Natural Antioxidant Compounds as Potential Pharmaceutical Tools against Neurodegenerative Diseases

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Review

Natural Antioxidant Compounds as Potential Pharmaceutical Tools against Neurodegenerative Diseases

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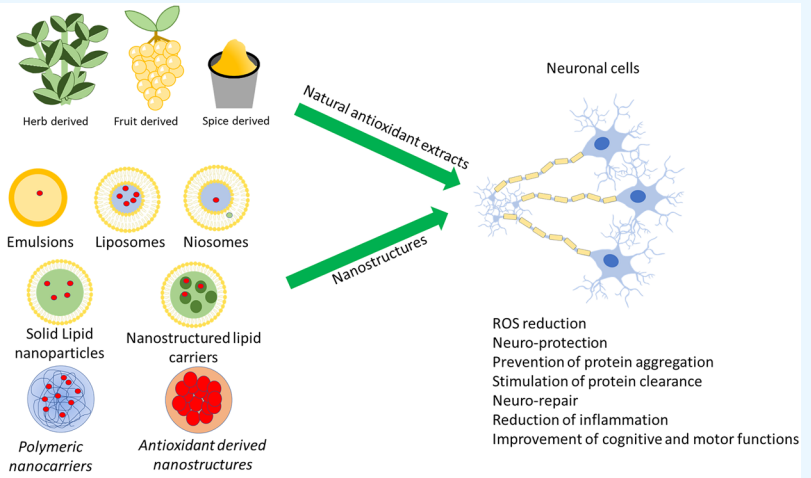

ABSTRACT: Natural antioxidants are a very large diversified family of molecules classified by activity (enzymatic or nonenzymatic), chemical-physical properties (e.g., hydrophilic or lipophilic), and chemical structure (e.g., vitamins, polyphenols, etc.). Research on natural antioxidants in various fields, such as pharmaceutics, nutraceutics, and cosmetics, is among the biggest challenges for industry and science. From a biomedical point of view, the scavenging activity of reactive oxygen species (ROS) makes them a potential tool for the treatment of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia, and amyotrophic lateral sclerosis (ALS). In addition to the purified phytochemical compounds, a variety of natural extracts characterized by a complex mixture of antioxidants and anti-inflammatory molecules have been successfully exploited to rescue preclinical models of these diseases. Extracts derived from *Ginkgo biloba*, grape, oregano, curcumin, tea, and ginseng show multitherapeutic effects by synergically acting on different biochemical pathways. Furthermore, the reduced toxicity associated with many of these compounds limits the occurrence of side effects. The support of nanotechnology for improving brain delivery, controlling release, and preventing rapid degradation and excretion of these compounds is of fundamental importance. This review reports on the most promising results obtained on *in vitro* systems, *in vivo* models, and in clinical trials, by exploiting natural-derived antioxidant compounds and extracts, in their free form or encapsulated in nanocarriers.

INTRODUCTION

The aerobic metabolism in mitochondria produces toxic byproducts such as reactive oxygen species (ROS; e.g., hydroxyl radical OH^-, hydrogen peroxide H_2O_2, superoxide ion O_2^-) and other free radicals.[1] Furthermore, specific genetic disorders (e.g., inherited mitochondrial diseases) and exogenous agents, such as pollutants, radiations, and smoke, increase ROS levels in organisms.[2] An imbalance between antioxidant systems and the production of oxidants, including ROS, is known as oxidative stress. Due to their highly unstable nature, ROS are prone to accept and donate electrons, interact with biological molecules, such as proteins, lipids, DNA, and RNA, and affect their structure/function. At the cell level, consequences of these phenomena include necroptosis and apoptosis induced by mitochondrial, death receptor, and endoplasmic reticulum pathways.[1,3]

The central nervous system (CNS) is extremely sensitive to ROS damage. Indeed, the CNS is a highly metabolically active

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organ that requires high concentrations of O_2.[4] In addition, many neurochemical reactions produce elevated doses of ROS due to the high content of oxidizable substrates, abundant redox-active metals, large dependence on oxidative phosphorylation in neural cells, and scarce levels of endogenous antioxidants.[4] Sustained levels of ROS in the CNS are implicated in the pathogenesis or progression of different neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS).[5]

Antioxidants are agents and molecules which stabilize or deactivate free radicals. Cells are protected by a synergistic combination of different antioxidant systems. Properties of biologically functional antioxidants include the ability to efficiently scavenge free radicals and chelate redox metals at physiologically relevant levels. Organic antioxidants are a very large diversified family of molecules divided into two different categories: endogenous, synthesized by our cells, and exogenous, obtained from the daily diet. Classifications are based on the type of activity (enzymatic or nonenzymatic), chemical-physical properties (e.g., hydrophilic or lipophilic), and chemical structure (e.g., flavonoids, polyphenols, etc.). A variety of phytopharmaceutical extracts show anti-inflammatory, antimicrobial, anti-infective, and antiapoptotic properties.[6] In this review, we report the properties and activities of the most promising natural-derived antioxidants that have been recently exploited to counteract neurodegeneration, highlighting the path from *in vitro* studies and preclinical investigations to the potential exploitation in clinics.

ENDOGENOUS ANTIOXIDANTS AND THEIR ROLE IN THE CNS

Endogenous enzymatic and nonenzymatic defenses protect our CNS from oxidative stress, preventing neurodegeneration and neuroinflammation. Genetic variants affecting functionality or normal expression levels of these biological defenses are frequently associated with the early onset or progression of neuropathological diseases, demonstrating their fundamental role in balancing ROS homeostasis in the CNS and in other highly metabolic organs.[2] In this section, the most relevant endogenous antioxidants and their role in neuroprotection will be reviewed.

Superoxide dismutase (SOD) is a highly efficient intracellular enzymatic antioxidant that catalyzes the dismutation of superoxide anions to molecular oxygen and hydrogen peroxide, according to reaction 1 in Table 1. SOD is expressed in nearly all living cells exposed to oxygen, except for *Lactobacillus plantarum*. Three isoforms of SOD are present in mammals: the cytosolic SOD1, the mitochondrial SOD2, and the extracellular SOD3. They differ not only in the amino acid sequence and intracellular/extracellular localization but also in terms of the reactive core, containing both Cu^{2+} and Zn^{2+} as metal cofactors in SOD1 and SOD3 and Mn^{3+} in SOD2. The decrease in SOD2 function is demonstrated to induce different pathological phenotypes, especially in the brain and in other metabolically active tissues. Animal models characterized by reduced SOD2 expression show neuronal effects also observed in AD, such as high levels of endogenous oxidative stress, hyperphosphorylation of the tau protein, and apoptosis.[7]

Human catalase is an enzyme characterized by a tetramer of four polypeptide chains, is present in the peroxisome of aerobic cells, and catalyzes the conversion of hydrogen peroxide to

Table 1. Main Properties of the Endogenous Antioxidants and Their Role in the CNS

endogenous antioxidant	type	main reactions	localization	role in CNS	ref
SOD	enzymatic	(1) $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$	cytosolic (SOD1), mitochondrial (SOD2), and extracellular (SOD3)	Reduced SOD2 gene dosage induces oxidative stress, tau hyperphosphorylation, and apoptosis.	7
catalase	enzymatic	(2) $2H_2O_2 \rightarrow O_2 + 2H_2O$ (3) $H_2O_2 + H_2R \rightarrow 2H_2O + R$	mainly in peroxisomes but also in cytoplasm and mitochondria	Overexpression of mitochondria-targeted catalase reduces the *Aβ* deposits in AD mice.	10
GPx	enzymatic	(4) $2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$	GPx1 is cytosolic, GPx2 extracellular, GPx3 in plasma, GPx4 nuclear, mitochondrial and cytosolic	GPx has a protective role on PD, AD, cerebral ischemia, and convulsive disorder. Suppression of GPx4 activates ferroptosis.	12−14
GST	enzymatic	conjugation of GSH to xenobiotic substrates	cytosolic, mitochondrial, and microsomal superfamilies	Genetic variants are linked to the onset of ALS, AD, and PD. Higher levels of GSTα-4 show neuroprotection.	15, 16
GSH	nonenzymatic	(5) $2GSH + R_2O_2 \rightarrow GS\text{-}SG + 2ROH$ (6) $GSH + R^{\bullet} \rightarrow 0.5GS\text{-}SG + RH$	intracellular (cytosol, nuclei, and mitochondria) and extracellular	GSH/GS-SG ratio decreases in PD patients. Lower GSH levels are associated with AD and MCI.	18, 19

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Table 2. Type of Exogenous Antioxidants and Main Applications in the Treatment of CNS Diseases

exogenous antioxidant	type	source	functions	exploitation in CNS disorder treatment	ref
ascorbic acid (vitamin C)	vitamins	vegetables and fruits	ROS scavenging, collagen synthesis	neuroprotection	20−24
α-tocopherol	vitamins	vegetable oils, dried fruits, and whole wheat	protection against lipid peroxidation	neuroprotection in PD model, prevention of AD progression	25−28
lutein	carotenoids	fruit, vegetables, and animal fat	protection of retina against light-induced damage	protection against age-related macular degeneration, improved cognitive functions	31−34
zeaxanthin	carotenoids	fruit, vegetables, and animal fat	protection of retina against light-induced damage	protection against age-related macular degeneration	31, 32
gallic acid	polyphenols (phenols)	extracted from gallnuts, tea leaves, olive oil, apples, and grapes	high antioxidant activity	anti-inflammatory, protection against AD and PD, protection against glutamate-induced neurotoxicity	36−41
hydroxycinnamic acids	polyphenols (phenols)	cinnamon oil and balsams	high antioxidant activity	protection against PD, suppression of inflammation mediated by microglia	42−45
resveratrol	polyphenols (phenols)	grapes, raspberries, and blueberries	antioxidant, protection from pathogens	anti-inflammatory and neuroprotective properties, improvement of cognitive and motor functions in HD and MS	46−50
quercetin	polyphenols (flavonoids)	fruits and vegetables	antioxidant and anti-inflammatory	neuroprotection in PD models, improved recovery in ischemia-reperfusion models	53−58
tannins	polyphenols (tannins)	fruits, vegetables, coffee, tea, and wine	no clear function in animals, mostly antioxidant and antimicrobial	inhibition of α-synuclein fibrilization	59, 60

water and molecular oxygen, as indicated in reaction 2 of Table 1. Catalase also promotes the oxidation of toxins by hydrogen peroxide, following reaction 3 of Table 1. It has been estimated that 6 million molecules of hydrogen peroxide are converted to water and oxygen each minute by a single molecule of enzyme. The lack of catalase in genetic mouse models is known to increase the occurrence of pathological conditions of diabetes mellitus, obesity, and fatty liver.[8,9] Concerning the CNS, overexpression of the mitochondria-targeted catalase inhibits the production of the amyloid β (Aβ) deposits and oxidative DNA damage in the AD mouse model carrying a mutant human amyloid precursor protein (APP).[10] Recent studies also reported a significantly higher catalase activity in both the blood and the cerebrospinal fluid of PD, cerebellar ataxia, and motor neuron disease patients.[11]

Glutathione peroxidase (GPx) is a family of eight different isozymes (GPx1−8). GPx converts the hydrogen peroxide or organic peroxide to water or ethanol, acting in combination with the reduced monomeric glutathione (GSH), as shown in reaction 4 of Table 1. In this reaction, GSH oxidizes to glutathione disulfide (GS-SG). GS-SG is then reduced by glutathione reductase to complete the cycle. GPx shows protective effects on various neurodegenerative conditions, including PD, AD, cerebral ischemia, and convulsive disorders.[12] Iron chelators and lipophilic antioxidants inhibit the activity of a specific class of GPx, GPx4, inducing uncontrolled oxidative stress and a regulated mechanism of neuronal death named ferroptosis,[13] known to play a key role in the progression of neurodegenerative diseases.[13,14]

Glutathione-*S*-transferase (GST) is a family of heterogeneous selenium-independent isozymes, which catalyzes the conjugation of GSH to electrophilic centers and detoxifies endogenous compounds. The omega-class GST is the only GST characterized by the presence of cysteine, a polar amino acid residue, in the active site.[15] This property allows for binding and reducing molecules that other GST members can not scavenge. Genetic variants inducing omega-class GST deficiency are linked to the early onset of ALS, AD, and PD.[15] Furthermore, the DA.VRA1 congenic rat strain expressing higher levels of GST-alpha-4 is genetically protected toward the degeneration of dopaminergic neurons of *Substantia nigra* in response to 6-hydroxydopamine (6-OHDA),[16] a toxin commonly used to induce PD models.

GSH is an endogenous nonenzymatic thiolic antioxidant, a tripeptide composed of cysteine, glycine, and glutamate. GSH not only is a cofactor of several antioxidant enzymes but also independently exerts an antioxidant function against free radicals, peroxides, and lipid peroxides in the cytosol, nuclei, and mitochondria, where it is particularly abundant (reactions 5 and 6 of Table 1).[17] In addition, GSH regenerates the exogenous antioxidant vitamins C and E back to their active antioxidant forms. Oxidative stress coupled with mitochondrial dysfunctions in the brain of PD patients decreases the GSH/GSSG ratio, which is considered a marker of the neuroinflammatory and neurodegenerative phenomena occurring in this disease.[18] Recent meta-analyses also highlighted a significant decrease in GSH in both cellular (erythrocytes and leukocytes) and extracellular (plasma and serum) components of AD patients' blood.[19] Reduced cellular, but not extracellular, GSH levels are associated with mild cognitive impairment (MCI).[19]

EXOGENOUS ANTIOXIDANTS

Exogenous antioxidants from fruits, vegetables, and other sources in the daily diet represent an essential supply supporting the endogenous antioxidant system. Exogenous antioxidants are typically grouped into vitamin and nonvitamin ones. In this section, the specific properties of the most relevant exogenous antioxidants and their role in neuroprotection will be reported (Table 2).

Ascorbic acid (the reduced form of vitamin C) is a water-soluble vitamin located in intracellular and extracellular hydrophilic compartments. Ascorbic acid is involved in collagen synthesis and ROS scavenging, especially superoxide.[20] Furthermore, ascorbic acid cooperates with vitamin E for the regeneration of α-tocopherol to prevent lipid oxidations. Vitamin C is an essential nutrient for humans, and it is widely available in vegetables and fruit. Among the main sources are citrus fruits, tomatoes, strawberries, blackcurrants, kiwis, dark leafy vegetables (e.g., broccoli, watercress, and spinach), cabbage, and potatoes. The relevance of this

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vitamin C for the CNS has been demonstrated in the knockout mice for the SVCT2 ascorbate transporter. In this model, the presence of vitamin C was not detected in the brain. The absence of this vitamin induced cerebral hemorrhages and death at postnatal day 1. This phenomenon may be attributed to the impairment of the ascorbate-dependent collagen synthesis that is necessary for both blood vessels and myelin formation.[21] Moreover, The role of ascorbic acid deficiency in AD was studied by Dixit et al. in biogenic mouse models heterozygous for the SVCT2 ascorbate transporter and with human AD mutations in the *APP* presenilin and (*PSEN1*) genes.[22] The deficiency of ascorbic acid in the CNS impairs cognition, enhances amyloid deposition, and increases oxidative stress in both the APP/PSEN1 model and in aging wild-type mice.[22] Furthermore, ascorbic acid displays a neuroprotection role against glutamate-dependent excitotoxicity and neurodegeneration in the developing postnatal rat brain.[23] Concerning HD, interesting work by Castro's group demonstrated that the SVCT2 ascorbate transporter of striatal neurons expressing the mutant huntingtin (*HTT*) gene failed the translocation to the plasma membrane, with consequent impairment of the ascorbic acid uptake.[24] The authors suggested that this phenomenon may produce early metabolic failure and neurodegeneration in HD.

Vitamin E is a class of liposoluble compounds including four tocopherols and four tocotrienols, with a crucial antioxidant function in lipids. Particularly, α-tocopherol is the most active in the protection against lipid peroxidation. After the transfer of hydrogen to a lipid peroxyl radical, conversion of α-tocopherol to the α-tocopherol radical occurs. Vitamin C reduces the α-tocopherol radical to its original form and recovers its scavenging activity.[25,26] Vitamin E can be sourced from many types of food such as vegetable oils (e.g., peanut, sunflower seed, wheat germ, palm, and olive oil), certain dried fruits (e.g., almonds, walnuts, and hazelnuts), and whole wheat. Vitamin E deficiency, although very rare, causes nerve problems. In a recent study by Schirinzi et al. on 100 PD patients and 100 healthy controls, a higher dietary intake of this vitamin was associated with an increase in PD occurrence independent of gender and age, although unrelated to clinical severity.[27] In the same work, the chronic administration of α-tocopherol fully rescued corticostriatal plasticity in the PTEN-induced kinase 1 knockout (PINK1−/−) PD model, highlighting the neuroprotective action of this vitamin. Furthermore, in a double-blind, placebo-controlled, parallel-group, randomized clinical trial (NCT00235716) involving 613 AD patients, participants receiving 2000 IU/day of α-tocopherol showed a significantly slower clinical decline as compared to placebo controls (19% delay in clinical progression per year, as measured by Cooperative Study/Activities of Daily Living).[28]

The most important exogenous nonvitamin antioxidant compounds are carotenoids and polyphenols. Carotenoids are a class of about 850 fat-soluble tetraterpenes biosynthesized by plants, algae, and photosynthetic bacteria. In plants, they are involved in photosynthesis and in the protection from photodamage. In animals, carotenoids can be supplied by various dietary sources (e.g., fruits, vegetables, and animal fat) and are stored in fatty tissues. Carotenoids in animals play different roles, the most relevant including as precursors of vitamin A, photoprotectors, antioxidants, and enhancers of the immunity system.[29] Carotenoids exert their antioxidant properties by scavenging ROS through physical reactions (i.e., accepting thermal energy from singlet oxygen)[30] and chemically by capturing radicals from peroxynitrite and/or nitrogen dioxide and inhibiting the nitration of tyrosine.[29] The macula of the human retina expresses three carotenoids which especially absorb in the blue wavelengths: lutein, zeaxanthin, and meso-zeaxanthin. The first two are obtained from the diet and are the only carotenoids able to cross the blood−brain barrier (BBB), while the last one is synthesized from lutein. Their main role is to protect the retina against light-induced oxidative damage, involved in age-related macular degeneration.[31] Different observational studies demonstrated that the supplemental intake of zeaxanthin and lutein decreases the risk of this pathology.[32] Of these two carotenoids, lutein preferably accumulates in the brain. Independent studies revealed that the dietary assumption of lutein produces cognitive health benefits,[33,34] and the concentration of this carotenoid in the brain is linked to the levels of cognitive functions.[35]

Polyphenols are a heterogeneous group of molecules generated by the secondary metabolism of plants. Chemically, they are characterized by aromatic rings and hydroxyl functions. More than 8000 different phenolic structures are known and grouped into phenols, flavonoids, and tannins.

Phenols display a phenolic ring and an organic carboxylic acid function. Among the phenols, hydroxybenzoic acids, such as syringic, vanillic, and protocatechuic acid, are extracted by angiosperm plants, particularly in acidic fruits. The availability of gallic acid, a highly investigated hydroxybenzoic acid, is more limited (for example, it can be extracted from gallnuts, tea leaves, olive oil, apples, and grapes). Gallic acid is characterized by a molar trolox-equivalent antioxidant activity (TEAC) of about 3-fold that of vitamin E and vitamin C.[36] Furthermore, gallic acid displays remarkable anti-inflammatory properties, as demonstrated in the zymosan-induced acute inflammation mouse model.[37] The multifaceted neuroprotective activities of gallic acid in different preclinical AD and PD models have been recently reviewed by Shabani et al.[38] In addition, this hydroxybenzoic acid has been efficiently exploited to counteract both the glutamate-induced neurotoxicity in primary rat cortex neurons[39] and the 6-OHDA-induced apoptosis in human dopaminergic neural-like cells.[40] Also, gallic acid derivatives such as glucose gallates prevent the isomerization and aggregation of the tau peptide, a hallmark of AD, and promote the dissociation of tau from microtubules.[41]

Another important group is represented by hydroxycinnamic acids, which are the most widely distributed phenolic acids in plants. They are hydroxylated compounds derived from cinnamic acid, a compound that can be obtained from cinnamon oil and balsams like storax. Cinnamic acid is slightly soluble in water and freely soluble in many different organic solvents. It is a typical component of the medicinal herbs in traditional medicine and of the Balsam of Matariyya, which was considered a panacea in Europe and the Middle East during the Middle Ages.[42] Oral administration of the cinnamic acid to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD was able to protect dopaminergic neurons in the substantia nigra and their fibers in the striatum from degeneration.[43] The antidegenerative mechanism involves the activation of the peroxisome proliferator-activated receptor α (PPARα), which is known to play a role in neuroprotection.[44] The research group of Pahan also demonstrated that cinnamic acid exerts an anti-inflammatory role by upregulating the expression of the suppressor of cytokine signaling 3 (SOCS3) in glial cells through the CREB pathway.[45]

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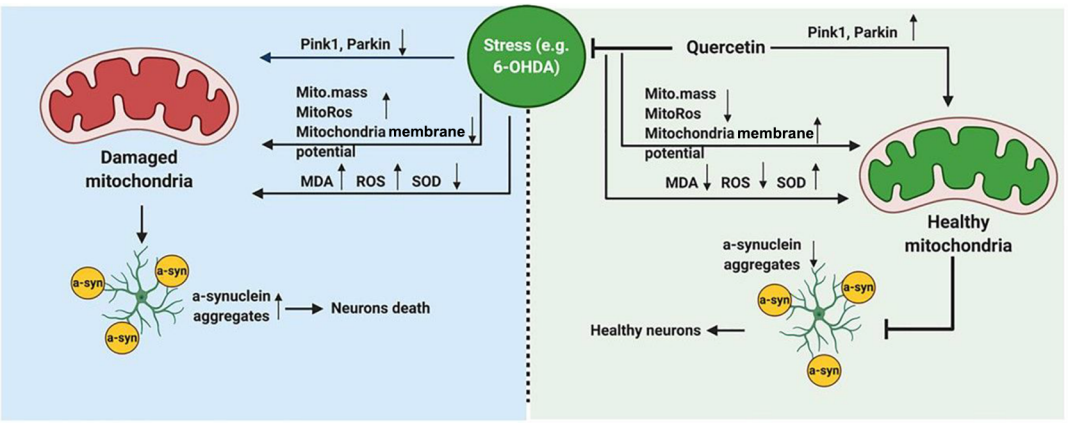

Figure 1. Neuroprotective molecular mechanisms of quercetin in the 6-OHDA-treated PD model. Adapted from ref 53 under a Creative Commons Attribution License (CC BY 3.0).

Resveratrol is another nonflavonoid phenolic acid intensively studied for its antioxidant, anti-inflammatory, and neuroprotective properties.[46,47] It is synthesized by different plants via resveratrol synthase enzyme to protect it from pathogens (e.g., bacteria and mushrooms). Higher concentrations of resveratrol can be found in grapes, raspberries, and blueberries. Biological targets of resveratrol include the quinone oxidoreductase 2 (NQO2), estrogen receptor-β (ER-β), glutathione sulfotransferase-π (GSTP1), carbonyl reductase 1, protein kinase B in interaction with NQO2, and integrin $\alpha V\beta$.[48] The scarce viability of this phenol associated with the oral administration can be attributed to its limited aqueous solubility, with a short half-life (~10 min) that reaches more than 9 h in the case of the sulfate and glucuronide forms.[49] In a recent interesting work by Belmonte-Reche et al., the authors synthesized different *O*-silyl derivatives of resveratrol to improve bioavailability.[50] Moreover, triethylsilyl and ditriisopropylsilyl resveratrol derivatives showed improved anti-inflammatory and neuroprotective capabilities compared to plain resveratrol *in vitro*. Among these synthesized prodrugs, the 3,5-triethylsilyl-4′-(6″-octanoylglucopyranosyl) resveratrol 26 was selected due to its superior biocompatibility and neuroprotection properties in zebrafish embryos. Such a compound reduced the severity of the motor dysfunctions in the 3-nitropropionic acid HD model and decreased the clinical score in an experimental autoimmune encephalomyelitis mouse model of MS.

Flavonoids, the major group of polyphenols, consist of a skeleton of two phenyl rings and one heterocyclic ring. The position of the substituents and the number of hydroxyl groups define their biological properties in terms of antioxidant efficacy and as modulators of enzyme activity.[51] Flavonoids exert their antioxidant function as terminators of radical chains by interacting with free radicals and as metal chelators. Phenolic antioxidants (PhOH) donate a hydrogen atom to radicals to inhibit oxidation. Legumes, medicinal herbs, and a wide range of fruits are rich in flavonoids (they can be extracted from celery, mint, *Ginkgo biloba*, chamomile, red peppers, parsley leaves, and peels of citrus fruits).[52] Leaves, flowers, and fruits contain flavones in the form of glucosides.

Flavonols are the most extensive subgroup of flavonoids in fruits and vegetables. They are constituents of proanthocyanins and are characterized by the presence of a ketone group and a hydroxyl group in position 3 of the C ring, which may also be glycosylated. The most interesting flavonols include quercetin, kaempferol, fisetin, and myricetin. In a recent work, a 20 μM quercetin treatment was demonstrated to improve mitochondrial function, decrease oxidative stress, and decrease α-synuclein protein expression in 6-OHDA-treated PC12 cells.[53] Moreover, oral administration of quercetin also significantly rescued the motor behaviors in the 6-OHDA PD rat model, by inhibiting mitochondrial damage, α-synuclein aggregation, and neuron apoptosis (the biological mechanism is shown in Figure 1).[53] Another independent proof of its neuroprotective role in the 6-OHDA PD rat model has been observed by Ghaffari et al. by using quercetin in the nanocrystal structure to improve its water solubility.[54] The protective mechanism of quercetin toward dopaminergic neurons involves the activation of Akt and protein kinase D1 (PKD1),[55] kinases known to play a key role in cell survival. Quercetin also protects the human brain endothelial cells upon hypoxia and reoxygenation damage[56] and was exploited to improve the functionality of the BBB in cerebral ischemia-reperfusion rat models.[57] The activation of the Wnt signaling and the Sirt1/Nrf2/HO-1 pathway seems to be involved in the quercetin-induced protection mechanism from cerebral ischemia-reperfusion injury.[58]

Other subgroups of flavonoids include the water-soluble anthocyanidin pigments (e.g., cyanidin, malvidin, pelargonidin, and delphinidin), the aromatic colorless flavanones (e.g., naringin, hesperetin, naringenin, and hesperidin), chalcones, isoflavonoids (e.g., daidzein and genistein), and catechins (e.g., epigallocatechin gallate and epicatechin gallate).

Tannins are water-soluble phenolic compounds characterized by high molecular weight (MW between 0.5 and 20 kDa) and by sufficient hydroxyl and carboxyl groups to complex with biomolecules. The peculiar property of tannins is indeed to bind to and precipitate amino acids, proteins, and alkaloids. Tannic acid, ellagic acid, gallic acid, and pyrogallic acid belong to this class, which is commonly presented in both angiosperms and gymnosperms (e.g., food grains, legumes, millets, sorghum, barley, fava beans, peas, pigeon peas, carobs, winged beans, and dry beans contain a large number of tannins). Despite different approaches being used for extracting tannins, solvent extraction with acetone is preferable to reduce tannin−protein complexes.[59] In a recent work by Hideshima et al., a two-step screening approach selected the tannic acid among 1262 FDA-approved small compounds as the most promising molecule in inhibiting the α-synuclein fibrilization without significant toxicity.[60]

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PHYTOPHARMACEUTICAL EXTRACTS

Instead of isolated antioxidant compounds, phytopharmaceutical extracts containing a complex variety of active molecules offer the potential of a multitargeting therapeutic effect. Different extraction techniques, including maceration, percolation, infusion, counter-current extraction, supercritical fluid extraction, phytonics process, pressurized liquid extraction, microwave-assisted extraction, and sonication, have been proposed depending on the type of vegetal source (e.g., leaves, fruits, or spices) and on the properties of the molecules to be extracted. For example, maceration allows for the extraction of caffeic acid, *p*-coumaric acid, ferulic acid, hydroxycinnamic acids, diterpenes, rosmarinic acid, and flavones from leaves of thyme, sage, and marjoram.[61] Monoterpenoids can be efficiently extracted by hydrodistillation of leaves and flowers (e.g., from rosemary and immortelle).[62] Instead, terpenes can be obtained by alcoholic maceration of flowers, seeds, leaves, and roots (e.g., from licorice, coriander, and southern blue gum).[63] However, classical extraction techniques (maceration, percolation, and infusion) usually require large amounts of organic solvents and show a scarce amount of bioactive molecules, and plant wastes can be still found in the extraction solution. In the recent work of Fierascu et al., the innovative and sustainable techniques used for extraction (e.g., sonication, microwaves, and pressurized liquid), the advantages/drawbacks of using these methods, the bioactive compounds extracted, and the extraction yields have been reviewed for different plant materials.[64] In the following part of the section, the phytopharmaceutical extracts used for rescuing *in vitro* and *in vitro* models of neurodegenerative diseases will be reviewed.

Curcumins are hydrophobic polyphenolic compounds extracted from the rhizome of *Curcuma longa*, a herbaceous tuberous plant widespread in South Asia, China, and India, belonging to the family of *Zingiberaceae*.[65] The curcumins comprise diferuloylmethane (curcumin I) and its derivatives, such as the *p*-hydroxycinnamyl-feruloyl-methane (curcumin II) and the *p*,*p*-dihydroxydicinnamoylmethane (curcumin III). The molecular targets of curcumins are quite wide, including growth factors and small noncoding RNAs. Moreover, curcumins are known to affect nucleosome remodeling, DNA methylation, and histone modification.[66] Curcumin I exerts its anti-inflammatory action by inhibiting the cellular signaling of the nuclear factor kappa B (NF-κB).[67] Early preclinical studies on the motor abilities and activity patterns of transgenic PD *Drosophila melanogaster* models treated with curcumin I showed the neuroprotective properties of this polyphenol.[68] The reduced PD mobility defects were associated with the curcumin treatment and accompanied by decreased lipid peroxidation and lower apoptosis levels. Also, curcumin I was demonstrated to improve the PD motor symptoms in the paraquat-induced *Drosophila melanogaster* model of PD.[69] Similarly, curcumin-induced neuroprotective effects have been demonstrated in 6-OHDA PD mouse models.[70,71] Its neuroprotective action on the nigrostriatal pathways of these mice was mediated by α7-nicotinic receptors.[71] Concerning AD, different independent *in vitro* experiments demonstrated that curcumin I binds the Aβ, inhibits the formation of its aggregates, and destabilizes the preformed fibrils.[72] However, its hydrophobic nature, poor bioavailability, rapid metabolism, limited BBB crossing ability, and quick excretion restrict the therapeutic effects of its free orally administered form.[73]

Ginkgo biloba is an ancient and tall Chinese tree (currently widespread throughout the world), belonging to the *Ginkgoaceae* family. *Ginkgo biloba* extract (GbE) is obtained from the dried leaves of the plant and results in a yellow powder. The registered standardized extract of *Ginkgo biloba* leaves EGb 761 is obtained by solid/liquid extraction using aqueous acetone and contains 24% flavonoids (quercetin, isorhamnetin, and kaempferol are the most represented), 6% terpene lactones (3.1% ginkgolides and 2.9% bilobalide), and other molecules (e.g., glucose, proanthocyanidins, and organic acids).[74] Different preclinical works reported protective effects of EGb 761 in cerebral-ischemia models. Interestingly, Xiaomei et al. observed that also long-term pretreatments (lasting 12 months before the injury via middle cerebral artery occlusion) with this extract significantly decrease the ischemia-induced neuronal damage in aged mice (24 months).[75] Specifically, reduced oxidative stress and infarct volume were found in treated mice compared to controls. The effects were associated with inhibition of the ERK activation. Furthermore, the use of EGb 761 in dementia patients has been investigated. A meta-analysis of seven placebo-controlled, randomized, double-blind clinical trials of at least 20 weeks in duration adopting EGb 761 to counteract dementia was carried out by Gauthier and Schlaefke.[74] The effect of 120 mg or 240 mg EGb 761 treatments versus placebo was considered for 2684 patients in total. Change in cognition, activities of daily living, and global rating significantly improved for EGb 761-treated participants compared to the placebo condition. No significant increase in the risk of adverse effects was observed compared to placebo, therefore confirming the good tolerability and efficacy of this extract for patients with dementia.

Grapes from the genus *Vitis* contain anti-inflammatory, antineoplastic, and antiatherosclerotic phytochemicals in their seeds, skins, and, in a lower amount, juice and stems. A large number of compounds can be extracted from grapes, including anthocyanidins, flavonoids (e.g., catechins, quercetin, and rutin), small phenolic acids (e.g., gallic, *p*-cumaric, *o*-cumaric, cinnamic, caffeic, gentisic, syringe, ferulic, and vanillic acids), a variety of polyhydro phenols, chalcones, and stilbenes (e.g., resveratrol), and numerous oligomeric and polymeric derivatives/conjugates with sugars. Depending on the variety of grapes, extraction approach, agricultural practices, and environmental factors (i.e., heat, drought, and light/UV intensity), the concentration and composition of the phenolic compounds are highly variable.[76] Leucoselectp-Phytosome is a standardized grape seed extract rich in oligomeric proanthocyanidins (OPC). Leucoselectp-Phytosome has been tested in a single-blind randomized, placebo-controlled crossover clinical study. An increase in the serum total antioxidant activity (TAG) was observed compared to the control group.[77] In other clinical trials, improvements in cognitive functions were found in elder people treated with grape polyphenol extracts, but no significant effects were found in healthy young adults.[78] Narita et al. demonstrated that polyphenols display high affinity with multiple biomolecules located in neurons of the hippocampus, where they exert remarkable BDNF-independent neuroprotective effects.[79]

Pomegranate (*Punica granatum*) belongs to the family *Punicaceae*, is native from Iran, and is one of the oldest known edible fruits. It contains high amounts of polyphenolic compounds. The soluble polyphenolic content of pomegranate juice is composed of anthocyanins, catechins, ellagic tannins, and gallic and ellagic acids.[80] The variable colors of the

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different pomegranate fruits, ranging from white to dark red, are directly related to the composition of anthocyanins, which changes during the development stages. Pomegranate is composed of three different parts: seeds (which represent 30% in weight of the fruit and are composed of sugars, vitamins, polysaccharides, polyphenols, and minerals), peels (26−30% of the total fruit weight), and juice, which is a good source of minerals like potassium, iron, phosphorus, calcium, manganese. Antioxidant, anti-inflammatory, antihypertensive, and antiatherogenic properties of its juice have been demonstrated in different *in vitro* and *in vivo* models as recently reviewed by Bonesi et al.[81] The neuroprotective effects of the juice are mainly attributed to ellagitannins (especially punicalin, punicalagin, pedunculagin, ellagic acid, and gallic and ellagic acid esters of glucose) and its derived metabolites, which contribute to its antioxidative, anti-inflammatory, and antiapoptotic activity. The oral preadministration of pomegranate extract was standardized to 40% ellagic acid before cerebral ischemia-reperfusion brain injury significantly protects adult rats from neuronal damage in a dose-dependent manner.[82] A reduced level of the nuclear factor NF-κB p65, tumor necrosis factor α, and caspase-3, as well as an increase in interleukin-10 and cerebral ATP, were associated with the neuroprotective antiapoptotic action of the extract.[82] Furthermore, several independent investigations carried out on *in vivo* AD models revealed strong neuroprotective effects of both pomegranate extract and juice.[83,84] In a recent interesting work by Malgorzata et al., administrations of the 6-fold concentrated pomegranate juice (500 mg/kg b.w./day) in rotenone-induced PD models (treatment with juice started 11 days earlier than rotenone administration) significantly decreased α-synuclein aggregation and neural apoptosis, with remarkable improvements on postural stability.[85] The presence of the ellagitannin-derived metabolites in the brain and in the plasma of the animal models was confirmed as well by ultraperformance liquid chromatographic tandem mass spectroscopy.

The culinary herb oregano is characterized by 70 species belonging to the genus *Origanum*, mainly localized in the Mediterranean territory. The most studied properties of oregano are antioxidant, antimicrobial, antispasmodic, and carminative.[86] Both oregano extracts and essential oils show a strong antioxidant and antimicrobial power, due to the high concentrations of the carvacrol and thymol phenols. Oral gavage with carvacrol in rats exposed to propiconazole reduces DNA damage and improves the neurobehavioral effects of this toxin due to its anxiolytic, antioxidant, and antigenotoxic activities.[87]

Leaves of *Camellia sinensis* and, less frequently, of *Camellia taliensis* are used for tea production. Green, oolong, and black tea are different in the method of production/fermentation and in the level of antioxidants, with green tea being the richest in antioxidants when compared to the others.[88] Black tea contains mainly tannins, while green tea contains high concentrations of antioxidant catechins. The red tea from *Camellia sinensis* is obtained from the oxidized bud leaves. The main antioxidant molecules present in green tea are catechin, epicatechin, gallocatechin, epigallocatechin, epigallocatechin-3-gallate, epicatechin-3-gallate, and gallocatechin gallate.[89] As already specified, exogenous antioxidants play an important role in preventing neurodegeneration induced by ischemic stroke. In a recent work, Alexandre et al. investigated the effect of preadministration with red, white, green, and black tea on both oxidative stress and memory loss in an ischemia-reperfusion rat model. Among tea types, only supplementation with green and red teas (the latter obtained from the oxidized bud leaves of *Camellia sinensis*) significantly reduced deficits in object and social recognition memories. Furthermore, only green tea was able to limit the deficits in spatial memory, scavenge the oxidative stress in the hippocampal region, and prevent the morphological alterations induced by a stroke.[90] The more efficient neuroprotective effects of green tea may be attributed to the superior antioxidant capacity of the catechins.

Ginseng (the root of the genus *Panax*) is characterized by the presence of polyphenols, flavonoids, vitamins, and ginsenosides.[91] The latter are a class of bioactive steroid glycosides and triterpene saponins with antimicrobial and antifungal properties produced by *Panax* for defense. The attention of the scientific community has been mainly focused on ginsenoside Rg1, a triterpenoid saponin with neuroprotective properties. Rb1 improves motor deficits in the MPTP mouse model of PD. Moreover, treatments with this saponin prevent PD-associated deficits in spatial memory and learning in the MPTP mice.[92] In the AD mouse models, the pharmacologic targets of Rg1 have been recently investigated by high-throughput metabolomics and include 14 metabolites involved in linoleic acid, arachidonic acid, tryptophan, and sphingolipid metabolism pathways.[93] A recent systematic review by Hai-Yong et al. reported the preclinical studies involving the Rg1 for the treatment of cognitive dysfunctions in AD models.[94] The review included 32 investigations, involving 1643 animals in total. This ginsenoside significantly improved the cognitive functions in most AD models and excluded SAMP8 transgenic mice and chronic stress-induced animals. The combination of the anti-inflammatory and antioxidant properties, together with the synaptic protection capacity of this molecule, seems to be involved in the Rg1-mediated improvement of cognitive behavior. However, it is important to highlight that the probability of publishing investigations with positive outcomes is higher compared to studies with negative or inconclusive results.[95,96] Moreover, although ginseng extracts are commonly used in traditional medicine, to date there is no substantial scientific evidence supporting their effectiveness in treating medical conditions in humans, and the medicinal use of these products is not approved by the FDA.

Finally, naturally derived extracts with neuroprotective activity also include those derived from berries,[97] olives/olive leaves,[98] *Nigella sativa*,[99] and other herbs/fruits.[100,101] However, a lower number of recent publications can be found using such natural sources against neurodegeneration processes, and therefore, a detailed description of their extracts is not the main scope of this review. It is also important to specify that, despite a large number of applications, the FDA approved only two botanical drugs for marketing as prescription drugs: the ointment against papillomavirus-induced external warts based on green-tea-derived catechins (sinecatechins, Veregen),[102] and the crofelemer (Mytesi), an oligomeric mix of randomly arranged catechin, epicatechin, gallocatechin, and epigallocatechin from the latex of the *Croton lechleri* tree used for the symptomatic relief of noninfectious diarrhea in HIV adult patients.[103] The FDA also highlighted the necessity to test botanical drug candidates with well-controlled and adequately designed clinical trials to achieve market approval.

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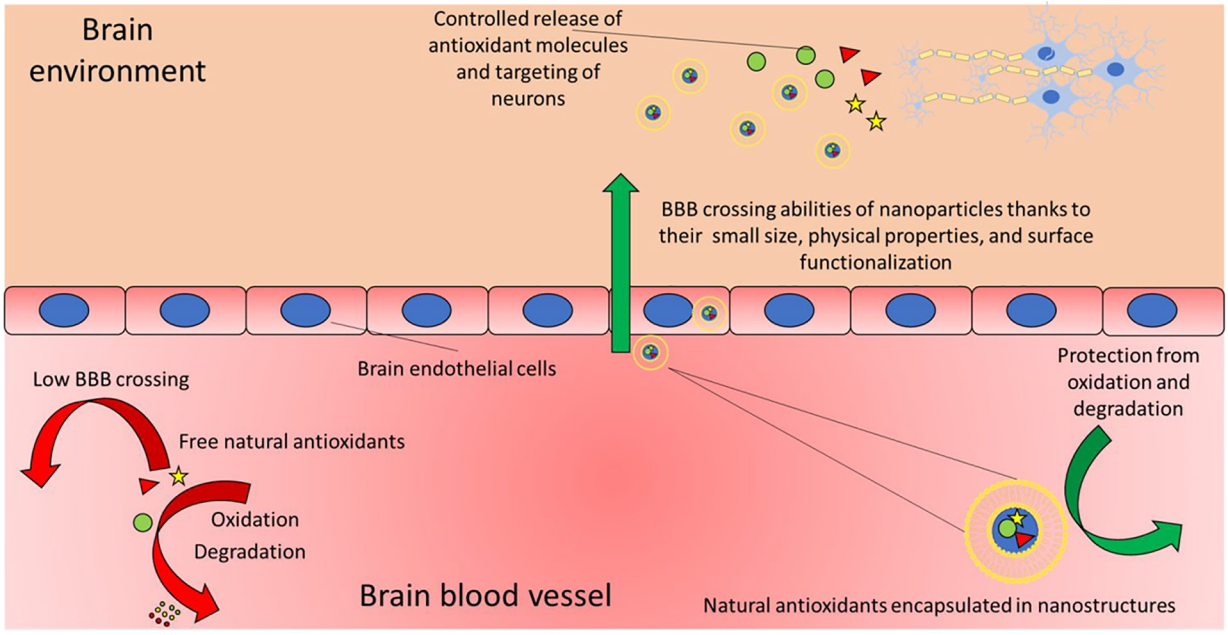

Figure 2. Scheme showing some of the limitations of free antioxidants in comparison to the advantages of nanostructures loaded with antioxidant molecules in the treatment of CNS disorders.

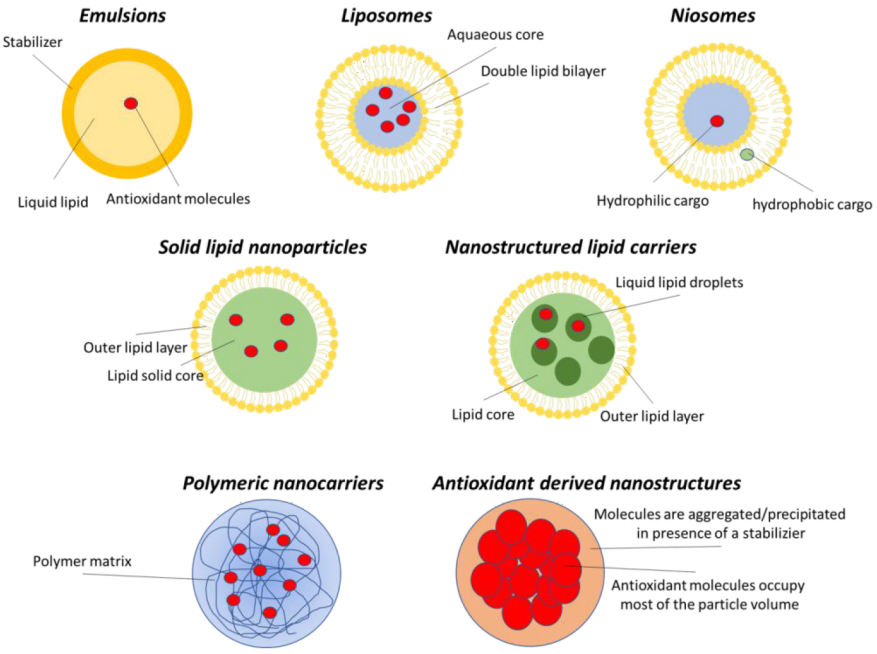

Figure 3. Different classes of nanostructured carriers exploited for improving the bioavailability and the scavenging efficiency of natural antioxidants.

ANTIOXIDANT EXTRACT-LOADED NANOCARRIERS

Despite the great benefits and promising effects of natural antioxidants, their use in CNS treatment is still somewhat limited by their ability to cross the BBB and to reach the brain, their susceptibility to oxidation, and their relatively poor bioavailability.[104] Nanotechnology-based approaches involving the use of nanocarriers to improve the limitations of natural antioxidants (Figure 2) represent one of the most promising tools for the future application of these compounds in clinical trials.[104] The main types of nanocarriers exploited for improving the bioavailability and the efficacy of natural antioxidants are shown in Figure 3. The properties and applications of lipid and polymeric nanostructures loaded with natural antioxidants for applications at the CNS level are summarized in Tables 3 and 4, respectively.

Lipid-based nanocarriers represent one of the most used approaches to improve the bioavailability, targeting, and delivery efficiency of therapeutic molecules. Lipid-based nanostructures offer several advantages over other solutions such as increased biocompatibility, relative easiness of fabrication and functionalization, relatively low cost, and

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Table 3. Examples of Lipid Nanostructures Loaded with Natural Antioxidants along with Their Properties, Fabrication Procedure, and Biomedical Applications

nanostructure	size	preparation method	application	ref
curcumin-loaded lipid-PLGA bubbles	400 nm	double emulsion evaporation	BBB crossing and potential PD treatment	108
curcumin-loaded SLNs	148 nm	hot mixing and homogenization	potential treatment of HD	111
N-trimethyl chitosan surface-modified curcumin loaded SLNs	412.0 ± 79.7 nm	high-shear homogenization and ultrasonication	enhancing curcumin brain delivery	112
curcumin-loaded niosomes	60 to 90 nm	thin-film hydration	improving neural stem cell therapy of TBI	113
Ginko biloba extract-loaded niosomes	141 nm	film dispersion−homogenization	improving oral bioavailability and brain targeting of *Ginko biloba* extract	114
thymoquinone-loaded SLNs	172.1 ± 7.4 nm	hot homogenization	potential treatment of HD	115
green tea polyphenol (−)-epigallocatechin-3-gallate loaded lipid nanoparticles	30 to 80 nm	co-solubilization	potential treatment of AD and HAD	116
lipid emulsion of pomegranate seed oil	180 nm	nanoemulsion by sonication	potential treatment of MS	117
lipid emulsion of pomegranate seed oil	135 ± 12 nm	nanoemulsion by sonication	potential treatment of CJD	118
lipid emulsion of pomegranate seed oil	//	nanoemulsion by sonication	potential treatment of AD	119
lipid core nanocapsules loaded with resveratrol	249 ± 5 nm	interfacial deposition	potential treatment of AD	120
resveratrol and grape extract-loaded SLNs	168 to 189 nm	combination of high-shear homogenization and ultrasonication	potential treatment of AD	121
apolipoprotein E-functionalized and resveratrol-loaded SLNs	155 nm	combination of high-shear homogenization and ultrasonication	improvement of resveratrol brain targeting	122
resveratrol-loaded NLCs	142 nm	high-temperature sonication	potential treatment of ARSACS	123
antitransferrin receptor antibody-functionalized and pomace seed extract-loaded liposomes	133 ± 27 nm	extrusion	enhancement of pomace seed extract BBB crossing and potential PD treatment	124

Table 4. Examples of Polymeric Nanostructures Loaded with Natural Antioxidants, along with Their Properties, Fabrication Procedure, and Biomedical Applications

nanostructure	size	preparation method	application	ref
curcumin-loaded PLGA	150−200 nm	single emulsion-solvent evaporation	potential treatment of AD	125
curcumin nanoparticles	127.0 ± 2.7 nm	antisolvent precipitation approach	potential treatment of intracerebral hemorrhage	126
curcumin-loaded lactoferrin nanoparticles	43−60 nm	sol-oil chemistry and ultrasonication	potential treatment of PD	128
curcumin and curcumin−coumarin hybrid analogue loaded PLGA nanoparticles	141−168 nm	nanoprecipitation	antioxidant effect on SH-SY5Y cells	129
PLGA nanoparticles modified with a BBB-penetrating peptide co-delivering the Aβ generation inhibitor and curcumin	139.8 ± 15.2 nm	emulsion-solvent evaporation	potential treatment of AD	130
curcumin nanoparticles	60−70 nm	antisolvent method	BBB crossing and potential treatment of AD	131
denondrosomal curcumin nanostructures	//	mixing of dendrosomes and curcumin	potential treatment of MS	132
curcumin nanoparticles	10 nm	encapsulation of curcumin in micelles	potential treatment of MS	133
curcumin nanoparticles	10 nm	encapsulation of curcumin in micelles	potential treatment for ALS	134
curcumin-loaded PLGA nanoparticles	80−120 nm	emulsion−diffusion−evaporation method	study of the protective effect of curcumin-loaded PLGA nanoparticles upon SK-N-SH cells	135
thymoquinone-loaded PLGA nanoparticles	97.3 ± 2.0 nm	emulsion solvent evaporation	potential treatment of epilepsy	137
anthocyanin-loaded PLGA-PEG nanostructures	120−165 nm	emulsification-solvent evaporation technique	protective effects against Aβ1−42-induced oxidative stress in SH-SY5Y cell line	140
anthocyanin-loaded PEG-gold nanoparticles	135 ± 5 nm	conjugation of anthocyanin to PEG-gold nanoparticles	potential treatment of AD	141
resveratrol-loaded PLGA-PEG nanostructures	70 nm	nanoprecipitation	protective effects against Aβ1−42-induced oxidative stress in the PC12 cell line	142
white tea extract-loaded PCL and alginate nanostructures	380.8 ± 37.9 nm	nanoprecipitation	white tea extract delivery and controlled release	143
rosmarinic-acid-loaded chitosan nanostructures	300 nm	ionic gelation	delivery of antioxidant rosmarinic acid	145
oregano essential oil-loaded chitosan nanoparticles	40−80 nm	oil-in-water emulsion and ionic gelation	delivery and controlled release of oregano essential oil	146
tannic acid and ferulic acid nanostructures	190−450 nm	flash nanoprecipitation	potential treatment of PD	144

higher affinity for biological structures (e.g., the BBB) due to their lipidic nature.[104] Lipid nanostructures include emulsions, which are liquid droplets of lipids stabilized by surfactants, liposomes, and niosomes, which are lipid vesicles with an

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aqueous core, solid−lipid nanoparticles (SLNs), that are lipid nanostructures characterized by an inner solid core entirely made out of solid lipids, and nanostructured lipid carriers (NLCs) that are characterized by a solid inner lipid core containing droplets of liquid lipids.[104,105] In general, the type of lipid nanostructure is chosen based on the nature of the cargo; in particular, structures characterized by an inner aqueous core are usually used for the delivery of hydrophilic substances, while nanostructures entirely composed of lipids are more efficient as carriers of hydrophobic moieties.[104,106]

Curcumin is one of the most investigated natural antioxidants in biomedical research. This is mainly due to the high potential of curcumin in terms of antioxidant activities, anticancer effects, and neuroprotective and anti-inflammatory capacities.[107,108] However, curcumin also presents severe drawbacks such as its relatively low solubility in water and its inability to cross the BBB in significant quantities.[108−110] To improve curcumin drawbacks, several delivery strategies based on the use of nanostructures have been developed and investigated.[108,111−113] *N*-Trimethyl chitosan (TMC)-functionalized SLNs loaded with curcumin (TMC-SLNs) were for example developed to improve its brain availability. TMC-SLNs of an average diameter of 412.0 ± 79.7 nm were prepared by a combination of shear homogenization and ultrasonication and demonstrated high stability and the ability to improve the curcumin BBB crossing efficiency and brain accumulation.[112] In another study, curcumin-loaded SLNs (C-SLNs) realized with a homogenization procedure and with an average diameter of 148 nm were tested on an *in vivo* model of HD. HD animal models treated with C-SLNs showed a significantly improved mitochondrial activity in striatum cells and a reduction of mitochondrial swelling, lipid peroxidation, and ROS accumulation.[111] An interesting example of lipid nanostructures loaded with curcumin is represented by the work of Yan and colleagues:[108] hybrid nanostructures composed of lipid and polylactic-*co*-glycolic acid (PLGA) and loaded with curcumin (Cur-NPs) were prepared through a double emulsion evaporation process. The obtained nanobubbles, characterized by an average diameter of 436.0 ± 58.3 nm, were administrated to PD animal models. Combining Cur-NBs with a low-intensity focused ultrasound (LIFU), Cur-NBs achieved brain accumulation thanks to the BBB opening action of ultrasound stimulation. Moreover, Cur-NBs were able to release curcumin at the CNS level and to improve the motor functions of the PD animal models.[108]

A particular class of lipid nanostructure is represented by niosomes, which are nonionic surfactant-based vesicles with a structure similar to liposomes. Niosomes can be loaded with both hydrophilic and hydrophobic compounds by exploiting the different characteristics of the various parts of the nanostructure.[105] Narouiepour et al. developed niosomal nanoparticles loaded with curcumin (CM-NS) to enhance the therapeutic potential of stem cell therapy in the treatment of traumatic brain injury (TBI). CM-NS with a diameter ranging from 60 to 90 nm were administrated orally to animal models of TBI subjected to stem cell implantations in the injury site. CM-NS demonstrated the ability to support stem cell therapy efficiency by reducing inflammation and brain edema and improving the overall motor activity of animals.[113] An interesting example of the application of niosomes is the use of *Ginko biloba* (GbE) extract-loaded niosomes (average diameter 141 nm), realized through a dispersion−homogenization procedure, able to cross the BBB and deliver GbE to the brain.[114]

Thymoquinone is an analgesic antioxidant phytochemical compound found in *Nigella sativa* and *Monarda fistulosa*, able to indiscriminately bind many different proteins (pan-assay interference compound). SLNs loaded with thymoquinone (TQ-SLNs) have been used as a countermeasure in an *in vivo* model of HD obtained using the mitochondrial complex-II inhibitor nitropropionic acid (3-NP). In particular, TQ-SLNs were obtained through a process of hot homogenization with an average size of 172.1 ± 7.4 nm. TQ-SLNs showed the ability to prevent the damages induced by 3-NP treatment, preventing the histopathological alterations caused by the increased oxidative stress caused by the toxin administration.[115] Smith et al. developed nanolipid particles loaded with green-tea-derived polyphenol (−)-epigallocatechin-3-gallate (EGCG) as a potential treatment for both AD and HIV-associated dementia (HAD).[116] In their work, they developed relatively small nanostructures with a size ranging from 30 to 80 nm through a cosolubilization methodology. The obtained nanostructures were able to significantly increase the bioavailability of EGCG compared to the normal administration of non-nanostructured polyphenol.[116]

An innovative approach consists of the formation of nanodroplets of pomegranate seed oil named Nano-PSO. These nanodroplets were obtained through a combination of stirring and sonication combining Tween 80, glyceryl monooleate, and glycerol. The obtained nanostructures, of an approximative size of 180 nm, showed interesting antioxidant activity, being able to reduce demyelination and oxidation of lipids on *in vivo* models of MS.[117] Nano-PSO of approximately 135 nm demonstrated the ability to prevent the oxidation and the consequent neuronal loss in the brain of TgMHu2ME199K mice, an animal model of the Creutzfeldt Jacob disease (CJD). Interestingly, the treatment with Nano-PSO did not cause any prevention or reduction of the prion accumulation typical of CJD, acting mainly on the reduction of lipid oxidation at the brain level.[118] Nano-PSO also demonstrated the ability to prevent Aβ accumulation in the brain of AD animal models, suggesting the possibility to utilize Nano-PSO and other nanostructure derivatives of pomegranate seed oil against AD.[119]

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound commonly present in the human diet, particularly in grapes and grape derivatives such as red wine. In recent years, the development of resveratrol-loaded nanostructures to achieve brain targeting has been investigated due to the pharmacological potential of resveratrol as an antioxidant and anti-inflammatory compound.[120] In one such approach lipid-core nanocapsules of approximately 249 ± 5 nm loaded with resveratrol (RSV-LPCs) were obtained through interfacial polymer deposition and tested on an animal model of AD. RSV-LPCs proved to be able to counteract the neuronal impairments caused by the treatment with Aβ1−42, improving memory function and reducing synaptic damage.[120] In a similar approach, Loureiro et al. developed SLNs loaded with resveratrol and grape extract and functionalized with an antitransferrin receptor monoclonal antibody (OX26 mAb) through a combination of ultrasonication and high-pressure homogenization. The obtained nanostructures, with a size ranging from 168 to 189 nm depending on synthesis parameters, demonstrated an improved ability to cross an *in vitro* model of the BBB and enhanced inhibitory activity against

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the Aβ.[121] Other strategies to achieve resveratrol BBB crossing include the encapsulation of resveratrol inside SLNs functionalized with apolipoprotein E (average size 150 nm), a protein able to target the LDL receptors overexpressed by brain endothelial cells and enhance brain targeting.[122] Lastly, nanostructured lipid carriers loaded with resveratrol (Res-NLCs) of approximately 142 nm, obtained through high-temperature ultrasonication, were tested on fibroblasts derived from patients affected by autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). Res-NLCs demonstrated the ability to reduce ROS accumulation and elicit an anti-inflammatory activity on ARSACS patient-derived cells, suggesting the possibility to exploit these nanostructures as a countermeasure for the pathological hallmarks typical of the disease.[123]

In a work recently published by our group, we proposed the preparation of liposomes loaded with polyphenol-rich grape pomace extracts (ext-LSs) as a potential treatment of PD. In our work, liposomes with an average diameter of 133.0 ± 27.0 nm realized through a coextrusion method were functionalized with an antitransferrin receptor antibody. The obtained ext-LSs showed the ability to cross an *in vitro* model of the BBB and to counteract some common features of PD in a rotenone-based *in vitro* model of the disease. In particular, ext-LSs were able to reduce ROS accumulation, apoptosis, and α-synuclein accumulation in neuronal-like cells treated with rotenone.[124]

Despite the advantages presented by lipid nanostructures, other approaches to manipulate the biodistribution and enhance the properties of natural antioxidants are described in the literature. Polymer-based nanostructures are a widely used and studied class of nanomaterials commonly exploited as nanocarrier systems. Similar to what has been previously discussed concerning lipid-based nanostructures, curcumin is once again one of the most studied natural antioxidants as cargo for nanocarriers.[125−135] The FDA-approved copolymer PLGA has been a widely used base for polymeric nanostructures loaded with curcumin due to its high biocompatibility and biodegradability.[136] Some examples of curcumin-loaded PLGA nanostructures include nanoparticles able to prevent ROS accumulation in the SK-N-SH cell line,[135] neuron targeting PLGA nanoparticles with antioxidant and antiamyloid properties,[125] and curcumin-loaded PLGA nanostructures cofunctionalized with a BBB targeting peptide and the Aβ generation inhibitor S1 (PQVGHL peptide), able to attenuate the behavioral and neuropathological feature of AD in animal models.[130] In an interesting work, Quezada et al. describe the synthesis of curcumin−coumarin hybrids and their loading in PLGA nanostructures. The obtained hybrid-loaded PLGA nanoparticles demonstrated the ability to prevent ROS accumulation in the SH-SY5Y cell line.[129] Lactoferrin-based nanostructures have also been proposed as a potential delivery system for curcumin. In particular, lactoferrin-loaded nanostructures obtained through sol-oil chemistry with an average diameter of 43−60 nm were employed as a countermeasure for ROS accumulation in a rotenone-based *in vitro* PD model.[128] One of the most promising approaches involving the use of curcumin is represented by the exploitation of nanostructures composed mostly of curcumin, commonly referred to as "nanocurcumin".[126,131−134] Nanocurcumin is commonly obtained through precipitation methods, usually in the presence of stabilizers such as polyethylene glycol (PEG)[126] or polyvinylpyrrolidone (PVP).[131] Nanocurcumin has shown potential for the treatment of neurological diseases not only in animals (such as on *in vivo* models of MS[132]) but also even in clinical trials.[133,134] The safety of nanocurcumin has been tested on patients affected by neurological diseases such as ALS, in which the administration of nanocurcumin did not cause any serious adverse effects.[134] Moreover, in other trials on human subjects, the administration of nanocurcumin to MS patients caused a significant downregulation of the expression levels of mRNA involved in neuro-inflammatory processes.[133]

Despite the attention given to curcumin, other natural antioxidants have also been studied as a cargo of polymeric nanostructures for the potential treatment of CNS diseases. For example, thymoquinone-loaded PLGA nanostructures (THQ-PLGA-NPs) have been proposed as a strategy to improve the brain accumulation of THQ. In particular, various nanoformulations of THQ-PLGA-NPs were realized through an emulsion solvent evaporation method and administrated to *in vivo* epilepsy models. The treated epilepsy animal models showed an enhanced accumulation of THQ at the brain level and an improvement in terms of seizure events.[137]

Anthocyanins are a class of flavonoids with promising antioxidant, anti-inflammatory, and neuroprotective effects.[138,139] However, anthocyanins are also highly unstable, due to their tendency to be oxidized, causing reduced biological activities.[140] To overcome these limitations, several approaches have been proposed involving the use of nanocarriers. For example, one strategy described in the literature involves the encapsulation of anthocyanins into PLGA-PEG nanoparticles (PLGA-PEG-NPs) through a solvent evaporation technique. The obtained anthocyanin-loaded PLGA-PEG-NPs of approximately 165 nm showed enhanced antioxidant properties compared to free anthocyanins, being able to prevent the toxicity induced by Aβ treatment on SH-SY5Y, acting as antioxidant, antiapoptotic, and anti-inflammatory agents.[140] In another approach, anthocyanins were conjugated to polyethylene glycol-gold nanoparticles (PEG-AuNPs).[141] The obtained PEG-AuNPs, of about 135 nm in diameter, showed once again interesting effects upon some of the common hallmarks of AD, being able to inhibit apoptosis and neurodegeneration in Aβ1-42-treated AD animal models.[141]

Polymeric nanocarriers have been exploited also for the delivery of the previously discussed resveratrol. In particular, Lu and colleagues were able to obtain resveratrol-loaded polymeric nanostructures composed of polycaprolactone (PCL) and PEG of approximately 70 nm in diameter through a coprecipitation synthesis method. The obtained nanostructures showed neuroprotective effects being able to reduce oxidative stress and caspase-3 activation in PC 12 cells caused by Aβ treatment.[142] Sanna et al. proposed a method for the encapsulation of white tea extracts in PCL and alginate nanoparticles.[143] The authors were able to obtain nanostructures of approximately 380.8 ± 37.9 nm average diameter through a nanoprecipitation method. The obtained nanostructures demonstrated good stability, high antioxidant capacity, and the ability to release tea extract in a controlled manner.[143]

Lastly, tannic-acid-based nanoparticles have also been proposed as antioxidant nanostructures for the treatment of chronic oxidative stress. In particular, tannic acid nanoparticles obtained through flash nanoprecipitation in the presence of ferulic acid with an adipic acid linker (FAA) were able to prevent αSYN fibrillization, reduce αSYN accumulation, and

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counteract inflammation, ROS, and NO production in microglial cells.[144]

CONCLUSIONS

Among the naturally derived antioxidant compounds, the most encouraging results in counteracting deficits caused by neurodegenerative diseases have been so far obtained by using epigallocatechin gallate.[106] This catechin from green tea is able to efficiently inhibit the progression of Alzheimer's disease symptoms in young adults with Down's syndrome (NCT01699711).[147] Clinical investigations involving a larger cohort of patients will be needed to evaluate the antidegenerative and neuroprotective effects of resveratrol (NCT00678431),[148] despite that its brain availability and antineuroinflammatory effects have already been demonstrated in humans (NCT01504854).[149] Instead, no clinical efficacy was demonstrated when using vitamin E (NCT00040378) and oral curcumin (NCT00099710) for the treatment of Alzheimer's disease symptoms. These negative results may be attributed to the limited bioavailability of these compounds, scarce brain targeting, or fast degradation. Therefore, future works should be directed toward the modification and nanoencapsulation of these molecules to protect them from oxidation in the blood and facilitate their release in the brain.[150]

Altogether, we believe that epigallocatechin-gallate and resveratrol are two naturally derived compounds that may have a clinical impact in the medium-/long-term for the treatment of CNS diseases due to their strong antioxidant and anti-inflammatory activities and thanks to the promising results demonstrated in clinical trials by using their free form. However, alternative administration routes (e.g., intranasal) should be tested to promote the accumulation of these antioxidants in the CNS.

Regarding antioxidant nanoformulations, clinical trials are very limited, and further in-depth preclinical investigations will be required to appropriately design efficient and safe nanomedicines for these applications, especially focusing on the targeted delivery of the cargo in the diseased CNS regions. However, recent clinical trials using nanocurcumin (Sinacurcumin) showed promising results in decreasing neuroinflammation in patients with multiple sclerosis (NCT03150966). Compared to the free form of curcumin, curcumin in nanomicelles shows a remarkably higher solubility, and therefore, an improved biodistribution is guaranteed. This may explain the different outcomes obtained by using the molecular and nanomicellar forms of curcumin in clinical trials. Finally, among phytopharmaceutical extracts, the standardized EGb 761 formulation from *Ginkgo biloba* leaves showed good efficiency and no significant risks of adverse effects in dementia patients, as demonstrated by meta-studies involving seven well-controlled clinical trials.[74] Finally, grape seed extracts showed a role in improving cognitive functions in elderly people (NCT03526406),[78] but further studies with standardized grape extracts on patients with CNS diseases will be required to verify their actual potential in clinics.

CNS is highly metabolically active, extremely sensitive to ROS damage, and prone to develop degenerative conditions attributed to or associated with oxidative stress. Natural product-derived molecules and extracts reported in this review show a series of properties potentially useful for protecting CNS from neurodegeneration, including antioxidant capacity, anti-inflammatory functions, antiaggregation activity toward misfolded proteins, antiferroptosis, and antiapoptotic roles. The difficulty to cross the BBB and reach specific CNS regions, the susceptibility to oxidation, and the relatively poor bioavailability represent the main limitations to their actual exploitation in the free-molecule forms. The recent development of nanomedicine, especially in the preparation of brain-targeting nanocarriers encapsulating molecules with different chemical-physical properties, promises the realistic use of these active principles in the treatment of CNS pathologies. We therefore expect a substantial increase in clinical interest toward these antioxidant nanoformulations. To achieve market approval, however, full compliance with the indications of the regulatory agencies, including adequately designed and well-controlled clinical trials, will be necessary.

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Notes

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REFERENCES

(1) Lee, Y. M.; He, W.; Liou, Y. C. The Redox Language in Neurodegenerative Diseases: Oxidative Post-Translational Modifications by Hydrogen Peroxide. *Cell Death Dis.* **2021**, *12* (1), 1−13.

(2) Hayashi, G.; Cortopassi, G. Oxidative Stress in Inherited Mitochondrial Diseases. *Free Radic. Biol. Med.* **2015**, *88*, 10.

(3) Redza-Dutordoir, M.; Averill-Bates, D. A. Activation of Apoptosis Signalling Pathways by Reactive Oxygen Species. *Biochim. Biophys. Acta - Mol. Cell Res.* **2016**, *1863* (12), 2977−2992.

(4) Clarke, D. D.; Sokoloff, L. Regulation of Cerebral Metabolic Rate. In *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*; Siegel, G. J., Agranoff, B. W., Albers, R. W., Fisher, S. K., Uhler, M. D., Eds.; Lippincott-Raven: Philadelphia, 1999.

(5) Liu, Z.; Zhou, T.; Ziegler, A. C.; Dimitrion, P.; Zuo, L. Oxidative Stress in Neurodegenerative Diseases: From Molecular Mechanisms to Clinical Applications. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 1.

(6) Rehman, M. U.; Wali, A. F.; Ahmad, A.; Shakeel, S.; Rasool, S.; Ali, R.; Rashid, S. M.; Madkhali, H.; Ganaie, M. A.; Khan, R. Neuroprotective Strategies for Neurological Disorders by Natural Products: An Update. *Curr. Neuropharmacol.* **2019**, *17* (3), 247−267.

(7) Dias-Santagata, D.; Fulga, T. A.; Duttaroy, A.; Feany, M. B. Oxidative Stress Mediates Tau-Induced Neurodegeneration in Drosophila. *J. Clin. Invest.* **2007**, *117* (1), 236.

(8) Góth, L.; Nagy, T. Acatalasemia and Diabetes Mellitus. *Arch. Biochem. Biophys.* **2012**, *525* (2), 195−200.

(9) Heit, C.; Marshall, S.; Singh, S.; Yu, X.; Charkoftaki, G.; Zhao, H.; Orlicky, D. J.; Fritz, K. S.; Thompson, D. C.; Vasiliou, V. Catalase Deletion Promotes Prediabetic Phenotype in Mice. *Free Radic. Biol. Med.* **2017**, *103*, 48−56.
(10) Mao, P.; Manczak, M.; Calkins, M. J.; Truong, Q.; Reddy, T. P.; Reddy, A. P.; Shirendeb, U.; Lo, H. H.; Rabinovitch, P. S.; Hemachandra Reddy, P. Mitochondria-Targeted Catalase Reduces Abnormal APP Processing, Amyloid β Production and BACE1 in a Mouse Model of Alzheimer's Disease: Implications for Neuroprotection and Lifespan Extension. *Hum. Mol. Genet.* **2012**, *21* (13), 2973−2990.
(11) Pandey, S.; Singh, B.; Yadav, S. K.; Mahdi, A. A. Novel Biomarker for Neurodegenerative Diseases- Motor Neuron Disease (MND), Cerebellar Ataxia (CA) and Parkinson's Disease (PD). *Clin. Chim. Acta* **2018**, *485*, 258−261.
(12) Sharma, G.; Shin, E. J.; Sharma, N.; Nah, S. Y.; Mai, H. N.; Nguyen, B. T.; Jeong, J. H.; Lei, X. G.; Kim, H. C. Glutathione Peroxidase-1 and Neuromodulation: Novel Potentials of an Old Enzyme. *Food Chem. Toxicol.* **2021**, *148*, 111945.
(13) Song, X.; Long, D. Nrf2 and Ferroptosis: A New Research Direction for Neurodegenerative Diseases. *Front. Neurosci.* **2020**, DOI: 10.3389/fnins.2020.00267.
(14) Liu, J.; Bandyopadhyay, I.; Zheng, L.; Khdour, O. M.; Hecht, S. M. Antiferroptotic Activity of Phenothiazine Analogues: A Novel Therapeutic Strategy for Oxidative Stress Related Disease. *ACS Med. Chem. Lett.* **2020**, *11* (11), 2165−2173.
(15) Board, P. G. The Omega-Class Glutathione Transferases: Structure, Function, and Genetics. *Drug Metab. Rev.* **2011**, *43* (2), 226−235.
(16) Jewett, M.; Jimenez-Ferrer, I.; Swanberg, M. Astrocytic Expression of GSTA4 Is Associated to Dopaminergic Neuroprotection in a Rat 6-OHDA Model of Parkinson's Disease. *Brain Sci.* **2017**, *7* (7), 73.
(17) Valko, M.; Rhodes, C. J.; Moncol, J.; Izakovic, M.; Mazur, M. Free Radicals, Metals and Antioxidants in Oxidative Stress-Induced Cancer. *Chem. Biol. Interact.* **2006**, *160* (1), 1−40.
(18) Bjørklund, G.; Peana, M.; Maes, M.; Dadar, M.; Severin, B. The Glutathione System in Parkinson's Disease and Its Progression. *Neurosci. Biobehav. Rev.* **2021**, *120*, 470−478.
(19) Chen, J. J.; Thiyagarajah, M.; Song, J.; Chen, C.; Herrmann, N.; Gallagher, D.; Rapoport, M. J.; Black, S. E.; Ramirez, J.; Andreazza, A. C.; Oh, P.; Marzolini, S.; Graham, S. J.; Lanctôt, K. L. Altered Central and Blood Glutathione in Alzheimer's Disease and Mild Cognitive Impairment: A Meta-Analysis. *Alz. Res. Ther.* **2022**, *14* (1), 1−17.
(20) Traber, M. G.; Stevens, J. F. Vitamins C and E: Beneficial Effects from a Mechanistic Perspective. *Free Radic. Biol. Med.* **2011**, *51* (5), 1000.
(21) Sotiriou, S.; Gispert, S.; Cheng, J.; Wang, Y.; Chen, A.; Hoogstraten-Miller, S.; Miller, G. F.; Kwon, O.; Levine, M.; Guttentag, S. H.; Nussbaum, R. L. Ascorbic-Acid Transporter Slc23a1 Is Essential for Vitamin C Transport into the Brain and for Perinatal Survival. *Nat. Med.* **2002**, *8* (5), 514−517.
(22) Dixit, S.; Bernardo, A.; Walker, J. M.; Kennard, J. A.; Kim, G. Y.; Kessler, E. S.; Harrison, F. E. Vitamin C Deficiency in the Brain Impairs Cognition, Increases Amyloid Accumulation and Deposition, and Oxidative Stress in APP/PSEN1 and Normally Aging Mice. *ACS Chem. Neurosci.* **2015**, *6* (4), 570−581.
(23) Shah, S. A.; Yoon, G. H.; Kim, H. O.; Kim, M. O. Vitamin C Neuroprotection against Dose-Dependent Glutamate-Induced Neurodegeneration in the Postnatal Brain. *Neurochem. Res.* **2015**, *40* (5), 875−884.
(24) Acuña, A. I.; Esparza, M.; Kramm, C.; Beltrán, F. A.; Parra, A. V.; Cepeda, C.; Toro, C. A.; Vidal, R. L.; Hetz, C.; Concha, I. I.; Brauchi, S.; Levine, M. S.; Castro, M. A. A Failure in Energy Metabolism and Antioxidant Uptake Precede Symptoms of Huntington's Disease in Mice. *Nat. Commun.* **2013**, DOI: 10.1038/ncomms3917.
(25) Chan, A. C. Partners in Defense, Vitamin E and Vitamin C. *Can. J. Physiol. Pharmacol.* **1993**, *71* (9), 725−731.
(26) Huang, H. Y.; Appel, L. J.; Croft, K. D.; Miller, E. R.; Mori, T. A.; Puddey, I. B. Effects of Vitamin C and Vitamin E on in Vivo Lipid Peroxidation: Results of a Randomized Controlled Trial. *Am. J. Clin. Nutr.* **2002**, *76* (3), 549−555.
(27) Schirinzi, T.; Martella, G.; Imbriani, P.; Di Lazzaro, G.; Franco, D.; Colona, V. L.; Alwardat, M.; Salimei, P. S.; Mercuri, N. B.; Pierantozzi, M.; Pisani, A. Dietary Vitamin E as a Protective Factor for Parkinson's Disease: Clinical and Experimental Evidence. *Front. Neurol.* **2019**, *10*, 148.
(28) Dysken, M. W.; Sano, M.; Asthana, S.; Vertrees, J. E.; Pallaki, M.; Llorente, M.; Love, S.; Schellenberg, G. D.; McCarten, J. R.; Malphurs, J.; Prieto, S.; Chen, P.; Loreck, D. J.; Trapp, G.; Bakshi, R. S.; Mintzer, J. E.; Heidebrink, J. L.; Vidal-Cardona, A.; Arroyo, L. M.; Cruz, A. R.; Zachariah, S.; Kowall, N. W.; Chopra, M. P.; Craft, S.; Thielke, S.; Turvey, C. L.; Woodman, C.; Monnell, K. A.; Gordon, K.; Tomaska, J.; Segal, Y.; Peduzzi, P. N.; Guarino, P. D. Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease: The TEAM-AD VA Cooperative Randomized Trial. *JAMA* **2014**, *311* (1), 33−44.
(29) Maoka, T. Carotenoids as Natural Functional Pigments. *J. Nat. Med.* **2020**, *74* (1), 1−16.
(30) Britton, G. Carotenoids, Vol. 4: Natural Functions. In *Carotenoids*; Britton, G.; Liaaen-Jensen, S.; Pfander, H., Eds.; Birkhäuser, 2008.
(31) Krinsky, N. I.; Landrum, J. T.; Bone, R. A. Biologic Mechanisms of the Protective Role of Lutein and Zeaxanthin in the Eye. *Annu. Rev. Nutr.* **2003**, *23*, 171−201.
(32) Mares-Perlman, J. A.; Millen, A. E.; Ficek, T. L.; Hankinson, S. E. The Body of Evidence to Support a Protective Role for Lutein and Zeaxanthin in Delaying Chronic Disease. Overview. *J. Nutr.* **2002**, *132* (3), 518S.
(33) Johnson, E. J.; McDonald, K.; Caldarella, S. M.; Chung, H. Y.; Troen, A. M.; Snodderly, D. M. Cognitive Findings of an Exploratory Trial of Docosahexaenoic Acid and Lutein Supplementation in Older Women. *Nutr. Neurosci.* **2008**, *11* (2), 75−83.
(34) Morris, M. C.; Evans, D. A.; Tangney, C. C.; Bienias, J. L.; Wilson, R. S. Associations of Vegetable and Fruit Consumption with Age-Related Cognitive Change. *Neurology* **2006**, *67* (8), 1370−1376.
(35) Johnson, E. J.; Vishwanathan, R.; Johnson, M. A.; Hausman, D. B.; Davey, A.; Scott, T. M.; Green, R. C.; Miller, L. S.; Gearing, M.; Woodard, J.; Nelson, P. T.; Chung, H. Y.; Schalch, W.; Wittwer, J.; Poon, L. W. Relationship between Serum and Brain Carotenoids, α-Tocopherol, and Retinol Concentrations and Cognitive Performance in the Oldest Old from the Georgia Centenarian Study. *J. Aging Res.* **2013**, *2013*, 1.
(36) Miller, N. J.; Begoña Ruiz-Larrea, M. Flavonoids and Other Plant Phenols in the Diet: Their Significance as Antioxidants. *J. Nutritional & Environ. Med.* **2009**, *12* (1), 39−51, DOI: 10.1080/13590840220123352.
(37) Kroes, B. H.; Van Den Berg, A. J. J.; Quarles Van Ufford, H. C.; Van Dijk, H.; Labadie, R. P. Anti-Inflammatory Activity of Gallic Acid. *Planta Med.* **1992**, *58* (6), 499−504.
(38) Shabani, S.; Rabiei, Z.; Amini-Khoei, H. Exploring the Multifaceted Neuroprotective Actions of Gallic Acid: A Review. *Int. J. Food Prop.* **2020**, *23* (1), 736−752.
(39) Maya, S.; Prakash, T.; Madhu, K. Assessment of Neuroprotective Effects of Gallic Acid against Glutamate-Induced Neurotoxicity in Primary Rat Cortex Neuronal Culture. *Neurochem. Int.* **2018**, *121*, 50−58.
(40) Chandrasekhar, Y.; Phani Kumar, G.; Ramya, E. M.; Anilakumar, K. R. Gallic Acid Protects 6-OHDA Induced Neurotoxicity by Attenuating Oxidative Stress in Human Dopaminergic Cell Line. *Neurochem. Res.* **2018**, *43* (6), 1150−1160.
(41) Hu, Y.; Yang, D.; Tu, Y.; Chai, K.; Chu, L.; Shi, S.; Yao, T. Dynamic-Inspired Perspective on the Molecular Inhibitor of Tau Aggregation by Glucose Gallates Based on Human Neurons. *ACS Chem. Neurosci.* **2021**, *12* (21), 4162−4174.
(42) El-Seedi, H. R.; Taher, E. A.; Sheikh, B. Y.; Anjum, S.; Saeed, A.; AlAjmi, M. F.; Moustafa, M. S.; Al-Mousawi, S. M.; Farag, M. A.;

Hegazy, M. E. F.; Khalifa, S. A. M.; Göransson, U. Hydroxycinnamic Acids: Natural Sources, Biosynthesis, Possible Biological Activities, and Roles in Islamic Medicine. *Stud. Nat. Prod. Chem.* **2018**, *55*, 269−292.
(43) Prorok, T.; Jana, M.; Patel, D.; Pahan, K. Cinnamic Acid Protects the Nigrostriatum in a Mouse Model of Parkinson's Disease via Peroxisome Proliferator-Activated Receptor α. *Neurochem. Res.* **2019**, *44* (4), 751.
(44) Roy, A.; Jana, M.; Kundu, M.; Corbett, G. T.; Rangaswamy, S. B.; Mishra, R. K.; Luan, C. H.; Gonzalez, F. J.; Pahan, K. HMG-CoA Reductase Inhibitors Bind to PPARα to Upregulate Neurotrophin Expression in the Brain and Improve Memory in Mice. *Cell Metab.* **2015**, *22* (2), 253−265.
(45) Chakrabarti, S.; Jana, M.; Roy, A.; Pahan, K. Upregulation of Suppressor of Cytokine Signaling 3 in Microglia by Cinnamic Acid. *Curr. Alzheimer Res.* **2018**, *15* (10), 894.
(46) Kaur, N.; Chugh, H.; Sakharkar, M. K.; Dhawan, U.; Chidambaram, S. B.; Chandra, R. Neuroinflammation Mechanisms and Phytotherapeutic Intervention: A Systematic Review. *ACS Chem. Neurosci.* **2020**, *11* (22), 3707−3731.
(47) Singh, N.; Agrawal, M.; Doré, S. Neuroprotective Properties and Mechanisms of Resveratrolin in Vitro and in Vivo Experimental Stroke Models. *ACS Chem. Neurosci.* **2013**, *4* (8), 1151.
(48) Vang, O. Resveratrol: Challenges in Analyzing Its Biological Effects. *Ann. N.Y. Acad. Sci.* **2015**, *1348* (1), 161−170.
(49) Baur, J. A.; Sinclair, D. A. Therapeutic Potential of Resveratrol: The in Vivo Evidence. *Nat. Rev. Drug Discovery 2006 56* **2006**, *5* (6), 493−506.
(50) Belmonte-Reche, E.; Peñalver, P.; Caro-Moreno, M.; Mateos-Martín, M. L.; Adán, N.; Delgado, M.; González-Rey, E.; Morales, J. C. Silyl Resveratrol Derivatives as Potential Therapeutic Agents for Neurodegenerative and Neurological Diseases. *Eur. J. Med. Chem.* **2021**, *223*, 113655.
(51) Kurutas, E. B. The Importance of Antioxidants Which Play the Role in Cellular Response against Oxidative/Nitrosative Stress: Current State. *Nutr. J.* **2016**, DOI: 10.1186/S12937-016-0186-5.
(52) Panche, A. N.; Diwan, A. D.; Chandra, S. R. Flavonoids: An Overview. *J. Nutr. Sci.* **2016**, DOI: 10.1017/jns.2016.41.
(53) Wang, W. W.; Han, R.; He, H. J.; Li, J.; Chen, S. Y.; Gu, Y.; Xie, C. Administration of Quercetin Improves Mitochondria Quality Control and Protects the Neurons in 6-OHDA-Lesioned Parkinson's Disease Models. *Aging (Albany. NY).* **2021**, *13* (8), 11738−11751.
(54) Ghaffari, F.; Hajizadeh Moghaddam, A.; Zare, M. Neuroprotective Effect of Quercetin Nanocrystal in a 6-Hydroxydopamine Model of Parkinson Disease: Biochemical and Behavioral Evidence. *Basic Clin. Neurosci.* **2018**, *9* (5), 317−324.
(55) Ay, M.; Luo, J.; Langley, M.; Jin, H.; Anantharam, V.; Kanthasamy, A.; Kanthasamy, A. G. Molecular Mechanisms Underlying Protective Effects of Quercetin against Mitochondrial Dysfunction and Progressive Dopaminergic Neurodegeneration in Cell Culture and MitoPark Transgenic Mouse Models of Parkinson's Disease. *J. Neurochem.* **2017**, *141* (5), 766−782.
(56) Li, Z.; Wang, F.; Liu, Y.; Zhai, D.; Zhang, X.; Ying, Q.; Jia, M.; Xue, X.; Meng, J.; Li, J.; Wu, X.; Li, M. The Protective Effect of Quercetin on Endothelial Cells Injured by Hypoxia and Reoxygenation. *Front. Pharmacol.* **2021**, DOI: 10.3389/fphar.2021.745646.
(57) Quercetin improves blood-brain barrier dysfunction in rats with cerebral ischemia reperfusion via Wnt signaling pathway - PubMed https://pubmed.ncbi.nlm.nih.gov/31497191/ (accessed May 5, 2022).
(58) Yang, R.; Shen, Y. J.; Chen, M.; Zhao, J. Y.; Chen, S. H.; Zhang, W.; Song, J. K.; Li, L.; Du, G. H. Quercetin Attenuates Ischemia Reperfusion Injury by Protecting the Blood-Brain Barrier through Sirt1 in MCAO Rats. *J. Asian Nat. Prod. Res.* **2022**, *24* (3), 278−289.
(59) Rowe, J. W. *Natural Products of Woody Plants*; Rowe, J. W., Ed.; Springer Series in Wood Science; Springer Berlin Heidelberg: Berlin, Heidelberg, 1989. DOI: 10.1007/978-3-642-74075-6.
(60) Hideshima, M.; Kimura, Y.; Aguirre, C.; Kakuda, K.; Takeuchi, T.; Choong, C. J.; Doi, J.; Nabekura, K.; Yamaguchi, K.; Nakajima, K.; Baba, K.; Nagano, S.; Goto, Y.; Nagai, Y.; Mochizuki, H.; Ikenaka, K. Two-Step Screening Method to Identify α-Synuclein Aggregation Inhibitors for Parkinson's Disease. *Sci. Rep.* **2022**, *12* (1), 1−11.
(61) Roby, M. H. H.; Sarhan, M. A.; Selim, K. A. H.; Khalel, K. I. Evaluation of Antioxidant Activity, Total Phenols and Phenolic Compounds in Thyme (Thymus Vulgaris L.), Sage (Salvia Officinalis L.), and Marjoram (Origanum Majorana L.) Extracts. *Ind. Crops Prod.* **2013**, *43* (1), 827−831.
(62) Mouahid, A.; Dufour, C.; Badens, E. Supercritical CO 2 Extraction from Endemic Corsican Plants; Comparison of Oil Composition and Extraction Yield with Hydrodistillation Method. *J. CO2 Util.* **2017**, *20*, 263−273.
(63) Rodríguez-Solana, R.; Vázquez-Araújo, L.; Salgado, J. M.; Domínguez, J. M.; Cortés-Diéguez, S. Optimization of the Process of Aromatic and Medicinal Plant Maceration in Grape Marc Distillates to Obtain Herbal Liqueurs and Spirits. *J. Sci. Food Agric.* **2016**, *96* (14), 4760−4771.
(64) Fierascu, R. C.; Fierascu, I.; Ortan, A.; Georgiev, M. I.; Sieniawska, E. Innovative Approaches for Recovery of Phytoconstituents from Medicinal/Aromatic Plants and Biotechnological Production. *Molecules* **2020**, *25* (2), 309.
(65) Yavarpour-Bali, H.; Pirzadeh, M.; Ghasemi-Kasman, M. Curcumin-Loaded Nanoparticles: A Novel Therapeutic Strategy in Treatment of Central Nervous System Disorders. *Int. J. Nanomedicine* **2019**, *14*, 4449.
(66) Ferrari, E. Curcumin Derivatives as Metal-Chelating Agents: Implications for Potential Therapeutic Agents for Neurological Disorders. *Curcumin Neurol. Psychiatr. Disord. Neurochem. Pharmacol. Prop.* **2019**, 275−299.
(67) Olivera, A.; Moore, T. W.; Hu, F.; Brown, A. P.; Sun, A.; Liotta, D. C.; Snyder, J. P.; Yoon, Y.; Shim, H.; Marcus, A. I.; Miller, A. H.; Pace, T. W. W. Inhibition of the NF-KB Signaling Pathway by the Curcumin Analog, 3,5-Bis(2-Pyridinylmethylidene)-4-Piperidone (EF31): Anti-Inflammatory and Anti-Cancer Properties. *Int. Immunopharmacol.* **2012**, *12* (2), 368.
(68) Siddique, Y. H.; Ara, G.; Jyoti, S.; Afzal, M. Protective Effect of Curcumin in Transgenic Drosophila Melanogaster Model of Parkinson's Disease. *Altern. Med. Stud.* **2012**, *2* (1), e3.
(69) Phom, L.; Achumi, B.; Alone, D. P.; Muralidhara; Yenisetti, S. C. Curcumin's Neuroprotective Efficacy in Drosophila Model of Idiopathic Parkinson's Disease Is Phase Specific: Implication of Its Therapeutic Effectiveness. *Rejuvenation Res.* **2014**, *17* (6), 481−489.
(70) Zbarsky, V.; Datla, K. P.; Parkar, S.; Rai, D. K.; Aruoma, O. I.; Dexter, D. T. Neuroprotective Properties of the Natural Phenolic Antioxidants Curcumin and Naringenin but Not Quercetin and Fisetin in a 6-OHDA Model of Parkinson's Disease. *Free Radic. Res.* **2005**, *39* (10), 1119−1125.
(71) El Nebrisi, E.; Javed, H.; Ojha, S. K; Oz, M.; Shehab, S. Neuroprotective Effect of Curcumin on the Nigrostriatal Pathway in a 6-Hydroxydopmine-Induced Rat Model of Parkinson's Disease Is Mediated by A7-Nicotinic Receptors. *Int. J. Mol. Sci.* **2020**, *21* (19), 7329−1.
(72) Pradeep, H.; Yenisetti, S. C.; Rajini, P. S.; Muralidhara, M. Neuroprotective Propensity of Curcumin: Evidence in Animal Models, Mechanisms, and Its Potential Therapeutic Value. *Curcumin Neurol. Psychiatr. Disord. Neurochem. Pharmacol. Prop.* **2019**, 301−323.
(73) Nelson, K. M.; Dahlin, J. L.; Bisson, J.; Graham, J.; Pauli, G. F.; Walters, M. A. The Essential Medicinal Chemistry of Curcumin. *J. Med. Chem.* **2017**, *60* (5), 1620−1637.
(74) Gauthier, S.; Schlaefke, S. Efficacy and Tolerability of Ginkgo Biloba Extract EGb 761 in Dementia: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. *Clin. Interv. Aging* **2014**, *9*, 2065−2077.
(75) Zhou, X.; Qi, Y.; Chen, T. Long-Term Pre-Treatment of Antioxidant Ginkgo Biloba Extract EGb-761 Attenuates Cerebral-Ischemia-Induced Neuronal Damage in Aged Mice. *Biomed. Pharmacother.* **2017**, *85*, 256−263.

https://doi.org/10.1021/acsomega.2c03291
ACS Omega 2022, 7, 25974−25990

(76) Teixeira, A.; Eiras-Dias, J.; Castellarin, S. D.; Gerós, H. Berry Phenolics of Grapevine under Challenging Environments. *Int. J. Mol. Sci.* **2013**, *14* (9), 18711.
(77) Nuttall, S. L.; Kendall, M. J.; Bombardelli, E.; Morazzoni, P. An Evaluation of the Antioxidant Activity of a Standardized Grape Seed Extract, Leucoselect. *J. Clin. Pharm. Ther.* **1998**, *23* (5), 385−389.
(78) Bell, L.; Whyte, A. R.; Lamport, D. J.; Spencer, J. P. E.; Butler, L. T.; Williams, C. M. Grape Seed Polyphenol Extract and Cognitive Function in Healthy Young Adults: A Randomised, Placebo-Controlled, Parallel-Groups Acute-on-Chronic Trial. *Journal of Nutritional & Environmental Medicine* **2020**, *25* (1), 54−63, DOI: 10.1080/1028415X.2019.1708033.
(79) Narita, K.; Hisamoto, M.; Okuda, T.; Takeda, S. Differential Neuroprotective Activity of Two Different Grape Seed Extracts. *PLoS One* **2011**, *6* (1), e14575.
(80) Chidambara Murthy, K. N.; Jayaprakasha, G. K.; Singh, R. P. Studies on Antioxidant Activity of Pomegranate (Punica Granatum) Peel Extract Using in Vivo Models. *J. Agric. Food Chem.* **2002**, *50* (17), 4791−4795.
(81) Bonesi, M.; Tundis, R.; Sicari, V.; Loizzo, M. R. The Juice of Pomegranate (Punica Granatum L.): Recent Studies on Its Bioactivities. *Qual. Control Beverage Ind. Vol. 17 Sci. Beverages* **2019**, 459−489.
(82) Ahmed, M. A. E.; El Morsy, E. M.; Ahmed, A. A. E. Pomegranate Extract Protects against Cerebral Ischemia/Reperfusion Injury and Preserves Brain DNA Integrity in Rats. *Life Sci.* **2014**, *110* (2), 61−69.
(83) Yuan, T.; Ma, H.; Liu, W.; Niesen, D. B.; Shah, N.; Crews, R.; Rose, K. N.; Vattem, D. A.; Seeram, N. P. Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites. *ACS Chem. Neurosci.* **2016**, *7* (1), 26−33.
(84) Essa, M. M.; Subash, S.; Akbar, M.; Al-Adawi, S.; Guillemin, G. J. Long-Term Dietary Supplementation of Pomegranates, Figs and Dates Alleviate Neuroinflammation in a Transgenic Mouse Model of Alzheimer's Disease. *PLoS One* **2015**, *10* (3), e0120964.
(85) Kujawska, M.; Jourdes, M.; Kurpik, M.; Szulc, M.; Szaefer, H.; Chmielarz, P.; Kreiner, G.; Krajka-Kuźniak, V.; Mikołajczak, P. Ł.; Teissedre, P. L.; Jodynis-Liebert, J. Neuroprotective Effects of Pomegranate Juice against Parkinson's Disease and Presence of Ellagitannins-Derived Metabolite-Urolithin A-In the Brain. *Int. J. Mol. Sci.* **2020**, *21* (1), 202.
(86) Marrelli, M.; Statti, G. A.; Conforti, F. Origanum Spp.: An Update of Their Chemical and Biological Profiles. *Phytochem. Rev.* **2018**, *17* (4), 873−888.
(87) Elhady, M. A.; Khalaf, A. A. A.; Kamel, M. M.; Noshy, P. A. Carvacrol Ameliorates Behavioral Disturbances and DNA Damage in the Brain of Rats Exposed to Propiconazole. *Neurotoxicology* **2019**, *70*, 19−25.
(88) Prasanth, M. I.; Sivamaruthi, B. S.; Chaiyasut, C.; Tencomnao, T. A Review of the Role of Green Tea (Camellia Sinensis) in Antiphotoaging, Stress Resistance, Neuroprotection, and Autophagy. *Nutrients* **2019**, *11* (2), 474.
(89) Khan, N.; Mukhtar, H. Tea Polyphenols in Promotion of Human Health. *Nutrients* **2019**, *11* (1), 39.
(90) Martins, A.; Schimidt, H. L.; Garcia, A.; Colletta Altermann, C. D.; Santos, F. W.; Carpes, F. P.; da Silva, W. C.; Mello-Carpes, P. B. Supplementation with Different Teas from Camellia Sinensis Prevents Memory Deficits and Hippocampus Oxidative Stress in Ischemia-Reperfusion. *Neurochem. Int.* **2017**, *108*, 287−295.
(91) Kim, J. S. Investigation of Phenolic, Flavonoid, and Vitamin Contents in Different Parts of Korean Ginseng (Panax Ginseng C.A. Meyer). *Prev. Nutr. Food Sci.* **2016**, *21* (3), 263.
(92) Qu, S.; Meng, X.; Liu, Y.; Zhang, X.; Zhang, Y. Ginsenoside Rb1 Prevents MPTP-Induced Changes in Hippocampal Memory via Regulation of the α-Synuclein/PSD-95 Pathway. *Aging (Albany NY)* **2019**, *11* (7), 1934.
(93) Li, G.; Zhang, N.; Geng, F.; Liu, G.; Liu, B.; Lei, X.; Li, G.; Chen, X. High-Throughput Metabolomics and Ingenuity Pathway Approach Reveals the Pharmacological Effect and Targets of Ginsenoside Rg1 in Alzheimer's Disease Mice. *Sci. Rep.* **2019**, *9* (1), 1−11.
(94) Liang, H. Y.; Zhang, P. P.; Zhang, X. Le; Zheng, Y. Y.; Huang, Y. R.; Zheng, G. Q.; Lin, Y. Preclinical Systematic Review of Ginsenoside Rg1 for Cognitive Impairment in Alzheimer's Disease. *Aging (Albany. NY).* **2021**, *13* (5), 7549−7569.
(95) Easterbrook, P. J.; Gopalan, R.; Berlin, J. A.; Matthews, D. R. Publication Bias in Clinical Research. *Lancet* **1991**, *337* (8746), 867−872.
(96) Rothstein, H. R.; Bushman, B. J. Methodological and Reporting Errors in Meta-Analytic Reviews Make Other Meta-Analysts Angry: A Commentary on Ferguson (2015). *Perspect. Psychol. Sci.* **2015**, *10* (5), 677−679.
(97) Miller, K.; Feucht, W.; Schmid, M. Bioactive Compounds of Strawberry and Blueberry and Their Potential Health Effects Based on Human Intervention Studies: A Brief Overview. *Nutrients* **2019**, *11* (7), 1510.
(98) Angeloni, C.; Malaguti, M.; Barbalace, M. C.; Hrelia, S. Bioactivity of Olive Oil Phenols in Neuroprotection. *Int. J. Mol. Sci.* **2017**, *18* (11), 2230.
(99) Salehi, B.; Quispe, C.; Imran, M.; Ul-Haq, I.; Živković, J.; Abu-Reidah, I. M.; Sen, S.; Taheri, Y.; Acharya, K.; Azadi, H.; del Mar Contreras, M.; Segura-Carretero, A.; Mnayer, D.; Sethi, G.; Martorell, M.; Abdull Razis, A. F.; Sunusi, U.; Kamal, R. M.; Rasul Suleria, H. A.; Sharifi-Rad, J. Nigella Plants − Traditional Uses, Bioactive Phytoconstituents, Preclinical and Clinical Studies. *Front. Pharmacol.* **2021**, *12*, 417.
(100) Patel, S. S.; Raghuwanshi, R.; Masood, M.; Acharya, A.; Jain, S. K. Medicinal Plants with Acetylcholinesterase Inhibitory Activity. *Rev. Neurosci.* **2018**, *29* (5), 491−529.
(101) Kure, C.; Timmer, J.; Stough, C. The Immunomodulatory Effects of Plant Extracts and Plant Secondary Metabolites on Chronic Neuroinflammation and Cognitive Aging: A Mechanistic and Empirical Review. *Front. Pharmacol.* **2017**, *8* (MAR), 117.
(102) Tyring, S. K. Sinecatechins: Effects on HPV-Induced Enzymes Involved in Inflammatory Mediator Generation. *J. Clin. Aesthet. Dermatol.* **2012**, *5* (1), 19.
(103) Sun, Y.; Qian, J. Botanical Drug Clinical Trial: Common Issues and Future Options. *Acta Pharm. Sin. B* **2021**, *11* (1), 300−303.
(104) Tapeinos, C.; Battaglini, M.; Ciofani, G. Advances in the Design of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Targeting Brain Diseases. *J. Controlled Release* **2017**, *264*, 306−332.
(105) Uchegbu, I. F.; Vyas, S. P. Non-Ionic Surfactant Based Vesicles (Niosomes) in Drug Delivery. *Int. J. Pharm.* **1998**, *172* (1), 33−70.
(106) Martinelli, C.; Pucci, C.; Battaglini, M.; Marino, A.; Ciofani, G. Antioxidants and Nanotechnology: Promises and Limits of Potentially Disruptive Approaches in the Treatment of Central Nervous System Diseases. *Adv. Healthc. Mater.* **2020**, *9* (3), 1901589.
(107) Zhai, K.; Brockmüller, A.; Kubatka, P.; Shakibaei, M.; Büsselberg, D. Curcumin's Beneficial Effects on Neuroblastoma: Mechanisms, Challenges, and Potential Solutions. *Biomolecules* **2020**, *10* (11), 1469.
(108) Yan, Y.; Chen, Y.; Liu, Z.; Cai, F.; Niu, W.; Song, L.; Liang, H.; Su, Z.; Yu, B.; Yan, F. Brain Delivery of Curcumin Through Low-Intensity Ultrasound-Induced Blood-Brain Barrier Opening via Lipid-PLGA Nanobubbles. *Int. J. Nanomedicine* **2021**, *16*, 7433−7447.
(109) Huerta-Ángeles, G.; Brandejsová, M.; Novotný, J.; Kopecká, K.; Šógorková, J.; Šmejkalová, D.; Velebný, V. Grafting of Steroids to Hyaluronan towards the Design of Delivery Systems for Antioxidants: The Role of Hydrophobic Core. *Carbohydr. Polym.* **2018**, *193*, 383−392.
(110) Leksiri, S.; Hasriadi; Dasuni Wasana, P. W.; Vajragupta, O.; Rojsitthisak, P.; Towiwat, P. Co-Administration of Pregabalin and Curcumin Synergistically Decreases Pain-Like Behaviors in Acute Nociceptive Pain Murine Models. *Molecules* **2020**, *25* (18), 4172.

(111) Sandhir, R.; Yadav, A.; Mehrotra, A.; Sunkaria, A.; Singh, A.; Sharma, S. Curcumin Nanoparticles Attenuate Neurochemical and Neurobehavioral Deficits in Experimental Model of Huntington's Disease. *Neuromolecular Med.* **2014**, *16* (1), 106−118.
(112) Ramalingam, P.; Ko, Y. T. Enhanced Oral Delivery of Curcumin from N-Trimethyl Chitosan Surface-Modified Solid Lipid Nanoparticles: Pharmacokinetic and Brain Distribution Evaluations. *Pharm. Res.* **2015**, *32* (2), 389−402.
(113) Narouiepour, A.; Ebrahimzadeh-Bideskan, A.; Rajabzadeh, G.; Gorji, A.; Negah, S. S. Neural Stem Cell Therapy in Conjunction with Curcumin Loaded in Niosomal Nanoparticles Enhanced Recovery from Traumatic Brain Injury. *Sci. Rep.* **2022**, *12* (1), 3572.
(114) Jin, Y.; Wen, J.; Garg, S.; Liu, D.; Zhou, Y.; Teng, L.; Zhang, W. Development of a Novel Niosomal System for Oral Delivery of Ginkgo Biloba Extract. *Int. J. Nanomedicine* **2013**, *8*, 421−430.
(115) Ramachandran, S.; Thangarajan, S. A Novel Therapeutic Application of Solid Lipid Nanoparticles Encapsulated Thymoquinone (TQ-SLNs) on 3-Nitropropionic Acid Induced Huntington's Disease-like Symptoms in Wistar Rats. *Chem. Biol. Interact.* **2016**, *256*, 25−36.
(116) Smith, A.; Giunta, B.; Bickford, P. C.; Fountain, M.; Tan, J.; Shytle, R. D. Nanolipidic Particles Improve the Bioavailability and Alpha-Secretase Inducing Ability of Epigallocatechin-3-Gallate (EGCG) for the Treatment of Alzheimer's Disease. *Int. J. Pharm.* **2010**, *389* (1−2), 207−212.
(117) Binyamin, O.; Larush, L.; Frid, K.; Keller, G.; Friedman-Levi, Y.; Ovadia, H.; Abramsky, O.; Magdassi, S.; Gabizon, R. Treatment of a Multiple Sclerosis Animal Model by a Novel Nanodrop Formulation of a Natural Antioxidant. *Int. J. Nanomedicine* **2015**, *10*, 7165−7174.
(118) Mizrahi, M.; Friedman-Levi, Y.; Larush, L.; Frid, K.; Binyamin, O.; Dori, D.; Fainstein, N.; Ovadia, H.; Ben-Hur, T.; Magdassi, S.; Gabizon, R. Pomegranate Seed Oil Nanoemulsions for the Prevention and Treatment of Neurodegenerative Diseases: The Case of Genetic CJD. *Nanomedicine* **2014**, *10* (6), 1353−1363.
(119) Binyamin, O.; Nitzan, K.; Frid, K.; Ungar, Y.; Rosenmann, H.; Gabizon, R. Brain Targeting of 9c,11t-Conjugated Linoleic Acid, a Natural Calpain Inhibitor, Preserves Memory and Reduces Aβ and P25 Accumulation in 5XFAD Mice. *Sci. Rep.* **2019**, *9* (1), 18437.
(120) Frozza, R. L.; Bernardi, A.; Hoppe, J. B.; Meneghetti, A. B.; Matté, A.; Battastini, A. M. O.; Pohlmann, A. R.; Guterres, S. S.; Salbego, C. Neuroprotective Effects of Resveratrol against Aβ Administration in Rats Are Improved by Lipid-Core Nanocapsules. *Mol. Neurobiol.* **2013**, *47* (3), 1066−1080.
(121) Loureiro, J. A.; Andrade, S.; Duarte, A.; Neves, A. R.; Queiroz, J. F.; Nunes, C.; Sevin, E.; Fenart, L.; Gosselet, F.; Coelho, M. A. N.; Pereira, M. C. Resveratrol and Grape Extract-Loaded Solid Lipid Nanoparticles for the Treatment of Alzheimer's Disease. *Molecules* **2017**, *22* (2), 277.
(122) Neves, A. R.; Queiroz, J. F.; Reis, S. Brain-Targeted Delivery of Resveratrol Using Solid Lipid Nanoparticles Functionalized with Apolipoprotein E. *J. Nanobiotechnology* **2016**, *14* (1), 27.
(123) Şen, Ö.; Emanet, M.; Marino, A.; Belenli Gümüş, M.; Bartolucci, M.; Doccini, S.; Catalano, F.; Genchi, G. G.; Santorelli, F. M.; Petretto, A.; Ciofani, G. Evaluation of the Therapeutic Potential of Resveratrol-Loaded Nanostructured Lipid Carriers on Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay Patient-Derived Fibroblasts. *Mater. Des.* **2021**, *209*, 110012.
(124) Marino, A.; Battaglini, M.; Desii, A.; Lavarello, C.; Genchi, G.; Petretto, A.; Ciofani, G. Liposomes Loaded with Polyphenol-Rich Grape Pomace Extracts Protect from Neurodegeneration in a Rotenone-Based in Vitro Model of Parkinson's Disease. *Biomater. Sci.* **2021**, *9* (24), 8171−8188.
(125) Mathew, A.; Fukuda, T.; Nagaoka, Y.; Hasumura, T.; Morimoto, H.; Yoshida, Y.; Maekawa, T.; Venugopal, K.; Kumar, D. S. Curcumin Loaded-PLGA Nanoparticles Conjugated with Tet-1 Peptide for Potential Use in Alzheimer's Disease. *PLoS One* **2012**, *7* (3), e32616.
(126) Yang, C.; Han, M.; Li, R.; Zhou, L.; Zhang, Y.; Duan, L.; Su, S.; Li, M.; Wang, Q.; Chen, T.; Mo, Y. Curcumin Nanoparticles Inhibiting Ferroptosis for the Enhanced Treatment of Intracerebral Hemorrhage. *Int. J. Nanomedicine* **2021**, *16*, 8049−8065.
(127) Ali, K. A.; El-Naa, M. M.; Bakr, A. F.; Mahmoud, M. Y.; Abdelgawad, E. M.; Matoock, M. Y. The Dual Gastro- and Neuroprotective Effects of Curcumin Loaded Chitosan Nanoparticles against Cold Restraint Stress in Rats. *Biomed. Pharmacother.* **2022**, *148*, 112778.
(128) Bollimpelli, V. S.; Kumar, P.; Kumari, S.; Kondapi, A. K. Neuroprotective Effect of Curcumin-Loaded Lactoferrin Nano Particles against Rotenone Induced Neurotoxicity. *Neurochem. Int.* **2016**, *95*, 37−45.
(129) Quezada, E.; Rodríguez-Enríquez, F.; Laguna, R.; Cutrín, E.; Otero, F.; Uriarte, E.; Viña, D. Curcumin−Coumarin Hybrid Analogues as Multitarget Agents in Neurodegenerative Disorders. *Molecules* **2021**, *26*, 4550.
(130) Huang, N.; Lu, S.; Liu, X.-G.; Zhu, J.; Wang, Y.-J.; Liu, R.-T. PLGA Nanoparticles Modified with a BBB-Penetrating Peptide Co-Delivering Aβ Generation Inhibitor and Curcumin Attenuate Memory Deficits and Neuropathology in Alzheimer's Disease Mice. *Oncotarget* **2017**, *8* (46), 81001−81013.
(131) Cheng, K. K.; Yeung, C. F.; Ho, S. W.; Chow, S. F.; Chow, A. H. L.; Baum, L. Highly Stabilized Curcumin Nanoparticles Tested in an in Vitro Blood-Brain Barrier Model and in Alzheimer's Disease Tg2576 Mice. *AAPS J.* **2013**, *15* (2), 324−336.
(132) Mohajeri, M.; Sadeghizadeh, M.; Najafi, F.; Javan, M. Polymerized Nano-Curcumin Attenuates Neurological Symptoms in EAE Model of Multiple Sclerosis through down Regulation of Inflammatory and Oxidative Processes and Enhancing Neuroprotection and Myelin Repair. *Neuropharmacology* **2015**, *99*, 156−167.
(133) Dolati, S.; Ahmadi, M.; Aghebti-Maleki, L.; Nikmaram, A.; Marofi, F.; Rikhtegar, R.; Ayromlou, H.; Yousefi, M. Nanocurcumin Is a Potential Novel Therapy for Multiple Sclerosis by Influencing Inflammatory Mediators. *Pharmacol. Rep.* **2018**, *70* (6), 1158−1167.
(134) Ahmadi, M.; Agah, E.; Nafissi, S.; Jaafari, M. R.; Harirchian, M. H.; Sarraf, P.; Faghihi-Kashani, S.; Hosseini, S. J.; Ghoreishi, A.; Aghamollaii, V.; Hosseini, M.; Tafakhori, A. Safety and Efficacy of Nanocurcumin as Add-On Therapy to Riluzole in Patients With Amyotrophic Lateral Sclerosis: A Pilot Randomized Clinical Trial. *Neurother. J. Am. Soc. Exp. Neurother.* **2018**, *15* (2), 430−438.
(135) Doggui, S.; Sahni, J. K.; Arseneault, M.; Dao, L.; Ramassamy, C. Neuronal Uptake and Neuroprotective Effect of Curcumin-Loaded PLGA Nanoparticles on the Human SK-N-SH Cell Line. *J. Alzheimers. Dis.* **2012**, *30* (2), 377−392.
(136) Anderson, J. M.; Shive, M. S. Biodegradation and Biocompatibility of PLA and PLGA Microspheres. *Adv. Drug Delivery Rev.* **2012**, *64*, 72−82.
(137) Ahmad, N.; Ahmad, R.; Al Qatifi, S.; Alessa, M.; Al Hajji, H.; Sarafroz, M. A Bioanalytical UHPLC Based Method Used for the Quantification of Thymoquinone-Loaded-PLGA-Nanoparticles in the Treatment of Epilepsy. *BMC Chem.* **2020**, *14* (1), 10.
(138) Joseph, J. A.; Denisova, N. A.; Arendash, G.; Gordon, M.; Diamond, D.; Shukitt-Hale, B.; Morgan, D. Blueberry Supplementation Enhances Signaling and Prevents Behavioral Deficits in an Alzheimer Disease Model. *Nutr. Neurosci.* **2003**, *6* (3), 153−162.
(139) Shih, P.-H.; Yeh, C.-T.; Yen, G.-C. Anthocyanins Induce the Activation of Phase II Enzymes through the Antioxidant Response Element Pathway against Oxidative Stress-Induced Apoptosis. *J. Agric. Food Chem.* **2007**, *55* (23), 9427−9435.
(140) Amin, F. U.; Shah, S. A.; Badshah, H.; Khan, M.; Kim, M. O. Anthocyanins Encapsulated by PLGA@PEG Nanoparticles Potentially Improved Its Free Radical Scavenging Capabilities via P38/JNK Pathway against Aβ(1−42)-Induced Oxidative Stress. *J. Nanobiotechnology* **2017**, *15* (1), 12.
(141) Ali, T.; Kim, M. J.; Rehman, S. U.; Ahmad, A.; Kim, M. O. Anthocyanin-Loaded PEG-Gold Nanoparticles Enhanced the Neuroprotection of Anthocyanins in an Aβ(1−42) Mouse Model of Alzheimer's Disease. *Mol. Neurobiol.* **2017**, *54* (8), 6490−6506.

https://doi.org/10.1021/acsomega.2c03291
ACS Omega 2022, 7, 25974−25990

(142) Lu, X.; Ji, C.; Xu, H.; Li, X.; Ding, H.; Ye, M.; Zhu, Z.; Ding, D.; Jiang, X.; Ding, X.; Guo, X. Resveratrol-Loaded Polymeric Micelles Protect Cells from Abeta-Induced Oxidative Stress. *Int. J. Pharm.* **2009**, *375* (1−2), 89−96.
(143) Sanna, V.; Lubinu, G.; Madau, P.; Pala, N.; Nurra, S.; Mariani, A.; Sechi, M. Polymeric Nanoparticles Encapsulating White Tea Extract for Nutraceutical Application. *J. Agric. Food Chem.* **2015**, *63* (7), 2026−2032.
(144) Zhao, N.; Yang, X.; Calvelli, H. R.; Cao, Y.; Francis, N. L.; Chmielowski, R. A.; Joseph, L. B.; Pang, Z. P.; Uhrich, K. E.; Baum, J.; Moghe, P. V. Antioxidant Nanoparticles for Concerted Inhibition of α-Synuclein Fibrillization, and Attenuation of Microglial Intracellular Aggregation and Activation. *Front. Bioeng. Biotechnol.* **2020**, *8*, 112.
(145) da Silva, S. B.; Amorim, M.; Fonte, P.; Madureira, R.; Ferreira, D.; Pintado, M.; Sarmento, B. Natural Extracts into Chitosan Nanocarriers for Rosmarinic Acid Drug Delivery. *Pharm. Biol.* **2015**, *53* (5), 642−652.
(146) Hosseini, S. F.; Zandi, M.; Rezaei, M.; Farahmandghavi, F. Two-Step Method for Encapsulation of Oregano Essential Oil in Chitosan Nanoparticles: Preparation, Characterization and in Vitro Release Study. *Carbohydr. Polym.* **2013**, *95* (1), 50−56.
(147) de la Torre, R.; de Sola, S.; Hernandez, G.; Farré, M.; Pujol, J.; Rodriguez, J.; Espadaler, J. M.; Langohr, K.; Cuenca-Royo, A.; Principe, A.; Xicota, L.; Janel, N.; Catuara-Solarz, S.; Sanchez-Benavides, G.; Bléhaut, H.; del Hoyo, L.; Benejam, B.; Blanco-Hinojo, L.; Videla, S.; Fitó, M.; Delabar, J. M.; Dierssen, M.; Civit, E.; Sanchez, G.; Dueñas-Espín, I.; Roca, L.; Legout, V.; Sánchez-Gutiérrez, J.; Trias, K.; Freixas, R. Safety and Efficacy of Cognitive Training plus Epigallocatechin-3-Gallate in Young Adults with Down's Syndrome (TESDAD): A Double-Blind, Randomised, Placebo-Controlled, Phase 2 Trial. *Lancet. Neurol.* **2016**, *15* (8), 801−810.
(148) Zhu, C. W.; Grossman, H.; Neugroschl, J.; Parker, S.; Burden, A.; Luo, X.; Sano, M. A Randomized, Double-Blind, Placebo-Controlled Trial of Resveratrol with Glucose and Malate (RGM) to Slow the Progression of Alzheimer's Disease: A Pilot Study. *Alzheimer's Dement. (New York, N. Y.)* **2018**, *4*, 609−616.
(149) Moussa, C.; Hebron, M.; Huang, X.; Ahn, J.; Rissman, R. A.; Aisen, P. S.; Turner, R. S. Resveratrol Regulates Neuro-Inflammation and Induces Adaptive Immunity in Alzheimer's Disease. *J. Neuroinflammation* **2017**, DOI: 10.1186/s12974-016-0779-0.
(150) Squillaro, T.; Cimini, A.; Peluso, G.; Giordano, A.; Melone, M. A. B. Nano-Delivery Systems for Encapsulation of Dietary Polyphenols: An Experimental Approach for Neurodegenerative Diseases and Brain Tumors. *Biochem. Pharmacol.* **2018**, *154*, 303−317.

https://doi.org/10.1021/acsomega.2c03291
ACS Omega 2022, 7, 25974−25990