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Effects of Chaihu-Shugan-San as an adjunctive intervention on psychosocial adaptation and meaning in life in patients with hepatocellular carcinoma comorbid with depression: a randomized controlled trial

Yiyuan Deng^{1,*}

¹ Yueyang Vocational Technical College, Yueyang County 414000, Hunan Province, China

* Corresponding author: Yiyuan Deng, dengyiyuan@163.com

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Abstract: Objective: This study aimed to evaluate the efficacy of Chaihu-Shugan-San (CHSGS), a classic Chinese herbal formula, as an adjunctive intervention on psychosocial adaptation and meaning in life in patients with hepatocellular carcinoma (HCC) comorbid with depression, and to preliminarily explore its potential mechanisms. **Methods:** A randomized, double-blind, placebo-controlled trial was conducted. A total of 132 eligible HCC patients (BCLC stage A/B) with comorbid moderate-to-severe depression (HAMD-17 score ≥ 17) were randomly assigned to either the combination group (conventional antitumor therapy plus CHSGS granule) or the control group (conventional antitumor therapy plus placebo) for a 12-week intervention. The primary outcomes were the total scores of the Chinese versions of the Psychosocial Adjustment to Illness Scale (PAIS-SR) and the Meaning in Life Presence Scale (MIPS). Secondary outcomes included the Hamilton Depression Rating Scale (HAMD-17) score, the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) score, and serum levels of inflammatory cytokines (IL-6 and TNF- α). Assessments were performed at baseline, week 6, week 12 (end of intervention), and at a 4-week follow-up. **Results:** A total of 123 patients completed the study. Repeated-measures analysis of variance revealed significant interaction effects between time and group on both psychosocial adaptation and meaning in life. Compared to the control group, the combination group demonstrated significantly higher PAIS-SR and MIPS scores at week 12 and at follow-up. Furthermore, the combination group showed significantly greater improvements in depressive symptoms and quality of life, as well as greater reductions in serum IL-6 and TNF- α levels than the control group. Correlation analysis indicated that the improvement in psychosocial adaptation was negatively correlated with the decrease in IL-6, and the enhancement of meaning in life was negatively correlated with the decrease in TNF- α . **Conclusion:** Adjuvant use of Chaihu-Shugan-San alongside conventional antitumor therapy effectively improves psychosocial adaptation and meaning in life, alleviates depressive symptoms, and enhances quality of life in HCC patients with depression. Its effects may be associated with the modulation of inflammatory responses. This formula provides a beneficial Traditional Chinese Medicine option for the integrated mind-body care of HCC patients.

Keywords: hepatocellular carcinoma; depression; chaihu-shugan-san; psychosocial adaptation; meaning in life; randomized controlled trial

1. Introduction

Hepatocellular carcinoma (HCC) is a leading malignancy in terms of global incidence and mortality. Although advances in treatment have prolonged patient survival, the physical suffering, changes in social roles, and fear of an uncertain future associated with the disease and its therapies render HCC patients a high-risk

population for psychological distress, particularly depression. Research indicates that the prevalence of depression in HCC patients is significantly higher than in the general population and patients with other cancers[1]. Depression not only severely impairs patients' quality of life, treatment adherence, and social functioning but may also influence tumor prognosis via neuroendocrine-immune pathways[2].

Modern psycho-oncology emphasizes comprehensive psychosocial care. However, the application of psychological interventions or antidepressant medications alone in cancer patients often faces challenges such as low acceptance, concerns about side effects, and potential interactions with antitumor therapies[3]. Traditional Chinese Medicine (TCM) has a long history in treating "emotional disorders", emphasizing a holistic view of "body-mind unity". In TCM theory, HCC is often attributed to "Liver Depression and Spleen Deficiency", while depressive mood is closely related to "Liver Qi Stagnation". Chaihu-Shugan-San (CHSGS), originating from Jingyue Quanshu, is a classic formula for soothing the liver, relieving depression, regulating Qi, and strengthening the spleen. Modern studies suggest it possesses antidepressant, anxiolytic, and immunomodulatory effects[4]. Nevertheless, research focusing on this formula for the specific population of HCC patients, particularly targeting core outcomes reflecting positive psychological resources and overall functioning such as "psychosocial adaptation" and "meaning in life", remains insufficient[5].

Therefore, we designed a randomized, double-blind, placebo-controlled trial to scientifically evaluate the effects of Chaihu-Shugan-San as an adjunctive intervention on psychosocial adaptation and meaning in life in HCC patients with comorbid depression, and to explore its association with inflammatory biomarkers, aiming to provide high-level clinical evidence for the integrated mind-body treatment of HCC patients.

2. Methods

2.1. Study design and ethics

This study was a prospective, randomized, double-blind, placebo-controlled trial. The protocol was approved by the Institutional Review Board of our hospital (Approval No. 20191210), and written informed consent was obtained from all participants prior to enrollment.

2.2. Participants

HCC patients attending the Hepatology Center of our hospital from January 2020 to June 2025 were recruited.

2.2.1. Inclusion criteria

(1) Age 18-75 years; (2) Diagnosis of HCC confirmed by pathology or imaging combined with alpha-fetoprotein (AFP), and classified as BCLC stage A or B (aiming to study patients with active treatment intent); (3) Meeting the diagnostic criteria for a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), with a 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 17 ; (4) Expected survival > 6 months; (5) Karnofsky Performance Status (KPS) score ≥ 70 .

2.2.2. Exclusion criteria

(1) Presence of severe cognitive impairment or psychiatric history (not due to depression); (2) Currently receiving standardized antidepressant drug therapy or systematic psychotherapy; (3) Allergy to any component of the study herbal formula;

(4) Coexistence of other uncontrolled malignancies or severe cardiac, pulmonary, or renal diseases.

Based on a pilot study, with an effect size $d=0.8$, $\alpha=0.05$ (two-tailed), and power $(1-\beta)=0.8$, calculation using G*Power software indicated a required sample size of 52 per group. Considering a 20% dropout rate, a total of 132 patients were planned for enrollment.

2.3. Randomization and blinding

A computer-generated randomization sequence was used to allocate eligible patients in a 1:1 ratio to either the combination group or the control group (Figure 1). The sequence was kept sealed by an independent statistician. All patients received conventional antitumor therapy (e.g., TACE, targeted therapy) and standard nursing care.

2.3.1. Combination group

Received oral Chaihu-Shugan-San granules (composed of *Bupleurum chinense* (Chaihu), *Paeonia lactiflora* (Baishao), *Citrus aurantium* (Zhiqiao), *Cyperus rotundus* (Xiangfu), *Ligusticum chuanxiong* (Chuanxiong), *Citrus reticulata* (Chenpi), *Glycyrrhiza uralensis* (Zhigancao), etc., conforming to the standards of the Chinese Pharmacopoeia, provided by the hospital pharmacy, with each bag equivalent to 15g of raw herbs), one dose daily, taken twice daily after being dissolved in water.

2.3.2. Control group

Received oral placebo granules identical in appearance, smell, and packaging to the treatment granules (primarily composed of dextrin and caramel pigment).

The intervention period was 12 weeks. Throughout the study, patients, assessing researchers, and data analysts were blinded to group assignment.

2.4. Outcome measures and assessment tools

2.4.1. Primary outcomes

Psychosocial adaptation: assessed using the Chinese version of the Psychosocial Adjustment to Illness Scale (PAIS-SR), which covers multiple dimensions including psychological state, social functioning, and patient-physician relationship. Higher total scores indicate better adaptation.

Meaning in Life: assessed using the Chinese version of the Meaning in Life Presence Scale (MIPS), which measures the extent to which an individual perceives meaning and purpose in life.

2.4.2. Secondary outcomes

Depressive Symptoms: assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17), administered by trained psychiatrists.

Quality of life: assessed using the liver cancer-specific Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.

Inflammatory biomarkers: fasting morning venous blood samples were collected at baseline and after the 12-week intervention to measure serum levels of Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF- α).

Assessment time points were baseline, week 6 of intervention, end of intervention (week 12), and 4 weeks after the intervention (follow-up).

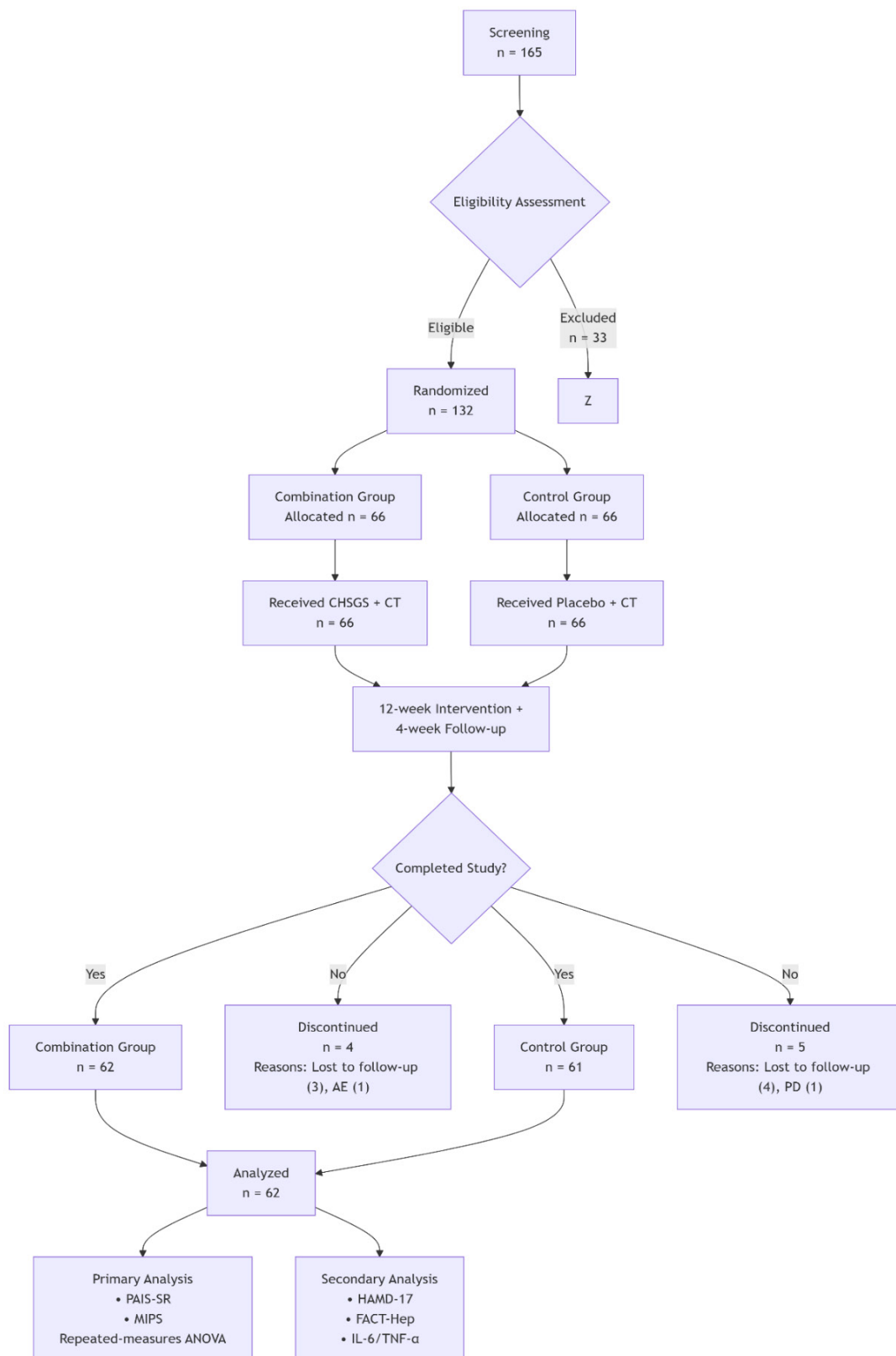


Figure 1. Simplified Study Flowchart.

Abbreviations: CHSGS: Chaihu-Shugan-San ; CT: Conventional Antitumor Therapy; AE: Adverse Event; PD: Disease Progression; PAIS-SR: Psychosocial Adjustment to Illness Scale; MIPS: Meaning in Life Presence Scale; HAMD-17: 17-item Hamilton Depression Rating Scale; FACT-Hep: Functional Assessment of Cancer Therapy – Hepatobiliary; ANOVA: Analysis of Variance.

2.5. Statistical analysis

Data analysis was performed using SPSS software (version 26.0). Continuous data are presented as mean $\pm$ standard deviation (SD) or median. For normally distributed data, within-group comparisons used paired-sample t-tests, and between-group comparisons used independent-sample t-tests or repeated-measures analysis of variance (ANOVA); non-normally distributed data were analyzed using non-parametric tests. Categorical data were analyzed using the chi-square test or Fisher's exact test. Pearson or Spearman correlation analysis was used to explore the relationships between changes in psychological indicators and inflammatory factors. All tests were two-tailed, and a P-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of participants

A total of 165 patients were screened, and 132 were enrolled and randomized. During the study, 4 patients in the combination group dropped out (3 lost to follow-up, 1 due to adverse reaction), and 5 in the control group dropped out (4 lost to follow-up, 1 due to disease progression), resulting in 123 patients who completed all assessments. The two groups showed no statistically significant differences in baseline characteristics, including age, gender, BCLC stage, baseline HAMD-17 score, PAIS-SR total score, and MIPS total score, indicating comparability (Table 1).

Table 1. Comparison of baseline characteristics between the two groups.

Characteristic	Combination Group (n=62)	Control Group (n=61)	Statistic	P-value
Age (years), M $\pm$ SD	58.3 $\pm$ 9.2	57.6 $\pm$ 8.7	t = 0.441	0.660
Gender (Male/Female), n	44 / 18	42 / 19	$\chi^2 = 0.081$	0.776
BCLC Stage (A/B), n	28 / 34	26 / 35	$\chi^2 = 0.077$	0.782
HAMD-17 Total Score, M $\pm$ SD	21.5 $\pm$ 3.2	22.1 $\pm$ 3.5	t = -1.034	0.303
PAIS-SR Total Score, M $\pm$ SD	52.8 $\pm$ 7.6	53.9 $\pm$ 8.1	t = -0.786	0.433
MIPS Total Score, M $\pm$ SD	35.2 $\pm$ 6.8	34.5 $\pm$ 7.2	t = 0.560	0.577

Note: M $\pm$ SD = Mean $\pm$ Standard Deviation; HAMD-17 = 17-item Hamilton Depression Rating Scale; PAIS-SR = Psychosocial Adjustment to Illness Scale-Self Report; MIPS = Meaning in Life Presence Scale.

3.2. Changes in primary outcomes

Repeated-measures ANOVA revealed significant interaction effects between time and group on both PAIS-SR and MIPS total scores. Post-hoc tests showed that the combination group had significantly increased PAIS-SR and MIPS total scores compared to baseline at week 6, week 12, and follow-up. Furthermore, its scores at week 12 and follow-up were significantly higher than those of the control group. The control group showed only a mild improvement in PAIS-SR at week 12, while the MIPS total score showed no significant change throughout the study period (Table 2).

Table 2. Comparison of psychosocial adjustment and meaning in life scores between the two groups.

Indicator / Time Point	Combination Group (n=62)	Control Group (n=61)	Between-Group P-value
PAIS-SR Total Score			
Baseline	52.8 $\pm$ 7.6	53.9 $\pm$ 8.1	0.433

Continuation Table:

Indicator / Time Point	Combination Group (n=62)	Control Group (n=61)	Between-Group P-value
Week 6	46.2 ± 6.9	51.4 ± 7.5	<0.001
Week 12	41.5 ± 6.1*#	49.8 ± 7.2*	<0.001
Follow-up	42.3 ± 6.3*#	50.5 ± 7.4*	<0.001
MIPS Total Score			
Baseline	35.2 ± 6.8	34.5 ± 7.2	0.577
Week 6	40.1 ± 6.0*	35.8 ± 6.5	<0.001
Week 12	45.6 ± 5.7*#	36.2 ± 6.9	<0.001
Follow-up	44.8 ± 5.9*#	35.9 ± 7.1	<0.001

Note: Data are presented as Mean ± Standard Deviation.

* P < 0.05 compared with the baseline within the same group.

P < 0.05 compared with the control group at the same time point.

3.3. Changes in secondary outcomes

Regarding depressive symptoms, the HAMD-17 total score in the combination group decreased significantly at all post-intervention time points, with a significantly greater reduction than in the control group. Regarding quality of life, the improvement in the FACT-Hep total score and most subdomain scores (except physical well-being) was superior in the combination group. Regarding inflammatory factors, serum IL-6 and TNF- α levels decreased significantly after the 12-week intervention in the combination group but showed no significant change in the control group (Table 3).

Table 3. Changes in depressive symptoms, quality of life, and inflammatory factors before and after intervention.

Indicator	Group	Baseline	Week 12	Within-Group P-value	Between-Group P-value
HAMD-17 Total Score	Combination	21.5 ± 3.2	12.1 ± 3.8*	<0.001	<0.001
	Control	22.1 ± 3.5	18.3 ± 4.1*	<0.001	
FACT-Hep Total Score	Combination	98.5 ± 15.2	118.6 ± 13.4*	<0.001	<0.001
	Control	96.8 ± 16.0	105.3 ± 14.9*	0.002	
IL-6 (pg/mL)	Combination	15.6 ± 4.3	10.2 ± 3.1*	<0.001	0.003
	Control	16.1 ± 5.0	15.3 ± 4.5	0.320	
TNF- α (pg/mL)	Combination	18.9 ± 5.8	13.4 ± 4.2*	<0.001	0.001
	Control	19.4 ± 6.2	18.7 ± 5.6	0.455	

Note: Data are presented as Mean ± Standard Deviation.

* P < 0.05 compared with baseline within the same group.

Between-group comparisons of score differences were performed using independent samples t-tests.

3.4. Correlation analysis

Pearson correlation analysis showed that within the combination group, the

degree of improvement in the PAIS-SR total score from baseline to week 12 was significantly negatively correlated with the decrease in IL-6 levels. Similarly, the increase in the MIPS total score was significantly negatively correlated with the decrease in TNF- α levels.

3.5. Comprehensive heatmap analysis of multi-dimensional changes over time

To comprehensively visualize the dynamic interrelationships among psychological, functional, and inflammatory changes throughout the study period, a correlation matrix heatmap was constructed based on the rate of change (slope) between consecutive assessment points for each outcome measure (**Figure 2**). The heatmap included slopes for psychosocial adaptation (PAIS-SR), meaning in life (MIPS), depressive symptoms (HAMD-17), quality of life (FACT-Hep), and inflammatory markers (IL-6, TNF- α) across three intervals: baseline to week 6 (S1), week 6 to week 12 (S2), and week 12 to follow-up (S3). The heatmap revealed several notable patterns: (a) Strong positive correlations within the same indicator across time (e.g., PAIS-SR_S1 with PAIS-SR_S2, $r = 0.85$), indicating consistent improvement trajectories. (b) Expected negative correlations between psychological improvements and inflammatory reductions were most pronounced in specific intervals: PAIS-SR improvement was strongly negatively correlated with IL-6 reduction in the early phase (S1: $r = -0.65$), while MIPS enhancement was strongly negatively correlated with TNF- α reduction in the mid-intervention phase (S2: $r = -0.70$). (c) Novel cross-domain synchrony: Improvement in quality of life (FACT-Hep) showed moderate to strong positive correlations with improvements in psychosocial adaptation and meaning in life, and negative correlations with depression and inflammation, suggesting a holistic recovery pattern. (d) Temporal specificity: The strongest anti-inflammatory effect of CHSGS appeared in the first 6 weeks (IL-6_S1 and TNF- α _S1 showing strong negative correlations with psychological metrics), while psychological gains were more sustained into the follow-up period. (e) This granular, time-sensitive correlational analysis underscores that CHSGS induces a synchronized, multi-system response, where psychological and functional improvements are temporally coupled with inflammatory downregulation, particularly in the early to mid-treatment phases.

3.6. Safety

During the study, the combination group reported 3 cases of mild diarrhea and 2 cases of mild nausea, all of which resolved spontaneously without affecting treatment. The control group reported 2 cases of mild gastrointestinal discomfort. No serious adverse events occurred.

4. Discussion

This study is the first to demonstrate through a rigorously designed randomized, double-blind, placebo-controlled trial that adjunctive use of Chaihu-Shugan-San alongside conventional antitumor therapy significantly improves psychosocial adaptation and meaning in life, concurrently alleviates depressive symptoms, enhances quality of life, and reduces serum pro-inflammatory cytokine levels in HCC patients with comorbid depression[6].

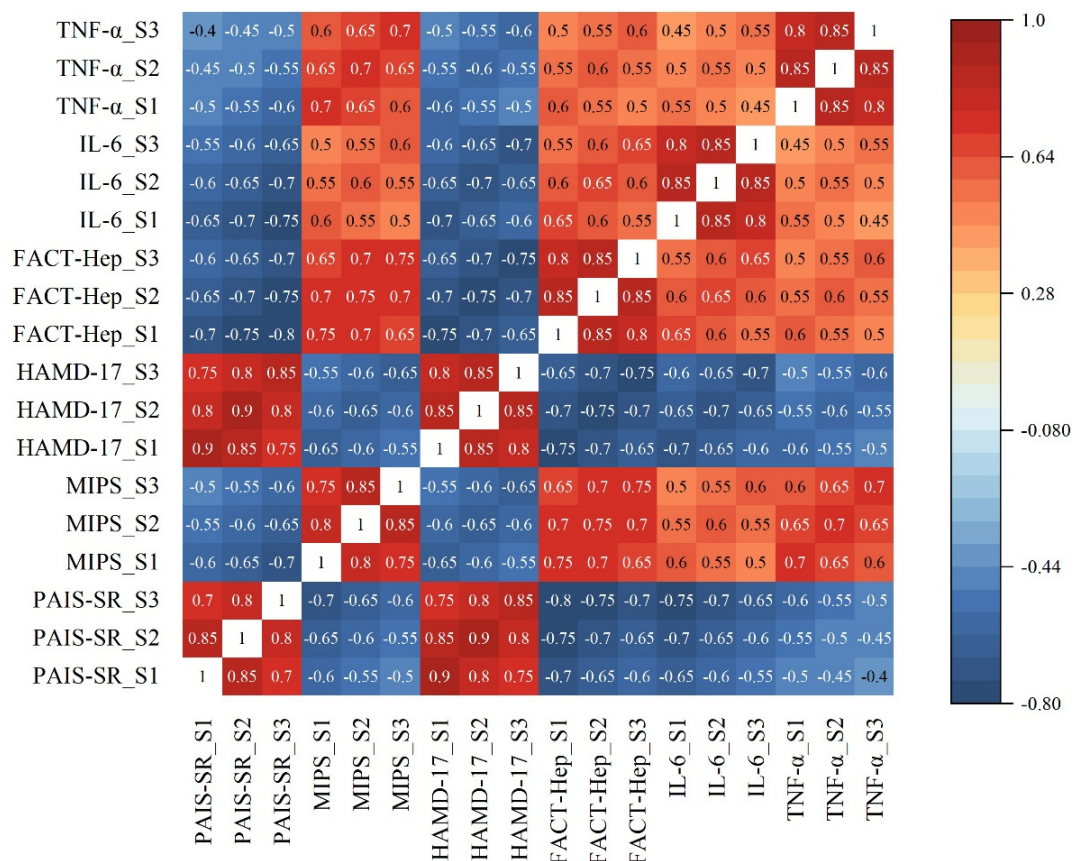


Figure 2. Correlations among psychosocial, functional, and inflammatory changes.

A key finding is the formula's pronounced effect on enhancing psychosocial adaptation and meaning in life. Unlike assessments focusing primarily on symptom reduction, psychosocial adaptation reflects an individual's overall capacity to cope with illness challenges and rebuild life balance, while meaning in life is a core element of positive psychological adjustment in cancer patients. The lack of significant improvement in meaning in life within the control group, which received standard medical care, suggests a potential limitation of conventional models in addressing patients' deeper existential needs[7]. In contrast, the combination group showed sustained and significant gains in both domains. This result can be interpreted through TCM theory: Chaihu-Shugan-San holistically regulates the patient's mind-body function at the level of "Qi" by soothing Liver Qi stagnation (improving mood), regulating Qi dynamics (alleviating somatic discomfort), and fortifying the spleen and stomach (improving functional status), thereby aiding patients in better adapting to their illness and rediscovering or establishing meaning and purpose in life while living with the disease[8].

Moreover, this study confirmed that Chaihu-Shugan-San effectively alleviated depressive symptoms and improved quality of life, consistent with previous clinical and preclinical research on its antidepressant effects[9]. Notably, quality of life improvements were observed not only in the emotional well-being domain but also in social/family well-being and functional domains, further supporting the TCM principle of "soothing the Liver" to promote holistic functional recovery[10].

On a mechanistic level, we observed that Chaihu-Shugan-San significantly reduced serum IL-6 and TNF-α levels, and these reductions were negatively correlated with improvements in psychosocial adaptation and meaning in life. Chronic

low-grade inflammation is considered a key biological bridge linking depression and cancer, as pro-inflammatory cytokines can directly affect the central nervous system, contributing to depressive-like behaviors[11]. Active components in Chaihu-Shugan-San (e.g., saikosaponins, paeoniflorin) have been confirmed to possess anti-inflammatory and immunomodulatory properties[12]. Therefore, we hypothesize that the formula may exert concurrent beneficial psychological and physiological effects by systemically downregulating excessive inflammatory responses, potentially disrupting the vicious cycle of “inflammation-depression-immune suppression”.

Furthermore, the comprehensive heatmap analysis of change rates across the intervention timeline provides a dynamic and integrative perspective on the treatment effects. The observed temporal specificity—where the strongest negative correlations between psychological improvements and inflammatory reduction were phase-dependent (e.g., early PAIS-SR gain with IL-6 decrease, mid-intervention MIPS enhancement with TNF- α decrease)—suggests that CHSGS may induce a sequential yet synchronized modulation across psychological and biological systems. This pattern aligns with the TCM concept of prioritizing “soothing Liver Qi” to release stagnation and alleviate emotional-somatic distress, which may subsequently facilitate deeper existential adjustment and functional recovery. Moreover, the sustained positive correlations within each outcome domain across time, coupled with cross-domain synchrony (e.g., between quality of life and psychosocial adaptation), reflect a holistic and coherent recovery process. These findings move beyond static biomarker associations and underscore CHSGS’s role in promoting an integrated mind-body trajectory toward better adaptation, supporting its use as a systemic intervention in psycho-oncology care. This provides a potential modern biological explanation for the traditional therapeutic effect of “soothing the Liver and relieving depression”.

This study has several limitations. First, the sample was from a single center; future multi-center studies are needed to verify the generalizability of the findings[13]. Second, the intervention duration was 12 weeks. Although short-to-medium-term sustained effects were shown, long-term follow-up data are lacking to assess its enduring impact. Third, the formula was administered in a fixed composition without modification based on TCM syndrome differentiation, which ensured consistency but might limit optimal efficacy in highly individualized TCM practice[14]. Fourth, the mechanistic investigation was limited to a few inflammatory cytokines; future research could explore deeper using multi-dimensional approaches such as metabolomics and gut microbiota analysis[15].

Despite these limitations, the findings hold significant clinical implications. They indicate that integrating classic formulas like Chaihu-Shugan-San into the comprehensive management of HCC is a safe, effective, and feasible strategy to address the prevalent yet often overlooked psychosocial and spiritual needs of cancer patients, moving towards genuine “body-mind-social-spiritual” holistic care[16]. This study demonstrates that Chaihu-Shugan-San as an adjunctive therapy can significantly improve psychosocial adaptation and meaning in life, alleviate depression, and enhance quality of life in HCC patients with comorbid depression[17]. Its effects may be related to the modulation of systemic inflammatory status[18]. This research provides high-quality evidence for the application of TCM in the field of psychosocial oncology and supports the inclusion of such formulas with “Liver-soothing and depression-relieving” properties into the multidisciplinary supportive care options for HCC patients[19-20].

5. Conclusion

This randomized, double-blind, placebo-controlled trial provides robust evidence that adjunctive use of the classic Chinese herbal formula Chaihu-Shugan-San (CHSGS) significantly improves psychosocial adaptation and meaning in life, alleviates depressive symptoms, enhances quality of life, and reduces systemic inflammatory markers in patients with hepatocellular carcinoma (HCC) comorbid with moderate-to-severe depression. The findings transcend the simple demonstration of symptomatic relief and invite a deeper, integrative discussion within the framework of modern psycho-oncology.

Firstly, this study underscores the critical importance of targeting positive psychological constructs alongside symptom reduction in cancer care. Psycho-oncology has progressively evolved from a focus on psychopathology (e.g., diagnosing and treating depression) towards a more holistic model that fosters resilience, well-being, and post-traumatic growth. Our primary outcomes—psychosocial adaptation and meaning in life—are cornerstones of this paradigm shift. Psychosocial adaptation reflects the dynamic process of achieving a new equilibrium between the demands of illness and personal resources, a process essential for long-term coping. Meaning in life represents a fundamental spiritual and existential resource that buffers against despair and fosters a sense of purpose, even in the face of a life-threatening illness. The significant and sustained improvements in these domains with CHSGS, contrasted with the stagnation in the control group, suggest that this herbal intervention actively facilitates a positive recalibration of the patient's psychological and existential stance towards their illness. This moves beyond palliative symptom management towards what can be termed therapeutic empowerment, enabling patients to live with and beyond their cancer diagnosis more fully.

Secondly, the results highlight the potential of Traditional Chinese Medicine (TCM) as a valuable, systematized resource within integrative psycho-oncology. The TCM diagnosis of “Liver Qi Stagnation” and the therapeutic principle of “soothing the Liver and relieving depression” offer a coherent, centuries-old framework for understanding and treating the emotional and somatic cluster of symptoms often seen in cancer-related depression. CHSGS operationalizes this principle. Its mechanism, as our correlational data tentatively suggests, may involve the modulation of the pro-inflammatory milieu (reducing IL-6 and TNF- α). Chronic inflammation is a recognized biological substrate linking depression, cancer progression, and sickness behaviors (fatigue, anhedonia). By potentially downregulating this inflammatory tone, CHSGS may simultaneously address the biological underpinnings of depressive affect and the physiological burden of cancer, thereby creating a conducive internal environment for psychological and functional improvement. This aligns with the psycho-neuro-immunology (PNI) model central to psycho-oncology, which seeks to understand and influence the bidirectional communication between psychological state, the nervous system, and immune/inflammatory function.

The practical implications for clinical psycho-oncology are multifaceted. For patients, CHSGS presents a complementary option that may be particularly appealing to those who are reluctant to engage with conventional psychotherapy, concerned about the side effects or stigma of psychiatric medications, or whose cultural background resonates with herbal medicine. Its positive effect on quality of life across multiple domains (emotional, social, functional) indicates a broad-based benefit. For clinicians, this study provides Level II evidence supporting the consideration of a

specific TCM formula within a multidisciplinary supportive care plan. It argues for collaboration between oncologists, psycho-oncologists, and trained TCM practitioners to identify patients who might benefit most. The intervention's safety profile, with only minor, self-limiting gastrointestinal events reported, supports its feasibility for use in a medically complex population.

However, this research also clearly delineates its boundaries and points the way forward. The single-center design and 12-week intervention period call for larger, multi-center trials with longer follow-up to confirm generalizability and durability of effects. The use of a fixed formula, while methodologically necessary for a controlled trial, departs from the highly individualized practice of TCM. Future research could explore efficacy-guided prescription variations or identify biomarkers predictive of response to CHSGS, thus moving towards a more personalized integrative approach. Mechanistically, our exploration was limited to two inflammatory cytokines. Future studies should employ broader omics technologies (e.g., metabolomics, proteomics) and neuroimaging to map the multi-system effects of CHSGS, further elucidating its pathways of action on the mind-body axis.

In conclusion, this investigation demonstrates that Chaihu-Shugan-San is more than an “herbal antidepressant”. It is an intervention that appears to positively influence the core psycho-social-spiritual challenges of living with advanced cancer. By providing high-quality evidence for its benefits, this study helps to bridge the gap between traditional healing systems and contemporary evidence-based psycho-oncology. It champions an inclusive, pluralistic model of care where empirically-validated complementary approaches like CHSGS are integrated into the supportive care arsenal, offering patients a broader range of tools to navigate the profound psychological journey of a cancer diagnosis. Ultimately, the goal of psycho-oncology is to alleviate suffering and enhance life. This study suggests that thoughtfully integrated herbal medicine can contribute meaningfully to achieving this goal for patients with hepatocellular carcinoma and depression.

Author contributions: Conceptualization, DY; methodology, DY; software, DY; validation, DY; formal analysis, DY; investigation, DY; resources, DY; data curation, DY; writing—original draft preparation, DY; writing—review and editing, DY; visualization, DY; supervision, DY; project administration, DY; funding acquisition, DY. All authors have read and agreed to the published version of the manuscript.

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