminished social engagement, and feelings of exclusion, which in turn are associated with a higher prevalence of depressive symptoms [3].

Additionally, adherence to a balanced diet, including moderation in alcohol consumption, is essential for preventing obesity and reducing the risk of type 2 diabetes. Persistent hypertension is correlated with an elevated risk of cerebrovascular deterioration, cognitive decline, vascular dementia, and Alzheimer's disease—conditions that constitute significant public health challenges. Research indicates that not only average blood pressure levels but also factors such as blood pressure variability or instability contribute to the development of cerebrovascular complications [4,5]. Moreover, hypertension compromises the integrity of the

blood-brain barrier, fostering neuroinflammation and exacerbating amyloid-related pathologies.

Serious neurological disorders have been linked to the toxicity of certain heavy metals, including cadmium, a non-essential metal recognized for its carcinogenic potential in humans. Exposure to cadmium arises from various sources, encompassing not only occupational hazards but also contamination through food, water, and tobacco consumption. Due to its slow elimination rate and prolonged biological half-life, cadmium accumulates in organs such as the kidneys, liver, lungs, and brain. In the bloodstream, cadmium exists in both ionic and molecular forms and is capable of crossing the blood-brain barrier to reach neurons, thereby inducing neurological damage affecting both the peripheral and central nervous systems. The neuronal injury involves disruption of endothelial reticulum permeability and integrity, leading to neuronal cell death. Additionally, cadmium exposure elevates the production of reactive oxygen and nitrogen species (ROS/RNS), compromising antioxidant defenses and resulting in neurodegeneration and memory impairment.

In the literature, there are no specific treatments to counteract cadmium toxicity, but many techniques have been proposed, such as the use of chelating agents that, by combining with the metal, would reduce its absorption by tissues or the elimination of the metal through excretion. Recently, the ability of antioxidant and anti-inflammatory agents to improve neurotoxicity by opposing oxidative stress has been highlighted.

Bioactive natural products play a key role in drug development due to their safety profile and strong antioxidant power. Most foods have a functional element responsible for improving health status. Fruit is a rich source of fiber, vitamins, polyphenolic compounds, and anthocyanins. These compounds perform numerous physiological functions and delay the onset of aging-related changes, help fight infections and chronic diseases, and hinder the progression of cancer, osteoporosis, and neurological diseases.

Natural extracts from plants with antioxidant molecules and pharmaceutical potential have attracted greater attention and the development of new research.

The Citrus genus includes many varieties of plants widely used both as a food source and in folk medicine to treat various pathologies. Citrus aurantium L. is a citrus species known as bitter orange that is used as a medical and nutritional supplement due to the presence of phytochemical substances, naringin and neohesperidin, which have

shown significant health benefits.

The antioxidant capacity of the peel and juice of *C. aurantium* has been evaluated and attributed to its essential oil, rich in linalool and limonene, and to the presence of ferulic and p-coumaric acids, recognized as the predominant phenolic compounds in methanolic extracts [6-8]. The peel and juice of *C. aurantium* are considered not only a potential source of natural antioxidants to be used in the food sector but also in the therapeutic sector due to the documented antibacterial and antifungal activity of its essential oils.

Recently, the neuroprotective effects of luteolin against cadmium-induced toxicity in cultured cells and murine models have been investigated. The results showed that luteolin, a carotenoid known for its important activity in eye health, protects hippocampal neurons from cadmium toxicity and mitigates cadmium-induced inflammatory responses in microglial cells. Previous studies have demonstrated that luteolin has anti-inflammatory effects and provides benefits for depression induced by chronic stress; recently, the molecular mechanisms through which luteolin regulates the functional phenotypes of microglia in mice with depression-like behaviors have been investigated. It was highlighted that luteolin administration significantly improved depression-like behaviors and reduced hippocampal inflammation [9].

Recent studies have shown that luteolin crosses the blood-brain barrier, an anatomical and functional structure that selects the metabolites that can enter the brain. Luteolin is the predominant carotenoid, naturally present in cabbage, kale, turnip greens, spinach, orange, papaya... and as a nutrient, it plays an important role in the overall health of the brain. Certain levels of lutein are positively connected with cognitive abilities: memory, attention, language, information processing, executive functions, and each function can be influenced by sleep, mood, stress, and diet. The eye and the brain share a common embryological origin and are characterized by a high content of polyunsaturated fatty acids and high metabolic activity, making them very sensitive to oxidative stress and free radical damage.

HEADACHES AND MIGRAINES

Headache is a generic term that indicates a headache, while migraine is a specific form of headache with well-defined characteristics. Migraine generally involves only one side of the head and is accompanied by symptoms such as nausea, vomiting, sensitivity to light and sound,

causing a pulsating, persistent pain that can last from 4 to 70 hours. Triggering causes can be stress, hormonal changes, diet, or lack of sleep. There are two main forms of migraine: migraine with aura, in which the headache is preceded by transient and reversible neurological symptoms, often visual, and migraine without aura, more common, in which these disturbances are absent. Headache can be primary, manifesting in a diffuse form or in a concentrated area of the head, of short duration, at most 7 days, without migraine symptoms; secondary, resulting from other conditions, such as infections or hypertension.

Tension headache, the most common type of primary headache, manifests with bilateral pain and is characterized by a sense of pressure or constriction around the head, of mild or moderate intensity, which can last from 30 minutes to a week, often related to muscle tension [10,11]. Headaches, as well as migraines, can affect a person's life due to the pain that interferes, making it difficult to concentrate on studying and work; sleep problems may occur, and the individual, in addition to the pain, must face fatigue and symptoms of physical weakness; constant or recurring pain can lead to stress, anxiety, or depression, while the fear of a sudden attack forces isolation and avoidance of social relationships. Therefore, the quality of life is greatly reduced, affecting physical, mental, and social well-being. To alleviate the suffering caused by headaches, a multifactorial approach is necessary, such as regular rest and sleep, stress management, proper nutrition, hydration, and moderate physical activity. If these measures do not have any effect, it is necessary to consult a doctor who can prescribe specific medications to relieve pain and prevent attacks, and in the case of very intense and frequent headaches, identify the cause and resort to personalized treatment. [12]

The treatment of migraine can vary depending on the severity and frequency of attacks, and currently the most commonly used drugs are triptans, which provide immediate relief because they act on serotonin receptors and help reduce pain and other symptoms; painkillers are useful in mild cases; antiemetics if the migraine is accompanied by nausea or vomiting. Triptans are specific drugs for the treatment of migraine and act on certain serotonin receptors (5-HT_{1B} and 5-HT_{1D}) present in cerebral blood vessels and neurons involved in pain. They work by reducing the abnormal dilation of cerebral blood vessels caused by migraine, alleviating the pain; they inhibit the release of substances such as CGRP (calcitonin gene-related peptide) and substance P (a neuropeptide of the

tachykinin family), a neurotransmitter and neuromodulator involved in numerous physiological processes that amplify inflammation and the perception of pain, relieving symptoms. They also act on neurons in the brainstem, reducing the perception of pain and other associated symptoms such as nausea and sensitivity to light and sound. They may be available in various formulations, both tablets and nasal sprays or injections, the latter being useful when tablets are poorly tolerated by the patient.

Triptans are generally well tolerated, but they can have side effects in some patients, among which the more frequent ones include: a sensation of tightness in the chest, throat, or head; nausea and dizziness; fatigue and drowsiness; tingling or a sensation of warmth on the face and limbs. Less common side effects involve blood pressure alterations; skin reactions; respiratory difficulties. More serious side effects are very rare and include: heart problems, as triptans act on vasoconstriction; serotonin syndrome, if taken with other drugs that increase serotonin levels, such as some antidepressants, which can cause symptoms like agitation, excessive sweating, and tachycardia[13,14].

The side effects of triptans can be reduced by following some precautions such as correct intake, which involves taking them before the attack occurs and avoiding excessive doses; it is recommended to take them on a full stomach and to drink water to prevent dehydration, which could worsen side effects such as dizziness and fatigue. To counteract side effects, CGRP receptor antagonist drugs and monoclonal antibodies that block this molecule and its receptors have been developed, representing a significant innovation as they are more targeted and have fewer side effects. Some examples of these drugs are erenumab, fremanezumab, galcanezumab, eptinezumab, which are injectable and indicated both for the prevention of frequent migraines and to reduce the severity of attacks. [15-18] Another class of drugs, especially useful for those with cardiovascular problems, are the ditans, such as lasmiditan, used to treat acute migraine attacks; they are agonists of the serotonin 5-HT_{1F} receptor, reducing the release of neuropeptides and influencing pain pathways without causing vasoconstriction. [19,20]

Of particular interest are mRNA drugs, an innovative technology that uses messenger RNA molecules to instruct cells to produce certain proteins. This technology gained notoriety for being used in COVID-19 vaccines, but it is also opening new avenues for the treatment of other diseases.

Regarding neurological disorders, mRNA drugs could be used to repair or replace defective proteins involved in degenerative diseases such as Alzheimer's and Parkinson's; provide therapeutic proteins directly to nerve cells, helping to slow down or stop the progression of the disease; modulate immune responses or inflammatory processes that contribute to brain disorders.

Migraines are often caused by alterations in nerve signals, inflammation, or chemical imbalances, and mRNA drugs could help regulate neurotransmitters or molecules involved in pain; send instructions to cells to produce proteins that strengthen the brain's protective barriers or reduce nerve sensitivity, thereby reducing the frequency and intensity of attacks; reduce inflammation. [21-23] This technology, however, is still in the research and development phase and is trying to understand which mRNA drugs are effective for treating neurological diseases and tolerable for patients.

Tension-type headache consists of a pain felt as a band tightening around the head, with intensity ranging from mild to moderate. They can occur from a few to many days per month, and the causes can be different: stress, sleep disorders, neck or jaw pain, eye strain. Tension-type headaches are rarely severe and generally do not interfere with daily activities; therefore, therapy involves the use of analgesics such as aspirin, paracetamol, or ibuprofen; behavioral and psychological interventions are often effective if used simultaneously with medications.

Non-pharmacological therapies can also be used: physiotherapy, for example, can help relax the muscles of the neck and shoulders, reducing the tension that contributes to the headache; yoga, meditation, and deep breathing can reduce stress; massages can improve circulation and reduce muscle tension. Lifestyle changes are very useful: improving posture to avoid incorrect positions; regulating sleep to prevent headaches; managing stress. [24]

Nutrition is fundamental for maintaining cognitive well-being and mental health, and it is therefore necessary to associate pharmacological therapies with a diet rich in functional foods to improve the conditions of patients suffering from neurological diseases. Due to the conditions of distress, many drugs must be used for a long time, resulting in undesirable and poorly tolerated side effects by patients. In these cases, food is not only a source of energy for the body, but following a certain dietary regimen provides essential elements for the protection of mental functions while keeping the ongoing pathology under control. The choice of

foods can influence brain processes through various mechanisms: regulating neurotransmitters, modulating synaptic transmissions, modifying the fluidity of cell membranes, and the pathways of nerve signal transmission. [25]

It has been observed that several nutrients have a protective effect against cognitive decline and the risk of developing dementia. Among these nutrients, the most studied are polyunsaturated fatty acids omega-3 found in fish and some vegetable oils such as flaxseed and hemp oil, carotenoids contained in orange-colored plant foods like pumpkin and apricots, polyphenols found, for example, in green tea or turmeric, vitamins, particularly vitamin C and E, vitamin D, and B vitamins, including B12 and folic acid.

Several studies recommend following diets containing fewer fried foods, dairy products, caffeine, and processed foods, such as white bread and processed meat, thereby favoring the reduction of symptoms or the frequency of migraine. It is often suggested to respect meal times suspecting a certain relationship with the onset of migraine; or that having nighttime snacks and eating late could reduce the risk of headache. [26] It should also be considered that stress must be given attention for its role in triggering headaches.

Some migraine triggers are known because they are related to diet and lifestyle, including chocolate, coffee, cheese, alcohol, or citrus fruits, whose consumption should be reduced or completely eliminated in the prevention and treatment of migraine.

Plant-based diets are the subject of particular attention due to the widely described benefits both for the improvement of cardiometabolic health and for the proven safety. A recent clinical study described the rapid and significant remission of migraine with a diet based on whole plant foods and rich in nutrients (WFPBD).

This diet (Whole Food Plant-Based Diet) is based exclusively on whole plant-based foods, avoiding animal products and highly processed foods. Fruits, vegetables, whole grains, legumes, nuts, and seeds constitute the basis of the diet: animal products are not consumed; processed foods such as baked goods, sugary drinks, and packaged snacks are avoided; the consumption of refined sugars and white flour is reduced. This diet is rich in fiber, which can promote better digestion and reduce the risk of constipation; antioxidants capable of reducing inflammation and oxidative stress; unsaturated fats, which can help reduce the risk of heart disease; it can contribute to weight loss, which can significantly reduce the risk of developing

diseases such as type 2 diabetes, cardiovascular diseases, certain types of cancer, and metabolic disorders.[27,28]

DEMENTIA

Dementia indicates a condition characterized by deficits in the cognitive sphere: attention, memory, language, orientation, reasoning, judgment, personality, and behavior. If this state occurs as a result of a natural process of brain aging, it should be considered a characteristic of advanced age, certainly bothersome, but it does not interfere with daily activities. If, with advancing years, the cognitive deficit increases and worsens to become a significant intellectual loss, in addition to limiting personal independence, it means that a pathological process is underway.

Although more frequent in old age, dementia is not an inevitable disease: there are risk factors that increase the likelihood of developing the disease such as age and sex; heredity. Dementia affects elderly people, more commonly women; regarding heredity, cases of dementia with genetic predisposition are only 1-2%

One of the main risk factors for the development of dementia is advanced age. Conditions such as diabetes, hypercholesterolemia, hypertension, obesity; an unhealthy lifestyle, lack of physical and mental activity, an unbalanced diet, and alcohol abuse can also contribute. In addition to cognitive and motor deficits, another very relevant aspect of dementias is represented by neuropsychiatric manifestations. In the early stage of the disease, depression and apathy are very common phenomena, to which agitation, irritability or aggressiveness, hallucinations, and delusions may later be added.

There are various forms of dementia that have different causes and symptoms: neurodegenerative dementias including Alzheimer's disease, Lewy body dementia, frontotemporal pathologies; vascular dementia.

Alzheimer's disease is a type of dementia that causes problems with memory, especially difficulty remembering recently learned information, because the changes caused by this disease involve the part of the brain related to learning.

The progression of Alzheimer's disease through the brain causes increasingly severe symptoms: disorientation, mood and behavior changes, difficulties in performing daily activities, problems with speaking, swallowing, and walking. Two abnormal structures are considered responsible for these transformations and the death of nerve

cells: plaques, consisting of deposits of a protein called beta-amyloid, which accumulates in the spaces between nerve cells, and neurofibrillary tangles, which are twisted fibers of the phosphorylated tau protein that accumulate inside the cells. Both play a role in blocking communication between nerve cells, hindering the processes necessary for their survival.

Other forms of neurodegenerative dementia are linked to the presence of different proteins: alpha-synuclein, a protein that plays an important role in the brain, particularly in synaptic transmission, and is associated with Parkinson's disease and dementia with Lewy bodies; the Tau protein or TDP-43 protein, the latter being essential for cellular function, especially for RNA control, in frontotemporal dementias. In these diseases, neuronal degeneration leads to a reduction in brain size either overall or in specific areas such as the frontal and/or temporal lobes, visible as atrophy upon macroscopic examination of the brain.

Lewy body dementia is the second most common form of dementia after Alzheimer's disease, and currently, there are no specific therapeutic agents available for it, but evidence of cholinergic deficits suggests that enhancing central cholinergic function may be a valid therapeutic approach. The purpose of the research was to evaluate cognitive changes in patients treated with cholinesterase inhibitors. Continuous use, for three years, of cholinesterase inhibitors significantly improved cognitive symptoms in patients with Lewy body dementia.[29]

In vascular dementia, dysfunction and neuronal death are due to reduced oxygen and nutrient supply and inflammatory reactions caused by the narrowing or occlusion of blood vessels in the brain.

Non-pharmacological interventions are considered the most important therapies as the first intervention for managing dementia symptoms, combined with pharmacological strategies, such as therapeutic gardens and horticultural interventions. A pilot study evaluated the effects of a six-month therapeutic garden intervention on psychological well-being, particularly on depression levels, to determine whether this treatment was effective for dementia. The study was conducted in a real setting, using multimodal stimulation, including sensory, motor, and cognitive elements. The results indicated a significant reduction in depression not after three months, but after six months, suggesting that a longer period is needed to achieve concrete benefits. Cognitive function, assessed based on the severity of dementia, did not show significant improvements.

These results highlight the potential of therapeutic gardens to provide significant psychological benefits by significantly reducing depression over time and emphasize the need for further research on long-term effects in dementia care.[30]

Dementia can also be diagnosed through postural control, which may indicate a dysfunction of the central nervous system. A study compared the characteristics of static postural control among patients with various types of dementia: Alzheimer's disease, Lewy body dementia, and vascular dementia. After asking the study participants to maintain a static standing position on a stabilometer for 60 seconds under conditions of eyes open and eyes closed, forty postural control parameters were calculated, including distance, position, and speed in the anteroposterior and mediolateral directions.

The very interesting results showed that patients affected by Alzheimer's disease, Lewy body dementia, and vascular dementia present disease-specific postural control characteristics, compared to cognitively normal individuals, and therefore this control is very effective for the diagnosis of the various types of dementia. [31]

The blood-brain barrier is made up of three cellular elements of the cerebral microcirculation: endothelial cells, astrocytic end-feet, and pericytes. It is a diffusion barrier that selectively prevents most substances carried by the blood from entering the brain. This impediment, caused by tight junctions between cerebral endothelial cells, nullifies the purpose of therapeutic strategies aimed at the prevention and chronic treatment of neurodegenerative conditions, as they cannot reach the target destination. [32]

Intranasal drug administration is one of the promising options to bypass the blood-brain barrier, offering greater bioavailability, fewer side effects, reducing systemic adverse effects of drugs, and the doses of administration. Much attention has also been given to the use of ultrasound, employed alone or with the contribution of drugs, as a new physical modulation technique, showing promising results in improving cognitive deficits. It has been observed that various ultrasound methods can open the blood-brain barrier, reducing the deposition of beta-amyloid plaques. [33,34]

Currently, there are no effective drugs available to treat the development and progression of the disease while also avoiding undesirable side effects, and research work is continuously increasing to use alternative therapies, such as phytotherapy, as support to improve the quality of life of patients. Many studies have shown that the bioactive substances present in plants can have

neuroprotective effects in the treatment of mental health conditions, such as depression and neurodegenerative diseases. The metabolites of these plants act by binding to neurotransmitter receptors, altering their synthesis and functions; they regulate the central nervous system and the endocrine system; they exert anxiolytic, hypnotic, antidepressant, nootropic, sedative, analgesic, tonic, and adaptogenic effects.

Sea buckthorn (*Hippophae rhamnoides* L.) is a wild plant belonging to the Elaeagnaceae family. It is rich in carotenoids, antioxidants, vitamins, minerals, polyphenols, and phytosterols; it contains high concentrations of natural omega 3, 6, and 9 fatty acids along with the rarer omega 7 fatty acids. The fruit has a vitamin C content higher than that of citrus fruits and a high vitamin E content. Sea buckthorn has many health benefits, such as antioxidant, antitumor, anti-hyperlipidemic, anti-obesity, anti-inflammatory, antimicrobial, antiviral, dermatological, neuroprotective, and hepatoprotective activities.

The presence of high amounts of polyphenols has aroused the curiosity of researchers interested in the antioxidant and neuroprotective properties of the total flavonoids of sea buckthorn. The results highlighted the plant's ability to remove 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals, hydroxyl radicals, and superoxide anions. The antioxidant and neuroprotective potential in vivo was explored using *Caenorhabditis elegans*, a small worm about 1 mm long, cylindrical, transparent, belonging to the phylum Nematoda. The results show that sea buckthorn in the longevity test significantly increased the lifespan of *C. elegans*; in oxidative stress induced by hydrogen peroxide, it significantly increased antioxidant capacity, and the neuroprotective effect was also found to be highly efficient, markedly delaying paralysis in *C. elegans*. [35]

Sea buckthorn is known for its medicinal properties in the treatment of various diseases, including neurological ones. A recent study tested the efficacy of sea buckthorn seed oil administered by nebulized inhalation in 9-month-old APP/PS1 mice affected by Alzheimer's disease. After 21 days of therapy, the results showed that the nebulized oil improved memory and cognitive functions; moreover, the enzyme-linked immunosorbent assay, ELISA, and pathological analyses indicated a reduction in neuroinflammation in plasma and brain, a decrease in neuronal necrosis, a reduction in β -amyloid ($A\beta$) protein levels, a reduction in amyloid deposition, and an increase in tyrosine hydroxylase activity. Nebulized inhalation therefore represents a

potential method to improve drug delivery across the blood-brain barrier with reduced systemic side effects. [36-38]

The study of the activity of functional products present in plants drives research towards the identification and development of new therapeutic products. Numerous studies have shown that polyphenols, due to their various pharmacological properties including antioxidant, anti-inflammatory, and neuroprotective effects, are of great help in the prevention and treatment of neurodegenerative diseases.

Nobiletin and **Tangeretin** are important flavonoids found in the peel of citrus fruits and other parts of the genus *Citrus* L., showing neuroprotective effects in vitro and in vivo. Nobiletin, a polymethoxylated flavone extracted from the peel of *Citrus depressa*, is a functional substance endowed with anti-dementia and neuroprotective activity.

In animal models, nobiletin has improved cognitive deficits and pathological features of Alzheimer's disease, attenuated cholinergic deficits, reduced beta-amyloid accumulation, improved ischemic damage, inhibited tau protein hyperphosphorylation, and reduced oxidative stress. The use of nobiletin increased levels of neprilysin, an enzyme that degrades vasodilatory peptides, such as natriuretic peptides and bradykinin, which play a fundamental role in regulating blood pressure, reducing the workload of the heart, and managing fluid and electrolyte balance. Motor and cognitive deficits in animal models of Parkinson's disease were also improved. These observations suggest that nobiletin has the potential to become a new drug for the treatment and prevention of neurodegenerative diseases. [39,40]

Tangeretin and nobiletin also influence the regulation of GSK-3 β (Glycogen Synthase Kinase-3 Beta), a serine/threonine kinase with the function of transferring phosphate groups between molecules, involved in numerous cellular processes, such as mood regulation, neuronal growth and development, with a fundamental role in the expression of Tau protein. Hyperphosphorylation of Tau protein destabilizes microtubule structures, leading to neuronal loss.

Tangeretin has been shown to be capable of preventing neuroinflammation and improving dementia in a murine model of Parkinson's disease induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This substance was injected into the compact zone of the substantia nigra of rats, an area of the brain that plays an important role in the coordination of movements,

learning, and memory, as well as performing a function in the organization of emotions. Oral administration of tangeretin was given three days before the MPTP injection and continued for 20 days after the injection, and the rats showed evident motor dysfunction. Treatment with tangeretin significantly attenuated memory deficits and improved motor and cognitive functions, and the experimental data support considering tangeretin a potentially effective drug for the prevention and treatment of neuroinflammation and dementia. [41]

Curcumin, a natural compound found in turmeric, has been shown to be effective in the treatment of brain diseases and the aging process. The antioxidant properties of curcumin include the removal of reactive oxygen and nitrogen species; metal chelation; regulation of antioxidant enzymes; anti-inflammatory properties; reduction of malondialdehyde; increase of total antioxidant potential. In vitro studies have demonstrated that curcumin inhibits the aggregation of β -amyloid protein (A β) and A β -induced inflammation, as well as the activity of β -secretase and acetylcholinesterase. [42,43]

In a study on homocysteine-induced neurotoxicity in rats, curcumin administered at doses of 5 and 50 mg/kg showed protective effects by reducing cognitive impairment and oxidative stress caused by homocysteine, reducing lipid peroxidation, and improving memory and learning in rats. [44]

Curcumin has also been recognized for its neuroprotective and cognitive enhancement properties, which may help delay or prevent neurodegenerative diseases, including Alzheimer's disease. In vitro studies have shown that A β metabolism is altered by curcumin, and animal studies report that curcumin can influence brain function and the development of dementia due to its antioxidant and anti-inflammatory properties.

Although research has highlighted various neuroprotective actions of curcumin, its clinical use is limited by its poor solubility, which prevents adequate absorption, by specificity, and by the difficulty of distribution to various targets. To avoid these drawbacks, other contact systems have been considered, such as bioengineering and systems biology, which integrates contributions from various disciplines, such as bioinformatics, mathematics, engineering, and molecular biology, to understand the functioning of biological systems. The multiple effects of curcumin, such as its impact on microRNAs and senescence markers, suggest new therapeutic targets in neurodegeneration. Furthermore, recent advances in delivery systems,

particularly brain-targeted nanocarriers such as polymersomes, micelles, and liposomes, have shown promising results in improving the bioavailability and therapeutic efficacy of curcumin in animal models. [45-47]

Cuscuta reflexa, belonging to the Convolvulaceae family, is a parasitic plant that has attracted the attention of pharmacological research due to the presence of various bioactive compounds and potential therapeutic applications. Its pharmacological activities have been validated by traditional uses in folk medicine and, according to tradition, it has been considered a plant with neuroprotective effects. To scientifically evaluate the pharmacological activity of the plant, a hydroalcoholic extract of *Cuscuta reflexa* was examined to highlight its ability to improve the neurodegenerative effect in rats affected by Alzheimer's induced by aluminum chloride. The *in vitro* study demonstrated that *Cuscuta reflexa* significantly reduced the cytotoxicity induced by aluminum chloride in PC12 cells; the *in vivo* study showed that treatment with the plant extract in rats improved learning and memory, also showing a reduction in oxidative stress in the brain following a significant decrease in malondialdehyde and an increase in antioxidant parameters such as reduced glutathione, catalase, and superoxide dismutase; it also showed its cholinergic activity by reducing the increased levels of acetylcholinesterase in the brains of rats. [48]

Due to its anti-inflammatory, antioxidant, cholinergic, and neuroprotective effects, its use is indicated in the treatment of progressive neural damage and cognitive deficits in patients affected by Alzheimer's.

The Snowdrop, *Galanthus nivalis* L., is a plant of the Amaryllidaceae family that presents various properties and benefits, mainly related to its chemical component, galantamine. This substance is studied for its potential ability to slow cognitive decline in people with Alzheimer's disease and also has an anesthetic effect.

Galantamine, an alkaloid present in the snowdrop, is the subject of studies for its possible effectiveness in the treatment of certain diseases, such as Alzheimer's disease, muscular dystrophy, and multiple sclerosis; it is known for its anesthetic properties, which makes it a potential tool in pain management; it is emmenagogue and emetic; it shows remarkable effectiveness as an acetylcholinesterase inhibitor.

Steroidal alkaloids are secondary metabolites present in plants, fungi, and sponges and are considered a source of bioactive compounds for

the treatment of chronic diseases. The various important neuroprotective activities and the different pharmacological effects of steroidal alkaloids, with polypharmacological modulatory effects, are important for the research of new drugs for the treatment of Alzheimer's. [49-51]

Ginkgo biloba is a plant used for thousands of years in China to treat a variety of disorders; several studies have shown that a *Ginkgo biloba* extract improves symptoms and slows the progression of Alzheimer's. The leaves, seeds, and exocarp of the *Ginkgo biloba* tree, including their extracts, have traditionally been used for thousands of years as medicine, food, insecticides, or bacteriostatic agents and for the improvement of age-related cognitive decline and quality of life in adults with mild dementia. [52] *Ginkgo biloba* leaves contain a multitude of bioactive components, such as flavonoids, lactone terpenes such as ginkgolides A, B, C, M, and J. [53,54] Flavonoids are important antioxidants and can also act as chelators for heavy metals [55]

Numerous flavonoids, both free and glycosylated, have been identified in *Ginkgo biloba* leaves, including isorhamnetin, quercetin, and kaempferol. [56] Several clinical studies have investigated the *in vivo* effects of this plant, focusing on degenerative cognitive diseases such as dementia, a syndrome characterized by gradual cognitive deterioration associated with behavioral disorders and reduced activities. Potentially beneficial effects have been observed for people with dementia when administered at doses higher than 200 mg/day for at least 5 months. [57,58]

Currently, it is one of the best-selling herbal products, being suitable for treating tinnitus, cognitive decline, and Alzheimer's; cardiovascular disorders, cerebrovascular ischemia, diabetic nephropathy, and other diseases. Several studies have shown that a *Ginkgo biloba* extract improves symptoms and slows the progression of Alzheimer's and that the use of the extract has led to significant improvements in blood flow and oxygen. A reduced blood and oxygen flow to the brain can indeed be an important factor in the development of Alzheimer's. However, to be certain of the effectiveness of the *Ginkgo* extract, the treatment should last without interruption for at least 12 weeks, a very difficult task for patients affected by Alzheimer's.

Resveratrol can be considered a functional food present in grapes and red wine and has been widely studied for its neuroprotective, anti-inflammatory, immunomodulatory effects and for its antioxidant properties. The neuroprotective mechanisms of resveratrol are related to the

inhibition of beta-amyloid aggregation and the inhibition of free radicals. Resveratrol is a powerful activator of sirtuins, a group of enzymes that play an important role in many cellular processes such as metabolism regulation, DNA repair, and aging. The activation of sirtuins can lead to various benefits, contributing to muscle protection, the prevention of metabolic and neurodegenerative diseases, and improved resistance to oxidative stress. [59,60]

Clinical studies on resveratrol have indicated that this polyphenol is well tolerated by young and elderly subjects when administered at 200 mg at 8-hour intervals, but it is rapidly metabolized and excreted. In healthy elderly individuals, resveratrol increases blood flow in a dose-dependent manner but without alterations in cognitive function. Currently, drugs for Alzheimer's such as rivastigmine, memantine, galantamine, and donepezil mainly address early symptoms but have limitations as they are not tolerated by all patients, have side effects, and are costly. To make resveratrol therapy acceptable especially for elderly people, bovine serum albumin nanoparticles coated with chitosan and loaded with resveratrol have been prepared to enhance its therapeutic properties and counteract Alzheimer's disease.

Using desolvation techniques, spherical and smooth nanoparticles were obtained, containing a dispersion of amorphous resveratrol powder inside, which showed stability for 90 days at refrigerated room temperature.

The safety of resveratrol-loaded nanoparticles was verified on Wistar rats, and furthermore, intranasal administration showed that they were more effective than the simple dispersion of resveratrol.

These results highlight the effectiveness of biodegradable and mucoadhesive nanoparticles as effective drug carriers for intranasal delivery to the brain, offering safety and high tolerability for the treatment of Alzheimer's disease. [61]

Phytochemicals of plant origin, such as resveratrol, huperzine, quercetin, galantamine, and rosmarinic acid, prove promising as potential treatments for Alzheimer's and are the subject of study for their ability to safely reduce the risk of this disease.

The prevention by resveratrol is based on the fact that this polyphenol also possesses anti-inflammatory and antioxidant properties; it prevents the aggregation of beta-amyloid and tau in the brain and inhibits neuronal apoptosis through the activation of sirtuins, minimizing oxidative stress. Furthermore, resveratrol can reduce the inflammatory response in leukocytes and inhibit

microglial neurotoxicity. Following recent research, grape seed extract containing polyphenols has been proposed as a dietary supplement with potential use in neurodegeneration.

PARKINSON'S DISEASE

Parkinson's disease is a common degenerative disease, the prevalence of which is increasing due to the aging of the global population, and it is believed that the cause of the disease involves multiple factors such as genetics, environment, and personal lifestyle. It is characterized by a movement disorder that mainly affects motor control; pathologically, the disease is characterized by the presence of Lewy body inclusions in the brain enriched with fibrillar forms of the presynaptic protein alpha-synuclein. [62]

Its identification is given by the progressive loss of dopaminergic neurons in the brain region of the pars compacta of the substantia nigra, for which mitochondrial dysfunction and oxidative damage are responsible. The loss of dopaminergic neurons affects the basal ganglia circuits, leading to the development of both motor symptoms such as bradykinesia, tremors, and postural instability, and non-motor symptoms such as insomnia, psychopathy, and cognitive deficits. Recently, a growing number of studies have revealed that Parkinson's disease also involves the gut, demonstrating an important bidirectional link between the brain and the gut, called the "gut-brain axis." Numerous clinical studies show that intestinal dysfunction often precedes motor symptoms in patients with Parkinson's disease, involving reduced intestinal permeability and increased inflammation of the microbiome. The deposition of α -synuclein has also been consistently observed in the intestines of patients with Parkinson's disease, suggesting a potential role in the onset of the disease. [63]

The current available therapy for Parkinson's disease is mainly based on levodopa, which offers the potential to slow the progression of the disease to some extent but involves numerous side effects.

Meals, especially those rich in proteins, can interfere both with the absorption of levodopa and with its entry into the brain, contributing to the decreased effectiveness of the drug. A predominantly vegetarian, low-protein diet is very important because it facilitates the absorption of levodopa, counteracting the decreased postprandial effectiveness observed especially in the advanced stages of the disease, which causes disability and risk of falls.

A proper diet in Parkinson's disease is essential to prevent malnutrition both from deficiency and excess, as cases of overweight and obesity are also common. Foods rich in saturated fats, refined sugars, and salt; processed foods, red meats, and high-fat dairy products; fried foods; commercial baked goods; and packaged snacks are discouraged. [64]

Plant-based products provide a rich supply of fiber and carbohydrates, counteracting body weight loss, and are easier to chew, a fundamental characteristic for patients in the mid-advanced stage of parkinsonism who have swallowing problems. Finally, minerals and vitamins, especially Vitamins C, D, E, iron, calcium, and magnesium, are essential for patients with Parkinson's Disease.

Among the causes of underweight are gastrointestinal disorders, increased energy expenditure, and the onset of mood changes; dysphagia among gastrointestinal disorders is common and appears in the advanced stages of the disease and, when present, requires specific nutritional rehabilitative treatment. Constipation is also very common, worsens with disease progression, causes a feeling of fullness, gastrointestinal disorders, and promotes food restriction.

Among the most frequent causes of overweight and obesity are the reduction in physical activity levels and a diet with excessive consumption of carbohydrates and lipids.[65]

Withania somnifera is an important medicinal plant used since ancient times for its aphrodisiac properties and a potential nerve tonic that improves learning and memory. The plant contains numerous bioactive compounds, such as withanolides, alkaloids, and saponins, which exhibit various biological activities; its roots are known for their anxiolytic, antidepressant, antioxidant, anti-inflammatory, anticancer properties, and for improving memory.[66]

Studies show that *Withania somnifera* can help reduce cortisol levels, the stress hormone, and improve mental well-being; it acts as an adaptogen due to its ability to help the body maintain internal balance; it may also have antioxidant properties and be used to improve energy and vitality. In particular, withanolides reduce the excessive activation of dopamine receptors caused by stress, improve antioxidant defenses in nervous tissue, and limit cellular damage caused by lipid oxidation.

In a study conducted on rats with Parkinson's disease induced by 6-hydroxydopamine, it was observed that administering an oral extract of *Withania somnifera* at doses of 100, 200, and 300

mg/kg of body weight for 3 weeks resulted in a significant reduction in peroxidation, significantly improving not only the biochemical parameters of Parkinson's disease but also reducing motor deficits compared to the control group.[67-69]

Bacopa monnieri is a perennial aquatic plant native to India, also known as Brahmi, which mainly grows in humid and marshy environments. The main bioactive compounds of *Bacopa monnieri* belong to the family of triterpenoid saponins and are known as bacosides. Bacosides A and B are the most therapeutically relevant compounds, for their neuroprotective effects, cognitive improvement, and antioxidant activity. Alkaloids: brahmine and herpestine may contribute to the neuroprotective effects; Flavonoids: known for their antioxidant properties, play a fundamental role in the pharmacological action of the plant, improving cognitive and neuroprotective abilities.

One of the most studied benefits concerns the ability to improve cognitive functions such as memory, attention, and information processing speed. According to the proposed mechanism of action, *Bacopa* has the ability to modulate neurotransmitter levels such as serotonin, dopamine, and acetylcholine while simultaneously improving synaptic plasticity, a fundamental process for learning and memory.[70]

Bacopa is also studied for its neuroprotective effects, protecting neurons from damage related to oxidative stress and inflammation: bacosides can inhibit the accumulation of beta-amyloid, a protein associated with Alzheimer's disease. [71]

A recent study focused on investigating the potential of chitosan nanoparticles in improving the bioavailability and efficacy of *Bacopa monnieri* extracts, known for their neuroprotective, antioxidant, and antitumor properties, by adding different concentrations of chitosan to the culture medium for in vitro regeneration of shoots. Antioxidant activity and cytotoxicity tests were performed, showing a significant increase in the antioxidant and antitumor properties of *Bacopa monnieri* extracts.[72]

The integration of nanoparticles in plant-based research has significantly improved the delivery and efficacy of plant-derived compounds following the increase in enzymatic antioxidant activity that stimulates the synthesis of phytochemical substances with potential therapeutic applications.

Mucuna pruriens, belonging to the Fabaceae family, endowed with various therapeutic

activities such as antioxidant, anti-inflammatory, antiepileptic, antimicro

bial, is a weed legume that grows spontaneously in tropical areas and contains a good percentage of levodopa, a precursor of dopamine used in the treatment of Parkinson's disease.

The healing properties of this plant make it an excellent ingredient for pharmaceutical and therapeutic applications: in addition to the high content of proteins and starch, it contains L-Dopa (3,4-dihydroxy-L-phenylalanine) and other important bioactive components such as ursolic acid and betulinic acid, which show similar neuroprotective activity. The antiparkinsonian activity of *Mucuna pruriens* has been explored in various models of Parkinson's induced by toxins such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), Rotenone, Paraquat, and different parts of the plant such as seeds, leaves, and stem have shown potent neuroprotective properties. [73]

The seeds of *Mucuna pruriens* also contain a wide range of phytochemical constituents such as alkaloids, glycosides, saponins, reducing sugars, and tannins, which offer an opportunity for exploration for broader applications. Nutraceuticals, including vitamins and phytochemicals present in the legume, have shown potential neuroprotective functions in preclinical and clinical studies, improving mitochondrial dysfunction, oxidative stress, and neuroinflammation, all factors involved in the pathogenesis of Parkinson's. [74]

Much importance has been given to the neuroprotective mechanisms of diet and plant extracts for Parkinson's therapy, without neglecting the control of dosage standardization, bioavailability, and variability of acceptance among patients.

Further in vitro and in vivo studies are also necessary to explore the potential of these seeds against numerous diseases, their use as a food source, antinutritional and harmful properties, and nutraceutical potential.

The pomegranate (*Punica granatum* L), belonging to the Lythraceae family, is cultivated both as a fruit tree and as an ornamental plant. The fruit of the pomegranate is rich in polyphenols that present many benefits for neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease in association with therapeutic treatment. The pomegranate is a good source of soluble and insoluble fibers, useful for good digestion and for protecting intestinal health; it promotes weight reduction, cholesterol control, improvement of immune defenses and the

cardiovascular system; it prevents the onset of tumors, particularly prostate cancer, and lymphomas. The intake of ellagitannins such as granatin B and punicalagin present in pomegranate juice can reduce cardiovascular risk by counteracting the action of free radicals.[75]

The pomegranate is a source of minerals, especially potassium, as well as phosphorus, sodium, magnesium, and iron; it is fairly rich in vitamin C and contains a decent level of provitamin A.

Scientific evidence has shown that changes in a healthy lifestyle, particularly in dietary patterns, can reduce the burden of age-related diseases; they have also reported that a large number of plant-derived components belonging to the polyphenol class possess neuroprotective benefits. Studies have been initiated on the effect of dietary polyphenols from *Punica granatum* L. on neurodegenerative diseases, including Alzheimer's disease, which is symptomatically characterized by impairment of cognitive functions.

The polyphenols ellagic acid, gallic acid, and punicalagin A and B, present in higher concentration in pomegranate, were extracted in ethyl acetate to evaluate the inhibitory effect of NO (nitric oxide) on the production of nitrogen nitrite NO₂ in culture media using the Griess reagent method.

Nitrite production was examined in RAW264.7 cells stimulated with lipopolysaccharides in the presence of ellagic acid, gallic acid, and punicalagin A and B at different concentrations for 24 hours: nitrite production was inhibited in a concentration-dependent manner; the maximum inhibition was obtained at a concentration of 200 µg/ml; ellagic acid showed the highest inhibitory effect compared to the other two compounds. The results indicate that ellagic acid, gallic acid, and punicalagin could be the compounds responsible for the anti-inflammatory potential of *Punica granatum*. [76]

A growing number of studies show that pomegranate extracts rich in polyphenols and their metabolites act on different types of brain cells, supporting their redox balance, proliferation, and survival. Ellagitannins are the most abundant components and have antioxidant activity much higher than that of red wine, green tea, or orange juice, which is increased by the presence of anthocyanins in the juice obtained from the arils. Their neuroprotective effects are mediated by antioxidant and anti-inflammatory factors, their chelating properties, and their ability to influence mitochondrial damage. Pomegranate polyphenols

act directly on both neuronal and glial cells and also influence the function of the blood-brain barrier, restoring redox balance in the blood and brain and increasing blood flow to the brain. In various rodent models affected by Alzheimer's disease, pomegranate extract improved behavioral performance and reduced amyloid accumulation in the hippocampus.

The effects of pomegranate juice have been studied on elderly people with memory problems: 250 ml of pomegranate juice taken daily for one month have been shown to improve verbal memory and neural activity during a visual memory task, highlighting the role of pomegranate juice in improving memory function by increasing functional brain activity.[77]

It is evident that pomegranate and its derivatives can modulate the expression and activity of various genes, enzymes, and receptors, influencing oxidative stress and inflammatory pathways. Different parts of the pomegranate (roots, bark, flowers, fruits, and leaves) contain various bioactive compounds, such as polyphenols, flavonoids, anthocyanins, and ellagitannins, which have preventive and therapeutic effects against numerous disorders, such as cardiovascular diseases, diabetes, neurological diseases, obesity, and tumors, without side effects.

Since the safety of the fruit, juice, and pomegranate extracts is proven, it is possible to design further studies focused on its antioxidant and anti-inflammatory active principles to discover new drugs.

II. CONCLUDING REMARKS

Functional foods, which promote health and help prevent diseases related to an aging society, have attracted much attention, being recognized as a valid complementary therapy. The health benefits are significant, including antioxidant, anti-inflammatory effects and strengthening of the immune system; they are well tolerated and can be used without undesirable effects.

Functional foods are very important for human health due to their content of physiologically active substances of both plant and animal origin. Composed of carbohydrates, vitamins, minerals, polyphenols, terpenes, phytosterols..., they are very useful for the various biochemical processes that develop in the body. Even if present in limited quantities, functional foods act effectively in the prevention of numerous diseases and also in long-term treatment, making the condition of patients more bearable. They not only contribute with a

balanced diet to improving lifestyle and preventing chronic diseases, but above all to obtaining benefits for personal well-being.

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