Clinical efficacy of Bupleuri Radix combined with syndrome differentiation behavior therapy in the treatment of non-suicidal self-injury depression

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Depression is a prevalent condition within the Psychiatry Department. Patients typically exhibit a diminished interest in external stimuli, persistent low mood, and in severe cases, a propensity for self-harm and suicidal ideation. Non-suicidal self-injury (NSSI) refers to the deliberate infliction of harm on one's body tissue without the intent to cause death. The common practices of NSSI include cutting, scalding, scratching, and biting. Treating depression in patients who engage in NSSI presents unique challenges. It requires an intensified focus on psychological and behavioural interventions alongside pharmacological treatment for optimal outcomes. Bupleuri Radix, a widely utilized traditional Chinese medicine, is known for its qi-regulating properties, offering a multifaceted approach to alleviating depressive symptoms by soothing the liver. Dialectical behaviour therapy (DBT), a structured cognitive-behavioural treatment, has demonstrated significant efficacy in reducing NSSI. This study explores the combination of Bupleuri Radix with DBT for the treatment of depression in patients with NSSI, yielding promising preliminary results and offering a novel perspective on the treatment of NSSI in depressive patients.

Keywords: Bupleuri Radix; Dialectical behavior therapy; Non-suicidal self-injury; Depression; Clinical effect

INTRODUCTION

Depression is a multifaceted condition, encompassing a range of emotional, cognitive, and physiological manifestations. It is typified by persistent low mood, waning interest, and slowed cognitive processing. As highlighted in studies, the depression's widespread nature coupled with its association with a high incidence of self-harm and mortality

rates, has emerged as a pressing global health issue [1-2]. Beyond the distressing emotional experiences it induces, depression often co-occurs with non-suicidal self-injury (NSSI), further complicating the clinical picture and patient management. NSSI encompasses a pattern of intentional, self-inflicted injuries to one's body, performed without the aim of suicide, and includes methods such as cutting, burning, scratching, colliding, and striking. Cutting is the most prevalent form of NSSI [3]. This behaviour intersects with the aetiology of depressive disorders, with the latter being a significant risk factor for NSSI. The primary motivation behind NSSI is to alleviate and regulate distressing emotions. While these acts are not life-threatening, in severe instances, the intense negative emotions they reflect can escalate to suicidal tendencies [4-5]. Current Western medical treatments for depression often face challenges of adverse effects and poor patient adherence. In contrast, Radix Bupleuri (Figure 1), a traditional Chinese medicine widely recognized for its qi-regulating properties, is known for its liver-soothing and depression-relieving effects. It exhibits a multi-component, multi-target, and multi-channel antidepressant profile, making it a favoured choice in clinical depression treatment with a proven track record of efficacy [6].

Figure 1 Bupleuri Radix.

Contemporary medical research indicates that the key antidepressant constituents of Bupleuri Radix (Figure 2) are saikosaponin A (SSA) and saikosaponin D (SSD).

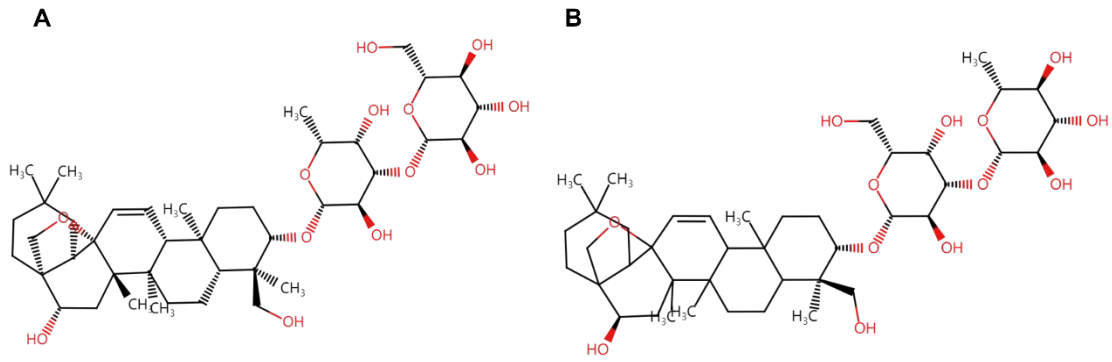


Figure 2 Active ingredients in bupleurum. (A) Saikosaponin A, (B) Saikosaponin D

These compounds exert their pharmacological influence in the prevention and management of depression by modulating monoamine neurotransmitters, enhancing brain-derived neurotrophic factors, regulating neuroinflammatory processes, and impacting the immune system's equilibrium [7-8]. Dialectical Behavior Therapy (DBT) is an innovative form of cognitive-behavioural therapy that extends upon traditional approaches. It aims to assist individuals in managing overwhelming emotions and bolstering their capacity to cope with distress without succumbing to loss of control or engaging in self-destructive behaviours [9]. To date, previous studies lack on the application of bupleurum in conjunction with DBT for NSSI patients. This paper investigates the therapeutic efficacy of this combined treatment for individuals with NSSI depression, offering novel insights and methodologies for addressing this complex condition, as detailed in the following report.

MATERIALS AND METHODS

2.1 Research object

Seventy participants diagnosed with depression and exhibiting NSSI and admitted to our facility between April 2022 and December 2023 were enrolled in this investigation. The participants were categorized based on their treatment protocols into a conventional treatment group (n=37) and a combined treatment group (n=33).

Eligibility for participation was determined by: (1) The individuals received a clinical diagnosis of depression following assessments conducted using established evaluation criteria; (2) The patient was more than 12 years old and exhibited clear-cut acts of self-harm; (3) The information in the patient's medical chart is comprehensive and accurate. Exclusion criteria included: (1) The individual exhibited intense negativity and engaged in a life-threatening act of self-harm; (2) The individual was diagnosed with one or more of the following conditions: schizophrenia, bipolar disorder, autism spectrum disorder, intellectual disability, or borderline personality disorder; (3) The individual had co-occurring non-psychiatric health conditions. The study protocol was reviewed and sanctioned by the institutional ethics board.

2.2 Intervention methods

2.2.1 Conventional Treatment Group

The conventional treatment involved the administration of sertraline hydrochloride tablets (manufactured by Pfizer Pharmaceutical Company, 50mg per tablet, batch number: H10980141). The sertraline hydrochloride tablets were taken orally daily, with an initial dosage of 50mg. The dosage could be incrementally adjusted based on the therapeutic requirements, not exceeding a maximum of 200mg. Once the desired therapeutic effect was achieved, the dosage was tapered down to the lowest effective amount for maintenance. The duration of this treatment phase was set at 8 weeks.

2.2.2 Integrated Therapy Approach

Patients were treated using a combination of Traditional Chinese Medicine (TCM) decoction, modified chaihu decoction, alongside DBT, the treatment was continued for a duration of 8 weeks.

The herbal formulation for modified chaihu decoction included the following ingredients: Radix Bupleuri 20g, Radix Scutellariae 15g, Rhizoma Pinelliae 10 g, Radix Pseudostellariae 10 g, Radix Paeoniae Alba 10 g, Turmeric 10 g, and Angelica 10 g, with Radix Glycyrrhizae at 5g. These medicinal materials were prepared by boiling in water to yield a liquid extract of 400 mL, which was then taken in two divided doses, morning and evening.

DBT is conducted by clinicians who are expertly trained to provide one-on-one therapy or group sessions for patients. The primary focus areas of this therapy include: (1) Fostering mindfulness, which involves guiding patients to practice deep breathing to maintain composure and steer clear of negative thoughts and impulsive actions. (2) Enduring distress, where patients are helped to assess the benefits of tolerating pain, using soothing and distraction techniques to prevent extreme emotional shifts. (3) Managing emotions through proactive communication between doctors and patients, delving into patients' inner thoughts, offering psychological support and positive reinforcement to enhance emotional regulation. (4) Enhance patients' social connections and equip their essential life skills. Encourage patients to maintain a calm and enjoyable emotional state, and practice active listening towards the experiences of others without resorting to judgment, intimidation, or aggression. Teach patients stress management techniques, help them recognize early indicators of relapse, and promote self-awareness of their condition's fluctuations. Subsequently, develop patients' social interaction abilities, engage them with their community and broader society, and support their gradual acquisition of self-sufficiency.

2.3 Monitoring Parameters and Assessment Standards

2.3.1 The Hamilton Depression Scale (HAMD)

The HAMD [10] comprises 24 items, with the majority being rated on a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). A few items are rated on a 3-point scale (0 = absent, 1 = mild to moderate, 2 = severe), and the cumulative score can vary between 0 and 74 points. An elevated score on the HAMD indicates a greater severity of depressive symptoms. A total score exceeding 35 points denotes severe depression, a score above 20 points suggests mild to moderate depression, and a score below 8 points indicates the absence of depressive symptoms.

2.3.2 The Hamilton Anxiety Scale (HAMA)

The HAMA [11] consists of 14 items, each scored on a five-point scale (0 = no symptoms, 1 = absent, 2 = mild, 3 = moderate, 4 = severe), with a total score ranging

from 0 to 56 points. An increased score on the HAMA corresponds to more severe anxiety symptoms. A score less than 7 points indicates the absence of anxiety, 7-13 points suggest the possibility of anxiety, 14-20 points indicate a definite anxiety disorder, 21-28 points reflect significant anxiety, and 29 points or above denote severe anxiety levels.

2.3.3 The Ottawa Self-Injury Inventory (OSI)

This inventory [12] comprises 27 items. The initial three questions conduct a comprehensive assessment of a patient's self-injury behaviour, while the subsequent 24 questions delve into the frequency of self-injury, the underlying motivations, the body sites involved, the techniques used, the drive to resist self-injury, and the treatment approaches employed.

2.3.4 Related serum indicators

The levels of serum inflammatory factors interleukin-6 (IL-6), tumour necrosis factor (TNF-α), norepinephrine (NE), 5-hydroxytryptamine (5-HT), dopamine (DA), neuron-specific enolase (NSE), neuropeptide Y (NPY) and brain-derived neurotrophic factor (BDNF) were detected by enzyme-linked immunosorbent assay (ELISA).

2.4 Quality control

The medical staff engaged in this project, comprising doctors, psychotherapists, and psychologists, are all duly certified with the appropriate degrees and professional licenses in their respective fields. They have additionally been trained in the specific methods of DBT. The intervention team underwent a unified training regimen to ensure strict adherence to the intervention protocol. The selection of subjects for the intervention was methodical, following the defined criteria for participation. Ensuring the accuracy and comprehensiveness of the collected data was a priority, with two committed team members assigned to oversee this process.

2.5 Data Analysis Techniques

Data were analyzed using SPSS version 23.0. Quantitative data that followed a normal distribution are presented as mean ± standard deviation ($\bar{x}$ ± s), with independent samples t-tests conducted to compare differences between groups. Categorical data are

represented as frequencies and percentages, with differences between groups assessed using the χ^2 test. Statistical significance was determined at the $P < 0.05$ level.

RESULTS

3.1 General Information

The conventional treatment group comprised 37 individuals, with 15 males and 22 females, ranging in age from 12 to 28 years and having a mean age of 19.19 ± 3.59 years. The combined treatment group consisted of 33 participants, including 14 males and 19 females, with ages spanning 13 to 25 years and a mean age of 19.30 ± 3.13 years. No disparities in gender distribution or age were observed between the two groups ($P > 0.05$).

3.2 Pre-Treatment Injury Patterns

According to the Ottawa Self-Injury Inventory, the predominant method of self-harm was cutting, practiced by 54.29% of the subjects. This was followed by 51.43% who inflicted skin punctures with sharp objects and 42.86% who opted for scratching as their self-harming behavior. For further details, refer to Figure 3.

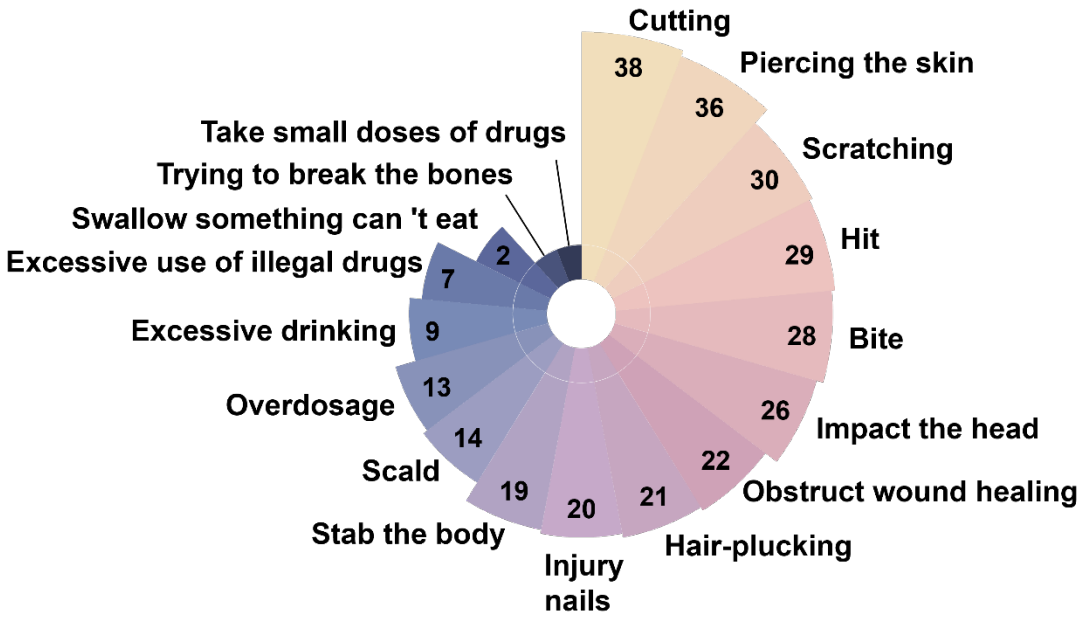


Figure 3 Self-Harm Modes Employed by Patients With NSSI. The number in the figure represents the cases of the method.

Findings from the Ottawa Self-Injury Inventory indicated that 70% of participants opted for the hand as their site of injury, while 48.57% targeted their upper arm or elbow, and 37.14% selected their lower arm or wrist for self-harm. This preference could be attributed to the accessibility of the upper limbs. Further insights are illustrated in Figure 4.

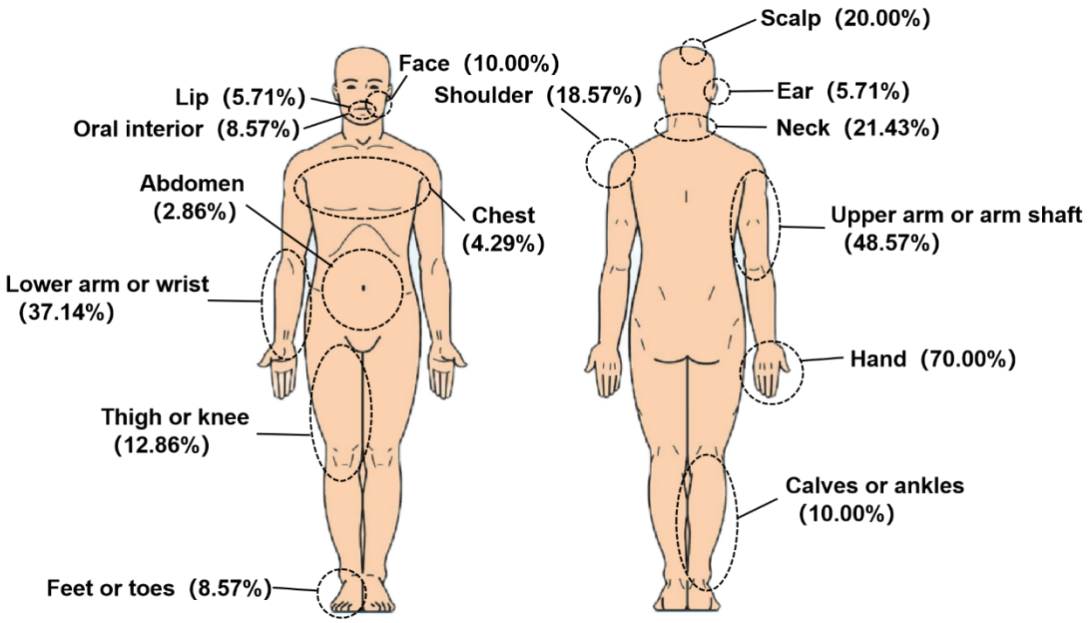


Figure 4 The Patient's Self-Harm Behavior Location. The percentage represents the proportion of NSSI in this site in this study.

3.3 Analysis of Hamilton Depression and Anxiety Scales Post-Intervention

Both groups exhibited comparable HAMD and HAMA scores at the outset and two weeks into the treatment, with close score ($P < 0.05$). However, at the 4-week, 6-week, and 8-week marks, the combined treatment group demonstrated a marked reduction in scores compared to the conventional treatment group ($P < 0.05$). For visual reference, see Figure 5.

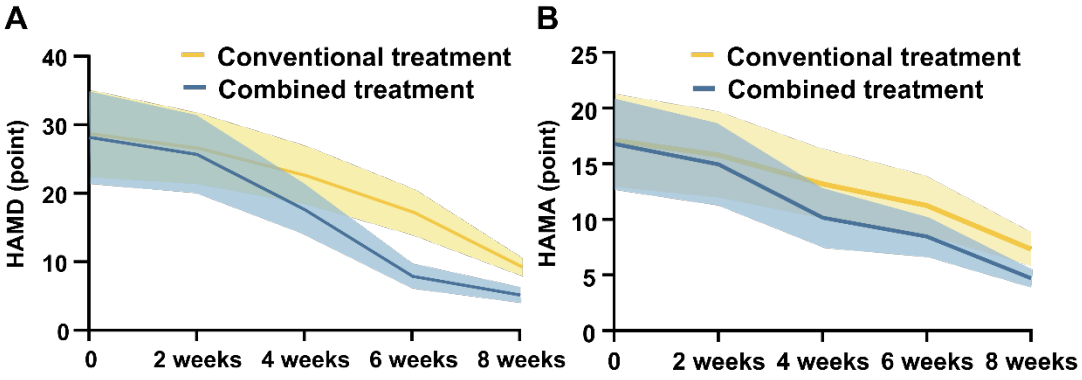


Figure 5 Depression and anxiety across four time points in two groups.

(A) Depression level; (B) Anxiety level.

3.4 Inflammatory Factor Levels

Initially, inflammatory concentrations of IL-6 and TNF-α were comparable between the two groups ($P > 0.05$). Following the intervention, both groups exhibited reduced levels of these inflammatory markers; however, the decline was more pronounced in the group receiving combined therapy as opposed to the conventional therapy group ($P < 0.05$). As shown in Figure 6.

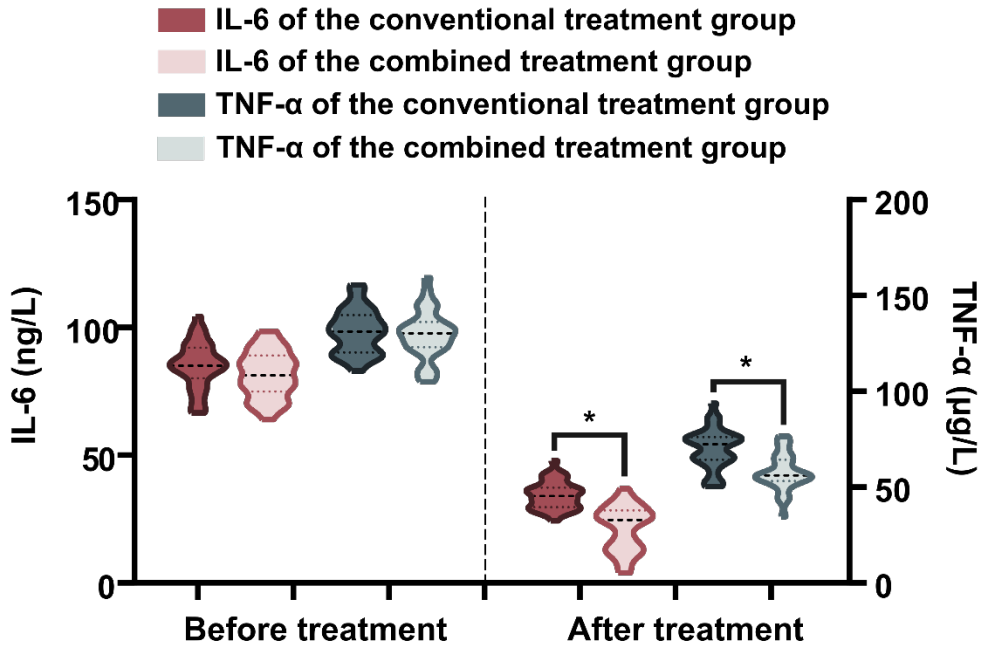


Figure 6 Analysis of Inflammatory Factor Concentrations in Two Patient Cohorts.

3.5 Analysis of Monoamine Neurotransmitter Levels

A comparative examination of the levels of monoamine neurotransmitters, specifically NE, 5-HT, and DA, in the serum of participants from both groups was conducted. Initially, it was observed that prior to the intervention, the serum concentrations of NE, 5-HT, and DA showed no notable variance between the two groups ($P > 0.05$). Post-intervention, an elevation in the serum concentrations of these neurotransmitters was noted in both groups. However, the serum concentrations of NE, 5-HT, and DA in the group that received the combined treatment were notably higher when compared to the group that underwent conventional treatment ($P < 0.05$). For further details, refer to Figure 7.

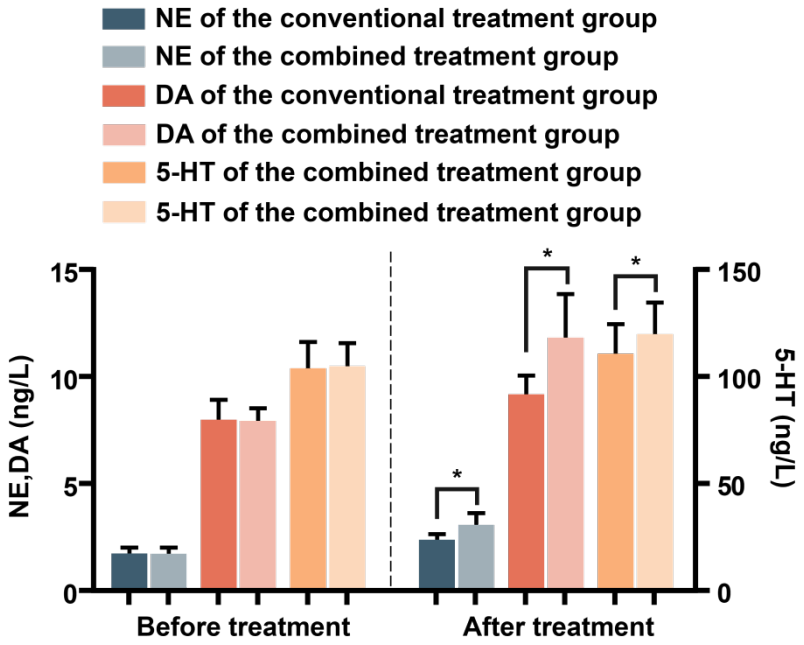


Figure 7 Analysis of Monoamine Neurotransmitter Levels Between Two Groups.

3.6 Levels of brain function injury-related factors

Following the treatment, the levels of NSE in both groups exhibited a decrease compared to pre-treatment levels. Notably, the reduction observed in the group receiving combined treatment was more pronounced than that in the group undergoing conventional treatment ($P < 0.05$). Conversely, the concentrations of NPY and BDNF both showed an increase post-treatment, surpassing their respective pre-treatment levels.

The combined treatment group also demonstrated higher levels of NPY and BDNF compared to the conventional treatment group ($P < 0.05$). For a detailed visual representation, refer to Figure 8.

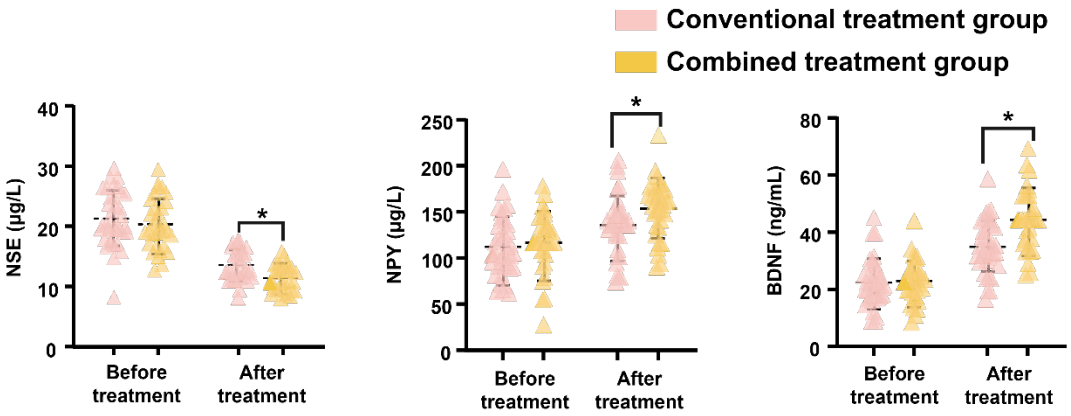


Figure 8 Evaluation of Brain Function Injury-Related Biomarkers in Both Groups.

DISCUSSION

Depression is categorized as a mental health disorder. Epidemiological data reveals that the lifetime prevalence rate of depression among the Chinese population stands at 3.4% [13]. In tandem with escalating life and work pressures, alongside heightened external stressors, the incidence of depression has witnessed a notable upsurge in recent years [14]. Symptomatically, the majority of patients present with delusions, hallucinations, persistent low mood, and fatigue, while a minority exhibit self-harm and suicidal tendencies. NSSI represents a unique form, serving as a maladaptive coping strategy employed by individuals facing psychological distress [15]. In the management of depression, pharmacological intervention forms the foundational approach, and psychotherapeutic interventions play a crucial role in alleviating distress, rehabilitating social functioning, and enhancing the overall quality of life for affected individuals.

Typical behaviours of NSSI encompass cutting, scratching, impeding wound healing, scalding, and biting, among others. These acts are frequently coupled with intense negative emotions, self-deprecating tendencies, and a deficiency in emotional regulation skills [16]. The results of this study findings indicate that among the 70 participants, the prevalent methods of self-harm include cutting, puncturing the skin

with sharp instruments, and scratching. The commonality among these behaviours is the infliction of harm through physical means. Such actions only necessitate simple tools and are not bound by specific circumstances, hence their high incidence. The most frequently targeted areas for self-injury are the hands, upper arms or arm shafts, and lower arms or wrists, likely due to the vulnerability of the upper limbs and the non-lethal nature of these sites. Patients exhibiting NSSI are prone to repeat such behaviours, potentially due to impaired function in their left superior frontal gyrus and weakened emotional control capabilities. Research indicates that individuals engaging in NSSI tend to experience more profound negative emotions, such as hostility and rage, and are inclined to channel these emotions into self-harm and aggressive behaviours [17]. The determinants and catalysts of NSSI behaviour predominantly stem from three spheres: personal characteristics, early life experiences, and interpersonal dynamics. Regarding personal factors, the inability to restrain impulsive actions, challenges in managing emotions, a negative self-body image, and issues related to self-esteem and personality can all influence an individual's likelihood of resorting to NSSI [18].

Bupleuri Radix is recognized for its properties of calming the liver, alleviating depressive symptoms, clearing heat, and uplifting yang energy. Contemporary pharmacological research has identified that Radix Bupleuri is rich in saponins, flavonoids, polysaccharides, coumarins, sterols, volatile oils, and other bioactive compounds, which contribute to its range of therapeutic effects, including hepatoprotection, choleresis, antipyresis, analgesia, anti-inflammation, antibacterial activity, antidepressancy, antioxidant properties, antitumor potential, and antiepileptic capabilities [19]. Saikosaponin, a key active constituent in Radix Bupleuri, is primarily responsible for the herb's antidepressant effects and exerts a multitude of pharmacological actions on the central nervous system. DBT, developed by Professor Marsha Linehan in 1991, is specifically tailored for individuals presenting with NSSI and suicidal tendencies. DBT has been established as an effective intervention for borderline personality disorders and has shown promise in addressing a variety of other psychiatric conditions [20]. The essence of DBT lies in assisting patients in enhancing

their capacity to tolerate distressing emotions, fostering self-acceptance, boosting adaptive coping mechanisms, preventing emotional dysregulation, diminishing the incidence of maladaptive and impulsive behaviors, and improving interpersonal communication skills. Professor Linehan posits that patients often harbour an excessive fear of their negative emotions, leading them to employ maladaptive coping mechanisms as a means of avoidance. DBT, when applied in the treatment of such patients, can empower them to develop a heightened tolerance for negative affect, embrace more constructive coping strategies, and mitigate the incidence of impulsive behaviours. It is only when patients learn to concentrate their attention on the present that they can free themselves from the torment of painful memories [21].

The findings of this study indicate that patients treated with a combination of Bupleuri Radix and dialectical behaviour therapy experienced a significant reduction in both depression and anxiety symptoms, with a more pronounced improvement compared to those treated with conventional approaches. Concurrently, the combined therapy group exhibited a notable increase in serum levels of NE, 5-HT, and DA. The monoamine neurotransmitter hypothesis [22], widely acknowledged in the field, posits that the onset of depression is intricately linked to diminished levels of the monoamine neurotransmitters 5-HT, NE, and DA. By targeting the neurotransmitters—5-HT, NE, and DA—increasing their concentrations in the brain's synaptic clefts and bolstering their physiological activities can yield antidepressant effects (Figure 9).

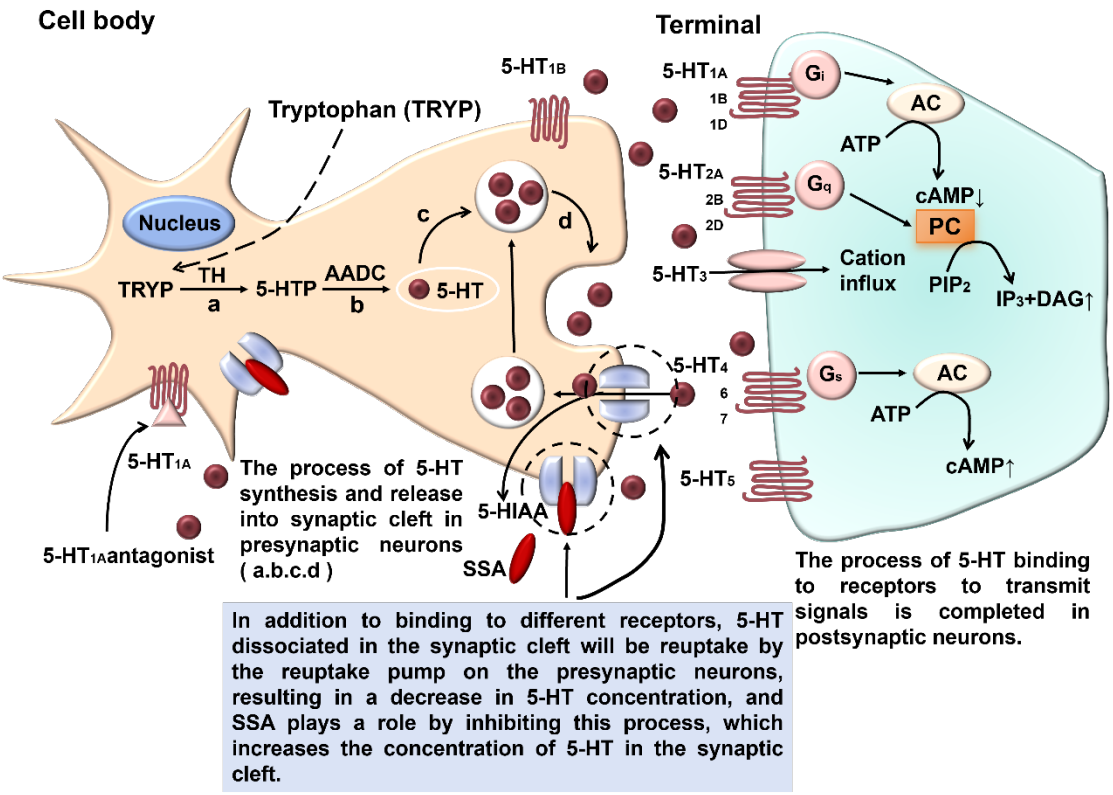


Figure 9 The mechanism of 5-HT and SSA.

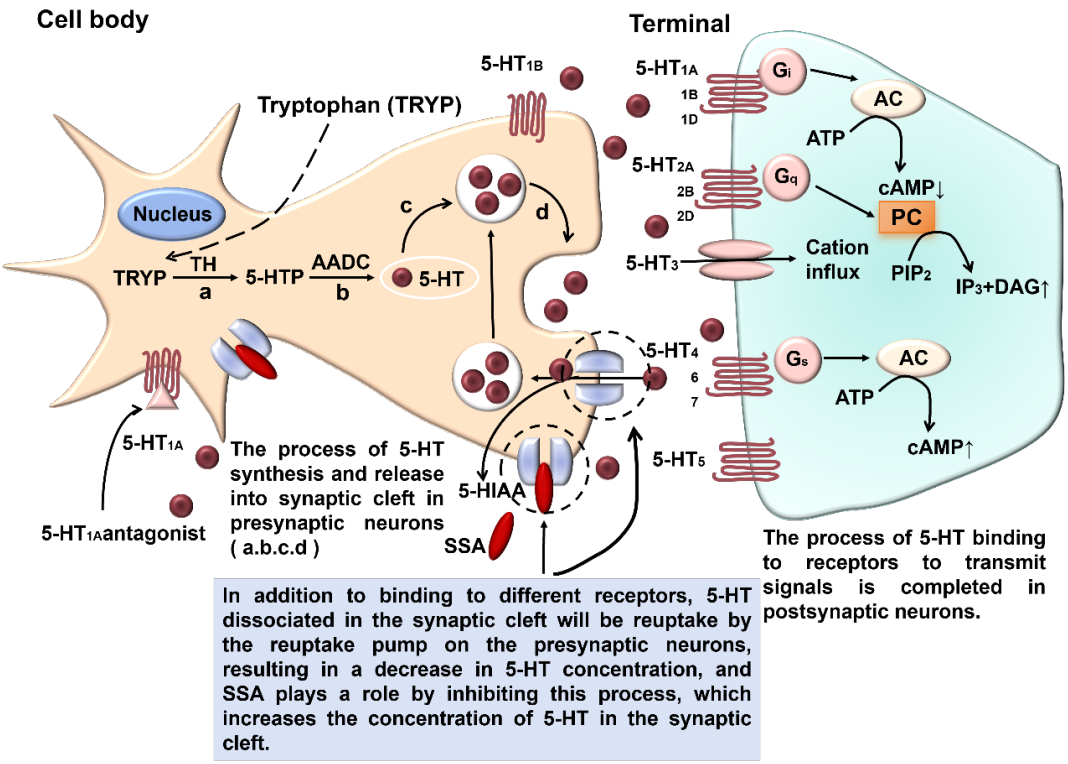
The study [23] showed that SSA could reduce the depressive symptoms of CUMS rats within 4 weeks, up-regulate DA content and proline-rich transmembrane protein 2 (PRRT2) expression level. It is suggested that SSA may exert its antidepressant effects by elevating the expression of PRRT2 and DA levels in the hippocampus. Serum inflammatory markers, such as IL-6 and TNF-α, indicate the extent of brain tissue damage. BDNF plays a pivotal role in the development and neuronal remodelling of the nervous system, influencing the differentiation, proliferation, nourishment, and maturation of various neuronal types. BDNF is a key regulatory factor in neuronal function, essential for the survival and regeneration of neurons following damage, and it represents one of the critical mechanisms in stress-induced hippocampal neuronal injury. NSE serves as a definitive marker of nerve injury, normally secreted by neurons and glial cells under physiological conditions and released into the peripheral bloodstream in substantial amounts upon nerve loss. Lower levels of NPY correlate with more severe depression, while a decrease in BDNF levels can precipitate

depressive episodes. This study's findings indicate that treatment with Bupleuri Radix in conjunction with DBT led to a significant reduction in IL-6, TNF-α, and NSE levels, along with a marked increase in NPY and BDNF levels. These results suggest that the combined therapy of Bupleuri Radix and DBT is beneficial in mitigating brain injury, facilitating neuronal repair, and lessening the severity of depression in patients with NSSI.

Nevertheless, the present study acknowledges certain inherent limitations that warrant further investigation. Since the participant pool was drawn solely from a single institution, the sample size remains modest, and the absence of long-term follow-up constrains the scope of the information and its representativeness. Subsequent research endeavours could refine the study's methodology, broaden the sample volume, enhance the diversity of the sample, and implement extended follow-ups with biological marker assessments, to further monitor the enduring efficacy of the combined treatment with bupleurum and dialectical behavioural therapy for depression and NSSI.

GRAPHICAL ABSTRACT

To explore the mechanism and clinical efficacy of Gastrodia elata in the treatment of hypertension based on intestinal flora-biliary acid axis



Depression, a prevalent condition within the realms of psychiatry and psychology, is characterized by a persistent lack of interest in usual activities and a prolonged state of low mood. This mental health challenge not only engenders a myriad of adverse emotional states but also frequently co-occurs with non-suicidal self-injury (NSSI) behaviors. Current conventional medical approaches to treating depression often face limitations, such as a propensity for side effects and suboptimal patient adherence to treatment regimens. In an innovative move, this study explores the integration of bupleurum with dialectical behaviour therapy for the treatment of individuals with depression who also exhibit NSSI behaviours, and obtain a satisfactory result. Preliminary findings suggest promising results, which may stem from the active constituents in bupleurum that modulate monoamine neurotransmitter levels, enhance brain-derived neurotrophic factors, and influence immune system equilibrium. This approach offers a novel perspective on the therapeutic management of depression in patients who engage in NSSI, potentially paving the way for more effective treatment strategies.

CONCLUSION

Depression, a significant health concern, continues to rise in prevalence annually. Its etiology remains elusive, and its pathogenesis is intricate, posing challenges for treatment. Radix Bupleuri, a widely utilized traditional Chinese medicinal herb, is recognized for its role in treating depression. DBT has shown promise in alleviating the negative mood states of NSSI patients and in the prevention and reduction of self-harm behaviors. The integration of these two modalities in treating NSSI depression has demonstrated a marked improvement in patients' depressive and anxiety symptoms, a reduction in IL-6 and TNF-α levels, an increase in monoamine neurotransmitter content, and a restoration of brain function injury-related factors. This combined approach exhibits a favorable clinical application profile.

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