https://doi.org/10.31925/farmacia.2025.1.21 **ORIGINAL ARTICLE**

EFFICACY OF ST. JOHN'S WORT EXTRACT IN PATIENTS WITH POST-STROKE DEPRESSION

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Abstract

This study examined the antioxidant properties of St. John's Wort (SJW) extract and its effects on post-stroke depression (PSD). Using high-performance liquid chromatography (HPLC), the main components of SJW extract were identified as rutin (24.78%), hyperoside (20.50%), and isoquercitin (26.15%). Eighty PSD patients were divided into control (routine treatment) and observation (routine treatment + SJW extract) groups. Neurological function, depression, anxiety and daily living ability were assessed using validated scales. Serum levels of oxidative stress markers (MDA, 8-OHdG, SOD, GSH-Px) and inflammatory cytokines (IL-2, IL-6, TNF-α, IFN-γ) were measured by ELISA. After 8 weeks, the observation group showed significant improvements in SSS, NIHSS, HAMD, HAMA, SDS, and Barthel Index scores compared to the control group ($p < 0.05$). Serum levels of oxidative stress and inflammatory markers decreased, while neuroprotective factors (BDNF, TrkB, NP, 5-HT) increased. The overall efficacy rate was 95% in the observation group *vs*. 75% in the control group, with fewer adverse reactions (5% *vs*. 12.5%). SJW extract demonstrated strong antioxidant properties, significantly improving neurological function, mood and daily activities while reducing oxidative stress and inflammation in PSD patients.

Rezumat

Acest studiu a examinat proprietățile antioxidante ale extractului de sunătoare (St. John's Wort, SJW) și efectele sale asupra depresiei post-accident vascular cerebral (AVC). Au fost identificate cu ajutorul cromatografiei lichide de înaltă performanță (HPLC), principalele componente ale extractului: rutină (24,78%), hiperozidă (20,50%) și isoquercitină (26,15%). Optzeci de pacienți cu depresie post-AVC au fost împărțiți într-un grup control (tratament de rutină) și un grup de observație (tratament de rutină + extract SJW). Funcția neurologică, depresia, anxietatea și capacitatea de viață zilnică au fost evaluate utilizând scale validate. Nivelurile serice ale markerilor de stres oxidativ (MDA, 8-OHdG, SOD, GSH-Px) și citokinele inflamatorii (IL-2, IL-6, TNF-α, IFN-γ) au fost măsurate prin ELISA. După 8 săptămâni, grupul de observație a prezentat îmbunătățiri semnificative ale scorurilor SSS, NIHSS, HAMD, HAMA, SDS și Barthel Index comparativ cu grupul de control ($p < 0.05$). Nivelurile serice ale stresului oxidativ și ale markerilor inflamatori au scăzut, în timp ce factorii neuroprotectori (BDNF, TrkB, NP, 5-HT) au crescut. Rata generală de eficacitate a fost de 95% în grupul de observație *vs.* 75% în grupul de control, cu mai puține reacții adverse (5% *vs.* 12,5%). Extractul SJW a demonstrat proprietăți antioxidante puternice, îmbunătățind semnificativ funcția neurologică, starea de spirit și activitățile zilnice, reducând în același timp stresul oxidativ și inflamația la pacienții cu depresie post-AVC.

Keywords: SJW extract, free radical scavenging activity, post-stroke depression, neurological function, oxidative stress, inflammation

Introduction

Depression is a common secondary mental complication after stroke, with a high incidence, and it is easy to occur in people who are middle-aged and elderly [1]. Statistics show that about 30% of patients have depressive symptoms within the first 15 days after a stroke, and the incidence of depression is as high as 40% to 50% within one year [2]. The incidence, disability, and mortality of post-stroke depression (PSD) are high, which has posed a serious threat to the life and health of patients. PSD is associated with factors including central neurotransmitter dysregulation, immune-inflammation, and oxidative stress (OS) injury [3]. During a stroke, OS, lipid peroxidation, and DNA damage in brain tissue can be caused by the generation of reactive oxygen species. Therefore, OS damage is an important mechanism that induces the occurrence of PSD [4].

Norepinephrine reuptake inhibitors and 5-HT reuptake inhibitors are first-line treatments for depression. However, their safety and tolerability in PSD have not been clearly established. SJW, also known as *Hypericum perforatum* L., is a perennial herb. It has the effects of clearing heat, detoxification, swelling, and pain relief. The major active constituents of SJW extract include propiophenone, flavonoids, essential oils, and phloroglucinol [5]. SJW extract is rich in flavonoids,

with a content of up to 11.7%, mainly hyperoside, quercetin, and rutin [6]. With the deepening of research, SJW extracts have become more and more prominent in anti-virus, anti-depression, and anti-tumour results. Hypericin and other components of SJW extracts have obvious antiviral effects. Pan *et al*. (2022) [7] found that hypericin has a significant inhibitory effect on the activity of the HIV virus. Clinical experiments have confirmed that hypericin in SJW extracts can be selectively accumulated around tumour tissues and has little damage to healthy normal tissues. Pietrzak *et al*. (2022) [8] confirmed that hypericin can form a complex with adriamycin and interact with flat aromatic compounds to be used as a blocking molecule for detoxification of cancer patients after chemotherapy. Hu *et al*. (2021) [9] confirmed that hypericin is a potent photosensitiser that can mediate the mitochondrial apoptosis pathway to regulate the cell cycle of cancer cells and induce apoptosis. SJW extract showed potent antioxidant activity. Selek *et al*. (2019) [10] found that after gavage treatment of SJW extract in mice with experimental autoimmune encephalomyelitis, the OS index of the mice was significantly reduced, while the total antioxidant status in brain tissue was increased. Uslusoy *et al*. (2019) [11] showed that SJW could upregulate the levels of glutathione and glutathione peroxidase in rats with sciatic nerve injury and play a protective role in brain injury caused by inflammation, oxidation, and apoptosis. However, the efficacy and safety of SJW extract in PSD need to be further investigated.

In this research, the main components of SJW extract were analysed, the efficacy and safety of its combination in PSD were investigated, and its results on the OS, inflammatory response, and neurological function in patients were examined. This study serves as a reference for the application of SJW extract in the clinical treatment of depression and PSD.

Materials and Methods

Analysis and Identification of SJW Extracts

A quantity of 0.3 g of SJW extract tablets was placed in 250 mL triangular bottles with 100 mL of methanol (Sigma-Aldrich, USA), treated with FS-1200N ultrasonic processor (Shanghai Acy Scientific Instrument Co., LTD., China) for 40 min, and the extract was evaporated by rotation to a small volume. The extract was transferred to a 50 mL volumetric flask with an appropriate amount of methanol, and the sample solution was filtered through a 0.45 μm microporous filter membrane. The filtrate was injected into the Vanquish Core liquid chromatograph (Thermo Fisher, USA) to determine the fingerprint of the SJW extract. Chromatographic conditions: ODS-C18 column (150 mm × 4.6 mm, 5 μm) (Waters, USA); detection wavelength was 254 nm. Column temperature: 27℃; mobile phase (A): acetonitrile-0.25% phosphoric acid aqueous solution (15:85); mobile phase (B): acetonitrile-methanol-1.5% triethylamine (49:49:3). The flow rate was 1.0 mL/min. Mobile phase gradient: 0-10 min: A (100%), B (0%); 10-30 min: A (92%), B (8%); 30-40 min: A (50%), B (50%); 40-45 min: A (0%), B (100%) (Shanghai Macklin Biochemical Co., Ltd., China).

Study subjects

In this study, 80 patients with PSD admitted to Changsha Hospital, Changsha, Hunan, China from June 2020 to June 2022 were enrolled. The experiment obtained the approval by the ethics committee of Changsha Hospital, Changsha, Hunan, China and the patients and their families signed the informed consent.

Inclusion criteria: (1) patients met the diagnostic criteria of stroke in the Chinese Guidelines for the Prevention and Treatment of Cerebrovascular Diseases and the diagnostic criteria of PSD in the Chinese Classification and Diagnostic Criteria of Mental Disorders, 3rd edition; (2) HAMD score more than 17 points; (3) patients had no depressive disorder before the stroke, the onset of the stroke lasted for 14 days or more, and did not receive antidepressant treatment; (4) patients had clear consciousness; (5) patients had good medication compliance.

Exclusion criteria: (1) severe dementia, cognitive impairment, schizoaffective disorder, schizophrenia, bipolar disorder, and other diseases; (2) family history of mental illness; (3) severe dysfunction of heart, liver, kidney, and other organs; (4) transient ischaemic attack; (5) pregnant or lactating women; (6) patients allergic or contraindicated to the use of drugs.

Grouping and treatments

According to the random number table method, the patients were divided into a control group and an observation group, with 40 cases in each group.

The control group received routine treatment, including routine rehabilitation training and drug therapy. Conventional rehabilitation training included smoking and drinking cessation, strengthening exercise, weight control, reasonable diet structure, etc. Medication included edaravone injection (China Resources Double-Crane Pharmaceutical Co., Ltd., China), 30 mg intravenously (30 mg dissolved in 100 mL normal saline), twice daily and escitalopram oxalate (Xian Janssen Pharmaceutical Ltd., China), oral, 10 mg once daily for 8 weeks.

Based on the control group, the observation group received SJW extract tablets (Dr. Willmar Schwabe

GmbH & Co.KG, Germany), orally, 300 mg twice daily for 8 weeks.

Observation indicators

Indicators of Neurological Function

The Scandinavian Stroke Scale (SSS) [12] and the National Institutes of Health Stroke Scale (NIHSS) [13] were used to evaluate the neurological function of the patients before and after treatment. The SSS included 9 items such as consciousness level, orientation, language, eye movement, facial and limb paralysis, and gait. The higher the SSS score, the better the recovery of neurological function. The NIHSS scale scores range from 0 to 42, with higher scores indicating more severe neurological impairment.

Indicators of depression degree

Before and following the treatment, the Hamilton Depression Scale (HAMD) [14] and Self-Rating Depression Scale (SDS) [15] were used to evaluate the degree of depression of patients, and Hamilton Anxiety Scale (HAMA) [16] was adopted to evaluate the degree of anxiety of patients. The lower the HAMD score, the better the condition of the patients. A score between 7 - 16 was defined as mild depression and a score between 17 - 24 was defined as severe depression. A score of more than 24 was defined as severe depression. The SDS scale includes 20 items that reflect subjective feelings of depression and is scored on a four-grade scale based on the frequency of symptoms, with 10 positive and 10 negative scores. The lower the SDS score, the better the condition of the patients. The score of 53 - 62 was mild depression, the score of 63-72 was moderate depression, and the score of > 73 was severe depression. The HAMA scale included 14 items such as fear, anxiety, and sensory system, and the total score is 56. The higher the score, the more serious the anxiety level of patients.

Barthel index

Barthel index [17] was adopted to evaluate the ability of daily living of patients before and following remedy. The Barthel index includes 10 items such as eating, bathing, and dressing. The total score is 100 points, and the higher the score, the more independent the patient's daily living ability is. Barthel Index scores of 60 to 99 were classified as mild dysfunction, 41 to 59 as moderate dysfunction, 20 to 40 as severe dysfunction, and less than 19 as complete disability.

Oxidative stress indicators

An amount of 5 mL fasting venous blood was collected before and after treatment, centrifuged at 3000 rpm for 10 minutes and the serum was separated. The thiobarbituric acid method was used to detect serum MDA level (Shanghai Beyotime Biotech, Inc., China), the xanthine oxidase method was used to detect SOD level and serum levels of GSH-Px and 8-OHdG were measured by competitive ELISA (Shanghai Beyotime Biotech, Inc., China) according to manufacturer's instructions.

Serum inflammatory factor index

The levels of IL-2, IL-6, TNF-α and IFN-γ before and after treatment were determined in the serum by ELISA commercial kits (Shanghai Beyotime Biotech. Inc., China) according to the manufacturer's instructions.

Serum neurotransmitter indicators

The levels of BDNF, TrkB, NSE, NP, SP and 5-HT before and after treatment were determined in the serum by ELISA commercial kits (Shanghai Beyotime Biotech. Inc., China) according to the manufacturer's instructions.

Clinical efficacy

Clinical efficacy was evaluated according to the following criteria: if after treatment the HAMD score was reduced by > 75% as cured, by 50 - 75% as markedly effective, by 25 - 50% as effective, and by < 25% as ineffective. Total efficacy rate = (number of cured + number of markedly effective + number of effective)/total number of people × 100%.

Occurrence of adverse reactions

The occurrence of adverse reactions such as nausea, vomiting, dizziness, fatigue, etc. during the treatment was recorded.

Statistical methods

SPSS 22.0 software (IBM, USA) was used. Count data were presented as case (%), and χ^2 test was used. The measure data were presented as mean ± standard deviation ($\bar{x} \pm s$). Independent sample *t-tests* and paired sample *t-tests* were adopted for comparison. When $p < 0.05$, the difference had statistical significance.

Results and Discussion

Analysis and identification of SJW extracts

As illustrated in Figure 1, SJW extracts mainly contained rutin (24.78%), hyperoside (20.50%), isoquercitrin (26.15%), quercitrin (4.91%), quercetin (20.46%), pseudohyperoside (1.69%) and hypericin (1.51%).

General information

Table I presents the subjects' general data. It was found that there were no significant differences in gender ratio, age, body mass index, course of stroke, and course of depression between the two groups ($p > 0.05$).

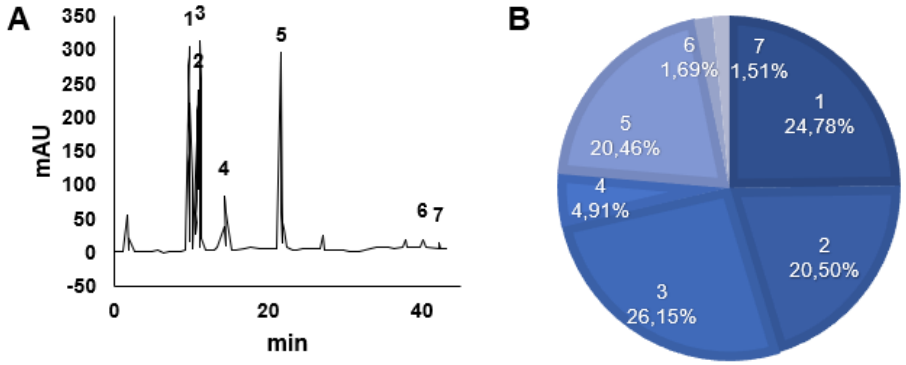

Figure 1.
Composition analysis of SJW extract
(A) HPLC fingerprint of SJW extract; (B) the ratio of the peak area of No. 1-7 to the total peak area
1: Rutin peak; 2: hyperoside peak; 3: isoquercitrin peak; 4: quercitrin peak; 5: quercetin peak;
6: false hyperoside peak; 7: hypericin peak

Table I
General data of subjects with PSD before treatment

Information	Control group (n = 40)	Observation group (n = 40)	t/χ^2	p
Male (n/%)	28/70.0	29/72.5	0.351	0.442
Age (years)	44.15 ± 3.82	44.21 ± 3.77	0.404	0.429
Body mass index (kg/m^2)	22.08 ± 1.03	22.10 ± 1.18	0.567	0.350
Stroke duration (months)	2.81 ± 0.75	2.88 ± 0.73	0.223	0.514
Duration of depression (months)	2.12 ± 0.48	2.13 ± 0.45	0.189	0.638

Neurological function
Figure 2 presents SSS and NIHSS scores of subjects before and after 8 weeks of treatment. Eight weeks later, the SSS and NIHSS scores of the subjects were visibly lower relative to before treatment. As compared to the control group, the observation group had visibly decreased SSS and NIHSS scores (all $p < 0.05$).

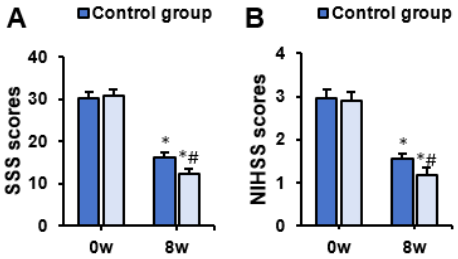

Figure 2.
Contrast of neurological function scores before and following treatment
(A) SSS score; (B) NIHSS score
. w: week. *compared with the same group before treatment (0w), $p < 0.05$; #compared with the control group, $p < 0.05$

Negative emotions and activities of daily living
Figure 3 illustrates the differences in HAMD, HAMA, SDS scales, and Barthel index scores of subjects before and 8 weeks following treatment. Eight weeks later, the scores of HAMD, HAMA, and SDS were visibly lower, and the Barthel index score was visibly higher relative to before the treatment. Compared with the control group, the observation group had the same results as above (all $p < 0.05$).

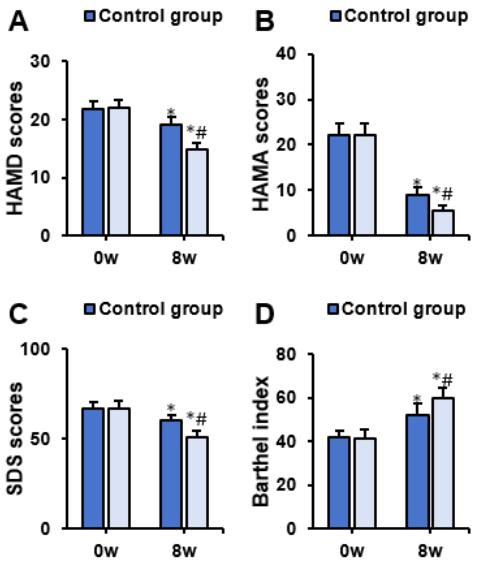

Figure 3.
Contrast of the scores of negative emotions and activities of daily living before and following remedy
(A) HAMD score; (B) HAMA score; (C) SDS score; (D) Barthel index score
*compared with the same group before treatment (0w), $p < 0.05$; #compared with the control group, $p < 0.05$

OS levels

Figure 4 presents serum levels of OS indicators MDA, SOD, GSH-Px and 8-OHdG in subjects before and after 8 weeks of treatment. Eight weeks later, the levels of MDA and 8-OHdG were visibly lower, while the levels of SOD and GSH-Px were visibly higher relative to before the treatment. Compared with the control group, the observation group had the same results as above (all $p < 0.05$).

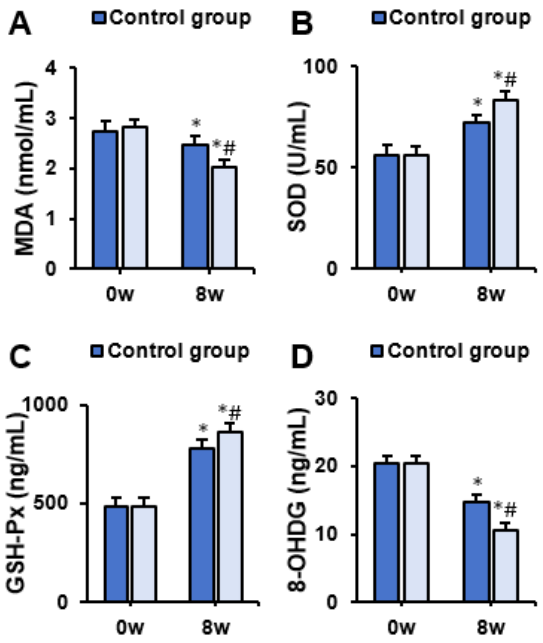

Figure 4.

Contrast of serum OS index levels before and following remedy

(A) serum MDA; (B) serum SOD; (C) serum GSH-Px; (D) serum 8-OHdG

*compared with the same group before treatment (0w), $p < 0.05$; #compared with the control group, $p < 0.05$

Level of inflammation

Figure 5 presents levels of serum inflammatory response markers IL-2, IL-6, TNF-α, and IFN-γ in subjects before and 8 weeks following treatment. Compared to the level before the treatment the serum levels of IL-2, IL-6, TNF-α, and IFN-γ in the subjects were visibly lower 8 weeks later. Compared with the control group, the observation group had the same results as above (all $p < 0.05$).

Neurotransmitter levels

Figure 6 presents the levels of serum neurotransmitter indicators BDNF, TrkB, NSE, NP, SP, and 5-HT in subjects before and after 8 weeks of treatment. Eight weeks later, the serum levels of NSE and SP were visibly lower, while the levels of BDNF, TrkB, NP, and 5-HT were visibly higher relative to prior to treatment. Compared with the control group, the changes in the observation group were the same (all $p < 0.05$).

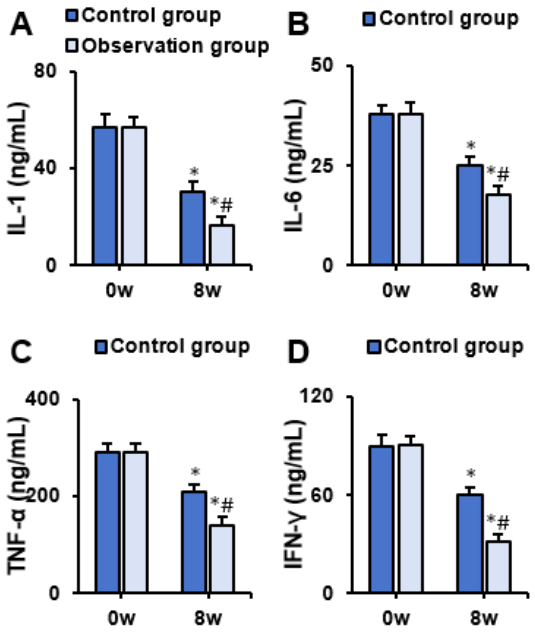

Figure 5.

Contrast of serum inflammatory markers before and following remedy

(A) serum IL-2; (B) serum IL-6; (C) serum TNF-α; (D) serum IFN-γ

*compared with the same group before treatment (0w), $p < 0.05$; #compared with the control group, $p < 0.05$

Efficacy of treatment

Table II presents the efficacy in subjects after treatment. In the control group, recovery in 8 cases (20.0%), 8 cases were markedly improved (20.0%), 14 cases (35.0%) were effective, invalid in 10 cases (25.0%), and the total effective 30 cases (75.0%). In the observation group, recovery in 13 cases (32.5%), 15 cases were markedly improved (37.5%), 10 cases (25.0%) were effective, invalid in 2 cases (5.0%), the total effective 38 cases (95.0%). The total response rate in the observation group was visibly higher as against the control group ($p < 0.05$).

The adverse reactions

The incidence of adverse events in subjects at 8 weeks post-treatment is shown in Table III. In the control group, nausea occurred in 2 cases (5.0%), vomiting in 1 case (2.5%), dizziness in 1 case (2.5%), fatigue in 1 case (2.5%), and the total adverse reactions occurred in 5 cases (12.5%). In the observation group, nausea occurred in 0 case (0.0%), vomiting in 0 case (0.0%), dizziness in 1 case (2.5%), fatigue in 1 case (2.5%), and total adverse reactions occurred in 2 cases (5.0%). The total adverse reaction rate in the observation group was markedly lower than in the control group ($p < 0.05$).

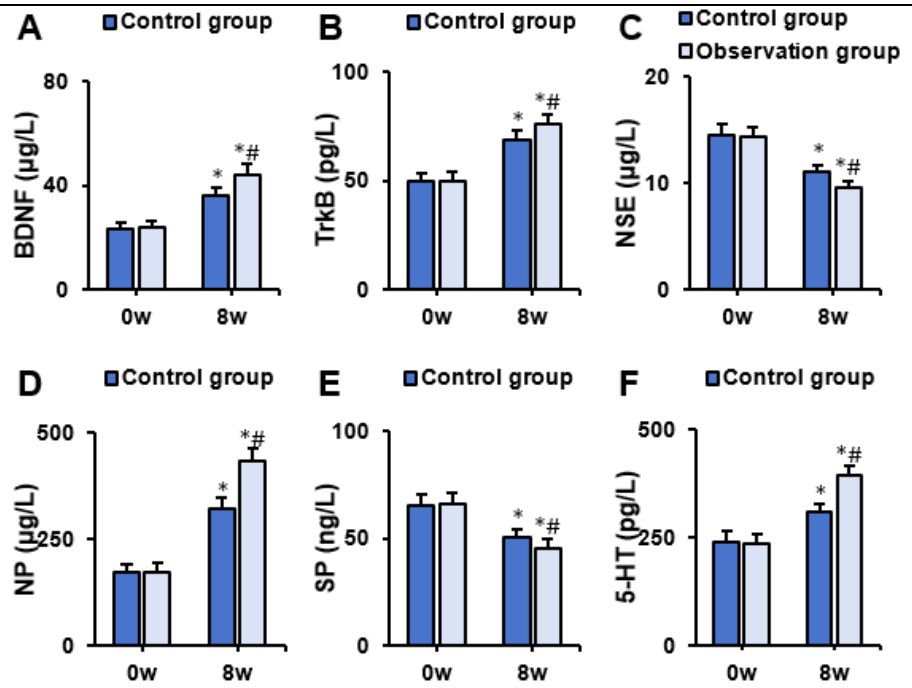

Figure 6.

Contrast of serum neurotransmitter indexes before and following remedy

(A) serum BDNF; (B) serum TrkB; (C) serum NSE; (D) serum NP; (E) serum SP; (F) serum 5-HT

*compared with the same group before treatment (0w), $p < 0.05$; #compared with the control group, $p < 0.05$

Table II

Contrast of treatment outcomes in subjects with PSD (*n*/%)

Grouping	Healed	Remarkable results	Effective	Invalid	Total response rate
Control group (*n* = 40)	8/20.0	8/20.0	14/35.0	10/25.0	30/75.0
Observation group (*n* = 40)	13/32.5	15/37.5	10/25.0	2/5.0	38/95.0
χ^2					5.039
P					0.031

Table III

Contrast of adverse reactions in subjects with PSD (*n*/%)

Grouping	Nausea	Vomiting	Dizziness	Fatigue	Total adverse reactions
Control group (*n* = 40)	2/5.0	1/2.5	1/2.5	1/2.5	5/12.5
Observation group (*n* = 40)	0/0.0	0/0.0	1/2.5	1/2.5	2/5.0
χ^2					3.197
P					0.044

At present, the pathogenesis of PSD is not completely clear, but it is believed that nerve function damage, neurotransmitter disorder and OS injury are important factors causing PSD [18]. The search for natural free radical scavenging drugs has attracted wide attention, and the antioxidant activity of free radicals such as DPPH·, ABTS+·, and ·OH of flavonoids and phenolic compounds in plants is also more and more widely studied [19]. This research found that SJW extract contained more than 70% of rutin, hyperoside, and isoquercitrin, all of which belong to flavonoids. Its own benzene ring and double-bond structure give it the ability to donate electrons or hydrogen atoms, thereby neutralising free radicals and reducing OS damage to cells and tissues [20, 21]. These results indicate that SJW extract has good free radical scavenging activity and a strong antioxidant effect.

OS injury is an important mechanism for the occurrence of PSD. OS occurs in the brain after stroke, which generates a large number of free radicals and leads to neuronal damage [22]. OS can hinder the repair and regeneration of neurones and affect neuroplasticity [23]. Other studies have confirmed that OS can affect the synthesis and secretion of BDNF, thereby aggravating brain damage [24]. Liu *et al*. (2018) [25] found that serum MDA and 8-OHdG levels were increased in subjects with PSD and were related to the severity of depression. This research found that the serum MDA and 8-OHdG levels of subjects were markedly reduced following the remedy, and the SOD and

GSH-Px levels were markedly increased, among which the serum OS index levels of patients with SJW extract tablets changed more markedly. Nabavi *et al*. (2018) [26] found that SJW extract could markedly improve the depressive-like behaviour of mice with PSD and increase GSH and SOD activities in brain tissue. These results suggest that SJW extract can markedly improve OS damage in subjects with PSD, and SJW extract can markedly improve OS damage in subjects with PSD.

According to the inflammatory factor hypothesis, stress stimulates the hypothalamic-pituitary-adrenergic system, which induces the secretion of typical inflammatory factors such as IL-2, IL-6 and TNF-α, thereby inhibiting the expression of cortical hormone receptors in the system and inducing depression [27]. This research observed that the expression levels of serum pro-inflammatory cytokines IL-2, IL-6, TNF-α, and IFN-γ in subjects were markedly reduced following remedy, and the serum pro-inflammatory cytokine levels in patients with SJW extract tablets were even lower. Khalil *et al*. (2023) [28] found that SJW extract and prepared nanoemulsion adopted for cisplatin in severe rats processing can enhance its antioxidant system function, reduce brain levels of proinflammatory cytokines, play a role in improving the neurotoxicity induced by chemotherapy. In conclusion, SJW extract can reduce the degree of inflammatory response in subjects with PSD, thus playing a therapeutic role.

According to the mechanism of the endogenous hypothesis, the occurrence of depression is a physiological basis for monoamine neurotransmitter in the brain's metabolic abnormalities, including 5-HT, dopamine, norepinephrine, *etc*. [29]. After a stroke, the lesions will affect serotonergic neurones, NE neurones, and their transmission pathways and inhibit the synthesis and secretion of monoamine neurotransmitters, thus leading to the occurrence of PSD [30]. SP is a kind of neuropeptide substance, which is involved in the regulation of emotional changes, inflammatory response, and immune function in the body. It belongs to the excitatory neurotransmitter and is highly expressed in patients with depression and anxiety [31, 32]. This research suggested that the serum NSE and SP levels of subjects decreased, while NP and 5-HT levels increased following remedy, and the changes of each index in patients with SJW extract tablets were more obvious. Pharmacological studies have confirmed that SJW extract can promote the content of neurotransmitters such as 5-HT, dopamine, and norepinephrine in the synaptic cleft, regulate the hypothalamic-pituitary-epinephrine axis, and play an anti-anxiety and anti-depression role [33]. Neurotrophins are closely related to the occurrence and development of PSD. BDNF is a kind of protein secreted by neurones and astrocytes, which can specifically bind to the TrkB receptor on the adjacent cell membrane and play a regulatory role in the growth of nerve cells and the repair and regeneration of neurones [34]. The BDNF/TrkB pathway plays a role in the regulation of the nervous system and is also a key target for antidepressant treatment [35]. This research suggested that the serum BDNF and TrkB levels of subjects increased following remedy, and the BDNF and TrkB levels of patients with SJW extract tablets increased more markedly; SSS, NIHSS, HAMD, HAMA, and SDS scores were smaller, and the clinical treatment efficiency was higher. Ng *et al*. (2017) [36] adopted meta-analysis and systematic evaluation to find that SJW extract can markedly improve the depressive symptoms of patients with mild to moderate depression, with high safety and efficacy. In conclusion, SJW extract can improve neurological function, depression and anxiety symptoms, and treatment effect in subjects with PSD by regulating monoamine neurotransmitter metabolism and the BDNF/TrkB pathway.

Conclusions

HPLC analysis suggested that the total flavonoid content of SJW extract was 74.63%, which had good free radical scavenging activity and a strong antioxidant effect. Clinically, the conventional treatment of stroke and oral escitalopram oxalate combined with SJW extract tablets can markedly improve the neurological function, depression and anxiety symptoms of stroke patients with depression. It can also reduce the degree of OS injury and inflammatory reaction, improve the clinical treatment effect, and reduce the incidence of adverse reactions. However, this research did not conduct a follow-up study, and the study time needs to be expanded in the future to analyse its effect on the long-term prognosis of patients.

Conflict of interest

The authors declare no conflict of interest.

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