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REVIEW

Recent trends in the development of nanophytobioactive compounds and delivery systems for their possible role in reducing oxidative stress in Parkinson's disease models

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Abstract: Oxidative stress plays a very critical role in neurodegenerative diseases, such as Parkinson's disease (PD), which is the second most common neurodegenerative disease among elderly people worldwide. Increasing evidence has suggested that phytobioactive compounds show enhanced benefits in cell and animal models of PD. Curcumin, resveratrol, ginsenosides, quercetin, and catechin are phyto-derived bioactive compounds with important roles in the prevention and treatment of PD. However, in vivo studies suggest that their concentrations are very low to cross blood–brain barrier thereby it limits bioavailability, stability, and dissolution at target sites in the brain. To overcome these problems, nanophytomedicine with the controlled size of 1–100 nm is used to maximize efficiency in the treatment of PD. Nanosizing of phytobioactive compounds enhances the permeability into the brain with maximized efficiency and stability. Several nanodelivery techniques, including solid lipid nanoparticles, nanostructured lipid carriers, nanoliposomes, and nanoniosomes can be used for controlled delivery of nanobioactive compounds to brain. Nanocompounds, such as ginsenosides (19.9 nm) synthesized using a nanoemulsion technique, showed enhanced bioavailability in the rat brain. Here, we discuss the most recent trends and applications in PD, including 1) the role of phytobioactive compounds in reducing oxidative stress and their bioavailability; 2) the role of nanotechnology in reducing oxidative stress during PD; 3) nanodelivery systems; and 4) various nanophytobioactive compounds and their role in PD.

Keywords: Parkinson's disease, phytobioactive compounds, nanotechnology delivery systems, nanocurcumin, nanoresveratrol

Introduction

The increase in the aging population in many countries is threatened by the second most common neurodegenerative disease, namely Parkinson's disease (PD).[1–3] Oxidative stress plays a key role in the development of PD, including several degenerative reactions, such as nitric oxide toxicity, mitochondrial toxicity, and development of several toxic components, leading to impaired neuronal function.[2,4,5] Synthetic bioactive compounds are extensively used to reduce oxidative stress but have toxicity limitations. Phytobioactive compounds serve as natural antioxidants to reduce toxicity, and are extensively used to reduce oxidative stress, repair the central nervous system, and prevent PD.[1,2] The phenolic compounds are the most beneficial, such as phenolic acids and flavonoids, which reduce disease by scavenging free radicals and limiting oxidative stress.[2,6] In addition, flavonoids chelate metal ions, preventing formation of free radicals and limits limiting the onset of PD.[6–8] Oral administration is the most

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convenient for the repeated and routine delivery of bioactive compounds.[9–11] However, it is most challenging due to the protection of brain by blood–brain barrier with the narrow diameter of approximately less than 20 nm that limits the entry of most bioactive molecules. Nanotechnology research has been utilized to enhance the permeability, solubility, and stability of bioactive compounds and to enhance delivery of phytobioactive compounds[12,13] to the various target sites including brain.

Natural polymer-based delivery systems have been used to deliver a variety of nanoscaled proteins and carbohydrates, including gelatin, whey proteins, zein, gum arabic, and maltodextrin.[14] These polymer-based nanoparticles are highly beneficial for delivering hydrophilic bioactive compounds, which bind to the membranes and increase the life of the bioactive compounds. In addition, nanosized bioactive compounds can be delivered to the plasma through transcellular or paracellular pathways or receptor-mediated endocytosis. Lipid-based delivery systems have been used to enhance delivery of a variety of digestible lipids, such as tocopherols, flavonoids, polyphenols, and oil soluble vitamins.[15,16] These digestible lipids greatly enhance the delivery of bioactive compounds in the small intestine by increasing the number of mixed micelles, which generally enhance solubility and transport of hydrophobic bioactive compounds.[17–23]

Many studies have focused on the health beneficial aspects of nanophytobioactive compounds to reduce oxidative stress and treat neurological disorders and PD.[24–28] Nanocurcumin shows a higher mean residential time in the mice brain than that of natural curcumin.[29] In addition, co-delivery of bioactive compounds greatly enhances the delivery rate of curcumin in the plasma.[30–32] Similarly, nano-resveratrol greatly reduces the oxidative stress of various cell and animal models of PD.[33–35] Bioactive nanoparticles enhance release of antioxidants to the brain with physical carrier properties of high biodegradability and lower toxicity. This review focuses on three main objectives: 1) the role of phytobioactive compounds in PD and their limitations; 2) nanotechnologies involved in the development of bioactive nanoparticles; and 3) the role of bioactive nanocompounds in reducing the rates of neurodegenerative diseases.

Phytobioactive compounds and PD

PD is a multifactorial neurological disorder characterized by loss of dopaminergic neurons leading to subsequent loss of dopamine in the midbrain region.[36] This causes an imbalance in neurotransmitters, such as dopamine and acetylcholine, which leads to various symptoms of PD. The major symptoms of PD include tremor, speech and writing changes, slowed movement, and rigid muscles.[37–39] Bioactive compounds play a major role in sustained protection against loss of dopaminergic neuron due to oxidative stress, among the various treatments to improve these symptoms in patients with PD.[3,36,40–43] Extensive animal model studies have been conducted about the sustained protective role of different synthetic and natural bioactive compounds against dopaminergic neuron loss in PD.[44–49] Based on limitations for using synthetic compounds,[50–52] natural phytobioactive compounds play an important role in preventing PD.[38,48] Phytobioactive compounds from various medicinal plants show neuroprotective effects in various animal models.[8,26]

Phytobioactive compounds are secondary metabolites with higher health beneficial activity that occurs in smaller amounts in various plant parts, such as leaves, fruits, seeds, nuts, and roots.[42,53–57] These include polyphenols, flavonoids, and triterpenoids, which contain one or more hydroxyl groups in their phenolic ring that scavenge free radicals and act as strong antioxidants. A diet rich in these bioactive compounds has a greater protective effect against neurodegenerative disorders.[3,58,59] Consuming tea rich in flavonoids reduces the risk of PD in human trials. Similarly, older rats fed a diet rich in fruits, such as blueberries and strawberries, and vegetables, such as spinach, showed had better cognitive function.[60] Figure 1 shows the possible preventive role of nanobioactive compounds in reducing oxidative stress and the onset of PD. Most polyphenols occur as methoxylated, hydroxylated, or glycoxylated derivatives and the linking sugars are glucose, galactose, or rhamnose.[61] The polyphenol is absorbed either in the small intestine or in the colon depending on the sugar linked to the polyphenolic group.[61,62] The activities of most polyphenols are linked with the number of hydroxyl groups present at the active site. For example, the hydroxyl groups present in the third and sixth positions determine the antioxidant potential of bioactive compounds. However, some hydroxyl groups present in the fifth and seventh dihydroxyl and fourth hydroxyl positions readily undergo degradation. Some acetylated flavonoids, such as epicatechin and epigalocatechin, are readily absorbed without hydrolysis.[63,64] A diet rich in plant foods with more bioactive compounds has a greater potential neuroprotective effect.[38,65]

Bioavailability of phytobioactive compounds

Most of the health benefits of bioactive phytobioactive compounds in vitro are associated with their capacity to scavenge free radicals, quench nitrogen species, and chelate

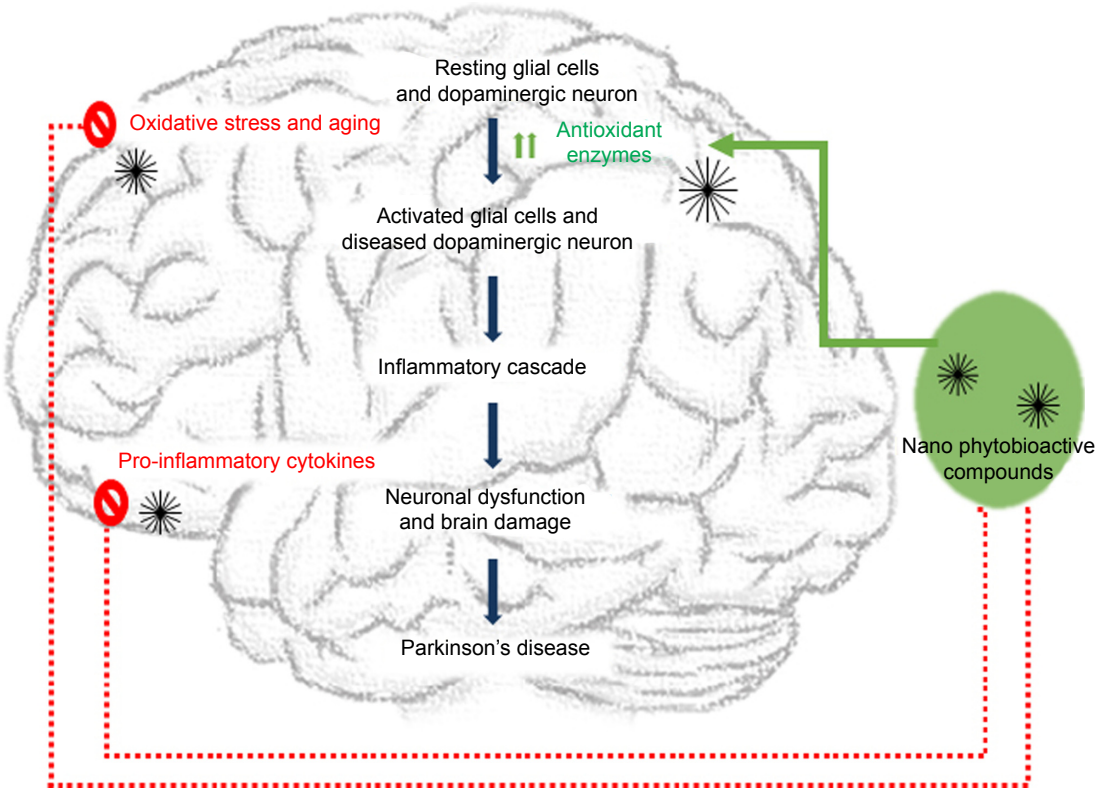

Figure 1 Nano phytobioactive compounds mechanism of action against Parkinson's disease pathway.
Notes: Phytobioactive compounds of its unique nanosize successfully cross the blood–brain barrier thereby inhibit the caspases activity and oxidative stress thereby inhibit further activation of glial cells and diseased dopaminergic neurons; also exhibit enhancement of endogenous antioxidant enzyme levels; inhibit the inflammatory cascade. These actions confirmed that phytobioactive compounds will be a successful therapeutic agent for Parkinson's diseases.

metal ions.[9,58,63] Different concentrations of various bioactive compounds that exert health beneficial activities in vitro are unlikely to be beneficial in vivo.[9] Individuals prefer the oral route for consuming bioactive compounds with higher health beneficial activities. Bioactive compounds undergo breakdown and antioxidant activity in the intestinal system, which limits their bioavailability to the brain.[9,62] Resveratrol-rich foods have higher absorption rates in humans but lower bioavailability in its active form in plasma.[66] Unlike other organs, the brain is well protected by the blood–brain barrier, which selectively filters molecules in and out of the brain. Oral administration of 100 mg/kg curcumin to mice results in only 0.4 μg curcumin/g brain.[67] Nanotechnology is an alternative approach to overcome these bioavailability challenges. Modifying phytobioactive compounds to a nanosize of 1–1,000 nm enhances their availability to cells, thereby enhancing activity. Trans-resveratrol loaded nanoparticle systems and optimized self nanoemulsifying systems enhance bioavailability fivefold to various target sites because of the optimum formulation.[68,69] Recently, nanotechnology-based approach of treatment gained more importance for the enhanced crossing blood–brain barrier through its unique nanosize to various brain diseases, such as PD, brain cancer, and Alzheimer's disease.[70]

The role of nanotechnology in reducing oxidative stress in PD

Nanotechnology plays a very significant role in reducing oxidative stress that occurs in various diseases, including cancers, Alzheimer's disease, and PD.[23,24,29,34] However, the role of this technology in various other diseases has not been elucidated. Among various ways of developing nanobioactive compounds, nanoparticles play a very significant role in reducing disease by reducing oxidative stress through their antioxidant mechanism.[71] The most common nanoparticle antioxidant mechanism involves reduction of the natural bioactive molecule (curcumin, resveratrol, or vitamin E) to a nanosize that can be readily absorbed and reach the target site without much loss in activity.[16,29,35] Nanosized bioactive compounds vary in the size from 10 to 1,000 nm, which increases bioactivity and target specificity, reduces toxicity, and enhances safety.[17,29,33,34,68,72,73] The most important characteristics of nanoparticles delivered to the PD brain include the size of the bioactive compound, surface activity, and carrier toxicity.[17,33,73]

Smaller bioactive nanoparticles release faster to the brain target compared with larger bioactive nanoparticles.[17] Hydrophilic coatings on nanobioactive compounds protect against phagocytosis. The carrier should also be highly biodegradable and nontoxic.[20] Nanoparticles or nanobioactive compounds can be placed in the core or on the surface, which depends on the method used to prepare the nanobioactive compound. The oxidization or hydroxylation of curcumin in the body can be prevented using nanocapsules in which curcumin is the core material.[13] Some nanobioactive molecules are designed on the surface, such as thiamine-coated nanoparticles, which enhances delivery of the antioxidant to the brain.[74,75]

Nanotechnological delivery systems used to develop nanobioactive compounds

Careful design of the delivery method is important for various neurodegenerative disorders.[13,22–24] The best nanotechnological methods deliver the bioactive compound efficiently to the target site without any side effects.[22,73] The activity of the bioactive compound also depends on the physicochemical properties at the target site. Numerous methods have been developed, such as solid lipid nanoparticles, liposomes, polymeric nanoparticles, nanoemulsions, and nanoniosomes.[16,24,76] The method is classified based on whether the compound is a solid or liquid, and each has distinct advantages and disadvantages based on the activity of the bioactive molecule. A few of these methods are shown in Figure 2.

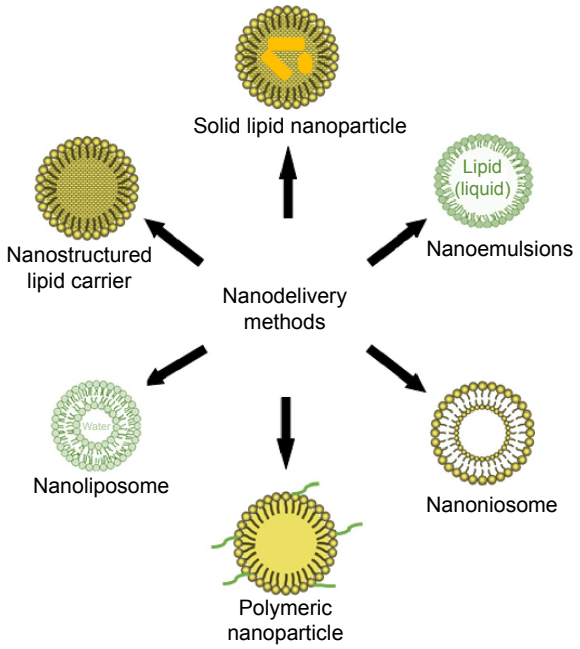

Figure 2 Nanotechnology delivery methods for producing nanosized phytobioactive compounds.

Bioactive nanoparticle delivery systems

Solid lipid nanoparticles

Solid lipid nanoparticles contain solid lipid as triglycerides, which incorporate the bioactive compounds in a lipophilic and hydrophilic shell surrounded by a phospholipid layer for controlled delivery of the bioactive compound to the target site.[72,77–81] The mobility of the bioactive compound is greatly reduced with a solid lipid core, so it remains in the gut, which enhances the sustained release of the compound for a prolonged period of time. Various methods have been used to develop solid lipid nanoparticles, including multiple emulsion, high-pressure homogenization, and ultrasonication.[82–86] Lipophilic bioactive compounds are highly dispersed in the lipid matrix, whereas the hydrophilic bioactive compounds are outside the lipid matrix. Dispersing the bioactive compounds in lipid involves the appropriate solvent or mechanical force. A polyethylene glycol (PEG) coating is used to stabilize nanoparticles incorporated in lipid. This coating enhances the stability of the bioactive compound in blood plasma by minimizing phagocytic uptake.[87] Several synthetic drugs are used to prepare solid lipid nanoparticles to prevent various conditions in PD.[88–91] Bromocriptine-loaded solid lipid nanoparticles have been developed and studied in patients with PD and are highly effective in reducing dyskenesia.[88] However, nanophytobioactive compounds developed using a solid lipid nanoparticle delivery system showed higher bioavailability.[92,93] Curcumin-loaded solid lipid nanocarriers achieved approximately 155 times higher curcumin delivery than that of natural curcumin in cancer cells.[94] Curcumin-loaded solid lipid nanoparticles are highly efficient and delivery to the brain delivery was approximately 16.5 and 30 times higher than that of natural curcumin treatment in rats via oral and intravenous routes, respectively.[95] The bioavailabilities of quercetin are also increased significantly in a formulation using solid lipid nanoparticles.[96–98] Similarly, resveratrol-loaded solid lipid nanoparticles also enhance bioavailability eightfold during oral delivery.[92,93]

Nanostructured lipid carriers

Nanostructured lipid carriers are prepared with a mixture of solid and liquid phase lipids in which the bioactive compound is incorporated.[92,99–104] Approximately 70% of the bioactive molecules incorporated into the mixture are well encapsulated into the carrier system and effectively reach the target site without much drop in bioactivity.[99,104,105] Solid phase lipids generally used to prepare nanostructured lipid carriers include acetyl alcohol, glycerol monosterate, and stearic acid and the liquid phase lipid includes caprylic

triglycerides, oleic acid, and cupric triglycerides.[106] The type of lipid also determines the stability of the bioactive compound in the bioactive compound-loaded nanolipid particles. The liquid lipid concentrations determine the size of the nanolipid particles.[92,104,107] Higher concentrations of the liquid lipid particles make a smaller sized nanolipid particle but a higher release rate of the bioactive particles.[107] Based on the structure of the matrix lipids, nanolipid carrier particles are subdivided into three types, such as the imperfect type, which contains less oil, leading to lower stability of the bioactive molecules. The imperfect type of nanostructured lipid carrier has significant advantages compared with solid lipid nanocarriers. The second type is the multiple nanostructured lipid carrier, which contains more oil, and can be loaded with more bioactive compound in their nanocompartments to enhance drug release.[92] The third type is the amorphous type of lipid, which lacks the crystalline structure of a solid lipid, and expels the bioactive compound during cooling. Baicalin-loaded nanostructured lipid carriers show enhanced bioavailability and sustained baicalin release.[105] Similarly, poorly soluble bioactive molecules, such as curcumin and genistein, have enhanced bioavailability in nanostructured lipid carriers and have a stronger effect inhibiting prostate cancer.[108,109]

Nanoliposomes

Nanoliposomes are phospholipids with a hydrophilic head and two hydrophobic tails. They range in size from 30 nm to a few microns and are formed by high-energy dispersion.[110–113] When the phospholipid bilayer is exposed to water it forms a continuous closed bilayer that encapsulates hydrophilic and hydrophobic bioactive compounds. Further aggregation of the nanoliposomes can be prevented by repulsion of the charged lipids in the membrane.[114–116] Many bioactive compounds encapsulated in nanoliposomes have prolonged antioxidant activity with more surface area exposed.[113,117,118] Extended circulation of bioactive compounds encapsulated in nanoliposomes in plasma is achieved through a modified surface. Several nanosynthetic compounds have been designed to effectively deliver drugs to the brain.[119,120] Similarly, phtobioactive nanoliposomes, such as *Orthosiphon stamineus* extract nanoliposomes, have higher bioavailability and in vitro antioxidant activity.[121] Curcumin encapsulated nanoliposomes show higher bioavailability after oral treatment in rats with enhanced antioxidant activity.[122] In vitro studies of multifunctional curcumin nanoliposomes proved their ability to cross the blood–brain barrier and were effective against Alzheimer's disease.[123]

Nanoniosomes

Nanoniosomes are liposomes made of nonionic surfactant type vesicles at a nanosize ranging from 10 to 1,000 nm. These niosomes can bind both hydrophilic and hydrophobic bioactive compounds for enhanced delivery.[124–127] They have advantages over other liposomes due to their higher chemical stability, enhanced protection of bioactive compounds, lower toxicity due to their nonionic nature, non-immunogenicity, and enhanced oral bioavailability.[126] Niosomes can leak their bioactive compound contents during dispersion and aggregation but this quite negligible. Furthermore, coating niosomes with PEG prevents their detection by Kupfer cells in blood plasma; thereby, enhancing delivery to the target site. In vitro and in vivo studies have confirmed that smaller sized niosomes are better able to retain a bioactive compound at the target site, regardless of the administration route.[128,129] Some bioactive compounds encapsulated in nanoniosomes have beneficial activities, including antioxidant, antimalarial, antifungal, and anti-Alzheimer's disease.[126,130] Nanoniosomes are frequently used to deliver bioactive compounds to the central nervous system with high efficiency and bioactivity. Ellagic acid-loaded nanoniosomes have been developed for optimal delivery of bioactive compounds to human dermal cells.[129] Synthetic compounds with diameters of 200 nm, such as doxorubicin, have been developed using the nanoniosome technique.[124] Similarly, nanosized ganciclovir niosomes were developed to enhance bioavailability of ganciclovir in plasma for at least 8 hours after administration.[131]

Polymeric nanoparticles

Polymeric nanoparticles are widely used as a carrier for phytobioactive compounds, such as curcumin and resveratrol, which are incorporated into the polymer or adsorbed on the surface by nanoprecipitation or emulsion-diffusion methods to form polymeric nanoparticles.[132] These nanosized particles are used to deliver phytobioactive compounds with minimal toxicity to the target site.[133] Polymeric nanoparticle such as polylactic-co-glycolic acid (PLGA) particles can be hydrolyzed into lactic and glycolic acids, which are readily excreted without much toxicity.[133] Quercetin and voglibose coated with poly-D,L-lactide-co-glycolide nanoparticles with a mean size of 41.3 nm have been developed using a solvent evaporation technique and showed good efficiency for treating diabetes through controlled trans-delivery systems.[134] Similarly, quercetin nanoparticles showed 20-fold increased efficiency and controlled ethanol-induced gastric ulcers in rats.[135] Synthetic PLGA-coated nanoparticles, such

as loperamide-loaded g7 and Pep TGN, were designed for controlled delivery to the brain.[136,137] Curcumin nanoparticles of 80 nm stabilized using poly ethylene glycol were highly stable in an in vitro blood brain mice model of Alzheimer's disease.[29] Similarly, curcumin-conjugated magnetic nanoparticles were used to detect Alzheimer's disease in mice.[138] Curcumin-loaded PLGA nanoparticles of 163 nm were highly bioavailable in liver, heart, spleen, kidney, and brain. In addition, these curcumin-loaded PLGA nanoparticles were effectively retained in brain.[13,139]

Nanoemulsions

Nanoemulsions are a mixture of two immiscible liquids to form a clear stable emulsion of particles <100 nm with higher optical clarity and greater bioavailability of the encapsulated functional compounds.[140] These emulsions are prepared by high-energy and low-energy methods. The high-energy method uses physical force, such as a homogenizer, to obtain the emulsion, and the low-energy method involves spontaneous formation of the nanoemulsion with a suitable surfactant, water, and oil under specified conditions.[141–143] A nanoemulsion is effective for encapsulating various bioactive compounds that are unstable under in vivo conditions for effective delivery to the brain.[144] Oral administration of nanoemulsified curcumin enhances bioavailability of curcumin in mice with reduced inflammation.[144] Similarly, a vitamin E-loaded resveratrol nanoemulsion with 102 nm particles was produced using the spontaneous emulsification technique and reduced brain-induced oxidative stress to treat PD.[145] A pomegranate seed oil nanoemulsion with 135 nm particles was produced using the sonication technique and reduced lipid peroxidation and neuronal loss with strong protective effects.[146] Several other plant bioactive compounds have been studied using nanoemulsion delivery methods, such as a betlunic acid nanoemulsion with 200 nm particles produced by sonication and enhanced bioavailability.[147] A resveratrol nanoemulsion with 128 nm particles produced by high-speed homogenization enhanced bioavailability.[148]

Nanophytobioactive compounds and their role in PD

Plant bioactive compounds are a large group that readily undergoes degradation during oral intake, leading to lower bioavailability to the brain.[9,11,60,66,149–151] Nanosizing of phytobioactive compounds along with suitable protective agents enhances the bioavailability of the compound to the brain.[24,72,95,145,152] A few of the bioactive nanosize compounds with enhanced bioactivity and less toxicity are discussed in this section. Some of these nanobioactive compounds are listed in Table 1.

Nanocurcumin

Curcumin is a highly hydrophobic water insoluble compound widely used in medicines and the pharmaceutical and food industries.[30,122,153,154] Curcumin has multiple health benefits, including antioxidant, antimicrobial, anti-inflammatory, anti-aging, anti-Alzheimer, anti-Parkinson, and anticancer activities.[30,32,94,144,153–155] A lower retention time in circulation leads to the lower therapeutic potential of this compound.[139,144] Reducing the size of the curcumin compound to the nanolevel and formulating it with polyesters leads to higher bioavailability in systemic circulation.[122,123,144,155] Many studies have confirmed that nanosizing curcumin enhances bioavailability and therapeutic efficiency for many diseases including PD.[6,13,29,31,67,94,108,122,138,139] Nanocurcumin greatly reduces the oxidative stress and apoptosis in the brain of PD flies.[156] Similarly, an alginate curcumin nanocomposite has a neuroprotective effect in a transgenic Drosophila PD model with reduced oxidative stress and brain cell death.[156] Choice of the delivery systems is more important to enhance the bioavailability of nanocurcumin in the circulatory system and for crossing the blood–brain barrier.[157] For example, curcumin-loaded PLGA nanoparticles show enhanced bioavailability compared with other nanodelivery systems.[158] The enhanced bioavailability of nanocurcumin in circulation systems has been studied but studies related to the distribution of those compounds in organs are limited. A few studies have confirmed that nanocurcumin is bioavailable in blood plasma and can readily cross the blood–brain barrier into the brain.[13,139] The bioavailability of solid lipid nanocurcumin is greatly enhanced in the mouse brain with significant pharmacological activity.[159,160] Similarly, the bioavailability of nanocurcumin is higher in mouse brain and has a protective effect against the oxidative stress in mice brain.[161] The bioavailability of nanosize curcumin is higher in various PD models, which will lead to the development of more nanodelivery techniques for curcumin treatments.

Nanoginsenosides

Ginsenosides are active compounds predominantly found in ginseng. The type of ginsenoside varies with ginseng variety.[162–164] Ginsenosides are broadly classified into 20(S) glycosides called protopanaxadiol and protopanaxatriol.[165,166] These compounds reduce oxidative

Table 1 Bioavailability of plant-based nanobioactive compounds and their production methods

Bioactive compounds	Production methods	Particle size (nm)	Experiment models	Bioavailability	References
Nanocurcumin	Alginate–curcumin nanocomposite	11.3	Drosophila model	Increase bioavailability and decrease oxidative stress and apoptosis in Parkinson's disease	Siddique et al (2013)[236]
	Solid lipid nanoparticle	190	Balb/c mice	Increase concentrations in lungs	Wang et al (2012)[237]
	PLGA nanoparticles	100–200	HeLa cells	Increase anticancer efficiency	Nair et al (2012)[238]
	PLGA nanoparticles	80–120	Human neuroblastoma SK-N-SH cells	Decrease neurons against oxidative damage in Alzheimer's disease	Doggui et al (2012)[239]
	PLGA nanoparticles	158	Sprague Dawley rats	Increase intravenous bioavailability	Tsai et al (2011)[13]
	PLGA nanoparticles	NA	Sprague Dawley rats	Increase neuroprotective effect	Chang et al (2015)[240]
Nanoginsenosides	Nanoliposome	150	L929 cells	Enhance the survival rate of H_2O_2-damaged cells	Tsai et al (2012)[172]
	Ginsenoside compound K-bearing glycol chitosan conjugate nanoparticles	255 and 296	Cancer cell lines	Exhibited higher cytotoxicity to HT29, HepG2, and HT22 cancer cells	Mathiyalagan et al (2014)[241]
Nanoresveratrol	Nanocapsule	241	Male Wistar rats	Enhanced bioavailability in Alzheimer's disease	Frozza et al (2010)[242]
	PCL–PEG polymeric micelles	100	PC12 cells	Enhanced bioavailability in Alzheimer's disease	Lu et al (2009)[243]
	Eudragit E100	73.8	Male Wistar rats	Decrease oxidative stress and prevent chronic liver disease	Lee et al (2012)[244]
	PEG–PLA–resveratrol conjugates	150	Rat C6 and Human U87 glioma cells	Increase antitumor activity	Guo et al (2013)[245]
	Resveratrol-loaded PEG–PLA polymeric NPs	120–233	Cultured CT26 colon cancer cells in vitro and in CT26 tumor-bearing mice in vivo	Higher antitumor activity	Jung et al (2015)[246]
Nanocatechin	Nanoencapsulation	432–440	Swiss outbred mice	Increase bioavailability	Dube et al (2010)[188]
	Tea polyphenol-loaded chitosan nanoparticles	400–452	HepG2 cells	Increase antitumor	Liang et al (2014)[247]
	Nanoliposome	71.7	In vitro	Increase bioavailability	Zou et al (2014)[187]
	Epigallocatechin-3-gallate gold nanoparticle	64.7	B16F10 murine melanoma cells	Improved anticancer efficacy	Chen et al (2014)[248]
	Epigallocatechin-3-gallate-loaded nanoparticles prepared from chitosan and polyaspartic acid	102	Oral administration to rabbits	Decrease atherosclerosis	Hong et al (2014)[249]
Nanoquercetin	Solid lipid nanoparticles	200	Male Wistar rats	Increase brain antioxidant capacity	Dhawan et al (2011)[197]
	Solid lipid nanoparticles	155.3	Male Wistar rats	Increase sustained release	Li et al (2009)[98]
	Nanosuspension	430	In vitro	Higher antioxidant activity	Karadag et al (2014)[250]
	Nanoliposomes	62.3–191.5	C6 glioma cells	Anticancer activity	Wang et al (2012)[251]
Nanolycopene	Nanostructured lipid carrier	150–160	In vitro	Higher antioxidant activity	Okonogi et al (2015)[215]
	Nanoemulsions	100–200	In vitro	Higher bioavailability	Ha et al (2015)[213]

Abbreviations: NA, not available; NP, nanoparticle; PCL, poly-caprolactone; PEG, polyethylene glycol; PLGA, polylactic-co-glycolic acid.

stress in the liver, brain, and other organs by scavenging hydrogen peroxide radicals. In addition, ginsenosides also play a critical role in reducing the oxidative stress of PD. Ginsenoside Rg1 protects cells against H_2O_2 induced oxidative stress and increases cell survival of a PD model in vitro.[167] Similarly, ginsenoside Rg1 protects neurons against 6-hydroxydopamine-induced death and iron-induced neuronal toxicity.[168,169] Although these compounds play a critical role in reducing oxidative stress, their activities are lower than those of some other compounds in several in vivo studies.[170,171] To increase the activity and bioavailability of these compounds or crude extracts, nanosizing the formulation is an alternative for an enhanced protective effect against PD. The nanoginsenosides Rg1 and Rb1 with 19.9 nm particles synthesized using a nanoemulsion technique have enhanced bioavailability in the brain. Intranasal delivery of these compounds results in better bioavailability in the brain with an enhanced protective effect compared with those of the intragastric administration.[165] In addition to the individual compounds, crude nanoextracts also have a beneficial effect against oxidative stress-related disease. Nanoliposomes of approximately 150 nm containing a ginseng crude extract rich in ginsenosides have been studied for their effect against hydrogen peroxide-induced oxidative stress in L929 cells. That study confirmed that liposomal nanovesicles effectively suppress hydrogen peroxide-induced oxidative stress.[172] Similarly, fabricated nanoginseng extracted powder with 300 nm particles has been synthesized using a ball mill technique and has enhanced bioavailability and antioxidant activity.[173] Similarly, nanoliposomal vesicles loaded with panax notoginsenoside have a protective effect against cerebral ischemia and myocardial ischemia in rats.[174]

Nanoresveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound found widely in grapes, peanut, peanut sprouts, blueberry, cranberry, and mulberry.[34,152,162] Resveratrol has multiple health benefits, including antiaging, anticancer, cardioprotective, and PD protective effects.[66,68,145] Resveratrol exists in cis and trans forms, in which trans-resveratrol is more stable than cis-resveratrol which is pharmacologically less active.[66] Trans-resveratrol is readily converted to cis-resveratrol when exposed to sunlight for 1 hour; therefore, protecting these compounds is biologically more important for a sustained effect. Nanoencapsulation protects trans-resveratrol from this rapid conversion and enhances its bioavailability in systematic circulation for prolonged activity.[68,175] PLGA-coated resveratrol nanoparticles enhance the bioavailability of resveratrol for up to 4 days in a rat model.[176] Their research group also studied sustained release of trans-resveratrol in vitro and found higher solubility and dissolubility of trans-resveratrol.[68,175,176] In addition, a combination of one or two nanosized bioactive compounds has multiple health beneficial effects for certain diseases, which further reduces the multiple drug load. Curcumin and resveratrol encapsulated nanoliposomes have an antitumor effect against prostate cancer. The role of nanoresveratrol in preventing PD and enhancing neuronal survival against oxidative stress has been shown certain study.[145] A vitamin E-loaded nanoresveratrol emulsion prepared with by self-emulsification followed by high-pressure homogenization with particles of 102 nm makes resveratrol available to the brain, thereby reducing the oxidative stress of PD.[145] Several other delivery techniques, such as solid lipid nanoparticles and nanostructured lipid carriers, have been studied for controlled delivery of resveratrol in the gastrointestinal tract. The same research group found that nanoresveratrol with 150–200 nm particles is biologically active with controlled delivery through the gastrointestinal tract in vitro.[92] Similar to PD, Alzheimer's disease can be controlled effectively by treatment with resveratrol-loaded lipid-core nanocapsules.[33,152] Nano resveratrol developed using a suitable delivery technique produces a sustainable protective effect against PD and will lead to the development of more nanodelivery techniques for controlled delivery to the brain and enhanced neuroprotective activity.

Nanocatechins

Catechins are a group of polyphenols in many plant foods, including tea, fruits, and beverages and show multiple health beneficial aspects, such as anti-aging, anticancer, antimicrobial, antiviral, anti-PD, and antioxidative effects.[177–180] The antioxidant activities of catechins are highly protective against oxidative stress-induced PD, as shown by various cell and animal models.[181–183] Although catechins have various health benefits, their bioavailability is low following oral consumption, resulting in reduced circulating levels.[184] Several nanotechnological approaches have been used to enhance their bioavailability with an enhanced protective effect against various disease models by reducing the size to the nanolevel or encapsulating the catechin in a suitable nanoencapsulating system.[185,186] Nanoliposome encapsulation of (−)-epigallocatechin gallate produced at a mean particle size of 71.7 nm enhances antioxidant activity and controls bioavailability.[187] Similarly, tea catechin-loaded

nanoparticles with sizes of 134–354 nm prepared from chitosan show enhanced transport to the intestine with higher antioxidant activity.[188,189] Some studies suggest that epigallocatehin-3-gallate reduced to approximately 50 nm by co-solubilization methods greatly enhances its bioavailability in a rat brain model of Alzheimer's disease.[190] These studies confirm that catechins can be efficiently encapsulated at a nanosize using a suitable nanotechnology involving nanoliposome, nanoemulsion, or nanoencapsulation techniques, thereby protecting the catechin from the gastrointestinal tract.

Nanoquercetin

Quercetin is found at high levels in plant foods, such as fruits, vegetables, and juices. This bioflavonoid has multiple neurobeneficial activities, such as free radical scavenging, antianxiety, neuroprotection, and cognitive enhancing effects.[191–193] Quercetin is chemo labile and thermo labile, which leads to lower bioavailability at the target site.[194] In addition, quercetin has poor solubility and distribution, resulting in less bioavailability to the brain.[194] Nanosizing quercetin greatly increases bioavailability and increases the protective effect at the target site without much loss in the gastrointestinal tract during oral administration.[98,135,195–197] Oral delivery of nanoencapsulated quercetin with a size of 270 nm protects rat brain and liver cells from toxicity induced by arsenic. These studies have confirmed that quercetin is highly protected in the gastrointestinal tract and can be safely delivered to the target site in the brain.[198] The same research group also studied quercetin encapsulated using an emulsion-diffusion-evaporation method to produce nanoquercetin with a size range of 20–50 nm, which showed higher bioavailability in various parts of the brain, such as hypothalamus, cerebellum, and hippocampus, in young and aged rats.[196] Similarly, nanoquercetin developed using a solid lipid nanoparticle delivery technique with a size of 200 nm showed enhanced permeability and a high brain protective effect from Alzheimer's disease.[197] Nanosized quercetin developed using a nanoliposome delivery technique with a size of 200 nm shows enhanced anti-inflammatory activity in MCF-10A cells and enhances cognitive function in a rat model.[199,200] Furthermore, quercetin encapsulated with poly-D,L-lactide nanoparticles with a size of approximately 130 nm produced using a solvent evaporation method enhances retention time to 96 hours.[55,201] These studies confirmed that nanosizing quercetin using various delivery techniques enhances its protective role against various neurological disorder animal models through its antioxidative effects.

Nanolycopene

Lycopene is a naturally occurring carotenoid compound widely found in tomato, watermelon, and pink guava.[54,56,57,202–204] Lycopene has a protective effect against neurological disorders including Alzheimer's and PD by reducing oxidative stress.[205–211] Lycopene supplementation of a rotenone-induced rat model of PD enhances the protective effect against oxidative stress and reduces neurobehavioral abnormalities.[208] However, bioavailability in the gastrointestinal tract was limited after oral administration.[212] Nanosizing lycopene using a self-emulsifying nanodelivery system or nanoemulsion greatly enhances bioavailability of the lycopene.[212–214] Nanosized lycopene prepared using a nanoemulsion delivery technique with a size of 100 nm enhances in vitro antioxidant activity[213] with increased bioaccessibility. Nanolycopene developed using a nanostructured lipid carrier delivery technique with a size of 150–160 nm shows less degradation and enhanced in vitro antioxidant activity.[215] These studies confirm that lycopene can be stabilized using various delivery techniques and is potentially bioavailable for an extended duration to protect against oxidative stress leading to PD. Nanolycopene developed using various delivery techniques will be used in future studies for its role in various diseases including PD.

Nanokaempferol

Kaempferol is a flavonoid found in many plant foods, including tea, broccoli, tomato, drumstick leaves, and beans. Kaempferol has a variety of beneficial effects, including antioxidant, anti-inflammatory, neuroprotective, and anticancer activities.[162,216–222] Kaempferol enhances autophagy in a rotenone-induced acute toxicity model of PD by enhancing mitochondrial antioxidant activity.[223] Kaempferol has a neuroprotective effect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in a mouse PD model.[224] However, bioavailability is limited to approximately 2% after oral administration.[225] Nanosized kaempferol enhances the antioxidant activity of kaempferol.[226] Nanokaempferol developed using a layer-bi-layer technique with a size range of 149–161 nm enhances the bioavailability of kaempferol in bone marrow.[227] Oral bioavailability of kaempferol is enhanced using self-nanoemulsifying drug delivery system and nanoniosome delivery techniques with a size range of 34–141 nm in dog and rat models.[228]

Nanosilibinin

Silibinin is a flavonoid found mostly in milk thistle that has a variety of bioactivities, including anticancer, antioxidant,

neuroprotective, and antidiabetic effects.[43,229–232] Silibinin protects against neuronal loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of PD by stabilizing mitochondria potential, antioxidative, and anti-neuroinflammatory reactions.[230] Similarly, silibinin attenuates mitochondrial dysfunction, oxidative stress, and neuronal loss following injection of MPP^+ in a rat model of PD.[229] Higher doses of silibinin enhance the protective effect in a 1-methyl-4-phenylpyridinium ion-treated animal model of PD in vivo.[43] However, the bioavailability of silibinin to various organs is limited but can be greatly enhanced by nanosizing the compound.[233,234] The bioavailability of silibinin-loaded nanotubes with a size range of 20–30 nm is greatly enhanced in cancer cell lines, even at very low concentrations.[234] PEG-loaded nanoliposomes with a size range of 164–194 nm have also been designed for controlled delivery of silibinin to the liver.[235] These studies confirm that silibinin, which has low bioavailability after oral intake, can be enhanced using a nanotechnological delivery method. Further herbal-derived nanoparticles are a budding approach to treat PD their toxicity was very minimal. It will be a future promising approach to treat PD.

Conclusion

The role of oxidative stress in PD is well understood but treatments using current phytotherapies are limited. Phytobioactive compounds are more vulnerable to various conditions during treatment, leading to lower bioavailability and lower anti-PD effects. Nanotechnology may solve these disadvantages and effectively deliver phytobioactive compounds with sustained activity. Development of nanodelivery techniques is more important for delivery to target organs and cross the blood–brain barrier. Delivery techniques can vary based on the bioactive compound. Several nanodelivery techniques and nanophytobioactive compounds discussed in this review increase the delivery efficiency of compounds to target sites. Further, research should focus on co-delivery of phytobioactive compounds to prevent oxidative stress that leads to various disorders including PD.

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Disclosure

The authors report no conflicts of interest in this work.

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