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Review Article

Lipid nanocarriers encapsulating herbal drugs for brain diseases therapy

Sara R. Gad*, Riham I. El-Gogary, Ahmed S. Geneidi, Rania M. Hathout

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt

ABSTRACT

The blood-brain barrier (BBB) is an essential component in safeguarding the brain and preserving its equilibrium. The BBB represents a challenge for various types of drug delivery systems, particularly in the context of treating numerous neuropathological disorders wherein the therapeutic agents cannot cross the BBB. Nonetheless, existing neurotherapeutics have drawbacks such as toxicity and lack of specificity. Advances in nano drug delivery systems, particularly lipid-based nanocarriers, aim to deliver active therapeutics across the BBB to improve neurological conditions such as Alzheimer's, Parkinson's, and brain tumors, offering a novel treatment strategy with enhanced drug delivery, increased target specificity, enhanced efficacy, and more significantly, minimized toxicity in a biomimetic manner. In this context, this review sheds light on the use of lipid nanocarriers loaded with drugs of natural origin such as ferulic acid, resveratrol, curcumin, and rosmarinic acid for their brain delivery with better bioavailability and exceptional improvement in their therapeutic potential to treat major neurological disorders in future clinics.

Keywords: *Blood-brain barrier; Alzheimer's disease; Parkinson's disease; brain Tumor; lipid nanocarriers; herbal drugs; brain delivery.*

***Correspondence** | **Sara R. Gad**; Department of *Pharmaceutical Technology, Faculty of Pharmacy, Misr International University, Egypt*. Email: sara.gad@pharma.asu.edu.eg

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1. INTRODUCTION

Brain diseases, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and brain tumors, have a tremendous impact on global health, being both the leading cause of disability-adjusted life-years and the second leading cause of deaths affecting a substantial number of people globally **[1]**. Among these disorders, neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, are especially challenging to manage. Neurodegenerative diseases are characterized by age-related decline in neurological functioning and often involve neuronal cell death **[2]**. This gradual decline results in debilitating long-term impacts on health and quality of life **[1]**. The etiology of neurodegenerative diseases has been related to several factors such as; mitochondrial dysfunction, the buildup of misfolded proteins, neuroinflammation, aging, oxidative harm, and sometimes inherited and molecular issues, which can either occur separately or combined, leading to disruption of neuronal communication and thus long-term cognitive and motor impairment **[1, 3, 4]**.

Because of our limited understanding of the complicated pathogenesis of neurological diseases, current therapies are only considered symptomatic treatment, and there are no disease-modifying drugs that can stop the progression of these diseases. The main challenges for creating new drugs for neurological diseases include identifying the right target and designing and specifically delivering the drugs to that target to ensure effective control of symptoms and avoid failure of treatment **[4, 5]**.

Besides the challenge of formulating a drug delivery system targeting the Central Nervous System(CNS), various physiological factors such as the blood-brain barrier (BBB), blood-cerebrospinal fluid barriers, and drug efflux systems also limit the access of drugs to the CNS **[6]**. To ensure the highest possible bioavailability with minimal side effects, it is essential to conduct a comprehensive investigation into the BBB to develop a drug and carrier system that can effectively reach the CNS.

Different brain delivery approaches have been reported in the literature, such as intra-cerebroventricular, and intra-cerebral delivery methods or transient disruption of the BBB in response to stimuli of different natures; physical, chemical, or biological. However, most of these approaches are not only invasive and costly but also lead to patient discomfort, undesirable side effects as well as potential infection or toxicity risks **[7]**. Therefore, several studies deliberated the use of nanoparticles for delivering drugs to the brain to surpass the aforementioned drawbacks of other delivery strategies **[8]**.

There is ample evidence that the intranasal administration of drugs, biotherapeutics such as peptides, proteins, gene vectors, and even mesenchymal stem cells is an effective way to bypass barriers in humans, non-human primates, and rodents. Intranasal delivery has many advantages, such as delivering drugs directly to the brain and bypassing the BBB, which is impenetrable to most of the small molecules and all the large molecules. Direct nose-to-brain administration eliminates systemic dilution and first-pass metabolism, and allows for the administration of low doses, reducing peripheral drug exposure and consequently, toxicity **[9, 10]**.

Simultaneously, advanced drug delivery systems such as lipid-based nanosystems have been developed as a front-line clinical therapeutic method that can overcome the hindrances associated with the BBB and the restrictions that occur when drugs are delivered to the CNS using traditional methods **[3, 5]**.

Among these carriers are solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), microemulsions (MEs), nanoemulsions (NEs), and lipid-based nanocapsules (LNCs).

By penetrating the BBB, SLNs, one of the safest and most cost-effective drug carriers, make it possible to treat neurological disorders in a non-toxic, safe, and efficient manner. The size, structure, and physicochemical characteristics of SLNs, as well as their synthesis methods, all affect how effective and functional they are. Second-generation nano-structured lipid carriers (NLCs), which are modified SLNs, have been developed to upgrade drug delivery to the brain by removing drawbacks like drug expulsion and abrupt release of active drug constituents **[11]**. By tailoring SLNs to boost drug delivery to the brain, they can become more effective in crossing the BBB and improving the bioavailability of the drug **[3]**.

These nanocarriers have a great capacity for administering therapeutic molecules to the brain, as their small size makes them capable of overcoming anatomical barriers such as the BBB. Combining these nanocarriers with nose-to-brain

delivery is an effective way to surpass the obstacle of the BBB and deliver a satisfactory dose of the therapeutic molecule to the CNS **[12]**.

Many phytochemicals proved to have neuroprotective properties mostly related to their anti-inflammatory and antioxidant capabilities. A crucial aspect of the bioefficacy of herbal bioactive components is their bioavailability, which may be constrained by some factors that these herbal drugs suffer from such as; minimal permeability, low water solubility, rapid metabolism, and instability in the CNS **[13, 14]**. Hence, nanoformulations of these natural substrates can be a compelling strategy to tackle the aforementioned problems hence increasing their bioavailability and efficacy **[13]** as shown in **Fig. 1**.

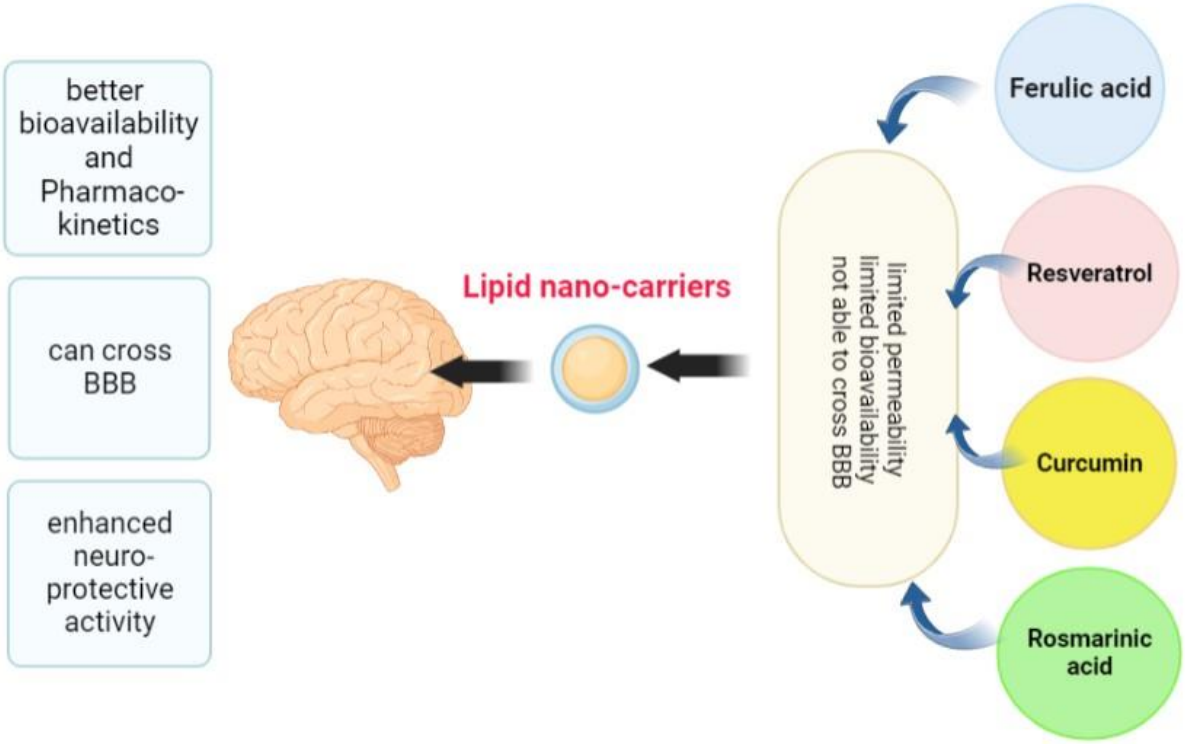

Fig. 1. Brain delivery for drugs of natural origin through lipid nanocarriers

In this context, this study will highlight different brain diseases, and the most recent efforts to treat them through the formulation of natural drugs using nanotechnology.

2. Brain Diseases

2.1. Alzheimer's disease

AD is an age-dependent neurodegenerative disease affecting more than 10% of elderly people aging 65 and more which accounts for about 50 million people around the world nowadays and is expected to exceed 150 million patients by 2050 **[15]**. Symptoms of AD are sequential beginning with a swinging of mood, short-term memory loss, gradual decline in cognition, behavioral and personal disturbances, dementia, and long-term memory loss ending with losing body functions and death **[16, 17]**.

The predisposing factors for the occurrence of AD are; aging, head traumas, different

infections, some environmental factors, and vascular diseases **[15]**.

There are two main suggested etiologies for AD. The first one is through β-amyloid protein (Aβ) accumulation outside the brain neurons together with tau protein accumulation inside, which results in pressure build-up on the neurons leading to their death and progression of neurodegeneration all over the brain **[13]**. The second cause is thought to be cholinergic dysfunction and neuroinflammation caused by induced neurotoxicity. Aβ-induced neurotoxicity leads to disruption of calcium ions homeostasis, mitochondrial dysfunction, raised oxidative stress, cholinergic dysfunction, and neuroinflammation **[18]**. Eventually, protein degradation pathways are interrupted, the metabolism of cholesterol and lipid is affected, the immune system loses its function, synaptic transfer of signals is lost and glutamatergic structures are altered **[19]**.

Unfortunately, there is no cure for AD but only medications for symptomatic treatment and the slowdown of dementia progression. Cholinesterase inhibitors and NMDA (N-Methyl D-Aspartate) receptor blockers are the two types of drugs used in symptomatic treatment. Cholinesterase inhibitors prevent the destruction of acetylcholine neurotransmitters which are essential for neuron communication and signal transmission thus they can improve some memory problems and reduce behavioral symptoms. Donepezil, Rivastigmine, and Galantamine are examples of these drugs **[20]**.

NMDA antagonists such as Memantine work by blocking NMDA receptors thus preventing binding of glutamate to them which stops neural excitation and release of calcium as excess calcium leads to damage of neurons **[21, 22]**.

Interestingly, the FDA approved monoclonal antibody, Aducanumab, as the first disease-modifying therapy for AD which has appeared to prevent AD progression in early stages by reducing amyloid protein deposition in the brain **[23, 24]**.

Throughout the last decade, research has concentrated on creating innovative techniques to circumvent some constraints against brain delivery and successfully deliver medications to the Brain. These constraints are the pervasive first-pass metabolism, the blood-brain barrier, decreased half-life, and potential negative consequences in non-target peripheral tissues **[21]**. Nanoparticles can penetrate the BBB to the CNS and can encapsulate pharmaceuticals with sustained drug release profiles. Nevertheless, nanotechnology offers new promise for the treatment of AD as a potent substitute for current drug delivery systems.

2.2. Parkinson's disease

Seven to ten million individuals worldwide are estimated to be affected by PD, the second most common neurodegenerative disease after AD. The prevalence rate for this condition is roughly 41 cases per 100,000 people in the fourth decade (people aged 30-39 years) and rises to approximately 1900 cases per 100,000 people in the 80+ age group **[10, 25]**.

The progressive degeneration of dopaminergic neurons in the substantia nigra and the ensuing shortage of dopamine in the basal ganglia are considered the major hallmarks of PD that can happen as a consequence of genetic mutations and several environmental toxins.

Sequentially, some harmful events take place, such as abnormal aggregation of α-Synuclein (αS) proteins, oxidative stress, mitochondrial dysfunction, and defective anti-apoptotic mechanisms, leading to loss of neurons. The depletion of dopamine brings about the trio of motor symptoms that typically characterize PD: bradykinesia, rigidity, and tremors.

Furthermore, mental health issues such as depression, sleep disturbances, and cognitive impairment can also arise during the early stages of the condition **[26, 27]**.

Levodopa (LD), Monoamine oxidase (MAO) inhibitors, anticholinergics, and dopamine (DA) agonists are some of the medications used to treat PD. These medications work to reduce dopaminergic insufficiency **[25]**. Since DA cannot cross the BBB due to its hydrophobicity or the lack of a particular transporter, LD, the metabolic precursor of DA, has been the preferred option for the earliest stages of treatment. LD-induced dyskinesia has been associated with long-term LD treatment, even though LD is beneficial for managing the motor disruption associated with PD. DA agonists are drugs that can bind to DA receptors and function by simulating DA in the body. All DA agonists have certain undesirable side effects, including valvular heart diseases, somnolence, and repetitive behavior. Anticholinergics act on muscarinic receptors by restoring the balance between acetylcholine and DA. Instead of directly acting on dopaminergic projections, they block neurotransmitters like acetylcholine that aid in regulating movement. Blurred vision, confusion, hallucinations, and drowsiness are some of the major side effects. MAO inhibitors block MAO that breaks down neurotransmitters like DA, thus increasing its concentration and activity. Combining LD with an MAO inhibitor in treatment increases the impact of LD. Selegiline and rasagiline are two examples of selective MAO-B inhibitors that are now available on the market, both of which have been shown to reduce the severity of PD **[25]**.

In summary, most of the current treatments for Parkinson's disease are symptomatic, with the main therapy focusing on replenishing dopamine and/or anti-cholinergic effect. Unfortunately, drugs have a limited capacity to cross the BBB, leading to peripheral side effects, and a lack of neuroprotective effects which only intensify the suffering **[25, 28]**. Over the years, countless attempts have been made to create a treatment therapy for PD that is non-invasive, biodegradable, capable of transporting drugs across the BBB, and delivering them to the site of action, while minimizing side effects. Nanocarriers are particularly beneficial for targeted drug delivery through BBB, providing greater patient compliance together with an increase in the efficacy of the drug, reduced side effects, and improved quality of life for PD patients **[25, 29]**.

2.3. Brain Tumors

Brain tumors can be divided into two major categories: primary brain tumors which originate in the brain, and secondary brain tumors which are formed by cancer cells that have spread from other parts of the body. Glioma is a cancerous growth of the glial cells that envelop nerve endings in the brain. It is the most prevalent primary brain tumor, constituting around 80% of all cases **[30, 31]**. Glioma patients can survive up to 2 years after diagnosis and According to reports, using authorized therapeutic options can increase this period by 20–25 percent **[32]**. The poor prognosis of glioma could be attributed to the shortage of targeted delivery systems that can overcome the BBB and the blood-tumor barrier (BTB) **[30]**.

As the tumor develops, the structure and function of the BBB become impaired to different extents, and new blood vessels, referred to as the Blood Brain Tumor Barrier (BBTB), are gradually formed. The BBTB in low-grade gliomas has a similar structure and activity to the normal BBB. However, in the case of high-grade gliomas, a heightened permeability can be observed on the BBTB **[30]**.

These two barriers, with their unique compositions, prevent drugs and their delivery systems from reaching the affected parts of the brain. In addition, gliomas also have a high metabolic rate, high cell division, and thus, high oxygen usage due to their solid tumor nature. With the continued growth of the tumor, angiogenesis is necessary to fulfill the increasing oxygen demands, and as a result, hypoxia occurs attributable to the unmet needs. These physiological modifications can compromise the integrity of BBB and render the BTB dysfunctional, but these impediments stay undamaged in most cases of glioma, thus posing a formidable challenge for drug delivery to the brain. For any therapeutic approach to be successful in gliomas, passage through both the BBB and the BTB is essential. Unfortunately, the majority of treatment options employed nowadays for gliomas are failing in pre-clinical and clinical trials, largely due to their incapacity to traverse these barriers **[31]**.

Glioma treatment typically involves surgical resection if possible, supplemented by radiotherapy and additional chemotherapy. Temozolomide (TMZ), an oral DNA alkylating drug, is the preferred chemotherapeutic. Notably, TMZ is amongst the few drugs that can pass through the BBB **[33]**.

Chemotherapy is generally considered to be a less invasive treatment in comparison to surgical operations. However, due to various limitations, it only plays an auxiliary role in the care of glioma patients. For example, gliomas, along with peripheral tumors, share some mutual characteristics, including increased interstitial pressure, low pH, reduced oxygen partial pressure, and infiltrative growth, all of which constitute major challenges in providing efficient penetration of drug moieties. Furthermore, the special microenvironments of glioma, such as severely decreased permeability and increased heterogeneity of the BBB and the BBTB make it even harder to reach a therapeutic dose or a homogeneous coverage of all infiltrated glioma **[34]**.

Although TMZ, the most commonly utilized treatment option for glioblastoma, can go across the BBB, its potency is much lower than other common cancer drugs used to treat conditions with limited BBB-crossing ability, such as paclitaxel, doxorubicin, vincristine and vinblastine **[35]**. As a result, higher doses of TMZ are required, which can lead to significant peripheral toxicity.

In this context, brain delivery systems for highly potent chemotherapeutics which can achieve enhanced effectiveness as well as safer pharmacokinetic profiles are in urgent demand **[36]**. Non-invasive nanoparticulate chemotherapeutic agents could be one of the most promising strategies **[34]**.

3. Herbal drugs

The significance of natural products in medicine and healthcare has been profoundly expanding throughout our evolutionary history. From ancient times to the present, natural products have been the secure mode of treating illnesses and injuries. They can get over the disadvantages of conventional treatment options and also prove effectiveness and safety **[37]**. But, with a majority of these natural products yet unexplored, more research is necessary on these compounds, as they play a crucial role in addressing this growing demand. Recently, scientists have shown greater interest in studying the biological effects of natural compounds, uncovering their potential therapeutic effects on the human body. In contrast to existing chemical therapeutics, plant products and their components offer remedies that have fewer side effects, while exhibiting a synergistic action through combinations of compounds **[38]**. As a result,

numerous natural substances have been researched to help comprehend their superior efficiency in improving many neurological disorders **[39]**.

However, the clinical applicability of most of these natural compounds is extremely limited because of their weak stability and low water solubility, rapid metabolism, minor permeability, and low bioavailability **[14]**. Hence, creating new drug delivery techniques, like using lipid nanocarriers, would probably be a potential answer to these issues.

3.1. Ferulic Acid (FA)

Polyphenols have shown prominent protective and modulatory effects in neurodegenerative diseases. The plant *Ferula foetida* extract contains one of the most promising bioactive polyphenols known as FA which is also found in many vegetables and fruits **[40]**. Being a potent multifunctional phenolic nutraceutical, FA shows multiple valuable applications in the biomedical field. FA is considered to be a good candidate for managing several cancers due to its strong antioxidant, reactive oxygen species (ROS) scavenging, protein inactivation, and strengthening of innate system properties **[41]**. It can reduce the Aβ fibrils formation, consequently, it may affect AD **[13]**. Besides, FA is also used for the treatment of heart-related, skin, and ischemic diseases **[42]**. Moreover, FA also shows peculiar hepatoprotective effects owing to its ability to decrease circulating levels of both triglycerides and cholesterol **[43]**.

Despite FA being a promising agent with multiple medical applications, FA suffers from poor membrane permeability and low aqueous solubility limiting its beneficial therapeutic application **[44]**.

Moreover, extensive first-pass metabolism of FA has led to the need for multiple dosing which resulted in both cost and patient compliance problems. In addition to the previous problems, FA has shown poor pharmacokinetic properties following oral administration, FA is either rapidly excreted through the kidney or converted into inactive conjugates by the liver while following intravenous administration, it shows rapid clearance and sub-therapeutic plasma levels. Despite the advantages of FA in passing the BBB, its application in neurodegenerative diseases is limited owing to its low reported concentration in the brain **[43]**.

Hence, it was postulated that incorporating FA in nano-targeted delivery systems would enhance its plasma levels, brain distribution, and overall pharmacokinetic properties. Encapsulating FA in versatile nano-delivery systems would improve its gastrointestinal delivery thus its stability in the body fluids either pre or post-absorption **[43]**. Several research articles have incorporated FA in various nano-delivery systems to overcome most of the innate drug problems and make it a good candidate for the treatment and protection of neurodegenerative diseases **[44, 45]**.

3.2. Resveratrol (RSV)

RSV is a phytochemical drug, classified as a non-flavonoid polyphenolic compound found in many natural sources such as roots, vegetables, seeds, fruits (i.e., peanuts and grapes), flowers and tea (i.e., black tea, green tea) **[46-49]**. It has multiple pharmacological actions such as antioxidant, antiaging, anticancer, and anti-inflammatory effects because of its ability to act on several molecular pathways. Its activity in AD treatment has been reported due to its crucial antioxidant effect which was proved by several studies **[47, 48, 50]**.

RSV exerts its antioxidant effect by acting as an iron chelator and ROS scavenger, also it has several mechanisms that can attenuate the

progression of AD through the reduction of Aβ production which decreases the amyloid toxicity and it can also interfere with the amyloid cascade through its anti-inflammatory effect **[48]**.

According to the Biopharmaceutical System (BCS), RSV is classified as class II which is characterized by low solubility and high permeability. This low water solubility is responsible for its minimal absorption therefore poor bioavailability. In addition, RSV is subjected to extensive systemic metabolism and photochemical decomposition **[51]**. As mentioned before, the application of nanotechnology would be of great interest in overcoming these limitations due to its huge benefits in enhancing bioavailability, targeting the drug to its site of action, improving its pharmacological actions, and reducing the adverse effects. Several studies have reported the encapsulation of RSV in different nanoparticulate systems, such as; SLNs, NLCs, NEs, and LNCs, that in turn resulted in an improvement in its *in-vivo* antioxidant and anti-inflammatory effects in neurological diseases **[52–56]**. Moreover, the usage of targeting moieties and surface modification of these nanosystems aid in BBB crossing and reaching the site of action **[46]**.

3.3. Curcumin

Curcumin is a natural lipid-soluble polyphenolic compound that was first extracted from *Curcuma longL*. Plant **[57]**. Curcumin was found to exhibit many therapeutic activities such as strong antioxidant, anti-inflammatory and anticancer actions **[58]**. Recent studies suggest that curcumin possesses therapeutic action against brain tumors by inhibiting their proliferation and inducing tumor apoptosis **[1]**. Curcumin also hinders brain disease progression and inhibits neurodegeneration in various conditions such as epilepsy, multiple sclerosis, glioblastoma, and PD **[39]**.

In the case of brain injury, curcumin was found to show neuroprotective activities where it increased the viability of cortal neurons which was reduced after the neuron's exposure to oxygen-glucose deprivation/reoxygenation cycle to mimic an ischemic injury *in-vitro*. Furthermore, curcumin was found to reduce the occurrence of thrombosis limiting cerebral ischemia **[38]**.

In addition, curcumin was found to be effective in the treatment of AD due to its ability to prevent the aggregation of Amyloid-β protein and the inflammation caused by the Amyloid-β protein, reduce the oxidative stress, improve the Amyloid-β uptake by macrophages as well as its ability to inhibit the action of Acetylcholinesterase enzyme with comparable effectiveness to the prescribed acetylcholinesterase inhibitors used as first-line management of AD **[59, 60]**. Research has also shown that nano-curcumin could dramatically reduce oxidative stress and apoptosis in the brains of individuals with PD **[61]**.

However, these promising therapeutic properties were hindered by the challenging process of crossing the BBB, the poor oral bioavailability of curcumin caused by its low water solubility as well as its accelerated metabolism and elimination caused by the presence of hydroxyl group in its structure thus impeding the curcumin’s ability to reach the brain **[58–60, 62]**. Fortunately, these drawbacks could be overcome by the nanoencapsulation of curcumin which lead to improved bioavailability and thus enhanced therapeutic properties **[58]**.

In recent years, novel curcumin- loaded nanoparticulate systems like polymeric nanoparticles, lipid-based nanoparticles, and liposomes started to become the object of interest since their properties could be designed and tuned to the desired values to improve the curcumin’s ability in treating many diseases like

tumors and neurodegenerative conditions. Such properties include particle size, surface charge, and functionality **[61, 63]**.

3.4. Rosmarinic acid (RA)

RA is a hydroxycinnamic acid, which can be isolated from *Rosmarinus officinalis* leaves, and found in many other plant species **[64]**. In terms of biological effects, RA has a wide range of uses such as; anti-aging, antiallergic, anticancer, antidepressant, antidiabetic, antimicrobial, and anti-inflammatory effects. Moreover, being an antioxidant, RA has protective effects on the heart, liver, and kidneys and most importantly, it has neuroprotective properties **[65, 66]**. Focusing on the later property, RA protects the neurons against any disease condition induced by oxidative stress. This occurs by attenuation of ROS generation and stimulation of apoptotic cell death **[64, 65]**.

Despite the numerous pros of RA, it is an unstable molecule and can be considered a class IV drug according to the BCS. It is characterized by low water solubility and permeability through any biological membrane including BBB leading to poor CNS bioavailability **[66]**. Therefore, some strategies were implemented to get over these limitations.

4. Blood Brain Barrier

The brain makes up just 2% of the body's weight, yet it consumes around 20% of the heart's blood supply, as well as 25% of the total oxygen and glucose needed **[31]**. The brain operates in an orderly yet dynamic setting and is disengaged from the peripheral circulation by three safeguards: the BBB, the blood–cerebrospinal fluid barrier, and the ependymal barrier. These impediments protect against the infiltration of toxins, at the same time, they permit entry of vital nutrients and neurotransmitters **[34]**.

The BBB is a complex structure that serves to shield the CNS from possibly dangerous bloodstream molecules. Concomitantly, it provides the CNS with the necessary nutrients and energy to ensure its typical performance **[5, 7]**. The BBB is comprised of endothelial cells, the basement membrane, pericytes, and astrocytes, which, in combination with the basal lamina, capillary neurons, and microglia, form a functional neurovascular unit **[67]**. Unlike peripheral vessels, the BBB's endothelial cells are joined by tight junctions (TJs), forming a compact, selective structure in which essential nutrients and oxygen can pass through yet it blocks large molecules and all hydrophilic molecules with a low log P value **[12]**.

Diffusion restriction is caused by different factors including structural characteristics of TJs and cell membranes, low levels of transcellular transport, ABC transporters (such as the well-known P-glycoprotein (P-gp)) which are efflux pumps that return endogenous and exogenous substances to the bloodstream, and drug-metabolizing enzymes across interfaces and intracellularly. These factors serve as the major hurdles to restricting drug entrance across the BBB, inhibiting their access to the CNS, and are the causes of the widely recognized impediment function **[5, 7]**.

The BBB serves as an actual physical shield that manages the transit of specific substances. Due to the noteworthy lipophilic surface area of the endothelial monolayer, the principal way that substances enter the CNS is through passive diffusion. This transport pathway is utilized by small lipophilic and gaseous molecules that permeate through the endothelial cells. On the other hand, small-sized hydrophilic molecules can go across the TJs between the endothelial cells through paracellular transport **[5]**. The BBB has a highly specialized capillary endothelial plasma membrane that facilitates the selective transport of nutrients or drugs. This process involves active efflux systems, active

transporters, and ectoenzymes **[68]**. Despite the availability of numerous drugs for treating neurological disorders, the BBB's specialized microvasculature allows only a few medicines to be transported following systemic administration, leading to insufficient efficacy **[3]**.

5. Strategies to overcome BBB, for brain delivery

As stated earlier, many medications either have very poor delivery efficacy or are unable to penetrate the BBB. Thus, more effective drug delivery methods to the brain have been proposed. These techniques can be divided into two groups; invasive and non-invasive techniques.

5.1. Invasive techniques:

A conventional solution to overcome the BBB involves direct delivery of drugs into the brain parenchyma or ventricles, utilizing intracerebral or intraventricular administration, respectively. Direct intracerebral therapies entail a bolus injection or infusion into the parenchymal region of the brain, whereas another approach involves using intracerebral implants that release the drug in a controlled pattern through a biodegradable polymer that incorporates the drug, leading to a prolonged neurotherapeutic release at the targeted site. These methods are especially beneficial in cases of brain tumors. However, although these delivery modes have been utilized traditionally, they are highly invasive and carry a significant risk of infection and neuropathological changes due to disruption of the BBB. Therefore, it is crucial to develop new non-invasive delivery strategies that minimize these risks **[7, 69, 70]**.

5.2. Disruption of BBB

By breaking down the TJs between endothelial cells in the brain capillaries, BBB disruption can make it simpler for medications to enter the brain **[1]**. Administration of osmotic solutions (such as mannitol hyperosmolar solution), usage of vasoactive chemicals (such as bradykinin), and application of physical stimuli, like ultrasounds, are examples of BBB disruption **[7]**. Even though this method can boost drug delivery to the brain, it has many drawbacks including neuronal damage and toxicity **[26]**.

5.3. Inhibition of efflux proteins

P-gp and other ATP-driven drug efflux pumps, such as multi-drug resistance proteins, are expressed by the brain endothelial cells and are in charge of moving drugs from the brain to the circulation. As a result, they act as one of the obstacles to brain targeting. While P-gp is in charge of the efflux of lipophilic substances, several multidrug-resistant proteins may also efflux out cationic, amphiphilic, and neutral molecules. Inhibiting these efflux pumps can therefore be a crucial strategy for brain targeting **[71]**. Reduced P-gp activity at the blood-brain barrier can make the brain more vulnerable to toxic substances, which can have a damaging impact on neurological function. Indeed, studies have shown links between aging and a decrease in P-gp expression or activity at the blood-brain barrier **[72]**.

5.4. Intranasal delivery as a strategy to overcome BBB

Numerous studies have demonstrated the effectiveness of intranasal delivery of both small and large molecules in directly targeting the brain. This is possible because the olfactory mucosa, an area not protected by the BBB, has direct contact with the brain **[73]**. The transportation of drugs through the intranasal route has been extensively researched as a potential treatment for CNS diseases. While the pathways for nose-to-brain delivery are not yet fully understood, recent studies suggested several major possibilities. One mechanism involves

direct drug transport to the brain through neuronal pathways, such as olfactory or trigeminal nerves **[74]**. Another proposed mechanism is indirect drug transport via the vasculature and lymphatic system, allowing for crossing the BBB **[73, 75]**.

The nose-to-brain delivery holds numerous benefits such as bypassing the BBB, enabling effective penetration of drugs, especially those of low molecular weight and lipophilic nature, and reducing systemic side effects. Moreover, this non-invasive, needle-free approach enhances patient compliance **[1, 76]**. Nonetheless, nose-to-brain delivery faces some challenges such as enhancing absorption across the nasal epithelium, optimizing mucus penetration, and mucociliary clearance, and overcoming local irritation and toxicity issues arising from long-term usage **[69, 73]**.

Therefore, the synthesis of more lipophilic analogs, the addition of permeation enhancers, and the formation of colloidal and bio-adhesive novel drug delivery systems such as lipid-based nanocarriers could aid in overcoming these challenges **[77].**

High surface area (150 cm^2), high permeability and vascularization, and low enzyme levels besides bypassing intestinal and hepatic metabolism in addition to the BBB, make the intranasal route a perfect option for brain delivery **[75]**. To give an illustration, Pangeni et al. formulated Resveratrol (RSV)-loaded Vitamin E NEs for brain delivery via the intranasal route. The oil phase was composed of vitamin E and propylene glycol mono caprylic ester (SefsolR) using tween 80 as the surfactant and transistor P as the co-surfactant. Treatment with the formulated NE could achieve high drug concentration and low degenerative changes in the brain of animals. In comparison to both RSV solutions administered through intravenous and intranasal routes, it was discovered that the concentration of RSV in the brain for RSV NE, taken intranasally, was significantly higher at all of the time points. When the latter was administered, RSV's highest concentration in the brain (3976.25 ± 118.62 ng mL^{-1}; Tmax 1.5 h) was much greater in comparison to RSV solution taken intravenously (1710.85 ± 64.92 ng mL^{-1}; Tmax 1.5 h) and RSV solution taken intranasally (2792.76 ± 137.21 ng mL^{-1}; Tmax 1.5 h). That, in turn, proves the potential of RSV NEs in nose-to-brain delivery of RSV. Considerably higher levels of glutathione and superoxide dismutase, and a decreased level of malonaldehyde, were found in the rats that received the formulated RSV NE intranasally when compared to haloperidol-induced rats and to the group that received resveratrol solution and haloperidol intravenously **[56]**.

Also, Omega-3 NEs loaded with curcumin and quercetin, are considered another promising phytochemical that can improve several brain diseases **[78]**, were prepared by Vaz et al. **[58]**. In this study, a high-pressure homogenization method was used for the preparation of NEs which resulted in NE that exhibited sustained release of the drugs formulae with remarkable characteristics for treating brain diseases due to their ability to confer nose-to-brain permeation of curcumin and quercetin, thus boosting treatment effectiveness.

Moreover, curcumin-loaded NEs were formulated by Vaz et al. in another study using hot solvent diffusion associated with phase inversion. The permeation of the prepared NEs across the porcine nasal mucosa was relatively high in comparison to free curcumin **[60]**. Fachel et al. explored the neuroprotective effect of RA chitosan-coated NEs administered intranasally on lipopolysaccharide (LPS)-induced memory deficit, neuroinflammation, and oxidative stress in Wistar rats. Results revealed that the RA chitosan-coated NEs nasal administration evoked

a protective effect on the neurons against LPS-induced damage, correlated with a recognition index that is 1.6 times higher. Moreover, RA chitosan-coated NEs treatment enhanced the brain bioavailability of RA, confirmed by quantitative analysis. Although no RA was quantified in the brain when free RA was used, a protective impact was found on some examined parameters **[79]**. The same research group used the aforementioned formulae to assess the protective and/or therapeutic benefits of RA chitosan-coated NEs in combating inflammation and oxidative stress caused by LPS in rat astrocyte primary cultures. In conclusion, prophylactic pre-treatment with RA chitosan-coated NEs before exposure to LPS, as a protective protocol, markedly decreased the LPS-induced damage to astrocyte cell viability, proliferation, and cell death by necrosis, which was not observed with the therapeutic protocol. RA chitosan-coated NEs prophylactic protocol also improved the anti-oxidative status by around 50%, minimizing oxygen reactive species production and nitric oxide levels. Accordingly, this study revealed the bioprotective potential of RA chitosan-coated NEs for the first time, associated with increased cell viability and proliferation, and prevention of death by necrosis **[77]**.

5.5. Lipid-based nanocarriers in brain diseases.

As previously noted, traditional methods for delivering drugs to the brain are invasive and costly, while also threatening patient comfort, sterility, and safety. As a result, their widespread use remains challenging. However, the emergence of nanotechnology-based delivery systems offers new opportunities to overcome these limitations and target drugs more effectively to the CNS **[7]**.

In general, colloidal drug carriers, including micelles, NEs, liposomes, and nanoparticles (nanospheres and nanocapsules), aim to increase the specificity toward cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes, and/or to protect them against enzymatic inactivation **[80]**. Numerous studies have demonstrated the importance and usefulness of drug-loaded nanosystems in treating neurological disorders **[6, 7, 81]**.

Lipid nanocarriers, in particular, offer several advantages over other nanocarriers, making them highly attractive for brain delivery. These nano-drug delivery systems elicit enhanced oral bioavailability, extended bloodstream half-life, and reduced side effects by modifying intrinsic drug properties such as solubility, bioavailability, diffusivity, drug release profiles, and immunogenicity **[26]**. These colloidal systems also have higher biocompatibility, biodegradability, and less cytotoxicity as benefits. The usage of physiological lipids and GRAS (generally regarded as safe) excipients is to account for this **[82]**. Additionally, they can incorporate both lipophilic and hydrophilic medications designed to be delivered to the brain, which can be given through several methods. These systems also allow access across the BBB, given their lipophilic nature and small size, as they can mask the physicochemical characteristics of nontransportable drugs and overcome their low permeability through their encapsulation **[7]**.

With the ability to evade phagocytosis by the reticuloendothelial system (RES) and naturally cross the brain capillary endothelial cells, lipid nanocarriers have become a major focus in CNS nanomedicine research. By modifying and coating their surfaces, these carriers may be designed to interact with particular BBB molecules or cell receptors, which improves their potential for brain targeting while increasing the bioavailability and concentration of some

medications that cannot typically cross the BBB. With these advances, the future of CNS drug delivery is promising **[7, 25, 29, 81]**.

Various lipid nano-carriers encapsulating herbal drugs are available depending on the lipid types, their physical state, composition, and formulation procedure **[6, 14, 67]**. Some of the conducted studies are shown in **Table 1**.

Table 1. Different lipid nanocarriers encapsulating drugs of natural origin to treat brain diseases

Drug	Disease	Nano-carrier	Route	Characteristic components	Remarks	References
FA°	Ischemic stroke	NLCs*	IV**	Cetyl palmitate Oleic acid poloxamer 188 Tween 80	marked reduction in I/R***-induced neurobehavioral issues lower cellular damage, and oxidative stress, while, free FA failed.	**[91]**
FA	AD•	SLNs••		compritol 888 ATO	Higher depletion in ROS••• production in comparison to the effect of drug alone.	**[86]**
FA	AD	Chitosan coated SLNs		Compritol polysorbate 80 Chitosan	Enhanced mucoadhesion, membrane permeability, and extended drug release along with improved pharmacological effect.	**[44]**
FA		SLNs		compritol-88	lower ROS formation and repaired mitochondrial membrane potential in neuroblastoma cell lines	**[45]**
FA	glioblastoma	NLCs		Oleth-20	Higher efficiency of FA-loaded NLCs relative to the free drug	**[92]**
RSV+++	AD	LNCs+	IP++	capric/caprylic triglyceride sorbitan monostearate	Higher concentration of encapsulated RSV in the brain, liver, and kidney tissues relative to free RSV. The harmful effects caused by Amyloid β were decreased by RSV-LNCs compared to free RSV	**[52, 53]**
RSV	AD	SLNs		Cetyl palmitate Polysorbate 80 DSPE-PEG LissRhod-PE	Prevention of Amyloid β fibrillation, better BBB▼ transport for the OX26-modified SLNs than for SLNs functionalized with LB 509 and four times higher relative to unfunctionalized SLNs	**[54]**
RSV	Brain targeting	SLNs		Apolipoprotein E	Achieved 1.8 higher penetration than free RSV.	**[87]**
RSV	glioma	SLNs		Compritol 888 ATO®	higher accumulation of RSV in rats' brains.	**[55]**
RSV	PD▼▼	NEs▼▼▼	IN♣	PVA or Tween 80 Vitamin E, Sefsol, Tween 80, Transcutol P	Degenerative changes decreased	**[56]**
RSV	PD	NLCs	IN	Cetyl palmitate, capmul mono-diglyceride of medium chain fatty acids, Acrysol K150, Poloxamer 188, Tween 80	Five-fold increase in the permeation across nasal mucosa compared to RSV suspension-based in situ gel.	**[93]**
Curcumin and Quercetin	Neuro-degenerative diseases	NEs	IN	Omega-3 fatty acids	Enhanced stability, no toxicity, and sustained release of curcumin *in-vitro*. The addition of fatty acids has improved the bioavailability of curcumin through increase its permeation from the nose to the brain.	**[58]**
Curcumin	AD	NLCs	IN		Higher drug entrapment, higher cell permeation, prolonged release, and better stability	**[94]**
Curcumin	Brain targeting	SLNs And		Transferrin for functionalization	Targeted brain drug delivery, higher encapsulation, and improved stability	**[62]**

Drug	Disease	Nano-carrier	Route	Characteristic components	Remarks	References
		NLCs				
Curcumin	AD	NLCs		Cetyl palmitate, oleic acid, and cholesterol	Optimized drug loading, enhanced brain uptake, and effective drug delivery.	**[95]**
Curcumin	AD	NEs	IN		Permeation improvement through the porcine nasal mucosa. No toxicity compared to free curcumin	**[60]**
Curcumin	AD	NLC	IV	LDL-mimic lactoferrin	Targeted brain drug delivery, sustained release, significant cell uptake, and enhanced therapeutic activity	**[96]**
Curcumin	Cerebral ischemia	SLNs	Oral	Soy Lecithin Tween 80 Compritol 888 ATO®	Better delivery and accumulation of curcumin in the brain compared with pure curcumin Better acetylcholine esterase activity compared to pure curcumin	**[88]**
Curcumin	Brain cancer	MEs$^{\clubsuit\clubsuit}$	IV and IN	Docosahexaenoic acid (DHA) rich oil	Higher brain concentrations of curcumin upon administration of DHA MEs than MEs without DHA and curcumin solution, when taken intranasally relative to the IV route.	**[103]**
RA$^{\circ\circ}$	Memory deficit	Chitosan coated NEs	IN	Egg- lecithin medium chain triglycerides (MCT) Low molecular weight chitosan	Higher neuroprotective effect against LPS-induced damage. Enhanced brain bioavailability of RA.	**[79]**
RA	glioma	Chitosan coated NEs	IN	Egg- lecithin medium chain triglycerides (MCT) Low molecular weight chitosan	Decreased LPS$^{\blacksquare}$-induced damage. Better oxidative status by 50%. Lower ROS and Nitrogen oxide levels.	**[77]**
RA	HD$^{\blacksquare\blacksquare}$	SLNs	IN	Glycerol monostearate tween 80 soya lecithin HSPC	A remarkable therapeutic action in comparison to the intravenous treatment	**[89]**

NLCs *	**Nanostructured lipid carriers**	**IP** $^{++}$	**Intraperitoneal**
IV **	Intravenous	**RSV** $^{+++}$	Resveratrol
I/R ***	Ischemia/reperfusion	**BBB** $^{\blacktriangledown}$	Blood-Brain Barrier
AD $^{\cdot}$	Alzheimer's disease	**PD**$^{\blacktriangledown\blacktriangledown}$	Parkinson's disease
SLNs $^{\cdot\cdot}$	Solid lipid nanoparticles	**NEs** $^{\blacktriangledown\blacktriangledown\blacktriangledown}$	Nanoemulsions
ROS $^{\cdot\cdot\cdot}$	Reactive oxygen species	**LPS** $^{\blacksquare}$	Lipopolysaccharide
LNCs $^{+}$	Lipid nanocapsules	**HD** $^{\blacksquare\blacksquare}$	Huntigon's disease
FA$^{\circ}$	Ferulic acid	**RA**$^{\circ\circ}$	Rosmarinic acid
IN$^{\clubsuit}$	Intranasal	**MEs**$^{\clubsuit\clubsuit}$	Microemulsions

5.5.1. Solid lipid nanoparticles (SLNs)

Since the early 1990s, SLNs have been established as a promising alternative to typical colloidal drug carriers such as microparticles, liposomes, MEs, and NEs **[83]**. Instead of relying on liquid lipids in emulsion systems, SLNs utilize solid lipids like triglycerides, fatty acids, or waxes to create a lipophilic core for the dissolution or dispersion of hydrophobic drugs. Hydrophilic molecules can be added at the surface of the NPs, which are stabilized by emulsifiers or stabilizing agents. With their nanometric size of around 40-200 nm, they can easily cross the BBB and escape from the RES.

SLNs are also highly reproducible, inexpensive, and do not require organic solvents for their synthesis. Furthermore, they can maintain stability for up to 3 years and facilitate controlled drug release for several weeks. As such, they are regarded as first-generation novel lipid drug carriers **[3, 26, 81, 84]**. As a result, SLNs hold great promise in surmounting the BBB and boosting drug concentration in the brain, thereby treating central CNS disorders **[85]**.

However, it is important to acknowledge that SLNs have their limitations, including less-than-optimal drug loading efficiency (especially for hydrophilic molecules) due to their rigid shape, and undesirable particle growth caused by the agglomeration or polymorphism of lipids, which can result in burst drug release **[26, 73]**.

FA is known to have a significant effect on AD patients which led to the development of several FA-loaded nano-delivery systems for alleviating disease-related symptoms. One study used compritol 888 ATO as the lipid phase to form SLNs by a microemulsion method and the formulae showed high stability, loading efficiency, optimum particle size, and exceptional reduction in ROS production in comparison to the effect of the drug alone. Elevated protection against human neuroblastoma cells was observed in FA incorporated SLNs group as compared to both empty SLNs and free drugs **[86]**.

Additional characteristics were obtained by coating FA-encapsulated SLNs with chitosan such as enhanced mucoadhesion, enhanced membrane permeability, and extended drug release along with improved pharmacological effect **[44]**.

Picone et al. utilized SLNs made up of comparison-88 to deliver the natural Aβ inhibitor, FA. This was done to prevent neurodegeneration induced by recombinant Aβ. It was observed that the FA-loaded SLNs could lessen ROS formation, decrease the level of cytochrome c and also restore the mitochondrial membrane potential in neuroblastoma cell lines **[45]**.

Active targeting is an attractive modality to enhance brain delivery via interaction with receptors on the BBB **[87]**. Loureiro et al. prepared RSV-SLNs that showed improvement in the anti-aggregation effect of RSV, thus preventing Aβ fibrillation. To direct the SLNs to the brain, they modified the surface of SLNs using OX26monoclonal antibody molecules (mAb), that bind to the transferrin receptors overexpressed in BBB, and compared that to brain targeting using LB 509 mAb, an antibody, that recognizes a non-specific protein to the BBB called α-synuclein.

Brain delivery of SLNs with OX26 surface modification was twofold higher than LB 509-SLNs, and four times higher than unfunctionalized SLNs **[54]**. Another study was carried out by Neves et al. who formulated RSV-SLNs functionalized with apolipoprotein E that can bind to the LDL receptors overexpressed on the BBB. The prepared SLNs showed high safety in the *in-vitro* cytotoxicity study. The permeability of the cell monolayers of hCMEC/D3 was studied using free RSV and the functionalized SLNs. The results showed that the functionalized SLNs had 1.8 times higher penetration than nonfunctionalized ones. This enhanced permeation may be attributed to the receptor-mediated endocytosis mechanism, which is a feature of the BBB. Thus, the use of functionalized SLNs has the potential to increase the permeability of the BBB **[87]**.

Additionally, numerous studies conducted both *in-vivo* and *in-vitro* experiments verified that RSV was capable of controlling every stage of carcinogenesis, including initiation, promotion, and progression **[38]**. One study group loaded RSV in SLNs prepared via solvent evaporation, high-speed homogenization, and

ultrasonic techniques **[55]**. They were composed of comparison 888 ATO® as the lipid excipient, generating particles with a particle size of about 250 nm with a negative charge and low entrapment efficiency (only about 35% of the used RSV) for the treatment of glioma. They could bypass the BBB and achieved higher drug concentration in the brain tissues of rats compared to the free resveratrol-treated group.

Neves et al. encapsulated curcumin in SLNs and NLCs functionalized with transferrin **[62]**. The results showed a 1.5-fold higher permeation of curcumin through hCMEC/D3 cell monolayers. Consequently, the incorporation of curcumin in SLNs and NLCs, along with the addition of transferrin to the surface of the nanoparticles, showed promising potential for curcumin brain delivery. Not only did this enhance the protection of the curcumin, but it also increased its brain-targeting efficiency due to transferrin affinity to receptors on BBB. Moreover, Kakkar et al. evaluated the effectiveness of curcumin-loaded SLNs in a rat model of cerebral ischemia (BCCAO) **[88]**. Considerable improvements: up to 90% better cognition, higher inhibition of acetylcholinesterase, and greater improvement in neurological scores were noticed. Gamma-scintigraphic studies revealed 16.4 and 30 times greater brain bioavailability when Curcumin-loaded SLNs were administered orally or intravenously, respectively, versus solubilized curcumin.

Bhatt et al determined the potential benefit of the intranasal administration of SLNs as a therapeutic delivery technology to improve the effectiveness of RA brain targeting. The hot homogenization method was used to formulate RA-loaded SLNs, in which glycerol monostearate (GMS) as lipid, tween 80, and soya lecithin was used as surfactant along with hydrogenated soya phosphatidyl choline (HSPC) as a stabilizer. Results showed that nasal delivery of optimized formulae produced a remarkable therapeutic action in comparison to the intravenous treatment. In conclusion, the optimized RA-loaded SLNs formulation following the non-invasive nose-to-brain drug delivery was proved to be a potential strategy for managing Huntington's disease effectively, one of the neurodegenerative brain diseases **[89]**.

5.5.2. Nanostructured lipid carriers (NLCs)

NLCs are modified and hybridized forms of SLNs, composed of a combination of both solid lipids (fatty substances) and liquid lipids (oils) at normal room temperature **[67]**. The most commonly used liquid lipids in the formulation of NLCs are oleic acid and caprylic/capric triglycerides **[90]**. Developed by Muller et al. in the 1990s, NLCs were created to get over the drawbacks of SLNs and other lipid-based nanocarriers. NLCs contain a partially crystallized lipid droplet or oil incorporated into an amorphous solid lipid core, with the drug already incorporated in the oily core **[67]**. When solid lipids are combined with liquid lipids, they create nanoparticles that have better drug loading and desirable release profiles. Consequently, utilizing liquid lipids can affect the entrapment efficiency, as a result of the many crystal defects found in solid lipids, causing imperfections in the matrix that provide sufficient space for the successful accommodation of a large number of drug molecules **[81]**.

Using NLCs as a drug delivery system helps to control drug release, achieve better stability of drugs, and incorporate both lipophilic and hydrophilic molecules without using organic solvents. NLCs display an initial burst release followed by sustained release. This biphasic drug release profile happens because the liquid lipid found in the outer NPs' layers forms a drug-enriched region that can cause the burst release. Drug molecules are preserved by NLCs in the

solid matrix and are shielded from deterioration **[67, 81]**. Therefore, NLCs are considered second-generation SLNs or smarter Nano-lipid carrier systems **[67]**.

Several techniques have been employed for the preparation of NLCs such as micro emulsification, solvent displacement, ultrasonication, double emulsion, microwave-assisted, and others. However, the most commonly used process is high-pressure homogenization as it is scalable for industrial applications and does not necessitate the use of toxic organic solvents, which would demand additional steps for washing and particle purification **[90]**.

Despite its advantages, NLCs have some drawbacks as well. For instance, the encapsulation efficiency may decrease when combining two or more therapeutic agents, and the drug loading capacity for hydrophilic drugs is relatively low **[73]**.

Hassanzadeh et al. encapsulated FA into NLCs using a high-pressure homogenization technique to enhance its efficacy against ischemic stroke which was observed by the significant reduction in I injury (I/R)-induced neurobehavioral issues **[91]**. FA-loaded NLCs were prepared by homogenization method using different amounts of FA. In another study, U87MG cells of human glioblastoma were used to test the improved bioavailability of FA-loaded NLCs **[92]**. NLCs were prepared by solvent-free inversion method. The selected formula showed better characteristics when compared to other lipidic delivery systems like NEs and SLNs. When the pharmacological effect was compared, FA-encapsulated NLCs showed significantly higher activation strength to apoptotic signaling pathway to idebenone (IDE) and IDE-encapsulated NLCs.

Additionally, the intranasal route was exploited to deliver RSV-loaded NLC *in situ* gel for the treatment of AD, resulting in a five-fold increase in the permeation, compared with RSV suspension. It was prepared *via* melt-emulsification probe sonication method using equal percentages of cetyl palmitate as solid lipid and capmul mono-diglyceride of medium chain fatty acids (MCM) as oil, Acrysol K150 as a solubilizer and Poloxamer 188 and Tween 80 as the surfactants. Improvement of memory function was observed in amnesia-induced rats, ensuring effective brain delivery **[93]**.

Agrawal et al. formulated curcumin in NLCs using the modified melt emulsification method followed by ultrasonication **[94]**. The prepared optimized formula showed a size of 124.37 nm, which could be suitable for high permeation when taken intranasally and therefore for brain delivery. The results showed high entrapment efficiency, a high drug release profile with an initial burst, and subsequent sustained release in comparison to drug solution.

Another research team aimed to enhance the efficacy of curcumin in treating AB-induced cognitive impairment in an animal model of AD, accomplished by loading it into NLCs. The results showed an increased accumulation rate of curcumin in the brain. Oxidative stress parameters including ROS formation, lipid peroxidation, and ADP/ATP ratio were lowered in the hippocampal tissue, leading to an improvement in spatial memory. Histopathological studies also suggested that curcumin–NLCs may have the potential to reduce the signs of AD in animal models **[95]**.

Similarly, Low-density lipoprotein (LDL) mimicking-NLCs, incorporating Curcumin, modified with lactoferrin were prepared for brain-targeted treatment of AD. A higher uptake in the brain capillary endothelial cells (1.39 folds greater than NLCs) and stability of the formulation while crossing the BBB was

observed. *Ex-vivo* imaging and histopathological evaluation showed that the prepared nanoparticles can permeate the BBB and accumulate in the brain (2.78 times greater than NLCs) and improve the damage caused by AD **[96]**.

5.5.3. Microemulsions (MEs) and Nanoemulsions (NEs)

MEs are thermodynamically stable and optically clear colloidal systems made up of water, oil, and amphiphiles **[97]**. It is important to note that the interfacial tension in MEs is exceptionally low, and to achieve values close to zero, co-surfactants, low molecular weight compounds that have a good affinity for both phases, are often used to enhance the effects of the surfactants **[98, 99]**. One key difference between emulsions and MEs lies in their thermodynamic stability; while emulsions may have excellent kinetic stability, they are ultimately unstable and will eventually separate **[100]**. Additionally, emulsions appear cloudy, while MEs are clear or translucent. Furthermore, their methods of preparation are distinct, with emulsions requiring a high input of energy while MEs do not **[101]**.

Three distinct systems and arrangements of MEs are formed based on the composition and proportion of oil, water, surfactant, and hydrophilic-lipophilic balance (HLB) of the surfactant. The presence of o/w MEs droplets is common in MEs where the volume fraction of oil is low while w/o droplets are common when the volume fraction of water is low. Meanwhile, when amounts of oil and water are similar, a bicontinuous ME may form and result in systems where both oil and water exist as a continuous phase, with a continuously fluctuating surfactant-stabilized interface and zero net curvature **[99, 101]**. MEs typically have droplet sizes of less than 200 nm. Moreover, oil-in-water MEs are a preferable option for incorporating poorly water-soluble drugs. Additionally, the solution-like feature of ME provides advantages such as the ability to be sprayed and dose uniformity. Thus, MEs are becoming a promising field for systemic and intranasal drug delivery, especially for targeting the CNS **[102]**.

Shinde et al. formulated curcumin MEs with docosahexaenoic acid (DHA)-rich oil for targeted brain delivery and treatment of brain cancer. The results showed a small globule size (<20 nm) with good stability. Upon intravenous administration, brain concentrations of curcumin were higher after administration of curcumin DHA-MEs in comparison to curcumin MEs without DHA and curcumin solution. However, when the intranasal route was used, brain concentrations were noticeably greater than intravenous delivery, especially with DHA-MEs compared to curcumin MEs without DHA and curcumin solution. Due to the effective targeting made possible by DHA-mediated transport across the BBB, curcumin DHA MEs showed these high brain concentrations **[103]**.

The term "microemulsion" can be considered misleading as it implies the presence of micrometer-sized particles. In reality, MEs are nanodispersions, as research has shown. Despite being thermodynamically different from NEs, MEs share several similarities, such as being composed of polar and non-polar phases, stabilized by one or more surfactants. NEs may be transparent or translucent and are kinetically stable. However, they occupy a metastable state and can potentially become destabilized over time. Despite this risk, physical factors such as steric and electrostatic repulsion, as well as Brownian motion, usually help to extend the destabilization time **[70]**.

Studies have shown that lipid-based carriers, such as MEs and NEs, are capable of crossing the BBB at a faster rate than polymeric particles. This suggests that utilizing lipidic carriers as

delivery vehicles for drugs may be a more efficient option **[99]**. Examples of herbal drugs loaded in MEs and NEs are outlined in **Table 1**.

5.5.4. Lipid Nanocapsules (LNCs)

LNCs are a type of smart drug delivery system that combines the best qualities of polymeric nanoparticles and liposomes **[104, 105]**. LNCs are formulated of less toxic biomimetic materials such as PEGylated surfactants, lecithin, and triglycerides **[106]**. They are prepared using a simple low-energy organic solvent-free phase inversion process that can be easily scaled up without heavy equipment. Owing to their narrow distribution and inner structure, LNCs remain physically stable for up to one year or even 18 months **[107, 108]**.

LNCs can be adjusted in size within the range of 20-100 nm, making them ideal for passing through endothelium fenestrations **[109]**. The incorporation of a PEGylated surfactant in the LNCs structure imparts stealth properties to them, enabling them to circulate without being detected by mononuclear phagocytic systems **[110]**.

The high drug loading, that can reach values above 90%, is one of the most significant advantages of LNCs, owing to their resemblance to MEs. Hydrophobic drugs can dissolve in the oily phase, consequently, they can be completely loaded **[111]**. In summary, LNCs provide a promising alternative to traditional drug delivery systems. Frozza et al. fabricated RSV-loaded LNCs of capric/caprylic triglyceride and sorbitan monostearate with appropriate size, high stability, and high encapsulation efficiency. The *in-vivo* study revealed high RSV concentration in rats' brain tissues **[52]**.

The efficacy of these nanocarriers as a neuroprotective agent against the harmful effects of Aβ was tested in rats. The outcomes demonstrated that RSV-loaded LNCs were more efficient than unloaded RSV in reducing memory loss, and learning difficulty, and reducing the levels of synaptophysin. Furthermore, the RSV-loaded NCs were observed to reduce the activation of astrocytes and microglial cells, indicating that they can act as a protective agent against Aβ-induced neurotoxicity **[53]**.

Conclusion

Treating CNS disorders remains a challenging target in the field of medicine, where mortality and morbidity rates persist as unresolved issues associated with complex neuropathologies. The BBB acts as a barrier for most therapeutic drugs, and the mechanisms behind the disorders remain unclear. When it comes to understanding the BBB as a potential target for brain drug delivery, recent research has made impressive strides. In this context, it is important to pay close attention to the BBB, both as a physical barrier and as a cutting-edge therapeutic target for a particular kind of drug delivery to the CNS for the treatment of brain diseases.

Among the advanced nano-drug-delivery carrier systems, lipid-based SLNs, NLCs, MEs, NEs, and LNCs and their surface modifications have shown improved pharmacological applications. They can deliver active drugs in a target-specific and controlled manner, with fewer possible toxicity issues, thereby resulting in promising results for effective brain drug delivery. Lipid nanocarriers loaded with drugs of natural origin such as FA, RSV, curcumin, and RA have shown exceptional neuroprotective activity with reduced side effects, increased drug half-life, higher bioavailability, and enhanced ability to cross the BBB compared to free drugs, in turn, can enhance their therapeutic impact, and offer a new solution to address severe health issues.

This review provided a summary of the most

current advances in phyto-nanomedicine for brain disease therapy. Nonetheless, more effective, non-toxic nanomedicine inventions are still required to address neurological conditions effectively.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Data analyzed during this study are all included in the main manuscript.

Competing interests

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