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Nanoformulation of Herbal Extracts in Treatment of Neurodegenerative Disorders

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Abstract: *Nanotechnology is one of the methods that influenced human life in different ways and is a substantial approach that assists to overcome the multiple limitations of various diseases, particularly neurodegenerative disorders (NDs). Diverse nanostructures such as polymer nanoparticles, lipid nanoparticles, Nano liposomes, nano-micelles, and carbon nanotubes (CNTs); as well as different vehicle systems including poly lactic-co-glycolic acid, lactoferrin, and polybutylcyanoacrylate could significantly increase the effectiveness, reduce the side effects, enhance the stability, and improve the pharmacokinetics of many drugs. The central nervous system (CNS) encompasses the brain and spinal cord and is considered the processing center and the most vital part of human body. The central nervous system (CNS) barriers are crucial interfaces between the CNS and the periphery. Among all these biological barriers, the blood-brain barrier (BBB) strongly impede hurdle for drug transport to brain. It is a semi-permeable diffusion barrier against the noxious chemicals and harmful substances present in the blood stream and regulates the nutrients delivery to the brain for its proper functioning. Neurological diseases owing to the existence of the BBB and the blood-spinal cord barrier have been terrible and threatening challenges all over the world and can rarely be directly mediated. There are some main possible reasons for failure in the treatment of neurodegenerative diseases such as limitations introduced by the blood–brain barrier (BBB), the Blood-Cerebrospinal Fluid Barrier (BCFB) and P-glycoproteins. Current advances in nanotechnology present opportunities to overcome mentioned limitations by using nanotechnology and designing nanomaterial improving delivering active drug candidates.*

Keywords: herbal extracts, nanoparticles, nanoformulations, neurodegenerative disorders

I. INTRODUCTION

In recent years, the increase in the proportion of the ageing population worldwide has escalated the incidence of Neurodegenerative disorders (ND) [1] ND, characterized by the progress've loss of structure or function of neurons, is often associated with neuronal death and morbidity. In spite of many studies and some progress, successful early diagnosis and treatment strategies of these diseases are still limited. Furthermore, the majority of current available treatments are symptomatic and unable to reform the quality of life and delay or ameliorate damage.[2]To maintain a perfect brain environment, the fluids surrounding neurons and shielding them from mechanical disturbances must be tightly regulated [3]. Brain cells are not only protected by fluids but also by the blood-brain barrier (BBB). The physical barrier known as the BBB comprises specialized endothelial cells, astrocytes, pericytes, and neurons that keep the brain in a state of homeostasis by closely maintaining the flow of chemicals into the CNS [4].

Neurodegenerative disorders:

Although the peripheral neurological system (PNS) is also affected, the CNS is affected the most among the aging population [5].Neuronal brain and spinal cord loss are a hallmark of many diseases. Alzheimer's, Parkinson's,

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Huntington's illnesses, multiple sclerosis, and amyotrophic lateral sclerosis are a few examples of neurodegenerative diseases (Figure 1).

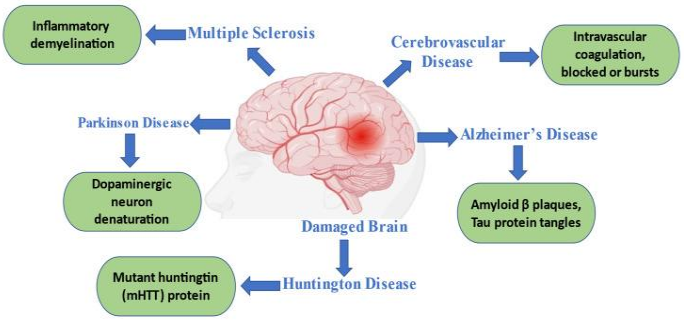

Figure 1.Common neurodegenerative disorders with their pathophysiological indications.

1. Alzheimer's Disease (AD)

The primary cause of dementia in late adulthood is Alzheimer's disease, which is recognized as a progressive, multifaceted neurological condition [6]. Alois Alzheimer first introduced the concept of AD in 1906. Amyloid- β is deposited extracellularly as plaques, hyperphosphorylated tau protein aggregates intracellularly as tangles, and intra-cortical projecting neurons gradually degenerate in AD [7].Acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists are two therapy options [8].

2. Parkinson's Disease (PD)

Dopaminergic neuron denaturation presence in substance causes striatal dopamine reduction in PD, the second most prevalent neurodegenerative illness [9-10] .The condition progresses with a gradual loss of motor control, which causes severe respiratory and gastrointestinal issues that ultimately result in the patient's death [11]. Although the cornerstone of PD treatment is dopamine supplementation, the acetylcholine, norepinephrine, and serotonin systems are also found to be defective in Parkinson's disease [12-16].

3. Cerebrovascular Diseases (CVDs)

All illnesses that predominantly affect the brain's blood arteries are called cerebrovascular disorders [17]. The most frequent symptom of cerebrovascular condition is stroke. It happens when a cerebral artery becomes blocked or bursts [18].There are two major types of strokes: ischemic stroke, which involves occlusions of cerebral vessels, and hemorrhagic stroke, which involves intracerebral hemorrhage (ICH) [19] .

4. Multiple Sclerosis (MS)

MS usually affects young people and causes non-traumatic debilitating conditions [20]. MS develops gradually, affecting the spinal cord, brain stem, basal ganglia, visual neurons, and other CNS white matter [21]. An individual's genetic makeup, Epstein-Barr virus, sunlight, smoking, and vitamin D play significant roles in MS development [22]. Disease-modifying medicines and symptomatic therapy are both used to treat the symptoms of MS, which are brought on by neurological problems [20].

5. Huntington's Disease (HD)

Dementia, behavioral and psychological issues, and uncontrollable choreatic movements indicate Huntington's disease (HD), a relatively uncommon neurodegenerative disease [23-24]. George Huntington originally described HD, also known as hereditary chorea, in 1872. He talked about the genetic origin of the condition, how the disease occurs in individuals between the ages of 30 and 40, and psychological and cognitive symptoms [25]. Chromosome 4 has the huntingtin (HTT) gene, which increases the CAG trinucleotide repeats and causes HD. It causes the development of a mutant huntingtin (mHTT) protein having an extensive polyglutamine repeat [26].

6. Amyotrophic Lateral Sclerosis

ALS is a progressive and fatal neurodegenerative disease due to the degeneration of motor neurons, with no effective treatment [27-28-29]. Recent studies showed that cerium oxide NPs or mesoporous silica NPs loaded with trophic factor peptide mimics preserved muscle function and prolonged the lifespan of ALS mice model [30]. Moreover, AuNPs loaded

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with FM19G11 (a hypoxia-inducible factor) may be a novel tailored approach to delaying ALS progression, as shown by the enhancement of proliferation and the self-renewal of ependymal stem progenitor cells in ALS mice . The dysregulation of the retinoic acid signaling pathway also plays an important role in the development of ALS [31]. Retinoid-activating NPs improved motor performance, prolonged lifespan, and played a neuroprotective role in the SOD1G93A mouse model of ALS Moreover, lactoferrin-functionalized lipid NPs facilitated the transport of riluzole across the BBB by interacting with lactoferrin receptors expressed on brain endothelium in ALS treatment . Collectively, these findings highlight the advantages and potential of NPs or NDDSs in the treatment of ALS.

7. Frontotemporal Dementia, Prion Disease, and Glioblastoma

FTD is a heritable dementia syndrome accompanied by frontotemporal lobe atrophy, personality changes, and cognitive impairment [32]. Prion disease is a neurodegenerative disease of humans and animals, in which prion protein plays a vital role in pathogenesis [33]. GBM is a kind of primary brain cancer, belonging to a heterogeneous collection of brain tumors [34]. There is currently no effective therapy for these diseases and new drug delivery technologies that can bypass the BBB need to be developed[33-34]. Binyamin et al. (2015) found that a Nano drop formulation of pomegranate seed oil (PSO) could greatly reduce demyelination and lipid oxidation in the brains of diseased animals, suggesting that nano-PSO may also be beneficial in the prevention and treatment of hereditary prion disease [35]. EI Moustaine et al. (2008) created amyloid nanofibrils and NPs from recombinant prion protein under high pressure, which provided an understanding of the misfolding of prion protein into amyloid [36]. Lin et al. (2016) developed BBB-penetrating albumin NPs for the dual-drug delivery of paclitaxel and fenretinide, and these albumin NPs exhibited improved treatment outcomes in glioma models with reduced toxic side effects [37-39].

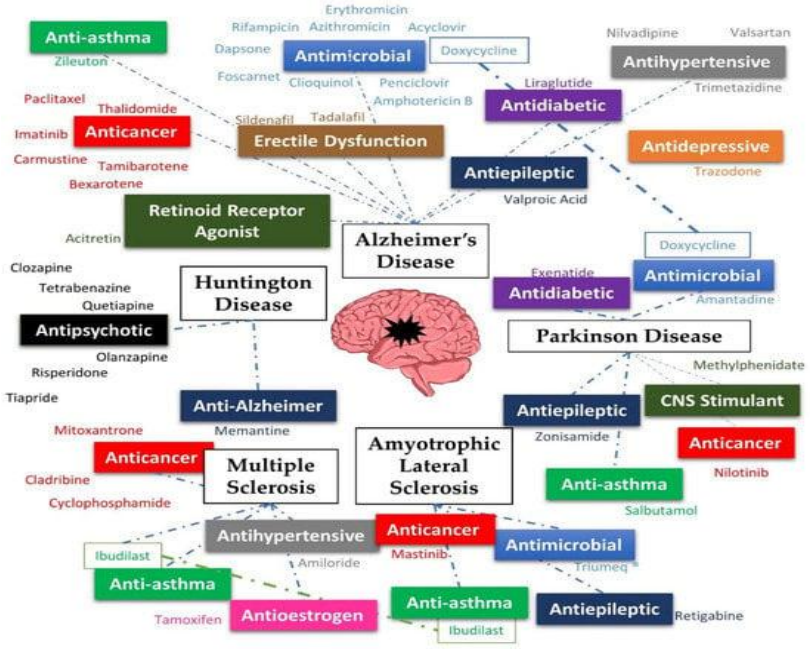

Figure 2 .Concepts of Neurodegenerative disorders

Medicinal Plants and Their Phytochemicals for NDs Treatment:

Numerous studies tried to characterize phytochemicals with positive effects on the neural system from medicinal, and even dietary plants[40].

Polyphenols

Polyphenols are the largest group of plant secondary metabolites, and their structures vary from hydroxyl groups attached to the aromatic ring in the simple phenols to highly complex polymeric compounds in tannins and lignin. Respecting their structures, polyphenols are strong antioxidant, and anti-inflammatory compounds with broad contribution to manage various diseases. To date, several clinical trials were proceeded to investigate the potency of polyphenols on different NDs [41].

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Flavonoids are the major bioactive group of polyphenols with more than 6000 members (Figure 3). Flavones (i.e., apigenin and luteolin),flavanol (i.e., epigallocatechin-3-gallate-EGCG) , flavones (i.e., QC and kaempferol), isoflavones (i.e., daidzein and genistein),flavanones (i.e., naringenin and hesperetin) , and anthocyanins (i.e., cyanidin and delphinidin) are the best known flavonoids with considerable medicinal and dietary values, particularly neuroprotective properties[42].

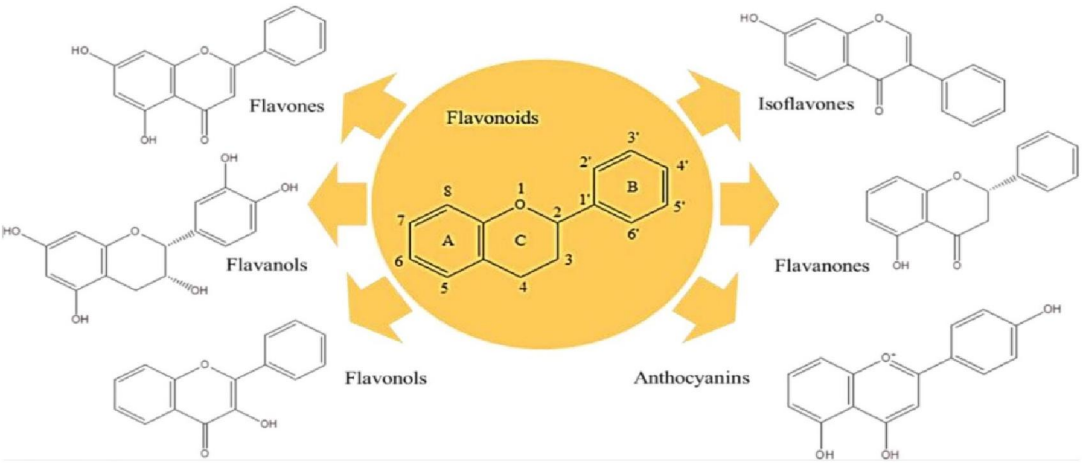

Figure 3. Flavonoids

Alkaloids

Alkaloids are organic natural compounds containing nitrogen in their structures. There are various classifications of alkaloids based on their chemical structures, biochemical precursors, and pharmacokinetics. Heterocyclic alkaloids (typical alkaloids) with nitrogen in their cyclic ring are more common. Berberine (Berberis vulgaris) , montanine (Rhodophiala bifida) , morphine (Papaver somniferum) , salsoline (Salsolaoppositifolia), and galantamine (Galanthusnivalis) belong to isoquinoline alkaloids, and proven to have positive effects on NDs. In addition, PIP (a piperidine alkaloid from Piper nigrum)[43].

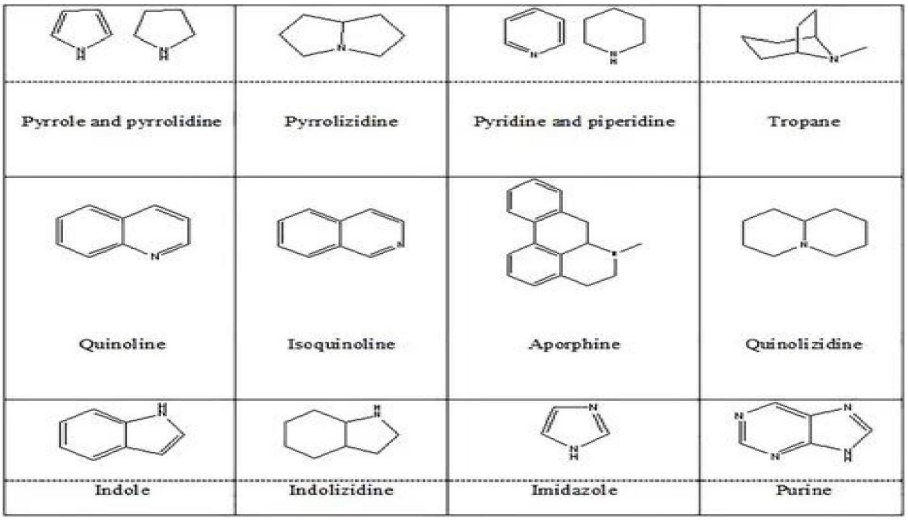

Figure 4.Heterocyclic Alkaloids

Herbal Medicines and Natural Compounds Nanoformulations :

Polymeric Nanoparticles (PNPs), Nanocapsules, and Nanospheres

Polymeric nanoparticles have high drug loading capacities, enabling the system to protect and support the incorporated drug against degradation. Therefore, there is an increasing chance of drug penetration and access to the brain. Due to

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their stable structures and unique features, they can evade macrophages, thus, facilitating the drug delivery to the CNS[44].Nanospheres are dense polymeric matrices that are prepared via micro-emulsion polymerization, while nanocapsules are developed by a thin polymeric envelope surrounding an oil-filled cavity .

Polymeric Nanogels and Nanosuspensions

Nanogels are described as highly cross linked nano-sized hydrogel systems that are either non-ionic- or ionic-monomers or copolymerized. The size of the nanogels varies from 20 to 200 nanometers[45].This system has a 40–60% capacity for drug loading. Previous studies suggested that nanogel structures could enhance the brain uptake and decrease the liver and spleen uptake of oligonucleotides.

Carbon Nanotubes (CNTs) and Nanofibers

Inorganic nano-drug delivery systems such as mesoporous silica nanoparticles, CNTs, layered double hydroxides, superparamagnetic iron oxide nanoparticles, and calcium phosphate nanoparticles emerged therapeutic applications in various diseases, particularly NDs. Inorganic nano-carbon systems are able to pass prolonged systemic circulation; while enhancing the drug accumulation, permeability, retention effect, stability, and availability to desire sites[46].

Polymeric Nanoliposomes

Nanoliposomes are phospholipids with two hydrophobic tails and a hydrophilic head. Their sizes differ from 30 nanometers to few microns. A significant amount of drugs can be incorporated into the lipid bilayers or within the liposome aqueous compartment[47].

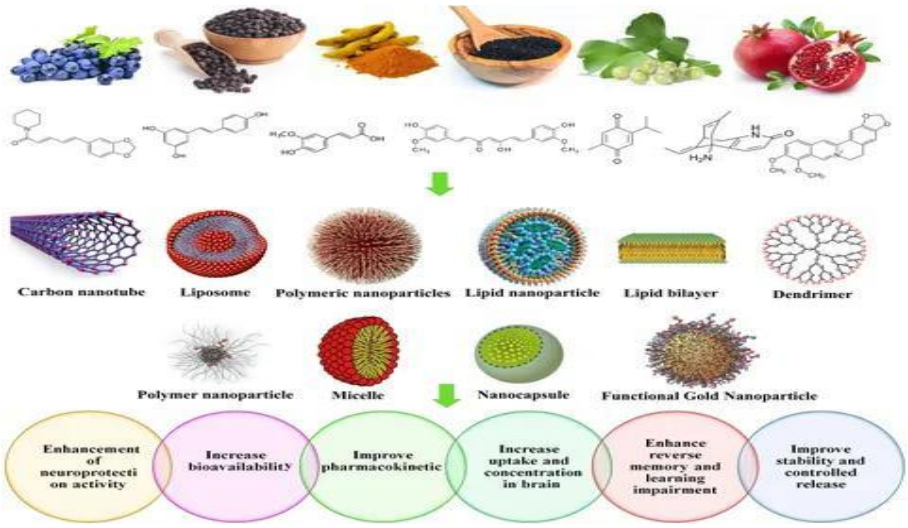

Figure 5. Nanoformulations used to improve the effectiveness of natural compounds.

Nanoformulations of Natural Products for NDs Treatment

Curcumin

Curcumin is one of the most popular and important natural polyphenols derived from Curcuma longa L. Cur has a distinctive chemical structure, making it susceptible to significant effects[48]. Cur affects many biological and pharmacological targets, such as transcription factors, growth factors, genes and cytokines.

In vitro Studies

Curcumin loaded lactoferrin NPs were developed to protect SK-N-SH dopaminergic cells from rotenone-induced neurotoxicity, a model that mimics symptoms similar to PD[49]. Besides sustained retention, the intracellular uptake, and the concentration of Cur increased, thereby, enhancing its neuroprotective effects.

In vivo Interventions

Curcumin encapsulated solid lipid nanoparticles (CSLNs) improved 3-nitropropionic acid (3-NP)-induced HD in rats. CSLNs treated animals showed significant enhancement of the antioxidant enzyme's activities (i.e., SOD and glutathione), while there was a significant decrease in mitochondrial swelling, ROS, protein carbonyls, and lipid peroxidation[50].

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Quercetin (QC)

Quercetin is a bioflavonoid found in diverse fruits, vegetables, and a number of herbal origin oils with well-known neuroprotective, and anti-inflammatory effects. Besides, QC has considerable potency to scavenge ROS. Despite its beneficial effects, poor solubility and low bioavailability hindered its clinical applications. Accordingly, to control such limitations, alternative QC formulations such as nanocapsules, nanogels, liposomes, nanosuspensions, and microsphere have been recommended, in which QC-nanocapsulation was shown to be the most proper form[51].

Resveratrol (RSV)

Resveratrol (3,5,4′-trihydroxy-stilbene) is a natural phytoalexin polyphenolic agent from the stilbene-class of compounds. Rapid metabolism, poor water solubility and low bioavailability are the main drawbacks of RSV[52].

Piperine (PIP)

Piperine (1-piperoylpiperidine) is a pungent alkaloid existing in the fruits of piper species. Bulk of evidence confirmed the effectiveness of PIP on the CNS, which is mainly implicated with the special consequences of PIP on acetylcholine[53]. The log P-value of PIP is 2.25, making this compound very lipophilic, with slight aqueous solubility. In addition, PIP has insufficient oral bioavailability.

Green-Extract Nanoparticles :

Ginkgo biloba

Ginkgo biloba (Ginkgoaceae) is an ancient Chinese tree, extensively cultivated for traditional and medical purposes. G. biloba extract contains flavonol glycosides, bilobalide, terpene trilactones, and varied forms of ginkgolides, and ginkgolic acid [54].

Thymoquinone (TQ)

The major active component of Nigella Sativa (Ranunculaceae) seed is TQ[55]. TQ a lipophilic compound with diverse pharmacological qualities in immunomodulation, neurodegeneration and cognitive deficits.

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III. CONCLUSION

Research is an ongoing process, and research on neurodegenerative disorders is the most prominent topic for several sectors, like pathology, pharmacology, medicinal chemistry, drug discovery, and drug delivery sciences. Many people suffer from various neurodegenerative disorders, and scientists worldwide are trying to find effective therapeutics for those diseases. Although, there are many studies reporting the restorative effect of NPs in preclinical models of neurological disorders, further research is requisite to address the safety issues related to these systems. In addition, clinical efficacy of NPs in the area of neurological medicine needs long term assessments. Design of nanoformulations with more specificity for different brain cells and for each type of NDs should also be noticed.

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