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A narrative review of potential neural repair poststroke: Decoction of Chinese angelica and peony in regulating microglia polarization through the neurosteroid pathway

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Abstract:

Ischemic stroke is a major global health crisis, characterized by high morbidity and mortality rates. Although there have been significant advancements in treating the acute phase of this condition, there remains a pressing need for effective treatments that can facilitate the recovery of neurological functions. Danggui-Shaoyao-San (DSS), also known as the Decoction of Chinese Angelica and Peony, is a traditional Chinese herbal formula. It has demonstrated promising results in the regulation of microglial polarization and modulation of neurosteroid receptor expression, which may make it a potent strategy for promoting the recovery of neurological functions. Microglia, which plays a crucial role in neuroplasticity and functional reconstruction poststroke, is regulated by neurosteroids. This review posits that DSS could facilitate the recovery of neuronal function poststroke by influencing microglial polarization through the neurosteroid receptor pathway. We will further discuss the potential mechanisms by which DSS could enhance neural function in stroke, including the regulation of microglial activation, neurosteroid regulation, and other potential mechanisms.

Keywords:

Danggui Shaoyao San, ischemic stroke, microglia, nature herbs, neuroprotection, neurosteroid

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Introduction

Ischemic stroke represents a global health crisis, responsible for significant morbidity and mortality.[1,2] While there have been considerable advancements in vascular reperfusion during the acute phase of this disease, approximately half of the survivors continue to live with permanent disabilities, resulting in an immense burden for families and society.[3-5] This highlights the urgent need for the development of effective stroke treatments that not only focus on neurological function recovery but also improve the prognosis of stroke.[6,7]

Microglia, the immune cells of the central nervous system, play a pivotal role in neuroplasticity and recovery poststroke. Depending on the microenvironment, microglia exhibit either pro-inflammatory or restorative phenotypes. Poststroke, microglia transition from a pro-inflammatory to a restorative phenotype, thereby facilitating functional recovery.[8]

Danggui-Shaoyao-San (DSS), a traditional Chinese herbal formula, has a long-standing history of use for the treatment of gynecological disorders, pain, and inflammation. Recent studies suggest that DSS exerts neuroprotective effects across various neurological disorders, including ischemic stroke.[9,10] Furthermore, DSS

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has demonstrated capabilities in regulating microglial polarization and modulating steroid hormone receptor expression, indicating its potential as a promising strategy for promoting neurological function recovery following a stroke.[11]

Numerous studies have underscored the importance of neurosteroids in microglia in regulating microglial function.[12] In this review, we posit that DSS may promote the recovery of neuronal function poststroke by regulating microglial polarization through the neurosteroid receptor pathway.

Our ultimate aim is to provide a comprehensive understanding of DSS's potential as a complementary therapy for ischemic stroke and contribute to the development of innovative therapeutic approaches for this devastating disease.

DSS is a traditional Chinese herbal formula with a history of usage spanning centuries, primarily for treating a variety of gynecological disorders such as irregular menstruation, dysmenorrhea, and infertility.[13] Nevertheless, recent studies have revealed DSS's effectiveness in treating conditions such as stroke and vascular dementia. DSS is a blend of six natural herbs: Radix Angelicae Sinensis, Radix Paeoniae Alba, Rhizoma Ligustici Chuanxiong, Poria, Rhizoma Alismatis, and Rhizoma Atractylodis Macrocephalae.[10,14] DSS facilitated the recovery of neurological function in rats subjected to transient middle cerebral artery occlusion (MCAO).[13] Li *et al*. also observed that DSS promoted long-term neurological outcomes in mouse models of MCAO.[9] When DSS was incorporated into conventional treatment regimens, there was a significant improvement in neurological function.[15] Similarly, when combined with rehabilitation training, DSS notably enhanced motor function and daily living abilities in stroke patients.[16] Furthermore, DSS has been administered to patients with asymptomatic cerebral infarction, where it improved microcirculation and blood flow in cerebrovascular disorders.[17] Another study discovered that combining the direct thrombin inhibitor argatroban with DSS significantly reduced neurological deficits and improved the hemorheological index, thereby positively affecting the long-term prognosis of patients with acute cerebral infarction.[18] Consequently, DSS holds substantial potential as a complementary therapy for stroke patients, underscoring the need for further investigation.

Mechanisms by Which Danggui-Shaoyao-San Enhances Neural Function Following Stroke

Microglial cells in poststroke neuroplasticity

Microglia, the resident macrophages of the central nervous system, play a crucial role in maintaining local homeostasis within the brain microenvironment.[19] These cells primarily mediate the inflammatory response poststroke.[20] Under physiological conditions, microglia remain dormant, but when activated, they present two polarized phenotypes: pro-inflammatory and restorative microglia.[19] Pro-inflammatory microglia generate substantial amounts of oxidative stress products and pro-inflammatory factors, which exacerbate cerebral ischemic injury.[11] Conversely, restorative microglia curtail the inflammatory response and facilitate tissue repair, a process that is critical for neuron survival through the promotion of angiogenesis, neurogenesis, differentiation of oligodendrocyte precursor cells, and myelin formation.[11,19,21] Thus, augmenting the population of restorative microglia and boosting their tissue-repair function bears significant clinical relevance in the treatment of ischemic stroke.[22]

Danggui-Shaoyao-San Modulates Microglial Activation

DSS's diverse protective effects on neuroinflammation and microglial activation. In an *in vitro* study, DSS was shown to guard against neuroinflammation in lipopolysaccharide-induced BV-2 microglia cells through the toll-like receptors/NF-κB signaling pathway.[23] DSS was also found to attenuate dopaminergic cell damage caused by 1-methyl-4-phenylpyridine toxicity and suppress microglial cell activation in primary mesencephalic culture systems.[24] In addition, DSS was observed to alleviate orthodontic pain in rats by inhibiting microglial activation in the trigeminal spinal nucleus caudalis in the brainstem.[25] Active components of DSS, such as tetramethylpyrazine and atractylenolide-III, were found to inhibit microglial activation in cerebral ischemia-reperfusion rat models and reduce pro-inflammatory factors in immortalized mouse microglia cell line IMG6, respectively.[26,27] Moreover, a study showed that DSS lowered the number of proinflammatory microglia, increased restorative microglia, reduced the expression of pro-inflammatory factors, and heightened the expression of anti-inflammatory factors following cerebral ischemia, positioning DSS as a promising treatment candidate for stroke and other neurological disorders.[9]

Danggui-Shaoyao-San's Role in Neurosteroid Regulation

DSS has demonstrated an ability to regulate neurosteroids, including estrogen, a hormone crucial to cognitive function.[28] Estrogen, synthesized in the brain, plays an instrumental role in memory formation by preserving hippocampal synapses.[29,30] Studies have illustrated that DSS treatment promotes estrogen synthesis in primary hippocampal cells and the hippocampus of

ovariectomized (OVX) mice, mitigating OVX-induced memory impairment.[31] Furthermore, DSS has shown potential in enhancing learning and memory abilities in female diabetic mice (db/db) and senescence-accelerated mice (SAM), likely by increasing the levels of estradiol (E2), nitric oxide (NO), and glycine.[32,33] The active ingredient in DSS, Z-ligustilide, has been associated with increased levels of neurosteroids, pregnenolone, and allopregnanolone, in brain tissue.[34] Intriguingly, previous network pharmacology studies have suggested that DSS might exert neuroprotective effects after stroke by modulating the steroid hormone signaling pathway and steroid hormone receptor activity, as evidenced by GO functional enrichment analysis and KEGG pathway enrichment analysis.[10] While the precise relationships between these targets and the potential of DSS in treating ischemic stroke are still under investigation, continued research could offer invaluable insights into the DSS's mechanisms of action and potential stroke treatment applications through the modulation of neurosteroid hormones.

Neurosteroid Hormone's Role in Microglia Function Regulation

Neuronal functions in the central nervous system are widely influenced by steroid hormones.[12,35] These "neuroactive" steroids, secreted by the adrenal glands, gonads, and placenta, can cross the blood–brain barrier, readily diffusing to their target cells.[12,36] In addition, steroid hormones can be synthesized within the central nervous system itself.[12] Evidence from a study using a mouse model of autoimmune encephalomyelitis showed that administration of estrogen receptor β (ERβ)-specific ligands that foster CtBP recruitment in microglia suppressed pro-inflammatory factors such as interleukin-6 (IL-6), IL-1, inducible NO synthase (iNOS), and cyclooxygenase-2.[37] When applied to brain trauma mouse models, 17β-estradiol can activate ERα and ERβ in microglia, inhibiting pro-inflammatory cytokines IL-6, IL-1β, and iNOS, thereby providing neuroprotection.[38] This supports the idea that bolstered ERαRERβ activity would suppress the expression of pro-inflammatory factors, serving a neuroprotective function.[12] Another mouse experiment confirmed that progesterone, secreted by astrocytes and oligodendrocytes, binds to the microglia receptor known as progesterone receptor membrane component 1 (PGMRC1), thereby boosting the expression of anti-inflammatory factors such as Cluster of Differentiation 206, arginase 1, and transforming growth factor-beta.[39] *In vitro* experiments demonstrated that elevated PGMRC1 expression amplifies the anti-inflammatory factor level in microglia under hypoxic conditions.[40] Thus, neurosteroid hormone receptors in microglia hold a significant role in microglia function regulation.[41] Overall, the studies suggest that the potential of DSS in stroke treatment is closely linked to its ability to regulate neurosteroid hormones, which in turn affect microglia function.

Additional Mechanisms

In vitro studies have suggested DSS's potential for anti-apoptotic effects.[42] In addition, it was reported that DSS can mitigate oxidative stress against cerebral ischemic reperfusion injury in a SIRT1-dependent manner.[43] DSS has been found to improve neurological dysfunction following cerebral ischemia by reducing infarct volumes and bolstering anti-apoptotic and antioxidant effects in a rat stroke model.[44] We also discovered that DSS stimulates focal angiogenesis and neurogenesis 14 days post-MCAO through the activation of vascular endothelial growth factor and endothelial NO synthase in the cortex and striatum.[13] Moreover, a protein microarray technology-based study found that DSS can boost the expression of basic fibroblast growth factor-2 and stromal cell-derived factor-1α, promoting angiogenesis in mice post-MCAO.[45] These findings underscore that DSS possesses multiple mechanisms of action and shows promise as a potential therapeutic agent for cerebral ischemia. Further investigation is vital to understand its mechanisms of action and explore its potential clinical applications.

Perspective and Prospective

At present, the studies suggest that DSS might stimulate neuronal function recovery following a stroke. This seems to be primarily achieved by directing the polarization of microglia cells through the neurosteroid receptor pathway [Figure 1]. The significance of these findings necessitates further research, to not only validate these results but also to delve deeper into the potential of DSS as an adjunctive therapy for stroke patients.

Traditional Chinese medicine, including treatments such as DSS, is gaining global recognition and acceptance. Given this trend, it is timely to rigorously examine the potential of DSS as a safe and efficient treatment option for ischemic stroke. The purported benefits of DSS need to be subjected to rigorous scientific scrutiny to establish its therapeutic value clearly.

Looking forward, our focus should be on several aspects. First, the precise molecular mechanisms underpinning the effects of DSS on microglial polarization and neurosteroid hormone regulation need to be elucidated. This understanding will build a solid scientific basis for its application in stroke management. Moreover, there is an urgent need to explore DSS's clinical applicability in stroke treatment. This is especially relevant when considering it as a complementary intervention in

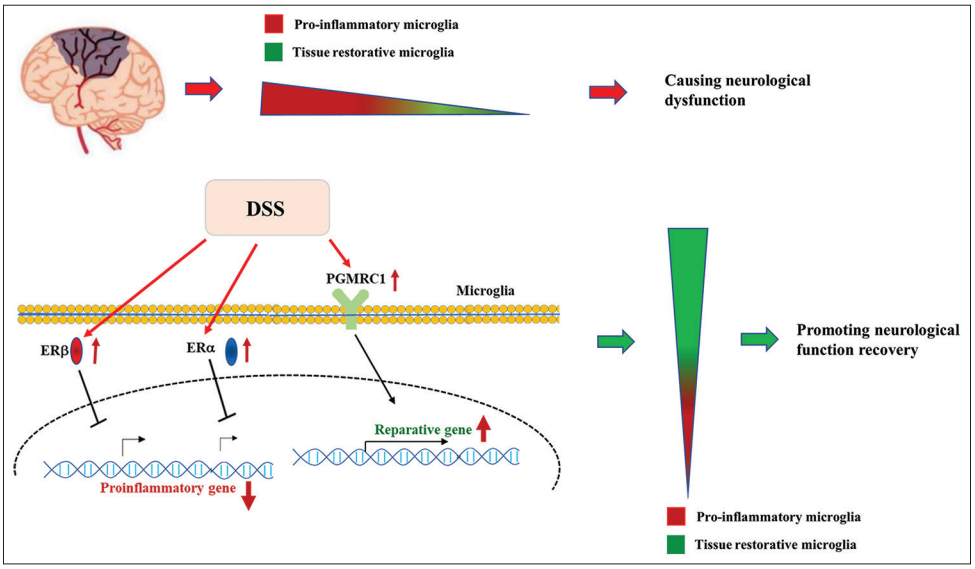

Figure 1: Schematic representation illustrating the potential mechanism by which Danggui Shaoyao San (DSS) promotes neuronal function recovery following a stroke. After a stroke, there is an increase in the pro-inflammatory phenotype of microglia and a decrease in the tissue repair phenotype, leading to exacerbated neuronal function damage. However, DSS, through the neurosteroid pathway on microglia cells, regulates microglial polarization. This leads to a reduction in the pro-inflammatory phenotype and an increase in the tissue repair phenotype of microglia. Consequently, DSS facilitates neuronal function recovery by promoting a favorable microglial polarization state. DSS: Danggui-Shaoyao-San, ERβ: Estrogen receptor β, ERα: Estrogen receptor α, PGMRC1: Progesterone receptor membrane component 1

conjunction with other established therapies, such as thrombolysis and rehabilitation training. An understanding of how DSS can synergize with these treatments could potentially unlock new avenues for stroke therapy, offering hope for better patient outcomes. Another crucial aspect to be investigated is the optimization of DSS administration. The ideal dosage, duration, and frequency of DSS treatment for stroke patients need to be established through meticulous research. This information is vital in ensuring the best possible therapeutic outcomes while minimizing any potential side effects. In parallel, large-scale clinical trials to assess the safety and efficacy of DSS are a necessity. Such trials will provide much-needed empirical evidence on DSS's utility as a stroke treatment. They would also shed light on any potential adverse effects, providing a more balanced view of DSS's therapeutic potential.

Understanding the effects of DSS on microglial polarization and neurosteroid receptor expression holds promise for the development of new therapeutic strategies for stroke patients. By regulating microglial polarization, DSS may help modulate the immune response and reduce neuroinflammation, which are key factors in stroke pathophysiology. This could potentially lead to improved neurological outcomes and functional recovery in stroke patients. In addition, modulating neurosteroid receptor expression, as observed with DSS, could have implications for the development of neuroprotective therapies. Understanding the mechanisms by which DSS regulates neurosteroid receptors may lead to the identification of novel targets for drug development. Overall, this knowledge may lead to the development of personalized treatment approaches and the repurposing of existing therapies for stroke patients. Further research is needed to elucidate these mechanisms and translate them into clinical applications for the benefit of stroke patients.

In summary, future studies focusing on these areas could potentially revolutionize our therapeutic approach to ischemic stroke. The results could lead to the development of novel strategies for stroke management, ultimately improving the prognosis and quality of life for stroke patients. The exploration of DSS's therapeutic potential represents an exciting frontier in stroke research, one that promises to blend traditional wisdom with modern scientific methodology.

Author contributions

Study design and concept were contributed by Changhong Ren and Yong Yang; manuscript writing was done by Linhui Qin, Peter Kamash, and Yuchuan Ding. All authors have approved the final version of the manuscript.

Ethical statement and patient consent

Not applicable.

Data availability statement

The datasets generated during and/or analyzed during the current study are available in the Pubmed repository, https://pubmed.ncbi.nlm.nih.gov.

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Conflicts of interest

Prof. Yuchuan Ding is an Associate Editor, Dr. Changhong Ren is an Editorial Board member of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the global burden of disease study 2019. Lancet Neurol 2021;20:795-820.
2. Lee H, Yun HJ, Ding Y. Timing is everything: Exercise therapy and remote ischemic conditioning for acute ischemic stroke patients. Brain Circ 2021;7:178-86.
3. Li F, Gao J, Kohls W, Geng X, Ding Y. Perspectives on benefit of early and prereperfusion hypothermia by pharmacological approach in stroke. Brain Circ 2022;8:69-75.
4. Yang P, Song L, Zhang Y, Zhang X, Chen X, Li Y, *et al.* Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): A multicentre, open-label, blinded-endpoint, randomised controlled trial. Lancet 2022;400:1585-96.
5. Yuan Y, Wei B, Zhu W, Liu Y, Wan Y. Systolic pressure target after endovascular thrombectomy in acute large-vessel occlusion ischemic stroke patients: Comment on ENCHANTED2/MT. Brain X 2023;1:e4.
6. Zhao W, Wu C, Dornbos D 3rd, Li S, Song H, Wang Y, *et al.* Multiphase adjuvant neuroprotection: A novel paradigm for improving acute ischemic stroke outcomes. Brain Circ 2020;6:11-8.
7. Wolf VL, Ergul A. Progress and challenges in preclinical stroke recovery research. Brain Circ 2021;7:230-40.
8. Shi L, Sun Z, Su W, Xu F, Xie D, Zhang Q, *et al.* Treg cell-derived osteopontin promotes microglia-mediated white matter repair after ischemic stroke. Immunity 2021;54:1527-42.e8.
9. Li H, Yang Y, Gao C, Ren C. Protective effects of Danggui Shaoyao powder on the brain of mice with cerebral ischemic stroke. Chinese J Inf TCM 2022;27:38-43.
10. Li S, Yang Y, Zhang W, Li H, Yu W, Gao C, *et al.* Systematic understanding of mechanism of Danggui Shaoyao San against ischemic stroke using a network pharmacology approach. Evid Based Complement Alternat Med 2022;2022:3747285.
11. Yu F, Huang T, Ran Y, Li D, Ye L, Tian G, *et al.* New insights into the roles of microglial regulation in brain plasticity-dependent stroke recovery. Front Cell Neurosci 2021;15:727899.
12. Yilmaz C, Karali K, Fodelianaki G, Gravanis A, Chavakis T, Charalampopoulos I, *et al.* Neurosteroids as regulators of neuroinflammation. Front Neuroendocrinol 2019;55:100788.
13. Ren C, Wang B, Li N, Jin K, Ji X. Herbal formula Danggui-Shaoyao-San promotes neurogenesis and angiogenesis in rat following middle cerebral artery occlusion. Aging Dis 2015;6:245-53.
14. Fu X, Wang Q, Wang Z, Kuang H, Jiang P. Danggui-Shaoyao-San: New hope for Alzheimer's disease. Aging Dis 2016;7:502-13.
15. Cui W, Zhao D. Connotation exploration of Danggui Shaoyao powder syndrome. Acta Chin Med 2021;36:2285-8.
16. Wang Y, Wang Y. Danggui Shaoyao powder combined with western medicine treating 60 cases of cerebral infarction. Guangming J Chin Med 2009;24:749-50.
17. Yi Y. Effect of Danggui Shaoyao powder on bulbar conjunctiva microcirculation and hemorheological factor in patients with asymptomatic cerebral infarction. Foreign Med Sci 2005;27:110.
18. Zhu Y, Wu Y. Efficacy and hemorheology of argatroban combined with Danggui Shaoyao powder in the treatment of acute cerebral infarction. World Latest Med Inf 2021;21:261-3.
19. Ma Y, Wang J, Wang Y, Yang GY. The biphasic function of microglia in ischemic stroke. Prog Neurobiol 2017;157:247-72.
20. Gonzales-Portillo BM, Lee JY, Vandenbark AA, Offner H, Borlongan CV. Major histocompatibility complex class II-based therapy for stroke. Brain Circ 2021;7:37-40.
21. Zhang LY, Pan J, Mamtilahun M, Zhu Y, Wang L, Venkatesh A, *et al.* Microglia exacerbate white matter injury via complement C3/C3aR pathway after hypoperfusion. Theranostics 2020;10:74-90.
22. Xue Y, Nie D, Wang LJ, Qiu HC, Ma L, Dong MX, *et al.* Microglial polarization: Novel therapeutic strategy against ischemic stroke. Aging Dis 2021;12:466-79.
23. Ding RR, Chen W, Guo CY, Liao WT, Yang X, Liao FE, *et al.* Dangguishaoyao-San attenuates LPS-induced neuroinflammation via the TLRs/NF-κB signaling pathway. Biomed Pharmacother 2018;105:187-94.
24. Hwang DS, Kim HG, Jang JB, Oh MS. Dangguijakyak-San protects against 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine-induced neuronal damage via anti-inflammatory action. Evid Based Complement Alternat Med 2013;2013:976270.
25. Li H, Gu Z, Wu L, Xia L, Zhou K, Lingling E, *et al.* Danggui-Shaoyao-San, a traditional Chinese medicine prescription, alleviates the orthodontic pain and inhibits neuronal and microglia activation. Chin Med J (Engl) 2014;127:3630-7.
26. Kao TK, Ou YC, Kuo JS, Chen WY, Liao SL, Wu CW, *et al.* Neuroprotection by tetramethylpyrazine against ischemic brain injury in rats. Neurochem Int 2006;48:166-76.
27. Novianti E, Katsuura G, Kawamura N, Asakawa A, Inui A. Atractylenolide-III suppresses lipopolysaccharide-induced inflammation via downregulation of toll-like receptor 4 in mouse microglia. Heliyon 2021;7:e08269.
28. Luine VN, Richards ST, Wu VY, Beck KD. Estradiol enhances learning and memory in a spatial memory task and effects levels of monoaminergic neurotransmitters. Horm Behav 1998;34:149-62.
29. Yun SH, Park KA, Kwon S, Woolley CS, Sullivan PM, Pasternak JF, *et al.* Estradiol enhances long term potentiation in hippocampal slices from aged apoE4-TR mice. Hippocampus 2007;17:1153-7.
30. Zhou L, Fester L, Haghshenas S, de Vrese X, von Hacht R, Gloger S, *et al.* Oestradiol-induced synapse formation in the female hippocampus: Roles of oestrogen receptor subtypes. J Neuroendocrinol 2014;26:439-47.
31. Hwang DS, Kim N, Choi JG, Kim HG, Kim H, Oh MS. Dangguijakyak-San ameliorates memory deficits in ovariectomized mice by upregulating hippocampal estrogen synthesis. BMC Complement Altern Med 2017;17:501.
32. Huang Y, Hu ZY, Yuan H, Shu L, Liu G, Qiao SY, *et al.* Danggui-Shaoyao-San improves learning and memory in female SAMP8 via modulation of estradiol. Evid Based Complement Alternat Med 2014;2014:327294.
33. Li HS, Ke J, Zhao GZ, Wu LA, Kou JP, Liu HC. Effects of Danggui-Shaoyao-San on the influence of spatial learning and memory induced by experimental tooth movement. Chin Med J (Engl) 2015;128:1948-55.
34. Ma JC, Zhang HL, Huang HP, Ma ZL, Chen SF, Qiu ZK, *et al.* Antidepressant-like effects of Z-ligustilide on chronic unpredictable mild stress-induced depression in rats. Exp Ther Med 2021;22:677.
35. Mellon SH, Griffin LD. Neurosteroids: Biochemistry and clinical significance. Trends Endocrinol Metab 2002;13:35-43.
36. Stárka L, Dušková M, Hill M. Dehydroepiandrosterone: A neuroactive steroid. J Steroid Biochem Mol Biol 2015;145:254-60.

37. Saijo K, Collier JG, Li AC, Katzenellenbogen JA, Glass CK. An ADIOL-ERβ-CtBP transrepression pathway negatively regulates microglia-mediated inflammation. Cell 2011;145:584-95.
38. Khaksari M, Hajializadeh Z, Shahrokhi N, Esmaeili-Mahani S. Changes in the gene expression of estrogen receptors involved in the protective effect of estrogen in rat's trumatic brain injury. Brain Res 2015;1618:1-8.
39. Lei B, Mace B, Dawson HN, Warner DS, Laskowitz DT, James ML. Anti-inflammatory effects of progesterone in lipopolysaccharide-stimulated BV-2 microglia. PLoS One 2014;9:e103969.
40. Habib P, Slowik A, Zendedel A, Johann S, Dang J, Beyer C. Regulation of hypoxia-induced inflammatory responses and M1-M2 phenotype switch of primary rat microglia by sex steroids. J Mol Neurosci 2014;52:277-85.
41. Franco R, Fernández-Suárez D. Alternatively activated microglia and macrophages in the central nervous system. Prog Neurobiol 2015;131:65-86.
42. Qian YF, Wang H, Yao WB, Gao XD. Aqueous extract of the Chinese medicine, Danggui-Shaoyao-San, inhibits apoptosis in hydrogen peroxide-induced PC12 cells by preventing cytochrome c release and inactivating of caspase cascade. Cell Biol Int 2008;32:304-11.
43. Luo Y, Chen H, Tsoi B, Wang Q, Shen J. Danggui-Shaoyao-San (DSS) ameliorates cerebral ischemia-reperfusion injury via activating SIRT1 signaling and inhibiting NADPH oxidases. Front Pharmacol 2021;12:653795.
44. Kim SH, Chung DK, Lee YJ, Song CH, Ku SK. Neuroprotective effects of Danggui-Jakyak-San on rat stroke model through antioxidant/antiapoptotic pathway. J Ethnopharmacol 2016;188:123-33.
45. Zhang W, Ren C, Wu X, Li H, Yang Y. Danggui Shaoyao San regulates angiogenesis in ischemic stroke mice through blood activating and or body fluidtransportation and transformation actions. Drug Eval Res 2020;44:56-62.