Natural Molecules for Neurodegenerative Diseases

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Contributor: Yan Dou, Dongju Zhao

Natural molecules with favorable safety profile and broad pharmacological activities have shown great promise in the treatment of various neurodegenerative diseases (NDDs). Studies applying natural molecules against NDDs mainly focus on well-recognized conventional pathogenesis, such as toxic protein aggregation, oxidative stress, and neuroinflammation. However, accumulating evidence reveals that some underlying pathogenic mechanisms are involved earlier and more deeply in the occurrence and development of NDDs, such as ferroptosis, energy metabolism disorders, autophagy-lysosomal dysfunction, endoplasmic reticulum stress, and gut dysbiosis. Therefore, determining whether natural molecules can play therapeutic roles in these emerging pathogenic mechanisms will help clarify the actual targets of natural molecules and their future clinical translation.

Keywords: neurodegenerative diseases ; natural molecules ; emerging pathogenic mechanisms

1. Introduction

Neurodegenerative diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS), are characterized by progressive degradation of neuronal structure and function in the central nervous system [1]. Among them, AD is the most common NDD with cognitive impairment as the main clinical performance, and its main pathological features are deposition of amyloid-β (Aβ) protein and neurofibrillary tangles composed of hyperphosphorylated tau protein. PD presents with movement disorders such as bradykinesia, tremor, and unsteady gait, commonly attributed to the loss of nigrostriatal dopaminergic neurons and aggregates of α-synuclein. HD is a devastating inherited NDD caused by the mutant huntingtin (mHTT) gene that induces non-functional or toxic misfolded proteins, characterized by choreiform movements, psychiatric abnormalities, and cognitive deficits. ALS is known for rapid progression of severe muscle weakness and atrophy owing to the degeneration of motor neurons in brain and spinal cord, usually leading to death due to respiratory failure within two to five years of onset.

Although the clinical symptoms and pathological manifestations of NDDs are well recognized, they are still incurable. The incidence of NDDs not only rises rapidly with the aging of the world's population, but also presents a younger trend in recent years. Existing drugs can only relieve some symptoms but fail to block disease progression, so there is an urgent need to explore effective therapeutic strategies to combat NDDs. Given that the pathogenesis of NDDs is complex and still not fully elucidated, there is a prevailing view that the most widely studied pathological manifestations such as characteristic protein aggregation are only the consequences rather than the causes of disease development. Some conventional pathogenic mechanisms, such as oxidative stress, neuroinflammation, and mitochondrial dysfunction, have been recognized to be closely related to the progression of NDDs. Specifically, oxidative stress caused by excessive production and weak clearance of reactive oxygen species (ROS) and reactive nitrogen species can lead to the oxidation of intracellular biomolecules for neuronal apoptosis. Aberrant activated glial cells can secrete large amounts of pro-inflammatory cytokines, inducing chronic neuroinflammation to damage neuronal structure and function. Abnormal mitochondrial division, fusion, and degradation can alter energy production and signal transduction in neurons or glial cells, resulting in neuronal death and synaptic loss. In contrast, several emerging pathogenic mechanisms have recently been discovered to be involved earlier and more deeply in the occurrence and development of NDDs, including ferroptosis, energy metabolism disorders, autophagy-lysosomal dysfunction, endoplasmic reticulum (ER) stress, and gut microbiota dysbiosis [2][3][4][5][6].

Among the numerous potential drugs, natural molecules mainly derived from plants show excellent biosafety and various beneficial pharmacological activities [7]. Many studies have revealed that natural molecules are effective against a variety of intractable diseases, such as cardiovascular disease, cancer, and NDDs [8][9][10][11][12]. At present, the potential targets of neuroprotective effects of natural molecules are mainly focused on well-recognized conventional pathogenesis, such as toxic protein aggregation, oxidative stress, and neuroinflammation [10][13]. For example, berberine and curcumin have been investigated to inhibit Aβ and α-synuclein accumulation in AD model APP/tau/PS1 transgenic mice and

lipopolysaccharide-induced PD mouse model, respectively [14][15]. 3-alkyl luteolin derivatives were found to decrease oxidative stress in HD mouse striatal cells [16], and Ginsenoside Re could attenuate neuroinflammation in a symptomatic human-superoxide dismutase 1 ($hSOD1^{G93A}$) mouse model of ALS [17]. However, due to the wide range of pharmacological effects of natural molecules, it is of great significance to determine whether natural molecules can play therapeutic roles in these above-mentioned emerging pathogenic mechanisms, which will contribute to clarifying the actual targets of natural molecules and their future clinical translation.

2. Intracerebral Administration Strategies for Natural Molecules

Although natural molecules in the existing studies were all tested in vivo by gavage and intraperitoneal injection for in vivo experiments, enhancing their bioavailability and efficiency into the brain remains challenging. The blood–brain barrier (BBB) protects the brain from exogenous toxic stimulation, but also prevents most poorly water-soluble natural molecules from entering the brain parenchyma. Therefore, enhancing the intracerebral bioavailability of natural molecules is beneficial to improve their efficacy against NDDs.

Nanotechnology-based drug carriers can not only improve the solubility and biocompatibility of natural molecules through entrapping, but also mediate the crossing of the BBB through surface-modified ligands, which have emerged as an effective alternative strategy for the delivery of natural molecules into the brain. A current study by Qu et al. showed that the relative bioavailability of nano-honokiol by gavage was significantly increased by 1.9-fold than that of free honokiol through improving its solubility, thereby better inhibiting neuropathology and modulating gut microbiota to alleviate cognitive impairment in TgCRND8 mice for AD treatment [18]. Li et al. designed resveratrol-based nanoparticles modified with the BBB transport-targeting peptide TGN (TGN-Res@SeNPs) for AD treatment, and their in vitro BBB transport efficiency was 75%, much higher than the 12% of the unmodified nanoparticles (Res@SeNPs) and 4% of free resveratrol [19]. Liu et al. used focused ultrasound and microbubbles to open the BBB to deliver quercetin for reducing ER stress-induced AD pathology [20]. Although natural molecule-based nanoformulations targeting emerging pathogenic mechanisms have been shown to be effective in AD treatment, their therapeutic effects in PD, HD, and ALS need further exploration. In addition, inconsistent criteria for assessing nanomedicine quality and efficacy are a major obstacle and challenge for natural molecule-based nanoformulations' development.

Intranasal administration has become a promising strategy to deliver drugs into the brain via bypassing the BBB [21]. Therapeutic agents are directly transported from the nose to the brain through olfactory and trigeminal nerve pathways, requiring shorter transportation time to enter the central nervous system than traditional administration routes into the systemic circulation. However, intranasal administration is usually suitable for a small volume administration of highly concentrated water-soluble drugs, while natural molecules are generally difficult to dissolve in water and have a limited ability to penetrate the nasal mucosa. Therefore, the therapeutic effect of using natural molecules alone via intranasal administration is not ideal enough [22]. Recently, intranasal administration in combination with nanoformulations is beneficial to fully exploit the advantages of intranasal administration. A previous work reported a nanoformulation of quercetin entrapped by human serum albumin to exert excellent antioxidant therapeutic effects in 11-month-old APP/PS1 mice via intranasal administration [23]. Liu et al. developed a self-assembled curcumin analogue nanoformula (NanoCA) that was delivered into the brain by a rapid arousal intranasal delivery system for PD therapy [24]. In the future, more focus should be placed on the pharmacokinetics, metabolism, and distribution of natural molecule-based nanoagents administered intranasally, which are currently few but crucial for clarifying pharmacological effects and promoting clinical translation of natural molecules.

3. Clinical Trails of Natural Molecules for NDD Treatment

Given the above-described excellent therapeutic potential and the natural safety profile, natural molecules show excellent promise for clinical translation into NDD treatment. Therefore, it is necessary to conduct clinical trials to test the actual therapeutic effects of natural molecules in human NDD patients. **Table 1** summarized natural molecule-based therapeutic agents currently in clinical trials for NDDs, screened by disease and drug as key items from the website (https://clinicaltrials.gov, accessed on 20 August 2022) of the Comprehensive Database of Clinical Trials administered by the U.S. Food and Drug Administration (FDA) or the National Institutes of Health. Most of the listed clinical trials have been approved for execution within the last 3–5 years, and less than half have just begun recruiting subjects. The goal of these clinical reagents is to demonstrate the safety and efficacy of natural molecule-based therapeutics, with little focus on specific mechanisms of action or only for conventional pathogenesis and lack of in-depth exploration of emerging pathogenic mechanisms. Among the current clinical trials targeting the four most common NDDs, AD is the most widely investigated disease treated by natural molecules, while the clinical research of natural molecules for the treatment of other NDDs needs to be further explored and carried out. In addition, clinical trials of natural molecule-based

nanomedicines are also highly anticipated in the future, but there are still many obstacles and more preclinical research support is needed.

Table 1. Natural molecule-based therapeutic agents currently in clinical trials for NDDs (available online: https://clinicaltrials.gov, accessed on 20 August 2022).

Natural Molecule-Based Agents	Disease	Status (CT.gov ID)	Phase	Date
Caffeine	AD	Recruiting (NCT04570085)	Phase 3	2021–2024
Colchicine	ALS	Active, not recruiting (NCT03693781)	Phase 2	2019–2022
Combination product: antioxidants	ALS	Recruiting (NCT04244630)	Phase 2	2022–2023
Conventional medication and chinese herbal medicine	PD	Not yet recruiting (NCT05001217)	Phase 2, 3	2021–2023
Curcumin and yoga	AD	Active, not recruiting (NCT01811381)	Phase 2	2014–2020
Dasatinib and quercetin	AD	Active, not recruiting (NCT04063124)	Phase 1, 2	2020–2022
Dasatinib and quercetin	AD	Enrolling by invitation (NCT04785300)	Phase 1,2	2022–2023
Dasatinib and quercetin	AD	Recruiting (NCT05422885)	Phase 1, 2	2022–2023
Dasatinib and quercetin	AD	Recruiting (NCT04685590)	Phase 2	2021–2032
DHA	AD	Active, not recruiting (NCT03613844)	Phase 2	2018–2025
Flos gossypii flavonoids tablet	AD	Recruiting (NCT05269173)	Phase 2	2020–2023
Ganoderma	PD	Recruiting (NCT03594656)	Phase 3	2018–2021
Huperzine A	AD	Not yet recruiting (NCT02931136)	Phase 4	2019–2025
Icosapent ethyl (IPE)	AD	Active, not recruiting (NCT02719327)	Phase 2, 3	2017–2023
Medical cannabis	PD	Recruiting (NCT05106504)	Unknown	2021–2024
Meganatural-Az grapeseed extract	AD	Active, not recruiting (NCT02033941)	Phase 2	2014–2021
Memantine and sodium oligomannate (GV-971)	AD	Not yet recruiting (NCT05430867)	Phase 4	2022–2024
Omega-3	AD	Recruiting (NCT03691519)	Phase 3	2018–2023
Omega 3 PUFA	AD	Active, not recruiting (NCT01953705)	Phase 2	2014–2021
Rapamycin	AD	Recruiting (NCT04629495)	Phase 2	2021–2024
Salsalate	AD	Active, not recruiting (NCT03277573)	Phase 1	2017–2021
Scopolamine, atropine, edaravone and dexmedetomidine	ALS	Not yet recruiting (NCT04391361)	Phase 2	2020–2023
SLS-005 (Trehalose injection)	AD	Not yet recruiting (NCT05332678)	Phase 2	2022–2024

Natural Molecule-Based Agents	Disease	Status (CT.gov ID)	Phase	Date
Sodium oligomannate capsules (GV-971)	AD	Recruiting (NCT05058040)	Phase 4	2021–2024
Sodium oligomannate (GV-971)	AD	Recruiting (NCT04520412)	Phase 3	2020–2026
Sodium oligomannate capsules (GV-971)	AD	Recruiting (NCT05181475)	Phase 4	2021–2025
Sulforaphane	PD	Not yet recruiting (NCT05084365)	Phase 2	2021–2022
Trehalose	AD	Recruiting (NCT04663854)	Phase 1	2020–2022
Trehalose	PD	Not yet recruiting (NCT05355064)	Phase 4	2022–2023
Yangxue Qingnao pills	AD	Recruiting (NCT04780399)	Phase 2	2021–2024

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