Protective effect of borneol combined with safflower on neurovascular unit in rats with ischemic stroke

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Author contributions
Gao L conducted the experiments; Liu FY and Qu XL preformed the data analysis; Lu ZY amended the paper; Gao HL designed the study, conducted the experiments and wrote the paper.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
NVU, neurovascular unit; MCAO, the middle cerebral artery; cerebral ischemia; SOD, superoxide dismutase; MDA, malondialdehyde; NO, nitric oxide; MMP-2, matrix metalloproteinase 2; ZO-1, tight junction protein 1; VEGF, vascular endothelial growth factor; BDNF, brain-derived neurotrophic factor.

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Abstract
Background: Compatibility is a characteristic of the clinical application of traditional Chinese medicine, often leading to enhanced therapeutic effects. In the treatment of cerebral ischemia, blood-activating and open orifices herbs are frequently used individually; however, their combination is not commonly practiced. This study aims to investigate the impact of combining safflower and borneol as examples of open orifices herbs and blood-activating herbs on the neurovascular unit in rats with ischemic stroke. The objective is to determine whether this combination exhibits superior therapeutic efficacy compared to using borneol or safflower alone while exploring its underlying mechanism. These findings may provide novel insights for clinical treatments. Methods: SD male rats were randomly divided into 6 groups: sham operation group, model group, borneol group (0.1 g/kg), safflower group (5 g/kg), borneol combined with safflower group (0.1 g/kg + 5 g/kg) and nimodipine group (0.01 g/kg). The middle cerebral artery cerebral ischemia (MCAO) model were prepared after continuous intragastric administration for 7 days in each group, the neurological function of each group were scored 24h after operation, and water content in brain tissue were measured by weighing method. The activity of superoxide dismutase (SOD) and the contents of nitric oxide (NO) and malondialdehyde (MDA) in brain tissue and serum were determined by spectrophotometry, and the mRNA expressions of matrix metalloproteinase 2 (MMP-2), tight junction protein 1 (ZO-1), vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) were detected by Real time PCR. Result: Compared with the model group, the group treated with borneol combined with safflower exhibited a significant decrease in the neural function score of MCAO rats (P < 0.01). Additionally, it led to a reduction in brain tissue water content (P < 0.01), elevated SOD activity, and reduced levels of NO and MDA in both serum and brain tissue (P < 0.01 or P < 0.05). Moreover, this treatment resulted in a decrease in the mRNA expression of MMP-2 and an increase in ZO-1 in brain tissue, along with an increase in the mRNA expression of VEGF and BDNF (P < 0.01). Conclusion: Borneol combined with safflower demonstrates a protective effect on the neurovascular unit in rats with ischemic stroke. This effect is likely associated with increased SOD activity, reduced MDA and NO content in both serum and brain tissue of MCAO rats, and a decrease in MMP-2 mRNA expression in brain tissue, coupled with an increase in ZO-1, VEGF, and BDNF mRNA expression. These effects were superior to those observed with borneol or safflower administered alone.

Keywords: borneol; safflower; neurovascular unit; combination; cerebral ischemia
In recent years, the understanding of brain ischemic injury has transitioned from a focus on single factors to a comprehensive understanding centered around the “neurovascular unit” (NVU). The concept of NVU was initially introduced by the National Institute of Neurological Disorders and Stroke [1], encompassing neurons, glial cells, and blood vessels. This concept not only considers their structural components and interactions as a whole but also elevates the approach to treating brain ischemic injury from the singular protection of neurons to the overall treatment of the NVU, offering new perspectives for brain ischemia treatment.

Traditional Chinese medicine, with its multi-target and multi-level treatment characteristics, align well with NVU treatment strategies. Gradually gaining recognition for its brain-targeting effects through component compatibility, traditional Chinese medicine employs blood-activating and stasis-removing herbs in ischemic stroke treatment, with Honghua (Safflower) being one of them. Ongoing research indicates that Honghua can prevent and treat ischemic stroke by exhibiting anti-inflammatory, antioxidant stress, inhibiting neuronal apoptosis, and protecting the blood-brain barrier [2–3]. Bingpian (Borneol), an office-opening drug, also finds application in brain ischemia, as studies have shown its ability to cross the blood-brain barrier and facilitate the penetration of other drugs [4].

Does the combination of blood-activating herb Honghua and office-opening drug Bingpian have a synergistic effect, providing overall protection to the NVU after brain ischemia? Preliminary experimental studies suggest that Bingpian combined with Honghua can reduce the protein expression of MMP-2 and MMP-9 in brain tissue while upregulating ZO-1. This, in turn, reduces MMP-9 and upregulates Claudin-5 mRNA expression, exerting brain-protective effects [5]. However, further research is needed to comprehensively explore the synergistic effects and mechanisms of this combination.

Materials and methods

Experimental animal
Male SPF-grade Sprague-Dawley (SD) rats, 114 in total, with a body weight of (220 ± 20) g, were provided by Jinan Pengyue Experimental Animal Breeding Co., Ltd. The qualification certificate number is SCXK (La) 20190003. The rats were housed in the Laboratory of Experimental Animals at the School of Pharmacy, Shandong First Medical University, and experiments were reviewed and approved by the Animal Ethics Committee of the Shandong First Medical University (ethics approval number: W202212010382).

Materials and reagents
Natural borneol (D-borneol, purity 96%) was purchased from Huanan Xinhuang Longnao Development Co., Ltd. Safflower (Honghua) was obtained from Tongrentang Pharmacy in Beijing and identified by Associate Professor Qu Xiaolan of the School of Pharmacy, Shandong First Medical University, as the dried flowers of Carthamus tinctorius L., a plant belonging to the Asteraceae family. Nimodipine tablets (30 mg/tablet, Shandong Xinhua Pharmaceutical, batch number 2105265) were used. Assay kits for MDA, SOD, NO, and protein quantification were from Nanjing Jiancheng (batch numbers: 20221007, 20221007, 20221009, 20220924). TRizol reagent was from Invitrogen (USA), and Real Time PCR primers were from Shanghai Sangon Biotech. The Prime Script™ RT Master Mix (Perfect Real Time) kit and qPCR reaction system kit were from TaKaRa (Dalian) Takara Bio Inc.

Safflower was extracted using a traditional method by soaking in distilled water for 30 minutes and then boiling twice for 30 minutes each time. After mixing and filtering, the extract was concentrated to a concentration of 1 g/mL and stored at 4 ℃. Borneol was prepared as a suspension with the desired mass concentration using 0.5% carboxymethyl cellulose sodium (CMC-Na) just before intragastric administration.

Instruments
Step One Plus Real-Time PCR System (Life Technologies, USA); UV-2700 UV-Visible Spectrophotometer (Shimadzu, Japan); INFINIT 200PRO Microplate Reader (TECAN, Switzerland); 3-30k Ultra-High-Speed Refrigerated Centrifuge (SIGMA, Germany), and others.

Methods
Grouping and administration
SD rats were randomly divided into six groups. The treatment groups included the borneol group (0.1 g/kg), the safflower (Honghua) group (5 g/kg), and the borneol combined with safflower group (borneol 0.1 g/kg + safflower 5 g/kg). The positive drug control group received nimodipine (0.01 g/kg). Sham surgery and model groups were also established. Each group received the corresponding treatment for 7 days, with intragastric administration once daily. The model group and sham surgery group received an equal volume of normal saline by intragastric administration.

MCAO rat model construction
One hour after the last drug administration in each group, the surgical procedure was performed to create the MCAO model, following the method described in reference [6]. Anesthesia was induced using intraperitoneal administration of chloral hydrate (350 mg/kg). A nylon thread (diameter 0.22–0.26 mm) was inserted into the internal carotid artery through a small incision made at the bifurcation of the common carotid artery. The insertion depth was approximately 18–20 mm from the bifurcation of the internal and external carotid arteries, stopping when slight resistance was encountered. In the sham surgery group, all procedures were the same except that the length of thread insertion was less than 10 mm.

Neurological function assessment
Two hours after surgery, neurological function was assessed in rats using a 5-level scoring system, following the method described by Longa [6]. Rats scoring 1–3 points were considered to have a successful MCAO model, and any rats not meeting this criterion were excluded from the experiment, with additional rats included as replacements if necessary. After 24 hours post-modeling, 10 rats from each group were subjected to neurological function deficit assessment.

Brain tissue water content measurement
Six rats from each group were anesthetized and decapitated rapidly. The brains were dissected to remove the olfactory bulb and lower brainstem. The ischemic side hemisphere of the brain was taken, and its wet weight was recorded. Then, it was placed in an oven at 105 ℃ for 48 hours until a constant weight was achieved, and the dry weight was recorded. The brain tissue water content was calculated using the formula: (wet weight - dry weight)/wet weight × 100%.

Serum SOD activity, MDA, and NO content measurement
For each group, 10 rats were anesthetized with an overdose of chloral hydrate, and blood samples were collected via the abdominal aorta. Serum was obtained after centrifugation. The levels of serum NO, MDA, and SOD were determined using a UV-Visible spectrophotometer or microplate reader according to the instructions provided with the assay kits.

Brain tissue SOD activity, MDA, and NO content measurement
After blood collection, eight rats from each group were decapitated rapidly, and brain tissue from the middle of the ischemic side was collected. Brain tissue was mechanically homogenized in a 1: 9 ratio with pre-chilled physiological saline. The homogenates were centrifuged to obtain 10% brain tissue homogenates. The protein concentration in brain tissue was determined using the Bradford assay. Brain tissue MDA, NO, and SOD levels were measured strictly according to the instructions provided with the assay kits.
Real-Time PCR detection of mRNA expression of MMP-2, ZO-1, VEGF, and BDNF in rat brain tissue

For each group, five rats were anesthetized with chloral hydrate and decapitated rapidly. Approximately 100 mg of brain tissue from the middle of the ischemic side cortex was collected, rapidly frozen in liquid nitrogen, and stored at −80 °C. Brain tissue was added to pre-chilled Trizol (1 mL) and RNA was extracted using routine methods to determine its purity and concentration. The RNA was reverse transcribed into cDNA, and real-time quantitative PCR (qPCR) was performed using the cDNA. The primer sequences for PCR are provided in Table 1, and GAPDH was used as an internal reference. After PCR reactions were completed, the amplification curves for the target genes and GAPDH were analyzed, and the Ct values for each well were obtained. The results were analyzed using the 2^−ΔΔCT method to reflect the fold change in the expression of the target genes.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Data were expressed as mean ± standard deviation (Mean ± SD). Group comparisons were conducted using One-Way ANOVA, and post hoc pairwise comparisons of means were carried out using the LSD test. A significance level of P < 0.05 was considered statistically significant.

Results

Effects on neurological function scores and brain tissue water content

In the sham surgery group, rats exhibited normal neurological function with a score of 0 at 24 hours post-surgery. In contrast, rats in the model group showed a significant increase in neurological function scores (P < 0.01), indicating impaired neurological function and successful replication of the MCAO model. In the different treatment groups, the borneol combined with safflower group significantly reduced the neurological function scores in the model rats (P < 0.01). The other treatment groups also showed varying degrees of reduction in scores (P < 0.01 or P < 0.05). Regarding brain tissue water content measurements, the model group had significantly higher brain tissue water content compared to the sham surgery group (P < 0.01). However, the borneol combined with safflower group significantly reduced brain tissue water content in the model rats (P < 0.01), outperforming the borneol-only or nimodipine group. The results are presented in Figure 1.

Table 1 PCR primer sequences

<table>
<thead>
<tr>
<th>Primer</th>
<th>Forward primer (5’–3’)</th>
<th>Reverse primer (5’–3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP2</td>
<td>AGTATGGGAACGCCTGATGGC</td>
<td>TTGTAGAGGTGCCCTGGAAG</td>
</tr>
<tr>
<td>ZO-1</td>
<td>GGGGCTACCTATGATGTCCT</td>
<td>GAGCGAACTGAATGGTCTGATG</td>
</tr>
<tr>
<td>VEGF</td>
<td>GCACITGGACCCCTGTTCCT</td>
<td>AACITCACCACCTCATGGGTTT</td>
</tr>
<tr>
<td>BDNF</td>
<td>GTGTGACATGATTAGGGATGGG</td>
<td>ACGATTGGATAGTTCCGGCATT</td>
</tr>
<tr>
<td>GAPDH</td>
<td>CTGGAGAAACCTGCCAAGTATG</td>
<td>GGTGGAAGAAATGGGAGTTGCT</td>
</tr>
</tbody>
</table>

Figure 1 Effects on neurological function scores and brain tissue water content in MCAO rats. (A) Neurological function score/points (n = 10); (B) Brain tissue water content/% (n = 6). *P < 0.01 versus sham group; **P < 0.01 versus model group; ***P < 0.05, ****P < 0.05 versus borneol and safflower combination group.
Effects on serum MDA, NO, and SOD

Compared to the sham surgery group, the model group exhibited a significant increase in serum MDA and NO levels ($P < 0.01$) while also showing a significant decrease in SOD activity ($P < 0.01$). In comparison to the model group, the borneol combined with safflower treatment group demonstrated a substantial improvement in the mentioned parameters, reducing MDA and NO levels, and increasing SOD activity ($P < 0.01$ or $P < 0.05$). Notably, the improvements in SOD and NO levels were superior to those in the borneol-only and safflower-only groups ($P < 0.01$ or $P < 0.05$), and regarding the reduction in MDA levels, it outperformed the borneol-only group ($P < 0.05$). Please refer to Table 2.

### Table 2 Effects on serum SOD, MDA, and NO in MCAO rats ($\bar{x} \pm s, n = 10$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose/g kg$^{-1}$</th>
<th>SOD/U mL$^{-1}$</th>
<th>MDA/nmol mL$^{-1}$</th>
<th>NO/μmol mL$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Surgery Group</td>
<td>-</td>
<td>270.82 ± 6.64</td>
<td>4.36 ± 0.58</td>
<td>2.34 ± 0.37</td>
</tr>
<tr>
<td>Model Group</td>
<td>-</td>
<td>242.28 ± 6.69</td>
<td>6.18 ± 0.47</td>
<td>4.73 ± 0.59</td>
</tr>
<tr>
<td>Borneol Group</td>
<td>0.1</td>
<td>255.74 ± 7.28</td>
<td>4.83 ± 0.49</td>
<td>3.47 ± 0.47</td>
</tr>
<tr>
<td>Safflower Group</td>
<td>5</td>
<td>259.68 ± 6.42</td>
<td>5.31 ± 0.79</td>
<td>3.39 ± 0.42</td>
</tr>
<tr>
<td>Borneol + Safflower</td>
<td>0.1 + 5</td>
<td>266.15 ± 7.83</td>
<td>4.72 ± 0.45</td>
<td>2.71 ± 0.31</td>
</tr>
<tr>
<td>Nimodipine Group</td>
<td>0.01</td>
<td>257.12 ± 6.56</td>
<td>5.42 ± 0.58</td>
<td>3.11 ± 0.39</td>
</tr>
</tbody>
</table>

Note: $^1P < 0.01$ versus sham surgery group; $^2P < 0.05$, $^3P < 0.01$ versus model group; $^4P < 0.05$, $^5P < 0.05$ versus borneol and safflower combination group.

Effects on brain tissue SOD, MDA, and NO

In the model group, there were significant alterations in brain tissue levels of MDA, NO, and SOD, with an increase in MDA and NO, and a decrease in SOD ($P < 0.01$). When compared to the model group, the borneol combined with safflower treatment group exhibited an elevation in SOD activity ($P < 0.01$) and a reduction in MDA and NO levels ($P < 0.01$). In terms of decreasing MDA and NO levels, this improvement was superior to both the borneol-only and safflower-only groups ($P < 0.01$ or $P < 0.05$). In enhancing SOD activity, it outperformed the borneol-only group ($P < 0.05$). Please refer to Table 3.

### Table 3 Effects on brain tissue SOD, MDA, and NO in MCAO rats ($\bar{x} \pm s, n = 8$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose/g kg$^{-1}$</th>
<th>SOD/U mg$^{-1}$</th>
<th>MDA/nmol mg$^{-1}$</th>
<th>NO/μmol g$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Surgery Group</td>
<td>-</td>
<td>409.33 ± 45.45</td>
<td>1.92 ± 0.26</td>
<td>1.76 ± 0.36</td>
</tr>
<tr>
<td>Model Group</td>
<td>-</td>
<td>249.08 ± 44.84</td>
<td>3.90 ± 0.49</td>
<td>4.67 ± 0.61</td>
</tr>
<tr>
<td>Borneol Group</td>
<td>0.1</td>
<td>306.33 ± 36.35</td>
<td>2.62 ± 0.41</td>
<td>3.59 ± 0.49</td>
</tr>
<tr>
<td>Safflower Group</td>
<td>5</td>
<td>333.57 ± 40.54</td>
<td>2.46 ± 0.23</td>
<td>3.36 ± 0.38</td>
</tr>
<tr>
<td>Borneol + Safflower</td>
<td>0.1 + 5</td>
<td>358.17 ± 47.10</td>
<td>2.16 ± 0.30</td>
<td>2.79 ± 0.45</td>
</tr>
<tr>
<td>Nimodipine Group</td>
<td>0.01</td>
<td>323.55 ± 44.75</td>
<td>2.26 ± 0.43</td>
<td>3.16 ± 0.34</td>
</tr>
</tbody>
</table>

Note: $^1P < 0.01$ versus sham surgery group; $^2P < 0.05$, $^3P < 0.01$ versus model group; $^4P < 0.05$, $^5P < 0.05$ versus borneol and safflower combination group.
Effects on brain tissue mRNA expression of MMP-2, ZO-1, VEGF, and BDNF

The real-time PCR results indicate that the mRNA expression of ZO-1 in the brain tissues of the model group rats was significantly decreased, while the mRNA expression of MMP-2 was significantly increased ($P < 0.05$). Compared to the model group, in the group treated with a combination of borneol and safflower, the mRNA expression of MMP-2 was significantly downregulated, and the mRNA expression of ZO-1 was significantly upregulated ($P < 0.01$). In terms of upregulating the mRNA expression of ZO-1, it was superior to the group using borneol alone and the group using safflower alone ($P < 0.01$ or $P < 0.05$). The mRNA expression of VEGF and BDNF in the model group showed only slight increases compared to the sham surgery group, with no significant differences ($P > 0.05$). In contrast, the mRNA expression of VEGF and BDNF in the group treated with a combination of borneol and safflower was significantly upregulated compared to the model group ($P < 0.01$), and it was superior to the group using borneol alone and the group using safflower alone ($P < 0.01$ or $P < 0.05$). See Figure 2 for details.

Discussion

Recent studies have confirmed that cerebral ischemia leads to the comprehensive disruption of the Neurovascular Unit (NVU). During ischemic stroke, various components of the NVU, including neurons, the blood-brain barrier, and glial cells, are differentially affected, leading to the disruption of NVU integrity [7]. Cerebral ischemic injury triggers a complex cascade of inflammatory responses that affect not only neurons but also microglia, microvasculature, astrocytes, and more, resulting in alterations in the intracellular and extracellular environment, thereby exacerbating brain damage [8]. This process involves various factors such as inflammatory mediators, oxidative stress, tight junction-related proteins, MMPs, among others. Consequently, comprehensive protection of the NVU is crucial for effectively treating cerebral ischemic injury rather than merely focusing on neuronal protection [9, 10].

Oxidative stress is considered one of the key pathogenic mechanisms during the early stages of cerebral ischemic injury [11–12]. Cerebral ischemia induces a series of cellular responses leading to the production of excessive reactive oxygen species, resulting in oxidative stress. Superoxide dismutase (SOD) is a crucial endogenous antioxidant enzyme, and malondialdehyde (MDA) is a final product of lipid peroxidation, both serving as essential indicators of oxidative stress. Nitric oxide (NO) is beneficial during the initial phase of cerebral ischemia; however, it later interacts with superoxide to form highly reactive nitrogen species, exacerbating oxidative stress [13]. Several traditional Chinese medicines also exhibit neuroprotective effects in cerebral ischemia by mitigating oxidative stress [14]. This study observed a decrease in SOD activity in cerebral tissue and serum alongside increased MDA and NO levels in MCAO model rats. Borneol combined with safflower significantly improved these indicators, outperforming both the borneol-only and safflower-only groups. Particularly, SOD and NO in serum and MDA and NO in brain tissue showed superior improvement with borneol combined with safflower. These results suggest that the observed effects may be attributed to the reduction of oxidative stress in MCAO rats.

![Figure 2](image_url)

**Figure 2** Effects on the mRNA expression of MMP-2, ZO-1, VEGF, and BDNF in MCAO rats. ($\bar{x} \pm s$, $n = 5$) (A) MMP-2/GAPDH mRNA expression; (B) ZO-1/GAPDH mRNA expression; (C) VEGF/GAPDH mRNA expression; (D) BDNF/GAPDH mRNA expression. $^*P < 0.01$ versus sham surgery group; $^*P < 0.05$ versus model group; $^*P < 0.05$, $^*^*P < 0.05$ versus borneol and safflower combination group.
In the acute phase of cerebral injury, matrix metalloproteinase-2 (MMP-2) plays a significant role in damaging the blood-brain barrier, subsequently exacerbating brain edema [15]. Up-regulation of MMP-2 expression can aggravate brain injury [16]. Additionally, zonula occludens-1 (ZO-1) is considered a hallmark protein in blood-brain barrier disruption and is closely related to blood-brain barrier damage [17]. Previous experiments of our research group have shown that borneol combined with safflower can reduce the protein expression of MMP-2 in the brain tissue of MCAO rats, and increase the protein expression of ZO-1 [5]. The current study found that MCAO rats had significantly increased cerebral tissue water content, along with markedly elevated MMP-2 mRNA expression and reduced ZO-1 mRNA expression. Borneol and safflower combination treatment reduced cerebral tissue water content, potentially through the upregulation of ZO-1 and downregulation of MMP-2 mRNA expression, thus ameliorating blood-brain barrier damage and reducing brain edema. In terms of up-regulating the mRNA expression of ZO-1, the borneol combined with safflower group was better than the borneol group or safflower group.

In the acute phase of cerebral injury, vascular regeneration is a critical factor determining the survival of neurons in the penumbra region. Vascular endothelial growth factor (VEGF) plays a key role in promoting angiogenesis and participates in post-cerebral ischemic injury blood vessel formation [18, 19]. Brain-derived neurotrophic factor (BDNF) is also highly expressed in neurons and glial cells following cerebral ischemia, contributing to neuroprotection and vascular remodeling [20]. Studies have found that borneol can promote angiogenesis and play a neuroprotective role by regulating VEGF and BDNF [21]. The current study observed that the borneol and safflower combination significantly upregulated the mRNA expression of VEGF and BDNF in the cerebral tissue of MCAO rats, suggesting their potential role in promoting vascular regeneration. The above effects were better than those of borneol alone and nimodipine positive drug group.

These results showed that borneol combined with safflower in the treatment of MCAO rats were better than the borneol group or the safflower group, especially better than the borneol group, some indexes were better than the Nimodipine group or there were no significant differences, indicating that borneol combined with safflower can enhance the efficacy of drugs.

Conclusion

This study found that borneol and safflower combination treatment could improve the neurological function scores of MCAO rats and reduce cerebral tissue water content. In combination with previous experimental research, this indicates that borneol and safflower may have anti-cerebral ischemic effects. The study suggests that their protective mechanisms may involve enhancing SOD activity in both serum and cerebral tissue while reducing MDA and NO levels. Furthermore, it may involve the downregulation of MMP-2 and upregulation of ZO-1 mRNA expression, along with the upregulation of VEGF and BDNF mRNA expression, ultimately exerting a protective effect on the neurovascular unit. The effects of borneol combined with safflower were better than those of borneol or safflower alone.

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