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Neuroprotective Action of Polyphenols and Phenolic Compounds: An Overview

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A central or peripheral somatosensory nervous system lesion or illness is a common cause of neuropathic pain. In this study, we address the most recent information on neuropathy, as well as the causes, symptoms, and treatments of neurodegenerative illnesses like Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis. While, in recent years, phenolic acid supplementation has been associated to enhanced cognitive function and the prevention of cognitive deterioration. The pharmacological effects of phenolic acid are discussed in this review. And gives the overview of role of Reactive oxygen Species (ROS), oxidative stress and antioxidants in neuropathy, and stated the strong relation between stress, tension, hectic lifestyle and neurodegenerative diseases.

Keywords: Free Radicals; Neuroprotective; Neuropathic pain; Neuropathy; Polyphenols; Phenolic Compounds; Reactive Oxygen Species.

The components of the nervous system that ordinarily transmit or send pain impulses are affected by abnormalities or diseases, leading to the development of chronic pain syndromes known as neuropathic pain illnesses. These are complex illnesses that are not caused by a single factor or particular condition[1]. Neuropathic pain is frequent in clinical practise and severely reduces patients' quality of lives.

The majority of patients fall into one of four broad categories include Central nervous system (CNS) lesions (such as Multiple Sclerosis, infarct, and spine injury), peripheral generalised polyneuropathies (toxic, metabolic, hereditary, or inflammatory), and focal and multi-focal neuropathic lesions in the periphery (distressing, ischemic, or inflammatory) (complex regional pain syndromes [CRPSs].

CRPSs (previously called as reflex sympathetic dystrophies, Subdeck's atrophy, or causalgia) are painful illnesses that primarily affect the limbs and can arise as a disproportionate result of trauma[2]. CRPS type I frequently occurs after a harmful damage to an extremity that does not result in a visible nerve lesion (e.g., bone fracture, surgery). After a trauma that is coupled with a significant nerve damage, CRPS type II occurs. However, CRPSs, unlike different types of neuropathic pain disabilities, include additional symptoms such as irregular perspiration and blood

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circulation as well as active and passive motor syndrome, indicating that they are systemic CNS illnesses.

One of the most common causes of early mortality in the world is neurodegenerative diseases. Peripheral alterations include, but are not limited to, oedema of the dermis and underlying tissues, systemic modifications, signs of inflammation, and a pain component supported by efferent sympathetic innervation. The continually growing life expectancy, the disease-related socioeconomic burden is predicted to rise[3]. Current scenario on numerous etiological pathways that lead to neurodegeneration. Neurodegeneration is a subsequent consequence of a main CVS cause, with artery or vein disease affecting the important homeostatic connections in between cerebral and the vascular, leading to cerebrovascular events, Alzheimer's disease, and cognitive deficits like stroke and second, that systemic metabolic problems combined with the presence of senescent cells in brain circuits may promote neurodegeneration[4]. The purpose of this literature review and overview is to explain the significance of polyphenols with radical-scavenging activity and the etiological role of oxidative stress or free radicals in neuropathy.

Distal symmetric sensory polyneuropathy, which is commonly accompanied with autonomic neuropathy, is the most prevalent kind of neuropathy related with diabetes mellitus[9]. Acute functional abnormalities in nerve fibres, followed by more chronic nerve fibre atrophy, damage, and complex loss due to microvascular dysfunction and slower nerve fibre regeneration, are characteristics of diabetic neuropathy, according to a growing body of research. The metabolic consequences of hyperglycaemia and/or other impacts of insulin insufficiency on the widely diversified cell components of peripheral nerve tissue and its associated connective tissue and vascular components are responsible for all of these problems[10]. Phenolic acids are among the most frequent kinds of polyphenol. They're plentiful in foods like berries[11], nuts[12], coffee, and tea[13] as well as entire grains[14]. Importantly, phenolic acid-rich meals have been found to reduce the incidence of depression in a recent meta-analysis[15]. Men from the Mediterranean region and "health-conscious" UK consumers are not included in the survey (most of whom are vegetarians). In all categories, phenolic acids made up the majority of the polyphenols (52.5–56.9% in the diets of men and women, respectively). In general, the primary sources of

Table 1. Types of Neuropathies

Type	Description
Peripheral Neuropathy	Peripheral neuropathy occurs when a neuropathic disease affects nerves that are located beside the brain and spine. Moreover, these kinds of nerves are a part of the peripheral neural network. On the other side, Peripheral neuropathy affects the nerves in the extremities, including all the toes, legs, fingers, and arms. Proximal neuropathy is a term that refers to nerve impingement that causes distress shoulders, quadriceps, and buttocks [5].
Cranial Neuropathy	Cranial neuropathy develops when one or more than 12 cranial nerves (nerves that directly leave the brain) are injured. Two different types of cranial neuropathy include optic neuropathy and auditory neuropathy. When the optic nerve, which transmits vision information from the retina to the brain, is injured, it is known as optic neuropathy. A disorder known as auditory nerve injury affects the nerve that controls hearing and transmits ear impulses that reach the auditory cortex of the brain, which is essential for hearing [6].
Autonomic neuropathy	A condition known as autonomic neuropathic pain affects the ANS's nerves. The heart and circulation (especially BP), digestive, gut and bladder activity, sexual response, and sweating are all controlled by these nerves. And other organs' Additionally, nerves may be harmed [7].
Focal Neuropathy	Focal neuropathy pain is a one of the certain kinds of neuropathy that only involves one nerve or a subset of nerve [8].

Table 2. Alzheimer's Disease

Drug	Description	Reference
Carmustine	Carmustine is a substance that fights cancer and is used to treat brain cancer. this can traverse the blood-brain barrier (BBB) since it is a tiny, non-charge, non-ionized, lipophilic molecule. In cells overexpressing amyloid-protein precursor at a non-toxic dose, carmustine significantly reduced the production of amyloid-protein precursor.	[32]
Bexarotene	Neurodegeneration was demonstrated to be reversed by bexarotene, a retinoid X blocker for the treatment of cutaneous T-cell lymphomas, improve cognition, and reduce amyloid-â in animals overexpressing hereditary Alzheimer's disease genes.	[33]
Tamibarotene	A retinoid receptor agonist called tamibarotene has been given the go-ahead in Japan to treat acute promyelocytic leukaemias, has also been demonstrated to enhance behaviour in mice with advanced ageing by lowering levels of cortical acetylcholine and inflammatory cytokines and chemokines released by brain cells. s	[34]
Paclitaxel	Alzheimer's is currently being researched as a major treatment with an antimitotic drug that has been approved for the management of semi-cell lung cancer, ovarian cancer, and cancer of breast. Therapy for tauopathies—disorders of the tau protein, which are common in brain cells and are responsible for stabilising microtubules —which are brought on by deficiencies in the protein—is especially effective in treating these illnesses. When a protein is phosphorylated, it loses some of its capacity to link to microtubules, increasing fibrillization. Paclitaxel is a medication that stops phosphorylation. Paclitaxel, like imatinib, has a drawback in that it may be a P-gp precursor and only partially penetrates the brain's nerves.	[35]
Thalidomide	Another chemotherapeutic drug with anti-AD properties, thalidomide, has been proven to reduce blood-brain barrier disruption, endothelial cell proliferation, and angiogenesis. Inhibiting tumour necrosis factor also resulted in less hippocampal neuronal death.	[36]
Tetracyclines	It functions as an antibacterial. Moreover, they have been shown to increase preformed fibril disintegration, decrease amyloid-, as well as its resistance to trypsin breakdown. They have a complex method of action since they also lessened oxidative stress.	[37]
Rifampicin	Rifampicin, the most often prescribed antibiotic for Mycobacterium exposure, has demonstrated dose-dependent benefits in the decline of amyloid-â, which is most likely owing to reduced formation and enhanced clearance of amyloid-â	[38]
Amphotericin B	It has been established and demonstrated that amyloid- formation is delayed by the antifungal activities of aminoglycosides B. The same outcomes were not reached in more recent studies, and amphotericin B's negative side effects would preclude it from being a serious candidate for the management of AD.	[39]
Clioquinol	Clioquinol is an antifungal and antiparasitic medication that has been demonstrated in transgenic mice to reduce amyloid plaques in the brain while still being tolerable.(40)	[40]
Valsartan	A medication used for the treatment of hypertension is valsartan, an angiotensin receptor inhibitor. The fact that long-term negative oxidative stress is the major primary environmental variables in the beginning and progression of disease, can cause increases in brain angiotensin II, which binds to AT1 and AT2 receptor subtypes, justifies the use of this class of medications to treat Alzheimer's disease.	[41]

	Additionally, angiotensin receptor blockers, which stop AT1, appear to be helpful in postponing cognitive deterioration. Elevated levels of angiotensin II have been associated to amyloidogenesis. sAlong with encouraging the release of acetylcholine, valsartan also lessens inflammation, vasoconstriction, and mitochondrial dysfunction. Valsartan medicine has been linked to decreased levels of amyloid- both in vitro and in vivo, and this evidence implies a decline in dementia. This medicine also penetrates the brain well, but further research is needed before it can be used to treat Alzheimer's disease.	
Trimetazidin	Trimetazidine is a piperazine-class anti-ischemic medication. It works through a number of different ways, including upregulating nitric oxide synthesis, reducing cell death, and serving as an antioxidant to enhance vascular tone. Due to its antioxidant characteristics, it can not only cross the BBB but also lower the production of free radicals. In both healthy and injured nerves, it can increase myelination and axonal regeneration.	[42]

total dietary polyphenols were hydroxycinnamic acids (varying from 27 percent in women from the "health-conscious" group in the UK to 53 percent in males from non-Mediterranean nations). cis-chlorogenic acid, (primarily 5-caffeoylquinic, 4-caffeoylquinic, and 3-caffeoylquinic acid) were the most widely distributed phenolic acids, followed by feruloylquinic, gallic, galloylquinic, 4-hydroxyphenylacetic, homovanillic, 3,4-dihydroxyphenylacetic, and dihydro-p-coumaric acids. Phenolic acids have the potential to be useful in the management of neurological illnesses in the future[16].

Neuropathy burden worldwide and their complications

Up to 50% of people with the condition get diabetic neuropathy, which is a serious side effect of the diabetes. Yet consistent blood sugar management and adopting a healthy lifestyle can usually prevent or slow the growth of diabetic neuropathy. Neuropathy can affect anybody with diabetes. However, the things increase your probability towards developing nerve damage are poor blood sugar control, longer diabetes has existed, the more probable it is that you will to develop diabetic neuropathy, especially if your blood sugar isn't adequately controlled[17]. Kidney disease, (Body Mass Index) BMI of 25 or more increases your probability towards developing diabetic neuropathy, Smoking causes your arteries to constrict and stiffen, limiting blood flow to your legs and feet. This makes wound healing more challenging and affects peripheral nerves[18].

Alzheimer's disease

The most prevalent neurodegenerative disease worldwide is Alzheimer's Disease (AD). Although AD affects everyone differently, these abnormalities in memory, cognition, and behaviour are the most common symptoms19. Sometimes early symptoms are mistaken for stress or advancing age. There is no denying that memory loss is common, and it causes problems remembering past events. Assessments of behaviour and cognition are frequently used to confirm a diagnosis. Confusion, impatience, violence, mood swings, and seclusion become more prevalent as the condition advances. Individuals with the condition are unable to participate in typical living activities, and long-term care and institutionalisation are frequently needed in the disease's latter stages[20]. The fundamental features of Alzheimer's diseases include loss of neurons of corticals and, to a lesser degree, neurons of subcortical area and synapses on a pathological level. As a result, a portion of the frontal brain, the cingulate gyrus, and the temporal and parietal lobes shrink[21]. The two types of different senile plaques are extracellular senile plaques and tangles in the brain lesions. Both are made up of aberrant amyloid-â (Aâ) aggregations[22]. These are the most prevalent histopathologic Alzheimer's symptoms, although it might be not an adequate to cause the disease's severe and profound neuronal loss[23]. AD is a frequent and well-known condition with a variety of prospective therapy alternatives, although only a few are now in clinical use. A few

more indications include the release of aggregated A, the decrease in neuro-inflammatory activity, the regulation of redox responses and oxidative stress, the suppression of ROS formation, immune-based neuro-degeneration in cells, tissues, and/or organs, and/or the protection and modulation of predictable biochemical responses[24]. Each of these would be vastly improved if medications could be administered selectively to damaged brain regions. If plaques, tangles, and/or neuropathological activity could be detected early in the course of the illness, and direct applications could enhance diagnoses. Hence, there has been a large effort in recent years to explore the application of nano formulations for detecting and treating Alzheimer's disease. The majority of the novel treatment methods target well-established pathogenic processes that are well-known to directly contribute to neurodegeneration[25,197].

Parkinson's Disease

Parkinson's disease was initially described in an 1817 medical text written by a London physician named James Parkinson. The symptoms unique to the affected brain subregion develop gradually. Balance problems, mobility problems, resting tremors, bradykinesia, and stiffness in the limbs and trunk are some of these indications and symptoms. Parkinson's disease is pathologically

Table 3. Parkinsonism Disease

Drug	Description	References
Nilotinib	Nilotinib is a tyr kinase Abl inhibitor is majorly part of the chronic myeloid leukaemia treatment. It was found that a rise in -synuclein expression, which results in accumulation, activates Abl in neurotoxicity. Nilotinib encourages the breakdown of -synuclein by preventing Abl phosphorylation.	[43]
Zonisamide	Zonisamide is a multimodal sulphonamide anticonvulsant drug that is used to treat a variety of illnesses. These modes of action include Na^{+} and Ca^{++} channel blocking, GABAA receptor modulation, carbonic anhydrase inhibition, and glutamate release inhibition. When therapeutic levels of dopamine were utilised in animal studies, there was an elevation in dopamine in the striatum. When greater amounts were employed, although, there was a drop in intracellular dopamine. In terms of Parkinson's disease, this medicine has had good results for both motor and non-motor complaints, but its precise mode of action is yet unknown. Zonisamide also inhibits monoamine oxidase-B. The breakdown of dopamine in neural and neuroglia caused by this enzyme, which is mostly present in astrocytes, results in the creation of free radicals, which can aid in the progression of PD. Its inhibition stabilises synaptic dopamine levels and increases dopamine's effect. The antiparkinsonian drug selegiline, which encourages astrocyte activation after striatal injury, is another monoamine oxidase-B inhibitor.	[44]
Methylphenidate	Methylphenidate, a CNS stimulant, blocks the presynaptic dopamine transporter and the noradrenaline transporter to prevent dopamine and noradrenaline from being absorbed in the striatum and prefrontal cortex. sADHD has been treated using it (attention deficit hyperactivity disorder). This medication has shown to be helpful in reducing non-motor symptoms and gait issues associated with Parkinson's disease in numerous studies. (45)	[45]
Exenatide	Exenatide, like liraglutide, is a glucagon-like peptide-1 that is employed to cure type 2 diabetes. It has been investigated as a potential treatment for Parkinson's disease and has demonstrated neuroprotection and advantageous neuroplastic change, which can halt the progression of the condition. It has the potential to pass the BBBs and protects the brain by activating GLP-1 receptors.(46)	[46]

identified by the death of dopamine secreting neurons in the substantia nigra because the striatal dopaminergic connections to the caudate and putamen are lost. compacted nigra pars[26]. Parkinson's disease is caused by a variety of factors, including misfolded proteins, neuronal damage, glial immune activation, ROS and free radicals' production, exposure to toxins, host genetics, and ageing[27]. Although autonomic anomalies and dysfunction may be signs of a disease, it is apparent that the illness process begins long before any symptoms arise[28]. The release of neurotoxic chemicals, which is started by immune activated glia, causes neuronal injury and the collapse of the BBB (Blood Brain Barrier), which is linked to motor and subsequently cognitive decline[29]. As the disease progresses, the blood-brain barrier becomes less intact, allowing leukocytes to enter the brain and feed the neuroinflammatory cascade[30]. The Parkinson's disease treatments that are currently available concentrate on the effects of the condition. They are used to replace missing dopamine, as D receptor agonists, or as selective monoamine oxidase inhibitors. The benefits and advantages of the dopamine substitute are extended by the latter's metabolism of dopamine. Tremors can be reduced with the aid of additional medications such amantadine or anticholinergic drugs[31]. Using nanomedicine techniques for Parkinson's disease, though, is focused on striking a balance between slowing the progression of the illness and improving the absorption of more traditional drugs used to treat symptoms.

Drug used in neurodegenerative diseases

Multiple Sclerosis

Role of ROS in Neuropathy/ Neurodegeneration

Denham Harman first recognized free radicals in 1956, and they are responsible for cellular destruction, mutation, cancer, and the degenerative process in biological ageing.[179] ROS and RNS are two different forms of free radicals. However, Super oxide (O–O-), triplet-state molecular oxygen (•O–O••), hydroxyl radical (•O–H••), and singlet oxygen (•O–O) are all examples ROS. NO radical (NO•), nitrosonium cation (NO+), nitroxyl anion (NO-), and peroxynitrate are

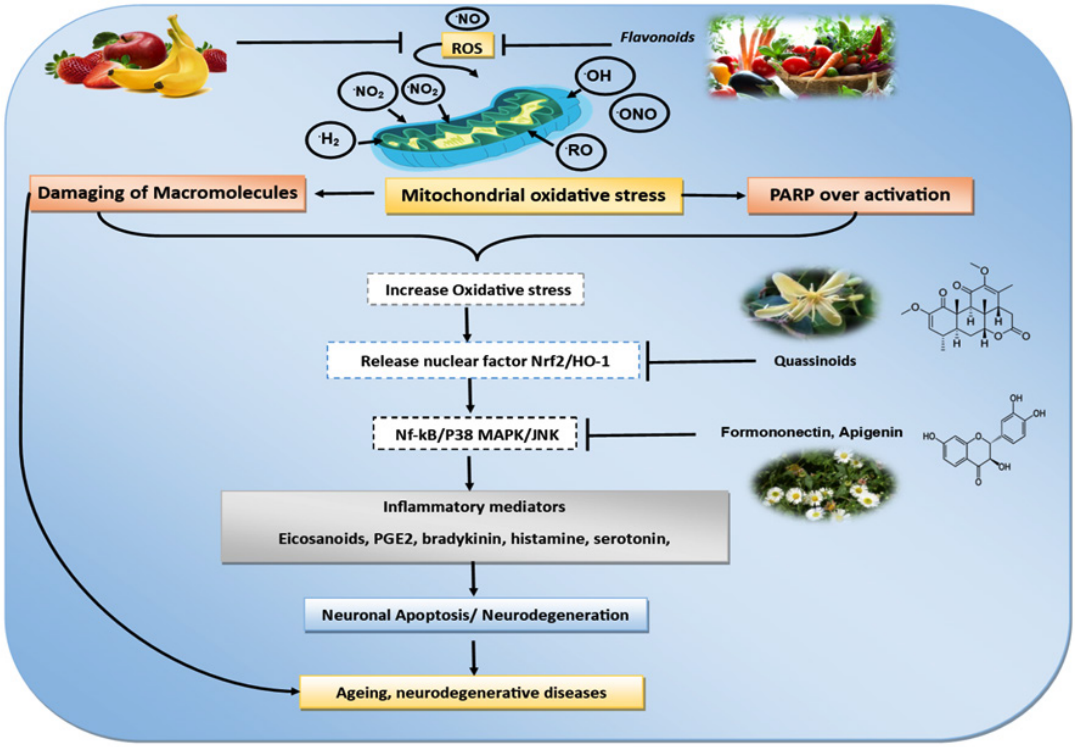


Fig. 1. Dietary polyphenols have neuroprotective and anti-aging effects. Abbreviations: P38 MAPK stands for protein 38 mitogen-activated protein kinase, JNK for Jun N-terminal kinase,

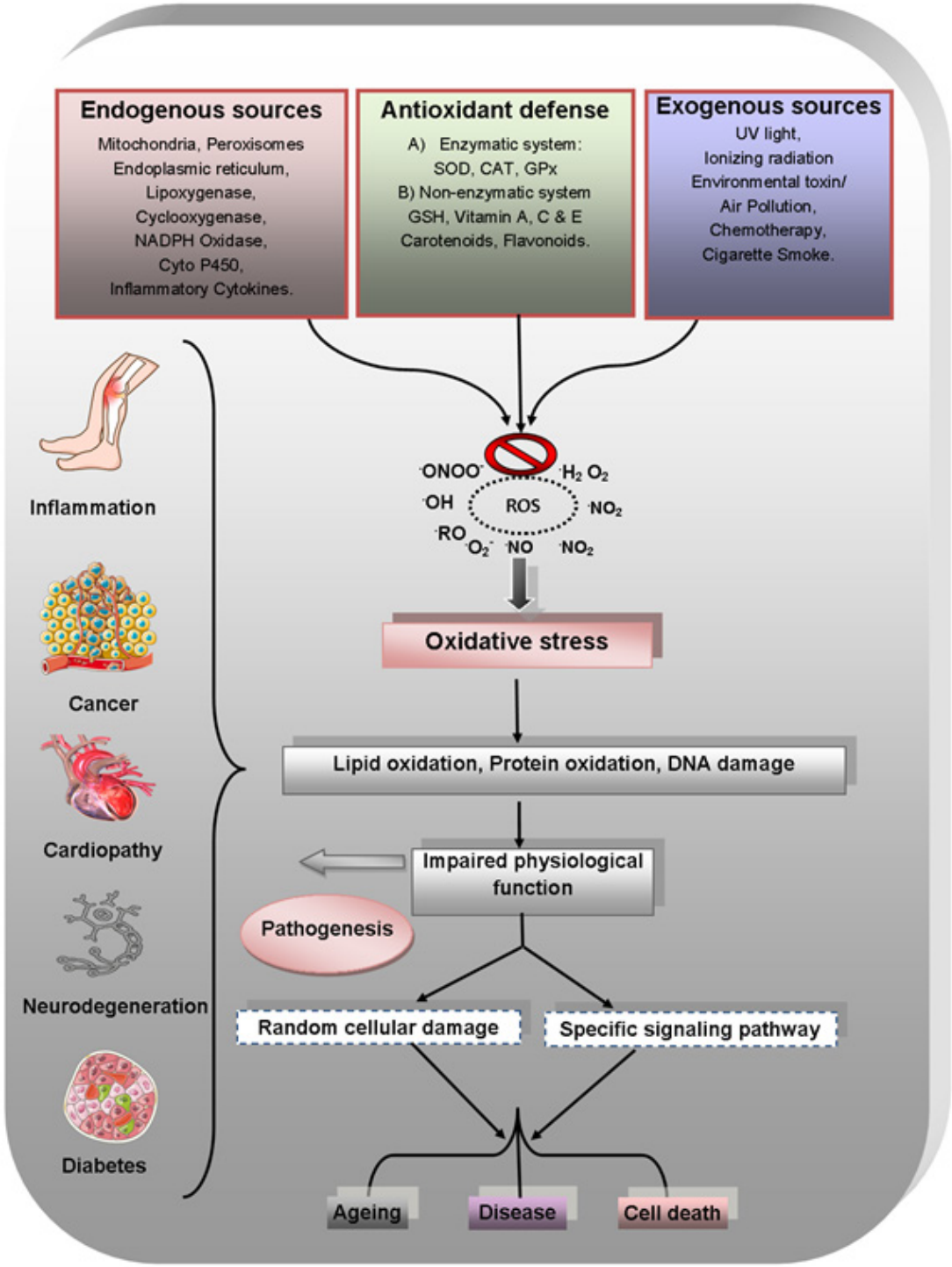


Fig. 2. The causes of human ailments brought on by OS. ROS produced by exogenous/endogenous sources causes OS, which contributes to the pathogenesis of a variety of human diseases by impairing physiological functioning,

examples of RNS (ONOO-) [180]. In cells, reactive species such as superoxide, hydrogen peroxide, and nitric oxide work as signaling pathways to trigger a plethora of intrinsic enzymes and proteins, such as the epidermal growth factor receptor, c-Src, and the p38 mitogen-activated protein kinase, Ras,[181]. Akt/ protein kinase B, and transcription factors like NF-êB/activator protein-1 (AP-1). The stimulation of numerous genes with vital functions in physiology and disease occurs when these signalling cascades and redox-sensitive transcription factors are triggered[182]. ROS concentrations in neurons subjected to 5 mM glutamate rises 5–10-fold in the first 10 hours and 200–400-fold later 10 hours [182] The slightly earlier moderate rise in ROS is related to glutathione depletion in the cytosol, whereas the late explosive increase in ROS is attributed to glutathione reduction in both the

ETC in the cytosol and mitochondria[182]. Increased ROS are known to cause apoptosis in smooth muscle cells via a p53-dependent mechanism. Our findings show that an abrupt rise in ROS lowers cell viability by triggering the production of proapoptotic proteinss, whereas a moderate spike in ROS enhances cell survival by inducing MAPK and transcription factors.[183] Many ROS are implicated in painful pathological circumstances, even though it is unknown if a particular ROS subtype is required for central sensitization in neuropathic pain[184.] Thus, radicals are the first species created during the creation of ROS and have the ability to control inflammatory pain.[184] When nitric oxide reacts with extremely high concentrations of SO, stable peroxynitrate molecules are created (NO). The SOD is prevented from conducting its catalytic action by these chemical nitrates. The hydroxyl radical is the most harmful ROS while being unstable[185.] Cyclooxygenase, peroxisomes, endoplasmic reticulum, mitochondria, and inflammatory cytokines are examples of endogenous generators of ROS. Moreover, some examples of external sources of ROS are ultraviolet radiation, air pollution, chemotherapy, cigarette smoke, and ionising sources. Oxidative stress is brought on by the ROS. As a result, activities like protein oxidation, lipid peroxidation, and DNA damage affect physiological performance. Impaired physiological performance is the main cause of random cellular damage and a specific signalling route that also accelerates ageing, causes neurological diseases, and causes cell death.

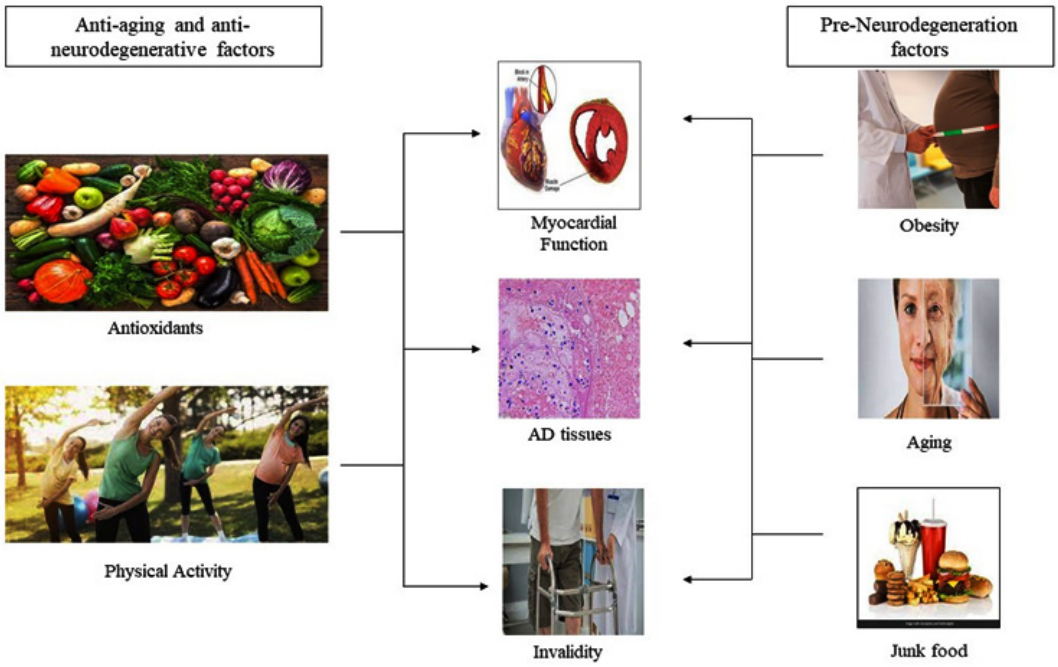


Fig. 3. Pro-neurodegenerative factors balanced by anti-aging and anti-neurogenerative factors 184.

Antioxidants and oxidative stress in neurodegenerative disorders

It is widely recognised that oxidative stress has a role in neurological disorders and the ageing process. By suppressing free radicals and regulating the expression of genes that cause inflammation, ascorbic acid has neuroprotective qualities that reduce neuroinflammation and the accumulation of amyloid-beta peptides. A decrease in the makeup of low-density lipoproteins and an increase in plasma levels of high-density lipoprotein were also linked to ascorbic acid administration. By reducing the conversion of macrophages to foam cells, ascorbic acid treatment may hence reduce atherosclerosis and the related systemic inflammation. Consuming ascorbic acid reduced miR155 levels by 90%, showing that ascorbic acid can reduce inflammation through controlling the levels of miRNA.[186] Curcuma's anti-oxidative effects on synapse-associated proteins were found in an AD animal model (APPswe/PS1dE9 double transgenic mice). The transgenic mice showed reduced PSD95 and Shank1 activity in the CA1 region of the hippocampus. Through altering PSD95 and Shank1 proteins, curcumin consumption may enhance synaptic structure and function[187]. In the CA1 region of the hippocampus, phosphatidylinositol-3 kinase, serine-threonine kinase, and their phosphorylated forms were expressed more, whereas the levels of insulin receptor and insulin receptor substrate-1 were reduced.[187] However, in double transgenic animals, the insulin receptor and insulin receptor substrate 1 were downregulated. The expression of insulin-like growth factor 1, insulin receptor substrate 2, phosphatidylinositol-3 kinase, and their phosphorylated forms all increased.

Relation between stress, tension, hectic lifestyle and neurodegenerative diseases

Because of urbanisation, changing

Table 4. Huntington's Disease

Drug	Description	References
Tetrabenazine	Tetrabenazine was created as part of an attempt to produce simple compounds with reserpine-like antipsychotic effects. It is a high-affinity, reversible inhibitor of monoamine absorption in presynaptic neurons and a modest blocker of D2 dopamine postsynaptic neurons. The medicine was repositioned for diseases like HD, which are typified by aberrant, hyperkinetic, uncontrollable movements, as the chemical's antipsychotic tests were unsatisfactory. Tetrabenazine has never been associated with dyskinetic symptoms, HD making it less risky than dopamine receptor blockers to use in HD.	[47]
Clozapine	Schizophrenia is treated with clozapine, a neuroleptic medication. It has a strong affinity for the D1 and D4 dopamine receptors and a weak antagonistic effect on the D2 dopamine receptors. It was proposed as a useful symptomatic treatment for chorea due to its infrequent extra pyramidal adverse reaction, yet clinical trials yielded mixed findings.	[48]
Olanzapine	The motor and behavioural signs of HD are usually treated with olanzapine, another antipsychotic medication. Despite blocking dopamine D2 receptors, this drug has a strong affinity for serotoninergic receptors.	[49]
Memantine	Alzheimer's disease is managed with a drug called memantine, an analogue of adamantane. It is a non-competitive inhibitor of N-methyl-D-aspartate (NMDA). Excessive NMDA receptor activation results in a significant amount of Ca++ entering the cell, which ultimately causes cell death. Memantine has the ability to block the entry of calcium into neuronal cells, hence avoiding the death of brain cells. Memantine has been investigated for its potential to cure Huntington's disease, and it has been found that it might make neurons less susceptible to glutamate-mediated excitotoxicity.	[50]

lifestyles, and ageing populations, stroke rates are rising globally. In their mid-forties, people who had healthy, low-risk lifestyles, such as stopping smoking, exercising frequently, consuming alcohol in moderation, and keeping a moderate weight, had a decreased incidence of neurodegenerative diseases. Hence, regular exposure to risk factors including stress, inactivity, poor nutrition, obesity, high plasma cholesterol, smoking, drinking, or arterial hypertension may be to blame for the comparatively high incidence of neurodegenerative diseases[188]. One of the main dietary factors associated with a higher risk of atherosclerosis and cerebrovascular disease has been identified

Table 5. Multiple Sclerosis

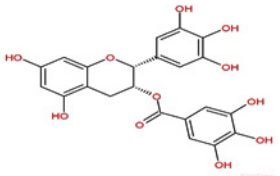
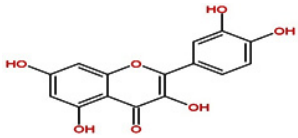
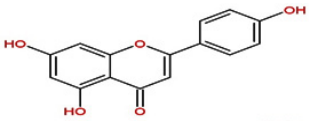
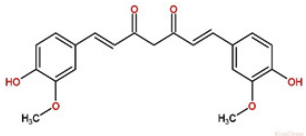
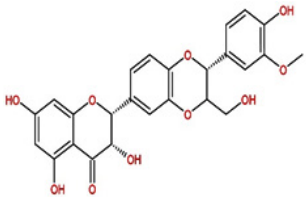
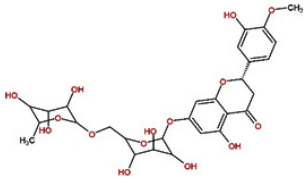
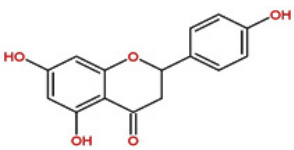
Drug	Description	References
Mitoxantrone	Due to its immunosuppressive properties, which have been related to unanticipated central nervous system reactions T- and Beta-cells to antigens, myelinsheath breakdown induced by macrophages, and axonal lesions, mitoxantrone has also been licenced for the management of MS. Mitoxantrone has the ability to block T-cell activation, limit T-cell and B-cell proliferation, reduce antibody production, and deactivate macrophages. Mitoxantrone was similarly well tolerated.	[51]
Cyclophosphamide	Cyclophosphamide is an alkylating agent that is licenced for the treatment of leukaemia, lymphomas, and breast cancer. It is also used to treat some solid tumours. It is similar to nitrogen mustards, targeting cells that divide quickly, and binds to DNA to stop mitosis and cell division. Cyclophosphamide is a drug used to treat MS because of its ability to act as an immunosuppressive and immunomodulatory agent. It specifically affects T- and B-cells, reducing both humoral and cell-driven immunity. Moreover, cyclophosphamide has been observed to increase the release of anti-inflammatory cytokines in the blood and brain while decreasing the pro-inflammatory T helper 1 cytokines interferon- and interleukin-12. T-lymphocytes' inflammatory behaviour is also altered. Additionally capable of penetrating the blood-brain barrier, cyclophosphamide exerts immunomodulation and immunosuppression, stabilising and delaying the development of sickness. It also has a high bioavailability in the central nervous system (CNS).	[52]
Amiloride	Amiloride is a diuretics medication used to cure and manage high blood pressure and oedema brought on by liver or heart failure. It has been studied for its ability to treat multiple sclerosis neuroprotectivity. Additionally capable of penetrating the blood-brain barrier, cyclophosphamide exerts immunomodulation and immunosuppression, stabilising and delaying the development of sickness. It also has a high bioavailability in the central nervous system (CNS).	[53]
Ibudilast	Ibudilast is a drug that has been approved in various nations to treat both bronchial asthma and cerebrovascular issues. It functions by preventing phosphodiesterases, which are known for their ability to reduce inflammation. It can also disrupt the pathways that produce leukotriene and nitric oxide, both of which have been related to MS. Ibudilast can suppress the release of TNF from microglia and astrocytes in the brain, by reducing neurons destruction. It is beneficial in MS because it can also prevent the death of astrocytes and lessen oligodendrocyte apoptosis and demyelination. At a high dose, Numerous studies stated that it is safe and tolerable, while also slowing the pace of brain shrinkage.	[54]

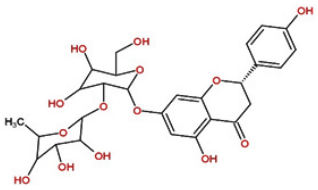
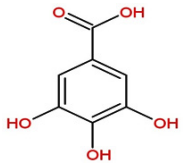
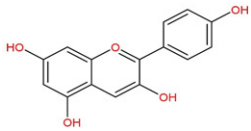
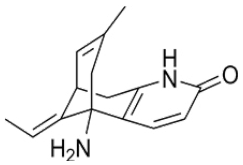
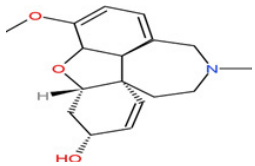
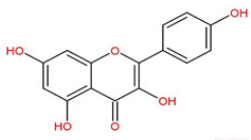
as a high-fat, high-cholesterol diet[189.] Poor eating habits, on the other hand, can aggravate metabolic diseases like high blood pressure, metabolic syndrome, cardiovascular disease, stroke, insulin resistance, and type 2 diabetes (T2DM), which are all brought on by systemic, persistent inflammation, also known as metabolic arthritis or meta-inflammation[190]. Along with cytokines and adipokines, sphingolipids and eicosanoids are hypothesised to contribute to this process by causing negative regulatory reactions in target cells like macrophages[191]. A high income, a shortage of food, dietary preferences, and lifestyle choices are all influences on the energy imbalance that the hypothalamus controls and which can result in weight gain. The hypothalamus functions at the molecular level. O-GlcNAc-transferase regulates body weight by catalysing the transfer of N-acetylglucosamine from uridine-diphosphate to the hydroxyl group of serine or threonine residues in nucleocytoplasmic proteins. O—N-acetylglucosamine transferase was inhibited, although obesity and insulin resistance were increased as a result of a high-fat diet[192]. A high income, a shortage of food, and dietary and lifestyle choices all contribute to an energy imbalance that the hypothalamus controls and can result in weight gain. By catalysing the transfer of -N-acetylglucosamine from uridine-diphosphate—N-acetylglucosamine to the hydroxyl group of serine or threonine residues in nucleocytoplasmic proteins, the hypothalamus O-GlcNAc transferase regulates body weight at the molecular level. O—N-acetylglucosamine transferase was disabled, yet high-fat diets led to a rise in obesity and insulin resistance.[193] An association between the disease and education was discovered in a recent study that examined the effects of 24 modifiable factors on the prevalence of Alzheimer's disease, demonstrating that genetically predicted greater levels of education were associated with fewer incidences of the illness. The following dietary and

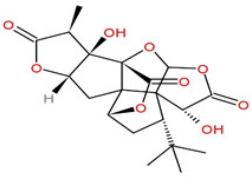
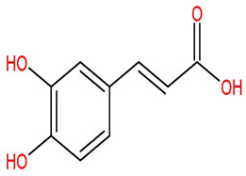
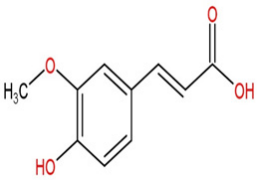
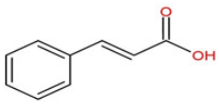
Table 6. Amyotrophic Lateral Sclerosis

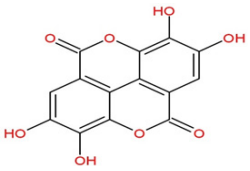
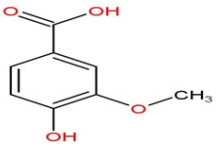
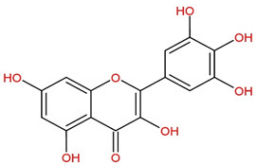
Drug	Description	References
Masitinib	Tyrosine kinase inhibition drugs are used in the treatment of ALS because they may be efficient in combating the disease's abnormal glial cells. Masitinib was found to lessen glial cell activation and boost survival in the relevant rat model. Tyrosine kinase inhibitors are used in the treatment of ALS because they may be effective against the aberrant glial cells that develop in the disease.	[55]
Triumeq®:	An antiretroviral used as an anti-HIV therapy was looked into for the treatment of ALS based on the discoveries that people with ALS have blood serum concentrations of reverse transcriptase comparable to HIV-infected patients and that a human endogenous retrovirus was expressed in the brains of ALS victims.	[56]
Retigabine	Retigabine, an approved anticonvulsant drug, increases the M-current via binding to voltage-gated potassium channels, inducing membrane hyperpolarization. Retigabine has the ability to prolong motor neuron life and diminish excitability, which is helpful in the treatment of ALS because the hyper-excited neurons in this condition fire more frequently than normal, eventually leading to death. This medication is still being tested in clinical trials for the management of ALS.(56)	[56]
Tamoxifen	Antioestrogen medication tamoxifen has been authorised for use in the diagnosis, treatment, and prevention of breast cancer. By chance, this medication was used to treat ALS after it was found that tamoxifen treatment improved neurological symptoms and stabilised the condition in ALS patients with breast cancer. It seems that its neuroprotective properties are related to the inhibition of protein kinase C, which is overexpressed in the spinal cords of ALS patients. Tamoxifen, which has been found to be an autophagy regulator, can alter a proteinopathy that is prevalent in ALS.	[57]

Table 7. List of polyphenols which are already reported with neuroprotective effect

No.	Polyphenols	Source	Structure	Pharmacological Activity
1	Epigallocatechin gallate	Dried leaves of green tea		Anti-oxidative [58], Anti-Inflammatory [59], Anti-cancer [60],
2	Quercetin	fruits, , leaves, seeds, and grains; capers, red onions, and kale, vegetables		Anti-oxidation [61], Anti-inflammatory [62], Anti-aging [63], Neuroprotective [64]
3	Apigenin	parsley, chamomile tea, celery and celeriac,		Anti-Depressant [65], Anti-inflammatory [66], Anti-Amyloidogenic [67], Anti-oxidant [68], Neuroprotective [69], Anti-spasmodic [70], Anti-Allergic [71], Anti-oxidation [72], Anti-inflammatory [73], Anti-dementia [74], Anti-pulmonary fibrosis[75], Anti-tumor [76, 196], Anti-lipidemic [77], Anti-diabetic [78], Immunomodulation [79], Cardiovascular protection [80], Antioxidant [81], Antimicrobial [82], Antiviral [83], and Anti-carcinogenic [84]
4	Curcumin	Curcumin longa		
5	Silymarin	Silybum marianum (L.) Gaertn		
6	Hesperidin	Citrus aurantium L.- Bitter Orange, grapefruit, juice, zanthoxylum gilletii, lemon, lime, agathosma serratifolia, peppermint, petitgrain, orange.		Anti-cancer [85], Anti-oxidant [86], Anti-inflammatory [87], Anti-allergic [88], Anti-diabetic [89], Antihyperlipidemic [90], Antihepatitis [91],
7	Naringenin	Orange, tart cherries, tomatoes, water mint, and Greek oregano, grapefruit, bergamot, chocolate		Anti-cancer [92], Anti-oxidant [93], Anti-allergic [94], Anti-inflammatory [95], Neuroprotective [96], Anti-diabetic [97].

8	Naringin	Grapefruit, Citrus fruit,		Neuroprotective [98], Anti-inflammatory [99], Anti-cancer [100], Anti-oxidant [101], Cardioprotective [102], effects on bone regeneration [103], metabolic abnormalities [104], genetic mutation and CNS diseases [105].
9	Gallic acid	Myriophyllum spicatum (aquatic plant), Microcystis aeruginosa (blue-green alga), Boswellia dalzielii (stem bark), fruits such as strawberries, carob fruit, grapes, bananas, as well as teas, cloves and vinegars Cynomorium coccineum (parasitic plant), Caesalpinia mimosoides (oak species)E		Antioxidant [106], Anti-inflammatory [107], Antineoplastic [108], Gastroprotective [109], neuroprotective [110], metabolic disorders [11], and cardioprotective [112].
10	Pelargonidin	Red geraniums, philodendron, orange coloured flowers of blue pimpernel (Anagallis monelli) red and pink roses, ripe rasberries, strawberriwes, blueberries, blackberries, cranberries, saskatoon berries, plums and pomegranates		Antithrombotic [113], Anti-inflammatory [114], Anti-cancer [115], Anti-oxidative [116], Neuroprotective [117].
11	Huperzine	Firmoss Huperzia serrata H. elmeri, H. carinat, H. aqualupian		Anti-inflammatory [118], Anti-convulsant [119], Neuroprotective [120], Antioxidant [121], Hepatoprotective [122].
12	Galantamine	Bulbs and flowers of Galanthus nivalis, Galanthus caucasicus, Galanthus woronowii. Amaryllidaceae family members such as Narcissus (daffodil), Leucojum aestivum (snowflake), Lycoris radiata (red spider lily)		Neuroprotection [123], Antiapoptotic [124], Antidiabetic [125], Antioxidant [126], Anti-inflammatory [127], Anti-athritic [128].
13	Kaempferol	Pteridophyta, pinophyte and Angiospermae. The various plant such as Coccinia grandis, Aloe vera, Cuscuta chinensis, Glycine max, Hypericum perforatum, Euphorbia pekinensis, Pinus sylvestris, Moringa oleifera, Rosmarinus officinalis Sambucus nigra Toona sinensis		Anti-oxidant [129], Anti-inflammatory [130], Anti-osteoporotic [131], Anti-depressant [132], Anthelmintic [133], Antibacterial [134].

		and llex. Common food such as Apples, grapes, tomatoes, green tea, potatoes, onions, broccoli, Brussels sprouts, squash, cucumbers, lettuce, green beans, peaches, blackberries, raspberries, and spinach are some of the other foods that are commonly eaten.		
14	Ginkgolides	Ginkgo biloba		Antioxidant [135], Antibacterial [136], Anti-inflammatory [137], Neuroprotective [138], anti-ischemic [139], cardioprotective [140].
15	Caffeic acid	Bark of Eucalyptus globulus, Horgenum vulgare (barley grain), Dipsacus asperoides (Herb), Salvinia molesta (freshwater fern), Phellinus linteus (mushroom). Coffee, herbs such as thyme, sage, spearmint. Spices such as Ceylon cinnamon, star anise and sunflower seeds. Red wines, apple sauce, apricots, prunes, black chokeberry, lingonberry, yerba mate. Grain such as barley and rye		Antioxidant [141], Anti-inflammatory [142], Neuroprotective [143], Antidiabetic [144].
16	Ferulic acid	Pectin and lignin, popcorn, bamboo shoots, flaxseed, barley grain, Asterid eudicot, leaves of yacon (Smallanthus sonchifolius), navy bean, Horse grams (Macrotyloma uniflorum). Chinese medicine such as Angelica sinensis, Cimicifuga heracleifolia, ligusticum chuangxiong, Centaurium erythraea. Rice brain oil, breads containing flaxseed, rye breads.		Antioxidant [145], Anti-inflammatory [146], Antiallergic [147], Antimicrobial [148], Antithrombotic [149], Anticarcinogenic [150], Hepatoprotective [151].
17	Cinnamic acid	Oil of cinnamon, balsams such as storax, shea butter.		Antioxidant [152], Antimicrobial [153], Antiinflammation [154], Anticancer [155], Antidiabetic [156], Antidepressant [157], Wound healing [158], Anti-obesity and and cardioprotective [159].

18	Ellagic acid	Oak species such as North American white oak (Quercus alba), European red oak (Quercus robur), Chestnuts, walnuts, pecans, cranberries, raspberries, strawberries, grapes, distilled beverages, peaches and pomegranates.		Antioxidant [160], Anti-inflammatory [161], Neuroprotective [162], Anticancer [163],
19	Vanillic acid	Root of Angelica sinensis, Acai oil derived from the acai palm's fruit		Antioxidant [164], Anti-inflammatory [165], Neuroprotective [166], Antiallergic [167], Cardioprotective [168].
20	Myricetin	Carob fiber, fennel leaves, fresh parsley, dried goji berry, frozen bog blueberry, carob flour, cranberry, raw dock, raw European black currant, crowberry, raw rabbit-eye blueberry, raw leaves sweet potato.		Antioxidant [169], Antibacterial [170], Anticancer [171], Antiviral [172], Anti-inflammatory [173], Antiepileptic [174], Cardioprotective [175], Hepatoprotective [176],

lifestyle factors, as well as cigarette, coca/coffee drinking, and 25(OH) vitamin D levels, were found to be strongly linked with AD. A decreased risk of AD has been associated with higher levels of 25(OH) vitamin D, coffee drinking, and cigarette smoking[194]. An increased risk of dementia and stroke is associated with increased use of artificially sweetened beverages. The risk of dementia and stroke has also been linked to sugary beverages or soft drinks with added sugar[195,196].

DISCUSSION AND CONCLUSION

This paper reviews the major neurodegenerative diseases that affect humans, including psychiatric conditions brought on by ageing and neuro-inflammation, as well as Alzheimer's Disease, Huntington's disease and multiple sclerosis. Neurodegenerative disorders currently have no known cure, and the medications that are available either treat the symptoms or slow the progression of the condition. The World Health Organisation (WHO) predicts that in 20 years, diseases with a focus on motor functions would surpass cancer as the second-leading cause of mortality, behind cardiovascular diseases. This underscores how important it is to treat ND. The majority of the research on neurodegenerative diseases has been conducted on amyotrophic lateral sclerosis, multiple sclerosis, huntington's disease, and Parkinson's disease, which are the focus of this pharmacological review. Polyphenols are micronutrients that occur naturally in plants. They can be found in a variety of foods, including fruits, vegetables, teas, spices, and a number of dietary supplements. There is now research being done on a number of the therapeutic biological effects that polyphenols have. They consist of cardiac protective, neuroprotective, anti-inflammatory, antioxidant, anti-carcinogenic, anti-diabetic, and anti-allergic properties. Reactive oxygen species are the main contributor to neurodegenerative diseases. The excessive creation of free radicals, or ROS, often known as "oxidative stress," has been linked to numerous molecular pathways of neuron and neurovascular injury. Antioxidants are therefore regarded as successful neuroprotection strategies. Neuroprotection has been significantly hampered by the increase in antioxidants' blood-brain barrier penetration. With a better understanding of oxidative pathways, the treatment's efficacy might be increased. Innate factors like ageing, neuroinflammation, brain injury, and oxidative stress can affect neurodegenerative illnesses, as can

lifestyle factors like high-sugar diets, alcohol and tobacco addiction, or high-fat diets. The good news is that calorie restriction, exercise, and a variety of nutrient-rich dietary components, including polyunsaturated fatty acids and antioxidants, can all work together to slow down the ageing process and the onset of neurodegenerative illnesses. So now a days ROS or oxidative stress is major etiological factor for various neurodegenerative diseases for this we have phytochemicals like polyphenols which are already registered with radical scavenging activity so might be they are good alternative in prophylactic manner to synthetic medications to overcome their side effects and ADR.

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Conflict of Interest

The authors declares that they have no conflict of interest.

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