中国临床研究
Chin J Clin Res, May 2026, Vol.39, No.5

Cite as: Shen JJ, Guo J, Qian YM. Research progress in the treatment of cognitive dysfunction in sepsis-associated encephalopathy [J]. Chin J Clin Res, 2026, 39(5):653-657.
DOI: 10.13429/j.cnki.cjcr.2026.05.001

Prof. QIAN Yiming, Doctor supervisor, Director of the Emergency Medicine Department, Director of the Integrated Traditional Chinese and Western Medicine Infection Center, and Director of the Western Internal Medicine Teaching and Research Office at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. He serves as Honorary Chairman of the Critical Care Medicine Committee and Chairman of the Emergency Medicine Committee of Shanghai Association of Integrated Traditional Chinese and Western Medicine. He has long been dedicated to the integrated traditional Chinese and Western medicine prevention and treatment of critical illnesses such as sepsis with organ dysfunction and severe pneumonia. Professor QIAN has led two projects funded by the National Natural Science Foundation of China and over 20 provincial, ministerial, and municipal-level research projects. He has published more than 140 academic papers in core journals both domestically and internationally, including over 10 indexed in SCI. He has contributed to the development of several clinical guidelines, including the "*Clinical Expert Consensus on Integrated Traditional Chinese and Western Medicine for Sepsis-Associated Acute Gastrointestinal Dysfunction*." He is the editor-in-chief of academic works and textbooks such as *Selected Medical Cases and Essays of He Liren* and *Practical Emergency Medicine*. His honors include the Third Prize of the Shanghai Integrated Traditional Chinese and Western Medicine Science and Technology Award in 2021 and the "Shanghai Benevolent Physician – Outstanding Specialist Physician Award" in 2024.

Research progress in the treatment of cognitive dysfunction in sepsis-associated encephalopathy

SHEN Junji*, GUO Jian, QIAN Yiming

**Department of Emergency Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine,*
Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China
Corresponding author: QIAN Yiming, E-mail: qianym2004@163.com

Abstract: Sepsis-associated encephalopathy（SAE）is a common neurological complication in sepsis, with an incidence rate of 70% in the intensive care unit, and approximately half of the patients suffer from long-term cognitive dysfunction. Currently, clinical treatment mainly focuses on anti-infection and supportive therapy, lacking specific intervention measures targeting core pathological processes such as neuroinflammation, blood-brain barrier disruption, mitochondrial dysfunction, and oxidative stress. This study systematically reviews the latest progress in the treatment of cognitive dysfunction in SAE and its transition from basic research to clinical practice, providing new strategies for the clinical treatment plan of SAE.

Keywords: Sepsis; Sepsis-associated encephalopathy; Cognitive dysfunction; Mesenchymal stem cells; Molecular hydrogen; Cholinergic pathway

Fund program: Natural Science Foundation of Shanghai Science and Technology Innovation Action Plan（23ZR1464200）

Sepsis-associated encephalopathy (SAE) is a common neurological complication in patients with sepsis, which is generally underappreciated clinically yet has an incidence rate as high as 70% in intensive care units [1]. This disease presents marked heterogeneous clinical manifestations ranging from mild disturbance of consciousness to deep coma, and is correlated with elevated in-hospital mortality risk in patients [2]. More than half of surviving patients develop persistent cognitive dysfunction, severely impairing their long-term prognosis and quality of life [3]. Existing pathological studies have demonstrated that the pathogenesis of SAE involves complex pathological processes including neuroinflammation, mitochondrial dysfunction and impaired integrity of the blood-brain barrier (BBB) [4]; nevertheless, its specific molecular and cellular mechanisms remain to be further elucidated. Given its complex pathophysiological characteristics and severe clinical consequences, SAE has become a crucial scientific issue urgently needing to be solved in critical care medicine.

Currently, the clinical treatment strategies for SAE are still dominated by non-specific supportive therapies, and a precise targeted therapeutic system has not yet been established. The mainstream therapeutic regimens mainly include infection control and organ function supportive treatment, which exert limited effects on inhibiting neuroinflammatory cascade reactions and promoting nerve repair [5]. Clinical studies have revealed that even after standardized anti-infective therapy and comprehensive organ function supportive care, the long-term incidence of cognitive dysfunction remains high among SAE patients [6]. Such therapeutic bottlenecks are closely associated with the pathophysiological heterogeneity of SAE, manifested as substantial individual differences in the characteristics of neuroinflammatory responses, the degree of BBB integrity damage and the status of mitochondrial dysfunction. In recent years, innovative breakthroughs have been made in the field of SAE treatment, and a variety of cutting-edge therapeutic strategies have shown broad prospects for clinical application [7]. These novel therapies are characterized by multi-target synergistic effects targeting the core pathogenic mechanisms of SAE, reflecting the translational significance of basic research findings into clinical practice.

1 Research on Intervenable Targets of SAE

1.1 Microglial Polarization and Astrocyte Activation

The neuroinflammatory mechanism underlying SAE is primarily attributed to the abnormal activation of microglia and astrocytes. Accumulating evidence indicates that microglia undergo M1/M2 phenotypic polarization throughout the entire course of sepsis. M1-type microglia are characterized by secreting pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), whereas M2-type microglia exert neuroprotective effects [8]. A study conducted by Jiang et al. [9] confirmed that pathological activation of these glial cells is closely linked to the occurrence and progression of cognitive dysfunction in SAE patients.

1.2 Blood-Brain Barrier Disruption

Impaired BBB integrity constitutes another core pathogenic mechanism of SAE. Accumulated studies have indicated that inflammatory factors in the peripheral circulation damage the BBB via dual mechanisms during sepsis progression: directly injuring cerebral microvascular endothelial cells and inducing the disintegration of tight junction structures. At the molecular level, activated endothelial cells markedly downregulate the expression of tight junction proteins occludin and claudin-5, and facilitate leukocyte infiltration, which collaboratively exacerbates BBB dysfunction [10-11]. Dynamic observational research adopting advanced photoacoustic microscopy has verified that abnormal BBB permeability is significantly correlated with morphological alterations of cerebral microvessels in septic mice models [12]. Such barrier destruction allows peripheral inflammatory mediators and neurotoxic substances to penetrate the BBB and enter the brain parenchyma, leading to direct neuronal injury.

1.3 Cholinergic Pathway

Current studies have demonstrated that α7 nicotinic acetylcholine receptor (α7nAChR), a core molecule in the cholinergic anti-inflammatory pathway, plays a pivotal role in neural and immune regulation. Vagus nerve activation can inhibit excessive microglial activation and overproduction of pro-inflammatory cytokines via α7nAChR. Dysfunction of this pathway results in imbalanced inflammatory regulation and aggravates neuropathological damage in SAE [13].

1.4 Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is a key link in the pathogenesis of SAE. Systemic inflammatory responses induced by sepsis and cerebral tissue hypoxia impair mitochondrial oxidative phosphorylation and trigger excessive reactive oxygen species generation [14]. Persistent oxidative stress directly induces neuronal damage and exacerbates neuroinflammation through activating the NLRP3 inflammasome. Experimental data have proven that abnormal release of mitochondrial DNA activates microglia, forming a vicious pathological cycle between oxidative stress and neuroinflammation [15]. Mitochondrial dysfunction also disturbs neurotransmitter synthesis and impairs synaptic plasticity, which are closely correlated with cognitive deficits in SAE patients [9].

2 Emerging Therapeutic Strategies

2.1 Mesenchymal Stem Cell (MSCs) Therapy

2.1.1 Basic Research of MSCs

Numerous recent studies have confirmed that MSCs exert multi-target therapeutic effects against SAE. A study by Ma LX et al. [16] revealed that umbilical cord-derived MSCs effectively suppress the activation of nuclear factor-κB (NF-κB) signaling pathway and markedly reduce the expression levels of pro-inflammatory factors including IL-6, IL-1β, TNF-α and high mobility group box 1 protein. Mechanistically, activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is essential for MSCs to exert neuroprotective functions. This pathway alleviates neuroinflammation, inhibits neuronal apoptosis and facilitates tissue repair [17]. Moreover, conditioned medium secreted by MSCs notably ameliorates anxiety-like behaviors in SAE model animals via paracrine effects.

2.1.2 Efficacy Verification

Multiple animal experiments have validated the therapeutic potential of MSCs for SAE. In lipopolysaccharide-induced SAE mouse models, intervention with umbilical cord-derived MSCs obviously alleviates cerebral cortical neuronal injury and suppresses cellular apoptosis. Morris water maze tests demonstrated that cognitive dysfunction was significantly improved in MSCs-treated SAE mice [18]. In cecal ligation and puncture (CLP)-induced septic rat models, MSCs intervention relieves acute-phase clinical manifestations, and peripheral transplantation improves long-term cognitive function in convalescent experimental animals [19]. Cumulative experimental evidence indicates that

MSCs treatment maintains BBB structural integrity in surviving septic mice, inhibits excessive astrogliosis and neuroinflammation, and promotes the recovery of cognitive function and behavioral ability [20].

2.2 Molecular Hydrogen Therapy

2.2.1 Basic Research of Molecular Hydrogen

As a promising medical gaseous molecule, molecular hydrogen exerts multi-mechanistic neuroprotective effects in SAE. Its neuroprotective mechanisms are mainly reflected in three aspects: first, molecular hydrogen modulates mammalian target of rapamycin signaling pathway to regulate microglial polarization, restraining pro-inflammatory M1 polarization and facilitating anti-inflammatory M2 phenotypic transformation [21]; second, the BBB-protective effect of molecular hydrogen has been validated, which is closely associated with peroxisome proliferator-activated receptor α activation and subsequent upregulation of ABC efflux transporter expression [22]; third, molecular hydrogen effectively inhibits NLRP3 inflammasome activation and mitigates neuroinflammation via activating nuclear factor erythroid 2-related factor 2 signaling pathway [23].

2.2.2 Experimental Evidence of Antioxidant and Anti-Apoptotic Effects

A series of animal experiments have confirmed the antioxidant and anti-apoptotic properties of molecular hydrogen. In CLP-induced SAE models, inhalation of 67% high-concentration hydrogen alleviates mitochondrial dysfunction by promoting mitochondrial biogenesis and regulating mitochondrial dynamic balance, thereby maintaining neuronal energy metabolism [24]. At the molecular level, hydrogen efficiently scavenges oxygen free radicals, markedly reduces abnormal tau protein hyperphosphorylation, and further improves resultant cognitive impairment [25].

2.3 Regulation Therapy Targeting Cholinergic Anti-Inflammatory Pathway

2.3.1 Basic Research of Vagus Nerve Stimulation

As the key anatomical foundation of the cholinergic anti-inflammatory pathway, the vagus nerve establishes an intact neuro-immune regulatory network via bidirectional afferent sensory and efferent motor fibers. Peripheral inflammatory mediators specifically activate vagal afferent fibers, transmit inflammatory signals to the central nervous system and trigger corresponding anti-inflammatory cascades. Animal model studies have proven that electrical stimulation of vagal efferent fibers or pharmacological specific activation of α7nAChR efficiently inhibits the secretion of pro-inflammatory cytokines [26]. Research by Goggins et al. [27] indicated that the anti-inflammatory effects of the vagus nerve are mainly mediated by norepinephrine release and α7nAChR signaling pathway-mediated regulation of macrophage functions. In recent years, non-invasive transcutaneous auricular vagus nerve stimulation has shown prominent translational medical prospects in clinical intervention for neurological diseases [28].

2.3.2 α7nAChR Agonists

α7nAChR serves as the core regulatory molecule of the cholinergic anti-inflammatory pathway, and decreased α7nAChR expression has been confirmed to be involved in sepsis pathogenesis [29]. Selective α7nAChR agonist GTS-21 exhibits dual effects of inhibiting pro-inflammatory factor release and protecting organ functions in various disease models, and alleviates inflammatory lesions such as acute lung injury via modulating splenic macrophage functions [30]. In SAE-related research, berberine has been verified to ameliorate glucose metabolism disorder through activating α7nAChR-dependent cholinergic anti-inflammatory pathways [31].

2.3.3 Targeted Intervention of Neuro-Immune Regulatory Network

Accumulated studies have illustrated that the cholinergic anti-inflammatory pathway forms a sophisticated neuro-immune regulatory network consisting of the vagus nerve, acetylcholine, nicotinic acetylcholine receptors, spleen and splenic nerves [32]. Notably, basal forebrain cholinergic neurons exert anti-inflammatory effects during sepsis progression, including suppressing hippocampal neuroinflammation and improving baroreceptor-mediated heart rate regulation [33]. In SAE animal models, acetylcholinesterase inhibitor huperzine A enhances cholinergic neurotransmission efficiency, facilitates hippocampal neuronal functional recovery and synaptic plasticity reconstruction, and relieves memory dysfunction [34].

2.4 Traditional Chinese Medicine Therapy

2.4.1 Pharmacological Research on Active Ingredients of Traditional Chinese Medicine

A large number of pharmacological studies have demonstrated that numerous traditional Chinese medicines and their active ingredients are effective for SAE treatment. Herbs including honeysuckle, coptis chinensis and phellodendron chinense exert anti-SAE effects by regulating key inflammatory factors such as TNF-α and IL-6 [35]. Flavonoids extracted from euphorbia helioscopia possess dual neuroprotective effects in SAE animal models, which suppress excessive microglial activation and ameliorate mitochondrial dysfunction simultaneously [36]. Resveratrol, the major active component of polygonum cuspidatum, treats SAE via regulating the p38 MAPK pathway mediated by miR-370-3p [37]. Modern pharmacological studies have revealed that traditional Chinese medicine polysaccharides intervene in the pathological progression of SAE by regulating the interaction between intestinal flora and the immune system [38]. Nevertheless, multiple scientific challenges remain in exploring the pharmacodynamic material basis of complex compound traditional Chinese medicines; the specific molecular targets and network regulatory mechanisms of clinically effective agents such as indigo naturalis still require further clarification [39]. The application of artificial intelligence has opened up new avenues for elucidating the synergistic mechanisms of multi-component traditional Chinese medicines, and computational methods based on data mining and molecular docking can effectively predict the interaction patterns between active herbal ingredients and SAE-related targets [40].

2.4.2 Proprietary Chinese Patent Medicines

Traditional Chinese medicine presents unique advantages in clinical intervention of SAE, and its multi-target regulatory mechanisms are complementary to modern precision medicine concepts. Animal experiments have verified that ginkgo biloba extract improves cognitive function in SAE mice by downregulating hippocampal Bax expression, upregulating B-cell lymphoma-2 expression and reducing hippocampal TNF-α and IL-6 levels [41]. Systematic reviews have confirmed that combined application of Xuebijing injection and conventional western medicine achieves synergistic effects, which effectively reduces mortality and improves neurological functional prognosis in SAE patients [42]. Current clinical practice indicates that proprietary Chinese medicines intervene in core pathological links of SAE including neuroinflammation, oxidative stress injury and BBB dysfunction via multi-dimensional regulatory strategies [43].

2.5 Exploration of Other Innovative Therapies

2.5.1 Biomaterial-Assisted Drug Delivery Systems

Breakthrough progress has been achieved in the application of biomedical materials for SAE treatment. Novel biomaterials with precisely controllable drug delivery systems enable targeted release of neuroprotective drugs, and the integration of photothermal and magnetothermal therapy provides innovative strategies for SAE management. Research by Song et al. [44] confirmed that multifunctional nanomaterials such as gold nanoparticles inhibit neuroinflammation via dual mechanisms and significantly alleviate cerebral dysfunction in septic animal models. Biomaterials with multi-tissue regenerative properties can precisely regulate local and systemic mechanical parameters, constructing an optimized microenvironment for nerve tissue repair.

2.5.2 Microbiome Intervention Strategies

Intestinal microbiota dysbiosis plays a critical role in the pathophysiological progression of SAE and is regarded as a promising therapeutic intervention target. Clinical observations reveal that the intestinal flora composition of SAE patients is characterized by marked oral flora ectopia, and such microbial ecological disturbance is significantly correlated with gastrointestinal symptoms and central nervous system inflammation [45]. Therapeutic strategies based on microbiota-metabolite axis regulation, including probiotic/prebiotic supplementation and fecal microbiota transplantation, have been proven to alleviate neuroinflammation by reshaping intestinal microecological balance [46]. Meanwhile, short-chain fatty acids, key signaling molecules mediating gut-brain bidirectional communication derived from intestinal commensal bacteria, exhibit obvious dose-dependent correlations with the severity of neuroinflammation in SAE patients [47]. Furthermore, the neuro-immune-microbiome interaction network constructed by vagal pathways, gut-derived neuropeptides and microbial metabolites exerts vital regulatory effects on the initiation and progression of SAE [48].

3 Summary and Prospect

The field of sepsis research has witnessed growing application of multi-omics technologies in recent years, among which combined genomic and transcriptomic analysis dominates, followed by integrated genomic and proteomic research models. The adoption of multi-omics integration strategies enables researchers to systematically dissect the molecular regulatory networks of SAE; for instance, the construction of gene-metabolite-phenotype composite networks facilitates the identification of core metabolic regulatory nodes in acute lung injury research. Multi-dimensional integrated analytical approaches combining proteomics, metabolomics data and organoid models provide novel research directions for clarifying the biological functions of specific molecular pathways in SAE pathogenesis [49].

In conclusion, the integration of multi-omics technologies and clinical data has brought novel ideas and methodologies for the research and treatment of SAE. Further optimization of the clinical application strategies of emerging therapies is expected to break through existing therapeutic bottlenecks and improve the prognosis of SAE patients. Future studies should continue to explore the molecular mechanisms of SAE and develop individualized therapeutic regimens to address this major challenge in critical care medicine.

Conflict of Interest: None

Reference

[1] Yang K, Chen JQ, Wang T, et al. Pathogenesis of sepsis-associated encephalopathy: more than blood–brain barrier dysfunction[J]. Mol Biol Rep, 2022, 49(10): 10091-10099.

[2] Zhao PP, Zhang W, Zhou XY, et al. Gypenoside XLIX alleviates sepsis-associated encephalopathy by targeting PPAR-α[J]. Exp Neurol, 2025, 383: 115027.

[3] Hoshino K. Targeting synaptic plasticity to bridge translational gaps in sepsis-associated encephalopathy[J]. Front Aging Neurosci, 2025, 17: 1616736.

[4] Ling JM, Wu YQ, Zou XJ, et al. (–)-epicatechin reduces neuroinflammation, protects mitochondria function, and prevents cognitive impairment in sepsis-associated encephalopathy[J]. Oxid Med Cell Longev, 2022, 2022: 2657713.

[5] Shehata AH, Anter AF, Ahmed AF. Role of SIRT1 in sepsis-induced encephalopathy: Molecular targets for future therapies[J]. Eur J Neuroscience, 2023, 58(10): 4211-4235.

[6] Gao SJ, Jiang Y, Chen ZY, et al. Metabolic reprogramming of microglia in sepsis-associated encephalopathy: insights from neuroinflammation[J].

Curr Neuropharmacol, 2023, 21(9): 1992-2005.

[7] Zhang Z, Wang L, Li F, et al. Therapeutic effects of human umbilical cord mesenchymal stem cell on sepsis-associated encephalopathy in mice by regulating PI3K/AKT pathway[J]. J Integr Neurosci, 2022, 21(1): 38.

[8] Hu JY, Xie SC, Zhang HS, et al. Microglial activation: key players in sepsis-associated encephalopathy[J]. Brain Sci, 2023, 13(10): 1453.

[9] Jiang JL, Zou Y, Xie CT, et al. Oxytocin alleviates cognitive and memory impairments by decreasing hippocampal microglial activation and synaptic defects via OXTR/ERK/STAT3 pathway in a mouse model of sepsis-associated encephalopathy[J]. Brain Behav Immun, 2023, 114: 195-213.

[10] Pu YH, Zhao L, Xi Y, et al. The protective effects of Mirtazapine against lipopolysaccharide (LPS)-induced brain vascular hyperpermeability[J]. Bioengineered, 2022, 13(2): 3680-3693.

[11] Gao QZ, Hernandes MS. Sepsis-associated encephalopathy and blood-brain barrier dysfunction[J]. Inflammation, 2021, 44(6): 2143-2150.

[12] Wang ZG, Ai CP, Sun T, et al. Photoacoustic imaging detects cerebrovascular pathological changes in sepsis[J]. Photoacoustics, 2025, 44: 100737.

[13] Barlow B, Ponnaluri S, Barlow A, et al. Targeting the gut microbiome in the management of sepsis-associated encephalopathy[J]. Front Neurol, 2022, 13: 999035.

[14]Ranjbaran M, Kianian F, Kadkhodaee M, et al. Mesenchymal stem cells and their conditioned medium as potential therapeutic strate-gies in managing comorbid anxiety in rat sepsis induced by cecal liga-tion and puncture[J]. Iran J Basic Med Sci, 2022, 25（6）: 690-697.

[15] Guo Y, Yu YH. PI3K/Akt pathway and neuroinflammation in sepsis-associated encephalopathy[J]. Open Med, 2025, 20: 20251248.

[18] Cao HH, Liu T, Xu MX. Senkyunolide I improves septicemia-induced brain dysfunction via regulating Nrf2 and astrocyte activity[J]. Biotech And App Biochem, 2025, 72(5): 1385-1394.

[19] Tan LJ, Cheng Y, Wang H, et al. Peripheral transplantation of mesenchymal stem cells at sepsis convalescence improves cognitive function of sepsis surviving mice[J]. Oxid Med Cell Longev, 2022, 2022(1): 6897765.

[20] Cui Y, Liu JF, Song Y, et al. High concentration hydrogen protects sepsis-associated encephalopathy by enhancing Pink1/parkin-mediated mitophagy and inhibiting cGAS-STING-IRF3 pathway[J]. CNS Neurosci Ther, 2025, 31(2): e70305.

[21] Zhuang XQ, Yu Y, Jiang Y, et al. Molecular hydrogen attenuates sepsis-induced neuroinflammation through regulation of microglia polarization through an mTOR-autophagy-dependent pathway[J]. Int Immunopharmacol, 2020, 81: 106287.

[22] Bai YY, Mi W, Meng XY, et al. Hydrogen alleviated cognitive impairment and blood–brain barrier damage in sepsis-associated encephalopathy by regulating ABC efflux transporters in a PPARα-dependent manner[J]. BMC Neurosci, 2023, 24(1): 37.

[23] Xie KL, Zhang Y, Wang YQ, et al. Hydrogen attenuates sepsis-associated encephalopathy by NRF2 mediated NLRP3 pathway inactivation[J]. Inflamm Res, 2020, 69(7): 697-710.

[24] E ZY, Cong Y, Wang YF, et al. Repair effect of 2% hydrogen inhalation on neurological function in rats with sepsis-related encephalopathy and its mechanism[J]. Shandong Med J, 2024, 64(35): 45-49. **[In Chinese]**

[25] Qi B, Song Y, Chen C, et al. Molecular hydrogen attenuates sepsis-induced cognitive dysfunction through regulation of tau phosphorylation[J]. Int Immunopharmacol, 2023, 114: 109603.

[26] Keever KR, Cui K, Casteel JL, et al. Cholinergicsignalingvia the α7 nicotinic acetylcholine receptorregulates the migration of monocyte-derived macrophages during acute inflammation[J]. J Neuroinflammation, 2024, 21(1): 3.

[27] Goggins E, Inoue H, Okusa MD. Neuroimmune control of inflammation in acute kidney injury and multiorgan dysfunction[J]. J Am Soc Nephrol, 2025, 36(12): 2473-2484.

[28] Ma L, Wang HB, Hashimoto K. The vagus nerve: an old but new player in brain–body communication[J]. Brain Behav Immun, 2025, 124: 28-39.

[29] Xue P. Effect of α7 nicotinic acetylcholinergic receptor on polarization anti-inflammatory microglia via JAK2/STAT3 pathway in septic encephalopathy rats and its mechanism[D]. Qingdao: Qingdao University, 2021. **[In Chinese]**

[30] Li RT, Hu XM, Chen HB, et al. Role of cholinergic anti-inflammatory pathway in protecting sepsis-induced acute lung injury through regulation of the conventional dendritic cells[J]. Mediat Inflamm, 2022, 2022: 1474891.

[31] Wang DK, Ren YL, Sun W, et al. Berberine ameliorates glucose metabolism in diabetic rats through the alpha7 nicotinic acetylcholine receptor-related cholinergic anti-inflammatory pathway[J]. Planta Med, 2022, 88(1): 33-42.

[32] Deng YQ, Gao M, Lu D, et al. Compound-composed Chinese medicine of Huachansu triggers apoptosis of gastric cancer cells through increase of reactive oxygen species levels and suppression of proteasome activities[J]. Phytomedicine, 2024, 123: 155169.

[33] Li N, Liao S, Liu L, et al. Pleiotropic role of endoplasmic reticulum stress in the protection of psoralidin against sepsis-associated encephalopathy[J]. Free Radic Biol Med, 2024, 221: 203-214.

[34] Yin L, Zhang JM, Ma HW, et al. Selective activation of cholinergic neurotransmission from the medial septal nucleus to hippocampal pyramidal neurones improves sepsis-induced cognitive deficits in mice[J]. Br J Anaesth, 2023, 130(5): 573-584.

[35] Liu PP, Zeng LN, Fu HY, et al. Investigating the therapeutic mechanisms of honeysuckle (China) in sepsis through network pharmacology and experimental validation[J]. Infect Drug Resist, 2025, 18: 3257-3277.

[36] Ding HG, Li Y, Chen SL, et al. Fisetin ameliorates cognitive impairment by activating mitophagy and suppressing neuroinflammation in rats with sepsis-associated encephalopathy[J]. CNS Neurosci Ther, 2022, 28(2): 247-258.

[37] Feng L, Peng HY, Wei XX, et al. Research of resveratrol regulating p38MAPK pathway through miR-370-3p in the treatment of sepsis related encephalopathy in rats[J]. Chin J Clin Pharmacol, 2025, 41(10): 1438-1443. **[In Chinese]**

[38] Bian ZY, Zhao AH, Wang QH, et al. Advancements in research on the anti-metabolic dysfunction-associated steatotic liver disease effects and mechanisms of action of traditional Chinese medicine polysaccharides: a review[J]. Int J Biol Macromol, 2025, 321: 146292.

[39] Zhou E, Shen Q, Hou Y. Integrating artificial intelligence into the modernization of traditional Chinese medicine industry: a review[J]. Front Pharmacol, 2024, 15: 1181183.

[40] Zhu JQ, Liu XN, Gao P. Digital intelligence technology: new quality productivity for precision traditional Chinese medicine[J]. Front Pharmacol, 2025, 16: 1526187.

[41] Wang X. Based on network pharmacology and animal experiments, the effect and mechanism of Ginkgo biloba extract on sepsis-related encephalopathy were explored[D]. Dali: Dali University, 2024. **[In Chinese]**

[42] Li XY, Xu XL, Zhang J, et al. Review of the therapeutic effects of traditional Chinese medicine in sepsis-associated encephalopathy[J]. J Ethnopharmacol, 2024, 334: 118588.

[43] Zhenxuan LI, Wang XR, Ulloa L, et al. Complementary and alternative medicine on cognitive defects and neuroinflammation after sepsis[J]. J Tradit Chin Med, 2024, 44（2）: 408-416.

[44] Song ZC, Chen HG, Xu WF, et al. The hexapeptide functionalized gold nanoparticles protect against sepsis-associated encephalopathy by forming specific protein Corona and regulating macrophage activation[J]. Mater Today Bio, 2025, 32: 101704.

[45] Póvoa P, Coelho L, Dal-Pizzol F, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians[J]. Intensive Care Med, 2023, 49(2): 142-153.

[46] Webster CI, Withycombe JS, Bhutada JS, et al. Review of the microbiome and metabolic pathways associated with psychoneurological symptoms in children with cancer[J]. Asia Pac J Oncol Nurs, 2024, 11(8): 100535.

[47] Zhang QL, Lu C, Fan WX, et al. Application background and mechanism of short-chain fatty acids in sepsis-associated encephalopathy[J]. Front Cell Infect Microbiol, 2023, 13: 1137161.

[48] Gareau MG. The microbiota-gut-brain axis in sepsis-associated encephalopathy[J/OL]. mSystems,(2022-08-30). https://escholarship.org/uc/item/2ck3v7sh.

[49] Jang WE, Park JH, Park G, et al. Cntnap2-dependent molecular networks in autism spectrum disorder revealed through an integrative multi-omics analysis[J]. Mol Psychiatry, 2023, 28(2): 810-821.

Submission Received: 2025-10-22 Revised: 2025-11-09

· 学术前沿 ·

脓毒症相关性脑病认知功能障碍治疗的研究进展

沈隽吉，　郭健，　钱义明
上海中医药大学附属岳阳中西医结合医院急诊医学科，上海 200437

钱义明教授，博士研究生导师，上海中医药大学附属岳阳中西医结合医院急诊医学科主任、中西医急症感染中心主任及西医内科学教研室主任。担任上海市中西医结合学会重症医学专业委员会名誉主任委员、急救医学专业委员会主任委员等职务，长期致力于脓毒症及其脏器损伤、重症肺炎等急危重症的中西医结合防治研究。主持国家自然科学基金项目2项及省部级、市局级课题20余项，在国内外核心期刊发表学术论文140余篇，其中SCI收录10余篇。参与制定《脓毒症急性胃肠功能障碍中西医结合临床专家共识》等多项指南，主编《何立人医论医案选》《实用急救医学》等专著与教材，获2021年上海中西医结合科学技术奖三等奖、2024年上海市“仁心医者·杰出专科医师奖”等荣誉。

摘要： 脓毒症相关性脑病（SAE）是脓毒症常见的神经系统并发症，重症监护病房中SAE发生率可达70%，其中半数遗留长期认知功能障碍。目前临床治疗以抗感染和支持疗法为主，缺乏针对神经炎症、血脑屏障破坏、线粒体功能障碍、氧化应激等核心病理环节的特异性干预手段。本研究系统回顾了近年来涌现的关于SAE认知功能障碍治疗及其从基础研究走向临床实践的最新进展，为SAE的临床治疗方案提供新思路。

关键词： 脓毒症；脓毒症相关性脑病；认知功能障碍；间充质干细胞；分子氢；胆碱能通路
中图分类号： R631　R459.9　**文献标识码：** A　**文章编号：** 1674-8182(2026)05-0653-05

Research progress in the treatment of cognitive dysfunction in sepsis-associated encephalopathy

SHEN Junji, GUO Jian, QIAN Yiming
Department of Emergency Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine,
Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China
Corresponding author: QIAN Yiming, E-mail: qianym2004@163.com

Abstract: Sepsis-associated encephalopathy (SAE) is a common neurological complication in sepsis, with an incidence rate of 70% in the intensive care unit, and approximately half of the patients suffer from long-term cognitive dysfunction. Currently, clinical treatment mainly focuses on anti-infection and supportive therapy, lacking specific intervention measures targeting core pathological processes such as neuroinflammation, blood-brain barrier disruption, mitochondrial dysfunction, and oxidative stress. This study systematically reviews the latest progress in the treatment of cognitive dysfunction in SAE and its transition from basic research to clinical practice, providing new strategies for the clinical treatment plan of SAE.

Keywords: Sepsis; Sepsis-associated encephalopathy; Cognitive dysfunction; Mesenchymal stem cells; Molecular hydrogen; Cholinergic pathway
Fund program: Natural Science Foundation of Shanghai Science and Technology Innovation Action Plan (23ZR1464200)

DOI: 10.13429/j.cnki.cjcr.2026.05.001
基金项目： 上海市“科技创新行动计划”自然科学基金项目(23ZR1464200)
通信作者： 钱义明，E-mail: qianym2004@163.com
出版日期： 2026-05-20

QR code for English version

脓毒症相关性脑病（sepsis-associated encephalopathy，SAE）是脓毒症患者常见的神经系统并发症，临床关注度普遍不足，但其在重症监护病房的发病率高达70%[1]。这种疾病的临床表现呈显著异质性，可从轻度意识障碍至深昏迷不等，且与患者住院期间死亡风险升高有关[2]。超过半数存活患者会留下持久性认知功能障碍，严重影响患者的预后及生活质量[3]。现有的病理学研究表明，SAE的发病机制包含神经炎症、线粒体功能障碍以及血脑屏障（blood-brain barrier，BBB）完整性受损等复杂病理过程[4]，但其具体分子与细胞机制仍有待进一步阐明，由于其复杂的病理生理学特征以及严重的临床后果，SAE已成为重症医学领域亟待攻克的关键科学问题。

目前对于SAE的临床治疗方案，仍以非特异性支持治疗为主，尚未形成精准靶向治疗体系，现有的治疗模式主要是控制感染与器官功能支持治疗，但在抑制神经炎症级联反应、促进神经修复等方面效果有限[5]。临床研究显示，即使进行了规范的抗感染治疗以及全面的器官功能支持治疗，SAE患者认知功能障碍的远期发生率仍居高不下[6]。这一治疗瓶颈与SAE病理生理的异质性密切相关，具体表现为个体间神经炎症反应的特点、BBB完整性受损的程度以及线粒体功能异常的状态存在显著差异。近年来，SAE治疗领域取得了创新突破，多种前沿治疗策略展现出广阔的临床应用前景[7]。这些创新疗法的共同特点是针对SAE关键病理机制的多靶点协同作用，体现了基础研究成果向临床实践转化的意义。

1　SAE的可干预靶点研究

1.1　*小胶质细胞极化与星形胶质细胞活化*　SAE的神经炎症病理机制主要与小胶质细胞和星形胶质细胞异常激活相关。研究表明，在脓毒症整个病程中，小胶质细胞可发生M1/M2表型极化，其中M1型的特点是分泌肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白细胞介素-1β（interleukin-1β，IL-1β）等促炎因子，而M2型则发挥神经保护作用[8]。Jiang等[9]的研究证实，这些神经胶质细胞的病理性激活与SAE患者认知功能障碍的发生发展紧密相连。

1.2　*BBB破坏*　SAE的另一核心病理机制为BBB完整性受损。有研究指出，在脓毒症的病理进程中，外周循环中的炎症因子通过双重机制破坏BBB：一方面直接损害脑微血管内皮细胞，另一方面致使紧密连接结构解体，从分子水平分析发现，活化的内皮细胞可显著下调紧密连接蛋白occludin和claudin-5表达，同时促进白细胞浸润，协同加重BBB功能障碍[10-11]。一项运用先进光声显微镜技术展开的动态观察研究证实，脓毒症模型小鼠的BBB通透性异常与其脑微血管形态学改变有明显关联[12]。这种屏障功能的破坏致使外周循环中的炎症介质以及神经毒性物质可穿透BBB进入脑实质，直接损伤神经元。

1.3　*胆碱能通路*　现有研究表明，α7烟碱型乙酰胆碱受体（α7 nicotinic acetylcholine receptors，α7nAChR）作为胆碱能抗炎通路中的核心分子，在神经与免疫调控过程中发挥着关键作用。迷走神经的活化可借助α7nAChR对小胶质细胞的异常活化以及促炎细胞因子的过度释放起到抑制作用，该通路功能异常时，可导致炎症调控失衡，加重SAE的神经病理损伤[13]。

1.4　*线粒体功能障碍与氧化应激*　线粒体功能异常是SAE发病机制中的关键环节，脓毒症所诱发的系统性炎症反应以及脑组织缺氧状况，可损伤线粒体氧化磷酸化功能，导致活性氧过量生成[14]。这种持续的氧化应激，会对神经元产生直接损伤，并通过激活NLRP3炎症小体加重神经炎症。实验结果表明，线粒体DNA异常释放可激活小胶质细胞，形成氧化应激与神经炎症相互促进的病理循环[15]。线粒体功能障碍还可干扰神经递质合成，损害突触可塑性，这些变化与SAE患者出现的认知功能障碍有关[9]。

2　新兴疗法

2.1　*间充质干细胞（mesenchymal stem cells，MSCs）治疗研究*

2.1.1　MSCs的基础研究　近年来开展的诸多研究已经证实，MSCs对SAE具有多靶点治疗效应。马礼秀等[16]研究显示，来自脐带的MSCs可有效地抑制核因子-κB（nuclear factor-κB，NF-κB）信号通路的激活，并可显著降低IL-6、IL-1β、TNF-α以及高迁移率族蛋白B1等促炎因子的表达水平。机制上，磷酸肌醇3-激酶（phosphoinositide 3-kinase，PI3K）/蛋白激酶B（protein kinase B，AKT）信号通路的激活是MSCs发挥神经保护功能的关键途径，此通路可减轻神经炎症反应，还可抑制神经元凋亡并且促进损伤修复[17]，MSCs分泌的条件培养基通过旁分泌显著改善SAE模型动物的焦虑样行为。

2.1.2　疗效验证　多项实验证实MSCs对SAE具有治疗作用。在脂多糖诱导的SAE小鼠模型中，脐带来源MSCs干预后，大脑皮层神经元损伤明显减轻，细胞凋亡过程也受到抑制；Morris水迷宫实验显示，MSCs治疗组的SAE小鼠认知功能障碍显著改善[18]。

在盲肠结扎穿刺(cecal ligation and puncture, CLP)诱导的脓毒症大鼠模型中,MSCs干预有效缓解了急性期临床症状,外周移植可改善恢复期实验动物的长期认知功能[19]。多项实验证据说明,MSCs治疗能维持脓毒症存活小鼠BBB结构完整性,抑制星形胶质细胞异常增生和神经炎症反应,促进认知功能和行为能力恢复[20]。

2.2 分子氢疗法研究

2.2.1 分子氢的基础研究 研究显示,分子氢作为一种有潜在临床应用价值的医用气体分子,在SAE神经保护中具有多重作用机制,从分子机制角度剖析,其神经保护效应主要体现在以下三个方面:其一,分子氢可借助调控哺乳动物雷帕霉素靶蛋白信号通路,对小胶质细胞的极化状态产生影响,抑制促炎M1型极化,并推动向抗炎M2型极化的转变[21];其二,分子氢对BBB的保护作用已得到证实,这与过氧化物酶体增殖物激活受体α的激活以及由其介导的ABC外排转运蛋白表达上调存在紧密联系[22];其三,借助激活核因子E2相关因子2信号通路,分子氢可有效抑制NLRP3炎症小体的活化,减轻神经炎症反应[23]。

2.2.2 抗氧化与抗凋亡作用的实验证据 多项动物实验研究结果显示,分子氢呈现出抗氧化特性以及抑制细胞凋亡的作用,在CLP诱导的SAE模型中,67%高浓度氢气吸入可有效缓解线粒体功能异常,其作用机制包括促进线粒体生物合成以及调控线粒体动力学平衡,以此来维持神经元的能量代谢[24]。从分子层面进行分析,氢气可依靠高效清除氧自由基,明显降低tau蛋白异常磷酸化的程度,改善因此引发的认知功能障碍[25]。

2.3 胆碱能抗炎通路调节治疗研究

2.3.1 迷走神经刺激的基础研究 迷走神经作为胆碱能抗炎通路的关键神经解剖学基础,借助其双向的感觉传入以及运动传出通路,构建起了完整的神经-免疫调控网络。现有证据表明,外周炎症介质可特异性地激活迷走神经的传入纤维,进而将炎症信号传递至中枢神经系统,触发相应的抗炎级联反应。一项动物模型研究表明,运用电刺激手段激活迷走神经传出纤维,或者凭借药理学方法特异性激动α7nAChR,可有效抑制促炎细胞因子的分泌[26]。Goggins等[27]的研究显示,迷走神经的抗炎效应主要依靠其释放的去甲肾上腺素及α7nAChR信号通路对巨噬细胞功能的调控。近年来发展起来的经皮耳迷走神经刺激技术,因其非侵入性的特点,在神经系统疾病的临床干预中呈现出了重要的转化医学前景[28]。

2.3.2 α7nAChR激动剂 α7nAChR作为胆碱能抗炎通路的核心调控分子,其表达水平降低已被证实与脓毒症的病理机制相关[29]。研究显示,选择性α7nAChR激动剂GTS-21在多种疾病模型中都呈现出抑制促炎因子释放以及保护器官功能的双重作用,借助调节脾脏巨噬细胞的功能状态,α7nAChR激动剂能有效缓解急性肺损伤等炎症性病变[30]。在SAE的研究中,小檗碱被证实可借助激活α7nAChR依赖的胆碱能抗炎途径来改善葡萄糖代谢紊乱[31]。

2.3.3 神经-免疫调控网络的靶向干预 当前已有研究指出,胆碱能抗炎通路借助迷走神经、乙酰胆碱、烟碱型乙酰胆碱受体、脾脏以及脾神经等多种成分构建起了一套精细的神经免疫调控网络[32]。需要注意的是,基底前脑胆碱能神经元在脓毒症的病理进程中呈现出抗炎效应,其作用机制包括对海马区神经炎症反应的抑制以及对压力感受器介导的心率调节功能的改进[33]。在SAE动物模型中,乙酰胆碱酯酶抑制剂石杉碱甲依靠提升胆碱能神经递质传递效率,可促进海马神经元功能恢复以及突触可塑性重建,缓解记忆功能障碍[34]。

2.4 中医药治疗研究

2.4.1 中药有效成分药理学研究 近年来,大量药理学研究表明,诸多中药或其有效成分可用于治疗SAE。研究显示,像金银花、黄连、黄柏这类药材,通过调节TNF-α、IL-6等关键炎症因子,呈现出抗SAE的作用[35]。泽漆中提取的黄酮类化合物,被证实对SAE动物有双重神经保护功效,可有效抑制小胶质细胞的异常活化,又可减轻线粒体功能障碍[36]。虎杖的有效活性成分白藜芦醇可以通过miR-370-3p调控p38 MAPK通路治疗SAE[37]。现代药理学研究表明,中药多糖类成分可依靠调控肠道菌群与免疫系统的相互作用起到干预SAE病理进程的作用[38]。然而中药复方复杂成分体系的药效物质基础研究仍存在不少科学难题,像临床疗效确切的青黛等药物,其具体分子靶点以及网络调控机制有待阐明[39]。人工智能技术的运用为解析中药多组分协同作用机制开拓了新路径,基于数据挖掘和分子对接的计算方法可有效预测中药活性成分与SAE相关靶点的相互作用模式[40]。

2.4.2 中成药治疗 中医药在SAE的临床干预方面有着独特之处,其多靶点调控机制能与现代精准医学理念相互补充。一项动物实验证明,银杏叶提取物可通过下调海马Bax和上调B细胞淋巴瘤因子2表达,降低海马TNF-α和IL-6含量,改善SAE小鼠的认知功能[41]。系统评价研究证明,血必净注射液和常规

西药联合使用可产生协同作用，在降低SAE患者病死率以及改善神经功能预后方面成效明显[42]。当前临床实践表明，中成药治疗方案主要针对SAE发病过程中的神经炎症反应、氧化应激损伤以及BBB功能障碍等核心病理环节展开多维度干预[43]。

2.5　其他创新疗法探索

2.5.1　生物材料辅助药物递送系统　近年来，生物医学材料在SAE治疗这一领域有了突破性的成果。研究显示，利用精确控制药物递送系统的新型生物材料可实现神经保护药物的靶向释放，同时光热以及磁热治疗技术的融合为SAE治疗提供创新性的策略。Song等[44]的研究证明，如金纳米颗粒这类多功能纳米材料凭借双重作用机制可有效抑制神经炎症反应，明显减轻脓毒症模型动物的脑功能障碍症状。拥有多组织再生特性的多种生物材料可精准调控局部与系统的机械性能参数，为神经组织修复营造出优化的微环境条件。

2.5.2　微生物组干预策略　肠道微生物群落失调在SAE的病理生理进程中发挥着关键作用，并被视为有很大潜力的治疗干预目标。临床观察可发现，SAE患者肠道菌群的组成呈现出显著的“口腔菌群异位”特点，这种微生物生态紊乱模式和消化道症状以及中枢神经系统炎症反应存在显著相关性[45]。以微生物-代谢轴调控为基础的治疗策略，像益生菌/益生元补充疗法以及粪便微生物移植技术，已被证实可通过重新塑造肠道微生态平衡来减轻神经炎症反应[46]。同时，肠道共生菌代谢产物短链脂肪酸作为肠-脑双向通信的关键信号分子，其水平变化和SAE患者神经炎症的严重程度有明显的剂量依赖性关系[47]。此外，由迷走神经通路、肠源性神经肽以及微生物代谢产物共同构建而成的神经-免疫-微生物组交互网络，在SAE的发生发展过程中起着极为关键的调控作用[48]。

3　总结与展望

当前脓毒症研究领域出现了多组学技术应用增长的态势，基因组学与转录组学联合分析方法处于主导地位，其次是基因组学与蛋白质组学相结合的研究模式，运用多组学整合策略，研究者可以系统剖析SAE的分子调控网络，比如在急性肺损伤研究中，基于基因-代谢物-表型复合网络的构建可有效辨认关键代谢调控节点。结合蛋白质组学、代谢组学数据与类器官模型的多维度整合分析方法，为阐明特定分子通路在SAE发病机制中的生物学功能提供了新的研究思路[49]。

总之，多组学技术与临床数据的整合为SAE的研究和治疗提供了新的思路和方法。通过进一步优化新兴疗法的临床应用策略，有望突破现有治疗瓶颈，改善SAE患者的预后。未来的研究应继续探索SAE的分子机制，开发个体化治疗方案，以应对这一重症医学领域的重大挑战。

利益冲突　无

参考文献

[1]　Yang K，Chen JQ，Wang T，et al. Pathogenesis of sepsis-associated encephalopathy：more than blood-brain barrier dysfunction[J]. Mol Biol Rep，2022，49(10)：10091-10099.

[2]　Zhao PP，Zhang W，Zhou XY，et al. Gypenoside XLIX alleviates sepsis-associated encephalopathy by targeting PPAR-α[J]. Exp Neurol，2025，383：115027.

[3]　Hoshino K. Targeting synaptic plasticity to bridge translational gaps in sepsis-associated encephalopathy[J]. Front Aging Neurosci，2025，17：1616736.

[4]　Ling JM，Wu YQ，Zou XJ，et al. (-)-epicatechin reduces neuroinflammation，protects mitochondria function，and prevents cognitive impairment in sepsis-associated encephalopathy[J]. Oxid Med Cell Longev，2022，2022：2657713.

[5]　Shehata AH，Anter AF，Ahmed AF. Role of SIRT1 in sepsis-induced encephalopathy：molecular targets for future therapies[J]. Eur J Neurosci，2023，58(10)：4211-4235.

[6]　Gao SJ，Jiang Y，Chen ZY，et al. Metabolic reprogramming of microglia in sepsis-associated encephalopathy：insights from neuroinflammation[J]. Curr Neuropharmacol，2023，21(9)：1992-2005.

[7]　Zhang Z，Wang L，Li F，et al. Therapeutic effects of human umbilical cord mesenchymal stem cell on sepsis-associated encephalopathy in mice by regulating PI3K/AKT pathway[J]. J Integr Neurosci，2022，21(1)：38.

[8]　Hu JY，Xie SC，Zhang HS，et al. Microglial activation：key players in sepsis-associated encephalopathy[J]. Brain Sci，2023，13(10)：1453.

[9]　Jiang JL，Zou Y，Xie CT，et al. Oxytocin alleviates cognitive and memory impairments by decreasing hippocampal microglial activation and synaptic defects *via* OXTR/ERK/STAT3 pathway in a mouse model of sepsis-associated encephalopathy[J]. Brain Behav Immun，2023，114：195-213.

[10]　Pu YH，Zhao L，Xi Y，et al. The protective effects of Mirtazapine against lipopolysaccharide (LPS)-induced brain vascular hyperpermeability[J]. Bioengineered，2022，13(2)：3680-3693.

[11]　Gao QZ，Hernandes MS. Sepsis-associated encephalopathy and blood-brain barrier dysfunction[J]. Inflammation，2021，44(6)：2143-2150.

[12]　Wang ZG，Ai CP，Sun T，et al. Photoacoustic imaging detects cerebrovascular pathological changes in sepsis[J]. Photoacoustics，2025，44：100737.

[13]　Barlow B，Ponnaluri S，Barlow A，et al. Targeting the gut microbiome in the management of sepsis-associated encephalopathy[J]. Front Neurol，2022，13：999035.

[14]　Ranjbaran M，Kianian F，Kadkhodaee M，et al. Mesenchymal stem cells and their conditioned medium as potential therapeutic strategies in managing comorbid anxiety in rat sepsis induced by cecal ligation and puncture[J]. Iran J Basic Med Sci，2022，25(6)：690-697.

[15]　Guo Y，Yu YH. PI3K/Akt pathway and neuroinflammation in sepsis-associated encephalopathy[J]. Open Med，2025，20(1)：20251248.

[16] 马礼秀. 诱导性多能干细胞外泌体来源的OIP5-AS1影响LPS诱导的小胶质细胞炎症反应的研究[D]. 南昌: 南昌大学, 2024.

[17] Hu JY, Xie SC, Chen T, et al. Glial vascular unit as a bridge between blood-brain barrier and glymphatic system: roles in sepsis-associated encephalopathy[J]. Neuroscience, 2025, 570: 68-71.

[18] Cao HH, Liu T, Xu MX. Senkyunolide Ⅰ improves septicemia-induced brain dysfunction *via* regulating Nrf2 and astrocyte activity [J]. Biotechnol Appl Biochem, 2025, 72(5): 1385-1394.

[19] Tan LJ, Cheng Y, Wang H, et al. Peripheral transplantation of mesenchymal stem cells at sepsis convalescence improves cognitive function of sepsis surviving mice[J]. Oxid Med Cell Longev, 2022, 2022: 6897765.

[20] Cui Y, Liu JF, Song Y, et al. High concentration hydrogen protects sepsis-associated encephalopathy by enhancing Pink1/Parkin-mediated mitophagy and inhibiting cGAS-STING-IRF3 pathway [J]. CNS Neurosci Ther, 2025, 31(2): e70305.

[21] Zhuang XQ, Yu Y, Jiang Y, et al. Molecular hydrogen attenuates sepsis-induced neuroinflammation through regulation of microglia polarization through an mTOR-autophagy-dependent pathway [J]. Int Immunopharmacol, 2020, 81: 106287.

[22] Bai YY, Mi W, Meng XY, et al. Hydrogen alleviated cognitive impairment and blood-brain barrier damage in sepsis-associated encephalopathy by regulating ABC efflux transporters in a PPARα-dependent manner[J]. BMC Neurosci, 2023, 24(1): 37.

[23] Xie KL, Zhang Y, Wang YQ, et al. Hydrogen attenuates sepsis-associated encephalopathy by NRF2 mediated NLRP3 pathway inactivation[J]. Inflamm Res, 2020, 69(7): 697-710.

[24] 鄂子玉, 丛岩, 王艳飞, 等. 2%氢气吸入对脓毒症相关性脑病大鼠神经功能的修复作用及其机制[J]. 山东医药, 2024, 64(35): 45-49.

[25] Qi B, Song Y, Chen C, et al. Molecular hydrogen attenuates sepsis-induced cognitive dysfunction through regulation of tau phosphorylation[J]. Int Immunopharmacol, 2023, 114: 109603.

[26] Keever KR, Cui K, Casteel JL, et al. Cholinergic signaling via the α7 nicotinic acetylcholine receptor regulates the migration of monocyte-derived macrophages during acute inflammation[J]. J Neuroinflammation, 2024, 21(1): 3.

[27] Goggins E, Inoue H, Okusa MD. Neuroimmune control of inflammation in acute kidney injury and multiorgan dysfunction[J]. J Am Soc Nephrol, 2025, 36(12): 2473-2484.

[28] Ma L, Wang HB, Hashimoto K. The vagus nerve: an old but new player in brain-body communication[J]. Brain Behav Immun, 2025, 124: 28-39.

[29] 薛萍. α7烟碱乙酰胆碱能受体通过JAK2/STAT3通路激活脑内抗炎性小胶质细胞对脓毒症脑病大鼠的脑保护作用及机制研究[D]. 青岛: 青岛大学, 2021.

[30] Li RT, Hu XM, Chen HB, et al. Role of cholinergic anti-inflammatory pathway in protecting sepsis-induced acute lung injury through regulation of the conventional dendritic cells [J]. Mediators Inflamm, 2022, 2022: 1474891.

[31] Wang DK, Ren YL, Sun W, et al. Berberine ameliorates glucose metabolism in diabetic rats through the alpha7 nicotinic acetylcholine receptor-related cholinergic anti-inflammatory pathway [J]. Planta Med, 2022, 88(1): 33-42.

[32] Deng YQ, Gao M, Lu D, et al. Compound-composed Chinese medicine of *Huachansu* triggers apoptosis of gastric cancer cells through increase of reactive oxygen species levels and suppression of proteasome activities[J]. Phytomedicine, 2024, 123: 155169.

[33] Li N, Liao S, Liu L, et al. Pleiotropic role of endoplasmic reticulum stress in the protection of psoralidin against sepsis-associated encephalopathy[J]. Free Radic Biol Med, 2024, 221: 203-214.

[34] Yin L, Zhang JM, Ma HW, et al. Selective activation of cholinergic neurotransmission from the medial septal nucleus to hippocampal pyramidal neurones improves sepsis-induced cognitive deficits in mice[J]. Br J Anaesth, 2023, 130(5): 573-584.

[35] Liu PP, Zeng LN, Fu HY, et al. Investigating the therapeutic mechanisms of honeysuckle (China) in sepsis through network pharmacology and experimental validation[J]. Infect Drug Resist, 2025, 18: 3257-3277.

[36] Ding HG, Li Y, Chen SL, et al. Fisetin ameliorates cognitive impairment by activating mitophagy and suppressing neuroinflammation in rats with sepsis-associated encephalopathy[J]. CNS Neurosci Ther, 2022, 28(2): 247-258.

[37] 冯林, 彭红艳, 魏晓星, 等. 白藜芦醇通过miR-370-3p调控p38MAPK通路治疗大鼠脓毒症相关性脑病的研究[J]. 中国临床药理学杂志, 2025, 41(10): 1438-1443.

[38] Bian ZY, Zhao AH, Wang QH, et al. Advancements in research on the anti-metabolic dysfunction-associated steatotic liver disease effects and mechanisms of action of traditional Chinese medicine polysaccharides: a review[J]. Int J Biol Macromol, 2025, 321(Pt 3): 146292.

[39] Zhou E, Shen Q, Hou Y. Integrating artificial intelligence into the modernization of traditional Chinese medicine industry: a review [J]. Front Pharmacol, 2024, 15: 1181183.

[40] Zhu JQ, Liu XN, Gao P. Digital intelligence technology: new quality productivity for precision traditional Chinese medicine [J]. Front Pharmacol, 2025, 16: 1526187.

[41] 王旭. 基于网络药理学和动物实验探究银杏叶提取物对脓毒症相关性脑病的作用及机制[D]. 大理:大理大学,2024.

[42] Li XY, Xu XL, Zhang J, et al. Review of the therapeutic effects of traditional Chinese medicine in sepsis-associated encephalopathy [J]. J Ethnopharmacol, 2024, 334: 118588.

[43] Zhenxuan LI, Wang XR, Ulloa L, et al. Complementary and alternative medicine on cognitive defects and neuroinflammation after sepsis[J]. J Tradit Chin Med, 2024, 44(2): 408-416.

[44] Song ZC, Chen HG, Xu WF, et al. The hexapeptide functionalized gold nanoparticles protect against sepsis-associated encephalopathy by forming specific protein corona and regulating macrophage activation[J]. Mater Today Bio, 2025, 32: 101704.

[45] Póvoa P, Coelho L, Dal-Pizzol F, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians[J]. Intensive Care Med, 2023, 49(2): 142-153.

[46] Webster CI, Withycombe JS, Bhutada JS, et al. Review of the microbiome and metabolic pathways associated with psychoneurological symptoms in children with cancer[J]. Asia Pac J Oncol Nurs, 2024, 11(8): 100535.

[47] Zhang QL, Lu C, Fan WX, et al. Application background and mechanism of short-chain fatty acids in sepsis-associated encephalopathy[J]. Front Cell Infect Microbiol, 2023, 13: 1137161.

[48] Gareau MG. The microbiota-gut-brain axis in sepsis-associated encephalopathy [J/OL]. mSystems, (2022-08-30). https://escholarship.org/uc/item/2ck3v7sh.

[49] Jang WE, Park JH, Park G, et al. Cntnap2-dependent molecular networks in autism spectrum disorder revealed through an integrative multi-omics analysis[J]. Mol Psychiatry, 2023, 28(2): 810-821.

收稿日期:2025-10-22　**修回日期:**2025-11-09　**编辑:**许煜晗