Research Progress on Nano-Delivered Plant Polyphenols in the Prevention and Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease(AD)is one of the most common neurodegenerative diseases with a complex pathological mechanism,and as the incidence of AD has increased recently,there is an urgent need to develop more effective prevention and treatment methods.Many studies have shown that plant polyphenols have great potential in the prevention and treatment of neurodegenerative diseases,but their bioavailability is poor,limiting their practical applications.The application of nanotechnology can be helpful for the delivery of plant polyphenols.This article aims to elaborate recent progress and challenges in the development of nano-delivery systems for plant polyphenols,and review the common plant polyphenols used for AD treatment and their action mechanisms.

Key words

Alzheimer's disease;plant polyphenols;nano-delivery

1. Introduction

Neurodegenerative diseases (NDs) are characterized by protein deposition and progressive neuronal loss, accompanied by progressive disease progression, physicochemical alterations and dysfunction in the brain and peripheral organs[1-3]. Alzheimer's disease (AD), the most prevalent type of NDs, has a long latent period[4]. Its typical clinical manifestations include progressive memory loss, cognitive impairment as well as psychiatric and behavioral disorders. The hallmark pathological lesions of AD consist of amyloid-beta (Aβ) plaques and neurofibrillary tangles formed by hyperphosphorylated Tau protein[5]. The pathogenesis of AD involves multiple pathways such as mitochondrial dysfunction, oxidative stress, neuroinflammation and dysregulation of the AGEs-RAGE axis[6, 7].AD has become the fifth leading cause of death among urban and rural residents in China. Acetylcholinesterase inhibitors are the primary FDA-approved drugs for AD treatment, whereas they are limited by obvious side effects and poor brain targeting due to the blood-brain barrier (BBB)[8]. Antioxidants and anti-inflammatory agents are commonly adopted as adjuvant therapies[9]. Plant polyphenols exhibit prominent antioxidant activity, yet their clinical application is restricted by low bioavailability. Nanoparticle-based delivery systems can stabilize polyphenols and exert targeted therapeutic effects. This review summarizes the latest research progress on plant polyphenols against AD and their nano-delivery strategies, so as to provide references for relevant research and development.

2. Preventive and Therapeutic Effects of Plant Polyphenols against Alzheimer's Disease and Underlying Mechanisms

Plant polyphenols are biologically active substances with high biosafety, exerting multiple neuroprotective effects including anti-oxidation and anti-inflammation. Studies have demonstrated that dietary polyphenols can modulate the AGEs-RAGE axis and microbiota-gut-brain axis, thereby preventing neurodegenerative diseases (NDs)[7]. Owing to their neuroprotective properties, plant polyphenols possess great potential for the prevention and treatment of AD.In recent years, nanotechnology has been widely adopted to improve the bioavailability of plant polyphenols. Quercetin (QT), curcumin (Cur), resveratrol (Res), anthocyanidin (An) and procyanidins (PCs) are the most frequently investigated polyphenols in nano-delivery systems. This review mainly elaborates the preventive and therapeutic effects of the first three polyphenols and their nanocomposites on AD..

2.1 QT

Quercetin (QT), a flavonoid widely distributed in plants, especially fruits and vegetables[10]. QT exerts multiple health-beneficial effects including anti-tumor, anti-oxidant, anti-inflammatory and anti-infective activities[11]. To date, extensive in vitro and in vivo studies have validated the preventive and therapeutic efficacy of QT against AD[12-14].QT suppresses the generation of reactive oxygen species (ROS) and ameliorates mitochondrial dysfunction. Its chemical structure contains two antioxidant moieties: the catechol group on the benzene ring and the hydroxyl group at the C3 position, which endow QT with free radical-scavenging capacity[15]. In addition, QT mitigates Aβ-induced neurotoxicity via inhibiting the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway and preserving cholinergic function[16].

2.2 Cur

Turmeric is a common food spice and colorant with a long application history in China and India, and curcumin (Cur) is extracted from the rhizome of turmeric[17]. Cur possesses antifungal, antiviral, anti-inflammatory and antioxidant properties. In vivo studies have verified that Cur can treat a variety of diseases including diabetes, obesity, neurological disorders and tumors[18].Existing research has confirmed

that Cur can inhibit Aβ aggregation and Tau protein hyperphosphorylation. Shimmyo et al.[19] demonstrated via in vitro experiments that Cur suppresses the upregulation of β-secretase 1, thereby reducing Aβ production. Moreover, Cur also exerts anti-inflammatory effects and metal ion chelating activity[20].

2.3Res

Resveratrol (Res) is abundant in berries, nuts and red wine, and exhibits anti-inflammatory, anti-tumor, anti-aging, antioxidant and neuroprotective activities[21]. Res protects the blood-brain barrier (BBB), inhibits Aβ aggregation and exerts anti-inflammatory effects in the nervous system. Moussa et al.[22] evaluated the anti-inflammatory mechanism of Res through clinical trials, and the results revealed that compared with the placebo group, Res significantly reduced the level of matrix metalloproteinase 9 (MMP9) in the cerebrospinal fluid of AD patients. Since MMP9 regulates BBB permeability, Res maintains BBB integrity by downregulating MMP9; meanwhile, Res decreases the levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), suppressor of cytokine signaling 2 and interleukin 12 (IL-12). In addition, Deng Haoyue et al.[23] found that Res could induce autophagy by upregulating the TyrRS-PARP1-SIRT1 signaling pathway, thereby alleviating neurotoxicity induced by $A\beta_{25-35}$.

3. Therapeutic Effects and Mechanisms of Nano-Delivered Plant Polyphenols against Alzheimer's Disease

Nanoparticles (NPs) range from 1 to 100 nm in diameter and can optimize the pharmacokinetic properties of drugs[24]. The complexes formed by drugs and NPs possess high stability, which can protect drugs from damages induced by internal and external environmental factors including temperature, pH and enzymes[25]. Furthermore, NPs can cross the blood-brain barrier for precise targeted drug delivery, achieve sustained drug release and reduce toxic side effects[26]. With favorable biocompatibility and biosafety, NPs loaded with plant polyphenols can improve their bioavailability and realize the protection and targeted release of active ingredients[27]. Common nanocarriers include liposomes, phospholipid complexes, nanobodies, protein-based nanoparticles, micelles, emulsions and metallic nanoparticles[28].

3.1 Nano-Delivered Quercetin (QT)

Despite the extensive pharmacological activities of QT, its low solubility, poor intestinal absorption and rapid in vivo metabolism lead to low bioavailability[29], which restricts its application in the prevention and treatment of AD. Sun Dongdong et al.[30] fabricated functionalized QT-loaded nanoparticles (PLGA@QT NPs). Relevant studies confirmed that PLGA@QT NPs could effectively inhibit Zn^{2+}-triggered $A\beta_{42}$ aggregation and elevate neuronal viability. Behavioral tests further demonstrated that administration of PLGA@QT NPs alleviated cognitive impairment in APP/PS1 mice. In addition, Moreno et al.[31] adopted zein nanoparticles as carriers to encapsulate QT and synthesized corn protein-quercetin nanoparticles (NPQ). The results revealed that zein nanocarriers markedly boosted the bioavailability of QT, and the resulting QT nanoparticles exerted moderate anti-inflammatory effects.

3.2 Nano-Delivered Curcumin (Cur)

To enhance the bioavailability of Cur, numerous studies have adopted diverse complexing agents such as cyclodextrins, phospholipids, gelatin, polysaccharides and proteins, as well as encapsulated Cur within biodegradable nanomaterials[32]. Nanoparticle encapsulation not only improves Cur solubility but also prolongs its systemic circulation time and cerebral retention duration[33]. Hoppe et al.[34] constructed curcumin lipid-core nanocapsules (Cur-LNCs). Their research indicated that Cur-LNCs at 1/20 of the effective dose of free Cur achieved equivalent neuroprotective efficacy. Both free Cur and Cur-LNCs significantly suppressed the upregulation of glial fibrillary

acidic protein (GFAP), Iba-1 and pro-inflammatory cytokines (TNF-α, IL-1β) induced by $A\beta_{1-42}$ peptide. Moreover, free Cur and Cur-LNCs exerted neuroprotective effects by upregulating the phosphorylation level of BDNF.

3.3 Nano-Delivered Resveratrol (Res)

In recent years, a variety of resveratrol-based nanocomposites have been developed. Res-loaded selenium nanoparticles (SeNPs) can inhibit Aβ aggregation and reduce reactive oxygen species (ROS) production. Selenium (Se), an essential trace element for brain function, exerts beneficial effects on human health. SeNPs feature high biosafety, favorable stability and intrinsic antioxidant capacity. Yang Licong et al.[35] synthesized Res@SeNPs by conjugating Res with SeNPs; Res and SeNPs displayed synergistic antioxidant activity. Res@SeNPs bind to $A\beta_{42}$ and block metal ion binding sites on $A\beta_{42}$, thereby mitigating metal-induced $A\beta_{42}$ aggregation and ROS overproduction. Dysregulation of intestinal microbiota facilitates Aβ generation and lipopolysaccharide (LPS) secretion, impairs the intestinal mucosal barrier, activates microglia and ultimately triggers neuroinflammation[36]. Li Changjiang et al.[37] modified the surface of Res@SeNPs with the BBB-penetrating TGN peptide to construct TGN-Res@SeNPs. Experimental outcomes illustrated that this biomimetic nanocomposite protected intestinal homeostasis, restored the disordered gut microbiota in aluminum chloride and D-galactose -induced AD mice, increased the diversity and abundance of intestinal flora, suppressed microglial activation and lowered the secretion of pro-inflammatory cytokines

In summary, nanocarrier-mediated delivery of plant polyphenols possesses multiple advantages and can effectively exert anti-AD effects, including anti-inflammatory activity as well as inhibition of Aβ production and deposition.

4. Conclusion

In addition to the polyphenols mentioned in this review, numerous plant polyphenols such as ferulic acid, chlorogenic acid, naringenin and apigenin exhibit neuroprotective activities. Liposomes, spherical nano/micro phospholipid vesicles widely used for polyphenol delivery, can improve the stability of polyphenols and facilitate their brain entry[38]. Liposomes are characterized by good biosafety, biodegradability, favorable blood-brain barrier permeability, prolonged in vivo circulation and low immunogenicity. Nevertheless, they generally suffer from low drug loading and encapsulation efficiency, and optimizing these two indicators remains an urgent challenge to be addressed. Novel biomimetic nanomaterials will become the mainstream direction of subsequent research and development.Nanocarrier-polyphenol composite systems can inhibit Aβ aggregation and Tau hyperphosphorylation, alleviate AD symptoms via anti-inflammation, reactive oxygen species scavenging and oxidative stress mitigation, and some systems can also regulate dysregulated intestinal microbiota. Polyphenols serve as the core active components, while nanocarriers improve blood-brain barrier penetration; modified nanocarriers also possess inherent neuroprotective effects. At present, this delivery system is limited by the single varieties of available polyphenols and carriers, and the transit time and targeted localization of nanoparticles across the blood-brain barrier cannot be accurately quantified. Comprehensive evaluation of the bioactivity and stability of encapsulated polyphenols as well as the biosafety of heavy metal-containing nanoparticles is also required. Future research should optimize the safety and pharmacokinetic properties of nanomaterials, and conduct clinical trials to verify the safety and therapeutic efficacy of nanoparticles on the basis of in vitro and in vivo experiments.

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