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REVIEW ARTICLE

Neuroprotective effects of natural polyphenol-loaded nanoparticles

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Abstract

Many natural polyphenolic agents, such as curcumin, catechin, or resveratrol may have significant neuroprotective benefits due to their antioxidant, anti-inflammatory, and antiproliferative effects. The main obstacles to the use of natural polyphenols are low stability, poor solubility, and low bioavailability. Several nano-formulations, including lipid nanoparticles, micelles, liposomes, and polymeric nanoparticles, have been formulated to increase the bioavailability and stability, and thus the therapeutic efficacy of natural polyphenols. In addition to prolonging the half-life, the role of nanoparticles in neuroprotection lies in their ability to cross the blood-brain barrier. Recently, some of these nanocarriers have already been modified with targeted molecules capable of recognizing defined areas of the brain. The review is focused on neuroprotective effects of curcumin-, catechin-, and resveratrol-loaded nanoparticles.

Introduction

Since they can cross the blood-brain barrier, curcumin, catechin, and resveratrol could be regarded as potential therapeutic agents for the treatment of central nervous system-associated diseases (Bandiwadekar *et al.* 2021; Maiti & Dunbar 2018; Shahbaz *et al.* 2021). Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington disease, or amyotrophic lateral sclerosis affect any part of the brain. Although the complete mechanism of neurodegenerative diseases is unknown, there are different molecular mechanisms and processes that could be positively affected. Compared with a classical treatment, natural compounds have better compatibility with the human body along with lesser side effects (Dayar *et al.* 2020,2021; Cebova & Pechanova 2020; Lietava *et al.* 2019; Cebova *et al.* 2017). Moreover, several studies have shown that various natural compounds have significant neuroprotective, antioxidant, and anti-inflammatory properties that might be beneficial in neurodegenerative diseases (Kovacsova *et al.* 2010; Maiti & Dunbar 2018). In addition, natural compounds also eliminate destructed biomolecules before their accumulation affects cell metabolism, thus improving the disease conditions (Bandiwadekar *et al.* 2021). Despite the beneficial effects of natural polyphenols, they have also a few limitations including poor water solubility, low bioavailability, and short systemic circulation which is restrained its clinical application (Na Bhuket *et al.* 2017; Obulesu 2021). To overcome these limitations and enhance the bioavailability, nanoparticle-based delivery systems have been developed and intensively studied (Pecha-

nova *et al.* 2019, 2020; Chen & Liu 2012). Liposomes, polymeric nanoparticles, and solid-lipid nanoparticles are the most studied nanoparticles (NPs) in terms of non-invasive brain drug-delivery materials with specific characteristics like biocompatibility, stability, low antigenicity, and high biodegradability. The capability of nano-systems to cross the blood-brain barrier (BBB) depends on their physicochemical properties, and therefore nanocarriers must meet several requirements as being non-toxic, able to carry the desired drug and able to interact with receptors present at the BBB (Chen & Liu 2012; Neves *et al.* 2016). The nanocarriers have emerged as one the most effective smart platforms for controlled discharge of their cargo in target sites (Masoudi *et al.* 2020). Some nanoparticles are designed to enhance the penetration of BBB and to target specific domains within cells. Their efforts focus on localization of intracellular or to reach extracellular molecules, such as amyloid-beta plaques in Alzheimer's disease (Masoudi *et al.* 2020).

Indeed, natural polyphenols-loaded nanoparticles showed improved effects in both *in vitro* and *in vivo* studies (Yavarpour-Bali *et al.* 2019; Obulesu 2021; Shahbaz *et al.* 2021). Recently it has been reported that curcumin-loaded nanoparticle systems increase the circulating levels of curcumin and improve the chemical stability that results in preventing its enzymatic and pH degradation (Yavarpour-Bali *et al.* 2019). The results of Marslin *et al.* (2017) even showed that curcumin-loaded poly (ethylene glycol) poly (ε-caprolactone) di-block copolymer nanoparticles possess significantly stronger neuroprotective effect in U251 human glioma cells compared to free curcumin and curcumin-loaded poly (ε-caprolactone) nanoparticles (Marslin *et al.* 2017). Smith *et al.* (2010) showed that forming nanolipidic (-)-epigallocatechin-3-gallate particles improves the neuronal (SweAPP N2a cells) alpha-secretase enhancing ability *in vitro* by up to 91% and oral bioavailability *in vivo* by more than two-fold over free (-)-epigallocatechin-3-gallate. Thus, because of better beneficial effects, some natural polyphenols-loaded nanoparticles may represent a useful tool for the treatment of neurodegenerative diseases like Alzheimer's or Parkinson's disease (Yavarpour-Bali *et al.* 2019; Andrade *et al.* 2018).

Curcumin

Curcumin isolated from a plant *Curcuma Longa L.* and presented in spice turmeric is known as a hydrophobic polyphenol (Fig. 1). It has pleiotropic actions and exhibits several therapeutical and pharmacological activities as well as anti-inflammatory, anti-amyloid, antioxidant, and neuroprotective effects. Since it can cross the blood-brain barrier, curcumin could be regarded as a potential therapeutic agent for the treatment of central nervous system-associated diseases (Maiti & Dunbar 2018; Shahbaz *et al.* 2021). Despite the beneficial effects of curcumin, it has also a few limitations including poor water solubility, low bioavailability, and short systemic circulation which is restrained its clinical application (Na Bhuket *et al.* 2017; Obulesu 2021; Barta *et al.* 2015). To overcome these limitations and enhance its bioavailability, nanoparticle-based delivery systems have been developed and showed improved effects of curcumin in *in vitro* and *in vivo* studies (Yavarpour-Bali *et al.* 2019; Obulesu 2021; Shahbaz *et al.* 2021).

Curcumin-loaded nanoparticle

In numerous studies, it has been reported that different curcumin-loaded nanoparticle systems including poly (lactide-co-glycolide) (PLGA), poly (ε-caprolactone) (PCL) or methoxy poly (ethylene glycol) poly (ε-caprolactone (MPEG-PCL), poly-ethylene glycol-polylactic acid co block polymer (PEG-PLA), alginate-curcumin nanocomposite, lipid-core nano-capsules, solid lipid nanoparticles and nanostructured lipid carriers (NLC), nano-emulsion are widely examined in central nervous system disorders. These curcumin-loaded nanoparticle systems increase the circulating levels of curcumin and improve the chemical stability that results in preventing its enzymatic and pH degradation (Yavarpour-Bali *et al.* 2019).

Curcumin encapsulation into PCL or MPEG-PCL in the form of nanoparticles enhanced the aqueous solubility of this compound. The cellular uptake of curcumin-loaded MPEG-PCL nanoparticles was greater than curcumin encapsulated in PCL nanoparticles and free curcumin (Marslin *et al.* 2017). Tsai *et al.* demonstrated that curcumin-loaded PLGA nanoparticles delivered to neuronal cells were present in several regions of the brain such as hippocampus and cerebral cortex (Tsai *et al.* 2011). Doggui *et al.* showed that these nanoparticles were nontoxic to human neuroblastoma SK-N-SH cells. Moreover, they could protect SK-N-SH cells against H_2O_2 and prevent the elevation of reactive oxygen species (ROS) and the consumption of glutathione (Doggui *et al.* 2012). It has been suggested that curcumin encapsulated-PLGA nanoparticles were able to destroy amyloid aggregates, exhibit antioxidative properties and can be used in treating Alzheimer's disease (Mathew *et al.* 2012). Curcumin-loaded PLGA nanoparticles increased the number of synapses, prevented inflammation by decreasing pro-inflammatory cytokines (IL-6, TNF-alpha), and restored antioxidant activity via decreasing the ROS level and increasing the level of superoxide dismutase in the mouse brain (Huang *et al.* 2014). Another study reported that curcumin-loaded PLGA nanoparticles may increase the action of curcumin on several pathways like inhibit the phosphorylation of Akt and Tau proteins in SK-N-SH cells induced by H_2O_2. Moreover, they displayed higher anti-inflammatory and antioxidant activities than free curcumin (Djiokeng Paka *et al.*

2016). PLGA nanoparticles thus represent a promising strategy for the brain delivery of drugs for the treatment of Alzheimer's but also other diseases. Similarly, curcumin-loaded lipid-core nano-capsules displayed significant neuroprotection against β-amyloid1-42 (Aβ1-42)-induced behavioural and neurochemical changes in Alzheimer's disease model (Giacomeli *et al.* 2019).

In an experimental model of epilepsy, curcumin-loaded nanoparticles effectively upregulated the levels of erythropoietin and klotho, which is a life extension factor. Moreover, mRNA level of TNF-α in the hippocampus was considerably reduced after the treatment with curcumin-loaded nanoparticles (Mansoor *et al.* 2018). Curcumin-encapsulated nanoparticles enter the cells and could reduce apoptosis in an *in vitro* model of Huntington's disease, a hereditary neurodegenerative condition. Moreover, curcumin-loaded nanoparticles were efficiently up-taken by a well-validated and widely used neuronal-like Huntington's disease model and no toxic effect was detected (Pepe *et al.* 2020).

Other promising drug delivery systems like SLNs and NLCs may enhance the efficacy of curcumin delivery to the brain. Using these systems, a 1.5-fold higher permeability of curcumin through the blood-brain barrier has been shown. However, the potential of these nano-systems needs to be further explored *in vivo* to demonstrate the interactions with plasma proteins and recognition by the immune system that nanoparticles encounter *in vivo*, as well as to study their biodistribution through body organs and tissues. Both SLNs and NLCs are promising for curcumin brain delivery, protecting the incorporated curcumin, and targeting the brain by the addition of transferrin to the surface of nanoparticles (Neves *et al.* 2021). Curcumin loaded SLNs and dexanabinol increased the mRNA and protein expression levels of the mature neuronal markers' neuronal nuclei, mitogen-activated protein 2, and neuron-specific beta-tubulin III, promoted the release of dopamine and norepinephrine, and increased the mRNA expression of CBR1 and the downstream genes *Rasgef1c* and *Egr1*, and simultaneously improved rat locomotor function. However, SLNs loaded with curcumin and dexanabinol had no antidepressant effects on the *CBR1*$^{-/-}$ mouse models of major depressive disorder (He *et al.* 2021).

Alkynylated cellulose nanocrystals (ACNC) nanoparticle system in alpha-synuclein-induced cytotoxicity in SH-SY5Y neuroblastoma cells (Parkinson's disease model) could reduce apoptosis, postpone the loss of climbing ability, and decrease the oxidative damage (Siddique *et al.* 2013). It has also been demonstrated that ACNC-curcumin can significantly reduce oxidative stress and apoptosis in the brain of Parkinson's disease files (Siddique *et al.* 2014). BSA-based nano-curcumin in SH-SY5Y cells improved p-Akt/t-Akt signalling and prevent cell death (Sookhaklari *et al.* 2018). Curcumin and fish oil-loaded spongosome and cubosome nanoparticles in SH-SY5Y cells decrease the H_2O_2-induced cell death and ROS accumulation (Rakotoarisoa *et al.* 2019). Ramires Junior *et al.* investigated the comparison between curcumin-loaded nano-emulsion and free curcumin in an experimental model of Parkinson's disease. It was reported that both curcumin-loaded nano-emulsion and free curcumin treatment significantly improved motor impairment, reduced lipoperoxidation, modified antioxidant defence, and prevented inhibition of complex I. However, curcumin-loaded nano-emulsion was more effective in preventing motor impairment and inhibition of complex I when compared to free curcumin. These results point to nano-emulsion as a promising nanomedical tool and a neuroprotective strategy for Parkinson's disease (Ramires Junior *et al.* 2021).

Catechins

Catechins belong to the group of flavan-3-ols (flavanols), part of the chemical family of flavonoids (Fig. 1). The main dietary sources of catechins are tea, pome fruits and cocoa. Usual, they are derived from green tea and began to be famous for their beneficial effects on several degenerative diseases (Thangapazham *et al.* 2007; Ananingsih *et al.* 2013). Epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid (EGCG) and is a type of catechin (Fig. 1). EGCG is the most abundant catechin in tea. These polyphenolic compounds are rich in phenolic hydroxyl groups which provide strong antioxidant activity and may play a serious role in protecting against cancer, cardiovascular disease, and other chronic conditions (Khan & Mukhtar 2007; Eng *et al.* 2018; Bernatova 2018). However, similarly to many other natural polyphenols, the pharmaceutical activity of catechins including EGCG is limited due to low bioavailability and chemical instability (Lambert & Yang 2003). For example, when taken orally, EGCG has poor absorption even at daily intake equivalent to 8–16 cups of green tea (Chow *et al.* 2003). It has been shown that different nano-systems serving as catechin carriers may overcome this problem (Yan *et al.* 2019; Kaur *et al.* 2019; Yang *et al.* 2021).

Catechin-loaded nanoparticle

Recently it has been documented that catechin-loaded polylactide nanoparticles further enhance cell survival against toxic protein aggregates. This nanoparticle system has been especially designed as delivery carrier of anti-amyloidogenic molecules (Mandal *et al.* 2020). The encapsulation of EGCG in caseinophosphopeptide (CPP) and chitosan (CS) (CS–CPP) nanoparticles could be a potential approach to enhance its antioxidant activity in biological systems. The encapsulation efficiency of EGCG in CS– CPP nanoparticle was considerably higher than that in CS–tripolyphosphate nanoparticles, and the burst release of EGCG was

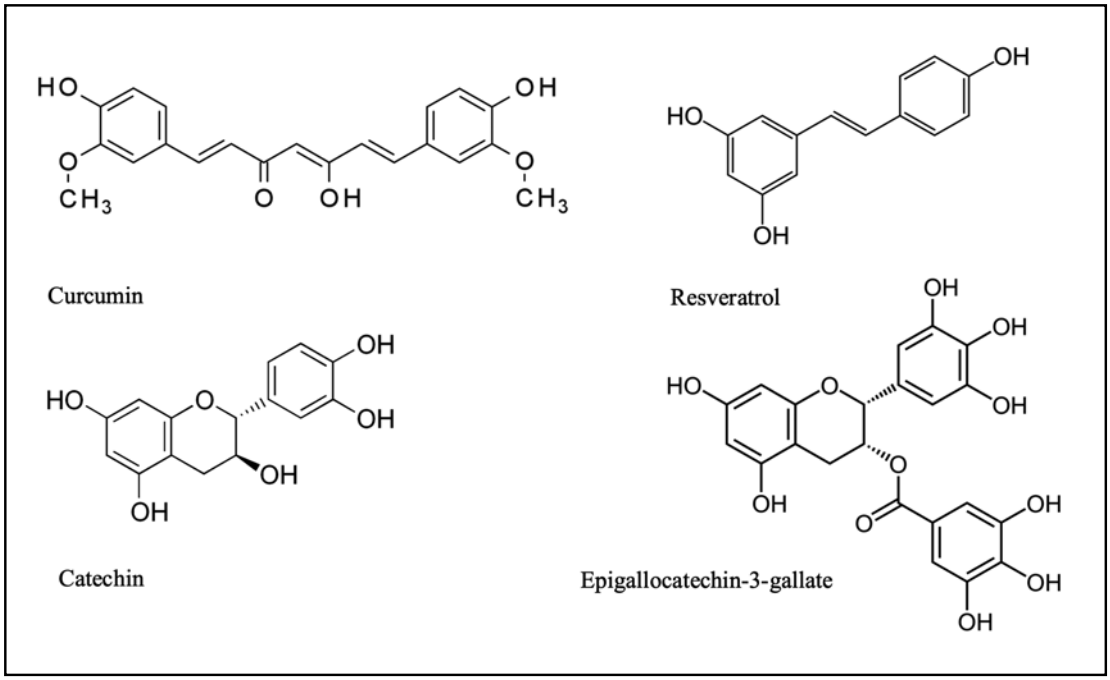

Fig. 1. Formulas of curcumin, resveratrol, catechin, and epigallocatechin-3-gallate.

slowed in a more controllable manner for CS–CPP nanoparticles as well. The nanoparticles assembled with bioactive polysaccharide and bioactive peptides should be efficient carriers for enhancing the bioavailability of EGCG (Hu *et al.* 2013). Combination therapy of curcumin and EGCG encapsulated biopolymer nanoparticle study even showed that presence of EGCG greatly improved the functional properties including the dispersibility, encapsulation properties, and antioxidant activity of curcumin (Yan *et al.* 2019).

In another approach as an oral delivery system, EGCG loaded solid lipid nanoparticles (SLN-EGCG) were developed. Results of this study showed that the SLN-EGCG did not show any acute or sub-chronic toxicity when compared with free EGCG in the rat model. Moreover, pharmacokinetic parameters indicated significantly improved bioavailability and protection of EGCG from degradation due to encapsulation into SLN. SLN-EGCG can enhance the bioavailability and stability and moreover ensure a slow and sustained release of EGCG which was indicative of reduced dosage frequency. Histopathology and toxicity studies further confirmed no treatment-related side effects and suggested that this formulation is safer for oral administration over a longer period (Ramesh & Mandal 2019). In a different study Kaur *et al.* have shown that SLN-EGCG enhanced brain EGCG bioavailability and penetration (Kaur *et al.* 2019).

Poly (ethyleneglycol) and cetyltrimethylammonium bromide (CTAB)-modified silica nanoparticles were synthesized to investigate potential effects of nano-encapsulated catechin on neuronal survival and morphological aberrations in primary rat hippocampal neurons. Catechin was loaded on silica nanoparticles in a concentration-dependent fashion, and release studies were carried out. The findings revealed that, under Cu (II)-induced oxidative stress, the loading ability of the PEGylated/CTAB silica nanoparticles was concentration-dependent, based on their catechin release profile. Catechin-loaded silica nanoparticles enhanced protective activity against oxidative stress and hippocampal cell survival compared to quercetin (Halevas *et al.* 2016).

Dual drug loaded PEGylated PLGA nanoparticles (EGCG/ Acetyl acid NPs) have the potential to be developed as a safe and suitable therapeutic alternative for the treatment of Alzheimer's disease. Oral administration of EGCG/Acetyl acid NPs in mice resulted in EGCG accumulation in all major organs, including the brain. It has been shown that this formulation could be able to increase drug permanence in blood stream and brain tissue (Cano *et al.* 2019). Recently, Yang *et al.* (2021) studied a nano-delivery system surface-modified with RD2 peptide (polypeptide sequence PTLHTHNRRRRR) for brain tissue penetration and β-amyloid (Aβ) binding. Epigallocatechin-3-gallate was selected for encapsulation and its therapeutic potential for Alzheimer's disease was investigated. The four-week RD2-NP/EGCG treatment significantly decreased the expression of the pro-inflammatory cytokine TNF-α and IL-1β, restored neuronal losses and hippocampal damage, and ameliorated spatial memory impairment in Alzheimer's disease model mice. Moreover, treatment with the RD2-NP/EGCG did not present organ toxicity. Surface modified RD2 peptide nano-delivery system can efficiently deliver drugs to Alzheimer's disease lesions and improve the therapeutic effect of EGCG on Alzheimer's disease (Yang *et al.* 2021).

Resveratrol

Resveratrol, known as 3,5,4'-trihydroxystilbene, is a polyphenolic phytoalexin (Fig. 1) that has been extensively studied recently due to its numerous beneficial activities. This natural polyphenolic compound is present in grapes, mulberries, rhubarb, some peanuts, and in several other plants (Galleano *et al.* 2010; Pechanova *et al.* 2020). The neuroprotective effects of resveratrol in neurological diseases, such as Alzheimer's and Parkinson's diseases, are related to the protection of neurons against oxidative damage and prevention of apoptotic neuronal death. Despite significant advantages, the effective use of resveratrol is limited due to its poor solubility, rapid metabolism, and photosensitivity, which severely reduce the bioavailability and bioactivity of resveratrol. Recently discovered nanotechnology appears to be a good strategy for overcoming the pharmacokinetic and absorption properties of resveratrol (Santos *et al.* 2019; Summerlin *et al.* 2015).

Resveratrol-loaded nanoparticle

To improve the solubility, stability, and cellular uptake of resveratrol Jeon *et al.* (2016) used nano-encapsulation with chitosan (CS) and γ-poly (glutamic acid) (γ-PGA). The solubility of resveratrol increases 3.2 and 4.2 times before and after lyophilization by this nanoencapsulation, respectively. Compared with non-nano-encapsulated resveratrol, the nano-encapsulated resveratrol tends to maintain its solubility and antioxidant activity during storage. Moreover, CS/γ-PGA nanoencapsulation was able to significantly enhance the transport of resveratrol across a Caco-2 cell monolayer (Jeon *et al.* 2016).

In a Sprague-Dawley rat model, the resveratrol-loaded polymer nanoparticles had more desirable improvements in resveratrol accumulation within the brain. Moreover, resveratrol-loaded polymer nanoparticles were able to inhibit ferroptosis induced by erastin in HT22 mouse hippocampal cells, which are commonly used in *in vitro* studies to examine neuronal differentiation and neurotoxicity implicated in neurological diseases. In an intracerebral hemorrhage mouse model, resveratrol-loaded polymer nanoparticles were a safer and effective treatment for intracerebral hemorrhage injury (Mo *et al.* 2021). Resveratrol-loaded transferosomes and nano-emulsions were developed and labelled with gold nanoparticles (GNPs). Salem *et al.* (2019) demonstrated that resveratrol-loaded transferosomes significantly enhanced behavioural acquisition and spatial memory function in amnesic rats compared with both the nano-emulsion formulation and the pure resveratrol. Computed tomography demonstrated the accumulation of GNPs in the brains of all treated rats, while superior accumulation of GNPs was observed in the rats that received the transferosome formulation. The histopathology also demonstrated GNP accumulation in the nuclei and cytoplasm in the brain tissues of both the transferosome- and nano-emulsion-treated groups (Salem *et al.* 2019).

Resveratrol-loaded nanoparticles showed positive effects also against rotenone-induced neurodegeneration in rats. The results showed that resveratrol-loaded nanoparticles had comparatively better efficacy than the resveratrol treatment in attenuating the rotenone-induced Parkinson's like behavioural alterations, biochemical and histological changes, oxidative stress, and mitochondrial dysfunction in rats (Palle & Neerati 2018).

In the study of Loureiro *et al.* (2017) it has been shown that solid lipid nanoparticles functionalized with an antibody, the anti-transferrin receptor monoclonal antibody (OX26 mAb), can work as a possible carrier to transport resveratrol to the brain. The cellular uptake of the OX26 SLNs in human brain-like endothelial cells was substantially more efficient than that of normal SLNs and SLNs functionalized with an unspecific antibody. Thus, the transcytosis ability of different SLNs is higher when functionalized with OX-26. In another study (Neves *et al.* 2016) resveratrol-loaded solid lipid nanoparticles were functionalized with apolipoprotein E which can be recognized by the LDL receptors overexpressed on the blood-brain barrier. These nanosystems appear to be a promising strategy for resveratrol delivery into the brain while protecting it from degradation in the blood stream.

Natural polyphenols-loaded nanoparticles and cognition

Several natural polyphenolic compounds have been reported to have positive role in different cognitive processes (Jagla & Pechanova 2015,2020). It has been documented that curcumin-loaded PLGA nanoparticles could activate neurogenesis and repair learning and memory impairments in an amyloid beta-induced rat model of Alzheimer's disease-like phenotypes (Tiwari *et al.* 2014). Also, oral administration of curcumin-loaded PEG-PLA nanoparticles in Tg2576 mice for 3 months remarkably enhanced memory in the contextual fear conditioning test and working memory in the radial arm maze test (Cheng *et al.* 2013). Moreover, EGCG/Acetyl acid nanoparticle treatment increased memory and learning process in the Alzheimer's disease mice model concomitantly with reduction of the Aβ plaques burden, Aβ42 peptide levels and neuroinflammation (Cano *et al.* 2019).

Frozza *et al.* (2013) tested lipid-core nanoparticles in rats exposed to Aβ, comparing the neuroprotective effects of resveratrol-loaded NCs with free resveratrol. The results demonstrated that resveratrol-loaded NCs decreased the harmful effects caused by Aβ, such as, memory loss, learning difficulty, but also reduced synaptophysin levels, activated astrocytes and microglial cells. Free resveratrol improved the adverse effects of Aβ only

partially (Frozza *et al.* 2013). Resveratrol-loaded polysorbate 80 (PS80)-coated poly(lactide) nanoparticles (but not bulk) displayed significant neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced behavioural and neurochemical changes, and social recognition memory (da Rocha *et al.* 2015). Li *et al.* (2021) prepared a small resveratrol-selenium-peptide nanocomposite to enable the application of resveratrol for eliminating Aβ aggregate-induced neurotoxicity and mitigating gut microbiota disorder in aluminium chloride (AlCl3) and d-galactose(d-gal)-induced Alzheimer's disease model mice. Oral administration of TGN-resveratrol@SeNPs improves cognitive disorder through interacting with Aβ and decreasing Aβ aggregation, effectively inhibiting Aβ deposition in the hippocampus, decreasing reactive oxygen species and increasing activity of antioxidation enzymes, and down-regulating Aβ-induced neuroinflammation via the nuclear factor kappa B/mitogen-activated protein kinase/Akt signal pathway.

Conclusion

The results presented in this review demonstrate that besides cell protection in the brain, polyphenol-loaded polyphenols may have serious potential in the prevention and treatment of cognitive disorders. The use of natural polyphenol-loaded nanoparticles also opens the question of possible experimental studies of the effects of polyphenols upon the selected mental operations like focussing the attention, support of memory mechanisms and several individual habits as e.g., professional skills.

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