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Research Progress in the Prevention and Treatment of Post-Stroke Depression with Traditional Chinese Medicine

Ruishan Yu[1], Xiaxia Jin[2], Jiaqi He[1], Nan Du[1], Gaofeng Wang[1], Yifan Yang[3], Tao Li[1], Yongmei Yan[1,2,3,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]National Resource Center for Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
[3]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author

Abstract: ***Post-stroke depression (PSD) is the most prevalent complication following stroke, which severely impairs neurological functional recovery and quality of life in affected patients. Traditional Chinese medicine (TCM) has demonstrated favorable clinical efficacy in the prevention and management of PSD. Accumulating evidence indicates that TCM monomers and their bioactive ingredients, compound preparations, and acupuncture therapy exert therapeutic effects against PSD by modulating multiple signaling pathways, including NF-κB, NLRP3, JAK/STAT3, BDNF/TrkB, Notch, PI3K/Akt/mTOR, and the hypothalamic-pituitary-adrenal (HPA) axis. This paper systematically summarizes the research advances in TCM interventions targeting the aforementioned signaling pathways, generalizes their underlying mechanisms of action, and discusses their potential value in PSD prevention and treatment. Existing findings suggest that TCM features multi-target and multi-pathway regulatory effects: it not only alleviates depressive symptoms but also promotes neurological functional recovery, providing novel insights and theoretical evidence for the clinical treatment of PSD.***

Keywords: Post-stroke depression, Traditional Chinese medicine monomer, Traditional Chinese medicine formula, Acupuncture, Signaling pathway.

1. Introduction

Post-stroke depression (PSD) is a common complication after stroke, affecting approximately one-third of stroke survivors. Its incidence can reach 11%–41% within 2 years after stroke onset [1]. Clinically, it is characterized by core symptoms including persistent low mood, anhedonia, and reduced energy, often accompanied by cognitive decline and suicidal ideation, which severely compromise patients' quality of life and hinder neurological rehabilitation [2].

In modern medicine, the pathogenesis of PSD is highly complex, with neuroinflammation as the central pathological link [3]. It also involves multiple interrelated mechanisms such as neurotransmitter imbalance, oxidative stress injury, neuroendocrine dysregulation, and decreased levels of neurotrophic factors [4]. Currently, Western pharmacotherapy for PSD is dominated by antidepressants such as selective serotonin reuptake inhibitors. Although these agents can ameliorate partial clinical symptoms, they are limited by delayed onset of action, frequent adverse reactions, and poor long-term tolerance [5].

In recent years, with the deepening understanding of the pathological mechanisms of PSD, research on its associated signaling pathways has attracted increasing attention. Studies have confirmed that signaling pathways including nuclear factor-κB (NF-κB), phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR), brain-derived neurotrophic factor (BDNF)/tyrosine protein kinase B (TrkB), and the hypothalamic-pituitary-adrenal (HPA) axis are closely implicated in key pathological processes of PSD, such as neuroinflammation, synaptic plasticity alterations, neuronal apoptosis, and stress response [6]. TCM treatment of PSD emphasizes holistic regulation and syndrome differentiation. Acupuncture and TCM formulas, with their inherent advantages of multi-target and multi-pathway modulation, exhibit unique efficacy in improving depressive mood and promoting neurological recovery. A large body of evidence indicates that acupuncture, single TCM herbs, and TCM formulas all exert therapeutic effects by intervening in the aforementioned signaling pathways. This paper systematically reviews the mechanisms of TCM (including acupuncture) in regulating relevant signaling pathways for the prevention and treatment of PSD, aiming to provide reference for clinical practice and further research.

2. Core Regulatory Signaling Pathways in PSD

2.1 Core Inflammatory Regulatory Pathways

Neuroinflammation is a pivotal pathological driver in the onset and progression of PSD [7]. Following cerebral ischemia, inflammatory pathways are overactivated, leading to massive release of pro-inflammatory factors including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These mediators damage brain regions such as the hippocampus, thereby inducing or exacerbating depressive phenotypes [3]. The NF-κB pathway, NOD-like receptor pyrin domain containing protein 3 (NLRP3) inflammasome, and Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway are critical signaling cascades involved in these inflammatory responses. Studies have shown that TCM modulates these pathways at multiple levels and targets, thereby exerting therapeutic effects against PSD.

2.1.1 NF-κB Pathway

Overactivation of the NF-κB signaling pathway is recognized as one of the primary pathological mechanisms underlying the development of PSD [8]. Upon activation, this pathway induces the expression of multiple pro-inflammatory factors such as IL-1β, IL-6, and TNF-α, and interacts with the NLRP3 inflammasome to jointly exacerbate neuroinflammatory responses [3], thus driving the pathological progression of PSD. In mammals, the NF-κB family comprises five members that collectively participate in this regulatory process [8].

2.1.2 NLRP3 Inflammasome Pathway

The NLRP3 inflammasome pathway is a key cytoplasmic pathway mediating innate immunity and inflammatory responses, composed of three proteins: NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and cysteinyl aspartate-specific protease 1 (Caspase-1) [9]. Aberrant activation of this pathway is considered an important mechanism in the development and progression of PSD. Activated NLRP3 inflammasome interacts with the NF-κB pathway to promote the release of pro-inflammatory cytokines such as IL-1β and interleukin-18 (IL-18), further activating microglia and promoting neuroinflammatory responses, ultimately causing damage to brain regions such as the hippocampus and exacerbating the pathological progression of PSD [10].

2.1.3 JAK/STAT3 Signaling Pathway

The JAK/STAT3 signaling pathway is the core cascade mediating signal transduction of cytokines and growth factors, with its core composed of the tyrosine kinase JAK family and the transcription factor STAT family [11]. Its abnormal activation plays a critical role in the pathological process of PSD: after stroke, pro-inflammatory factors such as IL-6 and TNF-α bind to cell membrane receptors, rapidly activating downstream JAK kinases, which mediate STAT3 phosphorylation and nuclear translocation. Nuclear p-STAT3 can specifically upregulate the transcriptional expression of pro-inflammatory factors including IL-1β and IL-6, triggering an inflammatory cascade and ultimately aggravating PSD progression [12].

2.2 Neuroprotection and Neurogenesis-Related Pathways

Impaired neurogenesis and disrupted synaptic plasticity are the core pathological basis for the difficulty in neurological recovery in PSD. Signaling pathways including BDNF-TrkB, PI3K/Akt/mTOR, and Notch coordinately regulate neuronal survival, neurogenesis, and synaptic plasticity. TCM can activate these pathways at multiple targets to promote nerve repair and exert therapeutic effects against PSD [13, 14].

2.2.1 BDNF-TrkB Signaling Pathway

BDNF is regarded as an important potential neurobiological biomarker for antidepressant therapy [15, 16]. BDNF and its specific receptor TrkB are widely expressed in multiple brain regions of the human brain. Their binding activates downstream pathways, regulating neuronal development, synaptic plasticity, and cell survival, and participating in glial function modulation and neurogenesis [17]. This signaling system plays a key regulatory role in the mechanism of action of antidepressant drugs.

2.2.2 PI3K/Akt/mTOR Signaling Pathway

PI3K belongs to the intracellular serine/threonine kinase and lipid kinase families, with AKT as its core downstream signaling molecule. In mammals, mTOR can form two functional complexes, mTORC1 and mTORC2 [18, 19]. In the canonical pathway, full activation of AKT requires sequential phosphorylation: first, phosphorylation at the Thr308 site by 3-phosphoinositide-dependent protein kinase 1 (PDK1), followed by phosphorylation at the Ser473 site by mTORC2 [20], which in turn activates downstream mTORC1 [21]. Studies have demonstrated that the PI3K/Akt/mTOR pathway is a core pathway regulating central nervous system function and oxidative stress homeostasis, and its abnormal activity is closely associated with the pathogenesis of various neurological disorders.

2.2.3 Notch Pathway

The Notch signaling pathway is one of the key pathways regulating neurological functional repair and neurogenesis in PSD [22]. Its core components include the Notch receptor family, homologous ligand family, and downstream target genes such as Hairy and Enhancer of Split 1 and 5 (Hes1, Hes5) [23]. Upon ligand-receptor binding, the Notch receptor undergoes proteolytic cleavage to release the Notch intracellular domain (NICD). NICD translocates into the nucleus and binds to recombination signal binding protein Jκ (RBP-Jκ) to regulate the transcription of downstream target genes. This pathway mediates hippocampal neurogenesis by regulating the proliferation and differentiation of neural stem cells, neuronal survival, and synaptic plasticity remodeling.

2.3 Neuroendocrine Stress Regulatory Pathway (HPA Axis)

The HPA axis is the core of the neuroendocrine system, composed of the hypothalamic paraventricular nucleus, anterior pituitary, and adrenal cortex. It regulates stress responses through the cascade of corticotropin-releasing hormone (CRH) – adrenocorticotropic hormone (ACTH) – glucocorticoids [24, 25]. Hyperactivation of the HPA axis leads to elevated levels of CRH, ACTH, and corticosterone, while reducing the content of monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA), resulting in neurotransmitter imbalance. This is one of the key mechanisms underlying the onset of depression and the exacerbation of PSD symptoms [26, 27]. TCM can exert regulatory effects in PSD treatment by inhibiting HPA axis hyperfunction and restoring neuroendocrine homeostasis.

3. Mechanisms of TCM Monomers in the Prevention and Treatment of PSD

Crocin is a class of water-soluble carotenoids with multiple pharmacological activities such as anti-inflammatory and neuroprotective effects [28]. Studies have found that the development and progression of PSD are closely associated

with central neuroinflammatory cascades mediated by overactivation of the Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88)/NF-κB signaling pathway [29]. Crocin can significantly inhibit the abnormal activation of the TLR4/MyD88/NF-κB pathway in the brain tissue of PSD rats, while downregulating the expression levels of pro-inflammatory factors, reducing cerebral inflammatory responses, and thereby alleviating depressive symptoms in PSD rats [30].

Astragalus polysaccharide, the main bioactive component of Astragalus membranaceus, is a mixture of acidic heteropolysaccharides and glucans with a wide range of pharmacological activities including antioxidant, anti-inflammatory, and immunomodulatory effects [31, 32]. Studies have shown that peroxisome proliferator-activated receptor γ (PPAR-γ) is a key upstream target regulating this inflammatory pathway; it can exert indirect neuroprotective effects by inhibiting NF-κB phosphorylation and attenuating NF-κB-mediated vascular wall inflammatory responses [33]. Astragalus polysaccharide can enhance PPAR-γ activity, suppress NF-κB phosphorylation and its activity, and thereby downregulate inflammatory responses to exert therapeutic effects against PSD [34].

Morinda officinalis oligosaccharides, derived from the root of the traditional Chinese herb Morinda officinalis, are the core active constituents responsible for its antidepressant effects [35]. Studies have found that these oligosaccharides can alleviate PSD by downregulating the expression of pro-inflammatory factors such as IL-1β and IL-18 and the NLRP3 inflammasome in hippocampal tissue, while reducing the protein levels of phosphorylated inhibitor of nuclear factor-κB (p-IκB), NF-κB, and phosphorylated p65 (p-p65), thus inhibiting the inflammatory process at multiple key nodes [36].

Liquiritin is a flavonoid active compound in the aqueous extract of Glycyrrhiza uralensis, with verified pharmacological effects including anti-ulcer, antiviral, and antidepressant activities [37, 38]. Studies have shown that synaptic plasticity impairment mediated by BDNF downregulation and neuronal apoptosis mediated by the imbalance of Bcl-2 associated X protein (Bax)/B-cell lymphoma 2 (Bcl-2) are closely related to the occurrence of PSD [39, 40]. Liquiritin has been shown to inhibit neuronal apoptosis and enhance synaptic plasticity by downregulating the expression of the pro-apoptotic protein Bax and upregulating the anti-apoptotic protein Bcl-2 and BDNF levels in the prefrontal cortex of PSD rats, thereby improving depressive-like behaviors in model rats [41].

Quercetin is a flavonoid compound with multiple biological functions such as antioxidant, anti-inflammatory, and neuroprotective effects, and its antidepressant effect has been verified in clinical trials [42, 43]. Studies have found that the BDNF/TrkB pathway can inhibit glycogen synthase kinase-3β (GSK-3β) activity and upregulate β-catenin expression by activating the PI3K/Akt pathway, thereby improving synaptic plasticity and promoting neurogenesis [44]. Animal experiments showed that 12-week intragastric administration of quercetin significantly reduced the levels of pro-inflammatory factors such as TNF-α and IL-1β in the serum and prefrontal cortex of PSD rats, while regulating the GSK-3β and BDNF/TrkB/β-catenin pathways, effectively improving depressive-like symptoms in model rats [45].

Sodium aescinate is a triterpenoid saponin sodium salt extracted from the dried mature fruits of Aesculus chinensis, with pharmacological activities such as anti-inflammatory, anti-exudative, and anti-edema effects [46]. Further studies have found that sodium aescinate can significantly reduce the adrenal index and serum corticosterone levels in PSD model rats, and exert antidepressant effects by correcting HPA axis hyperfunction and regulating HPA axis homeostasis [47].

Honokiol, isolated from the dried bark of Magnolia officinalis and Magnolia officinalis var. biloba, possesses multiple pharmacological activities such as antibacterial and anti-inflammatory effects [48, 49]. In a PSD mouse model established by middle cerebral artery occlusion (MCAO) combined with chronic unpredictable mild stress (CUMS) and single housing, after 28 days of continuous intragastric administration of honokiol, it was found that compared with the model group, the treatment group showed significantly downregulated expression of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α in the brain, as well as markedly reduced levels of CRH, ACTH, and serum corticosterone. The results suggest that honokiol can significantly improve depressive-like behaviors in PSD model mice through the synergistic multi-target effects of blocking central inflammatory cascades and inhibiting abnormal HPA axis activation [50].

In summary, a variety of TCM monomers exert definite antidepressant and neuroprotective effects in PSD intervention via the advantages of multi-target and multi-pathway actions. On one hand, they can target and inhibit core inflammatory pathways such as NF-κB and the NLRP3 inflammasome, upregulate PPAR-γ activity to block NF-κB phosphorylation, suppress the entire central inflammatory cascade, reduce the release of pro-inflammatory factors, and simultaneously correct HPA axis hyperfunction, restore the homeostasis of the neuro-endocrine-immune network, and halt the pathological progression of PSD. On the other hand, they can modulate the BDNF/TrkB/β-catenin signaling axis, upregulate Bcl-2 and downregulate Bax expression to inhibit hippocampal neuronal apoptosis, while enhancing synaptic plasticity and promoting neurogenesis, repairing post-stroke brain tissue damage, and improving depressive-like behaviors in model animals. These findings provide reliable experimental evidence for TCM treatment of PSD and identify multi-dimensional targets for the research and development of innovative clinical antidepressant drugs.

4. Mechanisms of TCM Formulas in the Prevention and Treatment of PSD

Xingshen Jieyu Decoction is a modified formulation derived from the combination of three classic TCM prescriptions: Kaixin San, Shengjiang San, and Banxia Xumi Decoction. It functions to replenish qi, activate blood circulation, refresh the mind, and resolve depression. Clinical studies have confirmed that it can improve cognitive dysfunction caused by PSD [51, 52]. After 14 days of intragastric administration of Xingshen Jieyu Decoction in MCAO+CUMS-induced PSD

rats, the formula significantly reduced the neurological function score of rats, alleviated hippocampal pathological damage, increased the number of neurons, downregulated the expression of ionized calcium-binding adapter molecule 1 (Iba-1), glial fibrillary acidic protein (GFAP), pro-inflammatory factors, and Cyclophilin A (CyPA)-extracellular regulated protein kinases 1/2 (ERK1/2)-NF-κB pathway-related proteins, and upregulated the level of the anti-inflammatory factor IL-10. These findings indicate that the formula can ameliorate neurological function in PSD rats by regulating this pathway to inhibit neuroinflammation [53].

Yinao Jieyu Formula is an effective clinical TCM formula for the treatment of PSD. Previous studies have shown that this formula can reduce hippocampal neuronal damage, inhibit apoptosis, increase the number of neurons in the hippocampal dentate gyrus, inhibit abnormal activation of astrocytes, and promote neurogenesis, exerting significant neuroprotective effects on the hippocampus [54, 55]. Further studies found that after 6 weeks of intragastric administration of this formula in PSD model rats, the number and layers of cells in the hippocampal CA3 region of the treatment group were significantly increased, and the expression of TLR2, TLR4, and NF-κB proteins was significantly downregulated, suggesting that Yinao Jieyu Formula exerts neuroprotective effects by attenuating immune inflammatory responses, repairing nerve damage, and inhibiting apoptosis [56].

Jieyu Pills are a pure TCM preparation developed on the basis of Ganmai Dazhao Decoction and Xiaoyao Powder with modern technology, with effects of tranquilizing the mind, soothing the liver, and relieving depression [57]. Studies have shown that this formula can directly improve depressive mood and promote neurological recovery in PSD patients, and its mechanism is related to increasing serum 5-HT levels while reducing the expression of NF-κB, miR-146, and miR-221-3p [57].

Modified Baishile Formula is an empirical formula of Professor Liu Lin from Hunan University of Chinese Medicine, with effects of activating blood and soothing the liver, resolving depression and phlegm, and calming the nerves and dredging collaterals. Numerous studies have verified its definite efficacy in the treatment of depression and PSD [58]. The P2X purinoceptor 7 (P2X7R)/NLRP3 pathway is a core cascade mediating the inflammatory cascade of PSD, and blocking this pathway exerts definite antidepressant effects [59, 60]. NLRP3 is a key molecule mediating inflammatory signal transmission in the brain-gut axis, which can affect cerebral homeostasis by regulating inflammatory responses [61]. Studies demonstrated that Modified Baishile Formula can significantly reduce the level of the pro-inflammatory factor IL-1β in the serum and intestinal tissue of PSD rats, while upregulating the content of brain-gut peptides such as neuropeptide Y (NPY), gastrin (GAS), and motilin (MOT). Ultimately, it effectively improves depressive-like behaviors in PSD model rats by inhibiting the inflammatory cascade and protecting neurological function [62].

Xuefu Zhuyu Decoction, originating from Correction of Medical Errors by Wang Qingren, is effective in activating blood circulation to remove stasis and moving qi to relieve pain. Its modern preparation, Xuefu Zhuyu Capsules, can effectively improve depressive symptoms and quality of life in PSD patients [63, 64]. As a key neurotrophic factor in depression research, BDNF is involved in regulating neuronal proliferation, differentiation, and regeneration [65]. Its expression is regulated by multiple signaling pathways such as cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), and it can only exert biological effects after binding to TrkB [66]. Modern studies have shown that Xuefu Zhuyu Capsules can significantly increase the levels of DA and 5-HT in the prefrontal cortex and hippocampus of PSD rats, and improve depressive-like behaviors in model rats by activating the BDNF/TrkB/p-CREB signaling pathway [67].

Shenjing Fuyuan Formula is a clinical empirical formula of Professor Li Rukui from Shanghai Municipal Hospital of Traditional Chinese Medicine, used for the recovery phase of nervous system injury. It functions to nourish yin and tonify the kidney, promote blood circulation and remove stasis, and resolve phlegm and relieve depression [68]. Current evidence suggests that reduced neuroplasticity is the core pathological basis of depression [69]. This formula can significantly upregulate the mRNA expression of BDNF and TrkB in the hippocampus of rats, promote the synthesis of Synapsin I (SYN I) and Syncytin-A (SYNA), and effectively improve neurological function and depressive-like behaviors in rats by enhancing synaptic plasticity [70].

Chaihu Shugan Powder, from Jingyue Complete Works, exerts effects of soothing the liver and activating blood, invigorating the spleen and regulating qi. Clinical studies have confirmed that it can effectively improve depressive symptoms in PSD patients [71]. After 21 days of continuous intragastric administration in PSD rats, the formula significantly upregulated the expression of BDNF and its receptor TrkB in the hippocampal region of rats, while reducing serum TNF-α levels and hippocampal NF-κB expression, thereby alleviating neurological deficits and improving depressive-like behaviors through the synergistic effects of neuroprotection and anti-inflammation [72].

Wuling Capsules are a single-ingredient Chinese patent medicine refined from deep-fermented mycelium of natural Xylaria nigripes via two national confidential technologies. They function to nourish the heart and tranquilize the mind, clear the heart and resolve phlegm, and tonify the kidney and benefit the brain, achieving good effects in the treatment of depression [73]. Studies have shown that this formula can increase the number of neurons in the hippocampal CA1 region of PSD rats and reduce brain tissue damage by upregulating the expression of proteins related to the PI3K/Akt/mTOR pathway, thereby exerting neuroprotective effects and promoting neuroplasticity [74].

Mongolian medicine Zadi-5 Pills (Roukou Wuwei Pills) is a classic Mongolian prescription for the treatment of emotional and heart diseases [75]. Clinical studies have shown that this formula can not only relieve anxiety and depression, improve sleep and cognitive function in PSD patients, but also reduce serum inflammatory factor levels, exerting multi-target therapeutic effects [76, 77]. Studies have shown that Mongolian medicine Zadi-5 Pills can promote the

proliferation and differentiation of hippocampal neural stem cells by upregulating the expression of Notch pathway components including NICD, Jagged 1 (Jag1), and downstream Hes1/5, thereby improving depressive-like behaviors in model rats [77].

Jieyu No.1 Formula is an empirical formula of the renowned TCM physician Professor Cai Yongliang, modified from Chaihu Shugan Powder. It functions to soothe the liver and regulate qi, and is an effective clinical TCM formula for PSD intervention [78]. Studies have shown that this formula exerts dual-target synergistic anti-PSD effects by activating the Notch signaling pathway and regulating the monoamine neurotransmitter system: on one hand, it upregulates the mRNA and related protein expression of Notch1 and Hes1 in the hippocampal region to promote neurogenesis and achieve neuroprotection; on the other hand, it increases the levels of 5-hydroxyindoleacetic acid (5-HIAA), NE, 5-HT, and DA in brain tissue to correct neurotransmitter imbalance. Ultimately, it effectively improves depressive-like behaviors and neurological deficits in PSD model rats through multi-pathway synergy [78].

Chaishao Anshen Jieyu Granules is a hospital preparation of Guangdong Second Provincial General Hospital of Traditional Chinese Medicine, with confirmed clinical efficacy against PSD after years of clinical application [79]. Its core mechanism of action is closely related to inhibiting excessive HPA axis activation and activating the PI3K/Akt/ribosomal protein S6 kinase (RPS6K) signaling pathway to exert neuroprotective effects. This formula not only significantly reduces the levels of hormones such as CRH, ACTH, and corticosterone (CORT) in PSD rats and inhibits HPA axis hyperfunction; it also upregulates hippocampal BDNF content and the protein expression of PI3K, Akt, and ribosomal protein S6 kinase A1 (RPS6KA1), reduces cerebral neuronal apoptosis, and ultimately effectively ameliorates depressive-like behaviors in PSD model rats [79].

Various TCM formulas for PSD, including classic prescriptions, clinical empirical formulas, Chinese patent medicines, and ethnic medicine preparations, all demonstrate definite antidepressant and neuroprotective effects, with the holistic advantages of multi-target and multi-pathway intervention. Taking NF-κB signaling as the core hub, these formulas inhibit central inflammatory cascades by targeting multiple pathways such as TLR2/4 and P2X7R/NLRP3, block abnormal glial activation, and balance the levels of pro-inflammatory and anti-inflammatory factors. Meanwhile, they can activate neurorestorative pathways including BDNF/TrkB, Notch, and PI3K/Akt/mTOR, inhibit hippocampal neuronal apoptosis, promote neurogenesis and synaptic plasticity remodeling, and repair cerebral pathological damage. In addition, they can simultaneously regulate monoamine neurotransmitter imbalance, correct HPA axis hyperfunction, and modulate brain-gut axis homeostasis, achieving multi-dimensional intervention in the pathological process of PSD. These findings provide sufficient experimental and clinical evidence for the clinical treatment of PSD with TCM, and also lay a theoretical foundation for the research and development of innovative therapeutic strategies for this disease.

5. Mechanisms of Acupuncture in the Prevention and Treatment of PSD

Acupoints such as Baihui, Dazhui, Neiguan, and Taichong are commonly used acupoints for the clinical treatment of mental disorders and depression. Acupuncture intervention exerts significant neuroprotective effects by regulating central neurotransmission and modulating immune-inflammatory cascades [80]. Leng et al. [81] found that after electroacupuncture stimulation at the above acupoints in PSD rats, the serum levels of TNF-α, TNF receptor-associated factor 6 (TRAF6), and interleukin-1β receptor (IL-1βR), as well as the protein expression of NF-κB, TRAF6, IL-1βR, and p38MAPK in hippocampal tissue, were significantly downregulated, confirming that electroacupuncture exerts therapeutic effects on PSD through the synergistic dual pathways of inhibiting inflammatory factor release and suppressing apoptosis.

Electroacupuncture is an acupuncture therapy that enhances therapeutic efficacy by delivering micro-pulse electrical stimulation after deqi (needle sensation) is achieved at the acupoints. Wangu is an acupoint of the Gallbladder Meridian of Foot-Shaoyang, with effects of tranquilizing the mind, refreshing the brain, soothing the liver, and relieving depression, and is commonly used in the treatment of mental and emotional disorders. In PSD rat models established by MCAO combined with CUMS, after 21 days of electroacupuncture stimulation at Wangu acupoint, the results showed that compared with the model group, the treatment group had downregulated NF-κB expression in hippocampal tissue, reduced TNF-α and IL-1β contents, significantly alleviated hippocampal neuronal damage, and markedly improved depression-related behavioral scores [82].

The Xingnao Kaiqiao (Brain-Refreshing and Orifice-Opening) Acupuncture Therapy was founded by Academician Shi Xuemin, with mind regulation and awakening as the core. It commonly uses acupoints such as Neiguan, Baihui, and Sanyinjiao, with significant efficacy and high safety. Clinical studies have confirmed that this therapy can effectively improve neurological function and depressive mood in PSD patients [83]. Basic research further demonstrated that this therapy can upregulate the expression of monoamine neurotransmitters and nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) proteins to enhance antioxidant capacity [84]; it also modulates the P2X7R/NLRP3/IL-1β pathway, inhibits NLRP3 inflammasome activation, reduces pro-inflammatory factor levels and alleviates oxidative stress damage, and also regulates the expression of apoptosis-related proteins to reduce neuronal apoptosis. It exerts neuroprotective effects through multi-pathway synergy, thereby achieving therapeutic effects against PSD [85].

The Siguan (Four Gates) acupoints are a classic compatible acupoint group in clinical acupuncture, consisting of Hegu (LI4, Large Intestine Meridian) and Taichong (LR3, Liver Meridian), with effects of regulating qi and blood, soothing the liver and relieving depression, and opening orifices and refreshing the mind [86]. Studies found that electroacupuncture stimulation at the Siguan acupoints in PSD rats can significantly upregulate the protein expression

of BDNF and its receptor TrkB in the hippocampal region, and effectively improve depressive-like behaviors in model rats by enhancing synaptic plasticity and improving neuronal survival and function [87].

Tongdu Tiaoshen (Governing Vessel-Unblocking and Spirit-Regulating) Acupuncture originates from the academic thought of Professor Zhang Daozong, a renowned veteran TCM physician, on the treatment of encephalopathy. It has confirmed efficacy in both generalized anxiety disorder and PSD [88]. Studies have shown that this acupuncture therapy can significantly improve depressive-like behaviors and alleviate neuronal damage in the hippocampal CA1 region of PSD model rats, and its mechanism is related to activating the PI3K/Akt/mTOR signaling pathway, downregulating the expression of autophagy-related proteins, and inhibiting excessive neuronal autophagy to exert neuroprotective effects [89].

Patients with depression are under chronic stress, and the HPA axis is the central link of stress response [90]. A study by Guo et al. [91] confirmed that acupuncture at acupoints including Baihui, Shenting, Yintang, Sishencong, Hegu, and Taichong combined with fluoxetine can treat PSD by regulating HPA axis function. This combination therapy not only significantly reduces plasma ACTH and CORT levels in patients, but also effectively improves depressive symptoms, with superior efficacy to fluoxetine monotherapy.

In summary, various acupuncture modalities, including single-point stimulation, classic compatible acupoint acupuncture, characteristic spirit-regulating acupuncture therapies, electroacupuncture, and combined acupuncture and medicine, all exert definite antidepressant and neuroprotective effects against PSD, with the characteristics of precise targeting, safety and flexibility, and the ability to synergize with Western medicine to reduce toxicity and enhance efficacy. From the single Wangu acupoint and the Siguan acupoint combination to the characteristic therapies such as Xingnao Kaiqiao and Tongdu Tiaoshen, all take the hippocampus as the core target region. Through meridian-brain axis signal transduction, they block inflammatory cascades via multiple pathways, reduce nerve damage, regulate central neurotransmitters, enhance antioxidant capacity, remodel synaptic plasticity, and correct HPA axis hyperfunction. Acupuncture is effective as monotherapy, and its combination with Western medicine achieves complementary mechanisms and improved efficacy. These findings elucidate the mechanism of acupuncture in regulating the mind and relieving depression, and provide experimental support for the optimization of clinical PSD regimens.

6. Summary and Prospect

Stroke is the leading cause of death and disability among Chinese residents. As its most common complication, PSD severely hinders the rehabilitation process of patients, and also significantly increases the risk of stroke recurrence and mortality. TCM possesses unique advantages in the prevention and treatment of PSD [92]. This paper systematically reviews the research progress of TCM in the prevention and treatment of PSD by regulating key signaling pathways such as NF-κB and PI3K/Akt/mTOR. The results indicate that multiple intervention methods including TCM monomers, formulas, and acupuncture can exert multi-target and holistic regulatory effects on multiple pathological processes such as inflammatory response, oxidative stress, neurogenesis, and synaptic plasticity, improving depressive mood while promoting neurological functional recovery, which provides an important basis for clinical prevention and treatment of PSD.

Nevertheless, current research still has certain limitations. The overall quality of clinical studies remains to be improved: most are small-sample, single-center trials lacking standardized and unified efficacy evaluation criteria, which limits the reliability and reproducibility of the results. Mechanistic investigations mostly focus on individual signaling pathways, and research on the interconnections and overall synergistic effects between pathways is still insufficient. In addition, there is no consensus on TCM syndrome differentiation, with diverse syndrome classifications and a lack of widely applicable standardized protocols, which affects the individualized treatment of PSD.

Future research can focus on the following directions: first, large-sample, multi-center, high-quality clinical studies should be conducted to establish a standardized evaluation system for TCM treatment of PSD; meanwhile, in-depth integrated mechanistic studies at multiple pathway levels are needed to systematically elucidate the multi-target mechanism of TCM. On this basis, the standardization of TCM syndrome diagnosis should be promoted, and the association between different syndromes and underlying biological pathways should be clarified with the help of modern technology; furthermore, attention should be paid to the formulation of clinical individualized diagnosis and treatment strategies. Finally, continuous efforts should be made to strengthen the screening and development of active TCM ingredients to promote their clinical translation and application.

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