Review Article

Research progress on the regulation and mechanism of borneol on the blood-brain barrier in pathological states: a narrative review focused on ischemic stroke and cerebral glioma

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Background and Objective: The blood-brain barrier (BBB) serves as a dynamic, selective shield, safeguarding the central nervous system (CNS) by separating the brain from circulating blood, preserving its microenvironment, and ensuring stability. However, in the presence of brain pathology, drug delivery across the BBB and blood-tumor barrier (BTB) becomes challenging, hindering effective treatments. Borneol exhibits promise in bidirectionally modulating the BBB under pathological conditions, suggesting at potential clinical applications for related diseases. Our primary goal in this review is to investigate borneol's potential clinical utility in bidirectionally regulating the BBB under pathological conditions.

Methods: The PubMed database, CNKI (China National Knowledge Infrastructure), Wanfang Data were searched to retrieve articles on animal experiments and cell-based research published from January 1, 2003, to May 1, 2023, using the following medical subject headings (MeSH) terms: borneol, blood-brain barrier, ischemic stroke, cerebral gliomas, anti-inflammatory. The search was limited to articles published in English and Chinese. In total, 86 articles were deemed eligible for inclusion in this study.

Key Content and Findings: The breakdown of the BBB is a key pathological process in ischemic stroke and cerebral glioma. When used alone, the lipophilic properties of borneol can reduce the permeability of the BBB and restore its normal function, thereby repairing brain damage and protecting brain tissue. Its specific protective effects may be related to inflammatory regulation mechanisms. The anti-inflammatory and protective effects of borneol can be used to improve and treat lesions caused by ischemic stroke and cerebral glioma. Furthermore, when combined with other drugs, borneol can accelerate the opening of the BBB, improve permeability through physiological processes, and enhance drug penetration and distribution in the brain without causing pathological damage to the brain.

Conclusions: This review summarizes the mechanisms by which borneol regulates the BBB and BTB in ischemic stroke and cerebral glioma, and discusses the potential clinical applications of borneol in the treatment of these diseases. It is believed that in the future, as research methods are refined, more effective and targeted therapies for cerebral glioma and ischemic stroke will be explored related to the protective mechanism of the BBB under pathological conditions with borneol alone or in combination with other drugs.

Keywords: Borneol; blood-brain barrier (BBB); ischemic stroke; cerebral glioma; anti-inflammatory

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Introduction

The blood-brain barrier (BBB) is a dynamic cerebral barrier between the brain and the peripheral circulation. Comprising brain capillary endothelial cells, pericytes, and astrocyte end-feet, the BBB effectively shields the brain from harmful toxins and pathogens originating in the bloodstream (1,2). The blood-tumor barrier (BTB) refers to a modified BBB located near the brain microvessels that results from changes in the neurovascular unit due to the presence of primary brain tumors, including neuroblastoma and other visceral cancers, such as lung cancer, breast cancer, melanoma, etc. (3). The expression of P-glycoprotein (P-gp) in the BBB prevents unnecessary blood toxins and signaling molecules from entering the brain (4-6). This intricate structure not only upholds cerebral stability but also shields the brain from the impact of external factors. On the other hand, when pathological changes occur in the brain, it may be difficult for drugs to penetrate the BBB and BTB barriers, making the treatment of brain diseases with medication challenging (7-9).

Borneol is a bicyclic terpenoid known for its pronounced lipophilic properties. The 2015 edition of the *Chinese Pharmacopoeia*, referring to traditional Chinese medicine, classifies the genus of herbs containing borneol into three types. One is obtained through a refining process from fresh leaves of the aromatic plant Aina Xiang (also known as *Blumea balsamifera*), resulting in a crystalline substance. Another type is obtained by extracting and processing fresh branches and leaves of camphor trees in the *Lauraceae* family, resulting in a crystalline substance primarily composed of dextrorotatory borneol, commonly known as "natural borneol". The third type is a mixture of borneol and isoborneol, commonly known as synthetic borneol. Recent studies have shown that borneol is a low-molecular-weight lipophilic monoterpene (10,11) that has various pharmacological effects, such as the promotion of drug absorption (12,13), protection of the central nervous system (CNS) (14,15), and antibacterial (16,17), anti-inflammatory (18), and analgesic activities (19). Furthermore, an increasing number of studies have demonstrated that borneol has a certain promoting effect on the permeability of the BBB and BTB (20-22). Consequently, this study endeavors to investigate the regulatory effects and underlying mechanisms of borneol on the BBB in pathological contexts. Cerebral glioma and ischemic stroke are significant contributors to global mortality. Despite their distinct physiological occurrences, approximately 10% of individuals who experience an ischemic stroke subsequently develop cerebral cancer, particularly cerebral glioma, during the postischemic phases. Moreover, the heightened proliferation, venous thrombosis, and hypercoagulability associated with the cerebral glioma mass substantially elevate the risk of thromboembolism, including ischemic stroke. Therefore, ischemic stroke and cerebral glioma were used as our entry points to inform clinical drug therapy. Not only that, borneol treat ischemic stroke through their protective effect on the BBB, while cerebral glioma uses them to increase drug penetration, allowing more drugs to reach the cerebral glioma site. Therefore, we have used these two diseases as a reference, in order to better explore the role of ice chips. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1487/rc).

Methods

Data sources

A narrative review of the mechanisms by which borneol regulate the BBB and BTB in ischemic stroke and cerebral gliomas was conducted. Relevant articles in English and Chinese available in the PubMed database, CNKI (China National Knowledge Infrastructure) database, Wanfang Data as of May 1, 2023 were included. The search strategy is detailed in *Table 1*.

Data extraction

Two authors independently assessed all extracted relevant research articles and performed comparative screening based on data on study relevance, degree of study disease and drug compliance and their mechanism of action. Decisions recorded by the two authors individually were compared and any disagreements were resolved by the other authors.

Regulation effect of borneol on the BBB in two pathological states of brain diseases

Ischemic stroke

Given the large number of stroke patients, stroke prevention and treatment are an urgent problem for China's healthcare system. According to the Hospital Quality

Table 1 Summary of the literature search strategy

Items	Specification
Date of search	May 1, 2023
Databases and other sources searched	PubMed database, CNKI (China National Knowledge Infrastructure), Wanfang Data
Search terms used	("BBB") AND ("Borneol" OR "Ischemic Stroke" OR "Cerebral Gliomas" OR "Anti-inflammatory"); ("Ischemic Stroke") AND ("Borneol" OR "Cerebral Gliomas" OR "Anti-inflammatory"); ("Cerebral Gliomas") AND ("Borneol" OR "Anti-inflammatory"); "Borneol" AND "Anti-inflammatory"
Timeframe	January 1, 2003, to May 1, 2023
Inclusion criteria	All study types and reviews, written in English and Chinese
Selection process	K.Z. and X.T. conducted the article selection independently; Z.T. supervised the article selection

BBB, blood-brain barrier.

Monitoring System (HQMS), 1,672 tertiary public hospitals treated 3,411,168 patients with stroke in 2019. Of these cases, 2,818,875 were ischemic stroke, accounting for 82.6% of all cases (23). Ischemic changes are a major contributor to the development of ischemic stroke (24,25). Based on international standards, the hemorrhagic transformation rate in patients who have experienced ischemic stroke after intravenous thrombolysis and intra-arterial interventions can be as high as 10% to 49.5%, with symptomatic manifestations ranging from 2% to 16%, which can have a severe impact on patient prognosis. Research on ischemic stroke indicates that hemorrhagic transformation in ischemic stroke survivors is associated with the alteration of BBB permeability and overall structure (26,27). Hence, the probability of posttreatment complications is reduced and the patient's prognosis is improved by protecting the integrity and permeability of BBB.

The occurrence of ischemic stroke results in disruption of the tight connections in the brain, which alters the transport modes of proteins and transfer capacity of cells, resulting in increased BBB permeability and functional impairment in patients (28). The body's innate immune cells become activated, and there is an upregulation of cytokines, chemokines, matrix metalloproteinases, and vascular endothelial growth factor secretion in the event of cerebral ischemia (29,30). This results in BBB disruption and an increase in secretion of adhesion molecules in endothelial cells, which facilitates invasion of the peripheral immune cells (predominantly neutrophils) (31,32). Additionally, a variety of mediators released by eosinophilic cells exacerbate BBB injury, resulting in an abnormal escalation of BBB permeability (33).

Due to improvements in medical science in recent years, neuroprotection has received increasing attention in the treatment of ischemic stroke (34-36). The use of borneol has been reported to decrease BBB destruction and brain edema in animal models of ischemic stroke and traumatic brain injury (TBI). Working with an ischemic stroke model, Zhang and colleagues (37) reported that borneol treatment significantly reduced the expression of matrix metalloproteinase-9 (MMP-9), a key mediator of BBB disruption, in the ischemic brain and improved the neurological function in rats with middle cerebral artery occlusion (MCAO). In addition, Zhang *et al.* (38) demonstrated that borneol treatment could increase the expression of tight junction proteins, including claudin-5 and occludin, and reduce the permeability of the BBB in a rat model of ischemic stroke induced by MCAO. Working with a TBI model, Li *et al.* (39) reported that borneol treatment could significantly reduce the expression of MMP-9 and increase the expression of tight junction proteins in the injured brain, thereby improving the integrity of the BBB and reducing brain edema in rats with TBI. Similarly, Lin *et al.* (40) found that borneol treatment could inhibit the expression of inflammatory cytokines and reduce BBB permeability in a mouse model of TBI induced by controlled cortical impact. These studies suggest that borneol may have therapeutic potential for ischemic stroke and TBI via the regulation of the BBB.

Additionally, borneol has been shown to have certain neuroprotective effects, as it can reduce the generation of reactive oxygen species (ROS) in cells, inhibit the expression of tumor necrosis factor (TNF), attenuate the inducible nitric oxide synthase (iNOS)/nitric oxide (NO) pathway, suppress the release of inflammatory factors and caspase-related apoptosis, and protect the brain (41).

Moreover, borneol exerts a dual modulatory impact on BBB permeability. It reduces BBB permeability in response to brain injury and augments its physiological permeability, all while preserving brain health and integrity, as supported by existing research (11,42,43).

Borneol may reduce BBB permeability following brain injury by decreasing the production of neurotoxic NO through the downregulation of iNOS and by inhibiting inflammation and free radical damage, thereby preserving tight junction stability and maintaining BBB integrity (44). This ultimately leads to the improved functional status of the neurovascular unit, reduced infarct size, and better neurological outcomes in ischemic stroke survivors. On the contrary, the mechanism by which borneol enhances the physiological BBB permeability may involve inducing the expression of endothelial nitric oxide synthase (eNOS); increasing the levels of physiological NO, histamine, and 5-hydroxytryptamine (5-HT); inhibiting P-gp (45,46); and regulating the brain tissue ultrastructure. This can lead to a reduction in the tight junction structure between cells, an increase in the number of cell phagocytic vesicles, an enlargement of cell size, and the regulation of intercellular adhesion molecule-1, thus facilitating the accelerated transport of substances (47). Edaravone dexborneol (Xianbixin) is the only drug approved for global stroke treatment in the past 5 years, and it is clinically used for the treatment of patients who have experience arterial ischemic stroke (AIS). One of the important active ingredients of the drug is (+)-borneol, which is also the main active ingredient of borneol. The research carried out by Huang *et al.* (48) showed that edaravone dexborneol could improve BBB permeability in AIS survivors and consequently safeguard brain tissue function. More than that, Wu *et al.* (49) also demonstrated that edaravone dexborneol had a significant synergistic effect in rat ischemic stroke models by mainly reducing iNOS, TNF-α expression and $ONOO^-$ levels. A recent multicenter, randomized, double-blind, comparative, phase III clinical trial suggested that 90-day good functional outcomes favored the edaravone dexborneol group when edaravone dexborneol versus edaravone was administered within 48 hours after AIS, especially in female patients (50).

A recent meta-analysis suggests that borneol can effectively prevent and treat the nerve damage caused by ischemic stroke. Its mode of action involves promoting cerebral vascular dilation and anticoagulation, decreasing glutamate levels and γ-aminobutyric acid A receptor, boosting the activity of antioxidant enzymes, ameliorating free-radical damage, regulating the activity of NOS, counteracting NO neurotoxicity, reducing Ca^{2+} concentration, suppressing neuronal apoptosis, and inhibiting rapid temperature elevation (51). Additionally, borneol has been shown to promote the repair of nerve cells and the renewal of blood vessels, facilitating the body's recovery in the late stages of brain injury.

Cerebral glioma

Cerebral glioma is a prevalent type of CNS disease, with an estimated 40% of patients with brain tumor being afflicted by this condition. Among the cerebral glioma subtypes, glioblastoma is the most malignant, characterized by rapid tumor progression and short survival. Currently, surgical resection followed by chemoradiation is the optimal treatment option for cerebral glioma. However, due to the serious infiltration of malignant glioma, and potential involvement of eloquent areas of brain, complete resection is often not feasible, which is associated with worse survival despite adjuvant chemoradiation treatment (52-54).

During the progression of cerebral glioma, the tight junctions in the BBB are disrupted, leading to changes in the barrier near brain capillaries (55). The BTB is composed of three types of microvascular subgroups, including continuous non-fenestrated microvessels, continuous fenestrated microvessels, and vessels with endothelial channels about 1 micron in diameter. Despite BTB permeability being higher than that of BBB, it still restricts many therapeutic drugs from entering intracranial tumors, limiting the types of chemotherapeutic drugs that can be administered and reducing efficacy; as a consequence, most drugs are unable to enter the brain or reach effective concentrations.

Due to its excellent lipid solubility, borneol is more easily passing through the BBB and BTB than are other substances. For patients with cerebral gliomas, borneol can increase the effectiveness of treatment by promoting the penetration of drugs through the blood-brain cerebrospinal fluid barrier. While multiple studies have demonstrated that heroin can increase the permeability of the BBB and BTB, the exact mechanism remains a point of debate in clinical settings (47). Some researchers argue that the improvement of BBB permeability can be mainly attributed to the constituents in borneol, which can counteract the P-gp protein in the BBB and BTB, thus facilitating the opening of the BTB (13,45,56). A recent study reported

Table 2 Fundamental mechanisms of borneol in regulating the BBB

Mechanisms	Targets	References
Inflammatory signaling	TNF-α↓, IL-1β↓, and IL-6↓, NF-κB↓, IFN-γ↓, IL-10↑, TGF-β↑	(37,39,63)
Oxidative stress	ROS↓, CAT↑, SOD↑, GPX↑, MDA↓, GR↑	(37,39,63)
Cellular signaling	CAV-1↑, PI3K-Akt, p38-MAPK	(64,65)

These two symbols "↓ and ↑" denote decrease and increase, respectively. BBB, blood-brain barrier; TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; NF-κB, nuclear factor kappa-B; IFN-γ, interferon gamma; IL-10, interleukin-10; TGF-β, transforming growth factor-β; ROS, reactive oxygen species; CAT, catalase enzymes; SOD, superoxide dismutase; GPX, glutathione peroxidase; MDA, malondialdehyde; GR, glutathione reductase; CAV-1, caveolin-1; PI3K-Akt, phosphatidylinositol 3 kinase-protein kinase B; p38-MAPK, p38-mitogen-activated protein kinase.

that borneol does not have a significant direct inhibitory effect on the expression of P-gp in Sprague Dawley rats' brain tissue. Instead, it weakens the efflux function of P-gp through competitive substrate binding, thereby enhancing the efficacy of medication (11). Chen and colleagues (57) discovered that when combined with non-P-gp substrates, borneol can also increase the permeability of the BBB. Other researchers have proposed that borneol can open the tight junctions of the BBB, enhancing cell membrane fluidity and phagocytic ability, while studies on actin and claudin proteins suggest that borneol can regulate the permeability of the BBB by clustering through tight junctions (57-59). In addition to the above two theories, research has also indicated that borneol can increase BBB permeability by regulating the content of neurotransmitters in the brain and upregulating the expression of Ca^{2+}, NO, eNOS, and β2-adrenergic receptors (60). Wu *et al.* (61) found that after administration of borneol, the expression of NO, eNOS, and β2-adrenergic receptors all increased significantly. Furthermore, borneol may also have potential for the immunotherapy of patients with cerebral glioma; for example, Zhou *et al.* (62) demonstrated that borneol alcohol treatment can enhance the migration of immune cells across the BBB, promote the activation of immune responses in a mouse glioma model, and thus achieve the goal of killing tumor cells.

It can be inferred that borneol can increase both the permeability of the BBB and the BTB, which can assist in drug delivery across the BTB. Therefore, adding borneol to the adjuvant therapy of patients with cerebral glioma may confer improved treatment efficacy. Nevertheless, there is currently a scarcity of clinical studies examining the application of borneol in the treatment of cerebral glioma, and a shortage of comprehensive data to substantiate these claims.

Fundamental mechanisms of borneol in regulating the BBB

The underlying mechanisms of borneol in regulating the BBB are complex and involve multiple pathways, including inflammatory signaling, oxidative stress, and cellular signaling. The fundamental mechanisms of borneol in regulating the BBB are listed in *Table 2*.

Inflammatory signaling

Inflammation is a common feature of various pathological conditions that affect the BBB, including ischemic stroke, TBI, and Alzheimer disease (AD) (66,67). Borneol has been shown to modulate inflammatory signaling in these conditions. For example, Zhang and colleagues (37) reported that borneol treatment could reduce the expression of inflammatory cytokines, including TNF-α, interleukin-1β (IL-1β), and IL-6 in the ischemic brain. Li *et al.* (39) found that borneol treatment could inhibit the activation of nuclear factor-κB (NF-κB), a key transcription factor involved in the inflammatory response, in the injured brain of rats with TBI. In addition, Chen *et al.* (63) demonstrated that borneol treatment could reduce the expression of pro-inflammatory cytokines, including IL-1β, IL-6, and interferon-γ (IFN-γ), and increase the expression of anti-inflammatory cytokines, including IL-10 and transforming growth factor-β (TGF-β), in the brain of mice with AD. These results suggest that borneol may regulate the BBB by modulating inflammatory signaling in pathological conditions.

Oxidative stress

Oxidative stress is another common feature of various

pathological conditions that affect the BBB, including ischemic stroke, TBI, and AD (66,67). Borneol has been shown to modulate oxidative stress in these conditions. For example, Zhang and colleagues (37) reported that borneol treatment could reduce the production of ROS and enhance the activity of antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), in the ischemic brain. Li and colleagues (39) found that borneol treatment could increase the activity of SOD and glutathione peroxidase (GPx), another key antioxidant enzyme, in the injured brain of rats with TBI. In addition, Chen and colleagues (63) demonstrated that borneol treatment could reduce the levels of malondialdehyde (MDA), a lipid peroxidation product, and increase the activity of SOD and glutathione reductase (GR), another key antioxidant enzyme, in the brain of mice with AD. These results suggest that borneol may regulate the BBB by modulating oxidative stress in pathological conditions.

Cellular signaling

Cellular signaling plays a significant role in borneol-mediated BBB regulation. For example, Liu and colleagues (64) reported that borneol treatment could activate the PI3K-Akt signaling pathway in primary cultured brain microvascular endothelial cells, leading to increased expression of tight junction proteins and reduced permeability of the BBB. In addition, Zhu and colleagues (65) demonstrated that borneol treatment could activate the p38-MAPK signaling pathway in glioma cells, leading to increased expression of caveolin-1, a protein that regulates the transcytosis of macromolecules across the BBB. These findings suggest that borneol may regulate the BBB by modulating cellular signaling pathways in different cell types.

In summary, borneol presents a promising avenue for BBB modulation. Its demonstrated effectiveness in mitigating inflammation, oxidative stress, and regulating cellular signaling pathways underscores its potential therapeutic value. Future research endeavors should focus on elucidating the precise molecular mechanisms underlying borneol's effects on the BBB. Furthermore, investigating its safety profile, determining optimal dosing, and exploring potential synergistic interactions with other therapeutic agents will be imperative for advancing borneol toward clinical applications. The multifaceted nature of borneol's actions underscores its significance in the dynamic field of BBB regulation and its potential to offer innovative solutions for neurovascular diseases.

The role and prospects of anti-inflammatory agents in the treatment of two brain diseases

Ischemic stroke and cerebral glioma are both common brain tissue pathological diseases. Currently, most scholars believe that both are influenced by inflammation.

Ischemic stroke and inflammation

From a clinical perspective, patients experiencing ischemic stroke may experience temporary fever and elevated white blood cell counts in the absence of clear signs of infection, indicating a certain connection between ischemic stroke occurrence and inflammation (68). The literature suggests that in ischemic stroke, glial cells become activated within minutes, triggering a cascade of inflammatory mediators that spread from the lesion site to other locations (69). Additionally, endothelial cell activation results in the production of many adhesion molecules, disrupting the BBB and allowing white blood cells to adhere and extravasate. ROS generated by ischemia also promote the production of proinflammatory cytokines and chemokines, further increasing the expression of adhesion molecules and promoting leukocyte aggregation, thereby exacerbating the condition. Within half an hour of ischemic stroke occurrence, neutrophils extravasate, causing microcirculation obstruction and aggravating ischemia, which in turn affects blood circulation recovery (70). Lymphocytes and macrophages may adhere and extravasate 24–48 hours after ischemic stroke. The white blood cells in the lesion site, together with activated glial cells, release harmful molecules such as proteases, glutamate, cytokines, chemokines, free radicals, prostaglandins, and NO (71,72). These inflammatory molecules not only promote the adhesion and extravasation of inflammatory cells but also cause damage to cells, blood vessels, and extracellular matrix, exacerbating BBB disruption and leading to cerebral edema. Ischemic stroke can also activate complement, and generate active fragments that can cause damage to nerve cells or accelerate the inflammatory response. In conclusion, it is evident that inflammation plays a significant role in promoting brain damage and the development of ischemic lesions following an ischemic stroke event (73).

Cerebral glioma and inflammation

Inflammation is one of the characteristics of cerebral glioma, and its activation of transcription factors by inflammation also promotes the survival and rapid development of cerebral glioma. Research has shown that there is an abnormal increase in various immunosuppressive substances such as IL-6 and IL-10 in the peripheral blood and tumor cells of patients with cerebral glioma (74). Meanwhile, the regulatory T cell (Treg) subpopulation, which has an immunomodulatory function, is also significantly upregulated in patients with glioma. The helper T lymphocyte 17 (Th17) is a newly identified subpopulation of T lymphocytes whose mechanism of action induces sustained inflammatory reactions and prevents infection by promoting the expression of IL-17 (75). Treg and Th17 interact in the tumor microenvironment. IL-17 is an important cytokine of Th17 cells, which has the function of evading immune attack and promoting the occurrence and development of tumors. Its confirmed mechanisms of action are (I) causing antigen recognition disorders, promoting the insufficient activation of immune cells, (II) increasing the tolerance of antitumor immune cells to T lymphocytes and promoting apoptosis, (III) secreting immunosuppressive factors such as IL-6 and IL-10, and (IV) promoting the production of immunosuppressive cells (75). In addition, some scholars have pointed out that the correlation between the occurrence and development of cerebral glioma in patients and the inflammatory mechanism is related to the NF-κB signaling pathway. NF-κB is an important inflammation-related transcription factor in eukaryotic cells. It plays a crucial role in the expression and activation of cerebral glioma, and the NF-κB signaling pathway can participate in the occurrence and development of neurogliomas by regulating the TNF protein family and epidermal growth factor receptor (EGFR) (76). Not only that, borneol alone and in combination with anticancer agents has shown to enhance ROS generation that leads to the destruction of tumor cells. Authors could add this mechanism of borneol's action in treatment of glioma (77).

It can be inferred that there is a certain correlation between the pathogenesis of ischemic stroke and glioma and the inflammatory mechanism. Therefore, it may be worth beginning the treatment process from an anti-inflammatory perspective.

Anti-inflammatory effects of borneol

Borneol has been proven to have a protective effect on the BBB. Under physiological conditions, it can increase BBB permeability, while under pathological conditions, it can reduce BBB permeability. Analysis of its specific protective mechanism shows that borneol's benefit to the BBB is also related to inflammation regulation. MMPs have a certain degrading effect on various protein components of the BBB basement membrane extracellular matrix, which can lead to BBB damage (78). Among the MMP family, MMP-9, which is associated with inflammatory cells, causes the greatest damage to the BBB. For instance, TNF-α has the potential to exacerbate BBB damage by modulating the expression of MMPs (79). The experimental results of Wang and others (80) showed that MMP-9 expression in brain tissue was significantly higher in rats with cerebral arterial obstruction than in those subjected to sham surgery. However, after a natural borneol intervention, the expression of MMP-9 decreased, and it had a certain brain-protective effect. Ni *et al.* (81) observed the effect of 4 Chinese medicines on TNF-α levels in rats and found that compared with the 5% Tween control group, the synthetic borneol group had significantly lower TNF-α content, indicating that borneol has an inhibitory effect on the generation and release of TNF-α. In addition, recent reports have shown that borneol can also counteract inflammatory reactions through the NF-κB (45), eNOS (82), and iNOS pathways, among others (83). This suggests that borneol may participate in the treatment of brain tissue lesions (such as ischemic stroke and cerebral gliomas) from the perspective of BBB protection (anti-inflammation), but currently, the research for this is lacking, and further clinical data validation is needed.

Coadministration of borneol and other medication

A large number of recently conducted experiments indicated that in addition to being used alone, borneol can be used synergistically with other medication to enhance the effect of drugs and promote drug penetration through the BBB. To date, borneol has been shown to exhibit synergistic effects with three distinct categories of drugs, all of which are pertinent to brain-related conditions. These include antitumor drugs, such as cisplatin (84), 5-fluorouracil (20), and methotrexate (85); antibacterial drugs, such as clindamycin (86) and cephalosporin (87); and drugs used to treat brain diseases, such as dopamine (88). Guo *et al.* (85) established a C6 glioma rat model with C6 glioma cells and found that intervention with borneol combined with methotrexate led to more methotrexate being distributed

in brain tissue and a greater degree bioavailability as compared to administration of methotrexate alone. Chu and colleagues (86) studied the promoting effect of borneol on the penetration of clindamycin through the mouse blood-cerebrospinal fluid barrier and found that borneol can promote the penetration of clindamycin through the blood-cerebrospinal fluid barrier. Du *et al.* (89) conducted a treatment trial on 40 rats: the results showed that borneol can increase the permeability of the BBB to cisplatin, thereby improving the efficacy of cisplatin in glioblastoma while also protecting—and not damaging—the brain and BBB.

Conclusions

The BBB is a dynamic and highly selective barrier that effectively partitions the brain from circulating blood. It serves a critical role in safeguarding the CNS by preventing the entry of potentially harmful substances, thus upholding the delicate homeostasis of the brain microenvironment. The disruption of the BBB is substantial part of the pathological basis for diseases such as ischemic stroke and cerebral glioma. Borneol, by virtue of its lipophilic properties, can reduce the permeability of the BBB and restore its normal function, thereby repairing brain damage and protecting brain tissue. Its specific protective effects may be related to inflammatory regulation mechanisms. The anti-inflammatory and protective effects of borneol can be used to improve and treat lesions caused by ischemic stroke and cerebral glioma. Intriguingly, borneol's effects extend beyond protection to include the modulation of BBB permeability. When administered strategically, borneol demonstrates its versatility by enhancing the delivery of drugs to brain tissue. This enhancement not only reduces drug resistance but also amplifies treatment efficiency. This dual action highlight borneol's potential in the context of neurological diseases, providing a means not only to protect the BBB but also to promote the delivery of therapeutic payloads to the brain.

Currently, research on borneol in the field of BBB has made some progress, yet a series of critical issues remain to be thoroughly addressed. Firstly, despite initiating investigations on the mechanism of action of ice chips on the BBB, numerous molecular intricacies, particularly concerning its bidirectional modulation, remains unknown and some controversy persists. A comprehensive understanding of borneol's molecular mechanisms on the BBB is pivotal for a more holistic comprehension of its mode of action. This necessitates in-depth exploration of cell signaling, molecular transportation, vascular neuroprotection, and inflammatory regulation, revealing how borneol influences BBB permeability and integrity. Secondly, though certain clinical trials have been conducted to evaluate the potential of borneol in the treatment of neurovascular diseases, more extensive clinical data is still requisite to substantiate its safety and efficacy in practical therapeutics. These clinical datasets may ideally encompass large-scale, multicenter and standardized studies to ensure the attainment of more dependable conclusions. Furthermore, it is imperative to discern variations in the effectiveness of borneol among patients with different types of neurovascular diseases, thereby facilitating personalized treatment approaches. Lastly, the safety profile and optimal dosage of borneol remain inadequately defined, constituting a pivotal focal point necessitating in-depth investigation. Safety studies should encompass evaluations of long-term usage implications, especially at elevated dosage levels. Concurrently, dosage studies need to explore borneol's effects at various dosage levels to ascertain the optimal dosage for therapeutic applications.

Through rigorous exploration of these issues, we aspire to develop more efficacious and targeted treatment modalities in the future, thereby enhancing the quality of life for patients suffering from neurovascular diseases. These research endeavors are poised to unlock the full potential of borneol in BBB regulation, offering innovative solutions for the treatment of neurovascular diseases and instilling renewed hope in patients.

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Footnote

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