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Transferosomes: A Promising Drug Delivery Tool in Neurodegenerative Disorders

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ABSTRACT

Background: Globally, neurodegenerative diseases (NDs) are complicated, progressive, and frequently lethal conditions that greatly increase mortality and disability. Because there are currently no effective treatments for conditions including Parkinson's disease, Alzheimer's disease, and numerous psychiatric diseases (such as depression, anxiety, bipolar disorder, and schizophrenia), these conditions continue to present significant healthcare issues. The blood-brain barrier (BBB), a highly selective membrane that prevents therapeutic medicines from entering the central nervous system (CNS), is a crucial obstacle in the development of effective treatments. Due to the poor brain bioavailability of conventional drug delivery systems, novel approaches are required to improve medication penetration and efficacy.

Purpose: This review examines the possibilities of nanocarrier-based systems, especially transferosomes; this review seeks to solve the shortcomings of traditional drug delivery techniques in the treatment of NDs. These ultra-deformable vesicles have demonstrated potential in overcoming BBB restrictions, boosting the distribution of neuroprotective medications to the brain, and enhancing therapeutic results.

Methods: The review summarizes the results of current studies on medication delivery systems based on transferosomes in relation to mental and neurodegenerative diseases. It reviews preclinical research on animal models, emphasizing enhancements in cognitive performance, locomotor activity, cerebral bioavailability, and biochemical indicators, including neurotransmitter levels and oxidative stress.

Conclusion: A promising development in medicine delivery for NDs driven by nanotechnology is transferosomes. They are a strong contender to replace conventional drug delivery techniques because of their capacity to increase brain bioavailability, reduce systemic side effects, and boost therapeutic efficacy. Preclinical research suggests that this relatively new method has great promise for treating a range of mental and neurodegenerative diseases. To prove transferosomes as a practical method for enhancing CNS medication distribution and patient outcomes, future studies should concentrate on refining formulations, carrying out comprehensive clinical trials, and resolving regulatory issues.

1. Introduction

An estimated 1 billion individuals worldwide are affected by neurodegenerative diseases (NDs), making them a major cause of ill health and an increasing cause of death, particularly in middle- and high-income nations. These conditions contribute significantly to the global disease burden, surpassing even cancer and cardiovascular disorders (Josephine Boder & Banerjee 2021). The number of diagnoses continues to rise due to increased awareness and information availability. However, the prevalence of these disorders is also significantly influenced by the increasing human life expectancy, as brain function naturally declines with age. Most drugs that are designed to target the brain struggle to effectively traverse the blood-brain barrier (BBB) (Hinge *et al.*, 2022). To overcome this problem and increase drug efficacy, reduce toxicity, enhance specificity, and prolong therapeutic residence time, various nanostructured drug delivery systems have been explored. The use of nanomedicines as drug delivery systems has vast potential (Arias, 2021). This approach possesses several significant advantages, including the controlled release of drugs at predetermined locations such as the brain and nerve tissue, which results in more precise therapeutic effects. It also enhances pharmacokinetics through increased cell membrane penetration and histo-hematic barrier penetration, as well as solubility and bioavailability. The approach also decreases side

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effects related to first-pass metabolism, thereby enhancing patient safety. Besides, it provides for other pharmaceutical forms made from non-toxic substances in the spirit of safer and more convenient drug delivery (Alonso *et al*., 2024). Transferosomes are a form of specialized vesicle with an ethanolic or aqueous core and phospholipid bilayers that are compositionally dense, cholesterol, and an edge activator (Cullinane *et al*., 2024). The major phospholipid present on eukaryotic cell membranes, phosphatidylcholine, reduces the risk of side effects as well as enhances drug delivery in sensitive areas. Such vesicles can deliver important biological signals that affect cell communication and general physiological function. Transferosomes are now being widely utilized for the encapsulation of various therapeutic agents, including proteins, peptides, nucleic acids, and hydrophilic as well as hydrophobic drugs. They also play a role in immunomodulation, neurogenesis, angiogenesis, and synaptic plasticity (Riccardi *et al*., 2024; Matharoo *et al*., 2024). The review is indicating the promising future of transferosomes in the management of neurological diseases. As ultra-deformable vesicular carriers, they have tremendous potential in addressing problems related to targeted drug delivery and entry through the BBB. Focusing on their uses, this review hopes to offer useful information to both medicinal chemistry and pharmacology researchers and clinicians looking for new treatments in neurological diseases (Yourdkhani *et al*., 2024). In recent research, formulated chrysin-loaded transferosome lipid vesicles and chitosan composite vesicles (CCV) to improve bioavailability and manage doxorubicin-induced chemotherapy-associated cognitive impairment, or "chemo brain." Transferosomes, which consist of phospholipids, edge activators (EAs), and single-chain surfactants, enhance membrane flexibility and deformability, enabling them to pass through pores smaller than their own diameter. This overcomes a major limitation of conventional liposomes. The formulations demonstrated nanometric size, controlled release over 72 hours, and high drug entrapment efficiency. Behavioral tests, acetylcholinesterase inhibition, and reductions in oxidative stress markers (catalase, reduced glutathione, lipid peroxidation, and hydrogen peroxide) showed that intranasal administration at a lower dose (0.5 mg/kg) improved memory impairment in rats. Furthermore, chrysin formulations suppressed apoptosis and NLRP3 inflammasome activation by downregulating caspase-3, TLR4, and NF-κB protein expression, suggesting their therapeutic potential against chemobrain (Ibrahim *et al*., 2021; Cardoso *et al*., 2020; Opatha *et al*., 2020). Similarly, quercetin (QER), a potent antioxidant that protects against oxidative stress, has limited oral bioavailability, restricting its therapeutic effectiveness. To enhance brain targeting, researchers developed QER-loaded transferosomal nanovesicles (QER-TFS) in an in-situ gel formulation for intranasal administration. The optimized formulation exhibited a vesicle size of 171.4 nm, high entrapment efficiency (78.2%), and sustained drug release while improving nasal mucosa permeability. CT scans confirmed efficient brain accumulation, and stability studies validated its robustness. In vitro cytotoxicity tests showed minimal toxicity, identifying QER-TFS in situ gel as a promising nanocarrier for neuroprotection via the intranasal route (Opatha *et al*., 2020). To improve the bioavailability of resveratrol (RES), a potent antioxidant with low oral absorption because of substantial hepatic and intestinal degradation, an intranasal transferosome mucoadhesive gel was also created. Optimized transferosomes with a vesicle size of 83.79 nm and an entrapment effectiveness of 72.58% were produced using a reverse evaporation vertexing sonication process. The formulation's safety was validated by histopathological investigations, which revealed strong ex vivo permeability (75.95%) and regulated drug release (65.87%). Pharmacokinetic research showed a 2.15-fold increase in Cmax and a 22.5-fold improvement in AUC when compared to oral administration, highlighting its potential for efficient drug delivery to the central nervous system (CNS) (Elkomy *et al*., 2023).

2. Transferosomes

Transferosomes are vesicular carrier systems specifically designed to contain an EA and at least one inner aqueous compartment enclosed by a lipid bilayer. This aqueous core, surrounded by a lipid bilayer, forms ultra-deformable vesicles with self-optimizing and self-regulating properties (Salem *et al*., 2019). Due to their elastic nature, transferosomes can compress and deform as whole vesicles, passing through minuscule pores or skin constrictions significantly smaller than their size without any noticeable loss. Unlike traditional liposomes, which are composed of synthetic phospholipids (such as dipalmitoyl phosphatidylcholine—DPPC, dimyristoyl phosphatidylcholine—DMPC, and dipalmitoyl phosphatidylglycerol—DPPG) or natural phospholipids (such as egg phosphatidylcholine—EPC and soybean phosphatidylcholine—SPC) (Çelik *et al*., 2020), transferosomes are a modified liposomal vesicular system composed of phospholipids and an EA, typically a single-chain surfactant (Chen *et al*., 2022). EAs act as membrane-destabilizing agents, significantly enhancing the deformability of vesicle membranes when combined with the appropriate lipid in the correct ratio. This optimal combination improves the transferosomes' ability to penetrate barriers by making them both highly flexible and ultra-deformable (Chen *et al*., 2024; Ahmed *et al*., 2025). Unlike traditional liposomes, which face limitations in penetration, transferosomes can pass through pores

much smaller than their diameter while maintaining their structural integrity, preventing fragmentation after crossing microscopic barriers. The inclusion of EAs in transferosomal formulations has led to superior performance compared to conventional liposomes (Matharoo *et al.*, 2024; Dudhipala *et al.*, 2020). The potential of transferosomes in the treatment of neurodegenerative disorders is shown in Figure 1. These ultra-flexible vesicles provide a promising therapy option for conditions including Alzheimer's, Parkinson's, and Huntington's illnesses by improving medication transport across the blood-brain barrier. By encapsulating medicinal chemicals, they improve bioavailability, reduce adverse effects, and provide a practical way to treat complex neurological conditions.

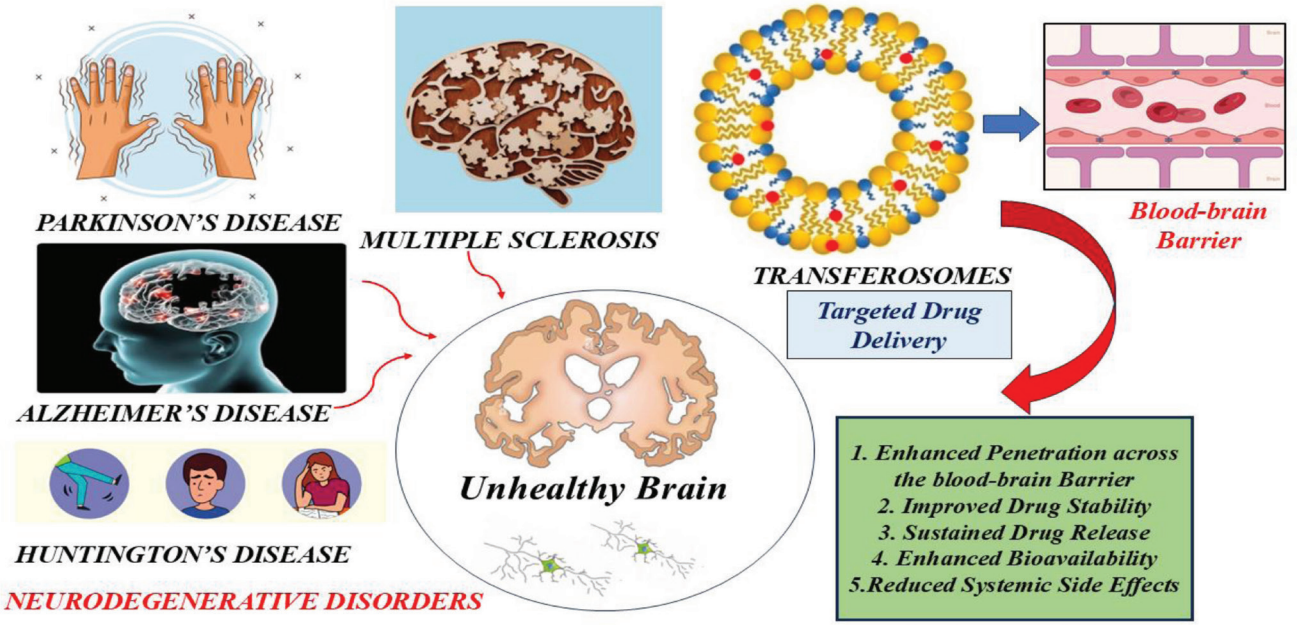

Figure 1: Transferosomes in Different Conditions like Alzheimer's, Parkinson's, and Huntington's Diseases

2.1. Mechanistic Approach of Transferosomes in Brain Targeting

Transferosomes are designed to provide medications for neurological conditions because of their capacity to cross the blood-brain barrier and overcome its challenges. Transferosomes' ultra-deformable vesicular structure allows them to effectively carry medications to the brain by piercing the blood-brain barrier's tight endothelial junctions. Targeting ligands like transferrin or lactoferrin added to the surface enhances receptor-mediated transcytosis or endocytosis, which makes it easier for these vesicles to enter certain brain regions (Cheng *et al.*, 2024; Malhotra *et al.*, 2017). Additionally, transferosomes can be administered intravenously, removing the need for systemic circulation and first-pass metabolism. This makes it easier for drugs to enter the brain directly through the trigeminal and olfactory nerve pathways. It is possible to load both hydrophilic and lipophilic medications onto these carriers, which will keep them stable until they travel to their destination and shield them from enzymatic breakdown in the blood. Transferosomes also guarantee regulated and prolonged drug release, which lowers the frequency of doses and prolongs the time that the medication is in the brain at a therapeutic concentration (Tan *et al.*, 2020). Neuropharmacological safety is improved by concentrating drug delivery on the brain, which limits adverse effects on systemic targets. Furthermore, to accomplish linked therapy and sensing, transferosomes can transport medicines in combination with one another or therapies in combination with diagnostic agents. With these benefits, transferosomes provide a flexible and effective way to address the difficulties in neurologic disease medication administration with the goal of optimizing treatment response and guaranteeing patient compliance (Puengel *et al.*, 2022; Tomar *et al.*, 2024).

3. Transferosomes' Potential for Treatment in Neurological Conditions

3.1. Multiple Sclerosis

Multiple sclerosis (MS) is a long-term, immune-mediated neurological condition that affects the central nervous

system (CNS), which includes the brain and spinal cord. The insulating covering of nerve fibers, myelin, is targeted by the immune system in multiple sclerosis (Misra & Pathak, 2023). This results in inflammation, demyelination, and damage to the underlying neurons. The disease also interferes with the normal conduction of electrical impulses through the nerves. MS can cause a wide range of symptoms, including fatigue, reduced mobility, tingling or numbness, muscle weakness, poor coordination, visual disturbances such as double or blurred vision, and cognitive impairments affecting memory and concentration (Portaccio *et al.*, 2024). MS is generally classified into three types:

- Relapsing-remitting multiple sclerosis (RRMS): Characterized by periods of partial or complete remission between flare-ups or relapses.
- Primary progressive multiple sclerosis (PPMS): Marked by a continuous progression of disability from the onset, without distinct relapses or remissions (López-Muguruza *et al.*, 2023; Cree *et al.*, 2021).
- Secondary progressive multiple sclerosis (SPMS): Initially begins as RRMS but later transitions into a phase of steadily worsening symptoms and disability.

While the exact cause of MS remains unknown, it is believed to result from a complex interaction between genetic and environmental factors. Potential risk factors include smoking, low vitamin D levels, and certain medical conditions (Bayas *et al.*, 2023; de Seze *et al.*, 2021). Diagnosing MS can be challenging due to the lack of a definitive diagnostic test. Neurologists typically rely on MRI scans, clinical history, physical examinations, and, in some cases, spinal fluid analysis to confirm the diagnosis. Currently, there is no cure for MS. However, several treatment strategies focus on symptom management, modifying disease progression, and improving overall patient well-being. One promising area of research involves transferosome-based nanosystems. These vesicular carriers contain numerous anti-inflammatory and neuroprotective agents that may help regulate the immune system, promote tissue repair, and support remyelination. This review will explore the potential of nanosystems in slowing the progression of MS, along with their role in targeting cell-specific diseases associated with the condition (Liu *et al.*, 2022).

3.2. Alzheimer's Disease

A degenerative neurological condition primarily affecting the brain causes memory loss, cognitive decline, and behavioral abnormalities. In the elderly population, it is the leading cause of dementia (Rosenberry *et al.*, 2022). Dr. Alois Alzheimer discovered the disease in 1906 AD, and one of its hallmarks is the accumulation of abnormal protein aggregates in the brain, including tau tangles and beta-amyloid plaques (Cenko *et al.*, 2021). These deposits obstruct the normal flow of signals between nerve cells, leading to cell death and the gradual deterioration of brain tissue (Tan *et al.*, 2021). Symptoms include memory loss, cognitive decline, behavioral changes, and functional impairments. Diagnosis is typically made through a comprehensive evaluation of the patient's medical history, cognitive assessments, and the exclusion of other potential causes of cognitive decline. In some cases, cerebrospinal fluid (CSF) analysis and advanced imaging techniques may be used. Alzheimer's disease (AD) is generally classified into three stages: mild (early stage), moderate (middle stage), and severe (late stage), each characterized by distinct symptoms and varying degrees of disability (Bis *et al.*, 2020). Currently, there is no known cure for AD. However, medications such as memantine and cholinesterase inhibitors can help alleviate symptoms and slow cognitive decline (Nojoki *et al.*, 2022). A previous study developed chitosan-transfersulin (CTI) nanovesicles as an intranasal drug delivery system for Alzheimer's disease treatment. The optimal formulation, prepared using the film hydration method, exhibited a zeta potential of +23.4 mV, a polydispersity index of 0.20, a particle size of 137.9 ± 28.2 nm, an encapsulation efficiency of 65.1 ± 0.9%, and a drug loading of 9.1 ± 0.4%. Fluorescence imaging and histological studies confirmed significant brain retention and neuroprotection in rats. Insulin encapsulated in CTI demonstrated stability, structural integrity, and effective nasal uptake, suggesting that CTI is a promising approach for treating Alzheimer's disease (AD) (Sakai *et al.*, 2023). Another study formulated ascorbic acid (AA)-loaded transferosomes (TRANS) with epigallocatechin-3-gallate (EGCG) for targeted brain delivery using the film hydration technique. In phosphate-buffered saline (pH 7.4), 61.65% ± 4.61 of EGCG was released over 72 hours, demonstrating sustained drug release. In vivo studies showed significant efficacy against Alzheimer's disease, with EGCG-AA-TRANS achieving 82.166% acetylcholinesterase (AChE) inhibition compared to 66.550% for EGCG-TRANS and 53.466% for AA-TRANS. Intranasal administration of EGCG-AA-TRANS improved memory approximately fivefold and facilitated the accumulation of EGCG and AA in the brain and other organs, highlighting its potential as a safe and effective Alzheimer's treatment (Gugleva *et al.*, 2022). In another study, curcumin-loaded transfersomes were formulated into an in-situ gel to enhance bioavailability and nasal delivery. The thin film hydration process was used to create curcumin transfersomes, and Design Expert software optimized the formulation. The optimized batch demonstrated stable drug content and pH, with an in vitro drug release profile suggesting non-

Fickian diffusion. The nasal in-situ gel extended drug contact duration and enabled controlled release, thereby improving bioavailability, reducing dosage requirements, and enhancing patient safety and compliance (Mishra *et al*., 2022). A separate study investigated transferosomes (TRANS) co-loaded with berberine (BBR) and curcumin (CUR) for Alzheimer's treatment. The BBR-CUR-TRANS formulation demonstrated sustained drug release, with 41.03 ± 1.22% release of BBR and 24.67 ± 1.94% release of CUR. In vivo studies showed increased antioxidant activity, reduced malondialdehyde levels, and improved spatial memory, with BBR-CUR-TRANS producing the most significant reduction in nitric oxide levels. These findings support transferosomes as effective vehicles for co-delivering neuroprotective agents to the brain (Langasco *et al*., 2019). Genistein, an isoflavone derived from soy, has neuroprotective and antioxidant properties but suffers from low oral bioavailability. To enhance its brain transport, lipid-based nanovesicles, particularly transfersomes, were developed for intranasal administration. The GEN-TF2 preparation, which contained Span 80, showed effective internalization in PC12 cells, lowering reactive oxygen species (ROS) generation and inhibiting H_2O_2-induced apoptosis. These results indicate that GEN-TF2 may be an effective antioxidant delivery system and hence a good adjuvant therapy for oxidative stress-related neurodegenerative diseases (Tekade *et al*., 2024). In recent work, researchers created hyaluronic acid-coated transferosomes (DPZ-HA-TFS) for the intranasal administration of donepezil hydrochloride (DPZ) to overcome gastrointestinal side effects in case of oral administration of DPZ for treating Alzheimer disease. DPZ-HA-TFS was prepared via the thin film hydration technique and was optimized by applying a 24-factorial design. The best formulation showed a vesicle size of 227.5 nm, an entrapment efficiency of 75.83%, and an eight-hour cumulative release of 37.94%. In vivo experiments evidenced extensive brain targeting and 547.49 μg/cm² nasal mucosa permeability for 24 hours, making it a good potential candidate as long-term non-invasive Alzheimer's disease therapy (Niazi, 2023). Lastly, transferosomes have vast possibilities for the delivery of tau and amyloid-beta proteins that contribute to Alzheimer's disease pathogenesis. By promoting improved drug delivery through the blood-brain barrier, transferosomes allow for targeted delivery and controlled release of drugs, which can enhance treatment efficacy. Future studies should aim to optimize transferosome formulations to allow for targeted delivery of gene therapies, monoclonal antibodies, or small molecules intended to modulate amyloid and tau aggregation, ultimately enhancing therapeutic outcomes for Alzheimer's and other neurodegenerative disorders (Chopra *et al*., 2022; Zhang *et al*., 2024).

3.3. Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder with progressive loss of motor function. It is mostly due to the gradual degeneration of brain neurons that produce dopamine, especially in the substantia nigra (Zhang *et al*., 2024). Dopamine is a neurotransmitter crucial for controlling and coordinating precise movements of muscles (Morris *et al*., 2024). Although the precise etiology of Parkinson's disease has not been identified, it is thought to be a product of both environmental and genetic influences. Some of the symptoms of PD are bradykinesia, postural instability, rigidity, and tremor (Zhu *et al*., 2024). Diagnosis of Parkinson's disease is primarily symptomatic and based on history, since no test can definitively establish the diagnosis. Imaging scans and neurological examinations may occasionally be employed to exclude other conditions (Roodveldt *et al*., 2024). Levodopa, a medication that replenishes dopamine, is commonly prescribed to manage motor symptoms. Additionally, physicians may recommend other drugs such as MAO-B inhibitors and dopamine agonists (Zarkali *et al*., 2024). The severity and progression of symptoms vary among individuals, and PD advances gradually over time. Ongoing research aims to further understand the underlying mechanisms of Parkinson's disease and develop more effective treatment strategies (ElShagea *et al*., 2023). A previous study sought to enhance the bioavailability of rasagiline mesylate (RSM), a hydrophilic drug with poor oral absorption, by encapsulating it in a transferosomal in-situ gel for intranasal (IN) administration. Transferosomes were formulated using the thin-film hydration method and optimized with Design-Expert® software. The formulation consisted of phosphatidylcholine and sodium deoxycholate as EA, with a particle size of 198.63 ± 34.98 nm and an entrapment efficiency of 95.73 ± 0.09%. The in-situ gel, which included pectin, Pluronic® F-127, and Pluronic® F-68, demonstrated successful brain targeting and improved bioavailability (131.17%), with a drug targeting efficiency of 304.53% and direct nose-to-brain transport of 67.16%. The findings indicate that this formulation is a safe, biocompatible, and promising approach for direct nose-to-brain delivery of RSM (Li *et al*., 2024). Rotigotine HCL (RTG) and rasagiline mesylate (RSM), which belong to separate Biopharmaceutics Classification System (BCS) classes (II and III, respectively), were used in a recent study to create transferosome patches for the treatment of Parkinson's disease. After being optimized by central composite design, the patches were created using the thin film hydration and homogenization casting process. They were then examined for a variety of factors, including drug content, tensile strength, in vitro release, and ex vivo permeability. The patches' rapid beginning of action,

prolonged drug release, and lack of in vivo skin irritation demonstrated the drugs' synergistic benefits. This mixture presents a viable approach to topical therapy of Parkinson's disease with fewer systemic adverse effects (de Oliveira *et al.*, 2021). In summary, transferosomes have great potential for dopaminergic drug delivery in the treatment of Parkinson's disease through enhanced blood-brain barrier penetration and compensation for low drug bioavailability. Their capacity for encapsulation and controlled release of dopamine or dopamine agonists increases the efficacy of treatment and the quality of patient outcomes. Current research centers on maximizing transferosome formulations for the co-delivery of neuroprotective therapeutics, gene therapies, or protein-based drugs to reduce side effects and maximize long-term control of Parkinson's disease. Furthermore, sustained-release formulations are also being designed to optimize therapeutic effectiveness (Feldman *et al.*, 2022).

3.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a degenerative neurological disorder characterized by the progressive deterioration of nerve cells in the brain and spinal cord. ALS leads to the degeneration of motor neurons, which are responsible for controlling voluntary muscle movements (Mead *et al.*, 2023). As motor neurons degenerate, the brain's ability to initiate and regulate muscle activity declines. While the exact cause of ALS remains unknown, both genetic and environmental factors are believed to contribute to its development. Common symptoms of ALS include muscle weakness, muscle wasting, difficulty speaking and swallowing, and breathing complications. The disease is classified into two types: familial ALS (inherited) and sporadic ALS (non-inherited) (Kiernan *et al.*, 2021). Since no definitive diagnostic test exists for ALS, diagnosis is primarily based on clinical symptoms and the systematic exclusion of other conditions. Electromyography (EMG) and nerve conduction studies are commonly used to assess motor neuron and muscle function. Although there is no cure for ALS, the FDA-approved drug riluzole can slow disease progression by reducing motor neuron damage (Yazdani *et al.*, 2022). Additionally, edaravone, another FDA-approved medication, can help slow the decline of physical abilities (Irwin *et al.*, 2024). Effective symptom management, including physical and occupational therapy, respiratory support, and communication aids, is essential for improving the quality of life of individuals with ALS (Masrori & Van Damme, 2020). Transferosomes offer promising advancements in ALS treatment by overcoming challenges related to inadequate drug delivery. Their ability to cross the blood-brain barrier enables the direct delivery of small and large molecules, such as RNA-based therapies or neuroprotective drugs, to motor neurons. Recent studies have investigated transferosome-based delivery systems for the targeted delivery of anti-inflammatory compounds, antioxidants, and gene editing tools such as CRISPR/Cas9 to alter the course of diseases. Furthermore, the integration of transferosomes with biomarkers of early diagnosis and personalized therapy can greatly enhance the quality of life and patient outcome (Rizea *et al.*, 2024; Stoker *et al.*, 2022).

3.5. Huntington's Disease

Huntington's disease (HD) is a genetic neurodegenerative condition that impacts both cognitive and motor abilities (Oosterloo *et al.*, 2021). HD results from a mutation in the huntingtin (HTT) gene, which creates a faulty version of the huntingtin protein (Raschka *et al.*, 2024). This mutation causes gradual degeneration of certain brain areas, leading to a broad array of neurological and psychological symptoms. HD has an autosomal dominant mode of inheritance, and only one mutated HTT gene from either parent is enough to have the disease. The disease is associated with a pathological expansion of CAG repeats in the HTT gene, with an increased number of repeats showing an association with increased severity and onset at an earlier age (Tabrizi *et al.*, 2020). Diagnosis would be by noting typical symptoms and assessment of family history. Genetic testing can confirm the presence of the HTT mutation. While there is no cure for Huntington's disease, supportive treatments can help manage symptoms. Medications are available to alleviate motor dysfunction and psychiatric symptoms, thereby improving overall quality of life. A multidisciplinary approach involving neurologists, psychiatrists, physical and occupational therapists, and genetic counselors is often necessary to address the diverse needs of HD patients (Jellinger, 2024). Recent research has identified transferosomes as a promising delivery system for gene therapy in Huntington's disease. These nanocarriers can efficiently transport genetic material into the brain to silence or modify the mutant huntingtin gene. Their ability to cross the blood-brain barrier and provide sustained release of therapeutic agents makes them well-suited for targeted gene therapy. Future research aims to refine transferosome formulations to deliver small interfering RNAs (siRNAs) or CRISPR-based gene-editing tools, offering the potential to reduce mutant huntingtin protein production and slow or halt disease progression (Ziehr & MacDonald, 2024).

Table 1 highlights advancements in brain-targeted drug delivery systems, emphasizing improved bioavailability, enhanced therapeutic efficacy, and innovative administration routes. The table also showcases how novel formulation techniques, overcoming challenges like poor solubility, limited bioavailability, and first-pass metabolism, ultimately enhance treatment outcomes for neurodegenerative and central nervous system disorders.

Table1: Advancements in Brain-Targeted Drug Delivery Systems

Active Ingredient	Method	Disease	Inference	Reference
Chrysin	Chitosan Composite Vesicles (CCVs) and Transfersomal Lipid Vesicles	Chemotherapy-induced Cognitive Impairmen	By inhibiting acetylcholinesterase, reducing oxidative stress, and modulating the TLR4-NF-Kb (p65)-NLRP3 axis, chrysin-loaded transfersomes and CCVs provide improved therapeutic potential against chemobrain.	(Opatha *et al.*, 2020)
Quercetin (QER)	Nanovesicle Development, In Situ Gel Preparation	Oxidative Stress-Induced Neurodegeneration: (Alzheimer's disease, Parkinson' 's disease)	Improved brain targeting by intranasal administration, enhanced quercetin bioavailability and medication stability, and decreased in vitro toxicity	(Elkomy *et al.*, 2023)
Resveratrol (RES)	Reverse evaporation vortexing sonication method	Central Nervous System Disorders	Overcome the drawbacks of resveratrol oral administration, and providing a viable substitute for CNS conditions that call for antioxidant treatment.	(Salem *et al.*, 2019)
Insulin	Film Hydration Method	Alzheimer's disease	Integrity and stability, and efficient intranasal administration	(Bis *et al.*, 2020; Nojoki *et al.*, 2022)
Epigallocatechin-3-gallate, Ascorbic Acid	Film Hydration Method	Alzheimer's Disease	Enhancement of memory, Acetylcholinesterase (AChE) inhibition, and brain targeting	(Gugleva *et al.*, 2022)
Curcumin	Thin Film Hydration Method	Anti-inflammatory or Antioxidant Effects	Better bioavailability, regulated drug release, advantages for patients, and possible uses	(Mishra *et al.*, 2022)
Berberine (BBR), Curcumin (CUR)	Synthesis of Transferosomes (TRANS)	Alzheimer's Disease	Better therapy results for Alzheimer's disease due to improved drug delivery to the brain	(Langasco *et al.*, 2019)
Genistein	GEN-TF2 (transfersomes containing Span 80).	Neurodegenerative Diseases	Antioxidant effectiveness, therapeutic potential, and adjuvant promise	(Tekade *et al.*, 2024)
Donepezil Hydrochloride (DPZ)	Thin film hydration method.	Alzheimer's Disease.	Facilitating efficient administration, guaranteeing medication stability, brain targeting, and therapeutic effectiveness with fewer systemic adverse effects	(Niazi, 2023)
RSM, Phosphatidylcholine, Sodium deoxycholate:	Thin-film hydration method	Parkinson's Disease, Epilepsy, and Alzheimer's	Improving brain bioavailability and achieving safe, biocompatible, and tailored brain delivery	(Li *et al.*, 2024)
Rotigotine Hydrochloride (RTG), Rasagiline Mesylate (RSM)	Thin Film Hydration and Homogenization Casting	Parkinson's Disease	Efficiency of medication delivery was increased by the transferosome patches' regulated drug release and rapid beginning of action	(de Oliveira *et al.*, 2021)

4. Recent Advancements in Neurodegenerative Disorders

4.1. Role of Mitochondria Oxygen Redox

Through oxidative phosphorylation, mitochondria produce ATP, which is essential for maintaining cellular energy balance. However, this process also generates reactive oxygen species (ROS) as byproducts. While ROS are crucial for normal cellular signaling, excessive production or impaired antioxidant defenses play a significant role in the pathophysiology of neurodegenerative diseases (NDs) such as Huntington's disease, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Minakhina *et al*., 2024). Oxidative stress leads to reduced ATP synthesis, mitochondrial DNA damage, and activation of pro-apoptotic pathways, ultimately resulting in neuronal dysfunction and cell death. Because of their intricate architecture and high energy requirements, neurons are especially susceptible (Zhang *et al*., 2022). Lipid vesicular structures known as transferosomes present a new solution in the form of facilitating targeted delivery of drugs through biological barriers like the blood-brain barrier. Transferosomes are best suited for the delivery of antioxidants—like chrysin, curcumin, and coenzyme—improving bioavailability and avoiding degradation. Moreover, transferosomes enhance the stability of drugs, minimize systemic side effects, and enable the co-delivery of therapeutic agents to multidirectional oxidative stress as well as mitochondrial dysfunction (Ji *et al*., 2020). These attributes render them well-suited for ND oxidative stress prevention. Future transferosome-based treatment targeting mitochondrial dysfunction has great potential for ND therapy. Research can be directed toward the creation of mitochondria-targeted transferosomes with ligands or peptides, assessing their efficiency in lowering oxidative stress and neuronal injury via clinical trials, and investigating their feasibility as adjuvants with gene therapies targeting mitochondrial DNA repair (Pekdemir *et al*., 2024). Transferosomes improve drug stability, bioavailability, and targeting, providing a viable avenue for creating long-term and effective treatments for neurodegenerative disorders.

4.2. Antioxidant Nutraceuticals Made from Plants to Treat Neurodegenerative Diseases

Since currently available drugs can only slow the progression of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease rather than completely halt them, treating these conditions remains one of the most challenging problems for physicians (Ramli *et al*., 2020). To address this issue, more effective therapeutic approaches are needed, particularly those based on natural medicines. Plant-derived antioxidant nutraceuticals, including curcumin, resveratrol, epigallocatechin gallate (EGCG), quercetin, and genistein, have shown promise in reducing inflammation and oxidative stress—two key factors in the development of neurodegenerative diseases such as Huntington's disease, Parkinson's disease, and Alzheimer's disease (Mursal *et al*., 2024). These bioactive compounds exhibit neuroprotective effects by scavenging free radicals, modulating signaling pathways, preventing neuroinflammation, and improving mitochondrial function. However, their clinical application is limited by their instability under physiological conditions, low bioavailability, and poor water solubility. To overcome these challenges, curcumin-loaded transferosomes have demonstrated improved brain absorption, prolonged release, and enhanced neuroprotective efficacy compared to traditional formulations. Similarly, transferosome-encapsulated EGCG and resveratrol have shown increased cellular absorption and antioxidant activity, reducing oxidative damage in neural models (Ashok *et al*., 2022; Alsaidan *et al*., 2024).

4.3. Transbilosomes

According to recent literature, bile salts such as sodium cholate, sorbitan tristearate, and deoxycholic acid act as EAs in biosomes, leading to the formation of "soft" lipid vesicular nanocarriers. The accumulation of these biosurfactants enhances the system's colloidal stability compared to conventional liposomes and transferosomes (AbouElhassan *et al*., 2022). Biosomes (BLs), a novel vesicular drug delivery system, are composed of non-ionic surfactants and bile salts (El Sisi *et al*., 2025; Kaurav *et al*., 2024). In membrane organization, they remain metastable until bile salt molecules are added, which lowers the phase transition temperature and makes them highly flexible and adaptable at physiological temperatures. Biosomes have been utilized in transdermal, ocular, and topical drug delivery (Khope *et al*., 2024). However, no published studies have specifically examined the effects of intranasal delivery of BLs loaded with medication on brain targeting and drug absorption. Despite the limited research on BL vesicles for intranasal drug administration, their small size and bile salt composition make them a promising alternative for drug transport from the nose to the brain (Abou Elhassan *et al*., 2022). Recently, hyaluronic acid-decorated transbilosomes (CIT-HATBLs) have been developed as an innovative intranasal drug delivery method to enhance brain targeting. This modified formulation has demonstrated improved brain penetration, sustained drug release, excellent entrapment efficiency, and nanoscale size. In vivo studies have shown improved cholinergic function, reduced oxidative and inflammatory markers, and decreased expression of Aβ1–42 and miR-137 in the hippocampus. Thermogel CIT-HATBLs hold significant potential as an effective therapeutic approach for Alzheimer's disease treatment (Sahu *et al*., 2024).

4.4. Nano Transferosomes

Patients with schizophrenia, a severe and common psychotic disorder, misinterpret reality and may exhibit various symptoms, including delusions, hallucinations, severely disordered thinking, and impaired behavior in daily functioning. Individuals with schizophrenia require lifelong therapy. Researchers are continuously working to discover new pharmaceutical compounds to improve the quality of life for people with schizophrenia (Pozo-Pérez *et al*., 2024). The antipsychotic drugs currently available for schizophrenia treatment need to be reformulated using lipid vesicular nanocarrier systems. These systems offer a promising platform for novel therapeutic approaches that target the brain through intranasal administration, thereby reducing systemic side effects. Additionally, nanoformulation has enabled the development of continuous or prolonged drug delivery systems, which may help reduce the need for frequent dosing (Kammoun *et al*., 2021). One of the hopeful strategies for treating schizophrenia effectively is the application of nano transferosomes—a novel evolution in intranasal drug delivery. These lipid-based, very flexible vesicles facilitate drug delivery by effectively permeating biological barriers like the blood-brain barrier and the mucosa of the nose. Intranasal administration speeds up and targets drug transport to the brain by avoiding first-pass metabolism, minimizing systemic side effects, and enhancing therapeutic results (Zarenezhad *et al*., 2024).

4.5. Transniosomes

Transniosomes are a novel and promising vehicle for intranasal administration of TQ because of the capacity to improve bioavailability, control drug release, and circumvent systemic barriers. This strategy could open the door for more patient-compliant and effective alternatives to Parkinson's disease therapy (Alhowyan *et al*., 2024). A novel study used a Box-Behnken design to formulate and optimize TQ-loaded transniosomes (TQ-TNs). The findings revealed nanoscale vesicles (102.2 nm) with better nasal permeability (245.24 μg/cm²) and controlled drug release (84.67% for 24 hours) than TQ suspension. The medication was formulated into an in-situ gel to improve mucosal adhesion, and studies of neuroprotection and antioxidant activity demonstrated its efficacy (87.09%). These findings demonstrate that transniosomes are a viable intranasal delivery technology that may improve Parkinson's disease therapy by resolving bioavailability concerns (Merlin & Abrahamse, 2024).

4.6. CRISPR/Cas9 Therapy

Transferosomes are innovative nanocarrier technologies that provide a possible solution by facilitating the co-delivery of therapeutic drugs that have been carefully chosen to target related medication classes or shared disease pathways. By offering a centralized method for accurate and efficient treatment, these systems improve safety and effectiveness. The advantages, drawbacks, and difficulties of different nanocarriers, such as transferosomes, in brain-targeted medication delivery are examined in comparative research. The research emphasizes how important it is to make strategic formulation changes to better improve transferosomal systems and ensure maximum absorption and prolonged release of medications. Additionally, transferosomes' potential to increase the precision of gene editing in the treatment of Parkinson's disease is highlighted by their conjunction with state-of-the-art technologies like CRISPR/Cas9. Two innovative strategies for achieving synergistic therapeutic advantages in the treatment of Parkinson's disease include the use of stem cell-derived therapies and the contemporaneous administration of synthetic and natural neuroprotective medications (Aljabali *et al*., 2024).

5. Patent Overview

A selection of patents showcasing current developments in transferosome-based medication delivery methods for neurological conditions is shown in Table 2. Innovative formulations that use transferosomes to improve brain permeability, increase medication bioavailability, and treat illnesses including Epilepsy, Parkinson's disease, Alzheimer's disease, and Stroke rehabilitation are highlighted in these patents.

Table 2: Highlighting Recent Advancements in Transferosome-Based Drug Delivery Systems for Neurological Disorders

Patent No.	Title	Assignee	Date of Publication	Summary of the Invention
JP5678901B2	Curcumin-loaded Transferosomes for Neurodegenerative Disorders	Kyoto Pharma Co	Feb 5, 2018	A formulation that uses transferosomes to increase curcumin's bioavailability in the treatment of neurological disorders

EP3345678A1	Transferosome-based Therapy for Epilepsy	Global Pharma Ltd.	Aug 10, 2019	A phenytoin-loaded transferosome formulation designed to reduce the frequency of seizures
US1234567B2	Transferosomal Drug Delivery for Parkinson's Disease	NeuroPharma Innovations	Jan 15, 2020	A Levodopa administration method based on transferosomes that increases brain permeability
WO2021123456A1	Transferosome Formulation for Alzheimer's Treatment	Brain Health Technologies	Mar 20, 2021	Donepezil is encapsulated in a new transferosome for enhanced absorption and decreased adverse effects
IN2023456789A	Transferosomes for Neuroprotective Peptides	Indian Bioinnovations	Dec 25, 2022	Neuroprotective peptides for stroke rehabilitation delivered via a transferosome method

6. Conclusion

By enhancing medication stability, brain-targeted delivery, and bioavailability, transferosomes have shown great promise in addressing challenges associated with neurodegenerative disorders. Their ultra-deformable vesicular architecture enables efficient traversal of the blood-brain barrier, thereby improving the therapeutic effectiveness of treatments for Parkinson's, Huntington's, Alzheimer's, and other diseases. Studies suggest that transferosomes are a safer alternative to traditional delivery systems, as they maximize drug release while minimizing systemic side effects. By encapsulating a variety of bioactive compounds, transferosomes provide a flexible framework for developing neurological therapeutics, paving the way for more effective and patient-centered treatment options.

7. Future Perspective

To improve targeting precision, future studies should focus on optimizing transferosome formulations for personalized therapy by incorporating ligands, peptides, or gene-editing tools. Treatment outcomes may be further enhanced by expanding their use to include the co-delivery of antioxidants, neuroprotective drugs, and RNA-based therapeutics. Clinical trials are necessary to confirm their efficacy and safety in larger populations, particularly for complex neurological disorders. Additionally, exploring scalable production methods and improved manufacturing processes will facilitate their commercial adoption. By integrating transferosome systems with biomarkers and diagnostic tools, these advancements have the potential to revolutionize the treatment of neurodegenerative diseases and significantly improve patients quality of life.

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Authorship Contribution

Neha Kanojia: conceived and designed the manuscript; Jatin Kumar collected data on recent studies. Aruna Sharma: contributed equally in writing, figure conceptualization, and drafting the manuscript; Amit Chaudhary critically reviewed and performed the final approval of the version to be published; all authors read and approved the final manuscript.

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