

Lipid nano-carriers with herbal extracts for targeted brain delivery and treatment of CNS disorders

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Neurodegenerative disorders

According to reports of the Global Burden of Disease Study (2016), the neurological disorders, among which are the neurodegenerative diseases (ND), are the leading cause of disability and the second leading cause of death worldwide. ND can be defined as conditions where the progressive neuronal loss in the central nervous system (CNS) provokes physical disability, cognitive deficits or both. The major basic mechanisms leading to slow progressive and irreversible dysfunction and loss of neurons and synapses can be result of different genetic, environmental and endogenous factors. Common pathological molecular mechanisms and pathways included in the ND development and progression include: abnormal protein dynamics, degradation, proteasomal dysfunction and aggregation; oxidative stress and formation of reactive oxygen species; mitochondrial dysfunctions and DNA damage; fragmentation of neuronal Golgi apparatus; disruption of cellular/axonal transport; neurotrophin dysfunction as well as different neuroinflammatory and neuroimmune processes which finally result in cell dysfunction and death (Jellinger, 2010).

Therapeutic treatments for ND

Since ND are disorders with a wide range of different pathophysiologies and insufficient information and understanding of the mechanisms and cascades involved, the therapeutic options for this type of diseases is quite limited (Duares et al., 2018). On the other hand, the complexity of the blood-brain barrier (BBB), the main

physiological barrier that selectively and specifically controls the entry of endogenous and exogenous molecules from the blood into the brain, additionally affects the efficacy of the treatment. Some of the therapeutic strategies currently used for AD treatment are: protein aggregation inhibitors ($iA\beta 5$ - Chaperon), cholinesterase inhibitors (Donepezil and Rivastigmine), regulation of Amyloid precursor protein by Latrepirdine, glutamate regulators (Memantine) and amyloid directed antibody (Aducanumab). Additionally, PD therapy is consisted of combination of Levodopa and Carbidopa, inducers of Hsp104 chaperones, targeting of α -synuclein misfolding with Hsp 70, anti-inflammatory drugs against Methyl-4-phenylpyridinium induced autophagy and knockdown of Sirt2 by siRNA, while the options for ALS is reducing the oxidative stress with Vitamin E and using glutamate receptor antagonists (Riluzole). Dopamine receptor blockers (phenothiazines), targeting of mHTT misfolding with Hsp70, immunomodulation therapy and Rapamycin-induced autophagy as well as RNAi-mediated silencing of host-encoded cellular prion protein (PrPC) are the treatment options for Huntington disease. Medication approaches for MS treatment include immunomodulation by beta-interferon, Ocrelizumab and hormonal replacement therapy (Lampteu et al., 2022; Poddar et al., 2021).

However, many of the approved drug regimens for ND help to treat the symptoms but do not prevent or reduce the progression of NDs.

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Herbal resources as therapeutic option for ND treatment

In the last two decades, the use of molecules from herbal sources is reported to complete and/or assist the traditional pharmacological agents in the treatment of ND, as a result of their numerous neuroprotective properties.

In the literature, there are several *in vivo* and *in vitro* studies confirming the antioxidant and anti-inflammatory activity of the phenolic acids (rosmarinic acid, chlorogenic acid, gallic acid), phenolic diterpenes (carnosic acid, carnosol), pentacyclic triterpenes (ursolic, oleanolic, butilic acid), flavonoids (derivatives of apigenin, luteolin and epicatechin gallate) present in the extracts of *Rosmarinus officinalis*, *Salvia officinalis* and Green tea. Apart from their free radical scavenging and metal chelating properties, the neuroprotective activity is enriched with decrease of apoptotic neuronal cell death, motor and memory impairment and protein aggregation and deposition by the inhibitory effect on dopamine transporters, activation of NF- κ B and ERK and p38 mitogen-activated protein kinase pathways, decrease of COX-2 expression as well as inhibition of brain secretases (Shalabaliija et al., 2021). Among the wide range of activities, the ginsenosides and saponins in Ginseng, Ginkgo Biloba constituents and Curcumin show inhibitory effect on the acetylcholinesterase and Caspase-3 activation, decrease of TNF- α , IL-1 β and IL-6 mRNA, decreased gene expression and proteins involved in metabolic pathways leading to neuronal death, as well as increased function of mitochondrial respiratory chain, thus resulting in prevention of the cascade reactions included in development and progression of AD and PD (Abdel-Salam, 2019). However, due to their low stability, fast metabolism, trivial permeability, poor water solubility leading to low bioavailability, their clinical use is quite limited. Hence, developing different drug delivery approaches would be a prospective solution to these problems.

Lipid nano-carriers with herbal extracts

Treatment of ND with lipid nano-carriers may have significant advantages in terms of proper biocompatibility and biodegradability, improvement of the drug pharmacokinetic and therapeutic efficacy, as well as reduction of the drug adverse effects. Literature data suggests that there have been developed many lipid-based nano-carriers with incorporated herbal extract components such as: wide range of Curcumin loaded nanoliposomes, lipid based NPs, solid lipid NPs (SLN) and lipid core NPs mainly intended for AD and PD treatment. On the other hand, many studies showed that

Quercetin loaded nano-lipid carriers, SNLs and liposomes, as well as Resveratrol into lipidic core NPs and nanoemulsions have improved bioavailability, transport and efficacy to the brain (Moradi et al., 2020).

In this sense, the application of lipid nano-carriers may significantly improve the clinical efficacy of herbal components in neurological disorders. Therefore, the activities of the Institute of Pharmaceutical Technology at the Faculty of Pharmacy in Skopje, in the last few years is oriented towards formulation, development and characterization of lipid nano-carriers loaded with herbal extracts intended for efficient brain delivery.

References

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