Tropical Journal of Pharmaceutical Research January 2025; 24 (1): 59-67
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v24i1.9

Original Research Article

Alleviation of cognitive impairments in ischemic stroke rat treated with baicalein-enriched fraction via JAKMIP1/GABRA6 pathway

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Sent for review: 2 November 2024 *Revised accepted: 4 January 2025*

Abstract

Purpose: *To investigate the therapeutic potential of baicalein-enriched fraction (BEF) extracted from Oroxylum indicum leaves on ischemic stroke in rat models induced with endothelin-1 (ET-1).*
Methods: *A total of 10 male Sprague Dawley rats were randomly assigned to the study (n = 5) and control (n = 5) groups. Study group received 50 mg/kg BEF treatment via oral gavage administration for 4 days prior to the induction of ischemic stroke using ET-1, while control group (n = 5) received normal saline. Neurological deficits, total infarct volume, histological scoring and expression of targeted genes were evaluated.*
Results: *The study group exhibited significantly improved motor function test, motor coordination and balance test, motor asymmetry test, and contralateral sensory test ($p < 0.05$) compared to control group. However, the reflex test was not significantly different between the study and control groups ($p > 0.05$). Furthermore, infarct volume, infarction area, and relative mRNA GABRA 6 expression were significantly lower in study group compared to control group while the relative mRNA expression of JAKMIP 1 was significantly higher ($p < 0.05$).*
Conclusion: *Baicalein-enriched fraction (BEF) extracted from O. indicum leaves improves motor coordination, lowers infarction parameters and therefore, may be a potential therapeutic agent for future clinical approaches to treat ischemic stroke disease.*
Keywords: *Phytotherapy, Ischemic stroke, Oroxylum indicum, Baicalein-enriched fraction, Neuroprotection*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Ischemic stroke is defined as a sudden disruption of blood flow to the brain, causing the brain cells deprived of oxygen and nutrients and ultimately leading to cell death in the affected area. Ischemic stroke is the second-leading cause of death and the top-leading cause of adult disability worldwide. In Malaysia, stroke is the third highest cause of death, closely trailing behind ischemic heart disease and pneumonia [1]. Currently, clinical treatment for ischemic stroke disease focuses on promptly reestablishing blood supply to areas affected by ischemia through the administration of recombinant tissue plasminogen activator (rt-

PA). However, the use of rt-PA is hampered by its narrow therapeutic window and rapid clearance from the body. As a result, the prognosis of ischemic stroke patients is low and approximately half the survivors of ischemic stroke still face an increased risk of recurrent stroke within days or weeks of the initial event [2].

Limitations in current ischemic stroke therapies have driven the exploration of alternative treatments that hold higher potential for promoting brain tissue repair and remodeling in patients with stroke-induced injuries. Recently, significant emphasis has been directed towards identifying and developing neuroprotective agents derived from natural products, aiming to achieve enhanced treatment efficacy while minimizing potential side effects. Among the plethora of studies conducted on plant-based remedies, particular attention has been drawn to *Oroxylum indicum,* a medicinal plant found in the tropical forests of Southeast Asia, especially Malaysia. This plant has been reported to possess various flavonoid compounds such as baicalein, chrysin and oroxylin with high antioxidant properties capable of scavenging free radicals and protecting cells against oxidative stress-induced injury. Furthermore, *O. indicum* has demonstrated diverse pharmacological effects such as anti-cancer, anti-bacterial, anti-adipogenesis, anti-inflammatory, wound healing and neurogenesis [3].

Among the phytochemicals present in *O. indicum*, baicalein is identified as a preeminent candidate for the treatment of neurological disorders due to its remarkable capability to transverse the blood-brain barrier (BBB) [4]. The therapeutic potential of baicalein has been reported in numerous neurodegenerative studies, demonstrating its capacity to reduce behavioral seizures, mitigate neuronal cell death, and foster neurite extension across diverse cellular and animal models [5]. Nonetheless, the potential effect of baicalein on ischemic stroke disease has not yet been explored. Therefore, this study investigated the effect of baicalein-enriched fraction (BEF) from the leaves of *O. indicum* in cognitive impairment following ischemic stroke.

EXPERIMENTAL

Extraction of baicalein-enriched fraction (BEF)

Leaves of *O. indicum* were collected from Kampung Pasir Parit, Pasir Mas, Kelantan, Malaysia, authenticated and deposited at Universiti Sains Malaysia (USM) Herbarium (voucher specimen 11751). Bioactive compounds of *O. indicum* were extracted using binary solvent soxhlet extraction procedure [6]. Powdered leaves (25 g) were loaded into a soxhlet extractor with 300 mL of petroleum ether and heated to 42 – 62 °C for 1 h. The solvent was discarded and the extraction was repeated for a second time. Thereafter, 500 mL of fresh methanol was added and heated to 62 – 65 °C for another1 h. The methanol solvent was collected, concentrated using rotary evaporator (Buchi AG, Flavil, Switzerland), weighted and stored at 4 °C until further use. The purpose of using binary solvents was to remove all non-polar compounds with petroleum ether and extract all targeted polar compounds with methanol. After crude extraction, baicalein was then enriched from the crude extract using a Diaion HP20 resin column and methanol-distilled water elution to obtain baicalein-enriched fraction (BEF).

Animals

A total of 10 healthy adult male Sprague Dawley (SD) rats of 8 - 12 weeks old weighing between 250-300 g were obtained from USM Animal Research and Service Centre (ARASC) and kept under standard conditions (12 h light / dark cycle, at room temperature, with unrestricted access to food and water). Ethical approval was obtained from the USM Institutional Care and Use Committee (IACUC; approval no. USM/IACUC/2019/(120(1019)) and complied with the recommendations of the National Research Council (US) for the Care and Use of Laboratory Animals [7].

Treatment with baicalein-enriched fraction (BEF)

The rats were randomly assigned study (n = 5) and control (n = 5) groups. Study group received 50 mg/kg of BEF while control group received normal saline (10 mL/kg). Both the vehicle solution and BEF were administered 4 days prior to the induction of ischemic stroke. Throughout the study, general behavior and signs of toxicity that include ataxia, tremors, hyperactivity, salivation, diarrhea, sleep, lethargy and convulsion were observed, and body weight was recorded weekly.

Induction of ischemic stroke using endothelin-1 (ET-1)

The rats were anesthetized using intraperitoneal injections of ketamine (100 mg/kg) and xylazine (5 mg/kg). Under anesthesia, the crown of the head was shaved, and a midline incision was

made using a scalpel. Then, a 21-gauge stainless steel guide cannula was stereotaxically implanted into right middle cerebral artery (1.6 mm anterior and 5.2 mm lateral to bregma), as previously described [8]. After fixation, the rats were housed in a controlled environment to facilitate recovery, before being subjected to perivascular administration of endothelin-1 (ET-1) to induce ischemic stroke. Following ET-1 administration, the rats were closely monitored in a transparent box for 60 min to assess stroke severity.

Evaluation of parameters/indices

Neurological deficits

Neurological deficit was evaluated based on the modified Neurological Severity Scores (mNSS) scoring system [9]. These evaluations were conducted on days 1, 2, 3, 4, 7 and 14 after the induction of stroke using ET-1 (n = 5 for each group). All the scores obtained were normalized against the baseline recorded on Day 1, allowing for the detection of any changes in scores over time following treatment. Five mNSS tests were conducted in this study, namely motor test, motor coordination and balance test, motor asymmetry test, contralateral sensory test, and reflex test.

Motor test

The rats were suspended by a tail 10 cm above the ground for approximately 5 seconds. Any flexion or twisting of the body towards the contralateral side was scored from 1 to 3. Those rats that showed no flexion or twisting of the body were scored 0.

Motor coordination and balance test

The rats were evaluated for motor coordination and balance tests using a beam-walking task. Rats that transverse the beam without slipping were scored 0, and those that transverse the beam with foot slip were scored between 1 to 3.

Motor asymmetry test

For the motor asymmetry test, small adhesive tapes (1 cm x 1 cm) were affixed to the palm of the rat forelimb. The time taken to remove the adhesive tape was recorded. Shorter time indicated better motor asymmetry function.

Contralateral sensory test

The rats were positioned with their vibrissae coming into contact with the wall. Thereafter, the number of successful placements of contralateral forepaw was recorded. Higher scores indicated better contralateral sensory function.

Reflex test

The reflex test was conducted to evaluate ear, eye, sound and tail reflexes. Sharp and immediate responses were scored 0, delayed or weak responses were scored 1, and no response was scored 0. Lower scores indicated better reflex function.

Cerebral infarct volume

After a 14-day experimental period, the rats were decapitated, and their brains were harvested for further analysis. The area of infarcted tissue in the experimental rat brains was determined with 2, 3, and 5-triphenyl tetrazolium chloride (TTC) stain. Infarct volume was measured by analyzing the TTC-stained sections using Image J software. Then, the brain tissues were fixed in a 10 % buffered formalin solution (pH 7.4) for preservation and subsequent histopathological assessment.

Histopathological assessments

After fixation, the brain tissues were embedded in paraffin and sliced using a microtome to obtain tissue slices of 3 µm in thickness. The tissue slices were then stained with hematoxylin and eosin (H & E) and examined under a light microscope to identify any potential histopathological changes. Photomicrographs were taken at three hotspots for every specimen slide for scoring analysis. Brain tissue integrity, severity of the lesions based on assessment of neuronal degradation, infiltration of inflammatory cells and density of blood vessels were used to assess histopathological staining [10].

Real-time polymerase chain reaction (qRT-PCR)

Total RNA was isolated from homogenized brain tissue using RNeasy lipid tissue mini extraction kit. Concentration of extracted RNA was then measured with a Nanodrop™ UV-visible spectrophotometer. Subsequently, RNA was converted into first-strand complementary deoxyribonucleic acid (cDNA) using the RevertAidTM H Minus Strand cDNA Synthesis Kit. For quantitative real-time PCR, the CFX96 real-time PCR detection system and qPCRBIO SyGreen Mix were employed according to the instructions provided by the manufacturer. Primers for genes of interest (JAKMIP1, STAT6 and GABRA6) as well as housekeeping genes (RPL13A and HRPT1) were designed using NCBI Primer BLAST software (Table 1). Protocol

for PCR included an initial activation phase at 95 °C for 2 min, succeeded by 40 repetitions of the denaturation phase at 95 °C for 5 s, an annealing phase at 60 °C for 30 s and an extension phase at 65 °C for 20 s. Data were analyzed using the relative threshold cycle (Ct) method, with results presented as fold differences normalized to reference genes (RPL13A and HRPT1).

Statistical analysis

Data was analyzed using Statistical Packages for Social Sciences (SPSS, version 22.0, IBM, Armonk, NY, USA). Data were presented as mean ± standard error mean (SEM). The student t-test was used to compare changes in body weight, relative organ weight (ROW) and the volume of infarction between study and control groups. One-way analysis of variance (ANOVA) was performed to analyze changes in behavioral scores within group. Post-hoc Tukey's test was performed to analyze multiple comparisons between groups. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of BEF on toxicity-related effects

There were no mortality or atypical behavioural changes like convulsions, twitching or epileptic episodes following treatment with BEF. Furthermore, throughout the 14-day study duration, all experimental rats exhibited consistent and stable weight gain (within 20 % of their initial weight per week), indicating normal growth trajectory following treatment with BEF compared to control group (Table 2).

Neurological deficit score

Study group showed significantly improved motor function (Figure 1 A), motor coordination and balance (Figure 1 B), more asymmetry (Figure 1 C), and contralateral sensory (Figure 1 D) effect compared to control group ($p < 0.05$). However, there was no significant difference in reflex functions (Figure 1 E) between study and control groups (Figure 1).

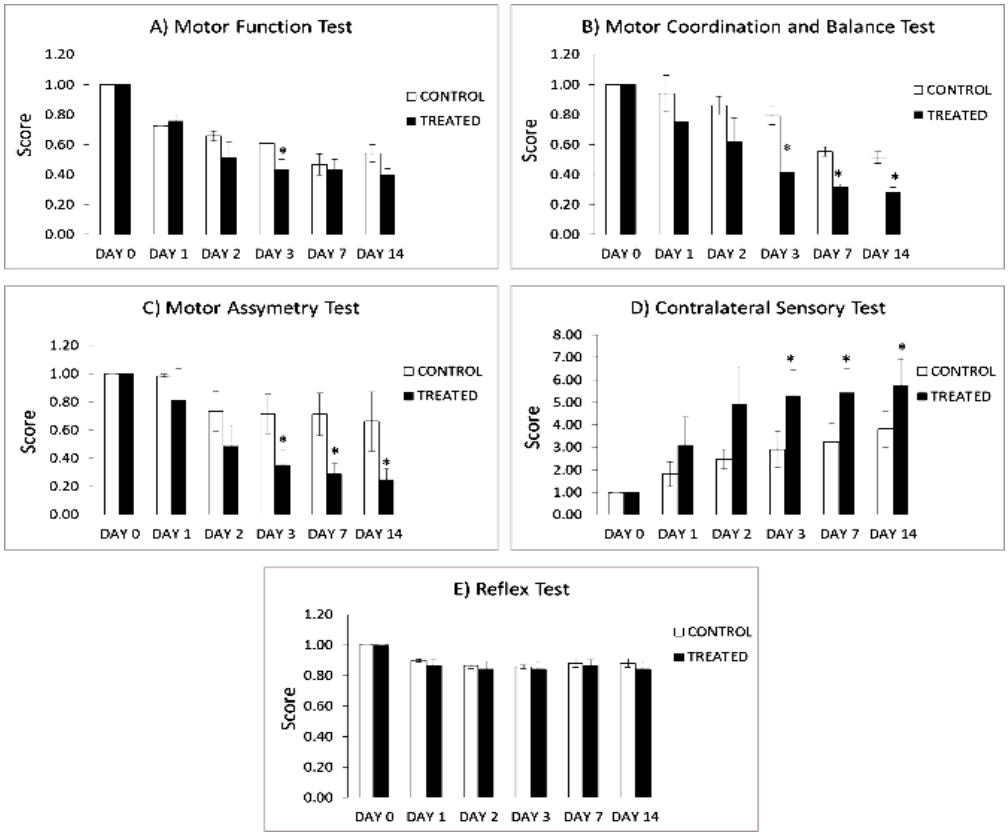

Figure 1: Behavioral scores in (A) motor function, (B) motor coordination and balance, (C) motor asymmetry, (D) contralateral sensory and (E) reflex tests of non-treated (control) and BEF-treated ischemic stroke rats. *$P < 0.05$ vs control group

Table 1: List of the gene name, symbol and nucleotide sequences of primers used in this study

Gene	Gene symbol	Forward primer (5' to 3')	Reverse Primer (3' to 5')	GenBank Accession no.
Janus kinase and microtubule interacting protein 1	JAKMIP1	TGACCAGGGAGTACC	AGGCTAAGTTG CTCCCGAGTCCGAG	001401057
Signal transducer and activator of transcription 6	STAT6	TGCCCTTGGTGGTCA	TCGTTAAGGGC ACTCGGTCCATCTC	NM_001044250
Gamma-aminobutyric acid type A receptor subunit alpha 6	GABRA6	TTGACAACT TGCTGGAGGGC	ACATCCATTGTGTACTCC ATCTCCA	NM_021841
Ribosomal protein L13A	RPL13A	GCTGCCGCACAAGACCAAAA	CCACCATCCGCTTTTTCTTGTCA	NM_173340
Hypoxanthine phosphoribosyltransferase 1	HRPT1	AGTCCCAGCGTCGTGATTAGT	CGAGCAAGTCTTTCAGTCCTGTC	NM_012583

Table 2: Body weight of control and treated rats (mean ± SEM, N = 5 in each group)

Group	Body weight (g) at Day 1	Body weight (g) at Day 7	Body weight (g) at Day 14	Body weight changes between D1 and D7*	Body weight changes between D7 and D14*
Control	222.80± 5.59	257.80±7.81	284.00±10.07	29 to 43 g (12.83 to 18.14 %)	21 to 32 g (8.89 to 11.42 %)
Study	330.00±18.06	339.00±16.34	342.40±18.94	-11 to 25 g (2.89 to 7.81 %)	-3 to 21 g (0.81 to 5.69 %)

All the weekly body weight changes recorded were within normal increment range (~ 20 % of initial weight). Each value represents the mean ± SEM (n = 5)

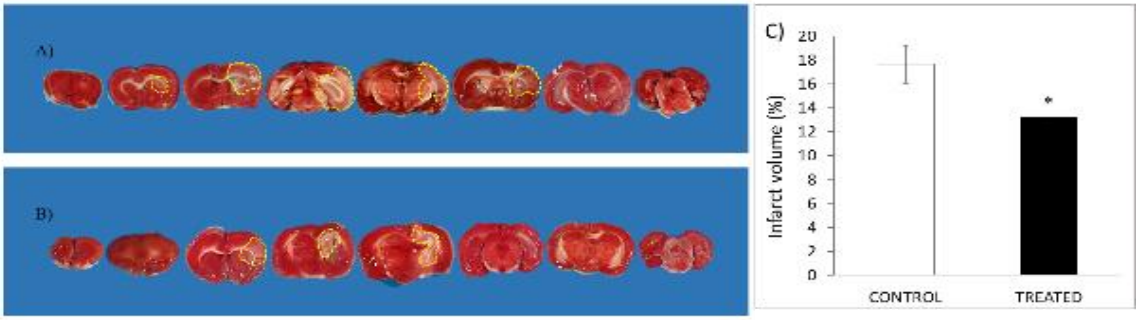

Figure 2: Coronal sections of brains with TTC staining of (A) control and (B) BEF-treated experimental rats 14 days after ET-1-induced ischemic stroke. Whitish area indicates the infarct area (visualized in yellow dash line) while the deep red staining area indicates the normal area of the brain. (C) Quantification of infarct volume of control and BEF-treated experimental rats 14 days after the induction of ischemic stroke. *P < 0.05 vs control group

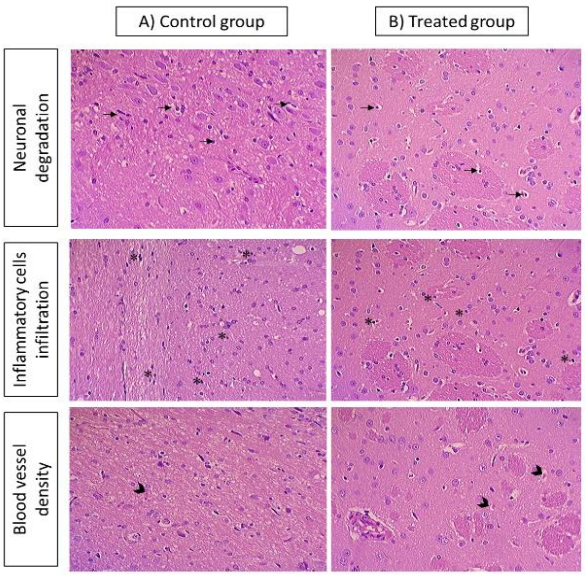

Figure 3: Representative images of brain tissue stained with H & E for (A) control and (B) Study group. Brain tissue showed neuropil vacuolation, necrosis, and pyknosis of certain neurons (indicated by arrow), infiltration of inflammatory cells (indicated by asterisk *) and blood vessels (indicated by arrowhead). x 40 magnification

Cerebral infarct volume

The extent of infarction in TTC-stained brain images was quantified using Image J software. Study group showed significant reduction (4.39 %) in infarct volume compared to control group (p < 0.05; Figure 2).

Histopathological scoring

Histological analysis of H & E-stained brain slices of BEF-treated ischemic stroke rats showed significant reduction in infarction area and neuronal degradation compared to control group (Figure 3 and Figure 4). However, there was no significant difference in histological scoring of inflammatory cell infiltration and blood vessel density between the two groups.

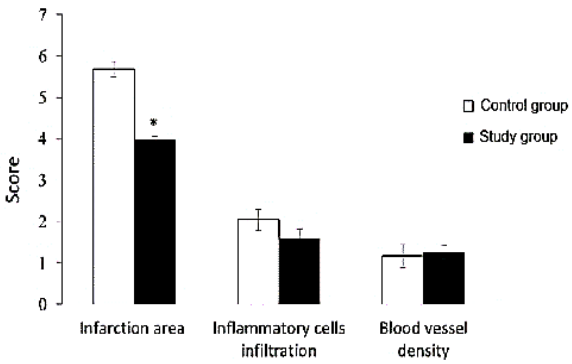

Figure 4: Histological scoring of infarction area, inflammatory cells infiltration and blood vessel density of brain tissues of study group compared to control. *P < 0.05 vs control

Relative quantification of genes of interest

Study group exhibited significant upregulation of JAKMIP1 (1.36-fold increase) compared to control group (Figure 5 A). Furthermore, the expression of GABRA6 demonstrated significant downregulation by 88 % in study group compared to control group (Figure 5 B). In contrast, study group demonstrated no significant difference in the expression of STAT6 compared to control (Figure 5 C).

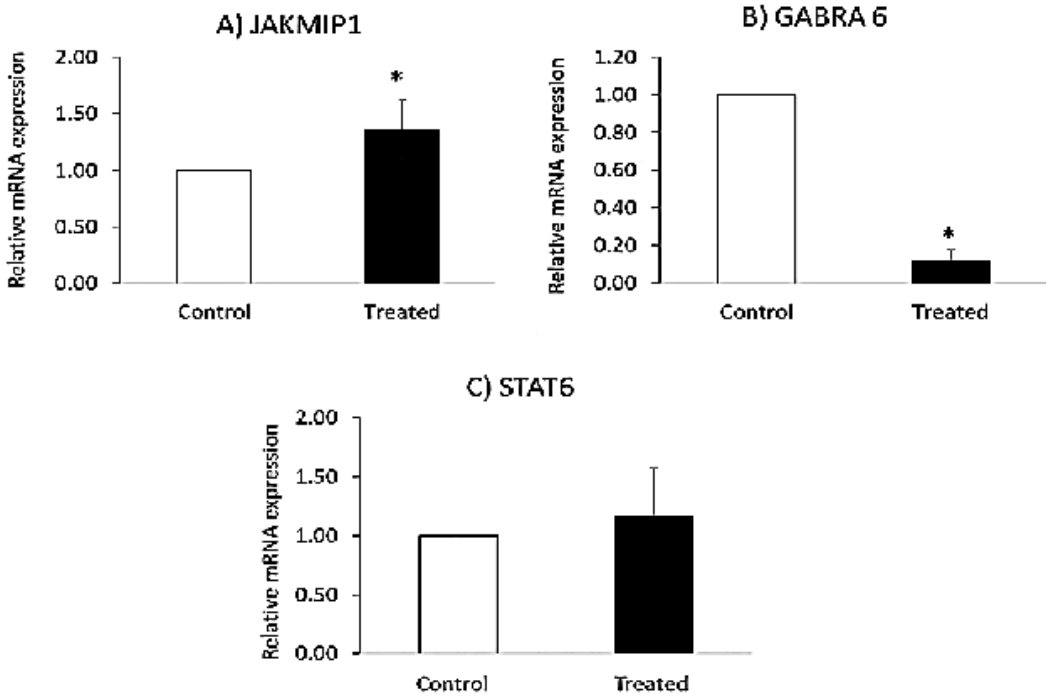

Figure 5: Relative mRNA expressions of (A) JAKMIP1, (B) GABRA6 and (C) STAT6 following BEF treatment. Relative mRNA expressions of genes of interest were normalized to HRPT1 and RPL13A genes. *P < 0.05 vs control group

DISCUSSION

Effects of BEF extracted from the leaves of *O. indicum* on behavioral neurological deficits were evaluated through a series of tests, where each test was analyzed independently. Results showed that study group exhibited remarkable improvement in motor function and contralateral sensory test compared to control group. These improvements strongly suggest that oral administration of BEF positively affects neurological function and aids recovery from ischemic stroke, mainly due to the presence of baicalein (a type of neuroprotective compound found in *O. indicum* plant to reduce inflammation and oxidative stress). It has been reported that baicalein compound plays pivotal role in key processes such as promoting survival of neurons, mitigating inflammation and preventing oxidative damage, thereby contributing to enhanced neurological health [11]. To strengthen the evidence for beneficial effects of BEF treatment for ischemic stroke rat model, this study also quantified the infarct volume in the affected brains.

The results obtained showed a significant decrease in the size of the infarcted area in study group presented by a distinct white, colorless region. These outcomes closely mirrored the findings by Elango *et al* [12] in which pretreatment with hawthorn extract exhibited a similar reduction in infarct area after middle cerebral artery occlusion. This improvement may help following BEF treatment may help restore blood flow and promote cell survival following ischemic stroke effects. This idea is supported by recent studies demonstrating that baicalein improves cerebral blood circulation in cases of brain ischemic injury [13,14]. Histological scoring of the brain was used to verify the extent of the infarcted area, where there was a decrease in neuronal degradation.

The underlying mechanism responsible for mitigating the severity of histological findings appears to stem from the enhancement of neurotrophic factors and reduction of reactive oxygen species (ROS) triggered by the bioactive compound in BEF [13]. Collaborative effects of

these mechanisms likely contribute to the regulation of neuronal survival, promotion of neurogenesis and control of oxidative stress, thereby leading to overall improvement in histological outcomes. However, the density of blood vessels did not show significant difference, suggesting the possibility that brain recovery is influenced by mechanisms apart from angiogenesis. Furthermore, the fast recovery observed in rats treated with BEF may be attributed to the capacity of BEF to cross the blood-brain barrier (BBB), thereby protecting brain tissues [14]. This theory was substantiated by previous evidence which demonstrated that baicalein was partially detected in the rat brain 30 min after oral intake [15].

In another study, baicalein was able to prevent BBB leakage, preserving its integrity in intracerebral hemorrhage animal models [14]. Besides the ability to cross BBB, baicalein also had been reported to possess neuroprotective benefits capable of protecting ischemic neurons in the brain from irreversible damage. This finding is in tandem with previous research on Parkinson's disease induced by 6-hydroxydopamine, both *in vivo* and *in vitro* [16]. Furthermore, the expression of JAKMIP1-STAT6-GABRA6 pathway also was investigated in this study. It was revealed that JAKMIP1 was significantly up-regulated while GABRA6 was downregulated in BEF-treated ischemic stroke rats. Expression of STAT6 was not significantly increased compared to control group.
The JAKMIP1 is implicated in regulating microtubule-associated processes critical for axonal growth and cellular transport. Expression of JAKMIP1 supports the structural integrity of neurons and facilitates xonal regeneration in affected areas [17]. On the other hand, GABRA6 is a subunit of the GABA-A receptor which plays a role in inhibitory neurotransmission. After stroke onset, overactive excitatory signaling may lead to further neuronal injury, a phenomenon known as excitotoxicity. Therefore, reduction of GABRA6 may trigger inhibitory neurotransmission and may play a role in balancing excitatory and inhibitory signals in ischemia. By balancing neural activity, GABRA6 may help to protect neurons and support the formation of new connections, a process necessary for regaining lost functions [18]. This protects surviving neurons and supports the formation of new neural connections, a key process in functional recovery.

Limitations of the study

This study has some limitations. Detailed characterization of the BEF compound was not performed. Hence, future studies should investigate phytochemical and physicochemical properties of BEF, as well as more detailed genomic and proteomic analysis on the brain tissue after treatment with BEF to comprehensively elucidate the underlying mechanisms and key regulators in modulating BEF-preconditioned NSCs for ischemic stroke treatment.

CONCLUSION

Baicalein-enriched fraction (BEF) extracted from *O. indicum* leaves improves motor coordination, and neurological behavioral function, lowers infarction parameters, promotes axonal repair through microtubule stabilization (via JAKMIP1), protects neurons from excitotoxic damage by balancing inhibitory and excitatory signaling (via GABRA6), and fosters the recovery of neural function through enhanced neuroplasticity. Thus, BEF may be a promising therapeutic strategy for managing ischemic stroke.

DECLARATIONS

Acknowledgement/Funding

The authors express their gratitude to the Universiti Sains Malaysia (USM) for the generous provision of facilities and resources, which were instrumental in the execution of this study.

This research was funded by Universiti Sains Malaysia Bridging Grant with Project No: R501-LR-RND003-0000000971-0000.

Ethical approval

Animal ethical approval was obtained from the USM Institutional Care and Use Committee (IACUC) - Approval no. USM/IACUC/2019/(120(1019).

Availability of data and materials

The datasets used and/or analyzed during the current study are available within the manuscript.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this

article will be borne by the authors. Othman FA and Mohd Satar A participated in the data curation and formal analysis of data. Othman FA and Tan SC wrote the article. Mustafa MZ and Tan SC conceived the idea and edited the article. All authors reviewed and approved the final version of the manuscript for publication.

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