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ISORHAMNETIN 3-O-GLUCOSIDE MECHANISTIC REVIEW IN NEUROINFLAMMATORY CONDITIONS

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ABSTRACT

A diverse collection of illnesses known as neurodegenerative diseases are distinguished by the progressive death and loss of function of particular neuronal populations, which results in the disease's clinical manifestation. Pathophysiologically, changes in particular proteins cause various cellular pathways to malfunction, such as elevated reactive oxygen species (ROS) from mitochondrial dysfunction, excitotoxicity, dysfunction of protein degradation systems, endoplasmic reticulum stress, DNA damage, inflammation, and cell cycle re-entry. Antioxidant-rich diets have been shown to lower Alzheimer's disease (AD) risk factors. Antioxidants found in Hippophae rhamnoides, also referred to as sea buckthorn (SB), may directly affect amyloid-beta (Aβ) levels and hence impact the pathophysiology of AD. SBO has a positive effect on APP/PS1 mice's cognitive impairment and protects against scopolamine-induced PC12 cell damage. As a result, SBO might be used clinically to treat cognitive impairment. The potential of sea-buckthorn flavonoids (SFs) as a nutraceutical to prevent cognitive deficits caused by high-energy density diets may be explained by their mediating effects on insulin signalling and inflammatory responses in the brain. There exists substantial evidence that suppressing Keap1 and activating Nrf2/ARE and downstream antioxidant enzymes may be helpful in treating AD. In order to counteract AD, the current review focuses on the neuroprotective effects of plant secondary metabolites by targeting Nrf2/Keap1/ARE and downstream linked mediators. Using the current electronic databases, such as PubMed, Medline, Web of Science, and Scopus, as well as relevant articles in the field, a thorough review was carried out for this study. Creating multi-target medicines that are more effective and have fewer adverse effects may open the door to managing or preventing neurodegenerative disorders. This review covered all the mechanistic views involved in causing neurodegenerative disorders and the use of Hippophae rhamnoides L. polysaccharide as well as flavonoids in various brain disorders.

KEYWORDS: Alzheimer's disease, Hippophae rhamnoides, Parkinson's disease, Antioxidant activity, Huntington's disease.

INTRODUCTION

Millions of people around the world suffers from a variety of neurological conditions known as neurodegenerative diseases (NDDs), which are characterized by the gradual loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS).[1] The loss of neurons that are terminally differentiated and unable to effectively renew themselves, as well as the collapse of neural networks' structure and function, lead to the breakdown of the fundamental interaction circuitry, which in turn impairs memory, cognition, behavior, sensory perception, and/or motor function.[2] Approximately 50 million people worldwide suffered from an NDD in 2019, which generally led to dementia. By 2060, this number is expected to increase to 152 million. Every age group and every geographic location suffers these disorders.[3] In Europe, the nationwide prevalence of NDD that results in dementia is 1.6% for men and 1% for women in the 65–69 age group, and it escalates to 11% and 12.6% for those in the 85–89 age group. According to a WHO research, the neurological burden will probably increase and constitute an uncontrollable hazard to public health unless swift worldwide action is taken. Research on a range of neurodegenerative diseases becomes particularly crucial because, according to the World Health Organization, neurodegenerative diseases like Huntington's disease, Parkinson's disease, progressive brain dysfunction, vascular dementia, cognitive impairment, Alzheimer's disease, and Amyotrophic Lateral Sclerosis cause more than seven million deaths and one billion cases of morbidity globally.[4]

Since neurons are responsible for communication, they are essential to the optimum functioning of the human brain. Although neurons are found throughout the body, the majority of them start in the brain. The bulk majority neurons are produced by neural stem cells throughout childhood, and as people age, their numbers substantially decline.[5] Neurodegeneration, the progressive loss of neurons, their structure, and/or their functions, is a major health problem and a key component of the pathogenesis of many brain illnesses, despite the fact that neurons are not eternal. Neurodegeneration is correlated with synapse and neural network dysfunction as well as the accumulation of physiochemically changed protein variations in the brain.[6] In lieu of selective static neuronal loss resulting from metabolic or toxic diseases, NDDs are identified by the gradual loss of preferentially vulnerable groups of neurons. Amyloidoses, tauopathies, and synucleinopathies are among the most prevalent neurodegenerative diseases that have been brought on by changes in proteins.[7]

Numerous NDDs as well as various Neurodegenerative inflammations are caused by common underlying pathways, such as.[8,9,10]

- Unusual protein dynamics, frequently accompanied by molecular chaperone mutations and activities, including misfolding of proteins, faulty degradation, proteasomal dysfunction, and aggregation.
- Oxidative stress (OS) and reactive oxygen species (ROS) and free radical production.
- DNA damage, mitochondrial malfunction, and compromised bioenergetics.
- Fragmentation of the Golgi apparatus in neurons.
- Cellular/axonal transport disruption.
- Neuroimmune and "Neuroinflammatory" processes.

Numerous forms of protein aggregation are present in the different neurological disorders. The presence of α-synuclein pathological inclusions is typical of Parkinson's disease and other disorders, such as Lewy body dementia, Lewy body variant of Alzheimer's disorder, and multisystem atrophy; Tau, a microtubule-associated protein, is the next misfolded protein frequently found in diseases such as Alzheimer's, Parkinson's, and Huntington's diseases; and β-amyloid plaques are a hallmark of Alzheimer's disease. Both frontotemporal dementia and ALS are associated with TAR DNA-binding protein 43 (TDP-43).[8,11,12]

The application of medications derived from plants has increased dramatically in the therapeutic sector in recent years. Plants contain over 4000 flavonoids, many of which have therapeutic qualities.

Mechanistic insights in neuro inflammation

Specifically, neuroinflammation is the inflammatory response caused by injury in the central nervous system (CNS). Neuroinflammation, also known as nervous system inflammation, is a complicated phenomena that can have both beneficial and harmful consequences in a range of neurological conditions. Inflammation helps limit damage, remove debris, and start the healing process. It first functions as a natural defensive mechanism during acute events like infections, injuries, or trauma. It is a very complicated process that involves in various cell types, such as oligodendrocytes, astrocytes, and microglia, all of that work in collaboration and synergistically. These cells use cytokines, neurotrophic factors, ions, and neurotransmitters to coordinate their interactions.[13,14] Microglia and astrocytes are the most common mediators of neuroinflammation within these cells. Long-term neuroinflammation can be harmful in chronic circumstances, feeding a vicious cycle of neuronal degeneration and destruction. The hallmark of chronic neuro-inflammation is the over-activation of glial cells, such as astrocytes and microglia. Similar to macrophages, microglia cells traditionally aid in maintaining brain homeostasis and carry out a number of neuronal reparative tasks, including the phagocytosis of strange proteins, synaptic organization, the biological response to biotoxins, and the removal of dendritic debris.[15] These cells emit chemokines, ROS, and pro-inflammatory cytokines, which can exacerbate neuronal injury and cause the progressive neurological deterioration associated with disorders like AD, PD, and HD.[16,17] Considering the fact that neuroinflammation is a significant protective mechanism. Excessive or persistent.

A group of illnesses that impact the brain and spinal cord and cause progressive degradation of neural tissue as well as death, are referred to as neurodegenerative conditions. They are often linked to neuroinflammation. Immune cells are released into the central nervous system (CNS) in various illnesses, producing inflammation and the destruction of brain structures. Although the symptoms and evolution of each of these illnesses vary, they are all characterized by neuroinflammation can negatively generate detrimental harm to the brain.[18]

Neuroinflammation, which is a major factor in their pathophysiology.[19,20,21]

In the case of AD, the neuroinflammation pathways include astrocyte and microglia activation, which results in the production of inflammatory cytokines. Amyloid beta, a protein essential for the development of neurofibrillary tangles, is also released as a result of this activation. One of the main features of AD is neuronal dysfunction, which is heightened by these tangles and proinflammatory cytokines.[21,22] Dopamine-producing cells in the substantia nigra (SN) are irreversibly reduced in Parkinson's disease (PD). A key factor in Parkinson's disease (PD) is the deposition of the synaptic protein α-synuclein, which can aggregate into fibrils or oligomers. α-synuclein aggregates to form clusters and interacts with TLRs to activate microglial cells.[23] This particular form of activation triggers a number of processes, such

as the production and release of cytokines that promote inflammation. Amplification of these pro-inflammatory cytokines causes cell death, which advances Parkinson's disease.[24]

ROS in Neurodegenerative Pathways

Many medical conditions have been connected to oxidative stress, which is currently implicated in the onset and/or progression of multiple neurodegenerative diseases. It has additionally been seen that oxidative stress alters the inflammatory response. Despite being two completely different disease processes, oxidative stress and neuroinflammation have similarities and have an impact on each other.[25] The excessive production of ROS can cause the oxidative breakdown of molecules implicated in aging progression and several kinds of ailments, including cancer, neurological disorders, and cardiovascular problems.[26]

A number of studies have been conducted to ascertain the part ROS plays in the growth of neurodegenerative disorders, and the findings have been encouraging. ROS can likely exacerbate the course of illness through oxidative damage and how they communicate with mitochondria, even if investigations have shown that they are not considered an initiating component in many diseases.[27,28] The brain becomes especially vulnerable to oxidative damage due to the combined effects of several factors (such as the brain's high level of oxygen consumption for high energy needs, a higher concentration of polyunsaturated fatty acids in neuronal membranes, high levels of redox transition metal ions, low levels of antioxidants, and neurotransmitter auto-oxidation).[30]

In case of PD, the overproduction of ROS has been experimentally linked to the degeneration of neurons that release dopamine. Both inflammation and dysfunction of mitochondria may be factors that lead to the excessive production of ROS. Neuroglia, which are cells that are not neurons but nonetheless provide protection, and the mitochondria in neurons are the primary sites in the brain where ROS is produced.[31,32]

Dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) are both of the primary defensive systems that can neutralize ROS produced by iron–dopamine chemistry. Free dopamine can be recovered from the synapses by these neurotransmitters transporters and preserved in synaptic vesicles in order to avoid oxidation. But as humans age, their nigral DAT expression gradually decreases, which suggests that their synaptic dopamine evacuation is hampered.[33,34] When we discuss about AD, Acoording to studies, ROS-induced oxidative stress has been connected to the production and deposition of β-amyloid, it is also regarded as an essential variable in the development of AD. In the patients who are in the early stages of the AD, it has been noted that Oxidative stress can be increased by the accumulation of β-which results in mitochondrial dysfunction.[35] It has been stated that oxidative dysregulation and neuronal alteration play an essential role in the beginning as well as the development of AD.[36]

Huntington’s disease HD is characterized as a protein-misfolding ailments which occurs when the HTT protein, a huntingtin-producing protein generated by the HTT gene, interacts with other proteins causing disruptions regular biological processes. One of the primary issues is that ROS-induced protein misfolding results in the development of bodies that cluster alongside neuronal axons and dendrites, obstructing neurotransmitter transmission. The excessive production of ROS/RNS and/or failure of the antioxidant defense mechanism may result from mitochondrial problems. As consequence, redox equilibrium is disrupted, which eventually results in a reduction in physiological cell functioning and cell death.[37,38]

The loss of motor skills is another brain disorder that is associated with amyotrophic lateral sclerosis (ALS). An etiological inquiry has been difficult because there are a number of different factors that can affect both the beginning and the progression of the disease. The precise role of OS in the development of the neurodegenerative disease remains unclear, despite the fact that it was one of the first components to be identified.[39] Nerve terminals have been observed to be sensitive to ROS, revealing that OS causes malfunctioning of mitochondria which further raised intracellular Ca2+ and worsen the presynaptic damage in neuromuscular junctions (NMJ). In addition, neurodegeneration can be promoted by nourishment loss and inflammatory substances.[40]

Hippophae rhamnoides pharmacological activity

Hippophae rhamnoides (Commonly known as sea buckthorn)[41] is a rich source of IGs.[42] Its berries have been designated as a "medicine food homology" fruit by China's National Health Commission for both nutritional and therapeutic applications.[43] Hippophae rhamnoides possesses a variety of beneficial biological, physiological, and therapeutic benefits, including antioxidant, anti-inflammatory, antidiabetic, anticarcinogenic, hepatoprotective, and dermatological properties.[44]

Compared to manufactured antioxidants, plants with varying chemical families and quantities of antioxidants have a higher bioavailability for the human body and cause less negative effects. Hippophae rhamnoides L. ssp. carpatica (Elaeagnaceae), also known as sea buckthorn (SB), is a thorny, nitrogen-fixing deciduous shrub native to Europe and Asia.[45] Sea buckthorn has around 150 cultivars, with fresh varieties being created all the time.[46] Sea buckthorn berries and leaves are thought to be high in bioactive compounds such as isoflavones and flavonoids, which have a number of health benefits, including anti-atherogenic, antioxidant, anticancer, and antibacterial properties.[47] The

antioxidative activities are attributed to hydrophilic and lipophilic substances such as ascorbic acid, flavonoids, proanthocyanidins, and carotenoids.[48,49,50] The sea buckthorn leaves, in particular, have been shown to have higher levels of phenolic compounds and antioxidant activity than the berries, as well as a higher content of nutrients and bioactive compounds such as minerals, vitamins, fatty acids, carotenoids, and phenolic compounds. Antioxidants protect the body from the harmful effects of free radicals produced as byproducts of normal metabolism, and they play significant roles in avoiding pathogenic processes associated with cancer and cardiovascular disease. They can also improve immunological function. In addition to their antioxidant properties, phenolic compounds from SB leaves have been shown to exhibit antibacterial action against a variety of pathogenic pathogens. Furthermore, sea buckthorn leaf extracts have been shown to have strong antibacterial, antitumoral, anti-inflammatory, and antioxidant properties.[51,52,53]

The antioxidant and antibacterial activity of sea buckthorn berries and leaf extracts can be attributed to their bioactive components (Phenolic, flavonoid, and carotenoid chemicals).[54,55] Although many studies have been carried out on sea buckthorn in other parts of the world, information regarding the amounts of biologically active substances as well as the antioxidant and antibacterial properties of cultivars developing in Romania is still based on a small number of studies. Thus, the goal of this study was to examine the bioactive chemicals that support the bioactive potential of four cultivars of Hippophae rhamnoides L. ssp. Carpatica in order to give information that will allow the selection of high-activity cultivars for future cultivation. The potential to create human and animal nutraceutical products based on sea buckthorn is one possible use of the data collected in the future. The substantial amount of sea buckthorn "waste," including leaves, fruit, pulp, and seed leftovers from juice and oil extraction, still contains useful chemicals that may be turned into an animal feed product with added value.

The human body gets advantages from phytonutrients, which are chemical substances found only in natural plants.[56] Because of their health-promoting properties, they frequently occur in food and nutraceuticals.[57] Numerous fruits, vegetables, and plants contain flavonoids, a type of polyphenolic substance.[58] Flavones (e.g., luteolin), flavonols (quercetin), flavanones (hesperidin), catechins or flavanols (epicatechin), anthocyanidins (cyanidin), and isoflavones (daidzein) are the six main subclasses of flavonoids that have been shown to make up different families of phytonutrients.[59] A plant-based diet high in fruits, vegetables, and whole grains has a definite impact in preventing a number of chronic diseases, according to growing data from observational and clinical research.[60] People also regularly consume dietary flavonoids from fruits and vegetables. The majority of flavonoids, which are present in many foods, are glycosidic.[61,62]

As naturally occurring flavonol chemicals, isorhamnetin glycosides (IGs) are mostly derived from a number of plant-based foods or medicinal herbs, including Ginkgo biloba, Opuntia ficus-indica, and Hippophae rhamnoides.[63,64,65] IGs are biologically significant flavonols that have been shown to have positive health effects, making them suitable for use in medicine.[66,67] They have a wide range of biological and pharmacological characteristics, including hepatoprotective, anti-inflammatory, anti-cancer, antidiabetic, and anti-obesity effects.[68,69,70,71,72] IGs have been considered a significant potential class of phytonutrients because of their advantageous biological activities, and more and more products containing IGs are available on the market in a variety of nations, including the US, Canada, Mexico, China, India, and some European nations.[73,74]

Antioxidant activity

Negative effects of oxidative damage brought on by free radicals include cellular malfunction and organic system failure.[75] It is important to note that a large number of in vitro and in vivo investigations have demonstrated that IGs have potent antioxidant and radical-scavenging capabilities.

Common indirect assays for determining antioxidant activity include β-carotene-linoleic acid, 2,2-diphenyl-1-picrylhydrazil (DPPH) scavenging, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS), oxygen radical absorbance capacity (ORAC), peroxyl radical-scavenging capacity (PSC), superoxide scavenging, peroxynitrite (ONOO(-)) assays, and CUPric reducing antioxidant capacity (CUPRAC). Using the DPPH and ONOO(-) tests, IGs extracted from Nelumbo nucifera stamens shown strong antioxidant activity. In addition to having DPPH radical- and ONOO(-)-scavenging activity,[76] brassicin shown a greater capacity to scavenge free radicals than vitamin C. A DPPH radical-scavenging activity experiment has been used to show that isorhamnetin 3-O-robinobioside, isorhamnetin 3-O-(2″,6″-O-α-dirhamnosyl)-β-galactoside,[77] typhaneoside, and isorhamnetin 3-O-neohesperidoside[50] have antioxidant activity. ABST was used to assess the antioxidant capacity of narcissin and astragaloside.[78] DPPH, β-carotene-linoleic acid, and ABST were used to determine the clear antioxidant activity of narcissin and isorhamnetin 3-O-rutinoside-7-O-glucoside. Superoxide anion scavengers and xanthine oxidase were both strongly inhibited by isorhamnetin 3-O-neohesperidoside.[79] Additionally, in every antioxidant activity test used, researchers have demonstrated the antioxidant qualities of isorhamnetin 3-O-glucoside and isorhamnetin 3-O-galactoside.[80,81,82,83]

Animal models and research with different cell types were also used to assess the antioxidant qualities of IGs.

When streptozotocin-induced diabetic rats received isorhamnetin-3,7-diglucoside orally, their levels of 5-(hydroxymethyl) furfural (5-HMF), a marker of stress and hemoglobin glycosylation, were dramatically decreased. The human chronic myelogenous leukemia cell line K562 also showed notable antioxidant benefits from isorhamnetin 3-O-robinobioside.[84] IGs were able to prevent the production of H2O2-induced radicals in the intestinal epithelial cells' immediate environment.[85] In addition, following incubation with isorhamnetin 3-O-neohesperidoside in pKS plasmid DNA, the transcriptional genes of the DNA repair pathway and the antioxidant system were elevated.[86] Reactive oxygen species (ROS) production in the oxidative burst activity of whole blood, neutrophils, and mononuclear cells was strongly inhibited by narcissin and isorhamnetin 3-O-glucoside.[87] Antioxidant action was also demonstrated by plant extracts high in IGs. Opuntia ficus-indica juice's IG-rich concentrate was able to prevent the production of H2O2-induced radicals in the intestinal epithelial cells' immediate surroundings.[88] generally phenolics, such as isorhamnetin-3-rutinoside and isorhamnetin-3-glucoside.[89] were substantially linked to the overall antioxidant activity of Hippophae rhamnoides berry extracts as assessed by ORAC and PSC.

Anti-Inflammatory activity

IGs work through a variety of mechanisms to reduce inflammation. High-mobility-group protein 1 (HMGB1) is a key inflammatory mediator that has a role in inflammation and organ damage.[90] It has been shown that isorhamnetin 3-O-galactoside(5 μM) dramatically suppresses HMGB1 release and lowers HMGB1-dependent inflammatory responses in human endothelial cells. It was discovered that (4.8 mg/mouse) could also inhibit the generation of tumor necrosis factor (TNF-α) in mice, the HMGB1-mediated activation of NF-kB, and the expression of the HMGB1 receptor.[91]

Inflammatory responses are significantly influenced by mitogen-activated protein kinase (MAPK) signaling pathways, which include p38, c-Jun N-terminal kinase (JNK), and extracellular regulated kinases (ERK).[92] The activation of p38 MAPK, ERK 1/2, and JNK was down-regulated by isorhamnetin 3-O-galactoside (50 μM), which also decreased cecal ligation and endothelin C receptor perforation-mediated shedding.[93] Similarly, in LPS-induced RAW264.7 macrophage cells, isorhamnetin 3-O-glucuronide demonstrated anti-inflammatory action by upregulating heme oxygenase-1 (HO-1) production and inhibiting the JNK and p38 signaling pathways.[94] Furthermore, isorhamnetin 3-O-glucuronide suppressed the upregulation of inducible nitric oxide synthase (iNOS) expression (5 μM) and inhibited the release of elastase and ROS (10 μM) in a human neutrophil model, suggesting that it has anti-inflammatory properties.[95,96]

By blocking inflammatory cytokines, IGs have been demonstrated in numerous trials to have anti-inflammatory effects. In phytohaemagglutinin-stimulated human peripheral blood mononuclear cells (PBMC), the inflammatory activity of narcissin(100 μM) and isorhamnetin 3-O-glucoside(100 μM) was mediated through the inhibition of nuclear factor kappa-B (NFκB) and inflammatory mediators like TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6).[97] Similarly, in RAW264.7 cells triggered by advanced glycation end product (AGE), narcissin (40 μM) inhibited inflammatory cytokines (TNF-α, IL-1β, and IL-6).[98] It was shown that isorhamnetin-3-O-[2,3-O-isopropylidene-α-l-rhamnopyranosyl]-(1→6)-O-β-d-glucopyranoside (25 μM) significantly inhibited the release of NO and the secretion of TNF-α and IL-6.[99] On TNF-α-stimulated human osteosarcoma MG-63 cells, isorhamnetin-3,4′-diglucoside (100 μg/mL) and isorhamnetin 3-O-glucoside(100 μg/mL) have demonstrated an inhibitory effect of IL-6 synthesis.[100] Compared to dexamethasone, isorhamnetin 3-O-glucoside (100 μg/mL) demonstrated clear anti-inflammatory action without causing any harm to RAW 264.7 macrophage cells.[101] Isorhamnetin-3-O-robinobioside is the product that has anti-inflammatory properties, according to research by Seddik Ameur et al. on the anti-inflammatory activity of IGs derived from Opuntia ficus-indica flowers.[102] The production of cyclooxygenase-2 (COX-2), TNF-α, and IL-6 was significantly inhibited by both Opuntia ficus-indica extract (OFI-E) and isorhamnetin-3-O-rhamnosylglucoside (125 ng/mL). Of these, 24 compounds have been proposed as potential natural ingredients for the creation of a novel anti-inflammatory ingredient.[103] Sea buckthorn's total flavonoid-rich IGs inhibited the ERK, PI3K/Akt, and PKCα pathways and reduced the production of IL-1β, IL-6, and COX2 in mice, protecting them against LPS/CS-induced airway inflammation.[104]

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