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Dual Role of *Ginkgo biloba* in Nanoparticle Biosynthesis and Parkinson's Disease Management

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Abstract: Parkinson's disease (PD) is a rapidly growing neurological disorder affecting millions globally, characterized by the degeneration of striatal dopaminergic neurons and reduced dopamine levels. With an estimated 12.9 million projected cases by 2040, current treatments, such as dopamine replacement, remain palliative and face significant challenges, particularly the blood-brain barrier (BBB), which limits effective drug delivery to the brain. Common databases such as PubMed, Medline, Scopus, and ScienceDirect were searched for relevant data on *Ginkgo biloba*, nanoparticles, lipids, and Parkinson's disease. Recent advancements in nanomedicine, especially lipid nanoparticles (LNPs), offer promising solutions to this problem. This review examines the potential of Ginkgo biloba extract (EGb) as both a therapeutic and a reducing agent in the development of innovative LNP-based delivery systems for PD treatment. EGb is renowned for its neuroprotective and antioxidant properties and can enhance BBB permeability while inhibiting monoamine oxidase, thus preventing dopamine breakdown. Studies indicate that EGb-loaded LNPs can improve drug delivery to the brain by leveraging ginkgolides and kaempferol, which activate adenosine receptors in the BBB, thereby enhancing their permeability. Furthermore, EGb has been shown to improve locomotor activity and muscle coordination and restore key brain enzymes. This dual-functional approach, combining the traditional medicinal benefits of EGb with modern nanomedicine, offers a novel and promising therapeutic strategy for PD and warrants further research.

Keywords: Parkinson's disease; lipid nanoparticles; *Ginkgo biloba*; blood-brain barrier; nanomedicine; biological synthesis.

1. Introduction

Parkinson's disease (PD) is one of the fastest-growing neurological disorders worldwide, with an estimated 12.9 million people expected to be affected by 2040, doubling the number reported in 2015 [1]. This debilitating motor dysfunction manifests as slowed gait, rigidity, and tremors, and often affects patients' mental health, leading to anxiety and depression. Treatment remains palliative, and diagnosis typically occurs after symptom onset, with the root cause rarely addressed. Diagnostic measures include physical examination focused on prodromal features such as rapid eye movement (REM) sleep behaviour disorder, constipation, hyposmia, cognitive or psychological difficulties, and characteristic movement impairments [2].

It is well established that degeneration of striatal dopaminergic (DAergic) neurons plays a pivotal role in PD pathogenesis. Therapeutic interventions, therefore, aim to increase dopamine levels or stimulate dopamine receptors, exemplified by drugs such as levodopa (L-Dopa), a naturally occurring dopamine precursor. Although effective, levodopa faces challenges including unpredictable absorption rates and excessive metabolism [3]. A significant obstacle to optimal therapy is the blood-brain barrier (BBB), which separates the central nervous system (CNS) from the bloodstream. The BBB consists of pericytes and neural endothelial cells regulated by tight junctions [4], controlling drug entry and limiting the transport and permeability of pharmacologically active agents [5].

Given the formidable nature of the BBB, recent research has focused on nanomaterials capable of traversing this barrier effectively. Nanoparticles (NPs) have emerged as a forefront technology due to their favorable size, structural versatility, and capacity to carry and protect therapeutic cargo,uch as drugs or genes, thereby enhancing solubility and bioavailability [6–8]. Lipid nanoparticles (LNPs), in particular, are promising delivery vehicles. The inclusion os sphingomyelin in their composition supports enhanced brain permeability via passive, specific, and non-specific diffusion [9]. Novel synthesis methods and various molecular conjugations can improve their targeting and therapeutic efficacy.

One innovative synthesis approach utilizes extracts of *Ginkgo biloba*, a tree native to China, renowned for its neuroprotective and antioxidant properties. *Ginkgo biloba* acts as a monoamine oxidase (MAO) inhibitor, preventing the enzymatic breakdown of dopamine. Early studies demonstrated that *G. biloba* extract (EGb) increased locomotor activity, muscular coordination, and restored glutathione and glutathione-dependent enzymes such as catalase and superoxide dismutase in the striatum. Additionally, an increased density of dopaminergic D2 receptors, alongside elevated density of tyrosine hydroxylase-immunoreactive (TH-IR) fibres,as observed [10].

The unique dual role of *Ginkgo biloba* as both a neuroprotective agent and a green reducing agent for nanoparticle synthesis positions it as an ideal candidate for developing synergistic delivery systems. Such dual-function vehicles, combining EGb with molecular conjugates and ligands, can produce formulations that simultaneously target multiple aspects of PD pathology. This review focuses on the formulation of EGb-based lipid nanoparticles and their potential applications in advancing the treatment and management of PD.

2. Parkinson's Disease: A Brief Overview

2.1. Epidemiology and etiology of Parkinson's disease.

PD is recognised as a global concern and one of the fastest-growing neurological diseases. The expected number of patients with PD is set to rise to an estimated 12.9 million people by 2040 [1]. Despite extensive studies, the etiology of PD is still under research and not completely elucidated. PD onset has been linked to both genetic and environmental contributors, as evidenced by single gene mutations in the familial form [11]. In addition to medication, therapeutic strategies have faced many challenges, of which the BBB is the greatest hindrance. Further strategies that have been implemented include cell therapy, neurotrophic agents, and electrical stimulation [12].

2.2. Pathophysiology and molecular mechanisms.

PD is associated with the progressive loss of dopaminergic neurons in the substantia nigra (SN) and their projections to the striatum. Consequently, the nigrostriatal pathway is disrupted, leading to reduced functionality and thus symptoms such as bradykinesia, tremors, impaired balance, rigidity, and mental health-related issues, including depression [13], as illustrated in Figure 1. Furthermore, Lewy bodies were found in all affected brain regions in patients presenting with PD. These intraneuronal proteinaceous cytoplasmic inclusions, including ubiquitin, α-synuclein, and neurofilaments, are among the pathological features of PD. Beyond this, oxidative stress, protein dysfunction, apoptosis, autophagy, inflammation, and mitochondrial dysfunction are the pathogenic mechanisms associated with PD onset [6,13]. Mutational events have also been noted to cause PD through protein dysregulation in the DJ-1, PINK1, FBXO7, PARKIN, and LRRK2 genes, with 5% of cases familial and 95% sporadic[14].

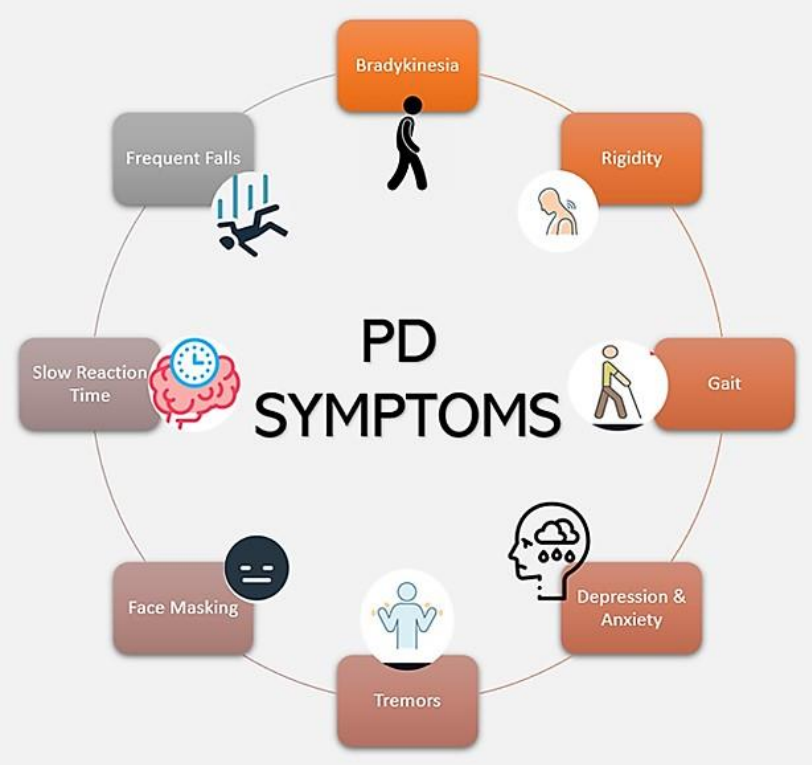

Figure 1. An illustration of the symptoms associated with Parkinson's disease.

2.3. Current therapeutics: pharmacological approaches.

The treatment against PD remains at a symptomatic level, with the gold standard treatment being in the form of dopamine replacement employing the use of levodopa. Following further research and alternative approaches, non-ergot dopamine agonists (DAs), catechol-O-methyl transferase (COMT) inhibitors, and monoamine oxidase-B (MAO-B) inhibitors have been used [15]. Combined with dopamine replacement options, complementary and alternative (CAM) and integrative medicinal approaches are performed [16]. The treatment of PD follows a five-step strategy commencing with rehabilitation, followed by therapy, restorative maintenance, and surgery [17].

Rehabilitative options are based on the effects of dopamine loss on the voice and movement, such as reduced volume and tone while speaking and limitations in movement. The

rehabilitation strategy employed is known as LSVT (Lee Silverman Voice Treatment)-LOUD and LSVT-BIG [18]. The former programme focuses on vocal exercise, thereby increasing vocal volume, while the latter is based onntensive exercise of large-amplitude movements to compensate for hypokinesia and bradykinesia [19].

The second strategy in the treatment of PD is the use of drugs to assist a patient with dopamine loss. Dopamine or 3,4-dihydroxyphenethylamine is a member of the phenethylamine and catecholamine molecular family [20]. This derivative of tyrosine (Tyr) is formed via the conversion of Tyr to levodopa (L-DOPA) to produce dopamine [21]. Dopamine agonists and replacement therapies, such as levodopa, were created to compensate for the loss of dopamine in PD. Simultaneous treatment with levodopa and carbidopa (an aromatic L-amino acid decarboxylase inhibitor) was shown to facilitate transport of levodopa into the CNS by preventing its conversion to dopamine ineripheral tissues [22]. Various other treatments have also been used (Table 1).

Table 1. Some approaches and drugs are used for the treatment of PD.

Compound	Drug	Mechanism of Action	Reference
Dopamine replacement	Carbidopa/ Levodopa	The blood-brain barrier permits entry of levodopa, leading to more dopamine being synthesized in the CNS.	[23]
Dopamine agonist	Ropinirole	Mimics dopamine by binding to dopamine receptors and stimulates the D2 dopamine receptors.	[24]
Monoamine oxidase-B (MOA-B) inhibitors	Selegiline	Prevents MAO from inactivating and breaking down excessive amounts of dopamine.	[17]
Catechol-O-methyl transferase (COMT)	Opicapone	It prevents the conversion of levodopa to 3-Omethyldopa and increases the half-life and retention time of levodopa in the CNS.	[2]
Anticholinergics	Trihexyphenidyl, Benztropine	Blocks acetylcholine receptors in the brain, balancing the dopamine-acetylcholine ratio.	[25]
Amantadine		It enhances dopamine release and blocks glutamate receptors, reducing dyskinesia and improving motor symptoms.	[26]
NMDA Receptor Antagonists	Memantine	Blocks N-methyl-D-aspartate glutamate receptors, potentially reducing dyskinesias and improving motor symptoms.	[27]
Adenosine A2A Receptor Antagonists	Istradefylline	Block adenosine A2A receptors, modulating dopaminergic signaling and reducing motor fluctuations.	[28]
Glutamate Receptor Antagonists	Riluzole	Inhibits glutamate release and blocks glutamate receptors, providing neuroprotective effects.	[29]

2.4. Rehabilitation and restorative therapies.

Another mitigation strategy against the pathogenic effects of PD is seen in exercise, known as restorative therapy. Exercise was shown to preserve undamaged dopaminergic neurons, increase brain-derived neurotrophic factor level and reduce pro-inflammatory markers in mice [30]. Strenuous aerobic exercise in humans also produced neuroprotective effects in PD patients while improving their quality of life [31,32].

2.5. Maintenance, adjunctive therapies, and surgical interventions.

As the name suggests, the maintenance approach maintains the remaining healthy dopaminergic cells by incorporating vitamins and other compounds. Traditional/ biological compounds form part of this therapy due to their properties. The exploration of adjunctive therapies in PD management offers promise but necessitates careful consideration of their efficacy and safety, particularly given their departure from established treatment guidelines. Vitamin D3 supplementation in PD remains debatable, with divergent findings on its cognitive

benefits, highlighting the need for further research to clarify its role. Conversely, challenges such as poor bioavailability and limited brain penetration hinder the translation of curcumin's antioxidant and anti-inflammatory effects into viable PD therapies. Similarly, while other adjunctive compounds show efficacy in preclinical studies, their clinical applicability lacks robustness [33].

Translating theoretical efficacy into practical applicability requires in-depth studies to assess the effectiveness and safety profiles of these adjunctive therapies. Caution must be exercised in their implementation, given the absence of definitive clinical evidence and their deviation from established treatment guidelines. Robust clinical trials are imperative for validating the therapeutic potential of adjunctive therapies and delineating their role in PD management. Until then, healthcare practitioners should judiciously consider adjunctive therapies and prioritize evidence-based approaches in PD treatment.

The option for surgery is reserved for individuals presenting with complications associated with long-term use of carbidopa/levodopa. Deep brain stimulation targets the thalamus, subthalamic nucleus, and globus pallidus [34]. While all strategies are productive in providing a band-aid approach to PD symptoms, a therapy option to treat the root causes of PD with limited side effects has not yet been established. Further research is imminent to treat PD patients more effectively, and this could involve looking back at traditional medicine and its adaptability to modern medicine. However, despite advances in symptomatic and surgical treatments, effective disease-modifying therapies remain elusive, necessitating exploration into novel therapeutic avenues such as traditional medicine and nanotechnology-based drug delivery systems. Among those emerging therapeutic strategies, EGb has attracted attention for its neuroprotective properties. While preclinical evidence supports its efficacy, further clinical trials are warranted to confirm its therapeutic role in PD patients.

3. Traditional Therapeutics: *G. biloba* Extract (EGb)

3.1. Bioactive compounds: their neuroprotective effects and limitations.

In light of these therapeutic challenges, *G. biloba*, a traditional medicinal plant, has been extensively studied for its neuroprotective and antioxidant effects relevant to PD. Due to its exhibited properties, *G. biloba* has long been utilized as a therapeutic agent. This endemic plant belongs to the genus Ginkgo and is the only species to have survived, known as the "living fossil" [35]. The tree has leathery, fan-shaped leaves with yellow, edible seeds. Historically, this tree has been used to treat bronchitis, renal dysfunction, asthma, and bladder complications [36,37].

In 1965, a German physician and pharmacist, Willmar Schwabe III, developed the initial standardised extract of dried *G. biloba*, known pharmacologically as EGb 761 [38]. This extract contained 6% terpenoids, 24% flavonoid glycosides, and 5-10% organic acids, each contributing distinct bioactivities relevant to various diseases (Figure 2).

The chemical compound found in the leaves of *G. biloba*, known as Ginkgetin (natural biflavonoid), presents further antioxidant capabilities and protects against 1-methyl-4-phenylpyridinium (MPP^+) induced cellular damage via the reduction of reactive oxygen species (ROS) levels. This was shown to improve sensorimotor coordination in a mouse model by regulating iron homeostasis[39]. Furthermore, pretreatment with ginkgolide B and bilobalide protectedH-SY5Y neuroblastoma cells against α-synuclein-induced apoptosis [40].

Additionally, MPP^+-induced SH-SY5Y cells treated with 60 to 120 µg/mL EGb761 were successfully protected with no significant cytotoxicity noted [41].

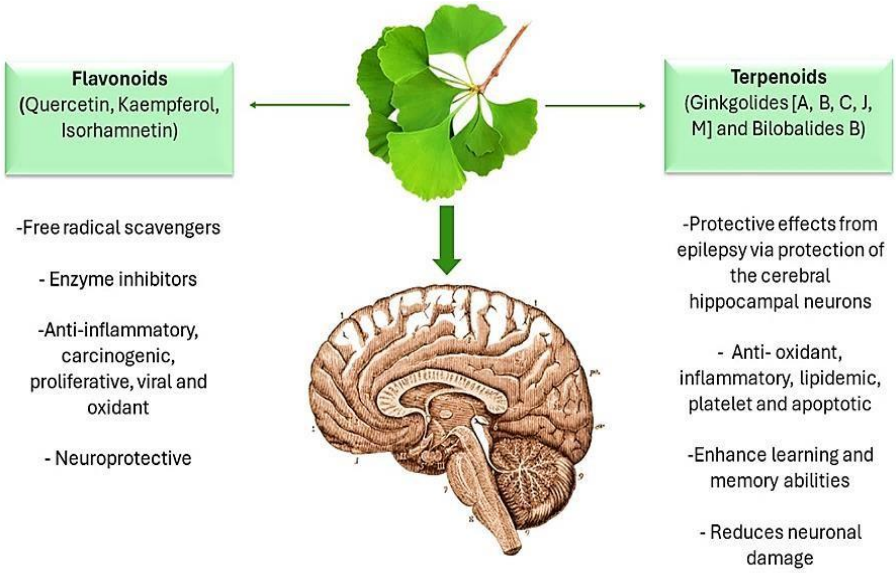

Figure 2. Chemical composition of *G. biloba* and its beneficial properties.

EGb761 also protected against paraquat-induced (a pesticide linked to PD) apoptosis of PC12 (rat pheochromocytoma) cells by increasing bcl-2 activation, decreasing mitochondrial caspase-3 activation, and maintaining membrane potential [42]. Overall, its advantages in PD treatment include its ability to decrease oxidative damage, regulate dopamine homeostasis, and enhance locomotor activity [43].

3.2. Mechanisms of action of bioactive EGb

The bioactive components of EGb have been shown to benefit many diseases. The terpenoids, especially ginkgolides A, B, and C, are antagonists of platelet-activating factor (PAF) receptors, inhibiting platelet aggregation and inflammatory signalling pathways [44], thereby reducing neuroinflammation. Furthermore, the terpene lactone bilobalide modulates mitochondrial function by stabilising the membrane potential and preventing apoptosis in neuronal cells [45,46].

The flavonoid glycosides quercetin and kaempferol are powerful antioxidants that directly scavenge ROS, such as superoxide anions and hydroxyl radicals [47]. The upregulation of antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase through activation of the Nrf2-ARE (nuclear factor erythroid 2–related factor 2–antioxidant response element) signalling pathway has been reported. This enhances endogenous defence systems against oxidative stress [48]. This dual action protects dopaminergic neurons from oxidative damage. Furthermore, these flavonoids are known to inhibit lipid peroxidation in neuronal membranes, thereby preserving the membrane integrity and function. Quercetin further modulates cell survival pathways by regulating apoptotic proteins, suppressing pro-apoptotic factors such as Bax and caspase-3, and promoting anti-apoptotic proteins like Bcl-2 [49].

The synergistic effects of terpenoids and flavonoids in EGb therefore contribute to neuroprotection by attenuating oxidative stress, inhibiting inflammation, stabilising mitochondrial function, and preventing neuronal apoptosis. These mechanisms underlie the therapeutic benefits of *G. biloba* in disorders including depression, cerebral insufficiency,

thrombosis, myocardial ischemia, peripheral occlusive arterial disease (POAD), memory impairment, and poor concentration [50].

3.3. Mechanisms of EGb in treating PD.

The chemical composition of *G. biloba* has been well elucidated, and its benefits have been successfully incorporated into PD therapeutics. One established mechanism is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- induced rat PD models. MOA-B has been noted to inactivate the dopaminergic nerve endings by converting MPTP to MPP^+. MPTP is considered a lipophilic compound, which can efficiently cross the BBB, followed by the subsequent metabolism by MOA-B [51]. This phenomenon occurs primarily in the glial cells, owing to the formation of MPP^+ in its ionic form [52]. Due to the structural similarities between dopamine and MPP^+, the DA neurons in the substantia nigra pars compacta (SNpc) take up the MPP^+ via the dopamine transporters (DAT) from the intercellular space [51].

Following neuronal uptake, MPP^+ accumulates in mitochondria and inhibits complex I of the electron transport chain, impairing oxidative phosphorylation and reducing ATP production. This dysfunction promotes excessive ROS production, leading to oxidative damage to mitochondrial DNA, proteins, and lipids. The resulting loss of membrane potential facilitates cytochrome c release and activation of caspase-9 and caspase-3, triggering intrinsic apoptosis [53-56]. MPP^+ also disrupts calcium homeostasis and activates microglia, intensifying neuroinflammation and loss of dopaminergic neurons [53-56]. Figure 3 summarises the bioactivities of *G. biloba* in PD.

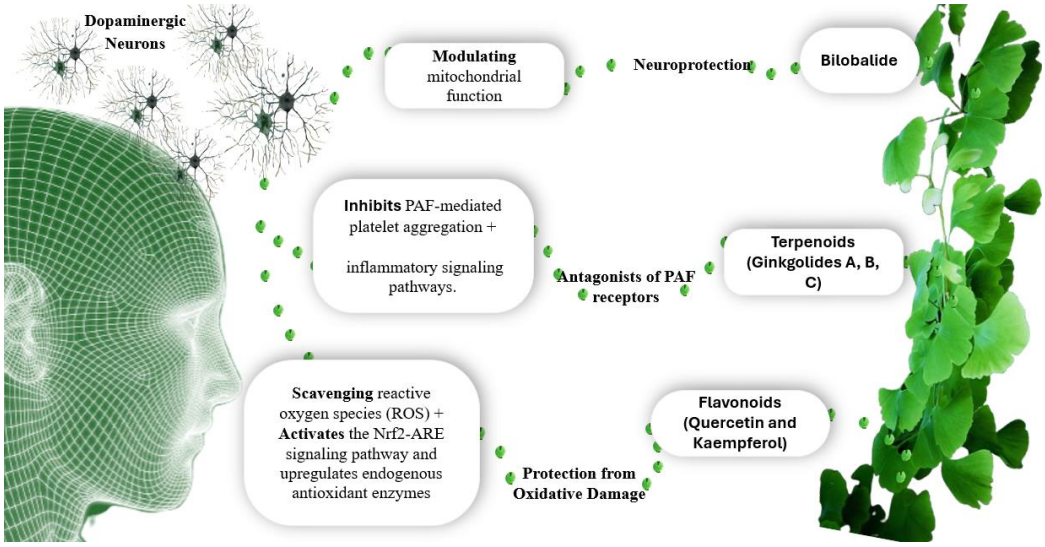

Figure 3. Neuroprotective mechanisms of *Ginkgo biloba* bioactives relevant to Parkinson's disease.

G. biloba extract EGb761 counteracts these pathological processes through multiple neuroprotective mechanisms. It stabilises mitochondrial membrane potential and enhances electron transport chain efficiency, thereby reducing ROS accumulation. EGb761 also upregulates endogenous antioxidant enzymes such as superoxide dismutase and catalase, and inhibits caspase activation to prevent apoptosis. Additionally, it modulates microglial activation and suppresses pro-inflammatory cytokine expression, fostering an anti-inflammatory environment conducive to neuronal survival [57-59].

Two independent studies demonstrated that EGb761 inhibits MPTP-induced dopaminergic neuron loss and preserves neuronal integrity, including protection of nerve terminals [59,60]. Histopathological analyses in PD mice revealed extensive striatal neuron

damage and glial hyperplasia, whereas treatment with *G. biloba* dropping pills preserved striatal architecture and prevented glial proliferation. Moreover, minimal loss of nerve fibre bundles in the EGb761-treated group highlighted its ameliorative effects on MPTP-induced neurodegeneration [60].

In 2003, the neurotoxic side effects of levodopa were noted, and EGb761 was found to possess additional neuroprotective properties by attenuating levodopa-induced neurotoxicity in 6-hydroxydopamine (6-OHDA) models [59]. This was later confirmed in a zebrafish model, which showed a significant reduction in 6-OHDA-induced dopaminergic neuron loss after treatment with 50 μg/mL of EGb 761 [41]. The neuroprotective properties were attributed to reduced oxidative stress, inhibition of lipid peroxidation, and attenuation of MPTP-induced neurodegenerationn the nigrostriatal pathway [13]. These early studies have paved the way for a better understanding of the vast range of beneficial properties associated with *G. biloba* uptake.

EGb761's efficacy has attracted attention for its multitarget neuroprotective mechanisms in addressing key pathological features. Its antioxidant capacity mitigates oxidative stress, thus permitting the protection of neurons from lipid, protein, and DNA damage [60]. It also exerts a pronounced anti-inflammatory effect via the modulation of microglial activation and downregulating pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). This is achieved primarily through the inhibition of the nuclear factor-kappa B (NF-κB) pathway. Resultingly, this reduces chronic neuroinflammation that accelerates dopaminergic neuronal loss [60].

Furthermore, due to the ability of EGb to stabilise the mitochondrial membrane potential, preserve electron transport chain function, and prevent ATP depletion, [61] was noted. This mitochondrial support inhibits intrinsic apoptotic pathways by regulating caspase activation and balancing pro- and anti-apoptotic protein expression, thereby enhancing neuronal survival [61]. Beyond this, a critical therapeutic mechanism is further noted in the inhibition of monoamine oxidase-B (MAO-B). This slows the deterioration of dopamine, thereby preserving synaptic dopamine levels and reducing the formation of toxic oxidative metabolites [62]. This directly counters the dopamine deficiency underlying PD motor symptoms.

EGb also affects protein homeostasis by preventing α-synuclein aggregation, a major component of Lewy bodies. As a result, clearance was promoted via autophagic and proteasomal pathways. This reduces proteinopathy-associated neuronal dysfunction and death [63]. EGb, thus, enhances neurotrophic support by upregulating brain-derived neurotrophic factor (BDNF) and related neurotrophins. This promotes synaptic plasticity and neuronal repair. Improved cerebral blood flow and mitochondrial bioenergetics complement these effects, fostering an environment conducive to neuronal health [64].

3.4. EGb limitations.

While EGb possesses several beneficial properties for BBB uptake, it faces various challenges in its pure form. Although EGb can be reduced to a nanoscale, size heterogeneity was observed, which reduced its targeting, therapeutic, and BBB-crossing potential[65]. EGb elicits immune or cytotoxic responses upon entry into the host, thereby reducing its biocompatibility [66]. This is evident for ginkgolic acid (GA), which had a reduced effect after fixation and fermentation. Unlike lipid or metal NPs, nanoscale EGb lacks versatility in terms of surface modifications, functionalization, and targeting efficiency.

4. Merging Traditional with Modern Medicine: Biological Nanoparticle Synthesis

The chemical constituents of EGb have been employed in NP synthesis, providing an innovative drug or gene delivery strategy with better efficacy and biocompatibility. Although plant extracts possess excellent therapeutic properties, their applications extend beyond traditional uses[67].

Biosynthesis, or green synthesis, is gaining prominence because it is environmentally friendly, low-toxic, and biocompatible. This is achieved by eliminating harmful chemicals commonly us in chemical NP synthesis [68]. In green synthesis, the bioactive phytochemicals (flavonoids, terpenoids, and phenolic acids) in *G. biloba* leaf extracts act as natural reducing and capping agents, donating electrons to metal ions (e.g., Au^{3+}, Ag^{+}) and reducing them to metallic NPs[69]. The adsorption of these compounds onto the NP surfaces further stabilizes the NPs and prevents aggregation, ensuring colloidal stability. This dual functionality facilitates controlled nucleation and growth of NPs, enabling the production of NPs with defined sizes and shapes suitable for biomedical applications [69].

Green synthesis using *G. biloba* further allows for the 'fine-tuning' of NP characteristics by varying different reaction parameters, including pH, extract concentration, reaction time, and temperature. Moreover, *G. biloba's* rich lipid content acts as a natural source of emulsifiers and structural components in the formulation of LNPs, including liposomes, solid LNPs(SLNPs), and nanostructured lipid carriers (NLCs) [67,70]. These LNPs benefit from *G. biloba's* antioxidant flavonoids, such as quercetin and kaempferol, which participate in redox reactions with lipid molecules. This neutralises free radicals, thus reducing oxidative damage to the lipid components, and stabilises the resulting NPs [71]. Flavonoids donate electrons to functional groups on unsaturated lipids, resulting in a conversion into more stable saturated forms, while acting as radical scavengers to prevent further oxidative reactions. This complex interplay of molecular interactions underscores *G. biloba's* multifaceted role as both a reducing and stabilization agent in NP synthesis. It also provides essential lipid building blocks for NP assembly and therapeutic efficacy [71–73].

The therapeutic advantage of this green synthesis approach lies in its ability to preserve the inherent bioactivity of the plant extracts within the NPs, while conferring improved stability, targeted delivery, and enhanced bioavailability. Consequently, *G. biloba*-derived NPs hold promise as versatile carriers capable of conjugating with pharmacologically active agents, thereby broadening their applicability in treating diseases such as PD. Using EGb in NP synthesis can mitigate the issues raised by the raw form of EGb while maintaining its inherent properties. This extract's use in synthesizing NPs, including metal and lipid NPs (LNPs), promotes colloidal stability, thereby maintaining drug integrity during passage through the BBB while preventing aggregation [74]. Furthermore, they can produce NPs of specific sizes through various optimizations, offering a more sustainable, eco-friendly green synthesis strategy [75,76].

4.1. Ginkgo biloba as a reducing agent.

In the bottom-up synthesis approach, the plant extract serves as a reducing agent to form NPs with varying sizes, shapes, and charges. This process requires the extraction of leaves, roots, or bark from trees, washing them in distilled water, and boiling to extract the chemical compounds into an aqueous solution, which is then added to the salts or lipids of the desired NP being synthesised (Figure 4). The amount of extract is related to NP size: more

extract yieldsmaller NPs, which are optimal for cell uptake [77]. The EGb contains many phytochemicals, including flavonoids, terpenoids, and phenolic acids, which exhibit antioxidant properties and can donate electrons, making them suitable candidates for reducing agents in NP synthesis.

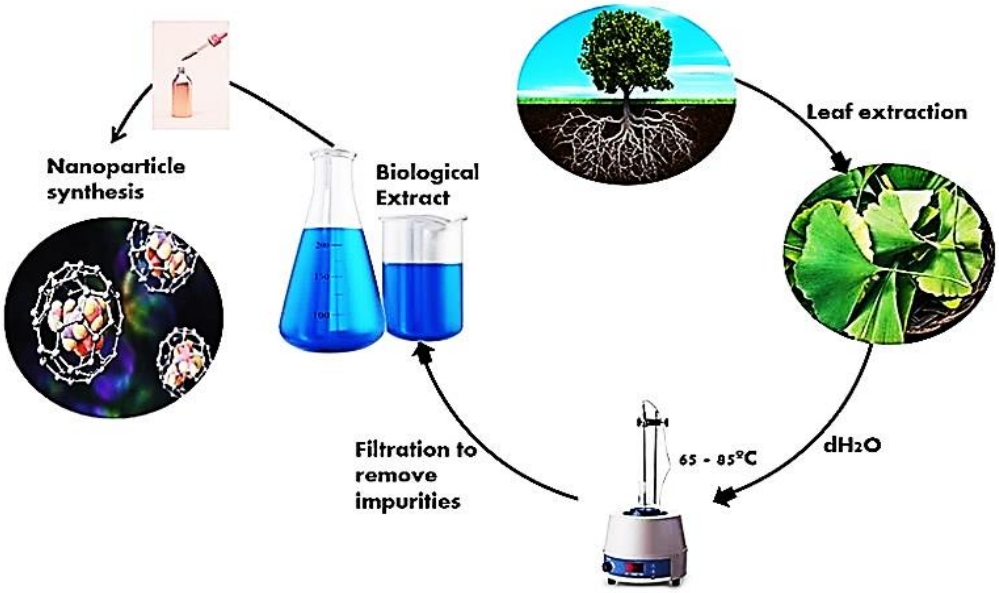

Figure 4. Bottom-up biosynthesis process using plant extracts.

Metallic NPs, such as gold NPs (AuNPs) and silver NPs (AgNPs), have been synthesized using EGb due to their rich composition of bioactive compounds. These compounds, particularly flavonoids such as quercetin and kaempferol, possess functional groups such as hydroxyl (-OH) and carbonyl (C=O) groups, which can reduce metal ions to form NPs. Quercetin has been shown to effectively reduce gold ions to form AuNPs with well-defined morphologies and sizes [78]. Using EGb in AgNP synthesis produced NPs with a mean size of 40.2 nm and a stable zeta potential of -34.56 mV [79]. The EGb extract's reducing potential was attributed to its ability to scavenge free radicals and undergo redox reactions. This antioxidant activity plays a crucial role in the reduction process by providing electrons to stabilise metal ions, neutralizing free radical formation [80], and promoting the nucleation and growth of NPs.

In the case of LNPs, EGb serves as a natural source of lipids and emulsifiers, which are essential components of lipid-based nanocarrier formulations. LNPs, including liposomes, SLNPs, and NLCs, are widely utilized for drug delivery applications due to their biocompatibility, controlled release properties, and ability to encapsulate hydrophobic and hydrophilic drugs. EGb orchestrates an intriguing and intricate process in synthesizing LNPs. An in-depth look into its mechanism of action for reducing lipids into NPs reveals a complex interplay of molecular interactions. Flavonoids, such as quercetin and kaempferol, interact with lipid molecules, initiating a series of redox reactions within a molecular framework. These redox reactions involve the transfer of electrons between the flavonoids and the lipid molecules. This donation of electrons to free radicals promotes the neutralization of NP components, thereby preventing oxidative damage [80,81]. These electrons are donated to the functional groups of the lipids present, and the reactions vary depending on the components used. Unsaturated lipids can become saturated, or the lipid hydroperoxides can be reduced to more stable forms [82]. The flavonoids act as radical scavengers, stabilizing the intermediates formed and preventing subsequenteactions [83].

As this process unfolds, the EGb would act as a catalyst for NP formation. Its bioactive components act as reducing agents and stabilizers, ensuring the growth and stability of LNPs. Lipids from the extract form the structural foundation of the NPs while also encapsulating hydrophobic substances within their lipid bilayers. Its multifaceted role underscores the versatility and sophistication of natural products in contemporary nanotechnology.

4.2. General benefits of plant extracts.

Plant extracts used in synthesis confer dual properties by allowing the extracts to retain their original therapeutic properties alongside the NP's favorable properties, enabling the NPs to conjugate to therapeutic agents. A recent study used extracts from Ocimum tenuiflorum L. inflorescences to synthesize silver and selenium NPs. *In vitro* studies revealed that these NPs exhibited dose-dependent cytotoxicity and strong antioxidant activity [84].

Loading plant extracts onto SLNPs has gained popularity in biomedical applications. SLNPs are submicron carriers of 50 to 1000 nm, and are usually made up of biodegradable and biocompatible lipids such as triglycerides, fatty acids, monoglycerides, or waxes [85]. This therapeutic approach can improveioavailability in CNS-related disorders [86]. A study examining the antidepressant effects using hibiscus extract-loaded SLNPs showed superior antidepressant activity compared to the crude drug extracts [87]. SLNPs have shown potential to treat CNS-related disorders, traverse the BBB, making them suitable vehicles for PD therapy.

5. The Blood Brain Barrier and *G. biloba* Synthesized Lipid Nanoparticles

Traversing the BBB has been daunting due to its impermeability to foreign molecules. Anatomically, the BBB inhibits direct interactions between the blood and the brain and is a vital part of the neurovascular unit, which communicates with the CNS [88]. This barrier comprises astrocytic end-feet links, tight junctions, pericytes, and endothelial cells, strictly controlling the movement of substances into the brain through the tight junctions and metabolic barriers (enzymes) (Figure 5) [89,90]. The main function of the tight intercellular junctions is to restrict the passage of molecules, toxic compounds, and pathogens [4,91–93].

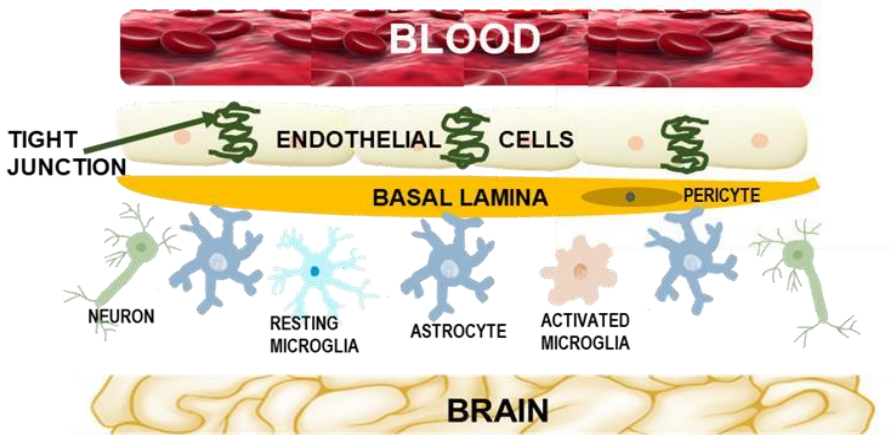

Figure 5. The composition of the blood-brain barrier.

The early processes of overcoming the BBB were highly invasive, requiring local brain site injections, catheters, or direct administration of the drugs via surgery [90]. Studies involving a carrier-mediated drug delivery system have been undertaken, with lipid

nanoparticles being favorably considered. It has been noted that lipids with a size of approximately 400 Da possess the ability to freely diffuse across the endothelial layer of the BBB [94]. Furthermore, SLNPs, with particle sizes ranging from0 to 1000 nm, play a significant role in evading and infiltrating the reticuloendothelial system (RES) [88].

These NPs traverse the BBB in four ways: paracellular pathway, adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis (RMT), and protein-mediated transport. The paracellular pathway, or the passive transmembrane diffusion, permits the entry of only hydrophilic molecules with a molecular weight of 400 Da [78]. The AMT depends on the carrier system's charge. A positively charged NP would interact favorably with the negatively charged luminal membrane [81]. The RMT is considered the most promising transport mechanism, allowing the entry of endogenous molecules across the BBB via endocytosis, intracellular vesicular trafficking, and exocytosis [95,96]. The protein-mediated transport involves binding the carrier system to transporter proteins for safe delivery into the cells. These passages are important in determining and creating a highly effective therapeutic approach.

EGb has been identified to enhance the BBB permeability through the pathways mentioned above. Besides improving stability and biocompatibility, their constituents also confer antioxidant properties, which would protect the LNPs from oxidative stress-induced damage[97]. The encapsulation of EGb-synthesized LNPs plays a synergistic role, enhancing neuroprotection and improving drug delivery efficiency [98]. This integrated approach can potentially mitigate neuronal damage, attenuate disease progression, and improve clinical outcomes in PD patients.

EGb, via its flavonoid constituent, increases the likelihood of LNPs binding to endothelial cell receptors on the BBB, thereby facilitating enhanced uptake via RMT. Hence, a higher dose of the therapeutic would be found in the brain. Furthermore, a targeted therapy can be formulated by exploiting specific receptor pathways [99]. This specificity reduces the off-target effects and effectively improves the therapeutic potency. Lastly, flavonoids possess inherent neuroprotective properties, including reducing oxidative stress and inflammation, owing to the synergism of the beneficial properties noted earlier. These properties, while stated expressly for LNPs and PD, could be effectively used for a wide range of neurodegenerative disorders, employing other NPs that act similarly with varied properties [100].

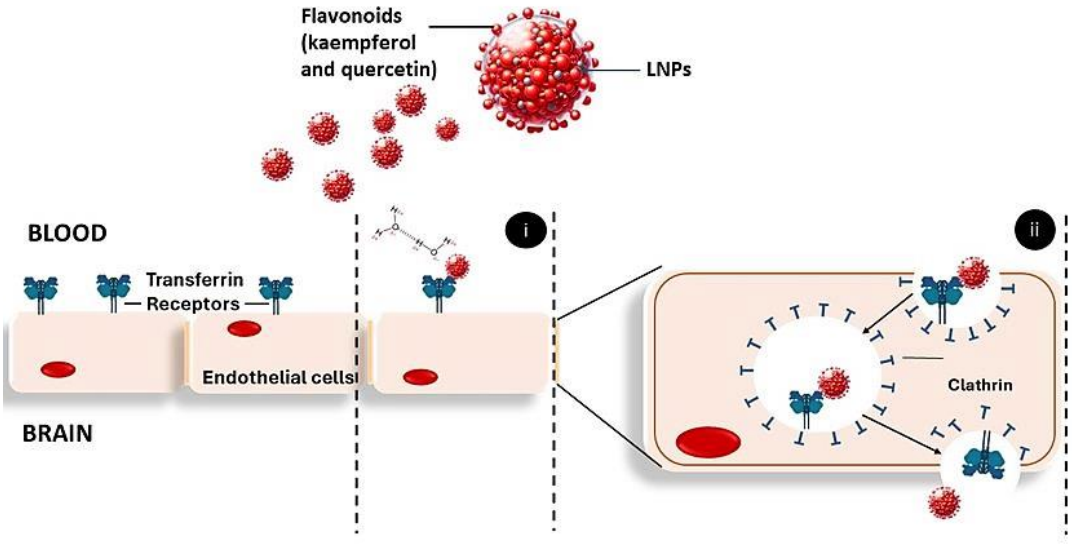

Figure 6. Receptor-mediated transcytosis across the blood-brain barrier utilizing LNPs synthesized with EGb.

The above is achieved through the flavonoids kaempferol and quercetin, which are critical in enhancing the delivery across the BBB. They bind specific receptors on the endothelial cells of the BBB, which include the low-density lipoprotein (LDLR) and transferrin receptors (Figure 6). The structural properties of flavonoids, particularly the presence of hydroxyl groups, enable high-affinity interactions with these receptors. These interactions typically involve hydrogen bonding and van der Waals forces, ensuring that flavonoids bind to and activate receptors [74]. Upon binding, a conformational change is induced, triggering endocytosis. Subsequently, endocytic vesicles form, engulfing the flavonoid-receptor complex, thereby permitting invagination of the endothelial cell membrane to form clathrin-coated pits. This results in the budding of vesicles, initiating an efficient transport system across the BBB [101].

Following this process, the vesicles are transported via the cytoskeleton, involving actin filaments or microtubules, directing the vesicles towards the abluminal side of the cell. At this point, the flavonoids exhibit their biochemical properties, ensuring that the vesicles are directed to this site for release into the brain parenchyma while avoiding lysosomal degradation. Flavonoids, particularly those found in *G. biloba*, possess the ability to inhibit efflux transporters, including P-glycoproteins (P-gp), which are known to actively pump many compounds out of the brain, thus rendering an increased accumulation of the LNPs in the brain [101]. Furthermore, flavonoids can modify LNP structure to release their therapeutic content in response to the lysosomal pH, thereby preventing LNP degradation. The fusion with endosomal membranes results in the release of contents before they reach the lysosomes. Once at the abluminal side of the endothelial cell, the vesicle fuses with the plasma membrane, thereby permitting the release of therapeutic agents. The LNPs and the conjugated flavonoids enter the extracellular space, ensuring efficient delivery of the LNPs to target sites [102,103].

5.1. Further enhancement of the BBB with EGb.

The BBB contains a class of G protein-coupled receptors (GPCRs) known as adenosine receptors (ARs), which play a crucial role in modulating its permeability. Notably, high levels of adenosine A1 receptors (A1R) are present in the brain [104]. Activation of A1R has been shown to improve the penetration of intravenously administered macromolecules and to induce cellular changes, such as increased formation of actinomyosin stress fibres, decreased transendothelial electrical resistance, and altered tight junctions [105,106].

In the case of EGb, it was demonstrated that the flavone in this extract could act as a P-glycoprotein (P-gp) inhibitor, increasing the intracellular drug concentration in the brain by enhancing uptake [107]. The main components of the extract, such as ginkgolides A, B, and C, kaempferol, and bilobalide, were reported to be present in the brain tissue, suggesting that they significantly contribute to BBB permeability and facilitate the entry of therapeutic agents. It was proposed that ginkgolides and bilobalide might enhance BBB permeability by modulating the A1R pathway, which influences endothelial cell function and tight junction integrity [108]. This temporary and reversible opening of the BBB can improve drug delivery to the brain. These findings were corroborated by an earlier study demonstrating that bilobalide, a prominent component of EGb, can efficiently cross the BBB, achieving significant extracellular concentrations in the brain and supporting its role in enhancing BBB permeability [109].

The BBB is often described as a 'double-edged sword' because crossing it poses challenges. Long-term administration of *G. biloba* has shown no apparent side effects while

reversibly opening the BBB for short periods, typically around four hours, without causing leakage. This reversible opening maintains the integrity of tight junctions, which is essential for brain homeostasis and protection [109]. Furthermore, EGb can potentially increase the phosphorylation of the ERM/MLC protein, which acts as a selective A1R antagonist. This increases gaps between cells by remodelling actin in cerebral microvascular endothelial cells, thereby enhancing cerebral microvascular permeability [108]. These properties make the biosynthesis of NPs with EGb highly beneficial for traversing the BBB and offer a promising therapeutic strategy against PD.

6. Conclusions

This review discusses the significant potential of EGb in developing novel dual-functional NPs for PD treatment. EGb demonstrates numerous beneficial properties, including neuroprotection, antioxidant activity, and the ability to cross the BBB, a significant challenge in treating neurological disorders. By acting as a reducing agent during LNPs synthesis, EGb stabilizes these NPs and enhances their delivery across the BBB. This innovative approach integrates the traditional medicinal benefits of EGb with advanced nanomedicine, offering a novel and promising therapeutic strategy for PD. Further clinical studies are necessary to fully understand the mechanisms involved and optimize the efficacy of EGb-loaded LNPs to advance treatment strategies for PD. The overall potential of EGb as a therapeutic and reducing agent shows promise for future research and clinical applicability. Several avenues can be explored further to unlock the multitude of beneficial properties exhibited in practical outputs. These could include efficacy studies on optimal dosages, formulation variations, and the extract's long-term effects in clinical trials. An in-depth look into the mechanism of action of EGb may significantly improve BBB permeability and its neuroprotective and antioxidant effects. These studies may aid in optimizing the synergistic effects of EGb-loaded LNPs when combined with therapeutic agents, such as drugs and therapeutic genes, to target specific diseases, such as PD. An exciting avenue that requires focus is personalised medicine, i.e., personalised treatment based on an individual's genetic profile, with the treatment protocol adjusted accordingly to develop an optimal therapeutic regimen tailored to a specific individual's needs. Continued interdisciplinary research and collaboration will be crucial in realizing the full potential of EGb-loaded LNPs and bringing these innovative therapies into clinical practice.

7. Summary and Future Outlook

The convergence and integration of G. biloba phytochemistry with nanotechnology are emerging as a compelling avenue in the quest for effective therapeutics against neurodegenerative disorders, particularly PD. Across various nanoplatforms, including metallic NPs, lipid-based carriers, and polymeric nano-formulations, researchers have successfully harnessed EGb as a bio-reducing and stabilizing agent. These formulations not only maintain the antioxidant and neuroprotective capabilities of the extract but further demonstrate an enhanced pharmacokinetic profile, notably improving bioavailability and targeted delivery across the BBB. AuNPs and AgNPs produced via EGb-mediated synthesis exhibit favourable physicochemical attributes, including controlled size and morphology, which support cellular uptake and offer inherent anti-inflammatory and antioxidant properties. LNPs further exploit the lipid affinity of EGb, forming biocompatible systems that can

effectively encapsulate both hydrophobic and hydrophilic payloads while supporting sustained release and BBB permeability. Likewise, EGb-decorated polymeric NPs introduce further opportunities for gene and drug co-delivery, leveraging their physicochemical tunability to enhance targeting precision and reduce systemic toxicity.

While the therapeutic potential is promising, key challenges persist. Standardisation of EGb composition remains a bottleneck for reproducibility, and NP size uniformity continues to influence biodistribution and therapeutic outcomes. Moreover, data on long-term *in vivo* behaviour, pharmacokinetics, and safety remain sparse, and clinical translation has yet to reach maturity. Moving forward, research efforts must focus on scalable synthesis methodologies for EGb-synthesized nanomaterials and on the design of multifunctional particles that integrate diagnostic and therapeutic capabilities. Surface engineering strategies to direct NPs towards dopaminergic neuronal populations will be critical, as will the exploration of synergistic interactions between EGb bioactives and co-administered drugs or genetic material. Rigorous toxicological assessments and methodologically sound animal and clinical studies are essential to affirm safety and efficacy in human cohorts.

If these challenges can be addressed through collaborative translational research, EGb-driven nanotherapies may well redefine PD treatment and extend their relevance to other complex CNS pathologies, thus bridging the gap between traditional botanical medicine and precision-targeted nanomedicine.

Author Contributions

Conceptualization, K.J., MS; methodology, K.J.; software, K.J.; validation, M.S.; formal analysis, K.J..; investigation, KJ.; resources, M.S.; data curation, K.J.; writing—original draft preparation, K.J.; writing—review and editing, M.S.; visualization, KJ., M.S; supervision, M.S.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

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Review paper. No new data were created or analyzed in this study. Data sharing is not applicable.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

References

1. Dorsey, E.R.; Sherer, T.; Okun, M.S.; Bloem, B.R. The Emerging Evidence of the Parkinson Pandemic. *J. Parkinsons Dis.* **2018**, *8*, S3-S8, https://doi.org/10.3233/JPD-181474.
2. Armstrong, M.J.; Okun, M.S. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA* **2020**, *323*, 548-560, https://doi.org/10.1001/jama.2019.22360.
3. Roco, M.C. Erratum to: The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. *J. Nanopart. Res.* **2011**, *13*, 1335, https://doi.org/10.1007/s11051-011-0323-1.
4. Kaya, M.; Ahishali, B. Basic physiology of the blood-brain barrier in health and disease: a brief overview. *Tissue Barriers* **2021**, *9*, 1840913, https://doi.org/10.1080/21688370.2020.1840913.
5. Preetam, S.; Jonnalagadda, S.; Kumar, L.; Rath, R.; Chattopadhyay, S.; Alghamdi, B.S.; Abuzenadah, A.M.; Jha, N.K.; Gautam, A.; Malik, S.; Ashraf, G.M. Therapeutic potential of lipid nanosystems for the treatment of Parkinson's disease. *Ageing Res. Rev.* **2023**, *89*, 101965, https://doi.org/10.1016/j.arr.2023.101965.
6. Jagaran, K.; Singh, M. Nanomedicine for Neurodegenerative Disorders: Focus on Alzheimer's and Parkinson's Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 9082, https://doi.org/10.3390/ijms22169082.
7. Venkatas, J.; Singh, M. Curcumin-Reduced Gold Nanoparticles Facilitate *Il-12* Delivery to A Cervical Cancer *In Vitro* Cell Model. *Nanomedicine* **2023**, *18*, 945-960, https://doi.org/10.2217/nnm-2023-0076.
8. Yavarpour-Bali, H.; Ghasemi-Kasman, M.; Pirzadeh, M. Curcumin-loaded nanoparticles: A novel therapeutic strategy in treatment of central nervous system disorders. *Int. J. Nanomed.* **2019**, *14*, 4449-4460, https://doi.org/10.2147/IJN.S208332.
9. Jagaran, K.; Singh, M. Lipid Nanoparticles: Promising Treatment Approach for Parkinson's Disease. *Int. J. Mol. Sci.* **2022**, *23*, 9361, https://doi.org/10.3390/ijms23169361.
10. Ahmad, M.; Saleem, S.; Ahmad, A.S.; Yousuf, S.; Ansari, M.A.; Khan, M.B.; Ishrat, T.; Chaturvedi, R.K.; Agrawal, A.K.; Islam, F. *Ginkgo biloba* affords dose-dependent protection against 6-hydroxydopamine-induced parkinsonism in rats: neurobehavioural, neurochemical and immunohistochemical evidences. *J. Neurochem.* **2005**, *93*, 94-104, https://doi.org/10.1111/j.1471-4159.2005.03000.x.
11. Day, J.O.; Mullin, S. The Genetics of Parkinson's Disease and Implications for Clinical Practice. *Genes* **2021**, *12*, 1006, https://doi.org/10.3390/genes12071006.
12. Yasuhara, T. Neurobiology Research in Parkinson's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 793, https://doi.org/10.3390/ijms21030793.
13. Corona, J.C. Natural Compounds for the Management of Parkinson's Disease and Attention-Deficit/Hyperactivity Disorder. *BioMed Res. Int.* **2018**, *2018*, 4067597, https://doi.org/10.1155/2018/4067597.
14. Deng, H.; Wang, P.; Jankovic, J. The genetics of Parkinson disease. *Ageing Res. Rev.* **2018**, *42*, 72-85, https://doi.org/10.1016/j.arr.2017.12.007.
15. Orayj, K.; Akbari, A.; Lacey, A.; Smith, M.; Pickrell, O.; Lane, E.L. Factors affecting the choice of first-line therapy in Parkinson's disease patients in Wales: A population-based study. *Saudi Pharm. J.* **2021**, *29*, 206-212, https://doi.org/10.1016/j.jsps.2021.01.004.
16. Pickut, B.A.; Mischley, L.K.; Joseph, R.R. Integrative Medicine and Parkinson's Disease. In Integrative Neurology, 1ST Edition; McBurney, J.W., Ruhoy, I.S., Eds.; Oxford University Press: **2020**; 141–183, https://doi.org/10.1093/med/9780190051617.003.0007.
17. Church, F.C. Treatment Options for Motor and Non-Motor Symptoms of Parkinson's Disease. *Biomolecules* **2021**, *11*, 612, https://doi.org/10.3390/biom11040612.
18. Bryans, L.A.; Palmer, A.D.; Anderson, S.; Schindler, J.; Graville, D.J. The impact of Lee Silverman Voice Treatment (LSVT LOUD®) on voice, communication, and participation: Findings from a prospective, longitudinal study. *J. Commun. Disord.* **2021**, *89*, 106031, https://doi.org/10.1016/j.jcomdis.2020.106031.
19. Yuan, F.; Guo, X.; Wei, X.; Xie, F.; Zheng, J.; Huang, Y.; Huang, Z.; Chang, Z.; Li, H.; Guo, Y.; Chen, J.; Guo, J.; Tang, B.; Deng, B.; Wang, Q. Lee Silverman Voice Treatment for dysarthria in patients with

Parkinson's disease: a systematic review and meta-analysis. *Eur. J. Neurol.* **2020**, *27*, 1957-1970, https://doi.org/10.1111/ene.14399.
20. Elsworth, J.D.; Roth, R.H. Dopamine Synthesis, Uptake, Metabolism, and Receptors: Relevance to Gene Therapy of Parkinson's Disease. *Exp. Neurol*. **1997**, *144*, 4–9, https://doi.org/10.1006/exnr.1996.6379.
21. Cookson, M.R. THE BIOCHEMISTRY OF PARKINSON'S DISEASE. *Annu. Rev. Biochem.* **2005**, *74*, 29-52, https://doi.org/10.1146/annurev.biochem.74.082803.133400.
22. Lees, A.J.; Tolosa, E.; Olanow, C.W. Four pioneers of L-dopa treatment: Arvid Carlsson, Oleh Hornykiewicz, George Cotzias, and Melvin Yahr. *Mov. Disord.* **2015**, *30*, 19-36, https://doi.org/10.1002/mds.26120.
23. Fox, S.H.; Katzenschlager, R.; Lim, S.-Y.; Barton, B.; de Bie, R.M.A.; Seppi, K.; Coelho, M.; Sampaio, C. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov. Disord.* **2018**, *33*, 1248-1266, https://doi.org/10.1002/mds.27372.
24. Carbone, F.; Djamshidian, A.; Seppi, K.; Poewe, W. Apomorphine for Parkinson's Disease: Efficacy and Safety of Current and New Formulations. *CNS Drugs* **2019**, *33*, 905-918, https://doi.org/10.1007/s40263-019-00661-z.
25. Rascol, O.; Goetz, C.; Koller, W.; Poewe, W.; Sampaio, C. Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet* **2002**, *9317*, 1589-1598, https://doi.org/10.1016/s0140-6736(02)08520-3.
26. Kuhn, W.; Müller, T. Amantadine for Treating Parkinson's Disease. In NeuroPsychopharmacotherapy, Riederer, P., Laux, G., Nagatsu, T., Le, W., Riederer, C., Eds.; Springer International Publishing: Cham, **2022**; pp. 3327-3332, https://doi.org/10.1007/978-3-030-62059-2_220.
27. Karimi Tari, P.; Parsons, C.G.; Collingridge, G.L.; Rammes, G. Memantine: Updating a rare success story in pro-cognitive therapeutics. *Neuropharmacology* **2024**, *244*, 109737, https://doi.org/10.1016/j.neuropharm.2023.109737.
28. Xiao-Zhong, J.; Xiang-Zhen, Y.; Xingguang, L.; Shu-Yun, Z.; Xiao-Ping, W. An Update on Nondopaminergic Treatments for Motor and Non-motor Symptoms of Parkinson's Disease. *Curr. Neuropharmacol.* **2023**, *21*, 1806-1826, https://doi.org/10.2174/1570159X20666220222150811.
29. Corcia, P.; Guy, N.; Pradat, P.-F.; Soriani, M.-H.; Verschueren, A.; Couratier, P. Treatment continuity of amyotrophic lateral sclerosis with available riluzole formulations: state of the art and current challenges in a 'real-world' setting. *Amyotroph. Lateral Scler. Front. Degener.* **2025**, *26*, 15-21, https://doi.org/10.1080/21678421.2024.2375330.
30. Zhou, W.; Barkow, J.C.; Freed, C.R. Running wheel exercise reduces α-synuclein aggregation and improves motor and cognitive function in a transgenic mouse model of Parkinson's disease. *PLOS ONE* **2017**, *12*, e0190160, https://doi.org/10.1371/journal.pone.0190160.
31. Oliveira de Carvalho, A.; Murillo-Rodriguez, E.; Rocha, N.B.; Carta, M.G.; Machado, S. Physical exercise for Parkinson's disease: Clinical and experimental evidence. *Clin. Pract. Epidemiol. Ment. Health* **2018**, *14*, 89–98, https://doi.org/10.2174/1745017901814010089.
32. Hall, M.-F.E.; Church, F.C. Exercise for Older Adults Improves the Quality of Life in Parkinson's Disease and Potentially Enhances the Immune Response to COVID-19. *Brain Sci.* **2020**, *10*, 612, https://doi.org/10.3390/brainsci10090612.
33. Fabbri, M.; Rosa, M.M.; Ferreira, J.J. Adjunctive Therapies in Parkinson's Disease: How to Choose the Best Treatment Strategy Approach. *Drugs Aging* **2018**, *35*, 1041-1054, https://doi.org/10.1007/s40266-018-0599-2.
34. Sharma, V.D.; Patel, M.; Miocinovic, S. Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches. *Neurotherapeutics* **2020**, *17*, 1525-1538, https://doi.org/10.1007/s13311-020-00939-x.
35. Nowak, A.; Kojder, K.; Zielonka-Brzezicka, J.; Wróbel, J.; Bosiacki, M.; Fabiańska, M.; Wróbel, M.; Sołek-Pastuszka, J.; Klimowicz, A. The Use of Ginkgo Biloba L. as a Neuroprotective Agent in the Alzheimer's Disease. *Front. Pharmacol.* **2021**, *12*, 775034, https://doi.org/10.3389/fphar.2021.775034.
36. Mansoor, M.; Brahmini, C.S.; Rao, S.D. Phytochemical and nephroprotective activity of *Ginkgo biloba* against gentamicin-induced nephrotoxicity in rats. *Int. J. Adv. Pharm. Med. Bioallied Sci.* **2015**, *3*, 98-101.
37. Rojas, C.; Rojas-Castaneda, J.; Rojas, P. Antioxidant properties of a Ginkgo biloba leaf extract (EGb 761) in animal models of Alzheimer's and Parkinson's diseases. *Curr. Top. Nutraceutical Res.* **2016**, *14*, 105-120.

38. DeFeudis, F.V. A brief history of EGb 761® and its therapeutic uses. *Pharmacopsychiatry* **2003**, *36*, 2-7, https://doi.org/10.1055/s-2003-40450.
39. Wang, Y.Q.; Wang, M.Y.; Fu, X.R.; Peng, Y.; Gao, G.F.; Fan, Y.M.; Duan, X.L.; Zhao, B.L.; Chang, Y.Z.; Shi, Z.H. Neuroprotective effects of ginkgetin against neuroinjury in Parkinson's disease model induced by MPTP via chelating iron. *Free Radic. Res.* **2015**, *49*, 1069-1080, https://doi.org/10.3109/10715762.2015.1032958.
40. Hua, J.; Yin, N.; Yang, B.; Zhang, J.; Ding, J.; Fan, Y.; Hu, G. Ginkgolide B and bilobalide ameliorate neural cell apoptosis in α-synuclein aggregates. *Biomed. Pharmacother.* **2017**, *96*, 792-797, https://doi.org/10.1016/j.biopha.2017.10.050.
41. Yu, D.; Zhang, P.; Li, J.; Liu, T.; Zhang, Y.; Wang, Q.; Zhang, J.; Lu, X.; Fan, X. Neuroprotective effects of Ginkgo biloba dropping pills in Parkinson's disease. *J. Pharm. Anal.* **2021**, *11*, 220-231, https://doi.org/10.1016/j.jpha.2020.06.002.
42. Kang, X.; Chen, J.; Xu, Z.; Li, H.; Wang, B. Protective effects of *Ginkgo biloba* extract on paraquat-induced apoptosis of PC12 cells. *Toxicol. In Vitro* **2007**, *21*, 1003-1009, https://doi.org/10.1016/j.tiv.2007.02.004.
43. Kuang, S.; Yang, L.; Rao, Z.; Zhong, Z.; Li, J.; Zhong, H.; Dai, L.; Tang, X. Effects of Ginkgo Biloba Extract on A53T α-Synuclein Transgenic Mouse Models of Parkinson's Disease. *Can. J. Neurol. Sci.* **2018**, *45*, 182-187, https://doi.org/10.1017/cjn.2017.268.
44. Shang, Q.; Zhou, X.; Yang, M.-R.; Lu, J.-G.; Pan, Y.; Zhu, G.-Y.; Jiang, Z.-H. Amide Derivatives of Ginkgolide B and Their Inhibitory Effects on PAF-Induced Platelet Aggregation. *ACS Omega* **2021**, *6*, 22497-22503, https://doi.org/10.1021/acsomega.1c01682.
45. Ding, X.; Tan, D.; Wang, Z.; Yin, H. Ginkgolide B regulates apoptosis, oxidative stress, and mitochondrial dysfunction in MPP^+-induced SK-N-SH cells by targeting HDAC4/JNK pathway. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2025**, *398*, 8899-8908, https://doi.org/10.1007/s00210-025-03815-7.
46. Feng, Z.; Sun, Q.; Chen, W.; Bai, Y.; Hu, D.; Xie, X. The neuroprotective mechanisms of ginkgolides and bilobalide in cerebral ischemic injury: a literature review. *Mol. Med.* **2019**, *25*, 57, https://doi.org/10.1186/s10020-019-0125-y.
47. Speisky, H.; Arias-Santé, M.F.; Fuentes, J. Oxidation of Quercetin and Kaempferol Markedly Amplifies Their Antioxidant, Cytoprotective, and Anti-Inflammatory Properties. *Antioxidants* **2023**, *12*, 155, https://doi.org/10.3390/antiox12010155.
48. Ngo, V.; Duennwald, M.L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. *Antioxidants* **2022**, *11*, 2345, https://doi.org/10.3390/antiox11122345.
49. Khan, A.; Ali, T.; Rehman, S.U.; Khan, M.S.; Alam, S.I.; Ikram, M.; Muhammad, T.; Saeed, K.; Badshah, H.; Kim, M.O. Neuroprotective Effect of Quercetin Against the Detrimental Effects of LPS in the Adult Mouse Brain. *Front. Pharmacol.* **2018**, 9, 1383, https://doi.org/10.3389/fphar.2018.01383.
50. Singh, S.K.; Srivastav, S.; Castellani, R.J.; Plascencia-Villa, G.; Perry, G. Neuroprotective and Antioxidant Effect of *Ginkgo biloba* Extract Against AD and Other Neurological Disorders. *Neurotherapeutics* **2019**, *16*, 666-674, https://doi.org/10.1007/s13311-019-00767-8.
51. Goloborshcheva, V.V.; Kucheryanu, V.G.; Voronina, N.A.; Teterina, E.V.; Ustyugov, A.A.; Morozov, S.G. Synuclein Proteins in MPTP-Induced Death of Substantia Nigra Pars Compacta Dopaminergic Neurons. *Biomedicines* **2022**, *10*, 2278, https://doi.org/10.3390/biomedicines10092278.
52. Langston, J.W. The MPTP Story. *J. Parkinsons Dis.* **2017**, *7*, S11-S19, https://doi.org/10.3233/JPD-179006.
53. Mustapha, M.; Taib, C.N.M. MPTP-induced mouse model of Parkinson's disease: A promising direction of therapeutic strategies. *Biomol. Biomed.* **2021**, *21*, 422-433, https://doi.org/10.17305/bjbms.2020.5181.
54. Wu, W.-J.; Lu, C.-W.; Wang, S.-E.; Lin, C.-L.; Su, L.-Y.; Wu, C.-H. MPTP toxicity causes vocal, auditory, orientation and movement defects in the echolocation bat. *NeuroReport* **2021**, *32*, 125–134, https://doi.org/10.1097/WNR.0000000000001574.
55. Haga, H.; Matsuo, K.; Yabuki, Y.; Zhang, C.; Han, F.; Fukunaga, K. Enhancement of ATP production ameliorates motor and cognitive impairments in a mouse model of MPTP−induced Parkinson's disease. *Neurochem. Int.* **2019**, *129*, 104492, https://doi.org/10.1016/j.neuint.2019.104492.
56. Prasad, E.M.; Hung, S.-Y. Behavioral Tests in Neurotoxin-Induced Animal Models of Parkinson's Disease. *Antioxidants* **2020**, *9*, 1007, https://doi.org/10.3390/antiox9101007.
57. Ramassamy, C.; Clostre, F.; Christen, Y.; Costentin, J. Prevention by a *Ginkgo biloba* Extract (GBE 761) of the Dopaminergic Neurotoxicity of MPTP. *J. Pharm. Pharmacol.* **1990**, *42*, 785-789, https://doi.org/10.1111/j.2042-7158.1990.tb07021.x.

58. Wu, W.-R.; Zhu, X.-Z. Involvement of monoamine oxidase inhibition in neuroprotective and neurorestorative effects of ginkgo biloba extract against MPTP-induced nigrostriatal dopaminergic toxicity in C57 mice. *Life Sci.* **1999**, *65*, 157-164, https://doi.org/10.1016/S0024-3205(99)00232-5.
59. Fei, C.; Shenggang, S.; E-tang, T. Experimental study on inhibition of neuronal toxical effect of Levodopa by Ginkgo Biloba Extract on Parkinson disease in rats. *Curr. Med. Sci.* **2003**, *23*, 151-153, https://doi.org/10.1007/BF02859941.
60. Sun, L.; Apweiler, M.; Tirkey, A.; Klett, D.; Normann, C.; Dietz, G.P.H.; Lehner, M.D.; Fiebich, B.L. Anti-Neuroinflammatory Effects of *Ginkgo biloba* Extract EGb 761 in LPS-Activated BV2 Microglial Cells. *Int. J. Mol. Sci.* **2024**, *25*, 8108, https://doi.org/10.3390/ijms25158108.
61. Abdel-Kader, R.; Hauptmann, S.; Keil, U.; Scherping, I.; Leuner, K.; Eckert, A.; Müller, W.E. Stabilization of mitochondrial function by Ginkgo biloba extract (EGb 761). *Pharmacol. Res.* **2007**, *56*, 493-502, https://doi.org/10.1016/j.phrs.2007.09.011.
62. Rojas, P.; Rojas, C.; Ebadi, M.; Montes, S.; Monroy-Noyola, A.; Serrano-García, N. EGb761 Pretreatment Reduces Monoamine Oxidase Activity in Mouse Corpus Striatum During 1-Methyl-4-Phenylpyridinium Neurotoxicity. *Neurochem. Res.* **2004**, *29*, 1417-1423, https://doi.org/10.1023/B:NERE.0000026406.64547.93.
63. Sahoo, S.; Padhy, A.A.; Kumari, V.; Mishra, P. Role of Ubiquitin–Proteasome and Autophagy-Lysosome Pathways in α-Synuclein Aggregate Clearance. *Mol. Neurobiol.* **2022**, *59*, 5379-5407, https://doi.org/10.1007/s12035-022-02897-1.
64. Toader, C.; Serban, M.; Munteanu, O.; Covache-Busuioc, R.-A.; Enyedi, M.; Ciurea, A.V.; Tataru, C.P. From Synaptic Plasticity to Neurodegeneration: BDNF as a Transformative Target in Medicine. *Int. J. Mol. Sci.* **2025**, *26*, 4271, https://doi.org/10.3390/ijms26094271.
65. Alqudah, A.; Aljabali, A.A.; Gammoh, O.; Tambuwala, M.M. Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier for precise CNS targeting. *J. Nanoparticle Res.* **2024**, *26*, 123, https://doi.org/10.1007/s11051-024-05983-8.
66. Boateng, I.D. A critical review of ginkgolic acids in *Ginkgo biloba* leaf extract (EGb): toxicity and technologies to remove ginkgolic acids and their promising bioactivities. *Food Funct*. **2022**, *13*, 9226–9242, https://doi.org/10.1039/D2FO01827F.
67. Ni, Q.; Zhu, T.; Wang, W.; Guo, D.; Li, Y.; Chen, T.; Zhang, X. Green Synthesis of Narrow-Size Silver Nanoparticles Using *Ginkgo biloba* Leaves: Condition Optimization, Characterization, and Antibacterial and Cytotoxic Activities. *Int. J. Mol. Sci.* **2024**, *25*, 1913, https://doi.org/10.3390/ijms25031913.
68. Edo, G.I.; Mafe, A.N.; Ali, A.B.M.; Akpoghelie, P.O.; Yousif, E.; Isoje, E.F.; Igbuku, U.A.; Ismael, S.A.; Essaghah, A.E.A.; Ahmed, D.S.; Ozsahin, D.U.; Umar, H.; Alamiery, A.A. Green Biosynthesis of Nanoparticles Using Plant Extracts: Mechanisms, Advances, Challenges, and Applications. *BioNanoScience* **2025**, *15*, 267, https://doi.org/10.1007/s12668-025-01883-w.
69. Liu, Y.; Xin, H.; Zhang, Y.; Che, F.; Shen, N.; Cui, Y. Leaves, seeds and exocarp of *Ginkgo biloba* L. (Ginkgoaceae): A Comprehensive Review of Traditional Uses, phytochemistry, pharmacology, resource utilization and toxicity. *J. Ethnopharmacol.* **2022**, *298*, 115645, https://doi.org/10.1016/j.jep.2022.115645.
70. Luo, J.; Lao, Z.; Chen, S.; Zheng, D.; Li, S.; Ma, G.; Fang, S.; Fang, B.; Wu, B. Green synthesis of silver nanoparticles using *Ginkgo biloba* seed extract: Evaluation of antioxidant, anticancer, antifungal, and antibacterial activities. *Nanotechnol. Rev.* **2025**, *14*, 20250160, https://doi.org/10.1515/ntrev-2025-0160.
71. Fermino, B.L.; Milanez, M.C.; Freitas, B.; Nunes da Silva, W.; Pereira, R.; Rocha, J.; Bonini, J. Ginkgo biloba L.: Phytochemical components and antioxidant activity. *Afr. J. Pharm. Pharmacol.* **2015**, *9*, 950-955, https://doi.org/10.5897/AJPP2015.4373.
72. Zeppilli, D.; Ribaudo, G.; Pompermaier, N.; Madabeni, A.; Bortoli, M.; Orian, L. Radical Scavenging Potential of Ginkgolides and Bilobalide: Insight from Molecular Modeling. *Antioxidants* **2023**, *12*, 525, https://doi.org/10.3390/antiox12020525.
73. Bajpai, V.K.; Kim, Y.; Baek, K.-H. Phenolic Content, Lipid Peroxidation Inhibition and Antioxidant Potential of Leaf Essential Oil of *Ginkgo biloba* in Various Scavenging Models. *Natl. Acad. Sci. Lett.* **2017**, *40*, 95-99, https://doi.org/10.1007/s40009-016-0530-5.
74. Shu, P.; Sun, M.; Li, J.; Zhang, L.; Xu, H.; Lou, Y.; Ju, Z.; Wei, X.; Wu, W.; Sun, N. Chemical constituents from *Ginkgo biloba* leaves and their cytotoxicity activity. *J. Nat. Med.* **2020**, *74*, 269-274, https://doi.org/10.1007/s11418-019-01359-8.

75. Kazemi, S.; Hosseingholian, A.; Gohari, S.D.; Feirahi, F.; Moammeri, F.; Mesbahian, G.; Moghaddam, Z.S.; Ren, Q. Recent advances in green synthesized nanoparticles: from production to application. *Mater. Today Sustain*. **2023**, *24*, 2586-2347. https://doi.org/10.1016/j.mtsust.2023.100500.
76. Saxena, R.; Kotnala, S.; Bhatt, S.C.; Uniyal, M.; Rawat, B.S.; Negi, P.; Riyal, M.K. A review on green synthesis of nanoparticles toward sustainable environment. *Sust. Chem. Clim. Act.* **2025**, *6*, 100071. https://doi.org/10.1016/j.scca.2025.100071.
77. Azad, A.; Zafar, H.; Raza, F.; Sulaiman, M. Factors influencing the green synthesis of metallic nanoparticles using plant extracts: a comprehensive review. *Pharm. Front.* **2023**, *5*, e117-e131, https://doi.org/10.1055/s-0043-1774289.
78. Zha, J.; Dong, C.; Wang, X.; Zhang, X., Xiao, X.; Yang, X. Green synthesis and characterization of monodisperse gold nanoparticles using Ginkgo Biloba leaf extract. *Optik* **2017**, *144*, 511–521. https://doi.org/10.1016/j.ijleo.2017.06.088.
79. Xu, Z.; Feng, Q.; Wang, M.; Zhao, H.; Lin, Y.; Zhou, S. Green Biosynthesized Silver Nanoparticles With Aqueous Extracts of *Ginkgo Biloba* Induce Apoptosis *via* Mitochondrial Pathway in Cervical Cancer Cells. *Frontiers in Oncology* **2020**, *10*, 575415, https://doi.org/10.3389/fonc.2020.575415.
80. Baliyan, S.; Mukherjee, R.; Priyadarshini, A.; Vibhuti, A.; Gupta, A.; Pandey, R.P.; Chang, C.-M. Determination of Antioxidants by DPPH Radical Scavenging Activity and Quantitative Phytochemical Analysis of *Ficus religiosa*. *Molecules* **2022**, *27*, 1326, https://doi.org/10.3390/molecules27041326.
81. Middleton Jr., E.; Kandaswami, C.; Theoharides, T.C. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol. Rev.* **2000**, *52*, 673-751.
82. Dennis, E.A.; Norris, P.C. Eicosanoid storm in infection and inflammation. *Nat. Rev. Immunol*. **2015**, 15, 511–523, https://doi.org/10.1038/nri3859.
83. Klotz, L.O.; Steinbrenner, H. Cellular adaptation to xenobiotics: interplay between xenosensors, reactive oxygen species and FOXO transcription factors. *Redox Biol*. **2017**, *13*, 646-654. https://doi.org/10.1016/j.redox.2017.07.015.
84. Olawale, F.; Ariatti, M.; Singh, M. Ocimum tenuiflorum L mediated green synthesis of silver and selenium nanoparticles: antioxidant activity, cytotoxicity and density functional theory studies. *Adv. Nat. Sci: Nanosci. Nanotechnol.* **2022**, *13*, 015015, https://doi.org/10.1088/2043-6262/ac5d4a.
85. Pandey, S.; Shaikh, F.; Gupta, A.; Tripathi, P.; Yadav, J.S. A Recent Update: Solid Lipid Nanoparticles for Effective Drug Delivery. *Adv. Pharm. Bull.* **2022**, *12*, 17-33, https://doi.org/10.34172/apb.2022.007.
86. Ravi, P.R.; Aditya, N.; Kathuria, H.; Malekar, S.; Vats, R. Lipid nanoparticles for oral delivery of raloxifene: Optimization, stability, *in vivo* evaluation and uptake mechanism. *Eur. J. Pharm. Biopharm.* **2014**, *87*, 114-124, https://doi.org/10.1016/j.ejpb.2013.12.015.
87. Vijayanand, P.; Jyothi, V.; Aditya, N.; Mounika, A. Development and Characterization of Solid Lipid Nanoparticles Containing Herbal Extract: In Vivo Antidepressant Activity. *J. Drug Deliv.* **2018**, *2018*, 2908626, https://doi.org/10.1155/2018/2908626.
88. Satapathy, M.K.; Yen, T.-L.; Jan, J.-S.; Tang, R.-D.; Wang, J.-Y.; Taliyan, R.; Yang, C.-H. Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB. *Pharmaceutics* **2021**, *13*, 1183, https://doi.org/10.3390/pharmaceutics13081183.
89. Cecchelli, R.; Berezowski, V.; Lundquist, S.; Culot, M.; Renftel, M.; Dehouck, M.-P.; Fenart, L. Modelling of the blood–brain barrier in drug discovery and development. *Nat. Rev. Drug Discov.* **2007**, *6*, 650-661, https://doi.org/10.1038/nrd2368.
90. Segarra, M.; Aburto, M.R.; Acker-Palmer, A. Blood–Brain Barrier Dynamics to Maintain Brain Homeostasis. *Trends Neurosci.* **2021**, *44*, 393-405, https://doi.org/10.1016/j.tins.2020.12.002.
91. O'Keeffe, E.; Campbell, M. Modulating the paracellular pathway at the blood–brain barrier: current and future approaches for drug delivery to the CNS. *Drug Discov. Today Technol.* **2016**, *20*, 35-39, https://doi.org/10.1016/j.ddtec.2016.07.008.
92. Habib, S.; Singh, M. Angiopep-2-Modified Nanoparticles for Brain-Directed Delivery of Therapeutics: A Review. *Polymers* **2022**, *14*, 712, https://doi.org/10.3390/polym14040712.
93. Chaichana, K.L.; Pinheiro, L.; Brem, H. Delivery of Local Therapeutics to the brain: Working Toward Advancing Treatment for Malignant Gliomas. *Ther. Deliv.* **2015**, *6*, 353-369, https://doi.org/10.4155/tde.14.114.
94. Pardridge, W.M. Drug Transport across the Blood–Brain Barrier. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 1959-1972, https://doi.org/10.1038/jcbfm.2012.126.

95. Zhu, X.; Jin, K.; Huang, Y.; Pang, Z. 7 - Brain drug delivery by adsorption-mediated transcytosis. In Brain Targeted Drug Delivery System, Gao, H., Gao, X., Eds.; Academic Press: **2019**; pp. 159-183, https://doi.org/10.1016/B978-0-12-814001-7.00007-X.
96. Pulgar, V.M. Transcytosis to Cross the Blood Brain Barrier, New Advancements and Challenges. *Front. Neurosci.* **2019**, *12*, 1019, https://doi.org/10.3389/fnins.2018.01019.
97. Gregory, J.; Vengalasetti, Y.V.; Bredesen, D.E.; Rao, R.V. Neuroprotective Herbs for the Management of Alzheimer's Disease. *Biomolecules* **2021**, *11*, 543, https://doi.org/10.3390/biom11040543.
98. Noor, E.T.; Das, R.; Lami, M.S.; Chakraborty, A.J.; Mitra, S.; Tallei, T.E.; Idroes, R.; Mohamed, A.A.-R.; Hossain, M.J.; Dhama, K.; Mostafa-Hedeab, G.; Emran, T.B. *Ginkgo biloba*: A Treasure of Functional Phytochemicals with Multimedicinal Applications. *Evid.-Based Complementary Altern. Med.* **2022**, *2022*, 8288818, https://doi.org/10.1155/2022/8288818.
99. Šamec, D.; Karalija, E.; Dahija, S.; Hassan, S.T.S. Biflavonoids: Important Contributions to the Health Benefits of Ginkgo (*Ginkgo biloba* L.). *Plants* **2022**, *11*, 1381, https://doi.org/10.3390/plants11101381.
100. Jung, U.J.; Kim, S.R. Beneficial Effects of Flavonoids Against Parkinson's Disease. *J. Med. Food* **2018**, *21*, 421-432, https://doi.org/10.1089/jmf.2017.4078.
101. Hasan, S.; Khatri, N.; Rahman, Z.N.; Menezes, A.A.; Martini, J.; Shehjar, F.; Mujeeb, N.; Shah, Z.A. Neuroprotective Potential of Flavonoids in Brain Disorders. *Brain Sci* **2023**, *13*, 1258. https://doi.org/10.3390/brainsci13091258
102. Wang, J.; Chen, R.; Xie, Y.; Qin, X.; Zhou, Y.; Xu, C. Endo/Lysosomal-Escapable Lipid Nanoparticle Platforms for Enhancing mRNA Delivery in Cancer Therapy. *Pharmaceutics* **2025**, *17*, 803. https://doi.org/10.3390/pharmaceutics17070803.
103. Desai, N.; Rana, D.; Salave, S.; Benival, D.; Khunt, D.; Prajapati, B.G. Achieving Endo/Lysosomal Escape Using Smart Nanosystems for Efficient Cellular Delivery. *Molecules* **2024**, *29*, 3131, https://doi.org/10.3390/molecules29133131.
104. Cheng, C.-C.; Yang, Y.L.; Liao, K.H.; Lai, T.W. Adenosine receptor agonist NECA increases cerebral extravasation of fluorescein and low molecular weight dextran independent of blood-brain barrier modulation. *Sci. Rep.* **2016**, *6*, 23882, https://doi.org/10.1038/srep23882.
105. Carman, A.J.; Mills, J.H.; Krenz, A.; Kim, D.-G.; Bynoe, M.S. Adenosine Receptor Signaling Modulates Permeability of the Blood–Brain Barrier. *J. Neurosci.* **2011**, *31*, 13272, https://doi.org/10.1523/JNEUROSCI.3337-11.2011.
106. Bynoe, M.S.; Viret, C.; Yan, A.; Kim, D.-G. Adenosine receptor signaling: a key to opening the blood–brain door. *Fluids Barriers CNS* **2015**, *12*, 20, https://doi.org/10.1186/s12987-015-0017-7.
107. Zhang, L.-D.; Ma, L.; Zhang, L.; Dai, J.-G.; Chang, L.-G.; Huang, P.-L.; Tian, X.-Q. Hyperbaric Oxygen and Ginkgo Biloba Extract Ameliorate Cognitive and Memory Impairment via Nuclear Factor Kappa-B Pathway in Rat Model of Alzheimer's Disease. *Chin. Med. J.* **2015**, *128*, 3088-3093, https://doi.org/10.4103/0366-6999.169105.
108. Liang, W.; Xu, W.; Zhu, J.; Zhu, Y.; Gu, Q.; Li, Y.; Guo, C.; Huang, Y.; Yu, J.; Wang, W.; Hu, Y.; Zhao, Y.; Han, B.; Bei, W.; Guo, J. *Ginkgo biloba* extract improves brain uptake of ginsenosides by increasing blood-brain barrier permeability via activating A1 adenosine receptor signaling pathway. *J. Ethnopharmacol.* **2020**, *246*, 112243, https://doi.org/10.1016/j.jep.2019.112243.
109. Lang, D.; Ude, C.; Wurglics, M.; Schubert-Zsilavecz, M.; Klein, J. Brain permeability of bilobalide as probed by microdialysis before and after middle cerebral artery occlusion in mice. *J. Pharm. Pharm. Sci.* **2010**, *13*, 607-614, https://doi.org/10.18433/j31c7q.

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