Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-508-2_3

Chapter 9: Recent Advancement of Phytosomes and Phytoconstituents for the Targeting Herbal PD Treatment and Current Status

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Abstract

Background: Parkinson disease (PD) is a slowly progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons and the presence of multi-faceted motor and non-motor symptoms. Partial symptom mitigation can only be performed pharmacologically and thus there is increased research to explore neuroprotective properties of herbal bioactives. However, poor solubility, lowered bioavailability, and weak ability to cross the blood-brain barrier limits the therapeutic efficacy of the usage of these compounds in clinical practice.

Objectives: The current chapter provides an overview of the recent developments of phytosome technology to deliver herbal phytoconstituents as a treatment against PD with focus on the major compounds, mechanisms, and current translational efforts.

Methods: literatures of the last decade, 2010-2025, were searched and questioned with special attention on phytosomes produced using neuroprotective phytoconstituents, which demonstrated anti-inflammatory, antioxidant, ant-aggregatory properties in the context of PD pathology.

Results: Phytosomes significantly improve the bioavailability and efficacy of important phytoconstituents such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and ginkgolides. The preclinical experiments exhibit improved motor performance, reduced oxidative stress, and inhibition of the alpha-synuclein aggregation. Despite the current stage of clinical evidence, data are also growing.

Conclusion: Phytosome delivery of herbal bioactives is a novel add-on approach to enhancing the treatment of PD that requires further clinical verification to streamline their therapeutic potential.

Keywords: *PD, phytosomes, phytoconstituents, neuroprotection, herbal therapy, targeted delivery.*

1. Introduction

Parkinson disease (PD) is a progressive neurodegenerative ailment hallmarked by the loss of dopaminergic neurons in substantia nigra selectively, a process that culminates in debilitating motor experience manifestations of tremor, stiffness, and bradykinesia [1]. Existing treatment methods, being more of symptomatic treatment rather than the barring of disease progression, have led to the researchers exploring alternative methods of treatment, especially herbal treatment, which might supplement conventional treatment regimens by directly intervening on pathophysiological processes.

Herbal medicines that have been used in global health systems due to their high bioactivities have shown antioxidant, anti-inflammatory and neuroprotective properties [2]. In preclinical PD models, polyphenols, terpenes, and alkaloids have demonstrated a specific potential with multifactorial therapeutic effectiveness and minimal toxicity. However, due to disadvantages in pharmacokinetic attributes of poor water solubility, fast metabolism, and minimal absorption in the central nervous system, these constituent parts often hinder their clinical translation. Phytosome technology counterbalances these issues. A phytosome is a lipid-compatible molecular complex, consisting of a conjugate of a phytoconstituent (or standardized extract) with phosphatidylcholine most often phospholipid [3]. This stabilized complex structurally resembles a cellular membrane and hence improves lipophilicity, membrane permeability and its general bioavailability over that of common herbal extracts. The secondary enhance-ment in pharmacokinetic and pharmacodynamic parameters has enabled clinicians to make dose reductions without affecting the therapeutic efficacy.

Recent systematic studies confirm the transformational nature of phytosome-based delivery complexes. *Mukhopadhyay et al. (2024)* define a phytosome as a nanomedicine that potentially increases the therapeutic activities of phytochemicals with poor bioavailability and present effective treatments of quercetin phytosome and silybin phytosome, which have shown better results in clinical practice in mediating cholesterol levels and cancer therapies [4]. Further, *Chauhan et al. (2024)* outline the phytosome nanotechnology with which vascular phytochemicals are stabilized and their therapeutic efficacy compounded, outlined a tangible prototype to later translate clinically [5].

In the case of PD, the hurdles of blood-brain barrier crossing and guaranteeing key central bioavailability are vital. The encapsulation of neuroactive phytoconstituents in phospholipid complexes may increase central nervous system penetration and enhance medicinal effect. This chapter consequently reviews new innovations in phytosome-based formulations with main herbal components to treat Parkinson diseases, explaining their mechanisms, preclinical and clinical findings, regulatory issues, and translational perspectives.

2. Pathophysiological Targets for Herbal Intervention in PD

Parkinson disease is a multifactorial neurodegenerative disorder with progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, loss that is clinically manifested by bradykinesia, rigidity, and tremor [6]. One core pathogenic mechanism is loss of the ability of a-synuclein to fold correctly and aggregate into insoluble fibrils, forming Lewy bodies, and disrupting neuronal function. Oxidative stress, which is an important contributor to PD pathogenesis, is closely linked to this phenomenon, as dopaminergic neurons exhibit high metabolic activity and are susceptible to reactive oxygen species (ROS) generated either by auto-oxidation of macromolecules or by ROS-mediated mitochondrial dysfunction. The excess ROS instigates macromolecular destruction, interferes with redox balance, and promotes lipid peroxidation, contributing to the escalation of the injury to the neurons [7]. At the same time, the inability to synthesize ATP in mitochondria, especially complex I of

the electron chain, reduces ATP synthesis and extends oxidative stress. These processes, in combination, create a vicious cycle of cell death and inability to use energy. Neurodegeneration is further perpetuated through chronic neuroinflammation: microglial activation leads to prolonged expression of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6), along with reactive nitrogen species, each of which maintains a degree of neurodegeneration. Apoptotic pathways also play an important role: upregulation of pro-apoptotic Bax proteins, high caspase-3 activity, and decreased anti-apoptotic Bcl-2 proteins ultimately lead neurons towards apoptosis. More important, protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and apoptosis represent interrelated processes that provide numerous targets of potential therapeutic interventions [8].

Recent studies prove that herbal phytoconstituents- curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, ginkgolides, andbacosides have strong pharmacological actions in relation to PD disease pathology. These agents have the ability to target and regulate various pathological pathways by means of antioxidant pathways, induction of mitochondrial biogenesis via activation of peroxisome proliferator-activated receptors gamma, inhibition of nuclear factor-kappaB-mediated inflammatory signaling, inhibition of the fibril formation in alpha-synuclein, and regulation of apoptotic protein expression. However, their clinical efficacy is limited due to low bioavailability, short half-life of systemic metabolism, and House would say their low blood-brain barrier (BBB) permeability [9]. The BBB poses an insurmountable barrier limiting most phytochemicals to penetrate the central nervous system. There is a hope that technological breakthroughs like phytosome formulation of phytoconstituent complexing with phospholipids to enhance lipophilicity and increase the permeability of the phytoconstituents across the membranes in the CNS can help address these shortcomings and, in turn, enable more effective delivery into the CNS, with or without enhanced neuroprotective capacity [10]. Based on this, advanced understanding of the pathophysiology of the disease results do not only inspire greater precision in pathways identification, but also in emphasizing the need to employ novel modalities of drug delivery, such as phytosomes so as to maximize the therapeutic potential of herbal medications in terms of disease modification in PD.

3. Phytosome Technology: Principles and Potential in PD

Phytosome technology is a pivotal advancement in providing bioactive molecules of plant origin, in response to a long-standing problem of low bioavailability limiting the therapeutic potential of many herbal phytoconstituents. Phytosome can be characterized as a molecular complex resulting due to covalent or non-covalent combination between a standardized vegetable extract or purified phytoconstituent with a phospholipid, usually phosphatidylcholine, at a specified stoichiometric ratio, usually 1:1 or 1:2 [11]. This interaction takes place at the molecular level where the polar head of the phospholipid binds the phytoconstituent polar groups with the help of the hydrogen bond, and the lipid-soluble tail orients to the exterior, which provides the lipophilicity to the rest of the complex. Compared to liposomes, where the active molecules are entrapped inside of a bilayer or a water-in-oil core, a phytosome forms an actual molecular complex, thus increasing stability as well as the potential to be miscible with cell membranes as well as expanding passive delivery through biological barriers [12]. Such attributes are particularly prominent in central nervous system (CNS) conditions like PD, wherein breaching the BBB is still a significant barrier to hydrophilic and unstable drug substances. The passive diffusion via lipophilic phytosomes and the potential to interact with the lipid transporters and receptors at the BBB could further increase active phytoconstituent reach to the brain. A variety of phytochemicals with relevance to PD, including curcumin, resveratrol, quercetin, and EGCG, have proven to have improved pharmacokinetics in formulations as phytosomes compared to their corresponding phytochemical reference extracts, where some pharmacokinetic profile comparisons found the

phytosomal form of these substances had plasma concentrations up to 20-fold higher than conventional extracts [12]. Besides facilitation of enhanced absorption, phytosomes protect vulnerable phytoconstituents against hydrolytic destruction by gastric acid, intestinal enzymes, and intestinal flora, extending systemic passage, sustaining therapeutic levels, and increasing therapeutic returns.

Particle size, zeta potential, and encapsulation efficiency are directly affected by the methodology chosen to manufacture the phytosomes through solvent evaporation, anti-solvent precipitation, or mechanical dispersion [13]. Particle size and polydispersity are particularly favorable in central nervous system targeting, wherein smaller particle sizes increase permeability and smaller colloidal fragments decrease opsonization by the reticuloendothelial system. Application of Generally Recognized as Safe (GRAS) phospholipids enhances biocompatibility and reduces toxicity thus facilitating the acceptance by the regulation. In Parkinson disease, an increase in antioxidant and neuroprotective phytoconstituents delivery through phytosomes can simultaneously regulate several pathways- reducing oxidative stress and α-synuclein aggregation, suppressing neuroinflammation, and maintaining mitochondrial integrity. Curcumin phytosomes (Meriva) represent this promise and have been demonstrated in animal models to enhance brain uptake, reduce loss of dopaminergic neurons, and enhance motor performance when compared to unformulated curcumin [14]. Similarly, resveratrol phytosomes achieve better blood-brain barrier transport and better neuroinflammation-reducing properties in models of PD. This group of results demonstrates the translational potential of phytosome technologies as applied to neurodegenerative disorders. The phytosome composition has previously proven to be commercially advanced in the context of other therapeutic areas such as silybin phytosome in hepatic disorders and *Ginkgo biloba* phytosome in cognitive decline, offering regulation precedent as well as market-proven use in PD [15]. Therefore, the discovery that phytosomes are not only a novel drug-delivery system but an essential enabling platform potentially holding the key to unlocking the therapeutic potential of herbal neuroprotectives in Parkinson disease. The mechanism by which phytosome formulation enhances bioavailability and neuroprotective efficacy in PD is illustrated in **Figure 9.1**.

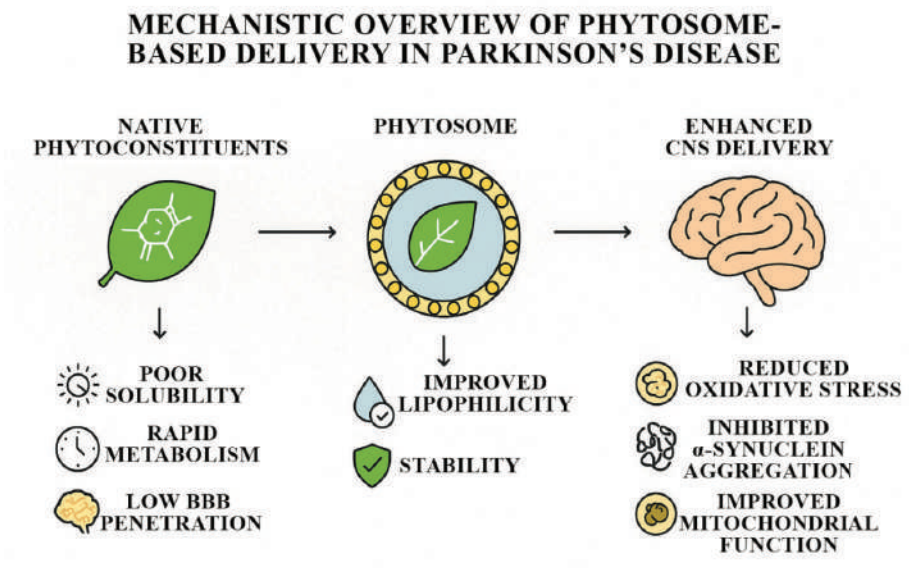

Figure 9.1 - Mechanistic Overview of Phytosome-Based Delivery in PD

4. Key Herbal Phytoconstituents for PD and Their Phytosome-Based Delivery

Phytochemical have been identified through plants that have shown therapeutic activity in PD by reducing oxidative stress, damping neuroinflammatory, interfering with alpha petalin packing, and reinstituting mitochondrial functions and apoptosis. Poor oral bioavailability, poor brain permeation, and fast hepatic metabolism, however, have hindered its clinical translation. Phytosome nano-formulations can break down these limitations as they serve to boost drug delivery to overcome biological barriers [16]. Curcumin is a polyphenolic derivative of *Curcuma longa* and occupies one of the important positions among the candidate agents. *In vitro* data suggest that curcumin inactivates reactive oxygen and reactive nitrogen species, chelates metal ions, activates phase II detoxification enzyme transcription through nuclear factor erythroid-2-related factor 2, and down-regulates pro-inflammatory transcription factor nuclear factor-kB. Curcumin interferes with the α-synuclein fibrillation and improves autophagy-induced removal of the harmful oligomers in animal models with PD. Low aqueous solubility and fast metabolic clearance, however, hinder the efficacy of native curcumin; phytosomal formulations, including Meriva, have been found to enhance systemic bioavailability by performing as much as 29-fold and significantly increase brain absorption as well, and show the potential to protect dopaminergic neurons and improve symptoms of motor disruption in MPTP-lesioned mice [17]. Stilbene, a component of grapes and peanuts, called resveratrol, has pharmacological activities through SIRT1 activation, an increase in mitochondrial biogenesis through peroxisome proliferator-activated receptor-gamma coactivator 1-alpha activation, and a decrease in microglia activation and neuroinflammatory markers. Its polyphenolic chemical framework also provides the ability to inhibit the monoamine oxidase B enzyme, which reduces catabolism of dopamine and the resulting generation of ROS [18]. However, the oral bioavailability is hampered by the rapid glucuronidation and sulfation that are characteristic of native resveratrol, nullifying the translation of its perceived neuroprotective capability. Subsequent use of phytosomes in resveratrol has resulted in a significant rise in plasma and cerebrospinal fluid concentration and relative therapeutic efficacy, leading to a reduction in nigrostriatal degeneration and behavioral parameters in animal models of PD.

The neuroprotective effects of epigallocatechin-3-gallate (EGCG), which is derived through extracts of green tea are multifaceted and include that such direct inhibitors of α-synuclein fibrillogenesis stimulation of protein refolding by molecular chaperones and inhibition of iron-induced oxidative stress [19]. Another way EGCG can have anti-inflammatory effects is by inducing neuronal survival-associated signals such as the mitogen activated protein kinase (MAPK) and phosphoinositide 3 kinase /protein kinase B (PI3K/Akt). However, the hydrophilic nature of the compound reduces its permeability through the BBB. Phytosomal formulations significantly boost lipophilicity and promote BBB permeability, ultimately boosting motor recuperation and conserving dopaminergic neurons in parkinsonian animal models [20]. Quercetin, a flavonol rich in onions and apples sequesters free radicals, inhibits lipid peroxidation, and inhibits mitochondrial depolarization. It also regulates neuroinflammatory processes mediated by nuclear factor-kB, including repression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and prevention of apoptotic cascades, including Jun N-terminal kinase (JNK) and p38 MAPK. Its low water solubility and insufficient intestinal uptake, however, limit its CNS penetration. Quercetin phytosomes offer better oral bioavailability and potent neuroprotection in rotenone-exposed PD-modeled-rat, which correlated with increased striatal dopamine accumulation and diminished alpha-synuclein clumping [21]. Ginkgolides and bilobalide are extracts of the Ginko biloba leaves which have neuroprotective effects like free radical scavenging, platelet-activating factor inhibition, glutamate excitotoxicity regulation, and enhancement of cerebral blood flow. They further increase mitochondrial respiration and reduce apoptosis of the neurons. *Ginkgo*

biloba phytosomes, such as Ginkgoselect Phytosome, have shown greater plasma and brain levels than crude extracts and provided better cognitive and motor performance in parkinsonian animal models and vascular protection against neuronal death. Isolated bacosides of Bacopa monnieri have been shown to have antioxidant and anti-inflammation actions, enhance synaptic plasticity, increase synaptophysin, and brain-derived neurotrophic factor (BDNF), and mitochondrial dysfunction [22]. Bacosides are amphiphilic however, they have unsatisfactory oral absorption. Bacoside phytosomes have a significant effect on bioavailability increasing dopaminergic neuron survival and enhanced motor performance in toxin-induced PD models.

Isolated withanolides of *Withania somnifera* (ashwagandha) show strong modulatory effect on the hypothalamic-pituitary-adrenal (HPA) axis, reduce neuro inflammatory molecules, reverse mitochondrial dysfunction, and neurogenesis [23]. The impact of these bioactive constituents on the gastrointestinal solubility, membrane permeability, and metabolic stability can be demonstrated using the mechanism of action of these bioactive constituents when formulated as withanolide phytosomes, such that therapeutically relevant concentrations may reach into the nigrostriatal pathway. The molecular affinity between the phytoconstituent and the phospholipid vesicle enhances more interaction with the intestinal enterocytes and its lymphatic absorption, which by-passes the extensive metabolism that is first-pass-that is, an issue of particular concern with polyphenolic reagents that have a quick rate of excretion in the liver [24]. The increased BBB permeability also provides the long-term target access in PD, a disorder which is associated with a simultaneous maladaptation in oxidative, inflammatory, and apoptosis-related pathways. Taken together, these data demonstrate that phytosome technology is not merely a pharmacokinetic adjuvant, but is a vital agent in translating *in vitro* neuroprotective properties to *in vivo* neurotherapeutic efficacies [25]. Future perspectives entail developing phytosomes into poly-faceted delivery platforms, such as mucoadhesive nanoparticles, nasal administration routes, and responsive carriers, to maximize CNS targeting, enhance brain retention dwell times, and permit multi-herb, synergetic formulations with the potential to address the heterogeneous pathological network of PD. The neuroprotective role of phytoconstituents and their enhanced bioavailability with phytosome formulations is presented (see **Table 9.1**)

Table 9.1 - Summary of key herbal phytoconstituents, their mechanisms of neuroprotection in PD, limitations in bioavailability, and improvements achieved through phytosome-based formulations

Phytoconstituent	Plant Source	Main Neuroprotective Mechanisms in PD	Bioavailability Limitations	Improvement with Phytosome Formulation	Preclinical/Clinical Evidence	Ref.
Curcumin	*Curcuma longa*	Antioxidant, anti-inflammatory, α-synuclein aggregation inhibition, mitochondrial protection	Low aqueous solubility, rapid metabolism	↑ bioavailability up to 29×; ↑ brain uptake	Motor improvement, dopaminergic neuron protection (MPTP model)	[26]
Resveratrol	Grapes, peanuts	SIRT1 activation, mitochondrial biogenesis, MAO-B inhibition, anti-inflammatory	Rapid glucuronidation and sulfation	↑ plasma & CSF levels, ↓ neuroinflammation	Reduced nigrostriatal degeneration in PD models	[27]

EGCG	Green tea	α-synuclein fibrillation inhibition, antioxidant, chaperone-mediated protein refolding	Hydrophilic, poor BBB permeability	↑ lipophilicity, ↑ BBB crossing	Improved motor recovery, dopaminergic neuron survival	[28]
Quercetin	Onions, apples	Antioxidant, anti-inflammatory (NF-κB inhibition), anti-apoptotic	Low solubility, poor intestinal uptake	↑ oral bioavailability, ↑ striatal dopamine	Reduced α-synuclein clumping in PD models	[29]
Ginkgolides	*Ginkgo biloba*	Antioxidant, cerebral blood flow improvement, anti-apoptotic	Limited CNS penetration	↑ plasma and brain levels	Better motor/cognitive performance in PD models	[30]

5. Recent Advances, Clinical Status, and Regulatory Trends

Over the last few years, significant developments have been made in the translation of phytosome-based herbal medicine models, to potential clinical use in PD, driven by developments in the fundamental science of formulation research, improved understanding of disease pathophysiology and an emerging interest in safer, multitargeted therapies [14]. In preclinical studies, phytosome administration has consistently been shown to greatly enhance the pharmacokinetic properties of neuroprotective phytoconstituents, including curcumin, resveratrol, EGCG, quercetin, and bacosides, enhancing antioxidant defense, reducing neuroinflammation, preventing fibrillation of α-synuclein, and protecting against toxin-induced PD. Several compounds have reached early-phase clinical development in PD and other neurodegenerative diseases [31]. In particular, curcumin phytosome (Meriva(R)) has enhanced bioavailability and better safety in healthy volunteers and demonstrates cognitive and mood improvements in the elderly, which appear to be translatable to PD-related cognitive decline. *Ginkgo biloba* phytosome (Ginkgoselect 10) also shows better vascular and neurocognitive results in mild cognitive impairment, with pathological overlap with PD dementia [32]. Even though no PD-specific clinical trials were available, these data provide strong preliminary evidence of effectiveness. In parallel, technological advancement has extended the capabilities of phytosome: new hybrid transport systems are being developed, such as phytosome-loaded nanoparticles, phytosome-micelle complexes, and thermoresponsive phytosomal hydrogels to offer controlled release, enhanced mucosal adhesion, and intranasal delivery to circumvent the blood brain barrier. In addition, combination therapy modalities are also emerging whereby phytosomes are co-formulated with synergistic herbal actives or standard PD drugs to achieve an additive neuroprotective effect and reduce levodopa-induced dyskinesia [33]. The development of regulation has also influenced the path of these innovations.

In the United States, the Dietary Supplement Health and Education Act (DSHEA) regulates dieting supplements that utilize phytosomes, and it provides access to the market without the strict clinical-efficacy requirements of pharmaceuticals and requires a demonstrable level of safety and manufacturing standards [34]. In comparison, the European Medicine Agency (EMA) has classified these formulations as a type of “herbal medicinal products” and regulates them based on either a traditional-use registration or a well-established-use process route, depending on the scientific evidence at hand [35]. In Asian countries, especially in India and China, pharmaceutical preparations of phytosomes in herbal form are common, often under traditional-medicine controls, which in turn leads to accelerated approval with increased expectations of standardization and evidence-based statements. In modern business trends,

the neuroprotective therapies based on phytosomes have become the scope of a steadily growing commercial interest, the driving force behind which is the modern consumers inclinations towards using more natural ways to ensure their health and the global nutraceutical market growing at a fast pace. However, the integration of phytosome-based therapeutics into PD care faces a number of obstacles to mainstream adoption: Clinical outcomes need to be demonstrated in larger scale, randomized, controlled trials directly in PD; the evidence of long-term safety is imperative owing to the chronic course of the disease; and the formulations should meet good manufacturing practice (GMP) standards to demonstrate batch-to-batch reproducibility [36]. In parallel, pharmacovigilance tools require close interventions to possible interactions of herb with drug, especially in elderly PD where polypharmacotherapy is frequently used. Future research is likely to focus on precision delivery, combining couple phytosomes with ligand-targeted nanocarriers to mediate selective neuronal uptake, evaluating the efficacy of phytosome preparations in prodromal PD to slow disease progression, and increasing phytoconstituent libraries via ethno-botanical inquiry. Overall, despite its relative youth in the translational process, the convergence of nanotechnology, phytochemistry, and regulatory freedom suggest that phytosome-based herbal medicines are deserving candidates as safe, effective, and holistic solutions to PD.

6. Challenges, Future Perspectives, and Conclusion

Herbal therapeutics in phytosomes are a promising therapeutic option in PD, but they still face a number of barriers in complete translation into clinical practice. The first and paramount is the lack of high-quality PD-specific randomized controlled trials to support preclinical findings and to identify effective dosing regimens to achieve long-term efficacy [37]. Phytoconstituents and phospholipid carriers must be standardized in order to guarantee interbatch reproducibility, which is a condition of regulatory acceptance as well as broader clinical acceptability. Moreover, the increased possibility of herb drug interactions, especially in the elderly patients undergoing polypharmacy, necessitates strict pharmacokinetic and pharmacodynamic analysis. The delivery mechanism should be focused in future on specific delivery domain such as ligand-functionalized phytosomes that will bind specifically to the dopaminergic neurons or internal delivery mechanism through existing pathways at blood-brain barrier [38]. Combination of the phytosome technology with other nanocarrier networks and personalized medicine strategies may also increase therapeutic efficacy. The discovery of unorchestrated phytoconstituents in ethnobraenic research also has the potential to identify new neuroprotective agents. Altogether, phytosomes are not the direct alternative to traditional PD therapies yet, but their potential to increase bioavailability, stability, and increase delivery to the CNS will make them a favorable choice as an adjunct to safer and multi-targeted management of neurodegenerative diseases [39].

Conclusion

In recent years, phytosome technology has been mentioned as a transformational platform to enhance the therapeutic potential of herbal phytoconstituents in PD. Phytosomes enhance the neuroprotective effects of curcumin, resveratrol, quercetin, and EGCG through their ability to increase bioavailability, stability, and blood-brain barrier permeability, extending the longevity and enhancing the intensity of their neuroprotective effects on various pathological processes, such as oxidative stress, neuroinflammation, and protein aggregation. Despite the plethora of preclinical data, clinical data in PD are limited, highlighting the need to develop well-designed large-scale trials. Their integration into everyday clinical practice will depend on standardization, overall safety profiling, and regulation harmonization. New technologies: Emergent technologies, including combination drug therapies, targeted drug delivery systems, provide possible opportunities to extend the phytosome-based therapeutic utility. To conclude, phytosomes represent a novel but promising adjuvant therapy to PD with a multitarget, multimodal, and naturally derived modality offering a scientifically supported trial with a lot of potential use in complementing traditional medicine and without unfilled regulatory niches in the way the treatments are handled significantly in the management of neurodegenerative disorders.

Acknowledgement: Authors would like to thank Editors, Deep Science Publishers and Department of Pharmacy, Jagannath University to provide this opportunity.

Author Contribution: All authors have equal contributions in completion of this book chapter.

Fundings: No funding.

Conflict of Interest: There is no conflict of interest.

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