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Review

Battle of the wall for aromatic "orifice-opening" agents: defending and breaching the blood-brain barrier

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ABSTRACT

The brain is the most stringently safeguarded organ in the human body. The 7-mm-thick cranial vault shields the central nervous system (CNS) from external damage, while the blood-brain barrier (BBB) functions as a specific physiological barrier, successfully safeguarding it from circulating toxins and pathogens. BBB disruption is closely linked to the emergence and development of various CNS disorders, and the strong constraints of BBB on substance exchange present a considerable obstacle to medicine administration for the treatment of neurological diseases. Aromatic orifice-opening agents (AOOAs), a specific class of traditional Chinese medicine (TCM), exhibit a unique bidirectional interaction with BBB. Such agents can loosen the BBB junctions, transiently enhance its permeability, and ease the passage of medications into the brain, a phenomenon referred to as the "permeability-promoting" effect on BBB. In contrast, under pathological conditions, AOOAs can preserve BBB integrity and exert a "permeability-restricting" effect by reducing inflammatory responses and alleviating oxidative stress. This review systematically analyzes the regulatory factors affecting BBB permeability, investigates the dual mechanisms by which AOOAs protect and penetrate the BBB, and highlights the innovative opportunities and significant potential these agents present for treating CNS disorders.

1. Introduction

The blood-brain barrier (BBB) is a highly selective, semi-permeable interface between the bloodstream and the brain. Its selectivity and permeability are predominantly influenced by the properties of brain microvascular endothelial cells (BMECs). Tight junctions (TJs) limit the paracellular transport of hydrophilic substances, whereas the transcytosis and leukocyte migratory mechanisms are rigorously controlled. Meanwhile, a range of transport proteins help maintain ionic homeostasis within the brain. BMECs additionally express several metabolic enzymes, thereby decomposing drugs or deleterious substances. Although BMECs are fundamental constituents of the BBB, they are part of a broader neurovascular unit (NVU). This unit comprises neurons, pericytes, astrocytes, microglia, oligodendrocytes, and basement membrane, together regulating the function of the BBB [1]. While BBB disruption is a consequence of pathological alterations in the brain parenchyma, such as inflammatory response and oxidative stress, it can also enable the influx of pro-inflammatory mediators, plasma proteins, and excitatory neurotransmitters into brain tissue, resulting in vasogenic edema and secondary brain injury [2]. Moreover, the highly selective nature of the BBB under normal conditions, along with the permeability alterations during pathology, poses considerable challenges for central nervous system (CNS) drug delivery.

Pharmaceuticals that predominantly enhance consciousness are termed orifice-opening agents. Owing to their aromatic characteristics, they are referred to as aromatic orifice-opening agents (AOOAs). The principal active components of AOOAs typically exhibit high lipophilicity and low molecular weight, facilitating rapid BBB penetration and access to cerebral tissue *via* passive diffusion [3]. When delivering such medications, the issue of barrier transport is not prominent. Furthermore, AOOAs administration can effectively regulate BBB permeability by temporarily and reversibly breaking the TJs or augmenting the expression of certain transporters, thereby enabling the ingress of co-administered medications into brain tissue, which broadens the range of pharmaceuticals accessible for addressing CNS disorders. Under pathological statement, AOOAs can reduce barrier permeability, maintain structural integrity, protect the damaged BBB, and enhance the efficacy of pharmacological treatments [4]. Last but not least, the distinctive fragrance of AOOAs suggests a high probability of direct entry into the brain *via* the olfactory bulb, later spreading to other cerebral areas *via* the olfactory nerve pathway [5]. This method circumvents the hepatic first-pass effect, reduces the drug's onset time, and provides an efficient and straightforward alternative for managing acute CNS diseases. This review systematically categorizes and analyzes the regulatory mechanisms of BBB permeability and investigates the dual action mechanisms of AOOAs in modifying the BBB. This not only establishes novel theoretical frameworks for comprehending the

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physiological and pathological mechanisms of BBB, but also paves the way for innovative treatments of CNS disorders.

2. Blood-brain barrier: the robust fortification of human brain

2.1. Brain microvascular endothelial cells

BMECs, integral to the BBB, create a trifecta of barriers: the cellular barrier, the transport barrier, and the metabolic barrier. The cellular barrier refers to the capability of BMECs to form highly specialised intercellular connections. This feature allows the BBB to effectively regulate paracellular transport pathways, markedly limiting the nonspecific diffusion of substances through the intercellular space. The transport barrier, an essential element of the transcellular transport pathway, comprises complex and exact molecular transport mechanisms. It selectively absorbs nutrients and vital chemicals required by the CNS while expelling metabolic waste and extraneous molecules that disturb CNS homeostasis. BMECs include many drug-metabolizing enzymes, notably the CYP450 enzyme system, which constitutes the metabolic barrier. These enzymes act as metabolic barriers by metabolising molecules that cross the BBB, hence affecting the quantity and rate of these substances' entry into the CNS.

2.1.1. Cellular barrier

The junctional complexes of BMECs consist of TJs, adherens junctions (AJs), and gap junctions (GJs) (Fig. 1). Claudin and occludin, as vital transmembrane components of TJs, tightly link adjacent BMECs, significantly reducing paracellular permeability. Junction adhesion molecule (JAM) and endothelial selective adhesion molecule (ESAM) are also essential components of TJs, playing a pivotal role in TJs' assembly and stability preservation. Zonula occludens (ZO), the auxiliary proteins of TJs, functions as a connector by securely attaching one end to the intracellular domains of claudin and occludin, while the other end binds to the actin cytoskeleton (AC), thereby firmly anchoring TJs to AC. Diverse isoforms of protein kinase C (PKC) and other cytoplasmic auxiliary proteins facilitate the precise regulation of TJs functions. The primary protein of AJs is vascular endothelial cadherin (VE-cadherin). By binding to the extracellular EF-hand motif of VE-cadherin, Ca^{2+} induces its conversion to a stretch-active conformation and the formation of a *cis*-dimer, forming the essential structure of AJs. BMECs bind homologously to platelet endothelial cell adhesion molecule-1 (PECAM-1) on the surface of leukocytes, mediating leukocyte-endothelial cell adhesion and its transendothelial migration in inflammatory states. Catenins are cytoplasmic auxiliary proteins linked to AJs. *β*-Catenin and *γ*-catenin firmly bind to the intracellular domain of VE-cadherin, whereas *α*-catenin connects *β*-catenin or *γ*-catenin to AC, forming a resilient complex that provides substantial mechanical stability to AJs. GJs are typically identified by connexin 43 (Cx43). Adjacent BMECs employ Cx43 to form channels that enable the transfer of small-molecule signaling elements, thus enhancing efficient and direct intercellular communication. AC is an essential element for the operation of cell junctions. AC substantially interacts with various TJs and AJs, providing strong mechanical support for these junctional complexes. Through the assembly, depolymerization, and rearrangement of actin filaments, AC can influence the permeability of TJs, the adhesion strength of AJs, and the functional status of GJs.

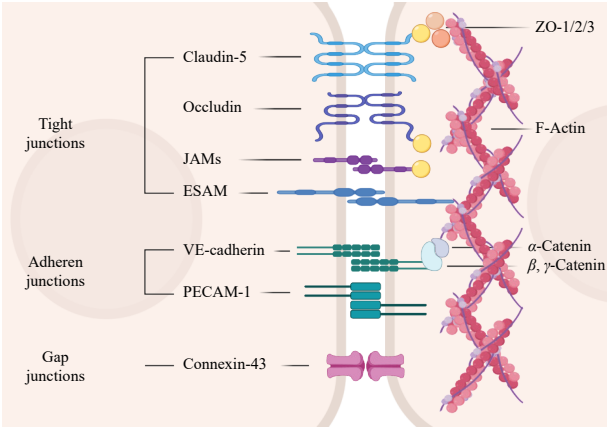


Fig. 1 Schematic representation of the endothelial cell junctions, including tight junctions, adherens junctions and gap junctions. Tight junctions comprise claudin, occludin, JAM, ESAM, among others; the auxiliary protein ZO links their intracellular domains with AC, ensuring strong anchorage. Adhesive junctions consist mostly of VE-cadherin and PECAM-1; *β*- and *γ*-catenin associate with their intracellular domains, while *α*-catenin links them to AC, so establishing a stable complex. Gap junctions primarily refer to Cx43.

2.1.1.1 Tight junction

Claudin participates in homotypic interactions with claudin on adjacent endothelial cells, with its carboxyl terminus associated with ZO, constituting the primary sealing layer of TJs. Among the 27 claudin genes in mammals, claudin-5 is the principal component in the establishment of TJs in the BBB, exhibiting an expression level that surpasses other claudins by a factor of one hundred. Mice possessing doxycycline-inducible shRNA genes targeting *claudin-5* exhibit death three weeks after the onset of protein knockdown [6]. After the initiation of chimeric endothelial-specific *claudin-5* gene ablation in adult mice, BBB permeability to tracers increased from the 6th day of induction, leading to mortality 10 days post-induction [7]. The analysis of the gene expression profile of claudin proteins in human and mouse BMECs indicates that *claudin-5* mRNA is only one of six other notably abundant transmembrane TJs transcripts. The mRNA levels of *claudins-11*, *-12*, and *-25*, as well as *occludin* (pertinent to both humans and mice), and *claudins-1* and *-27* (exclusive to humans) are comparable within the same organism [8]. Single-cell RNA sequencing in mice reveals that *claudin-5* is solely expressed in endothelial cells; *claudin-3* is found in four cell types, including endothelial cells; whereas *claudin-12* and *-25* demonstrate widespread expression [9-11]. In human brain slice capillaries, claudin-11 and claudin-5 display partial expression overlap, indicating a level of synergy and mutual compensation [8, 12]. Studies demonstrate that increased concentrations of claudin-25 interact with occludin, hence indirectly affecting the TJs functionality [13]. Claudins do not constantly operate synergistically. Research demonstrates that claudin-1 is upregulated at both the mRNA and protein levels post-stroke and competes with claudin-5 for binding ZO-1, leading to BBB permeability and impaired recovery [14].

Occludin belongs to the family of tight junction-associated MARVEL proteins (TAMPs). Occludin is often referred to as marvelD1, with the same family of marvelD2, known as tricellulin, and marvelD3. Occludin penetrates the extracellular loop into the intercellular space of the endothelium, interacting with corresponding segments on adjacent BMECs, so promoting the fusion of adjoining cell membranes that restricts paracellular diffusion [15]. Tricellulin is markedly localized in the tricellular contact area, where it plays a vital role in regulating the paracellular permeability of macromolecules [16]. When primary TJs are impaired or their expression reduced due to pathological conditions, marvelD3 can interact with the remaining TJs to form a more stable complex, thereby reducing intercellular gaps and compensating for functional deficiencies. TAMPs is crucial for maintaining the permeability characteristics of BBB [17]. Studies on both animals and humans have shown that occludin degradation is common in ischemic stroke, leading to BBB disruption [18]. The levels of blood occludin fragments during the early phase of cerebral ischemia were found to be positively correlated with the degree of BBB

disruption in a middle cerebral artery occlusion (MCAO) rat model [19]. Shenmai Injection promotes the correct incorporation of occludin into lipid rafts, hence maintaining the BBB integrity during focal cerebral ischemic injury [20].

JAMs and ESAM play a regulatory role in the formation and remodelling of other TJs. Studies demonstrate that JAM-A increases claudin-5 expression through exchange protein directly activated by cAMP, hence reducing endothelial permeability [21]. After the administration of anti-JAMs monoclonal antibodies, JAM-A faces difficulties in forming TJs, and the redistribution of occludin is obstructed [22]. Furthermore, JAM-A can regulate the transcellular migration of leukocytes. In cerebral ischemia/reperfusion injury (CIRI) injury, targeting JAM-A can reduce leukocyte infiltration and alleviate inflammation-induced cerebral damage. The JAM-A antagonist peptide inhibits the interaction between the C2 domain of JAM-A and lymphocyte function-associated antigen on neutrophils and monocytes/macrophages, thereby reducing the binding of JAM-A to leukocytes and lessening the infiltration of neutrophils and monocytes into the brain parenchyma induced by CIRI [23]. Metastatic breast cancer cells in the brain utilize the proteolytic activity of cathepsin S to cleave the extracellular domain of JAM-B, indicating that JAM-B inhibits tumor cell passage across the BBB [24]. Homozygous mutations in the gene that encodes JAM-C might cause abnormal mRNA splicing, resulting in premature stop codons that may lead to cerebral hemorrhage (CH) [25]. ESAM's precise co-localization with occludin, claudin-5, and ZO-1 indicates its presence on TJs [26]. The vascular system barrier in *ESAM*-deficient mice displays anomalies, evidenced by Evans blue leakage [27].

The ZO family interlinks and connects with several TJs and anchors to AC through the SH3 domain. Only ZO-1 and ZO-2 can connect TJs to AC. Studies demonstrate that fluctuations in ZO-1 protein concentrations are significantly associated with the degree of BBB compromise [28]. Post-cerebral IR injury, ZO-1 expression changes can affect the BBB structure and permeability, leading to cerebral edema. Repeated transcranial magnetic stimulation [29], systemic supplementation of *β*-hydroxybutyrate [30], extracellular vesicles (EVs) derived from mesenchymal stem cells and brain endothelial cells [31], USP14-specific inhibitor IU1 [32], *Rhodiola rosea* [33], rhubarb extract [34], and edaravone dexborneol (EDB) [35] can all effectively maintain BBB integrity by enhancing ZO-1 expression.

PKC participates in the regulation of TJs functionality. The suppression of NF1 enhances the PKCδ signaling, diminishing the protective impact of MLN4924 on BBB. PKCδ inhibitor rottlerin can significantly obstruct the increase in BBB permeability caused by *NF1* silencing [36]. The PKCδ-TAT peptide inhibitor demonstrates therapeutic potential in preventing or alleviating sepsis-induced cerebrovascular injury [37]. The suppression of PKC-β may reduce oxidative stress, AC remodeling, and cell apoptosis, thereby alleviating the harm caused by oxygen-glucose deprivation (OGD) to the integrity and function of the BBB formed by human brain microvascular endothelial cells (HBMECs) [38]. During ischemic stroke (IS), hyperglycemia-induced BBB impairment is primarily driven by the activation of PKC-β [39, 40]. After hypoxia treatment, the distribution of nPKC-θ in cortical microvessels undergoes morphological changes, the protein expression of nPKC-θ and aPKC-ζ increases, and nPKC-θ (Thr538) and aPKC-ζ (Thr410) residues are activated by phosphorylation [41].

2.1.1.2 Adherens junction

BMECs simultaneously express *N*-cadherin and VE-cadherin, the latter being specific to endothelial cells. The use of antibodies that block the function of the extracellular domain of VE-cadherin in adult mice can lead to impaired angiogenesis and exacerbated microvascular dysfunction [42]. Diverse signalings influence the VE-cadherin endocytosis process, including Class I PI3Kα, which destabilizes VE-cadherin *via* TNFα signaling [43]; interleukin-1β (IL-1β) binding to its receptor initiates the MYD88-ARNO-ARF6 cascade, hence modifying VE-cadherin localization [44]. Recent discoveries demonstrate that the interaction of p120 with VE-cadherin can inhibit its induced endocytosis [45, 46]. In CNS pathological state, inflammatory cytokines and oxidative stress mediators can facilitate the phosphorylation of VE-cadherin, leading to the disassociation of the VE-cadherin/catenin complex and increased vascular permeability [47]. Five possible phosphorylated tyrosine residues (Y645, Y658, Y685, Y731, and Y733) undermine the integrity of endothelial cell monolayer, while the phosphorylation of serine at VE-cadherin (S665) is involved in the regulation of AJs assembly [48-51]. Tissue inhibitor of metalloproteinases-2 (TIMP2) interacts with α3β1 integrin on endothelial cells, inhibiting Src-dependent phosphorylation of VE-cadherin, destabilization of complexes, and internalization processes, thus promoting the localization of VE-cadherin to the membrane and maintaining TIMP2-mediated barrier integrity. TIMP2 simultaneously promotes the membrane localization of VE-cadherin, which can increase active Rac1 levels and inhibit stress fibre formation [52].

PECAM-1, also known as cluster of differentiation 31 (CD31), is essential for the attachment of leukocytes to BMECs. Studies demonstrate a homophilic interaction between leukocytes and CD31 on the surface of BMECs, promoting adhesion and subsequently influencing leukocyte transendothelial migration to brain tissue [53]. PECAM-1 is also essential for regulating T cell translocation across the BBB [54].

Catenin is a cytoplasmic auxiliary protein of AJs. Wnt/*β*-catenin signaling is crucial for the BBB formation and maintenance. CNS-specific ligands Wnt7a, Wnt7b, and Norrin, secreted by glial cells, engage with Frizzled4 and LRP6 on BMECs, activating the receptors and promoting the translocation of *β*-catenin to the nucleus, which in turn activates the transcription factors TCF and LEF1. These transcription factors regulate the gene expression profile unique to the BBB by enhancing the expression of TJs, solute transporters, and efflux transporters [55]. Initial study suggests that the suppression of the immunoproteasome subunit LMP2 in rats can stimulate Wnt/*β*-catenin signaling, therefore mitigating BBB impairment caused by ischemia and hypoxia [56]. Overexpression of *β*-catenin improved the BBB defects in Unc5B mutant rats by activating this pathway [55]. In the study of attention deficit disorder, innovative optogenetic tools were utilized to manipulate the upstream regulator LRP6, activate the Wnt/*β*-catenin pathway, promote BBB repair, and alleviate related pathology [57]. Activation of the Wnt/*β*-catenin signaling can reinstate the reduced expression of ZO-1 and the transcytosis-inhibiting factor Mfsd2a in BMECs of endotoxemic mice, consequently impeding both paracellular and transcellular permeability of BBB [58]. Teriflunomide augments claudin-1 expression by this pathway in multiple sclerosis, hence strengthening BBB integrity [59]. *γ*-Glutamylcysteine increases BBB permeability and promotes neutrophil extracellular traps (NETs) formation after IS in mice by regulating Wnt/*β*-catenin signaling [60]. Researchers have recently engineered the Wnt7a ligand as a BBB-specific Wnt activator, employing the Gpr124/Reck receptor complex to protect BBB [61]. The precise delivery of Wnt7aK190A to the cerebral vasculature maintained BBB integrity in mice infected with SARS-CoV-2, while concurrently reducing T cell infiltration and microglial activation in the brain, hence improving learning and memory deficits [62].

2.1.1.3 Gap junction

BMECs express Cx37, Cx40, and Cx43, with Cx43 being crucial for maintaining the structural and functional integrity of the BBB. Research demonstrates that recombinant tissue-type plasminogen activator (rt-PA)-induced hemorrhage is substantially

associated with increased phosphorylation of Cx43 [63]. Further investigation reveals that during OGD and reduced extracellular calcium concentrations, pannexin 1 (Px1) and Cx43 hemichannels in BMECs are activated, leading to the release of intracellular taurine and adenosine triphosphate (ATP), which ultimately results in the impairment of BBB transport [64, 65]. In familial cerebral cavernous malformation type III (fCCM3) lesions, Cx43 protein is aberrantly raised, whereas fCCM3 lesions are characterized by high BBB permeability. *In vitro* evidence indicates that Cx43 regulates the localization of ZO-1, consequently limiting the formation of TJs and their *trans*-interactions, which contributes to BBB disruption; however, the Cx43 inhibitor GAP27 can obstruct these changes [66].

2.1.1.4 Actin cytoskeleton

Filamentous actin (F-actin) is a crucial component of AC that engages with the transmembrane proteins of TJs and AJs through cytoplasmic attachment proteins, thereby playing a vital role in their stability. During the early stage of stroke, the rupture of BBB transpires independently of MMPs, resulting from the rapid rearrangement of AC in BMECs. In response to specific stressors, BMECs rapidly polymerize globular actin (G-actin), initially existing as short filaments and dispersed monomers, into F-actin, leading to the development of linear stress fibres. The polymerisation process is linked to actin contraction and increased cytoskeletal tension, resulting in the morphological contraction of BMECs. By linking accessory proteins, TJs and AJs are promoted to be damaged, ultimately leading to BBB impairment [67]. Mild hyperthermia mitigates BBB permeability. RNA sequencing data from microvessels indicated that mild hyperthermia diminished the transcription of pathways associated with actin polymerization, attenuated the ROCK1/MLC pathway, and impeded the conversion of G-actin to F-actin [68]. Astragalus purpurascens significantly enhanced the expression of non-phosphorylated actin depolymerization factor (ADF) during the early CIRI phase, facilitating the depolymerization of stress fibers and preservation of AC [69]. In the late CIRI phase, it activated the Wnt pathway, suppressed MMP-9 expression, diminished extracellular basement membrane (BM) degradation, and elevated connexin expression. In an *in vitro* OGD model, endothelial overexpression of heat shock protein B8 suppresses abnormal actin polymerization, therefore preserving BBB integrity [70].

2.1.2. Transport barrier

The transport barrier of BBB is the essential mechanism for enabling transcellular selective transport of substances, comprising complex molecular transport networks (Fig. 2). Carrier-mediated transport (CMT) relies on specialist transporters. These transporters may precisely recognize and bind certain nutrients or substances, then translocating them across the membrane to the CNS through conformational alterations, so satisfying the metabolic demands of neurons and other brain cells. In receptor-mediated transcytosis (RMT), specific receptors on the cell membrane bind to ligands, forming a receptor-ligand complex that subsequently moves throughout the CNS through endocytosis and exocytosis. This approach has high specificity and efficiency. Adsorptive-mediated transcytosis (AMT) relies on the interaction of cell surface charges, allowing positively charged molecules to attach to the cell surface and then facilitate transcellular transport through endocytosis and exocytosis. It can recognize and bind to several endogenous and exogenous substances. Ion pumps enable the movement of ions against their concentration gradient by active transport, hence playing a crucial role in maintaining ionic balance. The efflux pump actively expels harmful substances and excess materials from the cell to the outside, thereby preserving a clean and stable CNS internal environment.

2.1.2.1 Carrier-mediated transport

The glucose transporter 1 (GLUT1) primarily enables the passage of glucose over the BBB into the brain. Inhibition of GLUT1 in mice can reduce the proliferation rate of the brain-derived endothelium bEND.3 cell line by 40% and delay angiogenesis [71]. In Alzheimer's disease (AD) murine models, the lack of endothelial cell GLUT1 can result in plasma protein extravasation, compromised TJs, and premature disruption of the BBB [72]. The knockout of GLUT1 in mice diminishes lactate production in endothelial cells, leading to reduced pericyte coverage in the retina and cerebral vasculature, which subsequently increases BBB permeability [73]. Pharmaceuticals can be conjugated with glucose to enhance their absorption in the brain, utilizing the characteristics of GLUT1. Studies formulated a lipophilic thiamine disulphide system that conjugates ibuprofen with L-ascorbic acid to produce a prodrug, demonstrating significant permeability across the BBB *via* GLUT1 and the sodium-dependent vitamin C transporter SVCT2 [74]. The researchers developed a galactose-modified

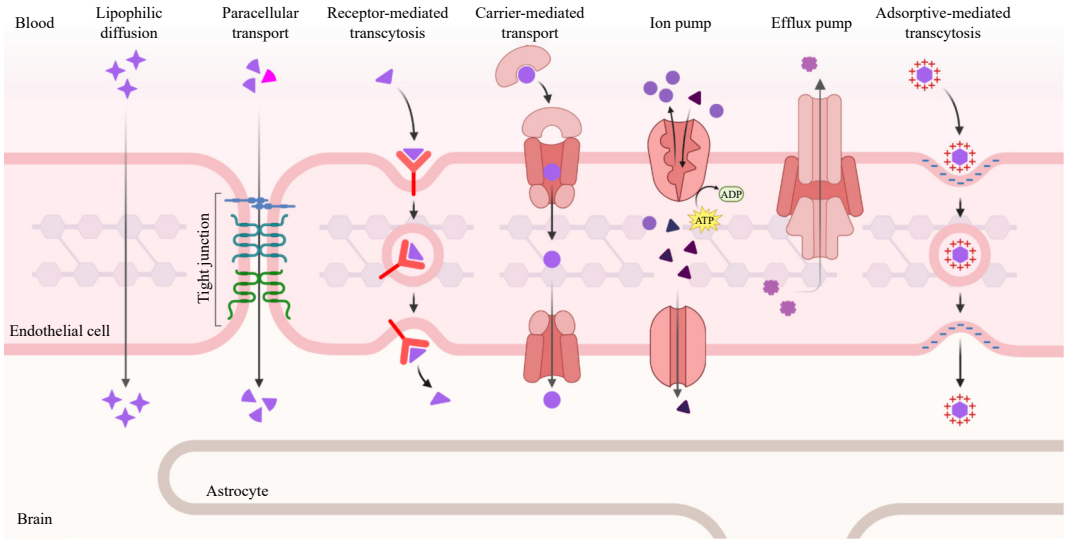


Fig. 2 Schematic representation of the transport systems across endothelial cells in the BBB. Lipophilic diffusion enables lipophilic compounds to permeate membranes according with the concentration gradient. Paracellular diffusion denotes the movement of substances through intercellular connections, governed by the integrity of these junctions. Receptor-mediated transcytosis entails the interaction of certain receptors on the membrane with ligands to create a complex, subsequently transferred through endocytosis and exocytosis. Carrier-mediated transport depends on transport proteins to selectively identify and bind substances, facilitating transport *via* conformational alterations. Ion pumps actively transport ions against their concentration gradient to sustain ionic equilibrium. Efflux pumps actively remove deleterious and surplus substances. Adsorptive-mediated transcytosis employs interactions with cell surface charges to attach positively charged molecules, subsequently transporting them through endocytosis and exocytosis.

nano-delivery system, employing GLUT1 to transport BACE1 siRNA across the BBB, therefore effectively reducing BACE1 expression in APP/PS1 transgenic mice [75]. Three major amino acid transport systems are present in the BBB: large neutral amino acid transporter (LAT), cationic amino acid transporter (CAT), and cysteine/glutamate exchange (system Xc-). LAT1 can transport only small molecule drugs that are coupled with natural amino acids or structurally similar molecules across blood-brain endothelial cells BMECs [76]. L-DOPA, a treatment for Parkinson's disease (PD), associates with the LAT1 recognition site and is transported into BMECs *via* LAT1 [76,77]. Furthermore, LAT1 can effectively enable the *trans*-BBB transport of several clinical CNS pharmaceuticals and prodrugs, such as baclofen, *α*-methyl-dopa, and gabapentin [78]. SLC22A17 belongs to the solute carrier family 22 (SLC22). After *in vivo* brain ischemia, the endothelial expression of SLC22A17 in the brains of both humans and mice increases with BBB permeability. In cultures of HBMECs, short interfering RNA (siRNA) targeting *SLC22A17* can impede TNF-α-induced ferroptosis and the downregulation of TJs, significantly improving BBB integrity in a localized cerebral ischemia animal model [79]. Multi-omics research demonstrates that Slc22a8 is downregulated in the BBB subsequent to middle cerebral artery occlusion (MCAO). The overexpression of the *Slc22a8* markedly preserves BBB integrity after MCAO [80]. Organic cation transporters (OCTs), members of SLC22 family, enable the transport of organic cations. OCT1 and OCT2 are situated on the luminal surface of the BBB and facilitate the translocation of cationic medicines, such as memantine and metformin, into the CNS [81].

2.1.2.2 Receptor-mediated transcytosis

The transferrin receptor (TfR) is crucial for the iron absorption facilitated by transferrin (Tf). In the early 21st century, drugs such as doxorubicin and cisplatin were utilised in cancer therapy through direct covalent linkage to Tf [82]. Subsequently, the academic community investigated the coupling methodologies of Tf/TfR with nanocarriers [83,84]. T7 is a peptide that associates with TfR. In a rat model of intracranial glioblastoma, tail vein injection of T7 peptide-modified exosomes containing microRNA-21 antisense oligonucleotides demonstrated efficient delivery of microRNA-21 antisense, leading to a reduction in tumour volume [85]. The amalgamation of Tf with the anti-*β*-secretase 1 antigen-binding fragment (ATV:BACE1) leads to increased levels of ATV:BACE1 in the brains of rodents and non-human primates, and intravenous injection causes a dose-dependent reduction in *β*-amyloid (Aβ) levels in CNS [86]. Recently, researchers engineered the adeno-associated virus BI-hTFR1, which can specifically bind to human TfR1. BI-hTFR1 can be actively transported by HBMECs, and relative to AAV9, the observed gene expression level in the CNS of human *TFRC* knock-in mice increased by 40 to 50 times [87]. Japan has approved Pabinafusp alfa (JR-141) from JCR Pharmaceutical Company, a fusion protein that combines an anti-TfR antibody with human iduronate-2-sulfatase (IDS), for the treatment of mucopolysaccharidosis II [88]. The insulin-like growth factor 1 receptor (IGF1R), insulin-like growth factor 2 receptor (IGF2R), and insulin receptor (INSR) are involved in the RMT mechanism at BBB. Research demonstrates that the ablation of *INSR* significantly alters the expression of TJs and several transport proteins in hCMEC/D3 cells [89]. The amalgamation of IGF-1 and methotrexate has successfully completed a Phase I trial targeting late-stage tumours that express IGF1R (NCT02045368). ABL Bio's bispecific antibody ABL301 targets IGF1R for trafficking across the BBB and aggregated *α*-synuclein (*α*-Syn). It is now in the preclinical development stage for the treatment of PD [90]. Scavenger receptors (SR) include SR-A, SR-B1, and SR-B2, among others. Researchers have engineered a biomimetic nanoparticle that enhances transport across the BBB by specifically targeting SR-B1 and CD15. This method combines apolipoprotein A1 and anti-CD15 to enhance the delivery effectiveness of sonic hedgehog (SHH) subtype medulloblastoma treatments [91]. A distinct study created a peptide-based carrier altered with the targeting ligand angiopep-2 for the transport of plasmid DNA across the BBB through low-density lipoprotein receptor-related protein-1 (LRP-1). This carrier can be given to BMECs by LRP-1 and can also infiltrate BMECs through SR-A and SR-B1 [92]. A separate research team developed a truncated mini LRP1 to function as a liposome carrier. This carrier can penetrate the BBB and transport the *γ*-secretase modulator BB25 from the luminal to the basolateral side, therefore reducing the expression of neurotoxic Aβ42 peptides [93].

2.1.2.3 Adsorptive-mediated transcytosis

Cell-penetrating peptides (CPPs) are a class of membrane transduction tools consisting of short amino acid sequences that can be modified to enhance the efficiency of transport of exogenous drugs across the BBB. CPPs are principally classified into three categories according to their physicochemical characteristics: hydrophobic peptides, cationic peptides, and amphipathic peptides [94]. *In vitro* studies indicate that specific amphiphilic CPPs had enhanced the BBB permeability; nevertheless, *in vivo* research shows that the penetration of cationic CPPs into brain parenchyma is significantly higher than that of amphiphilic CPPs [95]. Cationic cell-penetrating peptides are efficiently internalised by intracellular organelles through electrostatic interactions. Classical CPPs, such as the human immunodeficiency virus TAT peptide (YGRKKRRQRRR), bind to acetylheparan sulfate proteoglycans (HSPGs) on the surface of BBB endothelial cells *via* arginine-rich cationic sequences and enter the cells *via* adsorption-mediated endocytosis (AMT). It was shown that Ang and TAT dual peptide-modified sEVs not only show glioma cell and BBB selectivity but also can significantly enhance BBB permeation and glioma tumor penetration in the brain [96]. PepH3 is a cationic peptide derived from the capsid protein of Dengue Virus Type 2 (DENV-2) [97]. Research demonstrates that PepH3 exhibits a 24-h migration rate of 67.2% in an *in vitro* BBB migration assay and a brain biodistribution of 0.31% after 5 min in an *in vivo* context. Studies on endocytosis inhibitors suggest that the action mechanism of PepH3 corresponds with AMT [98].

2.1.2.4 Ion pump

Sodium-hydrogen exchanger isoform 1 (NHE1) is closely linked to BBB integrity. NHE1 dysregulation may affect the BBB integrity during cortical spreading depression events [99]. NKAα1 maintains BMECs functioning by inhibiting ferroptosis and regulating the autophagy-lysosome degradation pathway. Hamaudol, an NKAα1 activator, shows promise in improving endothelial dysfunction in diabetes [100]. During the early stage of ischemic stroke, the KCa3.1 inhibitor TRAM-34 significantly diminished edema formation and Na^+ accumulation in the rat brain [101]. A deficiency in TWIK-associated potassium channel-1 (TREK1) leads to increased synthesis of adhesion molecules, hence promoting immune cell migration and exacerbating symptoms of experimental autoimmune encephalomyelitis (EAE) [102].

2.1.2.5 Efflux pump

P-gp is the most well-known efflux pump. Notwithstanding possible threats to the integrity of the BBB, P-gp in the vasculature will persist in obstructing drug distribution and reducing therapeutic efficacy, impacting anticancer agents such as paclitaxel, doxorubicin, methotrexate, and vincristine; *β*-lactam antibiotics like ceftriaxone; and peptide therapeutics including pepstatin and valinomycin [103-106]. To improve the efficiency of CNS drug delivery, chemical modifications can be made to reduce the affinity of the drug for the efflux transporter or in combination with efflux pump inhibitors. Preclinical studies demonstrate that the inhibition of P-gp can significantly increase the brain permeability of P-gp substrate drugs by a factor of 2 to 100 [107]. However, in clinical applications, the majority of commercially available P-gp inhibitors, even at maximum dosages, demonstrate an inhibition rate of less than 50%, and the augmentation of therapeutic drug

permeability in the brain is under twice. Focused ultrasound (FUS) can enable limited and reversible disruption of the BBB. After ultrasonic therapy, the expression of P-gp in both the treated area and the contralateral brain region continues to decrease for up to three days [108]. The chemical derivative TX-67 of paclitaxel exhibits enhanced ability to penetrate the BBB relative to paclitaxel and can reduce the efflux activity of BMECs [109]. Analogues generated by the incorporation of carboxyl or amino groups at the C7 position of paclitaxel can likewise reduce P-gp efflux activity [110]. The multidrug resistance-associated protein (MRP) family and breast cancer resistance protein (BCRP) have analogous roles.The MRP family facilitates the movement of various endogenous and exogenous chemicals from cells, including intracellular glutathione conjugates, glucuronide conjugates, and numerous other compounds. These conjugates typically represent detoxified variants of intracellular metabolites or deleterious compounds, and the transporter function of the MRP family facilitates the expulsion of these substances from the cell, hence preserving the stability of the intracellular milieu [111]. BCRP facilitates the transfer of certain chemotherapeutic agents, riboflavin, and additional chemicals from intracellular to extracellular environments [112]. In tumor therapy, the presence of BCRP may induce resistance of tumor cells to chemotherapeutic agents; nevertheless, under normal physiological settings, it also participates in the metabolism and transport of chemicals, safeguarding the CNS from potentially deleterious compounds. Through collaborative function, the efflux pumps maintain the purity and stability of the CNS's internal environment, hence ensuring the normal operation of the nervous system.

2.1.3. Metabolic barrier

Phase I and Phase II drug-metabolizing enzymes expressed in BBB endothelial cells further limit CNS drug exposure by prescavenging drugs that enter the brain. The metabolizing enzymes synergize with ABC transporter proteins to reverse the efflux of drug metabolites out of the BBB, forming a "metabolism−exfiltration" double barrier. Phase I drug-metabolizing enzymes predominantly include various oxidoreductases and hydrolases, which introduce/expose polar groups of drugs primarily through oxidation, reduction, or hydrolysis to increase their water solubility. The most often expressed Phase I enzyme is CYP450. In recent years, more than twenty variations of CYP450 have been discovered in the brain. Research indicates that metabolites from CYP1B1, particularly hydroxyeicosatetraenoic acids (HETEs), reduce the inhibitory effect of manganese on TJs *via* PPARγ activation, while epoxyeicosatrienoic acids (EETs) alleviate manganese-induced oxidative stress by regulating the KLF/MAO-B axis and NRF2 expression [113]. Additionally, retinoic acid and 20-hydroxyeicosatetraenoic acid produced by CYP1B1 might respectively affect P-gp and TJs, hence modifying the characteristics of BBB. Inhibition of CYP1B1 *in vivo* increases BBB permeability, consistent with the downregulation of CYP1B1 in glioma endothelial cells [114]. The reduced expression of CYP2D4 in the brains of epileptic rats may alter the pharmacokinetics and pharmacodynamics of several medications in the brain [115]. The expression of CYP3A4 in the epileptic brain is associated with seizure frequency and is influenced by the combination of antiepileptic drugs (AEDs). The simultaneous injection of multiple CYP3A4 substrates significantly increases CYP3A4 expression. Fluctuations in CYP3A4 expression may serve as a criterion for adjusting AEDs therapy regimens [116]. CYP3A inhibitors may lead to the accumulation of the multi-target receptor tyrosine kinase inhibitor ponatinib and its active metabolite *N*-desmethyl ponatinib in the brain [117]. Phase II drug-metabolizing enzymes operate as conjugating enzymes, which catalyze the binding of drugs or Phase I metabolites to endogenous molecules to further facilitate excretion. Reports show that phase II drug-metabolizing enzymes in the brain include uridine 5'-diphosphate-glucuronosyltransferases (UGTs) and glutathione *S*-transferases (GSTs). Reports suggest that UGT1A can enhance the glucuronidation of various medicines, neurotransmitters, and neurosteroids in multiple brain regions of rats, hence altering the pharmacological actions of these compounds in brain [118].

2.2. Non-endothelial components

2.2.1. Pericytes

Pericytes (PCs) and BMECs are linked by a common basement membrane, facilitating direct interaction *via* *N*-cadherin and GJs [119]. BMECs secrete platelet-derived growth factor-BB (PDGF-BB), which engages with the heparan sulphate proteoglycans in BM, influencing PC proliferation, migration, and recruitment to the vascular wall through PDGFRβ receptors in PCs. Mice lacking PDGF-B or PDGFRβ exhibit a complete absence of PCs, leading to CNS microvascular rupture, the formation of microaneurysms, and embryonic mortality [120]. Conversely, PCs can also release signaling molecules that affect the BBB. The PCs respond within 1 h after ischemic stroke, before the deterioration of endothelial TJs, the death of BMECs, and the compromise of BBB [121]. In the Aβ oligomer stereotaxic injection animal model, elevated pro-inflammatory cytokine levels hinder the development of TJs in BMECs [122]. A deficiency in PCs will lead to the loss of components generated from the foot activities of astrocytes (ACs) [123]. Compared to mice expressing apolipoprotein E3 (APOE3), mice expressing APOE4 demonstrate reduced levels of type IV collagen, indicating that E4-type PCs may impair BBB integrity by altering the extracellular matrix (ECM) [124].

In aging or pathological conditions, elevated levels of PDGF-BB induce PDGFRβ to detach from the PCs cell membrane *via* MMP-14 [125]. The lack of PCs leads to heightened endothelial transcytosis, allowing toxins to infiltrate the brain parenchyma and causing damage to the BBB [126]. The deficiency of phosphocreatine may precipitate dementia by the disruption of BBB and insufficient perfusion [127]. APOE4 accelerates PCs loss and enhances the activation of the LRP1-dependent CypA-MMP-9 pathway, thus exacerbating the BBB disruption [128]. In traumatic brain injury (TBI), the suppression of the ETS transcription factor Fli-1 can reduce BBB compromise [129]. Furthermore, Foxf2 is solely expressed in PCs, and $Foxf2^{-/-}$ mice have intracranial hemorrhage, perivascular edema, weakening of BM, increased endothelial cell caveolae, and disruption of BBB. The adult inactivation of Foxf2 leads to the disruption of BBB, hypertrophy of endothelial cells, and increased transendothelial vesicular transport [130]. Mice deficient in activin receptor-like kinase 5 (ALK5) within PCs exhibit pronounced germinal matrix hemorrhage (GMH) throughout development, characterized by heightened endothelial cell proliferation, arterial dilation, and reduced PCs coverage. A deficiency of ALK5 in PCs diminishes TIMP3 expression, while the introduction of TIMP3 can improve endothelial cell morphogenesis, increase PCs coverage of endothelial cells, and alleviate GMH.

In terms of pharmacological intervention strategies, atorvastatin promotes the maturation of the BBB in newly created blood vessels, with its mechanism associated with the regulation of endothelial TJs formation by proliferating NG2-positive PCs [131]. EDB improves PCs coverage and prevents BBB disruption during CIRI through the laminin-integrin and PDGFB/PDGFR-β pathways [132]. Imatinib inhibits the conversion of progenitor cells into fibroblasts and reduces inflammation and vascular permeability after spinal cord injury (SCI) by blocking the PDGF-BB/PDGFR-β signaling [133]. PC-derived EVs reduce hypoxia-induced permeability in BMECs by upregulating the expression of ZO-1 and claudin5 [134]. Proteomic analysis indicates the presence of angiopoietin-1 (Ang-1) in the vesicles [135]. Ang-1 is continuously secreted by

PCs, engages the Tie2 receptor, activates the PI3K/Akt pathway, promotes the synthesis of proteins such as occludin and VE-cadherin, and stabilizes endothelial cells [136, 137]. miR-27a, released by PC-EVs, targets VE-cadherin, undermining BBB integrity, while miR-27b promotes interaction between BMECs and PCs, strengthening the endothelial barrier by targeting semaphorin 6A/D [138, 139]. Exosomes containing miR-210-5p can influence endothelial barrier function by inhibiting JAK1/STAT3 [140]. *In vivo* and *in vitro* models indicate that the mitochondrial-targeted antioxidant Mito-TEMPO can reduce mitochondrial oxidative stress, prevent PCs apoptosis, and alleviate BBB leakage [141]. Tunnelling nanotubes enable the transfer of mitochondria from healthy PCs and BMECs to damaged ACs, thereby protecting them from ischemia-induced apoptosis and aiding in the repair of BBB in neurological disorders [142].

2.2.2. Astrocytes

In physiological conditions, AC terminals connect to BM through aquaporin IV, dystroglycan-dystrophin complexes, and agrin. Research demonstrates that transforming growth factor-β1 (TGF-β1) secreted by ACs can enhance ZO-1 expression and augment endothelial barrier function through the non-canonical hedgehog signaling [143]. ACs can also influence BBB integrity and permeability through the Slc4a4-CCL2 and endothelial CCR2 pathways [144].

Quiescent ACs can transform into the A1 phenotype when stimulated by pro-inflammatory stimuli [145]. Semaglutide can obstruct this transition, hence reducing BBB damage [146]. A1-type ACs can directly undermine the integrity of the BBB by upregulating cytokines, chemokines, proteases, and reactive oxygen species (ROS) [147]. In PD, oligomeric *α*-Syn activates adenylate cyclase, leading to increased production and release of VEGF-A and nitric oxide, which causes BBB disruption [148]. RNA sequencing of reactive ACs revealed that *CCL5* is one of the most significantly upregulated genes. *CCL5* deletion in ACs can reduce $CD8^+$ T cell invasion, increase ZO-1 and occludin expression, and decrease Evans blue leakage [149]. In multiple sclerosis (MS), fingolimod and siponimod can inhibit the transendothelial migration of peripheral blood mononuclear cells (PBMCs) by decreasing the release of CCL2 [150]. Post-stroke, polymerase *δ*-interacting protein 2 (POLDIP2) is elevated in ACs, augmenting BBB permeability by facilitating the secretion of IL-6, chemokine (C-C motif) ligand 2 (CCL2), TNF-α, VEGF, and MMPs [151]. Inhibiting MMP3 *in vitro* or specifically reducing MMP3 *in vivo* in reactive ACs, can both alleviate hemorrhagic BBB breach [152]. Moreover, Exenatide can reduce the levels of ACs-derived VEGF-A, MMP-9, chemokine ligand 1 (CXCL-1), and monocyte chemoattractant protein 1 (MCP-1) in the cerebral tissue of MCAO rats, with the reduction in VEGF-A and MMP-9 associated with an increase in TJs expression [153]. ROS can directly promote the production of A1-type ACs, and the ROS produced by microglia can exacerbate this change [154]. In contrast, A2-type ACs secrete growth factors, cytokines, and other compounds that can accelerate the anti-inflammatory response. IGF-1 released by ACs can promote the transformation of immune cells into an anti-inflammatory phenotype, hence maintaining BBB integrity following stroke [155]. In a rat photothrombotic stroke model, the synthesis of TGF-β and VEGF in A2-type ACs increased, leading to reduced BBB permeability, improved vascular integrity, and heightened angiogenesis [29].

Various factors influence the effect of ACs on the BBB. Studies demonstrate that APOE4 disrupts BBB integrity through an ACs-specific mechanism. Eradicating APOE4 produced by ACs can restore the integrity of the BBB [156]. ACs-expressing dentin matrix protein 1 (Dmp1) can transport mitochondria to BMECs. Inhibiting the mitofusin 2 (*Mfn2*) gene in Dmp1-positive ACs will obstruct mitochondrial transport and undermine BBB integrity [157]. The glycosylation of Dmp1 can maintain the integrity and functionality of BBB by regulating the expression of ECM constituents [158]. The absence of neogenin-1 (NEO1) in ACs leads to increased proliferation of BMECs and modifications in BBB structure. Hepcidin treatment can effectively improve endothelial dysfunction and restore BBB integrity in NEO1 deletion models and subarachnoid hemorrhage (SAH) models [159]. A recent study indicates that ACs can maintain vascular coverage in the brain. An isolated ACs ablation triggers a replacement mechanism of ACs end-feet, with pSTAT3 playing a crucial role in this process. Inhibiting its phosphorylation reduces the replacement process [160]. However, after tamoxifen-induced ACs ablation, disruption of the BBB persists for several weeks. Adjacent astrocytes display elevated GFAP levels and morphological changes; nevertheless, a significant proliferative response is not observed [161]. Post-MCAO, the expression of *N*-Myc downstream-regulated gene 2 (NDRG2) in ACs increases, potentially influencing BBB permeability *via* enhancing MMPs expression following cerebral ischemia [162]. Glutathione (GSH) released by ACs can alleviate damage-induced endothelial permeability, while exogenous GSH can prevent the disruption of TJs [163]. In NHE1 gene knockout rats in ACs, occludin expression is increased, MMP-9 is reduced, BBB disruption is mitigated, and 24 h post-MCAO, cerebral blood flow in the ischemic region significantly increases [164]. Mutant superoxide dismutase 1 (SOD1) and sporadic amyotrophic lateral sclerosis (ALS) inappropriately release glutamate, which can increase the expression of P-gp in endothelial cells *via* *N*-methyl-D-aspartate receptor (NMDAR) activation [165]. TIMP1 can protect the BBB during SAH by inhibiting the ubiquitination of AC β1 integrin [166]. The ACs p75 neurotrophin receptor (p75NTR) enhances NF-κB and hypoxia-inducible factor-1α (HIF-1α) signaling, leading to the upregulation of MMP-9 and VEGF production, which subsequently results in TJs disruption following ischemia [167]. EVs derived from OGD-activated ACs influence the ARHGAP25/Wnt/*β*-catenin pathway and alleviate BBB damage by transferring miR-27a-3p to bEnd.3 cells [168].

2.2.3. Basement membrane

Reports indicate that leukocytes take approximately 5 min to cross the endothelial layer, whereas penetrating the underlying BM requires 20 to 30 min [169]. BM, a unique acellular component of the neurovascular unit, is a highly dynamic portion of the BBB, synthesized and deposited by several cell types, including BMECs, ACs, and PCs [170]. The principal proteins of BM are laminin, collagen type IV, nidogen, and perlecan. These components operate as ligands, binding to two ECM receptors, talin and integrins, thereby initiating a signaling cascade that regulates barrier function [171]. The human IgG monoclonal antibody L13 significantly reduces BBB disruption in two stroke models, specifically cerebral IR and intracerebral hemorrhage (ICH), by inhibiting the breakdown of BM and TJs facilitated by MMP-9 activity [172].

Laminin is a key ECM protein in the BM, composed of three subunits: α, β, and γ. Currently, five types of α subunits, four types of β subunits, and three types of γ subunits have been identified, which can combine to generate up to 20 unique laminin isoforms [173]. Research shows that nestin-Cre-mediated laminin γ1 conditional knockout (γ1-NKO) mice exhibit considerable breakdown of BBB and spontaneous ICH, primarily in deep brain regions such as the hypothalamus, thalamus, and basal ganglia [174, 175]. Subsequent mechanistic studies demonstrated that the absence of AC-derived laminin-γ1 impedes smooth muscle cell maturation, leading to vascular rupture, while facilitating the differentiation of PCs from a quiescent to a contractile state, thereby transforming their function from protecting the BBB to undermining it [174, 175]. A recent *in vivo* study revealed that the conditional deletion of Dab1 in BMECs leads to BBB permeability and reduced coverage of AC endfeet on cerebral capillaries. This indicates that Dab1-activated BMECs engage with ACs through

laminin α4 to maintain the barrier [176]. A distinct study created a dual mutant lacking laminin-α5 in both BMECs and mural cells (α5-TPKO). Endothelial-specific conditional knockout (α5-TKO) and selective mural cells laminin-α5 knockout (α5-PKO) mice exhibited no significant BBB impairment, but α5-TPKO mice demonstrated BBB disruption [177, 178]. This indicates that BMECs and mural cells-derived laminin-α5 actively maintain neurovascular integrity through a transcellular mechanism rather than a paracellular one. Although α5-TKO and α5-PKO animals exhibit no significant impairments under homeostatic conditions, both models display increased BBB permeability and leukocyte infiltration during ICH and IR events [177, 179, 180]. Subsequent research demonstrated that mural cell-derived laminin obstructs transcellular transport by reducing caveolin-1 expression in BMECs, hence alleviating BBB damage [181]. In a mixed FVB/C57Bl6 background, pericyte-specific conditional knockout (γ1-PKO) mice exhibited BBB dysfunction and hydrocephalus [182]. Due to the potential disruption of BBB integrity by hydrocephalus, γ1-PKO mice were subsequently crossbred with pure C57Bl6 background mice. γ1-PKO rats exhibited little disruption of BBB in advanced age rather than in youth, and in the absence of hydrocephalus, indicating that PC-derived laminin-γ1 is crucial for maintaining BBB integrity [183]. Mutant mice lacking laminin γ1 in oligodendrocyte lineage cells (γ1-OKO) exhibit signs of BBB breakdown. In these mutations, transcellular transport is enhanced, while paracellular transport is erratic [184]. Mice lacking laminin-α2 throughout the brain (lama2$^{-/-}$) exhibit BBB disruption and vascular abnormalities at three weeks of age, marked by compromised TJs, reduced PCs coverage, and hypertrophy of AC endfeet [185].

Collagen type IV is also a predominant element of BM, comprising three *α* chains. Currently, six varieties of collagen type IV *α*-chains (COL4A1–6) have been identified, with COL4A1 and COL4A2 present in almost all BM. The deletion of exon 41 from COL4A1 in ACs leads to negligible intracerebral bleeding; however, the same mutation in BMECs or PCs causes fully penetrant ICH and incompletely penetrant hole malformations [186]. In Fgfbp1 knockout mice, the buildup of collagen type IV in BM is reduced, leading to compromised connections between BMECs and PCs, along with increased neurovascular permeability [187]. Nidogen can stabilize networks of collagen type IV and laminin. Currently, two isoforms of nidogen (nidogen-1 and nidogen-2) have been identified; however, the exact processes by which they bolster BBB integrity remain unclear [188]. Perlecan is a macromolecular protein found in most BM. Studies have demonstrated that perlecan promotes the endocytosis of FGF in endothelial cells of the BBB, with FGF considered an essential soluble factor for maintaining the integrity of the BBB [189]. Studies demonstrate that the proteolysis of ECM components post-stroke produces ECM protein fragments, notably the *C*-terminal domain V (DV) of perlecan, which may enhance angiogenesis [190]. Further research demonstrates that the DV segment of perlecan enhances the phosphorylation of PDGFRβ, SHP-2, and FAK, induced by PDGF-BB through integrin α5β1, hence promoting PCs migration and contributing to the maintenance and recovery of BBB after ischemic stroke [191].

2.2.4. Neurons

Neurons secrete GDNF, which enhances the expression of claudin-5 and VE-cadherin, hence augmenting BBB integrity [192]. In ischemic stroke, zinc transporter 3 (ZnT3) promotes the excessive release of Zn from neurons into the synaptic cleft, where Zn interacts with MMP-2, enhancing its activity and leading to the degradation of TJs and compromise of BBB [193]. Neurons were co-cultured with BMECs and ACs after a 3-h OGD treatment. The findings suggested that ischemic neurons activate ACs to augment VEGF synthesis, consequently resulting in the disruption of the endothelial barrier [194]. Serpina3n, a serine protease inhibitor, was significantly elevated in ischemic brain neurons, diminished the activities of granzyme B and neutrophil elastase released by T cells and neutrophils, and alleviated BBB disruption and immune cell infiltration post-stroke [195]. In herpes simplex virus (HSV)-1 encephalitis, the IL-1-dependent chemokine CXCL1, produced by perivascular ACs and neurons, is essential for the CXCR2-mediated migration of neutrophils across the endothelium into the brain, resulting in their accumulation in the lacunae; these neutrophils may substantially enhance the permeability of BBB [196]. In the cerebral tissue of mice infected with the rabies virus, the expression of chemokine CXCL10 was first detected in neurons three days post-infection, resulting in the activation of microglia (MG) and ACs, infiltration of inflammatory cells, upregulation of chemokines and cytokines, diminished expression of TJs, and increased permeability of BBB [197]. Adenosine produced by neurons and adenylyl cyclase increases BBB permeability through A1 and A2A adenosine receptor signaling located on BBB cells. Selective agonist-induced adrenergic receptor signaling transiently enhances BBB permeability, allowing macromolecules to enter the CNS; antagonism of adrenergic receptor signaling prevents the infiltration of inflammatory cells and soluble substances into the brain [198]. Furthermore, neuronal activity regulates the expression of circadian rhythm genes in BMECs, hence affecting the function of BBB efflux transporters [199].

2.2.5. Microglia

Multiple studies demonstrate that quiescent microglia play a role in maintaining the BBB phenotype. Co-culturing mouse BMECs with quiescent MG can enhance the expression of occludin and ZO-1 [200]. *In vivo* tests indicate that MG can directly provide claudin-5 to BMECs, promoting the establishment of TJs [201]. The maintenance of the BBB in adult mice depends on the secretion of PDGFB by MG. The sudden loss of microglial PDGFB markedly compromises BBB integrity, leading to the death of mice exposed to lipopolysaccharide (LPS) stimulation [202].

In a chronic inflammatory state, MG phagocytose AC endfeet, compromising the integrity of BBB [201]. The introduction of LPS-activated MG to the luminal surface of the BBB model may lead to BBB rupture, accompanied by a significant increase in 19 types of cytokines and chemokines on the luminal side [203]. Pro-inflammatory cytokines produced by M1-type MG can promote the excessive generation of ROS and nitric oxide (NO), together with the activation of MMP-9, therefore undermining the integrity of BBB [204, 205]. IL-1β increases BBB permeability *via* reducing the expression of ZO-1, occludin, and claudin-5 [206, 207]. TNF-α stimulates PCs to release MMP-9 [208]. Moreover, TNF-α therapy can eliminate the efflux activity of P-gp mediated by the endothelin B receptor [209]. Interferon-γ (IFN-γ) compromises the integrity of the BBB and promotes the migration of CD4 T cells [210]. IL-6 can reduce the levels of claudin-5 and occludin in isolated ovine cerebral microvessels [211]. Increased secretion of CCL2 promotes the migration of monocytes and macrophages across the BBB. CXCL10 can promote the migration of monocytes and macrophages over the BBB, a phenomenon noted in ischemic stroke [212], AD [213], and TBI [214]. Research indicates that the NLRP3 inflammasome increases the expression of MMP-2 and MMP-9, reduces the expression of TJs, and raises endothelial cell permeability [215]. Acteoside can inhibit inflammation and pyroptosis through the HMGB1/TLR4/NLRP3 pathway, hence safeguarding the BBB from ischemic stroke injury [216]. Fibrinogen triggers the NLRP3 inflammasome in MG and transmits pro-inflammatory signals through EVs, thereby affecting BBB integrity [217]. Research indicates significant alterations in circadian rhythms affecting inflammation-induced disruption of the BBB, demonstrating that the exacerbation of barrier damage at night is alleviated by microglial clearance or housing mice in a constant dark environment [218]. Conversely, ROS operate as a ubiquitous activator for several downstream path-

ways that directly impact and undermine the BBB [219]. ROS transiently stimulates the PI3K/AKT pathway through its upstream mediator Rho, resulting in the breakdown of TJs [220]. Inducible nitric oxide synthase (iNOS) promotes the production of NO and peroxynitrite during the reoxygenation phase after stroke, thereby reducing ZO-1 expression [221]. In murine models of CIRI, pharmacological inhibition of iNOS can attenuate the activity of MMP-2/-9, hence mitigating BBB disruption [222]. Activation of cannabinoid receptor 2 (CB2R) on MG may reduce the number of $p44/P42^{(+)}$/Iba-$1^{(+)}$ MG, decrease evans blue extravasation, and inhibit the activities of MMP-9/-12. CB2R stimulation has been shown to inhibit MG/macrophage migration, which may be involved in thrombin-induced cerebral edema and in reducing BBB damage [223]. Further research indicates that M1 microglia, through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, induce P-gp dysfunction in BMECs, resulting in the accumulation of neurotoxic chemicals in the brain [224]. The removal or inactivation of MG can prevent the activation of MMP-2/-9 induced by celastrol, significantly reducing the increase in BBB permeability resulting from celastrol [225].

M2 microglia can synthesize many anti-inflammatory cytokines [226, 227]. IL-10 exerts its anti-inflammatory actions by suppressing NF-κB, reducing harmful ROS-producing enzymes, and promoting antioxidant pathways, so preserving the integrity of BBB function [228]. Promoting M2 microglial polarization in EAE model mice helps maintain the functional integrity of the blood-spinal cord barrier [229]. Recent research has developed lipid nanoparticles targeting M2 microglia (MLNP), which can selectively deliver mRNA encoding the phenotypic switch mIL-10 to the ischemic brain, thereby facilitating microglial polarization towards the protective M2 phenotype and enhancing the delivery of mIL-10-loaded MLNP to the ischemic region. The intravenous delivery of mIL-10@MLNPs in MCAO mice restored the impaired BBB and exhibited considerable potential to extend the post-stroke treatment window to at least 72 h [230]. Furthermore, miR-23a-5p derived from M2 microglial EVs may reduce the synthesis of TNF, MMP-3, and NFκB p65 in ACs under conditions of OGD, hence promoting the expression of ZO-1 and claudin-5 in bEnd.3 cells [231].

2.2.6. Oligodendrocyte precursor cells

In physiological conditions, oligodendrocyte precursor cells (OPCs) support the maintenance of BBB integrity and promote the development of TJs [232]. OPCs possess several processes, and in the brains of juvenile C57BL/6J mice, a single OPC process can interact with several blood vessels [233]. In the CNS development, OPCs can activate the TGF-β signaling in BMECs, leading to the overexpression of occludin and claudin, so improving the integrity of BBB [234]. Further study has shown that OPCs can migrate to cerebral blood vessels, hence influencing endothelial cell permeability and the TJs between ACs and BMECs [235, 236]. Simultaneously, OPCs can enhance BBB integrity through the PDGF-BB/PDGFRα signaling [236]. Variations in the number of OPCs inside the white matter can lead to significant changes in vascular density, as OPCs interact with endothelial cells through Wnt-dependent signaling and other mechanisms [237].

In certain active lesions of MS, aberrantly clustered OPCs encircling blood vessels can compromise the integrity of AC endfeet and endothelial TJs, leading to changes in vascular permeability and subsequently provoking CNS inflammation [235]. In diabetes, OPCs can activate Wnt/*β*-catenin signaling, increase MMP-9 expression, and compromise TJs, resulting in the deterioration of the structure and function of the BBB [238]. In the white matter injury model induced by extended cerebral hypoperfusion, OPCs can rapidly respond before the disruption of the BBB, releasing MMP-9 to promote neutrophil infiltration [239]. Studies demonstrate that cerebral hypoperfusion causes hypoxia in deep cortical areas, affecting OPCs and promoting the synthesis of VEGFA, which increases BBB permeability through HIF1a and EPAS1 pathways [240]. OPC transplantation can significantly reduce cerebral infarction volume and the degree of brain edema after ischemia, while maintaining BBB integrity [241]. Moreover, OPCs are crucial for maintaining MG homeostasis and have the ability to differentiate into reactive ACs after prolonged cerebral ischemia, providing new insights for related therapies [242, 243].

2.2.7. Oligodendrocytes

In the pathological state of neuronal demyelination, isolated oligodendrocytes (OLs) lesions often occur before the disruption of BBB [244]. Recent *in vivo* studies demonstrate that HIF-α in OLs regulates CNS angiogenesis through Wnt-independent and VEGF-dependent pathways [245]; furthermore, OLs can improve BBB function *in vitro* by releasing soluble chemicals [236]. Co-culturing rat BMECs with OPCs and OLs at different densities led to a significant decrease in the permeability of BMECs to Na-F, a behavior associated with cell density. The study demonstrated that OLs may enhance BBB function through different mechanisms outside the non-PDGF-BB/PDGFRα signaling [236]. A distinct investigation revealed that WNT/*β*-catenin signaling promotes the interaction between BMECs and OLs as well as OPCs. Disruption of this connection may hinder the remyelination of white matter lesions (WML) and lead to BBB permeability [246]. The MMP-9 produced by OLs after WML alters vascular architecture, indicating that the influence of these OLs on angiogenesis may pertain to damaged white matter [247].

OLs release EVs that convey proteins, including myelin-associated proteins, to neurons. EVs can improve the integrity of the BBB by regulating neurovascular coupling [248]. The regulation network of numerous non-endothelial components on the BBB is summarized in Fig. 3.

3. Aromatic "orifice-opening" agents: special opponents of blood-brain barrier

Natural musk is obtained from the dried secretion of the mature male musk glands of *Moschus berezovskii* flerov, *Moschus sifanicus* przewalski, and *Moschus moschiferus* linnaeus. Musk is mostly obtained from Asia, with China as the main producer, and it is also found in North Korea, India, and the Eastern regions of Russia. The chemical composition of musk includes macrocyclic ketones, polypeptide proteins, and steroid compounds. Muscone, the primary component responsible for the pharmacological properties of musk, is officially required by the *Chinese Pharmacopoeia* to contain a minimum of 2% in musk, calculated on a dry weight basis. Muscone possesses a unique hydrophobic pocket and high lipid solubility, facilitating its effortless traversal of the BBB. Experimental tests have indicated that peak muscone concentration in the brain was attained 5 min post-injection into the tail vein of rats. Utilizing the gavage approach, the concentration of muscone in the brain tissue peaked at 1.5 h [249]. Muscone readily traverses the BBB, and its concentration in brain tissue diminishes gradually, resulting in prolonged accumulation. Pharmacological study indicates that musk has a bidirectional regulatory effect on the CNS: it stimulates the CNS at low doses, while at high concentrations, it suppresses CNS activity, and at the same time enhances tolerance to hypoxia and improves cerebral circulation. Moreover, musk has exhibited significant effects in cardiotonic, anti-inflammatory, anti-fertility, anti-tumor, and immunological regulation. By the end of the 20^{th} century, the musk deer population in China had sharply decreased to fewer than 100 000. As a result, musk has been classified in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora and designated as a first-level protected species in China's List of Key Protected Wild Animals.

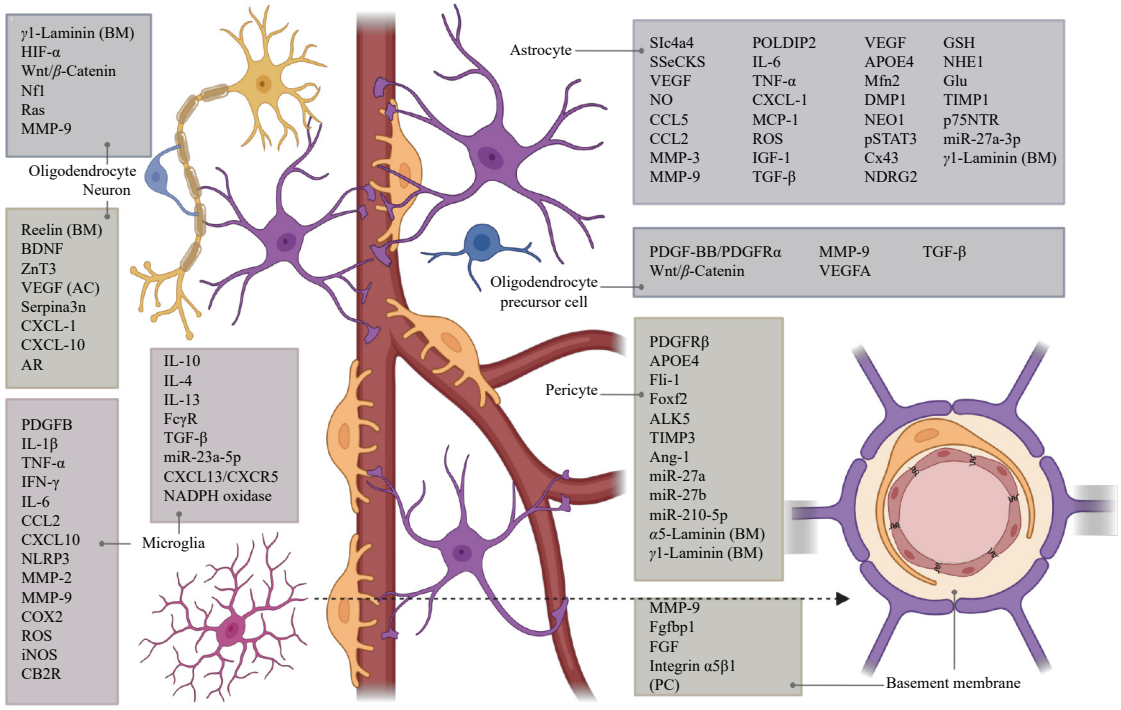


Fig. 3 The various types of cells in the NVU and their associated molecular regulatory networks that regulate the BBB. The cells include neurons, pericytes, astrocytes, microglia, oligodendrocytes, and oligodendrocyte precursor cells. The boxes encompass the relevant targets or signaling pathways.

Natural borneol is derived by the extraction and processing of the fresh branches and leaves of *Cinnamomum camphora*. This species is native to Southeast Asian countries such as Malaysia, Brunei, and Indonesia, and it also exists in limited quantities in China. Natural borneol consists of two varieties: (+)-borneol and (−)-borneol. Traditionally, (+)-borneol is extracted from the resin of *Dipterocarpus aromatica*, primarily found in Southeast Asia. Owing to the restricted availability of *Dipterocarpus aromatica* resources, essential oil extracted from the fresh branches and leaves of *Cinnamomum camphora* has been widely employed as an alternative source of borneol. Levomenthol is extracted from the fresh leaves of *Blumea balsamifera*, a traditional medicinal plant extensively employed by the Miao people in China. Borneol is a small-molecule bicyclic terpenoid, characterized by its ability to traverse the BBB efficiently. It was identified in mice brain tissue within 5 min post-gavage, with concentrations reaching a peak approximately 1 h later, indicating that borneol can readily penetrate the BBB [250]. Pharmacological studies indicate that borneol has a dual regulating effect on the CNS, eliciting both sedative and activating responses. Moreover, borneol demonstrates significant pharmacological properties, such as anti-inflammatory analgesia, anti-myocardial ischemia, inhibition of pathogenic microorganisms, prevention of thrombus formation, enhancement of transdermal drug absorption, and reversal of multidrug resistance in tumors. In the last thirty years, the population of camphor trees has significantly decreased by as much as 50% owing to deforestation and the timber industry. As a result, camphor trees have been listed in the International Union for Conservation of Nature (IUCN) Red List of Threatened Species. The *Chinese Pharmacopoeia* stipulates that the purity of (+)-borneol must be no less than 96.0%, the purity of (−)-borneol must be no less than 85.0%, and the purity of (±)-borneol must be no less than 55.0%.

Acori Tatarinowii Rhizoma is the dried rhizome of a plant in the Araceae family. Geographically, it is widely distributed in Southeast Asia, extending from Northeastern India to Northern Thailand, and is cultivated in many locations in China. Volatile oil is the principal active component of Acori Tatarinowii Rhizoma, with *β*-asarone, *α*-asarone, and elemicin as significant constituents exhibiting pharmacological activity. The *Chinese Pharmacopoeia* mandates that the volatile oil concentration of Acori Tatarinowii Rhizoma must be at least 1.0%. Employing the GC-MS technique, *β*- and *α*-asarone were identified in rat brain tissue 5 min post gavage administration of Acori Tatarinowii Rhizoma volatile oil, suggesting their ability to traverse the BBB [251]. Pharmacological study indicates that Acori Tatarinowii Rhizoma has a variety of effects. In the CNS, it protects neurons, regulates neurotransmission, and thereby improves cognitive performance; in the cardiovascular system, it exhibits effects such as anti-myocardial ischemia and cholesterol reduction through the modulation of vascular dynamics and cardiac function. Furthermore, Acori Tatarinowii Rhizoma offers significant medicinal advantages, such as mitigating asthma and allergies, decreasing gastrointestinal smooth muscle contraction, displaying antibacterial properties, exhibiting anti-tumor effects, avoiding osteoporosis, and ensuring fetal protection.

Storax is obtained from the aromatic resin exuded by the trunk of *Liquidambar orientalis*. Historically, it was mostly produced in regions including Africa, India, and Turkey. Artificial cultivation has begun in Guangxi, China. Storax's chemical composition is intricate, mostly consisting of cinnamic acid, benzoic acid, benzyl benzoate, and benzyl cinnamate. The *Chinese Pharmacopoeia* mandates that the cinnamic acid concentration in storax must be at least 5%, contingent upon the dried product. Pharmacological studies indicate that storax has significant medicinal potential. In the CNS, it can effectively combat brain ischemia and hypoxia; in the cardiovascular system, it may alleviate symptoms of myocardial ischemia; simultaneously, storax exhibits significant efficacy in antibacterial and anti-inflammatory areas. Nonetheless, rampant deforestation and environmental degradation have severely impacted the storax tree population. Since the mid-20th century, the area of storax forests has drastically decreased from 7000 hectares to a little over 1000 hectares now. The storax tree has been classified as an endangered species.

Benzoin is derived from the dried resin of *Styrax tonkinensis*. Historically, benzoin primarily relied on imports. Research conducted by the Institute of Medicinal Plant Development at the Chinese Academy of Medical Sciences indicates that Chinese spe-

cies, such as *Styrax hypoglaucus*, *Styrax chingii*, and *Styrax tonkinensis*, have the ability to produce benzoin. The principal volatile components of benzoin are benzoic acid and cinnamic acid. Also, benzoin contains aromatic aldehydes as well as esters. The *Chinese Pharmacopoeia* mandates that benzoin must have a total resin acid, quantified as benzoic acid, of at least 27.0%. Current pharmacological research indicates that benzoin possesses several pharmacological characteristics. In the CNS, it provides a protective effect against cerebral ischemia and hypoxia, and it exhibits anti-inflammatory and antipyretic properties in immune and inflammatory responses. Additionally, benzoin shows significant anti-tumor activity and promotes oestrogen secretion. Fig. 4 contains general information regarding AOOAs. The chemical details of the main components of AOOAs are presented in Table S1.

4. Mechanism of aromatic "orifice-opening" agents in blood-brain barrier integrity protection

4.1. Musk

In an *in vitro* BBB model, established by co-culturing rat ACs with human umbilical vein endothelial cells, muscone was observed to modify the model's permeability after OGD treatment, with the mechanism related to inhibition of MMP-9-mediated TJs degradation [252]. Furthermore, muscone and (+)-borneol can substantially decrease cerebrovascular permeability, and protect claudin5 in mice following stroke. This mostly stems from their inhibition of ROS formation and modulation of MG inflammatory infiltration [253]. A research team has just developed an inducible transgenic technique employing muscone, called AAVMUSE. The method enabled the continuous and controlled synthesis of therapeutic proteins in the liver or lungs of mice *via* the inhalation of muscone. The AAVMUSE system demonstrated significant therapeutic efficacy and showed acceptable safety and biocompatibility in animal models of non-alcoholic fatty liver disease and allergic asthma [254]. This intranasal route offers a fresh approach for applying muscone in addressing BBB dysfunction.

4.2. Borneol

Borneol has demonstrated considerable synergistic enhancement and detoxifying effects in combination therapy. EDB, a potent new neuroprotective compound, comprises edaravone and (+)-borneol in a 5∶1 ratio. Research indicates that Y-2 Sublingual Tablets at doses of 1, 3, and 6 mg·kg^{-1} can markedly maintain the BBB integrity in rats affected by ICH. The mechanism may be related to reduced inflammatory response and oxidative stress near the haematoma core [255]. Similar studies have shown that EDB can activate the Keap1/Nrf2 signaling, alleviating oxidative stress and damage to the BBB in the murine model of SAH. In the study of ischemic stroke, EDB alleviates BBB damage by preserving TJs integrity and reducing the accumulation of peripheral leukocytes [256, 257]. Morover, EDB can improve PCs coverage through vitronectin-integrin and PDGFB/PDGFR-β signaling, hence preventing the BBB disruption [132]. A study has developed a nasal thermosensitive hydrogel (EDA-BP TSGS) that integrates an edaravone and borneol inclusion complex, which can both overcome the occlusion of BBB and avoid the impracticality and delay of intravenous administration, thereby enhancing the drug delivery efficiency to the ischemic lesions [258]. *Ligusticum chuanxiong* is widely employed in China for the treatment of ischemic stroke, with significant efficacy. Chuanxiong predominantly promotes the proliferation of neural stem cells, neurogenesis, and the preservation

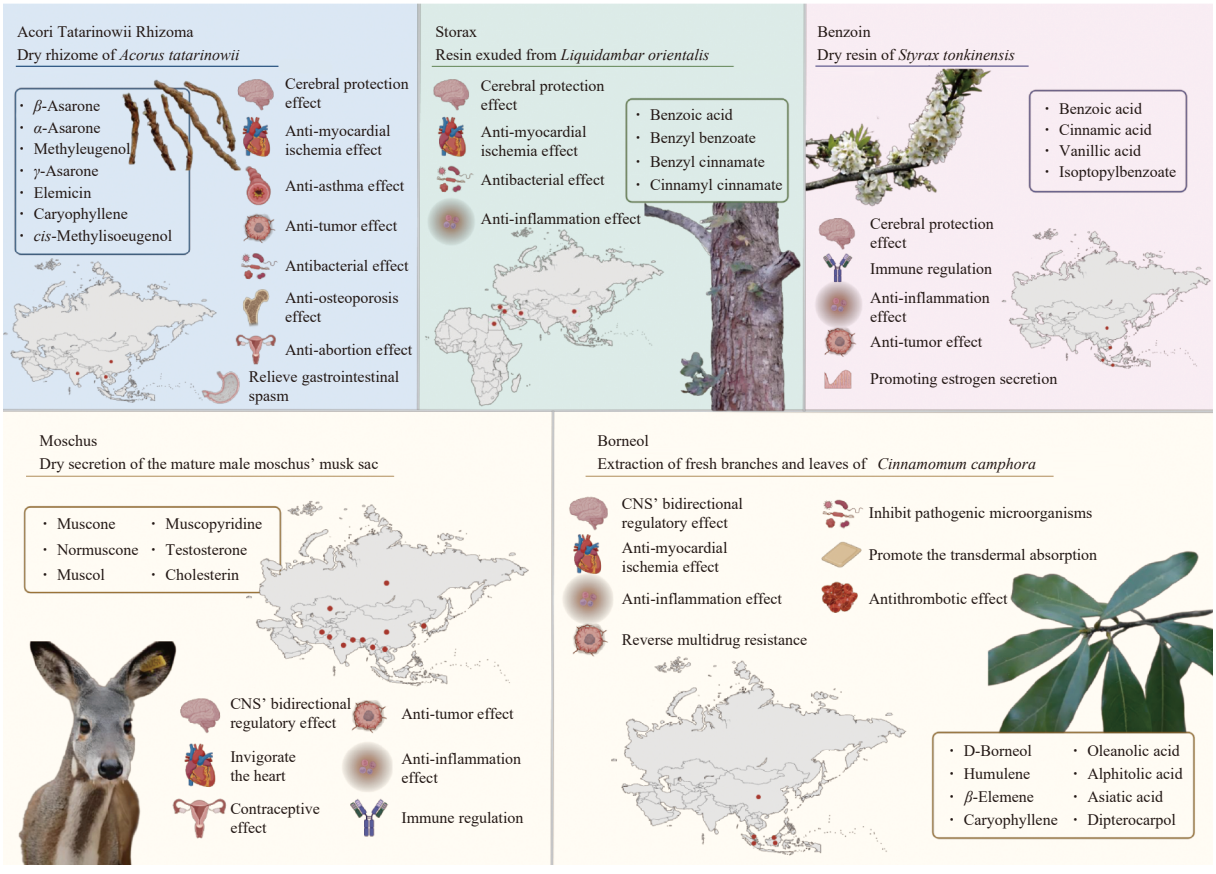


Fig. 4 Schematic representation of the main information on the five AOOAs. The AOOAs include musk, borneol, Acori Tatarinowii Rhizoma, storax andbenzoin. The main information covers their zoological/botanical sources, geographical distributions, main active components, corresponding pharmacological effects, etc.

of mature neurons; in contrast, borneol underscores the maintenance of BBB integrity. The concurrent use of the two not only enhances the previously mentioned therapeutic effects but also produces other advantages, including the lowering of evans blue permeability and the improvement of TEER values [259,260]. Ultrasound-targeted microbubble destruction (UTMD) and borneol both augment the delivery of therapeutic medicines to cerebral lesions. The research indicated that the application of UTMD intensified evans blue leakage, microvascular ultrastructural changes, cerebral edema, and even precipitated CH in ischemic stroke mice. However, pre-treatment with borneol markedly mitigated the aforementioned detrimental effects induced by UTMD on the BBB. The concurrent application of UTMD and borneol in the treatment of ischemic stroke may be a safer approach for BBB permeability than the exclusive use of UTMD [261].

4.3. Acori Tatarinowii Rhizoma

Transmission electron microscopy analysis indicates that Acori Tatarinowii Rhizoma can synergistically interact with Kaixin San to repair the impaired BBB in mice with AD [262]. After the administration of *α*-asarone and *Acorus calamus* extract, the BBB integrity showed a dose-dependent recovery [263]. Research indicates that *α*-asarone, when converted into a dry powder and administered intranasally, can access the brain by two pathways: the systemic circulation and the olfactory bulb. In the systemic circulation pathway, *α*-asarone is absorbed into the bloodstream and later crosses the BBB to reach the brain; in the olfactory bulb channel, *α*-asarone travels from the nasal olfactory epithelium through the olfactory bulb directly to the brain tissue. Intranasal delivery of *α*-asarone in dry powder form promotes rapid absorption, averting overly high drug levels in the blood and liver, while attaining brain concentrations similar to those achieved with intravenous injection and oral administration [264].

4.4. Storax and benzoin

Research indicates that a dosage of 0.4 $g \cdot kg^{-1}$ storax can significantly reduce the intensity of fluorescent albumin expression in the brain parenchyma and decrease the number of caveolae in endothelial cells. 6 h after stroke onset, this dose of storax substantially reduced damage to the ultrastructure of BBB [265]. Benzoic acid obtained from benzoin can augment the expression of claudin5, maintain the integrity of the BBB and substantially reduce ischemic injury [266]. Research on the neuroprotective effects of vanillin against hypoxic-ischemic injury in neonatal rats demonstrates that vanillin treatment vanillin partially inhibited the activation of MMP-2 and MMP-9 induced by hypoxia-ischemia. Compared to the model group, vanillin significantly increased the levels of ZO-1, occludin, and claudin-5, hence further stabilizing the BBB structure [267]. The mechanism by which AOOAs protect BBB integrity is shown in Fig. 5.

5. Mechanism of aromatic "orifice-opening" agents in blood-brain barrier permeability enhancement

5.1. Muscone

Muscone can inhibit the expression of P-gp under both normal and OGD conditions [268]. Inhibition of P-gp expression results in a significant increase in the muscone concentration in brain. It can be inferred that the translocation of muscone *via* BBB is closely linked to the P-gp transport system. The absorption efficiency of geniposide across the BBB is somewhat inadequate. Muscone as a potent absorption enhancer, may significantly boost the absorption efficiency of geniposide by facilitating transcellular and paracellular transport [269]. The research team co-modified docetaxel (DTX) liposomes with muscone and the mouse monoclonal antibody RI7217, which demonstrates superior affinity and specificity for the transferrin receptor (TfR). The modified liposomes significantly improved the absorption of DTX by hCMEC/D3 and U87-MG cells, enhanced the drug's penetration into the deeper areas of U87-MG tumour spheroids, increased *in vivo* brain targeting, and markedly extended the survival of tumor-bearing nude mice [270]. Consequently, the team created dual-modified liposomes combining lactoferrin (Lf) receptors and muscone (Lf-LP-Mu-DTX). The Lf-LP-Mu-DTX further increased the apparent permeability coefficient of the *in vitro* BBB model to 51.0%, which was 1.6 times higher than that of the Lf-LP-DTX group, and

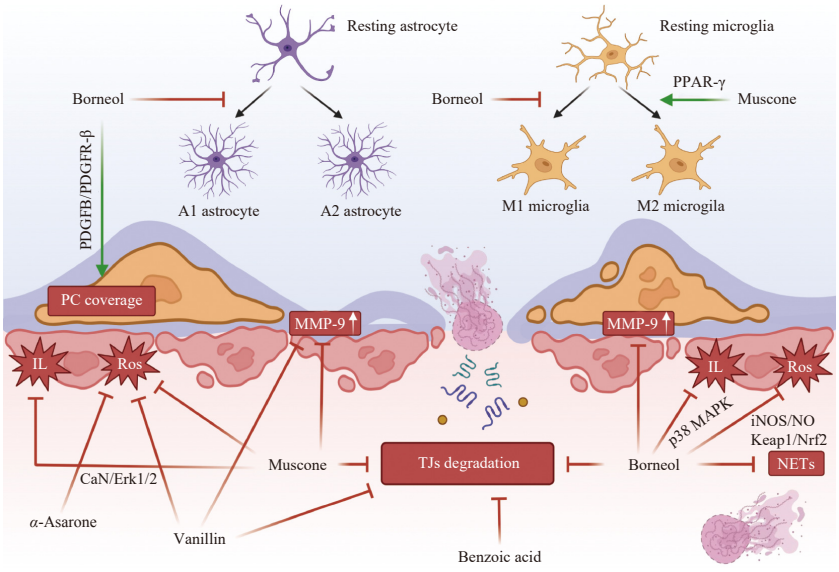


Fig. 5 Schematic representation of the molecular mechanisms by which the five AOOAs protect the BBB integrity. The AOOAs include musk, borneol, Acorus Tatarinowii Radix, storax and benzoin. TJs degradation, ROS, IL, NETs, MMP-9 activation, etc., can all lead to endothelial dysfunction and BBB disruption. In addition, A1-type astrocytes and M1-type microglia can damage the BBB integrity. The red arrows indicate the inhibitory effect of the main active components of AOOAs on these processes. The transformation of M2-type microglia and the enhancement of PC coverage are beneficial to BBB permeability. The green arrows indicate the promoting effect of the main active components of AOOAs on these processes.

resulted in more than 2-fold the efficiency of tumor sphere penetration and cellular uptake of the Lf-LP-DTX group [271].

5.2. Borneol

Additional research has investigated the effects and processes of borneol in various brain areas. Following the administration of a 0.2 $g \cdot kg^{-1}$ dose of borneol to the experimental subjects, the architecture of the TJs was compromised, resulting in the formation of gaps between the endothelium and thylakoid cells. Pharmacokinetic studies indicate that borneol is predominantly distributed in the cerebral cortex, minimally in the striatum, with intermediate distribution in the hippocampus and hypothalamus. The regulation of the ultrastructure of the hippocampus and hypothalamus by borneol is coupled with the modulation of the expression of multidrug resistance gene 1a (*Mdr1a*), multidrug resistance gene 1b (*Mdr1b*), and multidrug resistance-associated protein 1 (*Mrp1*) [272].

Borneol has been thoroughly investigated for its capacity to facilitate medication permeation across the BBB and to augment therapeutic outcomes in neurological disorders. In the domain of CNS ischemic disorders, the concurrent administration of edaravone and (+)-borneol can provide a synergistic effect. Borneol can improve the transport of edaravone across the BBB by promoting transcellular transport facilitated by P-gp and OAT1/3 [273]. Grapefruit extracellular vesicles (GEVs) were utilised to encapsulate Xingnaojing Microemulsion (XNJM), with borneol (Bo) employed for modification, yielding Bo-GEVs/XNJM having neuro-targeting capabilities. Both *in vivo* and *in vitro* studies have validated its substantial effects in preserving the BBB [274]. A novel tanshinone IIA (TSA) loaded nanoparticles, Bo-TSA-NP, has been developed, with its surface modified by borneol. The Bo-TSA-NP showed sustained release and P-gp inhibition property. It demonstrated a significantly higher uptake by 16HBE cells *in vitro* [275]. The research developed borneol-modified ginkgolide liposomes (GGB-LPs). Borneol markedly enhanced the transport of ginkgolide across the BBB, while greatly optimising the pharmacokinetic properties of GGB-LPs [276]. Puerarin (PUE) and tetramethylpyrazine (TMP) are potential CNS pharmacological agents for the treatment of cerebral ischemic disorders. The combined delivery of borneol and *α*-asarone during oral intake markedly enhances the accumulation of PUE and TMP across the BBB. Borneol and *α*-asarone concurrently diminish the expression of ZO-1 at the BBB, while augmenting the expression of A1 adenosine receptors and A2A adenosine receptors [277]. Recent research utilised borneol as a functional component to synthesise an amphiphilic borneol-based copolymer p(PB)10/(TB)30. In the MCAO mouse model, this nanoformulation can facilitate reversible disruption of the BBB. 3 h post-injection, the brain bio-distribution level attained 12.7% ID/g of the total administered dose [278].

Borneol is pivotal in the domain of medication delivery for brain tumours. Glioma is the most prevalent primary brain tumour. Research has prompted the creation of a dual-functional carmustine-loaded micelle (Pep-1/Bor/CMS-M). This micelle improves BBB permeability through camphor and specifically targets glioma cells *via* Pep-1. This effectively addresses the issues of carmustine's brief half-life, limited selectivity, and the obstacle of big molecules traversing the BBB [279]. A separate study developed a dual-functional doxorubicin glioma-targeted delivery system utilising PAMAM G5 dendritic polymer (FA-BO-PAMAM/DOX). This approach markedly diminishes the cytotoxicity of PAMAM to HBMECs and C6 cells by conjugating borneol to the carrier's surface, while substantially improving BBB permeability. In comparison to the unaltered borneol conjugate, its transport ratio has doubled [280]. The combined action of borneol and CGKRK peptide-modified paclitaxel prodrug self-assembled redox-responsive nanoparticles (CGKRK-PSNPs) significantly improves the nanoparticles' capacity to penetrate the BBB and enhances the efficacy of targeted tumour delivery. In a nude mouse model with cerebral implantation of U87MG glioma, real-time fluorescence imaging demonstrated that the accumulation of nanoparticles at the tumour site markedly increased following the simultaneous administration of borneol [281]. DTX is a prospective therapeutic agent for brain tumours; however, its bioavailability is limited, and it readily causes resistance in tumour cells. Tetrahydropalmatine (TET) can mitigate tumour cell resistance to chemotherapeutic agents. A study developed borneol-modified DTX plus TET micelles to address chemotherapy resistance. The micelles promoted drug uptake in bEnd.3 cells, contributing to drug passage across the BBB *in vitro* [282]. Studies demonstrate that natural borneol can facilitate the cellular uptake of doxorubicin *in vitro*, hence synergistically augmenting the anticancer efficacy of doxorubicin [283]. Glioblastoma is the most aggressive variant of gliomas. Doxorubicin-loaded nanomicelles (DOX BO-PMs) were subsequently synthesised utilising DSPE-PEG2000-BO *via* electrostatic interactions. DOX BO-PMs markedly improved the transport efficiency of doxorubicin across the BBB, resulting in its fast accumulation in cerebral tissue [284]. Paediatric brainstem glioma (PBSG) arises in the brainstem. Nonetheless, the tumor's hypoxic microenvironment and the existence of BBB significantly restrict the efficacy of cisplatin in the treatment of PBSG. The research documented the nasal delivery of borneol/R8dGR peptide-modified poly nanoparticles, which simultaneously encapsulated curcumin and cisplatin. The modification of borneol improves the brain penetration capacity of nanoparticles by decreasing the expression of ZO-1 and occludin in the nasal mucosa; the R8dGR peptide modification facilitates the binding of nanoparticles to the integrin αvβ3 receptor on paediatric brainstem glioma cells, enabling targeted delivery [285]. Metastatic brain tumours represent the predominant form of cerebral malignancy. Studies indicate that the bioactive compounds borneol and tetrandrine can augment the permeability of the chemotherapeutic agent 5-fluorouracil (5-FU) across the BBB and blood-tumor barrier (BTB) models. It can partially impede the efflux pump activity of P-gp [286]. Dioleoylphosphatidylethanolamine (DOPE) is a crucial constituent of liposomes and serves to encapsulate anticancer pharmaceuticals. Chemically altering DOPE with borneol and employing it as a lipid component for solid lipid nanoparticles (SLN). SLN with chemically modified borneol (BO-SLN/CM) demonstrate reduced cytotoxicity, enhanced cellular uptake rates, and superior BBB permeability compared to SLN with physically modified borneol (BO-SLN/PM) and SLN [287].

In neurodegenerative disease research, the clinical management of PD encounters significant obstacles. Exenatide, a peptide medication with potential disease-modifying properties, encounters challenges in traversing the BBB owing to its substantial molecular weight. Related study has developed multifunctional Lpc-BoSA/CSO with BBB targeting, improved permeability, and responsive release capabilities. Camphor and stearic acid are chemically bonded to improve BBB permeability. Immunofluorescence tests conducted on the brain tissues of 15-month-old C57BL/6 mice revealed that Lpc-BoSA/CSO penetrated the BBB and diffused into the brain parenchyma 4.21 times more effectively than typical lipid nanoparticles [288]. The limited permeability of octahedral palladium nanoparticles (Pd NPs) across the BBB constrains their application in AD treatment. A study has developed a borneol-modified octahedral palladium nanoenzyme platform that effectively eliminates intracellular ROS and improves the permeability of epithelial cells. Research has demonstrated that this nanoenzyme can swiftly accumulate in the brains of AD mice, mitigating pathogenic characteristics such as Aβ plaque deposition, neuronal degeneration, and neuroinflammation [289]. Kaempferol (KA) exhibits a notable anti-AD action, is safeguarded by the

BBB, and its concentration in the brain is exceedingly little. The combination of 15 and 30 mg·kg^{-1} of borneol markedly enhances the brain bioavailability and delivery of KA. The area under the drug-time curve of KA in the brain increased by 1.84-fold and 2.19-fold, respectively, while the maximum blood concentration rose by 2.09-fold and 3.18-fold, respectively, in comparison to the absence of ice tablets. The cerebral blood distribution ratio of KA rose by 48.68% and 57.97%, respectively, compared to the absence of borneol [290]. A separate study detailed a novel mesoporous selenium (MSe) release delivery system (MSe-Res/Fc-β-CD/Bor) developed with a borneol-targeted β-cyclodextrin nanovalve (Fc-β-CD) encapsulating resveratrol (Res). MSe-Res/Fc-β-CD/Bor initially engages with esterases in the bloodstream or intracellularly, liberating borneol, thereby facilitating the nanosystem's traversal of BBB. Consequently, Fc-β-CD reacts to redox agents and undergoes a conformational change, thereby releasing resveratrol at the site of injury [291]. Salvianolic acid A (SAA) and puerarin exhibit potential efficacy in the management of neurodegenerative disorders. Research indicates that the SAA borneol ester (SBE) demonstrates considerable benefits by enhancing BBB permeability and by the prolonged inhibitory action of borneol on P-gp efflux [292]. Puerarin exhibits low water solubility, leading to inadequate oral absorption and challenges in traversing the BBB. Related studies employed borneol as an oral brain-targeting enhancer to formulate three types of puerarin oral preparations: nanocrystal suspensions (NCS), inclusion complex solutions (ICS), and self-microemulsifying drug delivery systems (SMEDDS). *In vitro* BBB modeling studies revealed a substantial increase in geraniol permeability and a notable decrease in trans-epithelial resistance at 2 h when the borneol concentration surpassed 12.5 μg·mL^{-1}. Pharmacokinetic findings indicated that the intestinal absorption and intracerebral penetration of geraniol were markedly improved when the borneol dosage surpassed 50 mg·kg^{-1}. When administered simultaneously with 100 mg·kg^{-1} borneol, the area under the drug-time curve in plasma and the area under the drug-time curve in the brain of puerarin in SMEDDS were significantly elevated compared to the NCS and ICS groups [293].

Depression, a persistent mental condition that poses a substantial risk to human health and life, is strongly impeded by the BBB, which markedly limits the penetration of pharmaceuticals into the brain, leading to inadequate distribution of antidepressants inside this organ. The research team has created an innovative brain-targeted medication delivery system utilising borneol-modified polyethylene glycol-graphene oxide (GO-PEG-BO). The incorporation of borneol enables GO-PEG-BO to efficiently traverse the BBB by disrupting TJs and suppressing the efflux mechanism. Administering ginsenoside Rg1 (GRg1) onto GO-PEG-BO markedly enhanced anhedonia, despair, and anxiety elicited by stress in a rat model of depression, thoroughly mitigating depressive symptoms [294]. Aripiprazole (ARP) is an antipsychotic medication sanctioned for the management of schizophrenia. Relevant investigations utilised Soluplus and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) to construct aripiprazole micelles (ARP-MM), and furthermore developed micelles using borneol as a permeation enhancer (ARP-B-MM). In the parallel artificial membrane permeability assay BBB model, ARP-MM and ARP-B-MM augmented the effective permeability of aripiprazole by approximately twofold. ARP-B-MM decreased P-gp-mediated efflux by roughly fourfold compared to ARP that was not encapsulated in micelles. Pharmacokinetic parameters demonstrated that the peak plasma concentration, area under the plasma concentration-time curve, and half-life all elevated, substantiating that both formulations of mixed micelles containing ARP significantly enhanced the bioavailability of ARP [295].

Itraconazole (ITZ) is an efficacious medication for the treatment of cryptococcal meningitis and aspergilloma. The hydrophobicity of ITZ and the existence of BBB significantly restrict its use. Researchers encapsulated ITZ within bovine serum albumin nanoparticles (ITZ-NPs) and subsequently modified these nanoparticles with borneol and polyethylene glycol (PEG), resulting in the successful synthesis of PEG/BO-ITZ-NPs. The outcomes of cellular uptake assays indicated that the absorption of PEG/BO-ITZ-NPs in bEnd.3 cells was markedly higher than that of ITZ-NPs, and the cellular uptake of the nanoparticles correspondingly increased with the concentration of borneol. Moreover, following intravenous administration, the area under the drug-time curve of PEG/BO-ITZ-NPs in rats was roughly 3.5 times greater than that of sporanox spironolactone (ITZ solubilised by hydroxylpropyl-β-cyclodextrin), while the distribution in the mouse brain was approximately doubled [296].

Research on the treatment of other diseases has demonstrated that the combination of borneol with self-emulsifying agents (SE) has led to the successful preparation of borneol-dimethylbiguanide hydrochloride water/oil/water composite submicroemulsions (B-Met-W/O/W SE). This composite submicroemulsion can efficiently facilitate the drug's traversal of BBB, markedly enhancing the distribution of metformin (Met) in the brain. Mechanistic investigations demonstrate that B-Met-W/O/W SE can markedly reduce the expression levels of occludin, ZO-1, and P-gp [297]. Furthermore, borneol in *in vitro* models can facilitate the translocation of verapamil and digoxin across the BBB and diminish the expression levels of mdr1a and P-gp. The applications of borneol in enhancing BBB permeability are shown in Fig. 6.

5.3. Acori Tatarinowii Rhizoma

Acori Tatarinowii Rhizoma facilitated the transfer of GRg1, GRb1, and farnesolone III across the BBB in Kaixin San, resulting in the elevation of their levels in the cerebrospinal fluid by 1.47-fold, 1.39-fold and 2.02-fold, respectively. Mechanistic studies revealed that Acori Tatarinowii Rhizoma enhanced the expression of claudin5, occludin, and ZO-1 proteins, dramatically up-regulated the expression of OCT3/OATP2 uptake transporter proteins, and down-regulated the expression of P-gp/MRP1 efflux transporter proteins in AD mice [265]. Levodopa (L-DOPA), a highly successful pharmacological agent for PD, exhibits a permeability of less than 5% across the BBB. Following the co-administration of *β*-asarone and L-DOPA, the concentrations of L-DOPA, dopamine, 3,4-dihydroxyphenylacetic acid, and homovanillic acid in the striatum, together with the level of S100β protein in plasma, were assessed. Concurrently, the concentrations of neuron-specific enolase, P-gp, ZO-1, occludin, and claudin-5 in the cerebral cortex were diminished, leading to disruptions at the TJs between striatal BMECs. Furthermore, in the combination therapy cohort and the *β*-asarone treatment cohort, a strong inverse connection was seen between L-DOPA or dopamine and P-gp or TJs [298]. *β*-Asarone can facilitate the transmembrane passage of temozolomide (TMZ) into human glioma U251 cells. In contrast to monotherapy, the combination of *β*-asarone with TMZ has enhanced inhibitory effects on cell growth in U251 and C6 cells, concurrently diminishing the expression of P-gp and MDR1 [299]. A separate study integrated liposomes with Tf and included the cell membrane proteins of RG2 glioma cells into the liposomes, successfully formulating eleutherol (ELE) and cabazitaxel (CTX) actively targeted biomimetic liposomes (Tf-ELE/CTX@BLIP). These liposomes demonstrate high-efficiency penetration of the BBB and targeting capabilities for gliomas. *In vitro* tests demonstrated that it had markedly substantial homologous targeting and immune evasion capabilities. Bioluminescence imaging revealed augmented drug accumulation in the brain and improved tumour penetration of Tf-ELE/CTX@BLIP in nude mice, a model of glioma *in situ*. The method of action involves the suppression of P-gp, enhancing BBB permeability and facilitating the entry of CTX into the brain [300].

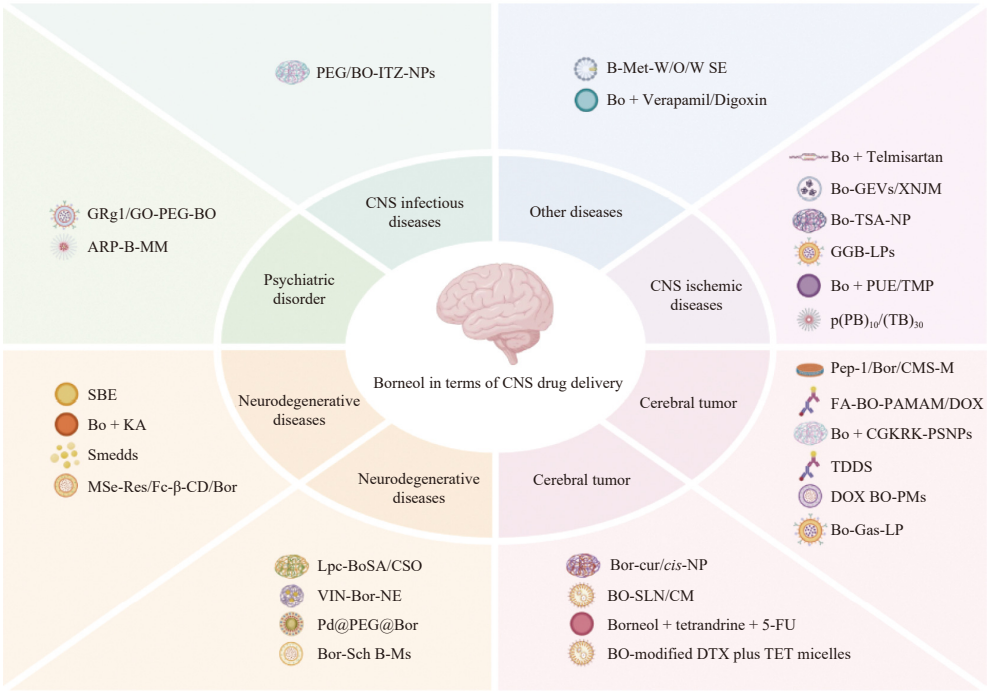


Fig. 6 Specific applications of borneol in CNS drug delivery systems. These applications cover CNS ischemic diseases, cerebral tumor, neurodegenerative diseases, psychiatric disorders, CNS infectious diseases and other diseases.

6. Conclusion and perspective

The pharmacological history of AOOAs is well-documented, featuring a variety of bioactive compounds including muscone, borneol, *α*-asarone, benzoic acid, vanillin, and etc. These compounds exhibit diverse pharmacological effects, including anti-cerebral ischemia, anti-myocardial ischemia, anti-inflammatory properties, immunological modulation, and etc., highlighting the importance of AOOAs in disease prevention and treatment. Especially, on the one hand, AOOAs can swiftly penetrate the BBB and exhibit significant therapeutic effectiveness on the impaired barrier in CNS disorders; on the other hand, AOOAs enhance the penetration of other medications into the brain, exhibiting considerable potential in CNS drug delivery. Current preclinical research has predominantly investigated single occurrences, but the mechanisms and targets of this bidirectional regulatory role remain largely unexamined. TJs are the central focus of most pharmacological researches; however, transport proteins and other cellular elements of the BBB remain insufficiently studied. The structural alteration of the key active components of AOOAs to enhance efficacy, reduce toxicity, or improve pharmacokinetics represents a significant research direction, which may provide a solid basis for new drug development. As science advances, it is highly expected that these powerful natural compounds will become a great treasure for the development of new medications.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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