Chapter

Recent Advancements in Phyto Component Based Nanocarriers for Improved Treatment of Brain Disorders

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Abstract

Effective treatment of brain disorders remains a tough task in medical science. Age-old brain disorders like Parkinson's (PD) and Alzheimer's (AD) are yet to be managed effectively in spite of fabulous scientific progress over the last decades. Presently available treatment strategies have been found insufficient to tackle the out bursting cases of AD and PD. Indeed, presence of blood-brain barrier (BBB) highly hijacks success of conventional drug therapy. In this regard, phyto bioactive components delivered through nanocarrier (NCs) systems hold ray of hope in improving treatment benefits in brain disorders. Several NCs including polymeric nanoparticles, nanoliposomes, micelles, dendrimers have now being heavily researched to effectively deliver the phyto active components to brain tissue. NCs owing to their structural and physiological uniqueness have now been evolved with great potential for the treatment of brain disorders. Functionalization of brain specific ligands on the surface of NCs further makes them target specific, which might significantly improve bioavailability or reduce the off-target adverse effects. This chapter primarily focuses on recent advancements in phyto component loaded NCs employed for the treatment of brain disorders. The chapter especially covers existing impediments of phyto component based NCs for Parkinson and Alzheimer's disease.

Keywords: phyto component, nanocarriers, blood-brain barrier, brain disorder, treatment strategies, recent advances

1. Introduction

Brain disorders refer to non-transmittable but widely inherited disease problems caused by disruptions in normal body structure and functioning caused by birth

abnormalities or genetic malfunctions [1]. There are many different types of brain problems and diseases that impact the brain, such as infections, tumors, traumas, and neurological abnormalities [2]. Present time demands rapid development of diagnostic, therapeutic, and effective preventive agents to tackle the rising prevalence of cerebral illnesses brought on by the aging global population. The BBB, a unique brain capillary control mechanism that prevents the majority of blood molecules from accessing the central nervous system, has severely hampered brain drug development [3]. As a result, unlike other organs, over than 98% of micro therapeutic compounds and about 100% of bigger therapeutic molecules are unable to reach the brain via the circulatory system. Researchers have found that because of their small size, nanocarriers (NCs) can enter most cells through endocytosis and transcytosis. NCs are sub micrometer objects that act as a unified entity in terms of transport and characteristics. NCs have been extensively researched in recent times for brain medication delivery [4]. Previously, various co-solvents/surfactants like dimethyl sulfoxide, polysorbate 80, ethyl alcohol etc. were used with medications to promote BBB penetration. However, such substances pose high risk for integrity of BBB and might disrupt its protective features. NCs-based therapeutics have recently emerged as a prospective therapeutic for brain diseases and disorders due to their easy transportability across the BBB and distinctive qualities like low toxicity, specificity, biocompatible, tiny size, and solubility [5]. However, conventional drugs used for brain disorders possess lots of severe healthy tissue toxic effects along with low bioavailability at brain tissue, which limits their effective clinical application. In view of this, the secondary metabolites of plants known as phytochemicals or phytonutrients such as alkaloids, saponins, indoles, phytosterols, phenolic acids, isothiocyanates, and phytoprostanes/furanes etc. are being largely investigated in recent days [6]. Phyto bioactive constituents have a long history of use in the management of illnesses and brain disorders in people. Nanocarriers are intended to more effectively carry phytochemicals to the target region (brain). Depending on the carrier material, both hydrophilic and hydrophobic molecules can be loaded inside them. For instance, polar and non-polar molecules are both transported by lipid-based nanocarriers (in the aqueous core and the membrane, respectively) [7]. Owing to their nanosize, tunable surface nature, several nanocarriers like polymeric nanoparticles, nanoliposomes, niosomes, magnetic nano-carriers, dendrimers etc. have been investigated largely over the past years to improve treatment outcomes in brain disorsders. Many phytochemicals delivered through polymeric/lipid based nanocarriers have already shown effective potential in increasing the therapeutic efficacy of phytochemicals. In the present chapter, we want to highlight the major phytocomponents those have been delivered through nanocarriers for improved therapeutic effect in brain disorders. We have mostly covered two important brain disorders, *Viz*. Parkinson's (PD) and Alzheimer's disease (AD) with their recent reports on the use of phtonanocarriers. We summarized potential targets, phytoconstituents, brain medication delivery methods, and nanocarrier systems used in the disease management and therapy in this chapter.

1.1 Blood brain barrier (BBB)

BBB is essential for allowing biomolecules to enter and exit the brain's neuronal system. Therefore, comprehension of the functional structure and characteristics of BBB is required to increase medication transport to the brain. This protective unit component helps to stop the shuttling of chemicals between the blood and the brain [8]. It consists of layers of vascular endothelial cells that are restrained by tight junctions and other supporting structures. The astrocyte end-feet of the basement

membrane surround the endothelial cells discontinuously scanned by microglial cells. Endothelial cells cohesive regions give persistence for the deliberate movement of tiny substances across the BBB. Transcytosis is a type of regulated intracellular transport that occurs to meet the protein and peptide needs of the brain [9]. Depending on the type of molecules, endothelial cells may be able to promote transfer with the help of numerous unique transporting proteins (hydrophilic or hydrophobic) [10]. In recent times, many NCs based novel formulations have been investigated at pre-clinical stage to treat brain disorders like AD and PD. The NCs can encapsulate anti-AD/anti-PD drugs and can efficiently transport them across the BBB.

1.2 Role of P-gp in brain disorders

The most difficult challenges have been passing the BBB and the blood-cerebrospinal fluid (CSF) barrier in treating brain diseases and disorders. As P-gp carefully mediates material efflux across the BBB, its down-regulation has been linked to the advancement of neurodegenerative disorders and tumors [11]. P-gp inhibition improves medication penetration and subsequent effects across the BBB. Poly(butylcyanoacrylate) NCs have been shown to reduce with P-gp-mediated phenytoin tolerance in rats [12]. Furthermore, when compared to free drug, the incorporation of andrographolide (a neuroprotective agent) into solid lipid NCs increases their permeation to the BBB. In summary, the data suggest that by controlling p-gp, NCs can improve predicted drug penetration and targetability [13].

1.3 Types of nanodrug carriers for brain targeting

1.3.1 Solid lipid nanoparticles (SLNs)

SLNs are nanoscale dispersal made of fatty acids, biocompatible triglycerides, or waxes that have been steady by emulsifiers with HLB values less than 12 [14]. SLNs are unique lipid-based biocompatible nanocarrier systems mainly constituting lipid or modified lipid (triglycerides, fatty acids, or waxes) nanostructures (10–1000 nm diameter size range). SLNs have a solid hydrophobic lipid core, in which both hydrophilic and lipophilic drugs can be dispersed. In vitro, SLNs containing stearic acid and pluronic®F68 were added to demonstrate the ability of Atazanavir to successfully penetrate human brain vascular endothelium. In vivo testing on rats revealed that Riluzole-loaded SLNs were more effective at transporting the medication into the brain [15]. Docetaxel-loaded SLNs composed of soya lecithin, monostearin, vitamin E, and stearyl amine-betreliesoxybutyric acid (HBA, a ketone body and substrate for the monocarboxylic acid carrier conveyed on the BBB) conjugation showed effective permeation across the intact BBB. Despite the fact that SLNs are easily cleared by the reticuloendothelial system due to their hydrophobicity, they have demonstrated the benefits, biocompatibility, good degradability, and the ability to be surface-covalently for brain targeting [16].

1.3.2 Nanoemulsions

Nanoemulsions are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant. These are the thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, i.e., surfactant and co-surfactant [17]. Nano emulsions are promising drug delivery vehicles across the BBB, because they

can solubilize either hydrophilic (W/O nanoemulsions) or hydrophobic (O/W nanoemulsions) drugs. The typical mean droplet diameter of nanoemulsions obtained is around 500 nm or smaller [18]. They have a transparent or hazy look due to their small droplet size, as opposed to the milky white due to attachment with coarse emulsion (whose micron sized droplets partake in multiple light scattering). Additionally, surface functionalization for targeting may make it easier for cells to take up nanoemulsions and the drugs they contain through receptor-mediated endocytosis [19].

1.3.3 Gold NPs

Gold nanoparticles (AuNPs) provide non-toxic carriers for drug and gene delivery applications. AuNPs have been widely studied for their neuroprotective and BBB penetration characteristics in the diagnosis of AD [20]. AuNPs use their special chemical and physical characteristics to load and unload medicines. The gold core is basically inert and non-toxic, which is the first advantage. Another benefit is their simple steps of production. A study reported the production of Au-NPs in the range of 150 nm and the experimental Au-NPs conjugated with glutathione were examined for potential anti-AD effect and it was found that these nanoparticles prevented amyloid aggregation and had a strong anti-AD effect [21].

1.3.4 Nanoliposomes (NLs)

NLs are lipid based nanoparticles with one or more layers of phospholipid bilayers [22]. Natural sphingomyelin, phosphatidylcholine, and glycerophospholipids are common elements of the phospholipid bilayer. NLs have received a lot of attention because of their good biocompatibility and potential for uploading pharmaceuticals in the aqueous core for systemic therapeutic medication delivery [23]. Another strategy to increase the penetration rate of NLs crossing the BBB is cationization of the conjugated ligands. Other challenges affecting NLs brain delivery include poor stability and low drug loading capacity. Due to the limited number of accessible surface groups, binding ligands to the surface is problematic, and steric hindrance exists [16].

1.3.5 Polymeric nanoparticles (PNPs)

PNPs have attracted considerable interest over the last few years due to their unique properties and behaviors resulting from their small size. PNPs have the potential for a variety of uses including medication delivery and diagnostics. PNPs are formed of natural or synthetic polymers and have a diameter of 1 to 1000 nm [24]. Depending on the drug-loading techniques, PNPs can either form thermodynamically stable nanocapsules (drugs are encircled by a polymeric shell) or nanospheres (drugs are embedded into polymeric matrix) [25]. PNPs possess certain qualities such as controlled and/or sustained medication release profiles, better half-life, along with easy surface manipulation for site-specific targeting [26].

One of the best-studied biodegradable copolymers is poly (lactic-co-glycolic acid) (PLGA), which breaks down into non-toxic chemicals that the body excretes (H2O and CO2). Through hydrolysis of the ester linkages to its monomeric anions, the polymer degrades in vivo (lactate and glycolate). PEG-PLGA/PLA-PEG NPs were only used in one Phase II clinical trial for metastatic castration-resistant cancer (BIND-014) [27]. There is no PLGA NPs available for the clinical trial in the market for treatment of brain disorders right now. In reality, a variety of pre-clinical studies

based on drug-loaded NCs are being done. Drugs like curcumin, levodopa, cholesterol, rapamycin etc. have already been investigated for the treatment of AD, PD, high blood pressure, and multiple sclerosis [28]. As a result of the lack of drug-specific transport systems at BBB, many neuroprotective medications are unable to reach the brain. PLGA NPs in such cases have the capacity to carry the loaded drugs across BBB to elicit improved brain delivery [29].

1.3.6 Dendrimers

The symmetric monodispersed macromolecules known as dendrimers are built from a collection of branching units that are clustered around in an inner core [30]. When there are numerous responsive groups on the surface, the number of arms and

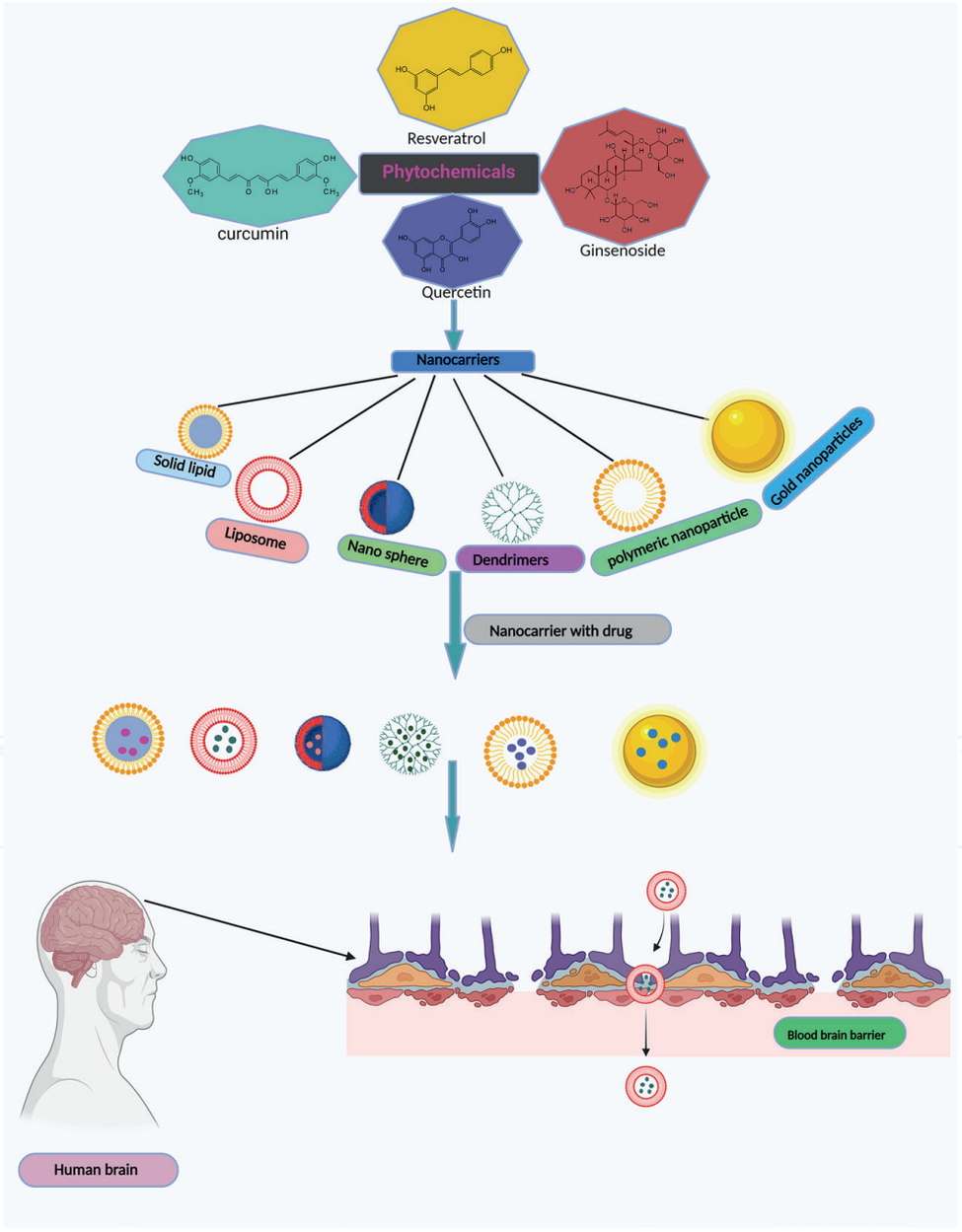

Figure 1.
Selected phyto chemicals and their delivery mechanism through various nanocarrier platforms for improved brain permeation.

surface groups increases dramatically with each generation [31]. They can be used to determine receptor-ligand affinities, administer targeted drugs, or to conduct imaging studies. In case of insoluble and hydrophobic drugs, it is considered as a useful nanocarrier. The interaction of dendrimers with cells is dependent on the hydrophobic contact between the dendrimer arms and the lipid chains of the cell membrane's phospholipid bilayer. Drug distribution to the target site is enabled by the functional groups on the dendrimer's exterior because they act as attachment sites for ligands [32]. Drug is released from dendrimers either through enzymatic dendrimer-drug bond degradation or as a result of environmental changes like temperature and pH [33].

1.3.7 Carbon dots (CDs)

The performance of CDs, a new type of zero-dimensional carbonaceous nanomaterials, is superior to that of novel metal nanoclusters or inorganic nanocrystals, making them potentially effective information-carrying nanomaterials [34]. The ability to easily modify the surface of CDs for targeted distribution and their tunable fluorescence, which is completely color-tunable from blue to close, regions are two of its most notable things [35]. These novel carriers could be used for chemo- or bio sensing due to their customizable luminous capabilities.

1.3.8 Micelles

These are single-layered amphiphilic NCs that enable for regulated drug release. These NCs boost the BBB's ability to absorb hydrophobic medicines for the purpose of treating the brain disorders [36]. Micelles have also demonstrated encouraging outcomes to carry different potent compounds, including peptides and small molecules [37]. It has been observed that micelles deliver magnetic resonance imaging for strokes and brain swelling, as well as possesses effective potential for treating AD [38].

Basic mechanism of action of phyto components delivered through NCs has been presented in **Figure 1**.

2. Widely used diagnostic tools in brain disorders

2.1 Molecular imaging (MI)

An important area of biomedical science called MI examines pathogenesis or bodily processes at the molecular level. With great sensitivity and specificity, imaging techniques make it simple to visualize, characterize, and quantify activities of interest in the body [39]. It uses cutting-edge methods with a variety of capabilities, including as bioluminescence imaging, microscopy, magnetic resonance imaging, ultrasound, single-photon, x-ray radiography emission computed tomography, and positron emission tomography etc. Infections, brain tumors, and neurological illnesses are just a few of the several brain diseases that have been analyzed and characterized using MI techniques [40].

2.2 Biomarker detection

Basically, a biomarker is a distinguishable molecule that is linked to a specific disease or protein. A biomarker's ability to distinguish between healthy and ill

persons, as well as its precision in determining illnesses stage is the critical component in disease management [41]. Many biomarkers for illnesses and abnormalities of the brain have been identified. However, the lack of suitable methodologies makes its clinical application difficult. Ubiquitin-C-terminal hydrolase-L1 (UCH-L1) plasma limits have been found to be significantly higher in TBI patients than in healthy people, implying that UCH-L1 could be a viable diagnostic marker for the situation [42]. An innovative technique based on the surface plasmon resonance of Au NPs has recently been shown to successfully and swiftly identify the biomarker UCH-L1 in TBI patients with 100% sensitivity and specificity [43].

3. Some important brain disorders, their etiology and treatment strategies

3.1 Alzheimer's disease (AD)

AD is caused by a mix of genetically determined and environmental risk factors. Age is the most major risk factor [44]. At the age 65, the chance of developing this disease is about 3 percentages and increasing in to more than 30 percentages by the age of 85. Although the frequency of AD among persons under the age of 65 is unclear, it is estimated that this age group accounts for around 3 percentages of all AD patients [45]. While overall numbers of AD continue to rise with the aging population, age-specific incidence too appears to be declining in a number of countries [46]. The accumulation of amyloid-β protein on neuronal cells after exposure to iron, copper, aluminum, cadmium, and zinc chloride salts suggests that heavy metals might be associated with the development or progression of AD [47]. Researchers have also interlinked the AD pathogenesis with presence of toxic metals such as vanadium, nickel, lead etc. Along with that, certain gases like SO2, NOx, and CO found in polluted air may cause chronic neuroinflammation, cerebrovascular damage, oxidative stress reactive oxygen species (ROS) production, neuron damage/loss and peptide accumulation [48]. Also exposure to high amount of pesticides and insecticides in the environment has also been assigned as other major contributing factors for the progression of AD [49]. The etiology of AD has been summarized in **Figure 2**.

Current therapeutic approaches give symptomatic relief of AD, but do not ensure complete recovery. Phytochemical components in this regard are getting more importance owing to their neuroprotective properties, less toxicity and potential to target various pathogenic pathways implicated in AD. Given the limits of currently available AD medications, the different types of phytocompounds have been suggested as therapeutic agents for the disease management. However, phyto components in their native form show poor bioavailability, low solubility and insufficient BBB permeability, which restrict their effective application. Nanotechnology in this regard has been accepted as an innovative technique to overcome these brain medication delivery restrictions [50]. Phyto constituents loaded NCs have the potential to overcome these challenges while also improving neuroprotective effects in BBB. A numbers of pre-clinical studies on phyto component loaded NCs nanocarriers to treat AD have been reported [28, 50]. However, development of NCs for delivery of phyto componets in AD is still limited due to challenging formulation procedures at industrial prospects [51]. Though, several in-vitro and in-vivo studies have been carried out; however, detailed studies by using small laboratory animals to human testing is still very necessary. When administering medicines for the treatment of AD, precise analysis of important parameters like physicochemical

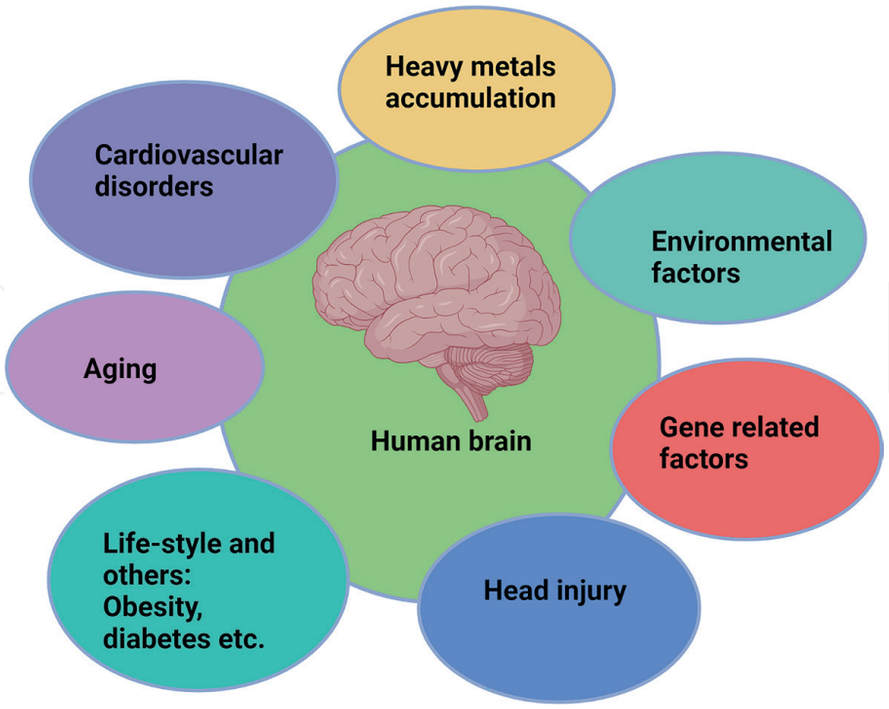

Figure 2.
Probable causes/risk factors involved in the progression of Alzheimer's disease.

properties, particle size, biodistribution, and bioavailability of loaded drug(s) is extremely necessary [52]. Furthermore, the stability of NCs is another striking factor in decreasing the toxic metabolites agglomeration in the BBB. While the conventional formulation of compounds remains difficult to show their action at brain tissue, NCs could be alternative strategy for effective permeation across the BBB with utmost specificity. Problems of instability, limited solubility, low bioavailability issue associated with phytocomponents could be sufficiently addressed by suitable NCs. Clinical studies have also demonstrated efficacy of phyto component loaded NCs in various brain disorders [53].

Further, concerns of safety and brain absorption of NCs must be addressed in AD patients. At present, creating nano phytopharmaceuticals for large-scale production in line with good laboratory practice standards is required to maintain the quality of end product, while retaining patient compliance.

3.1.1 Recent research findings on phyto component based NCs for AD

Over the past years, many active phyto components have been delivered through NCs and have been shown to elicit better pharmacological effect than the free phyto components. Multi-functional liposomal NPs were prepared and coated with an amyloid-binding curcumin-lipid ligand to target amyloid. Along with that two other ligands were also conjugated with the liposomal NPs to target transferrin and LDL receptors present over BBB. The study indicated excellent brain targeting and amyloid peptide aggregation of experimental NCs [54].

The functionalization of NPs with plant phytochemicals has been investigated by Zhang J. et al., 2014. Polyphenols were used to functionalize selenium NPs. The nanosized selenium in the study was coated with epigallocatechin gallate (EGCG), a polyphenol found in green tea. EGCG is well-known for its neuroprotective

properties, specifically its ability to limit the formation of many amyloid-forming proteins engaged in the course of Alzheimer's disease. The EGCG-stabilized selenium prevented atrial fibrillation while also dissolved the developed fibrils. Furthermore, at very low concentrations, the specified NCs was observed to decrease DNA fragmentation and ROS generation [55].

In another research, A. Mathew, et al., 2012 investigated the potential of curcumin loaded NCs in in neuronal targeting in vitro. Curcumin is one of the widely investigated phytocomponent over the past decade for the treatment of several brain disorders. In the study, Tet-1 targeted PLGA loaded curcumin nanoparticles with anti-amyloid and anti-oxidant capabilities was found effective in the diagnosis of AD. The incorporation of Tet-1 neuropeptide into the PLGA-curcumin nanoparticle increased its neuronal targeting efficacy in vitro. Although additional conclusions can only be formed after extensive in vivo research, the findings of this exploratory investigation suggested that curcumin could be a promising drug in the treatment of AD [56]. Resveratrol is another important phytocomponent, which is now heavily investigated for its neuroprotective properties. Grape seed and grape skin extracts containing resveratrol were shown to be more efficient at suppressing aggregation. However, after the intravenous injection, resveratrol is quickly metabolized (in less than 2 hours) in the liver and intestinal epithelial cells into glucuronic acid and sulphate conjugations of phenolic groups, which are subsequently excreted. According to a recent study, anti-transferrin receptor monoclonal antibody (OX26 mAb) functionalized SLNs was found as an efficient carrier system for transporting the extract into the target encephalon [57]. In vitro studies on human brain like endothelial cells showed that OX26 SLNs were significantly more effective at cellular absorption than conventional SLNs and SLNs functionalized with an unspecific antibody. Experimental SLNs functionalized with OX-26 showed higher transcytosis capacity [57].

3.2 Parkinson's disease (PD)

PD is a complicated condition with biological as well as environmental origins. The common major risk factor for PD is age, with a median onset age of 60 years. The prevalence of the condition rises with age, peaking at 93.1 (per 100,000 person-years) in people aged 70 to 79 [58]. Though, the exact etiology of PD is yet to be understood. But several risk factors like accumulation of heavy metals, cigarette smoking, pesticides, herbicides, genetic factors, high amount caffeine consumption etc. have been identified for the development and progression of PD. The basic etiology of PD has been summarized in **Figure 3**.

Nanosizing the formulation is an option for increased PD protection to improve the efficiency and bioavailability of crude extracts. Furthermore, adding one or two phytonanocarrier of nano-sized range bioactive chemicals delivers considerable health advantages for specific conditions, thus reducing the need for several drugs. Example like Curcumin and resveratrol NLs exhibited anticancer activity against prostate cancer. According to research curcumin loaded NCs improved the therapeutic and bioavailability efficacy during PD [59]. Experimental NCs significantly lowered oxidative stress and apoptotic cell death in fly model of PD. Similarly, an alginate curcumin nanocomposite also showed a lowering in brain oxidative stress and cell death in a transgenic Drosophila PD model [60]. Curcumin loaded NCs improved bioavailability of curcumin in the blood circulation and also the brain pharmacokinetic [61, 62]. The methods of administration utilized were more significant in increasing nanocurcumin bioavailability in the circulatory system and penetrating to the BBB. Ginsenoside also

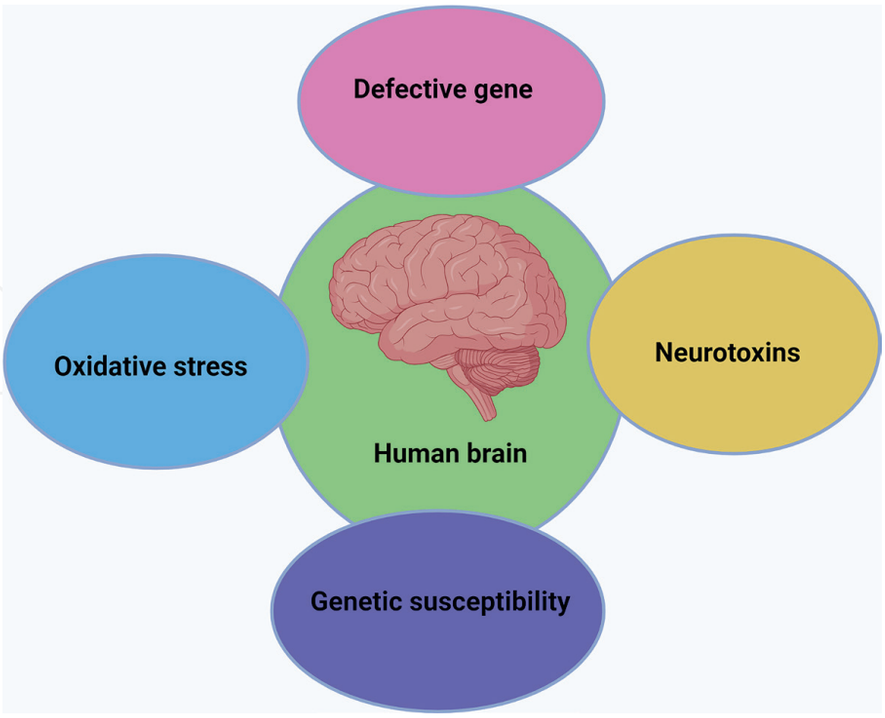

Figure 3.
Probable causes/risk factors involved in the progression of Parkinson's disease.

protects neurons against 6-hydroxydopamine- and iron-induced neurotoxicity. These compounds have an important role in lowering oxidative stress as reported in the recent experiment [63]. Various studies have also indicated that nanoresveratrol can aid in the prevention of PD and enhance neuronal survival in the face of oxidative stress [64].

3.2.1 Recent research findings on phyto component based NCs for PD

Aggregation of amyloid protein in the brain as a result of oxidative stress causes the formation of Lewy bodies and the selective death of dopamine neurons [65]. Polyphenolic substances have poor oral bioavailability, higher metabolic turnover, and decreased BBB permeability. The effect of a produced alginate-curcumin nanocomposite on the climbing capacity of PD model flies, apoptosis, and lipid peroxidation in the brain of PD model flies was investigated in a recent work [65]. The chow was supplied at the known concentrations of 105, 103, and 101 g/mL of alginate-curcumin nanocomposite, and the flies were allowed to consume for 24 days. In the Drosophila model of PD, there was a substantial dose-dependent delay in the reduction in climbing ability, as well as a lowering in apoptosis and oxidative stress.

Another recent work highlighted the neuro protective effect of *Bacopa monnieri* loaded SLNs in vivo. The work involved incorporation of *Bacopa monnieri* extract into SLNs to develop dissolvable microneedle arrays and evaluate its neuroprotective activity. Quality by design approach was employed for optimizing the SLNs formulations based on several in vivo and in vitro properties. Mechanical strength, in vitro release studies, permeation studies, skin irritation test, histopathological analysis, biochemical studies, and behavioral tests of SLNs loaded microneedle arrays were performed. The experimental phyto constituent loaded microneedle patches were shown to be mechanically robust, nonirritant. The optimized formulation was also found to produce decreased degree of bradykinesia along with high motor coordination, and balance ability [66].

In another study, neuronal protective effect of photoactive component of Ginsen delivered in nanoparticle formulation was investigated. The principal active component of the plant, ginsenoside (Rg1) has been reported to protect the neurons against 6-hydroxydopamine-induced death and neuronal toxicity [67]. Although the photoactive components of Ginsen play a critical role in reducing oxidative stress, but the poor bioavailability problem has always been an issue In the work, Rg1 loaded nanoparticles were found to enhance the in vivo activity and bioavailability of these compound than the crude extracts. Nanosizing the formulation showed an enhanced protective effect against PD. The nano ginsenosides were developed using a nanoemulsion technique with average particle diameter of 19.9 nm. Bioavailability of the selected Rg1 loaded nanoparticles showed significantly higher bioavailability than the crude extract in the rat brain tissue [63].

Numerous studies have reported that different nanoparticle-loaded phytochemicals (e.g., vitamin E, resveratrol, curcumin, and hyaluronic acid) with an average particle size of 100 nm resulted in higher ROS scavenging efficiency and lower lipid peroxidation in patients with PD. A work by Pangeni R et al., evidenced antioxidant and neuroprotective effect of nanoencapsulated thymoquinone (TQ) in PD induced rat model. The experimental TQ-loaded mesoporous silica NPs (90 nm in size) were able to cross the BBB. Results showed that the experimental silica NPs enhanced drug delivery to all major brain areas including cortex, thalamus, midbrain, and hypothalamus and significantly reduced oxidative stress biomarkers [64]. Few significant recent research outcomes on phyto component based NCs on AD and PD has been summarized in **Table 1**.

Name of the plant	Major active biocomponent	Nano carrier formulation	Model	Outcome	Reference
Turmeric	Curcumin	Alginate–curcumin nanocomposite	In-vivo	In Parkinson's disease, improve bioavailability while decreasing oxidative stress and apoptosis.	[65]
		Caprylic and capric triglycerides, sorbitan monostearate	In-vitro	Curcumin-NPs protect against A42-induced behavioral and neurochemical alterations in AD mice model.	[68]
		PLGA nanoparticles	In-vitro	Reduced the protection of neurons protected against oxidative damage in AD.	[69]
		curcumin-loaded NP	In-vivo	synergistic delivery of Levodopa curcumin that would be able to pass the blood–brain barrier	[70]

Name of the plant	Major active biocomponent	Nano carrier formulation	Model	Outcome	Reference
Panax ginseng	Ginsenosides	Nanoliposome	In-vitro	Improved the survival of H2 O2-damaged cells	[71]
		PGL-1 nanoparticles	In-vivo	protective effect on apoptosis SH-SY5Y induced by Aβ25–35	[72]
		glipopolysaccharide	In-vivo	ginsenoside Rg3 effective for slowing the development of neurological disorders	[73]
Grapes (*Vitis vinifera*), Cranberry (*Vaccinium macrocarpon*), and Peanut (*Arachis hypogaea*)	Resveratrol	Nanocapsule	In-vivo	Bioavailability enhancement in AD sickness	[74]
		PCL–PEG polymeric micelles	In-vitro	Bioavailability improvement in AD dementia	[75]
		RSV loaded lipid nanocarrier	In-vivo	Induced AD rat model Restoration of the deteriorative effects of Aβ1–42 in animals	[76]
Tea, red wine, apples, parsley, citrus fruits, sage and onions	Quercetin	Solid lipid nanoparticles	In-vivo	Increased the antioxidant capacity of the brain.	[77]
		Nanoliposome	In-vitro	Improved bioavailability	[78]
		(QC- and RA-loaded liposome with conjugated phosphatidic acid and grafted apolipoprotein E	In-vivo	Neurotoxicity was recovered and drug was able to penetrate BBB in AD induced rat model	[79]
		Epigallocatechin-3-gallateloaded nanoparticles	In-vivo	Reduced atherosclerosis	[80]

Table 1.
List of some important phyto components delivered through nanocarrier systems for the treatment of Parkinson (PD) and Alzheimer's disease (AD) [63].

4. Conclusion

Technological advancements in the scientific tools along with exploration of novel formulation strategies have made a substantial impact on diagnosis and treatment of major brain disorders like AD/PD. Undoubtedly, delivery of phyto components through nanocarrier based platforms will bring significant impact on the

management and treatment outcome of AD and PD in future days. Most phyto active components show poor BBB penetration capacity, yet possess effective brain therapy potential, which can be overcome by loading the phyto active components suitable nanocarriers. Further, the nanocarriers could be functionalized with brain-specific ligands for effective BBB permeation. However, despite of huge progress in disease diagnosis, health infrastructure, and newer treatment strategies, the clinical use of phyto nanotherapeutics has yet to gain commercial acceptance. There still exists long gap between in vivo data and effective clinical use. Poor yield percentage, low encapsulation efficiency, lack of efficient purification techniques, high production cost, stability issues are some of the crucial problems, which need to be addressed cautiously. Some of the key factors that need urgent attention include: Optimization and standardization of laboratory techniques for effective isolation of phyto active components, optimization of formulation steps of nanocarriers to achieve reasonable loading capacity and stability, in vitro- in vivo correlation, establishment effective process for technology transfer etc. Seeing the diversifying area of brain diseases, interdisciplinary research should be the need of the hour. Neurosurgeons/neuroscientists, formulation scientists, industrial experts and drug researchers should come together for continuous research collaboration to utilize the power of nanotechnology and phyto pharmaceuticals for effective treatment of brain diseases. Only a well-organized, planned interdisciplinary research outlook could offer promising avenue for phyto active chemicals to get clinical approval.

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Disclosure statement

The authors of the article have no conflict of interest to declare.

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