International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 24s, 2025
https://theaspd.com/index.php

Blood–Brain Barrier Modulation By Herbal Compounds: Implications For Neuroprotection

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Abstract:
The blood–brain barrier (BBB) is a highly selective physiological interface that regulates the passage of molecules into the central nervous system (CNS). While this barrier is essential for neuronal protection, it poses a major challenge for drug delivery in treating neurodegenerative and neuropsychiatric disorders. Recent advances highlight the potential of herbal compounds, many of which possess neuroprotective, antioxidant, anti-inflammatory, and anti-apoptotic properties, to cross or modulate the BBB. Compounds such as withanolides, bacosides, ginsenosides, and flavonoids have demonstrated significant roles in enhancing cognitive function, reducing oxidative stress, modulating neurotransmitter systems, and protecting synaptic integrity. Pharmacokinetic features such as lipophilicity, molecular size, and interactions with efflux transporters strongly influence their BBB permeability. Preclinical and clinical studies support their therapeutic promise in conditions including Alzheimer's disease, Parkinson's disease, stroke, epilepsy, and mood disorders. Furthermore, synergistic approaches employing nanocarriers or combined herbal–synthetic therapies show potential for overcoming delivery challenges and maximizing therapeutic efficacy. Despite encouraging outcomes, critical issues remain regarding dose optimization, herb–drug interactions, and standardization of herbal extracts. Future directions point toward advanced herbal nanosystems, omics-based exploration, and AI-driven screening for identifying BBB-active compounds, along with addressing regulatory and translational hurdles. Overall, herbal compounds offer a promising and multi-targeted strategy for BBB modulation and neuroprotection, warranting further scientific validation for clinical translation.

Keywords: *Blood–brain barrier, Herbal compounds, Neuroprotection, Alzheimer's disease, Parkinson's disease, Stroke, Epilepsy, Depression, Nanocarriers, Pharmacokinetics*

INTRODUCTION:

Importance of the blood–brain barrier (BBB) in CNS physiology

The central nervous system (CNS) is protected by the blood–brain barrier (BBB), a highly selective physiological barrier that regulates the movement of molecules between the bloodstream and neural tissue. The BBB is composed of endothelial cells interconnected by tight junctions, supported by astrocytic end-feet, pericytes, and the basal lamina, which together maintain CNS homeostasis.[1] This barrier ensures that essential nutrients such as glucose and amino acids enter the brain, while potentially harmful substances and pathogens are excluded.[2] Additionally, the BBB plays a critical role in controlling the ionic microenvironment necessary for neuronal signaling and synaptic plasticity. By tightly regulating entry and clearance processes, the BBB maintains a delicate equilibrium between protection and metabolic support, thereby preserving neural function and cognitive health.[3]

Challenges in drug delivery across BBB

While the BBB safeguards the brain, it simultaneously represents a formidable obstacle in delivering therapeutic agents for neurological disorders. Only small, lipophilic molecules with molecular weights typically below 400–500 daltons and high lipid solubility can passively diffuse across the BBB. Large polar molecules, peptides, and most hydrophilic drugs face substantial restrictions.[4] Moreover, efflux transporters such as p-glycoprotein (p-gp), multidrug resistance-associated proteins (mrps), and breast cancer resistance protein (bcrp) actively pump many xenobiotics and therapeutic agents back into the circulation, further reducing drug availability in the brain. Consequently, the effectiveness of many promising neuroprotective drugs is limited by their poor penetration through the BBB, contributing to the high rate of failure in developing CNS-targeted pharmacotherapies.[5] This challenge underscores the urgent need to explore alternative strategies and bioactive molecules with inherent BBB-crossing abilities.[6]

Table 1. Challenges in BBB penetration and the role of herbal compounds in overcoming them[7-9]

Challenge in BBB drug delivery	Description	Impact on neuro-therapeutics	Role of herbal compounds

Molecular size limitation	Molecules >500 Da rarely cross by passive diffusion	Restricts delivery of peptides, proteins, and large phytoconstituents	Some herbal compounds (e.g., ginsenosides, bacosides) show BBB penetration despite high MW, possibly via carrier-mediated or vesicular transport
Lipophilicity requirement	Hydrophilic drugs poorly penetrate BBB	Limits access of polar drugs to CNS	Flavonoids, terpenoids, and alkaloids exhibit balanced lipophilicity, enabling partial passive diffusion
Efflux transporters (P-gp, BCRP, MRPs)	Actively pump drugs out of CNS endothelial cells	Reduces brain concentration of many synthetic drugs	Flavonoids (quercetin, baicalin) and saponins inhibit efflux pumps, increasing CNS drug retention
Enzymatic metabolism in BBB endothelial cells	Phase I/II enzymes degrade xenobiotics	Lowers effective CNS drug levels	Polyphenols and terpenoids exhibit enzyme-inhibitory effects, stabilizing bioactive molecules
Endothelial tight junctions	Maintain barrier integrity, preventing paracellular transport	Prevents entry of hydrophilic molecules	Some herbal extracts modulate tight junction proteins (occludin, claudin-5), improving permeability
Inflammatory and oxidative stress responses	BBB disruption occurs in neurodegeneration	Leads to impaired CNS drug delivery	Herbal compounds (e.g., withanolides, asiaticoside, salvianolic acids) protect BBB by reducing inflammation and oxidative stress

Growing interest in herbal compounds for neuroprotection

In recent decades, there has been a surge of interest in natural products, particularly herbal compounds, as potential neuroprotective agents capable of modulating BBB function. Phytochemicals such as flavonoids, terpenoids, alkaloids, and saponins have demonstrated antioxidant, anti-inflammatory, anti-apoptotic, and neuroregenerative activities in both preclinical and clinical studies. Many of these compounds also interact with transporters or signaling pathways at the BBB, thereby enhancing their own delivery or facilitating the entry of co-administered drugs. For example, ginsenosides from *panax ginseng*, withanolides from *withania somnifera*, and bacosides from *bacopa monnieri* have shown not only therapeutic effects in models of alzheimer's and parkinson's disease but also influence on endothelial barrier integrity. Furthermore, some herbal compounds with molecular weights exceeding the conventional 500 dalton threshold have been reported to penetrate the BBB, challenging long-held assumptions about molecular size limitations. This unique property positions herbal molecules as valuable candidates for next-generation neuroprotective interventions.[10-11]

The present review aims to provide a comprehensive overview of the role of herbal compounds in modulating the BBB and their implications for neuroprotection. First, the structure and function of the BBB will be outlined, with emphasis on its regulatory mechanisms and barriers to drug delivery. The review will then focus on different classes of herbal compounds, summarizing their sources, molecular characteristics, mechanisms of BBB interaction, and neuroprotective potential. Special attention will be given to compounds with high molecular weights that defy conventional BBB permeability criteria, highlighting their unique modes of transport. Furthermore, pharmacokinetic considerations, preclinical and clinical evidence, as well as safety concerns, will be critically examined. Finally, emerging strategies such as combining herbal agents with nanocarriers and advanced delivery technologies will be discussed. By consolidating current evidence, this review seeks to clarify the potential of herbal compounds as BBB modulators and establish their relevance in the development of novel therapeutic approaches for neurodegenerative and neuropsychiatric disorders.[12-13]

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The blood–brain barrier: structure and function

Anatomy of the BBB

The blood–brain barrier (BBB) is a dynamic, highly specialized structure that maintains the biochemical stability of the central nervous system (CNS). At its core, the BBB is formed by brain microvascular endothelial cells (bmecs), which differ from systemic endothelial cells due to the presence of continuous tight junctions, minimal pinocytotic activity, and an extensive network of transport proteins. These endothelial cells are supported by pericytes, astrocytic end-feet, and the extracellular matrix, collectively forming the neurovascular unit (nvu). Tight junction proteins such as claudins, occludins, and junctional adhesion molecules prevent paracellular leakage and ensure selective permeability. Astrocytes regulate barrier integrity and mediate crosstalk with neurons, while pericytes modulate angiogenesis, vascular tone, and immune cell infiltration. In addition, the luminal and abluminal membranes of bmecs are enriched with efflux pumps such as p-glycoprotein (p-gp), breast cancer resistance protein (bcrp), and multidrug resistance-associated proteins (mrps), which actively expel xenobiotics. This intricate organization of cellular and molecular components ensures the BBB serves as both a physical and biochemical barrier, safeguarding the CNS from toxins while allowing nutrient exchange.[14-16]

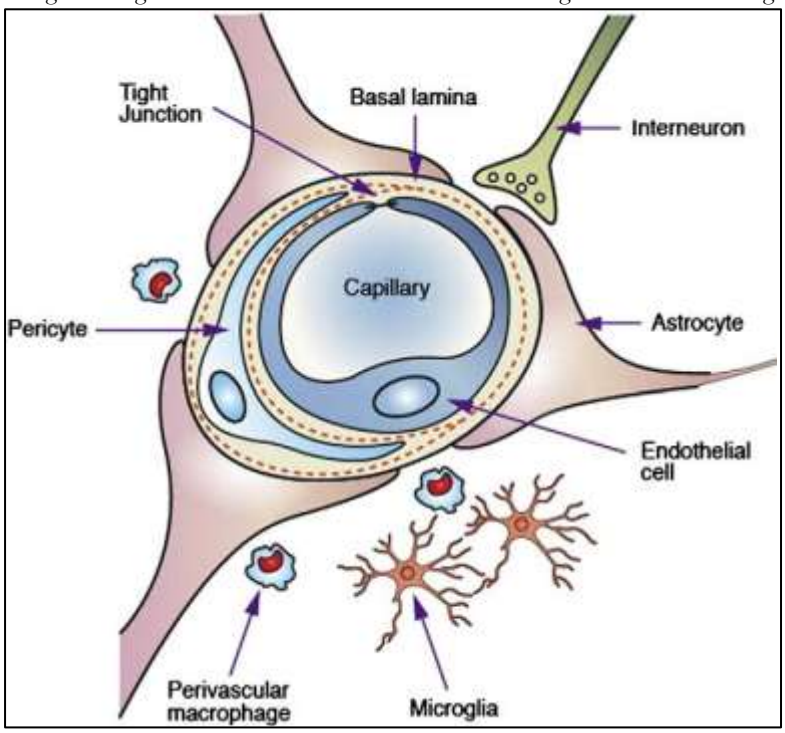

Figure 1. Blood–brain barrier (BBB) [15]

Mechanisms of transport across the BBB

Despite its restrictive nature, the BBB is not an impenetrable wall; rather, it employs selective transport mechanisms to regulate molecular flux between blood and brain. The simplest mode of entry is passive diffusion, which permits the movement of small, lipophilic, and uncharged molecules such as oxygen, carbon dioxide, and some lipophilic drugs. However, most essential nutrients rely on carrier-mediated transport (cmt), mediated by specialized transporters. For example, glucose enters via glut1, while amino acids are transported through lat1 and other solute carrier proteins. Larger biomolecules, including insulin, transferrin, and certain peptides, exploit receptor-mediated transcytosis (rmt), wherein binding to specific receptors triggers vesicular internalization and transcytotic delivery across endothelial cells. Additionally, positively charged proteins and peptides can traverse the BBB via adsorptive-mediated transcytosis (amt), which is driven by electrostatic interactions with negatively charged endothelial membranes. Together, these mechanisms maintain a balance between protecting the brain from harmful agents and supplying it with vital nutrients and regulatory molecules.[17-21]

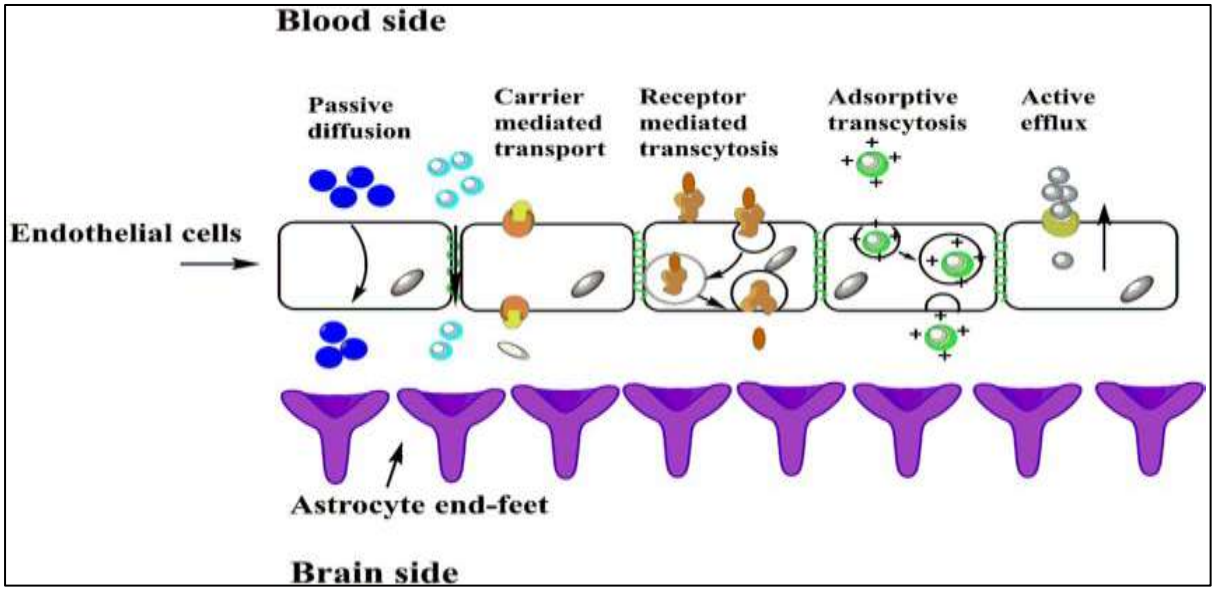

Figure 2. Mechanisms of transport across the BBB [22]

Limitations for drug delivery

While the BBB is indispensable for CNS protection, it presents formidable challenges for drug development and therapeutic interventions. The barrier restricts the entry of approximately 98% of small molecules and nearly 100% of large-molecule drugs into the brain. One critical limitation is molecular weight: compounds exceeding 400–500 daltons typically fail to cross the BBB via passive diffusion. Lipophilicity is another determinant; while moderate lipophilicity facilitates passive diffusion, excessive lipophilicity can lead to sequestration within endothelial membranes, reducing CNS availability. Additionally, efflux transporters such as p-gp, bcrp, and mrps pose a major hurdle by actively pumping a wide range of drugs, including anticancer agents, antiepileptics, and antibiotics, back into the bloodstream. This significantly lowers therapeutic concentrations within the CNS, often necessitating higher systemic doses and leading to off-target side effects. The combined impact of molecular size restrictions, physicochemical constraints, and active efflux makes the BBB one of the primary bottlenecks in developing effective treatments for neurodegenerative and neuropsychiatric disorders.[23-28]

Table 2. Transport mechanisms across the BBB and their relevance to drug delivery

Transport Mechanism	Key Features	Representative Substrates	Relevance for Drug Delivery
Passive diffusion	Lipophilic, small (<400–500 Da), uncharged	Oxygen, CO_2, ethanol, some lipophilic drugs	Favours small lipophilic herbal compounds like flavonoids and terpenoids
Carrier-mediated transport (CMT)	Transporters for nutrients and metabolites	Glucose (GLUT1), amino acids (LAT1), monocarboxylates	Potential route for herbal glycosides and amino acid–conjugated phytochemicals
Receptor-mediated transcytosis (RMT)	Ligand binding to endothelial receptors triggers vesicular transport	Insulin, transferrin, leptin	Exploitable for herbal compounds with structural similarity to natural ligands
Adsorptive-mediated transcytosis (AMT)	Electrostatic interaction with negatively charged endothelial membranes	Cationic proteins, peptides	May facilitate entry of positively charged herbal alkaloids and saponins
Efflux transport (P-gp, BCRP, MRPs)	Active extrusion of xenobiotics	Anticancer drugs, antivirals, some phytochemicals	Limits brain penetration of many drugs; some herbal flavonoids act as efflux inhibitors

Blood–Brain Barrier–Targeted Delivery Strategies[29-34]

Passive diffusion enhancement

One of the simplest approaches to enhance drug delivery across the BBB is to modify compounds to increase lipophilicity or reduce molecular size. Herbal flavonoids and terpenoids often possess physicochemical properties that favor passive diffusion, especially when delivered in lipophilic formulations such as lipid nanoparticles. This strategy is particularly relevant for small polyphenols like quercetin and baicalin, which demonstrate neuroprotective effects in alzheimer's disease models.

Carrier-mediated transport (CMT)

The BBB expresses numerous transporters to supply the brain with essential nutrients, including glucose, amino acids, and monocarboxylates. Herbal compounds can be structurally modified or conjugated to exploit these carriers. For instance, glycosylated ginsenosides and paeoniflorin utilize glucose transporters for CNS uptake. Delivery systems that incorporate transporter-targeting ligands, such as glycosylated nanoparticles, have shown promise in enhancing herbal drug delivery for ischemic stroke and parkinson's disease therapy.

Receptor-mediated transcytosis (RMT)

Large biomolecules such as insulin and transferrin enter the brain via receptor-mediated vesicular transport. Herbal compounds can be loaded into nanocarriers decorated with receptor-specific ligands to exploit this pathway. Withanolides from *withania somnifera* and bacosides from *bacopa monnieri* are examples of phytochemicals investigated for receptor-targeted delivery. This strategy is particularly valuable in models of alzheimer's disease and vascular dementia, where sustained delivery is crucial for therapeutic success.[35-39]

Adsorptive-mediated transcytosis (AMT)

Electrostatic interactions between positively charged drug carriers and the negatively charged endothelial surface can trigger non-specific uptake and vesicular transport. Herbal alkaloids and saponins, due to their amphiphilic structures, are well-suited for amt-based delivery systems such as cationic liposomes and chitosan nanoparticles. These carriers have been explored in glioblastoma and neuroinflammation models, where enhanced brain uptake is required.

Efflux pump modulation

Efflux transporters such as p-gp, bcrp, and mrps pose a major barrier to CNS drug accumulation. Interestingly, several herbal flavonoids and alkaloids act as natural efflux inhibitors. For example, baicalin and berberine have been shown to inhibit p-gp activity, thereby enhancing brain retention of co-administered drugs. Co-delivery of efflux modulators with herbal neuroprotective compounds holds potential in treating epilepsy, depression, and alzheimer's disease.

Nanotechnology-assisted delivery

Nanotechnology offers an advanced platform to bypass BBB restrictions by encapsulating herbal drugs in lipid-based, polymeric, or vesicular systems. Nanoemulsions, solid lipid nanoparticles, and ethosomes protect bioactive compounds from degradation, improve solubility, and facilitate uptake via multiple BBB pathways. For example, salvianolic acid b, crocin, and bacosides have been successfully delivered using nanosystems, showing enhanced neuroprotective efficacy in preclinical studies.

Tight junction modulation

Transient modulation of BBB tight junctions offers another strategy to enhance drug delivery. Herbal compounds such as resveratrol and astragalosides have been shown to influence tight junction proteins, improving paracellular permeability without permanently damaging the BBB. This approach is being explored in stroke and ischemia models, where rapid neuroprotection is needed.

Table 3. Blood–brain barrier targeted delivery strategies[35-44]

No.	BBB-targeting strategy	Mechanism of action	Delivery system	Therapeutic drug/compound	Disease/organ/model
1	Passive diffusion enhancement	Increases lipophilicity or reduces molecular size to favor diffusion	Lipophilic prodrugs, nanoparticle surface modification	Flavonoids (e.g., quercetin, baicalin)	Alzheimer's disease models

2	Carrier-mediated transport (CMT)	Utilizes nutrient transporters (GLUT1, LAT1, monocarboxylate transporters)	Ligand-conjugated nanoparticles, glycosylated herbal derivatives	Ginsenosides, paeoniflorin, salidroside	Ischemic stroke, Parkinson's disease
3	Receptor-mediated transcytosis (RMT)	Exploits receptor binding for vesicular transport across endothelial cells	Transferrin- or insulin-decorated liposomes, polymeric nanoparticles	Withanolides, asiaticoside, bacosides	Alzheimer's and vascular dementia models
4	Adsorptive-mediated transcytosis (AMT)	Driven by electrostatic interactions with negatively charged BBB endothelium	Cationic liposomes, dendrimers, chitosan nanoparticles	Alkaloids and saponins (e.g., saikosaponin, guggulsterone)	Glioblastoma, neuroinflammation
5	Efflux pump modulation	Inhibits P-gp, BCRP, and MRP to improve CNS drug retention	Co-delivery systems, efflux inhibitor–loaded nanoparticles	Baicalin, curcumin, berberine	Epilepsy, depression, Alzheimer's disease
6	Nanotechnology-assisted delivery	Protects drugs from metabolism and improves BBB uptake	Solid lipid nanoparticles, nanoemulsions, ethosomes, exosomes	Salvianolic acid B, bacosides, crocin	Neurodegenerative disorders
7	Disruption or modulation of tight junctions	Transiently opens BBB by modulating tight junction proteins	Peptide-based modulators, herbal extract preconditioning	Resveratrol, astragalosides	Brain ischemia, stroke models

Mechanisms of BBB modulation by herbal compounds[45-58]

Modulation of tight junction proteins

Tight junctions, composed of proteins such as occludin, claudins, and zonula occludens (zo-1), form the structural backbone of the blood–brain barrier and regulate paracellular transport. Disruption of these proteins can lead to uncontrolled entry of xenobiotics and toxins into the central nervous system (CNS). Several herbal compounds have been reported to enhance or stabilize tight junction integrity. For example, withanolides from *withania somnifera* and asiaticoside from *centella asiatica* have shown potential in maintaining BBB integrity by upregulating the expression of tight junction proteins. These effects not only protect against barrier leakage during neurodegenerative conditions but also help improve the delivery of beneficial neuroprotective compounds.

Inhibition of efflux transporters

Efflux pumps such as p-glycoprotein (p-gp), breast cancer resistance protein (bcrp), and multidrug resistance-associated proteins (mrps) play a significant role in limiting drug entry into the brain. Many synthetic drugs are substrates of these transporters, resulting in reduced bioavailability within the CNS. Herbal flavonoids like quercetin, kaempferol, and baicalin are known inhibitors of p-gp and bcrp. By modulating transporter activity, these compounds can increase the retention of therapeutic molecules in the brain. For instance, quercetin has demonstrated p-gp inhibitory activity, which enhances the CNS availability of co-administered drugs. This property makes flavonoids promising adjuvants in drug delivery strategies targeting neurological disorders.

Oxidative stress and neuroinflammation contribute to BBB dysfunction by damaging endothelial cells and altering tight junction protein expression. Herbal compounds rich in polyphenols and terpenoids possess strong antioxidant and anti-inflammatory properties. For example, curcumin, resveratrol, and ginsenosides have demonstrated the ability to reduce reactive oxygen species (ros) production, inhibit nf-

κb signaling, and suppress pro-inflammatory cytokines such as tnf-α and il-6. Through these actions, herbal compounds not only protect the BBB from oxidative damage but also restore its selective permeability, thereby facilitating controlled drug delivery into the brain.

Role of nanocarriers and natural glycosylation in transport

Poor solubility and instability of many herbal constituents limit their effectiveness in crossing the BBB. Nanotechnology-based systems such as liposomes, nanoparticles, and solid lipid carriers have been employed to improve the transport of herbal actives. For instance, curcumin-loaded nanoparticles and ginsenoside-based liposomes have shown enhanced brain penetration compared to free compounds. Additionally, natural glycosylation of certain phytochemicals, such as glycosylated flavonoids, improves solubility, stability, and affinity toward endogenous transporters, thus facilitating BBB passage. These strategies represent a promising approach to integrate herbal medicine with advanced drug delivery systems.

Influence of glycosides and saponins on membrane permeability

Glycosides and saponins are amphiphilic compounds commonly found in medicinal plants that interact with lipid bilayers of cellular membranes. Their surfactant-like properties can transiently increase membrane permeability, which may support enhanced paracellular transport across the BBB. For example, saponins from *panax ginseng* have been reported to modulate BBB permeability, potentially through reversible interactions with cholesterol-rich domains of endothelial membranes. This property may be beneficial for controlled drug delivery when combined with neuroprotective agents. However, excessive disruption may cause cytotoxicity, and therefore precise dose optimization is required.

Table 4. Mechanisms of BBB modulation by herbal compounds

Mechanism	Herbal Compounds / Extracts	Mode of Action	Neuroprotective Outcome
Modulation of tight junction proteins	Withanolides (*Withania somnifera*), Asiaticoside (*Centella asiatica*)	Upregulation of occludin, claudins, ZO-1	Stabilization of BBB integrity
Inhibition of efflux transporters	Quercetin, Kaempferol, Baicalin	Inhibition of P-gp and BCRP	Increased CNS drug retention
Regulation of oxidative stress & inflammation	Curcumin, Resveratrol, Ginsenosides	Antioxidant activity, suppression of NF-κB and pro-inflammatory cytokines	Protection of BBB from oxidative damage
Role of nanocarriers & glycosylation	Curcumin nanoparticles, Ginsenoside liposomes, Glycosylated flavonoids	Improved solubility, stability, and transporter affinity	Enhanced brain penetration
Influence on membrane permeability	Saponins (*Panax ginseng*), Glycosides from medicinal plants	Interaction with lipid bilayers, transient permeability increase	Facilitated paracellular transport

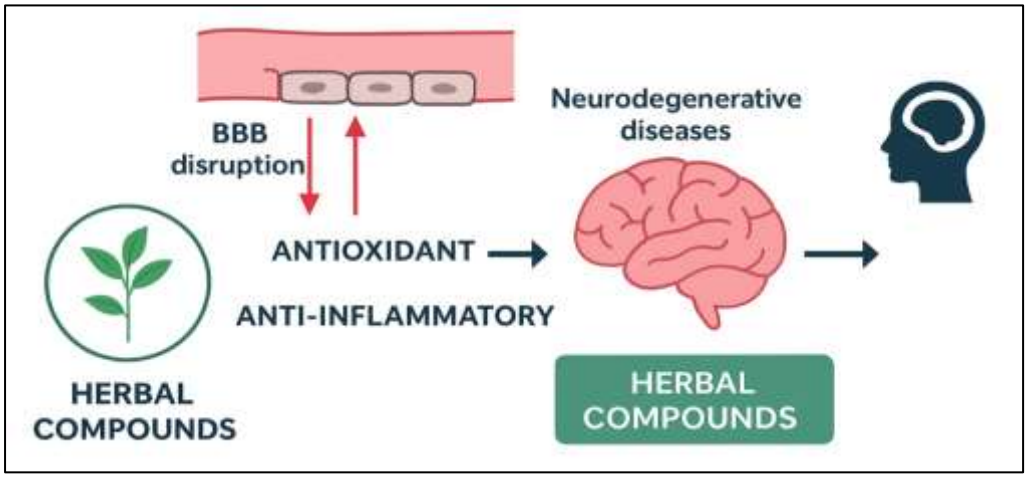

Figure 3. Pathophysiological role of BBB disruption in neurodegenerative diseases and how herbal compounds intervene

Herbal compounds crossing or modulating the BBB

The ability of herbal compounds to either cross the blood–brain barrier (BBB) or modulate its permeability has become a key area of research in neurotherapeutics. The traditional view that only low molecular weight (mw < 500 da), lipophilic molecules can effectively penetrate the BBB has been challenged by emerging evidence showing that several high molecular weight (mw > 500 da) herbal constituents are capable of reaching the CNS. These effects are often attributed to carrier-mediated transport, receptor interactions, glycosylation, or vesicular mechanisms that allow selective entry or modulation of barrier function.

Low molecular weight herbal compounds (<500 da)

Low molecular weight compounds typically exhibit greater potential for passive diffusion across the BBB due to their lipophilic nature and smaller size. Many plant-derived flavonoids, alkaloids, and terpenoids fall into this category. For instance, quercetin from *ginkgo biloba* and withaferin a from *withania somnifera* have mw values well below 500 da, enabling them to cross the BBB and exert neuroprotective effects. These compounds often act as antioxidants, anti-inflammatory agents, and modulators of efflux transporters, thereby not only penetrating but also stabilizing BBB function.

High molecular weight herbal compounds (>500 da)

Traditionally, high molecular weight molecules face significant challenges in BBB penetration. However, certain phytoconstituents, particularly saponins, glycosides, and polyphenolic acids, have shown CNS activity despite exceeding the size threshold. Compounds like ginsenosides from *panax ginseng* (mw ~800–1200 da) and bacosides from *bacopa monnieri* (mw ~900–1200 da) utilize mechanisms such as carrier-mediated transport, interaction with membrane proteins, and vesicular transcytosis to bypass restrictions. This highlights the ability of natural compounds to exploit physiological transport pathways for CNS access.

Case studies of herbal compounds[59-67]

***Withania somnifera* (withaferin a, withanolides)**

Withania somnifera (ashwagandha) is widely studied for its neuroprotective role in neurodegenerative conditions. Withaferin a (mw 470 da) and withanolides exhibit strong antioxidant and anti-inflammatory properties. They cross the BBB efficiently due to their relatively low molecular weight and lipophilicity. Preclinical studies have shown improvements in memory, synaptic integrity, and protection against β-amyloid neurotoxicity, making ashwagandha a promising candidate for alzheimer's and other dementias.

Panax ginseng (ginsenosides)

Ginsenosides, a group of triterpenoid saponins, are high molecular weight molecules (mw ~800–1200 da) that surprisingly demonstrate CNS penetration. Their transport is believed to occur via transcytosis and efflux pump modulation. They provide neuroprotection in models of ischemia, alzheimer's disease (ad), and parkinson's disease (pd) by reducing oxidative stress, modulating neurotransmitter release, and stabilizing BBB integrity. Clinical studies have also suggested cognitive benefits in elderly populations.

Bacopa monnieri (bacosides)

Bacopa monnieri, commonly used in ayurvedic medicine, contains bacosides (mw > 900 da), which improve cognitive functions. Despite their large size, bacosides have demonstrated CNS effects, likely through glycoside-mediated transport and vesicular pathways. Experimental data show enhancement of learning, memory, and synaptic plasticity, making bacopa a well-validated nootropic herb.

Centella asiatica (asiaticoside, madecassoside)

Compounds such as asiaticoside and madecassoside (mw ~900–1000 da) from *centella asiatica* are known for their roles in BBB repair and synaptic plasticity. These triterpenoid glycosides may cross via facilitated transport mechanisms and exhibit strong neurorestorative effects in models of traumatic brain injury and neurodegeneration. Their ability to upregulate tight junction proteins further suggests a dual role in both protecting and modulating the BBB.

Salvia miltiorrhiza (salvianolic acid b)

Salvia miltiorrhiza (danshen) contains salvianolic acid b (mw ~718 da), a polyphenolic compound that enhances cerebrovascular function. Although it exceeds the classical size restriction, it demonstrates activity in stroke and ischemic brain injury models by improving blood flow, scavenging free radicals, and modulating endothelial function.

Hypericum perforatum (hypericin)

Hypericum perforatum (st. John's wort) contains hypericin (mw ~504 da), a relatively small lipophilic molecule capable of crossing the BBB. It has been shown to regulate mood disorders by modulating monoamine neurotransmitters, particularly serotonin and dopamine. Its dual properties as an antidepressant and neuroprotective agent make it an attractive compound in the management of depression-related neurological changes.

Ginkgo biloba (bilobalide, flavonoids)

Ginkgo biloba extracts are rich in bilobalide (mw 326 da) and flavonoids such as quercetin and kaempferol, all of which fall under the low molecular weight category. These compounds cross the BBB via passive diffusion and provide antioxidative, anti-inflammatory, and vasodilatory effects, thereby improving cerebral blood flow and modulating BBB integrity. They are widely used in the management of cognitive decline and dementia.

Table 5. Herbal compounds crossing or modulating the BBB

Compound / Extract	Molecular Weight	Source Plant	Proposed Mechanism of BBB Interaction	Neuroprotective Effects
Withaferin A, Withanolides	<500 Da	*Withania somnifera*	Passive diffusion, antioxidant & anti-inflammatory actions	Memory improvement, anti-amyloid activity
Ginsenosides	>800 Da	*Panax ginseng*	Transcytosis, efflux pump modulation	Neuroprotection in ischemia, AD, PD
Bacosides	>900 Da	*Bacopa monnieri*	Glycoside-mediated transport, vesicular entry	Cognitive enhancement, synaptic plasticity
Asiaticoside, Madecassoside	~900–1000 Da	*Centella asiatica*	Tight junction modulation, facilitated transport	BBB repair, neuroregeneration
Salvianolic acid B	~718 Da	*Salvia miltiorrhiza*	Vascular modulation, ROS scavenging	Cerebrovascular protection, anti-ischemic effect
Hypericin	~504 Da	*Hypericum perforatum*	Lipophilic BBB penetration, neurotransmitter modulation	Mood regulation, antidepressant effect
Bilobalide, Quercetin, Flavonoids	<500 Da	*Ginkgo biloba*	Passive diffusion, antioxidant & anti-inflammatory actions	Cognitive protection, BBB stabilization

Pharmacokinetic and molecular aspects[68-73]

The pharmacokinetic and molecular properties of herbal compounds play a central role in determining their ability to cross the blood–brain barrier (BBB) and exert neuroprotective effects. One of the most important factors is lipophilicity, since compounds with moderate to high lipid solubility can diffuse across endothelial membranes more effectively. Several herbal constituents, including flavonoids and terpenoids, possess favorable lipophilic properties that allow them to enter the CNS. At the same time, compounds that are excessively hydrophilic face greater challenges in reaching therapeutic concentrations within the brain, and their activity often depends on alternative mechanisms of transport or modulation of BBB function.

Another critical determinant is the interaction of herbal compounds with active efflux transporters located on BBB endothelial cells. Proteins such as p-glycoprotein (p-gp), breast cancer resistance protein (bcrp), and multidrug resistance-associated proteins (mrps) limit CNS accumulation of xenobiotics by pumping them back into circulation. Many phytoconstituents are substrates for these efflux systems, resulting in reduced brain penetration. However, certain flavonoids and polyphenols act as natural inhibitors of these transporters, thereby enhancing the delivery of not only themselves but also co-

administered neuroprotective drugs. This dual role of being both efflux substrates and modulators highlights the complex interactions between herbal molecules and the BBB transport machinery.

Metabolism is another layer of complexity influencing BBB permeability. Herbal compounds often exist in glycosylated forms that are more hydrophilic and less likely to cross the barrier through passive diffusion. However, their aglycone counterparts, generated through enzymatic hydrolysis, are more lipophilic and can penetrate more efficiently. For instance, baicalin, a glycosylated flavone from *scutellaria baicalensis*, demonstrates poor BBB permeability in its native form, but its aglycone baicalein shows markedly improved transport into the CNS. Similarly, glycosylated saponins such as bacosides or ginsenosides may undergo metabolic modification that alters their bioavailability and enables them to exploit alternative uptake pathways. This highlights the significance of considering metabolic transformations when evaluating the pharmacokinetics of herbal neuroprotective agents.

The classical restriction that molecules above 500 da cannot efficiently cross the BBB has been challenged by several large phytoconstituents, particularly saponins, glycosides, and polysaccharide derivatives. These compounds often rely on natural transport mechanisms such as receptor-mediated endocytosis, vesicular trafficking, or membrane interaction to achieve CNS penetration. Ginsenosides, bacosides, and asiaticosides are prime examples, as they exceed the molecular weight threshold yet consistently demonstrate neuroprotective efficacy in experimental and clinical studies. Their ability to influence membrane permeability, interact with transport proteins, or modulate tight junction integrity allows them to bypass size-related restrictions that typically hinder synthetic drugs. Thus, herbal compounds represent a unique pharmacokinetic class where structural complexity and natural glycosylation provide novel routes of BBB modulation and transport, offering significant promise for the development of effective neuroprotective therapies.

Table 6. Pharmacokinetic and Molecular Aspects of Herbal Compounds in BBB Modulation[74-79]

Herbal compound	**Molecular weight (da)**	**Lipophilicity (BBB penetration)**	**Efflux transporter interaction**	**Metabolic form (aglycone vs glycoside)**	**Observed neuroprotective effect**
Withaferin A (*Withania somnifera*)	470	Moderate lipophilicity, favorable for passive diffusion	Not a major efflux substrate	Exists mainly as aglycone	Improves memory, reduces amyloid toxicity
Ginsenosides (*Panax ginseng*)	780–1200	Low lipophilicity, poor passive diffusion	Substrates for P-gp, some act as P-gp modulators	Glycosylated; metabolism enhances BBB penetration	Protects against ischemia, AD, PD
Bacosides (*Bacopa monnieri*)	900–1200	Amphiphilic, limited passive entry	Possible efflux modulation	Glycosylated; partial hydrolysis improves absorption	Enhances cognition, synaptic plasticity
Asiaticoside & Madecassoside (*Centella asiatica*)	975–1000	Hydrophilic, restricted passive diffusion	Not fully established, may interact with efflux	Glycosylated; aglycone forms more permeable	BBB repair, neuroregeneration
Salvianolic acid B (*Salvia miltiorrhiza*)	718	Polar, limited diffusion	Possible efflux inhibition	Polyphenolic form, limited aglycone conversion	Improves cerebral blood flow, anti-ischemic
Hypericin (*Hypericum perforatum*)	504	Lipophilic, good diffusion potential	Limited evidence for efflux interaction	Exists as aglycone	Mood regulation, antidepressant effect

Bilobalide & Quercetin (*Ginkgo biloba*)	326–450	High lipophilicity, efficient passive penetration	Quercetin inhibits P-gp and BCRP	Both aglycone forms, readily absorbed	Antioxidant, anti-inflammatory, BBB stabilization
Baicalin/Baicalein (*Scutellaria baicalensis*)	446 (Baicalin), 270 (Baicalein)	Baicalin poorly lipophilic; Baicalein lipophilic	Baicalin efflux substrate, Baicalein avoids efflux	Glycoside (Baicalin) vs Aglycone (Baicalein)	Neuroprotection in ischemia, reduces oxidative stress

This table highlights that herbal compounds vary widely in their pharmacokinetic behavior depending on molecular weight, lipophilicity, efflux interaction, and metabolic form. Smaller aglycone forms such as withaferin a, baicalein, and bilobalide penetrate the BBB efficiently by passive diffusion. In contrast, large glycosylated molecules such as ginsenosides, bacosides, and asiaticosides face greater challenges but overcome them through vesicular transport, efflux modulation, or metabolic conversion into more lipophilic derivatives. Efflux transporter interactions are particularly important, as compounds like quercetin act as natural inhibitors of p-gp and bcrp, thereby enhancing not only their own CNS uptake but also the uptake of co-administered neuroprotective agents. This interplay between molecular structure, metabolism, and transporter modulation demonstrates the unique pharmacokinetic strategies by which herbal compounds exert neuroprotection despite classical BBB restrictions.

Neuroprotective implications of BBB modulation[80-87]

The modulation of the blood–brain barrier by herbal compounds offers significant therapeutic potential in the management of neurodegenerative and neurological disorders. In alzheimer's disease, impaired clearance of amyloid-β peptides and heightened oxidative stress contribute to progressive neuronal loss and cognitive decline. Herbal bioactives such as polyphenols and flavonoids enhance amyloid-β clearance by modulating efflux transporters and reducing oxidative injury, thereby preserving synaptic function. In parkinson's disease, the accumulation of α-synuclein aggregates and mitochondrial dysfunction are central pathological mechanisms. Herbal molecules like ginsenosides and curcuminoids counteract these processes by reducing protein misfolding, stabilizing mitochondrial function, and alleviating neuroinflammation. Stroke and cerebral ischemia represent conditions where oxidative stress and apoptosis dominate the pathophysiological cascade. Herbal compounds with strong antioxidant and anti-apoptotic properties, such as resveratrol, baicalein, and asiaticoside, protect neuronal integrity and improve post-stroke recovery by stabilizing the BBB and enhancing cerebral blood flow. In epilepsy, the excitability of neurons is often heightened due to ionic imbalance and oxidative burden; herbal interventions like flavonoids and terpenoids exert anticonvulsant effects by modulating gabaergic signaling and attenuating excitotoxicity. Similarly, in depression and anxiety, herbal compounds influence neurochemical and trophic pathways, including regulation of monoaminergic transmission and upregulation of brain-derived neurotrophic factor (bdnf), which contribute to mood stabilization and neurogenesis. These diverse neuroprotective roles highlight how BBB modulation by herbal agents extends beyond barrier permeability to the regulation of key pathological mechanisms across neurological diseases.

Table 7. Neuroprotective implications of BBB modulation by herbal compounds[88-105]

Disease/Condition	Key Herbal Compounds	Mechanism of Action	Neuroprotective Outcomes
Alzheimer's disease	Curcumin, Resveratrol, Ginkgo biloba flavonoids	Enhance Aβ clearance, reduce oxidative stress, stabilize synaptic proteins	Memory preservation, reduced neuronal loss
Parkinson's disease	Ginsenosides (Panax ginseng), Withanolides (Withania somnifera), Baicalein	Reduce α-synuclein aggregation, protect mitochondria, modulate dopamine levels	Improved motor function, slowed neurodegeneration
Stroke/Ischemia	Asiaticoside (Centella asiatica), Salvianolic acid B	Antioxidant and anti-apoptotic effects, promote	Reduced infarct size, improved recovery

	(Salvia miltiorrhiza), Resveratrol	angiogenesis, enhance BBB integrity	
Epilepsy	Flavonoids (Quercetin, Apigenin), Terpenoids	Modulate GABAergic signaling, reduce excitotoxicity, stabilize ion channels	Reduced seizure frequency, improved neuronal stability
Depression/Anxiety	Hypericin (Hypericum perforatum), Bacosides (Bacopa monnieri)	Regulate monoaminergic pathways, upregulate BDNF, reduce neuroinflammation	Mood stabilization, enhanced neurogenesis

This table highlights how diverse herbal compounds modulate the blood–brain barrier and exert disease-specific neuroprotective effects. In Alzheimer's disease, polyphenols such as curcumin and resveratrol enhance amyloid clearance and preserve memory. For Parkinson's disease, herbal adaptogens like ginsenosides and withanolides protect dopaminergic neurons from mitochondrial stress and protein aggregation. Stroke and ischemia benefit from compounds like asiaticoside and salvianolic acid B, which maintain BBB integrity and limit neuronal apoptosis. In epilepsy, flavonoids and terpenoids reduce hyperexcitability and stabilize neuronal signaling, while in mood disorders, compounds such as hypericin and bacosides regulate neurotransmitters and neurotrophic factors. The table thus provides a concise overview of how herbal agents contribute to neuroprotection via BBB modulation across different neurological diseases.

Synergistic approaches

The integration of herbal compounds with advanced delivery strategies and combinatorial therapies has further enhanced their neurotherapeutic efficacy. Nanocarriers such as liposomes, polymeric nanoparticles, ethosomes, and exosomes improve the bioavailability of poorly soluble herbal molecules and facilitate their targeted delivery across the BBB. This not only ensures higher CNS accumulation but also prolongs therapeutic action. Beyond nanocarriers, synergistic combinations of herbal and synthetic drugs are emerging as a promising strategy, where herbal agents may modulate efflux transporters or oxidative stress, thereby improving the penetration and efficacy of co-administered pharmaceuticals. For example, combining flavonoids with standard anti-alzheimer's or anti-parkinson's drugs can improve drug retention in the brain and enhance clinical outcomes. Moreover, herbal compounds are particularly effective due to their multi-target nature, acting simultaneously as antioxidants, anti-inflammatory agents, and anti-apoptotic protectors. Such pleiotropic actions are advantageous in complex neurological disorders where single-target therapies often fail. Overall, these synergistic approaches underscore the importance of integrating traditional herbal medicine with modern pharmacological and nanotechnological advances to achieve enhanced and sustainable neuroprotection.[106-128]

Safety, toxicity, and pharmacological challenges

Although herbal compounds hold promise for modulating the blood–brain barrier and exerting neuroprotective actions, safety and pharmacological challenges remain significant considerations. One of the foremost concerns is dose dependency, since many phytochemicals display biphasic effects where low doses can be therapeutic but higher concentrations may induce cytotoxicity or impair neuronal functions. For example, flavonoids such as quercetin exhibit antioxidant activity at physiological doses but may paradoxically act as pro-oxidants when consumed in excess. Another key limitation arises from herb–drug interactions at the BBB level. Many herbal constituents inhibit efflux transporters such as p-glycoprotein (p-gp), which, while enhancing brain penetration of therapeutic drugs, also carries the risk of altering the pharmacokinetics of co-administered synthetic medications, leading to potential toxicity. In addition, variability in herbal extracts due to differences in plant source, geographical conditions, extraction methods, and storage can result in inconsistent therapeutic outcomes. The lack of standardized formulations makes it challenging to establish reproducible safety profiles, and impurities or adulterants in poorly regulated herbal products may exacerbate adverse effects. Addressing these challenges requires rigorous pharmacological testing, standardization of extracts, and careful monitoring of potential interactions with conventional drugs to ensure safe translation of herbal therapies for neurological applications.[129-136]

Clinical and preclinical evidence

Evidence from preclinical and clinical studies provides valuable insights into the potential of herbal compounds to modulate the BBB and confer neuroprotection. Animal studies using advanced techniques

such as imaging, liquid chromatography–mass spectrometry (lc–ms), and intracerebral microdialysis have confirmed that several herbal constituents, including resveratrol, ginsenosides, and bacosides, are capable of crossing the BBB and accumulating within brain tissue. These preclinical findings often demonstrate strong antioxidant, anti-apoptotic, and anti-inflammatory activities, translating into measurable improvements in memory, motor control, or neuronal survival in animal models of alzheimer's disease, parkinson's disease, stroke, and epilepsy. In clinical settings, compounds such as ginkgo biloba extracts, bacopa monnieri, and panax ginseng have been evaluated for their cognitive-enhancing and neuroprotective effects. Some trials have reported modest benefits in memory, attention, and overall cognitive function, while others show variable or inconclusive results, often due to small sample sizes, differences in extract preparation, and limited follow-up periods. A persistent gap exists between promising preclinical efficacy and consistent clinical translation, which underscores the need for large-scale, well-designed trials with standardized formulations. Bridging this gap will require harmonization of preclinical and clinical methodologies, better pharmacokinetic profiling, and more precise biomarkers to validate the therapeutic potential of herbal compounds for central nervous system disorders.[137-141]

FUTURE PERSPECTIVES:

The future of research on blood–brain barrier modulation by herbal compounds lies in integrating traditional knowledge with cutting-edge scientific innovations. One of the most promising directions involves the use of advanced delivery systems, particularly herbal nanosystems such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, and exosome-based carriers. These systems not only improve solubility and stability of phytochemicals but also provide targeted and sustained release within the brain, thereby overcoming some of the natural limitations posed by molecular weight and efflux transporters. Such nanosystems hold the potential to transform poorly bioavailable herbal constituents into clinically viable neuroprotective agents.

Alongside delivery innovations, omics-based research approaches such as proteomics, metabolomics, and transcriptomics are expected to play a crucial role in understanding how herbal compounds interact with the BBB at a molecular level. These techniques can unravel the specific pathways and biomarkers associated with tight junction regulation, efflux inhibition, and neuroinflammation, thereby enabling precision-based interventions. When combined with systems biology, omics studies can provide a holistic picture of how phytochemicals exert their pleiotropic effects on the central nervous system.

Another emerging frontier is the integration of artificial intelligence (ai) and computational modeling for drug–herbal compound screening. Predictive algorithms can be used to assess BBB permeability, identify synergistic combinations with synthetic drugs, and optimize structural modifications of phytochemicals to enhance their transport across the barrier. This approach could significantly reduce experimental burden, shorten discovery timelines, and accelerate the translation of promising herbal compounds into therapeutic candidates.

Despite these advances, regulatory aspects and standardization remain critical challenges. Variability in herbal preparations due to differences in plant sources, extraction protocols, and formulation quality continues to hamper reproducibility in clinical outcomes. International harmonization of guidelines, establishment of reference standards, and stringent quality control will be necessary to ensure safety, efficacy, and acceptance of herbal neuroprotectants in mainstream medicine. Overall, future perspectives highlight a multidisciplinary approach that combines nanotechnology, omics sciences, artificial intelligence, and regulatory rigor to unlock the full therapeutic potential of herbal compounds in blood–brain barrier modulation and neuroprotection.

CONCLUSION:

The blood–brain barrier plays a pivotal role in maintaining central nervous system homeostasis, but its highly selective nature remains a major hurdle in the development of effective neurotherapeutics. Conventional small molecules and biologics often fail to achieve therapeutic concentrations in the brain, highlighting the urgent need for novel strategies to modulate BBB permeability without compromising its protective functions. Herbal compounds have emerged as promising candidates in this regard, offering multi-targeted actions such as modulation of tight junctions, inhibition of efflux transporters, regulation of oxidative and inflammatory pathways, and facilitation of receptor- or carrier-mediated transport.

The extensive range of herbal compounds documented, from low molecular weight flavonoids like baicalin and withaferin A to high molecular weight glycosides and saponins such as bacosides, asiaticoside, and ginsenosides, underscores the diversity of natural scaffolds capable of interacting with the BBB.

Interestingly, several compounds with molecular weights well above 500 Da have demonstrated the ability to penetrate or modulate the barrier, often via natural transport mechanisms like glycosylation or through nanoscale delivery systems. Representative examples, including Withania somnifera, Panax ginseng, Bacopa monnieri, Centella asiatica, Salvia miltiorrhiza, and Ginkgo biloba, have shown preclinical and clinical potential for neuroprotection in disorders such as Alzheimer's disease, Parkinson's disease, stroke, epilepsy, and depression.

Pharmacokinetic complexities remain a central challenge. Variability in bioavailability due to differences in lipophilicity, metabolism, and interactions with efflux transporters necessitates further refinement of delivery approaches. Nanocarrier-assisted delivery, synergistic herbal–synthetic combinations, and structural optimization of phytochemicals provide new opportunities to enhance BBB penetration and therapeutic outcomes. However, issues related to safety, dose dependency, herb–drug interactions, and variability in extract standardization cannot be overlooked. Rigorous toxicological studies and harmonized regulatory frameworks are critical to ensuring reproducibility, safety, and clinical acceptance.

Evidence from animal studies using advanced tools such as imaging, microdialysis, and LC–MS strongly supports the BBB permeability of many phytochemicals, yet translation into human trials remains limited and often inconsistent. This gap highlights the necessity for well-designed, large-scale clinical studies with standardized formulations to validate the neuroprotective potential observed in preclinical settings.

Looking ahead, the integration of advanced nanosystems, omics-based molecular profiling, and AI-driven screening platforms offers exciting avenues to unlock the full therapeutic value of herbal compounds in BBB modulation. Such multidisciplinary strategies, combined with regulatory rigor and global standardization, can pave the way for herbal-based interventions to move from experimental promise to established therapeutic reality. Ultimately, harnessing the unique properties of herbal compounds for BBB modulation may provide a transformative approach to managing neurodegenerative and neuropsychiatric disorders, bridging traditional medicine with modern drug discovery.

ACKNOWLEDGEMENT: The author sincerely acknowledge the support and facilities provided by the **School of Pharmacy, Vishwakarma University, Kondhwa Budruk, Pune, Maharashtra**, which enabled the successful compilation of this review article. The academic environment, access to scientific resources, and continuous encouragement from the faculty have been instrumental in completing this work. The authors also extend their gratitude to all researchers whose valuable contributions in the field of blood–brain barrier modulation and herbal neuroprotection formed the foundation of this review.

CONFLICT OF INTREST: The author declares no any conflict of interest.

FUNDING: None

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