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EDITED BY

Sheema Khan,
The University of Texas Rio Grande Valley,
United States

REVIEWED BY

Ruo Wang,
Shanghai Jiao Tong University, China
Dalinda Isabel Sánchez-Vidaña,
Hong Kong Polytechnic University, Hong Kong
SAR, China

*CORRESPONDENCE

Lianfang Yin,
✉ 1833654734@qq.com

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Xiaoyaosan formula augments adjuvant therapy and enhances postoperative breast cancer care

Chao Wang and Lianfang Yin*

Department of Chinese Medicine, The First Affiliated Hospital of Bengbu Medical University, Bengbu,
Anhui, China

Introduction: Xiaoyaosan (XYS), a traditional Chinese formula, not only has good antitumor effects but also attenuates distress, anorexia, and quality of life (QoL) by regulating neurology, the microbiota, immunology, and oxidative stress. This study aimed to assess the effect of YYS on QoL, psychological pressure, and spiritual well-being in breast cancer patients undergoing adjuvant chemotherapy.

Methods: This prospective cohort study enrolled 176 postoperative breast cancer patients who received adjuvant chemotherapy combined with ($n = 81$) or without ($n = 95$) YYS for comparison. The Quality-of-Life Questionnaire Core-30 (QLQ-C30), Hospital Anxiety and Depression Scale (HADS), University of California Los Angeles (UCLA-LS), and Functional Assessment of Chronic Illness Therapy–Spiritual Well-being (FACIT–Sp) scores were evaluated before adjuvant chemotherapy (T_0) and after the first (T_1), second (T_2), third (T_3), and fourth cycles (T_4) of adjuvant chemotherapy.

Results: YYS improved the QLQ-C30 score at T_2 ($p = 0.043$), T_3 ($p = 0.021$), and T_4 ($p = 0.040$) and the QLQ-C30 score at T_4 ($p = 0.027$); moreover, YYS attenuated the QLQ-C30 score at T_2 ($p = 0.040$), T_3 ($p = 0.023$), and T_4 ($p = 0.027$). Regarding distress, YYS reduced the HADS-anxiety score at T_2 ($p = 0.010$), T_3 ($p = 0.025$), and T_4 ($p = 0.019$) and the HADS-defined anxiety score at T_3 ($p = 0.038$). YYS also decreased the HADS-depression score at T_2 ($p = 0.016$), T_3 ($p = 0.018$), and T_4 ($p = 0.017$) and the HADS-defined depression rate at T_2 ($p = 0.047$), T_3 ($p = 0.012$), and T_4 ($p = 0.013$). In addition, YYS decreased the UCLA-LS at T_2 ($p = 0.023$) but enhanced the FACIT–Sp at T_2 ($p = 0.029$) and T_4 ($p = 0.026$). Furthermore, after adjustment via propensity score matching, most of the significant findings remained.

Discussion: The addition of YYS to adjuvant chemotherapy improved QoL, psychological health, and spiritual well-being in breast cancer patients.

KEYWORDS

postoperative breast cancer, Xiaoyaosan, adjuvant chemotherapy, quality of life, psychological pressure

1 Introduction

According to a recent global cancer statistical report, breast cancer ranks high among all cancer cases in terms of both incidence and mortality (Sung et al., 2021). Profiting from screening technology and national health literacy education, an increasing number of breast cancer patients are being diagnosed at an early stage and are able to receive mastectomy, with a good prognosis estimation (Yang S. et al., 2022a; Ren et al., 2022; Alkabban and Ferguson, 2023). However, a large proportion of patients are indicated to receive adjuvant chemotherapy with or without anti-HER2 agents based on the type of agent used after surgery, which has a considerable impact on patients' quality of life (QoL), vasomotor symptoms, distress, social functions, and so on (Grimison and Stockler, 2007; Liu et al., 2022; Pereira et al., 2022). These factors make improving QoL, mental health, and spiritual well-being essential for postoperative breast cancer patients undergoing adjuvant chemotherapy (Krzyzanowska et al., 2021; He et al., 2022).

Xiaoyaosan (XYS) is a traditional Chinese formula commonly consisting of eight main components, Radix Bupleuri, Radix *Angelicae sinensis*, Radix Paeoniae alba, Rhizoma *Atractylodis macrocephala*, Poria, Rhizoma Zingiberis Recens, Radix Glycyrrhizae, and Herba Menthae, which can also be modified by the addition of other individual components (Hu et al., 2021). Multiple types of YYS have been shown to have good antitumor effects on several cancers, such as ovarian cancer (Li et al., 2021), colorectal cancer (Zhang et al., 2020), and especially breast cancer (Chen et al., 2012). Moreover, numerous studies have reported the excellent effects of YYS on depression, anxiety, anorexia, and QoL, which may be attributed to its regulation of the hypothalamic–pituitary–adrenal axis, neural and synaptic plasticity, neuronal loss, microbiota components, immunology, and oxidative stress, as well as its ability to modify several key biological pathways, including the PI3K/AKT, TLR4/NLRP3, RAGE, and JAK/STAT pathways (Li et al., 2017; Zhao et al., 2020; Zhou et al., 2021; Zhu et al., 2021; Chen et al., 2022; Yan et al., 2022; Zeng et al., 2022; Jiao et al., 2023). Recently, YYS has been applied along with adjuvant chemotherapy in breast cancer patients, which attenuates the postoperative complications and toxic reactions of chemotherapy and prolongs disease-free survival and overall survival to some degree (Wang et al., 2006; Du et al., 2015; Suo et al., 2018; Lu, 2019). However, its impact on QoL, psychological pressure, and spiritual well-being regarding adjuvant therapy in breast cancer patients has been less reported.

The current study compared adjuvant chemotherapy plus YYS versus adjuvant chemotherapy alone in postoperative breast cancer patients, aiming to investigate the effect of YYS on QoL, anxiety, depression, loneliness, and spiritual well-being in postoperative patients with breast cancer.

2 Methods

2.1 Subjects

This prospective cohort study enrolled 176 breast cancer patients who planned to receive adjuvant chemotherapy or

adjuvant chemotherapy plus YYS between August 2020 and October 2022. The inclusion criteria were as follows: 1) histologically confirmed breast cancer; 2) aged older than 18 years; 3) scheduled for adjuvant chemotherapy or adjuvant chemotherapy plus YYS; 4) adequate hepatic, kidney, and bone marrow function according to the investigator; and 5) willing to cooperate with this study. The exclusion criteria were as follows: 1) had other primary cancers; 2) had malignant hematological diseases; 3) had distant metastases; 4) had allergies or physical intolerance to the study drugs; and 5) were pregnant women or nursing mothers. Approval for this study was granted via the Ethics Committee of The First Affiliated Hospital of Bengbu Medical University with the approval number 2020159. After explaining the details of the study to the patients, the investigator asked the patients whether they would participate in the study. The participants signed the consent form if they agreed to participate in this study.

2.2 Data collection and sample detection

Clinical characteristics, which included the age, marital status, employment status, education level, residence status, lesion site, histologic grade, and tumor–node–metastasis (TNM) stage, were collected for all subjects. In addition, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki67 expression were detected in the tumor tissue by immunohistochemistry.

2.3 Treatment

Patients received adjuvant chemotherapy or adjuvant chemotherapy plus YYS. This study did not intervene in patients' treatments, which were based on their disease status, their own wishes, or doctors' suggestions. YYS was administered once a day, 30 min prior to a meal, for four cycles (3 weeks per cycle). The contents of YYS included bupleurum (10 g), white peony (15 g), Tuckahoe (15 g), *Atractylodis Macrocephalae* Rhizoma (10 g), *Angelica sinensis* (10 g), Radix glycyrrhizae preparata (10 g), *Zingiber officinale* (5 g), jujube (10 g), and Mentha (4 g) (Hu et al., 2021). Furthermore, the YYS regimen was adjusted according to the condition of the patients. In detail, patients with diarrhea received *Dioscorea opposita* Thunb. or *Lablab purpureus* (L.) Sweet; patients with poor sleep quality (such as insomnia) received Semen Ziziphi Spinosae. In addition, adjuvant chemotherapy included the following regimens: AC-T, AC-TH, AC, AC-THP, and AC + H. 'A' represents anthracyclines, 'C' represents cyclophosphamide, 'T' represents taxane, 'H' represents trastuzumab, and 'P' represents pertuzumab. Conventionally, four cycles of adjuvant chemotherapy ('A,' 'C,' and 'T') were administered (3 weeks per cycle). Patients with a HER2-positive status received 1 year of targeted therapy ('H' and 'P') in addition to adjuvant chemotherapy. The detailed regimen used was described in the guidelines of the Chinese Society of Clinical Oncology (CSCO) for breast cancer 2020 and is available at <http://www.cSCO.org.cn/cn/index.aspx>.

2.4 Questionnaires

The Quality-of-Life Questionnaire Core 30 (QLQ-C30) is a scale that contains 30 items. The first 28 items of the questionnaire used a four-point response scale ranging from 1 to 4. Items 29 and 30 were designed to evaluate global health status and quality of life (QoL), respectively, and used a response scale ranging from 1 to 7. All the raw data were transformed to a 0- to 100-point scale. Higher scores for the functional scales and global health status indicated better functioning and overall QoL, while a high score for the symptom scale represented a high level of symptom distress. The Cronbach's α coefficient for this QLQ-C30 exceeded 0.70 (Tung et al., 2016). The Hospital Anxiety and Depression Scale (HADS) for anxiety (HADS-A) subscale comprises seven items with scores ranging from 0 to 3 for each item, and the total scores range from 0 to 21; the higher the score is, the more severe the anxiety. The HADS for depression (HADS-D) subscale comprises seven items with scores ranging from 0 to 3 for each item, and the total score ranges from 0 to 21; the higher the score is, the more severe the depression. A previous study reported good internal consistency for both the anxiety (0.71) and depression (0.67) subscales (Su et al., 2012). The University of California Los Angeles Loneliness Scale (UCLA-LS) scale contains 20 items (each item has a four-point frequency score ranging from 1 to 4), of which nine items are scored in a reverse order. The higher the total score is, the greater the degree of loneliness. The internal consistency of the UCLA-LS was good (Cronbach's α coefficient was 0.94) (Liu and Guo, 2008). The Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing (FACIT-Sp) scale contains 12 items, which involves three dimensions. Each item was scored from 0 to 4 by the Likert 5 grading method. The Cronbach's α coefficient for the FACIT-Sp subscales ranged from 0.711 to 0.920 (Liu et al., 2016). These questionnaires were administered in written form in Chinese.

2.5 Outcome measures

The QLQ-C30, HADS-A, HADS-D, UCLA-LS, and FACIT-Sp scores were used for evaluating quality of life, anxiety, depression, loneliness, and spiritual well-being, respectively (Aaronson et al., 1993; Russell, 1996; Peterman et al., 2002; Snaith, 2003). The above parameters were assessed before adjuvant chemotherapy (T_0) and after the first (T_1), second (T_2), third (T_3), and fourth cycles (T_4) of adjuvant chemotherapy.

2.6 Statistics

SPSS (IBM, United States) version 26.0 was used for data processing. Student's *t*-test, the Mann-Whitney *U* test, the χ^2 test, and Fisher's exact test were utilized for comparison analyses. To adjust the imbalance of the characteristics between the two groups, propensity score analysis with the nearest neighbor matching method was used. The matched analysis included a comprehensive assessment of various factors, including the age,

marital status, employment status, level of education, place of residence, lesion site, histologic grading, TNM stage, ER status, PR status, HER-2 status, and Ki67. Thus, the two study groups were matched at a 1:1 ratio. $p < 0.05$ indicated statistical significance.

3 Results

3.1 Patient characteristics

A total of 176 eligible patients were analyzed in the study, consisting of 81 patients in the adjuvant chemotherapy plus XYS group and 95 patients in the adjuvant chemotherapy group (Table 1). In the adjuvant chemotherapy plus XYS group, the mean age was 51.0 ± 10.3 years; 9.9%, 69.1%, and 21.0% of patients were at TNM stage I, II, and III, respectively; and 55.6%, 25.9%, 9.9%, 7.4%, and 1.2% of patients received AC-T, AC-TH, AC, AC-THP, and AC + H as adjuvant chemotherapy regimens, respectively. In the adjuvant chemotherapy group, the mean age was 51.8 ± 10.7 years; 14.7%, 60.0%, and 25.3% of patients were at TNM stage I, II, and III, respectively; and 60.0%, 18.9%, 9.5%, 9.5%, and 2.1% of patients received AC-T, AC-TH, AC, AC-THP, and AC + H as adjuvant chemotherapy regimens, respectively. In comparison, most of the patients' characteristics did not differ between the two groups, but the level of education was greater in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group ($p = 0.020$).

3.2 QoL comparison

Generally, in both the adjuvant chemotherapy plus XYS group and the adjuvant chemotherapy group, the QLQ-C30 global health status and functional scale showed a decreasing trend from T_0 to T_1 and then gradually increased thereafter to T_4 (Figures 1A, B); the QLQ-C30 symptom scale revealed the opposite trend (Figure 1C).

In comparison, the QLQ-C30 global health status did not differ between T_0 ($p = 0.406$) and T_1 ($p = 0.672$) but was greater at T_2 ($p = 0.043$), T_3 ($p = 0.021$), and T_4 ($p = 0.040$) in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group (Figure 1A). The QLQ-C30 functional scale did not vary at T_0 ($p = 0.586$), T_1 ($p = 0.452$), T_2 ($p = 0.122$), or T_3 ($p = 0.078$) and was greater only at T_4 ($p = 0.027$) in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group (Figure 1B). In addition, the QLQ-C30 symptom scale did not differ at T_0 ($p = 0.258$) or T_1 ($p = 0.146$) but was lower at T_2 ($p = 0.040$), T_3 ($p = 0.023$), and T_4 ($p = 0.027$) in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group (Figure 1C).

3.3 Anxiety comparison

The HADS-A score did not differ at T_0 ($p = 0.902$) or T_1 ($p = 0.146$) but was lower at T_2 ($p = 0.010$), T_3 ($p = 0.025$), or T_4

TABLE 1 Clinical characteristics of breast cancer patients.

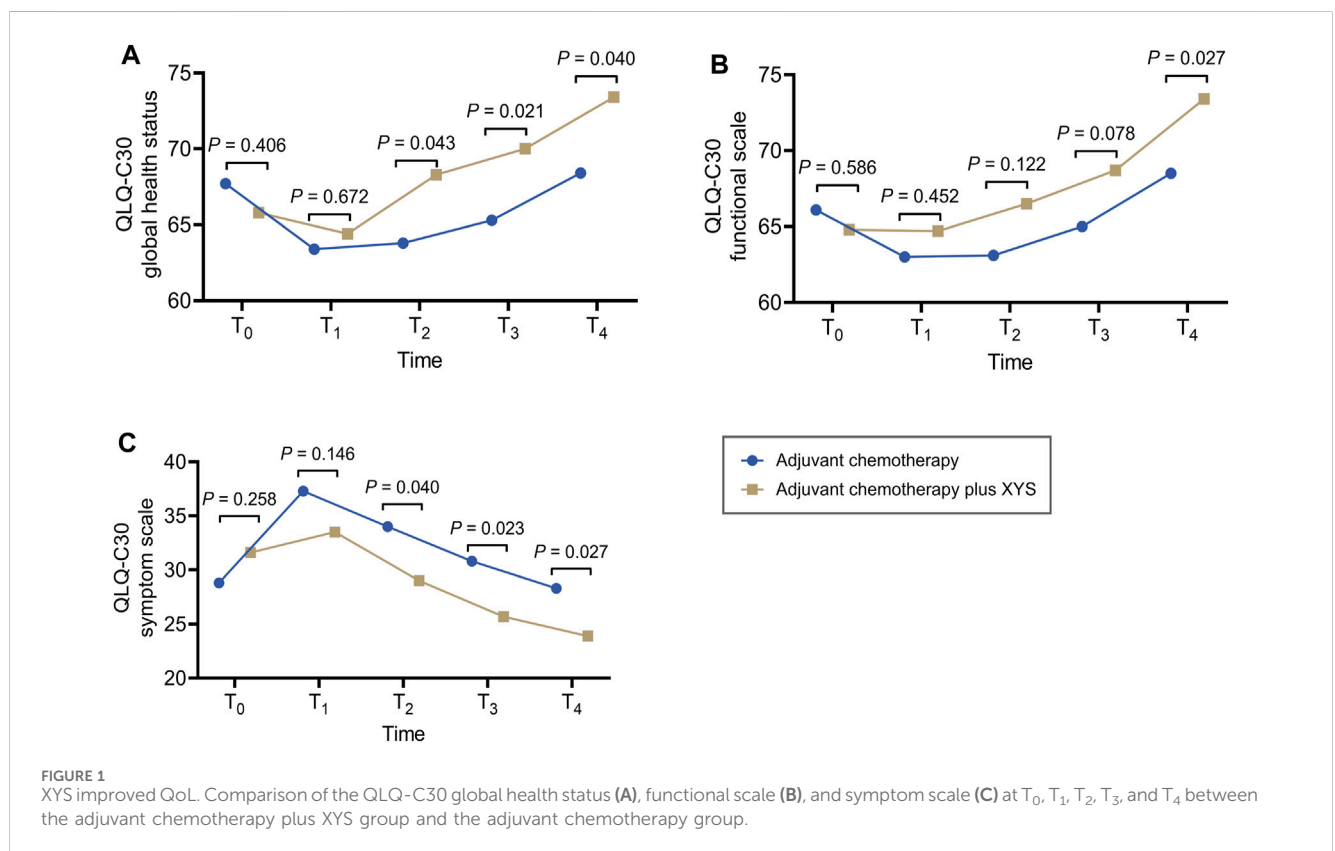
Characteristic	Adjuvant chemotherapy (N = 95)	Adjuvant chemotherapy plus XYS (N = 81)	p-value
Age (years), mean \pm SD	51.8 \pm 10.7	51.0 \pm 10.3	0.599
Married, No. (%)	84 (88.4)	66 (81.5)	0.196
Employed, No. (%)	45 (47.4)	44 (54.3)	0.358
Level of education, No. (%)			0.020
Primary school	8 (8.4)	2 (2.5)	
Middle school	28 (29.5)	14 (17.3)	
High school	40 (42.1)	44 (54.3)	
Undergraduate or above	19 (20.0)	21 (25.9)	
Residence, No. (%)			0.673
Rural	10 (10.5)	7 (8.6)	
Urban	85 (89.5)	74 (91.4)	
Lesion site, No. (%)			0.391
Unilateral	85 (89.5)	69 (85.2)	
Bilateral	10 (10.5)	12 (14.8)	
Histologic grading, No. (%)			0.084
Grade I	24 (25.3)	12 (14.8)	
Grade II	48 (50.5)	43 (53.1)	
Grade III	23 (24.2)	26 (32.1)	
T-stage, No. (%)			0.083
1	25 (26.3)	11 (13.6)	
2	58 (61.1)	58 (71.6)	
3	12 (12.6)	12 (14.8)	
N-stage, No. (%)			0.175
0	50 (52.6)	52 (64.2)	
1	24 (25.3)	14 (17.3)	
2	19 (20.0)	13 (16.0)	
3	2 (2.1)	2 (2.5)	
M-stage, No. (%)			1.000
0	95 (100.0)	81 (100.0)	
TNM stage, No. (%)			0.999
I	14 (14.7)	8 (9.9)	
II	57 (60.0)	56 (69.1)	
III	24 (25.3)	17 (21.0)	
ER positive, No. (%)	55 (57.9)	47 (58.0)	0.986
PR positive, No. (%)	52 (54.7)	41 (50.6)	0.585
HER-2 positive, No. (%)	29 (30.5)	28 (34.6)	0.568
Ki67 \geq 30%, No. (%)	31 (32.6)	32 (39.5)	0.343

(Continued on following page)

TABLE 1 (Continued) Clinical characteristics of breast cancer patients.

Characteristic	Adjuvant chemotherapy (N = 95)	Adjuvant chemotherapy plus YYS (N = 81)	p-value
Adjuvant chemotherapy regimen, No. (%)			0.827
AC-T	57 (60.0)	45 (55.6)	
AC-TH	18 (18.9)	21 (25.9)	
AC	9 (9.5)	8 (9.9)	
AC-THP	9 (9.5)	6 (7.4)	
AC + H	2 (2.1)	1 (1.2)	

YYS, Xiaoyaosan; SD, standard deviation; TNM, tumor–node–metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; A, anthracycline; C, cyclophosphamide; T, taxane; H, trastuzumab; P, pertuzumab.



($p = 0.019$) in the adjuvant chemotherapy plus YYS group than in the adjuvant chemotherapy group (Table 2). Moreover, the HADS-defined anxiety rate did not vary at T₀ ($p = 0.717$), T₁ ($p = 0.275$), T₂ ($p = 0.052$), or T₄ ($p = 0.064$) but was lower at T₃ ($p = 0.038$) in the adjuvant chemotherapy plus YYS group than in the adjuvant chemotherapy group.

3.4 Depression comparison

The HADS-D score did not differ at T₀ ($p = 0.538$) or T₁ ($p = 0.255$) but was lower at T₂ ($p = 0.016$), T₃ ($p = 0.018$), or T₄ ($p = 0.017$) in the adjuvant chemotherapy plus YYS group than in the adjuvant

chemotherapy group (Table 3). Moreover, the HADS-defined depression rate did not differ at T₀ ($p = 0.485$) or T₁ ($p = 0.393$) but was lower at T₂ ($p = 0.047$), T₃ ($p = 0.012$), or T₄ ($p = 0.013$) in the adjuvant chemotherapy plus YYS group than in the adjuvant chemotherapy group.

3.5 Loneliness and spiritual well-being comparison

UCLA-LS increased from T₀ to T₁ and then continuously decreased from T₁ to T₄ in both the adjuvant chemotherapy plus YYS group and the adjuvant chemotherapy group. In comparison,

TABLE 2 Comparison of HADS-A scores and anxiety rates between the two groups.

Item	Adjuvant chemotherapy	Adjuvant chemotherapy plus XYS	p-value
HADS-A score, mean ± SD			
T ₀	7.7 ± 3.8	7.6 ± 3.1	0.902
T ₁	8.2 ± 2.9	7.6 ± 2.2	0.146
T ₂	8.2 ± 3.0	7.1 ± 2.2	0.010
T ₃	7.9 ± 3.0	6.9 ± 2.3	0.025
T ₄	7.7 ± 3.3	6.6 ± 2.6	0.019
Anxiety rate*, %			
T ₀	36.8	39.5	0.717
T ₁	46.2	37.8	0.275
T ₂	46.1	31.0	0.052
T ₃	43.7	27.5	0.038
T ₄	40.2	26.1	0.064

HADS-A, Hospital Anxiety and Depression Scale for anxiety; XYS, Xiaoyaosan; SD, standard deviation; T₀, before adjuvant chemotherapy; T₁, first cycle after adjuvant chemotherapy; T₂, second cycle after adjuvant chemotherapy; T₃, third cycle after adjuvant chemotherapy; T₄, fourth cycle after adjuvant chemotherapy. *, a HADS-A score of more than 7 was defined as anxiety.

UCLA-LS was not different at T₀ ($p = 0.473$), T₁ ($p = 0.219$), T₃ ($p = 0.093$), or T₄ ($p = 0.159$) but was lower at T₂ ($p = 0.023$) in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group (Figure 2A).

FACIT-Sp did not fluctuate obviously from T₀ to T₂ and then greatly increased from T₂ to T₄ in the adjuvant chemotherapy plus XYS group; however, it decreased from T₀ to T₂ first and then gradually increased from T₂ to T₄ in the adjuvant chemotherapy group. In comparison, FACIT-Sp did not vary at T₀ ($p = 0.815$), T₁ ($p = 0.300$), or T₃ ($p = 0.090$) but was greater at T₂ ($p = 0.029$) and T₄ ($p = 0.026$) in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group (Figure 2B).

3.6 Findings after the adjustment by propensity score matching

Considering that some of the characteristics differed between the adjuvant chemotherapy plus XYS group and the adjuvant chemotherapy group, propensity score matching was performed for adjustment. All of the characteristics did not differ between the two groups after adjustment by propensity score matching (Table 4).

After adjustment, the QLQ-C30 global health status ($p = 0.991$), functional scale score ($p = 0.909$), symptom scale score ($p = 0.645$), HADS-A score ($p = 0.700$), HADS-defined anxiety rate ($p = 0.389$), HADS-D score ($p = 0.749$), HADS-defined depression rate ($p = 1.000$), UCLA-LS score ($p = 0.570$), and FACIT-Sp score ($p = 0.558$) were not different at T₀ between the adjuvant chemotherapy plus XYS group and the adjuvant chemotherapy group. Importantly, the QLQ-C30 global health status ($p = 0.013$), QLQ-C30 functional scale score ($p = 0.010$), and FACIT-Sp score ($p = 0.035$) were greater at T₄ in the adjuvant chemotherapy plus XYS group than in the adjuvant chemotherapy group. Moreover, the HADS-D ($p = 0.002$) and HADS-defined depression rates ($p = 0.010$) were lower at T₄ in the adjuvant chemotherapy plus XYS group than in the adjuvant

TABLE 3 Comparison of HADS-D scores and depression rates between the two groups.

Item	Adjuvant chemotherapy	Adjuvant chemotherapy plus XYS	p-value
HADS-D score, mean ± SD			
T ₀	7.6 ± 3.0	7.4 ± 2.9	0.538
T ₁	7.9 ± 2.8	7.4 ± 2.8	0.255
T ₂	8.1 ± 3.1	6.9 ± 3.0	0.016
T ₃	7.8 ± 2.4	6.9 ± 2.4	0.018
T ₄	7.7 ± 2.8	6.6 ± 2.6	0.017
Depression rate*, %			
T ₀	40.0	34.6	0.485
T ₁	43.0	36.5	0.393
T ₂	44.9	29.6	0.047
T ₃	47.1	27.5	0.012
T ₄	43.7	24.6	0.013

HADS-D, Hospital Anxiety and Depression Scale for depression; XYS, Xiaoyaosan; SD, standard deviation; T₀, before adjuvant chemotherapy; T₁, the first cycle after adjuvant chemotherapy; T₂, the second cycle after adjuvant chemotherapy; T₃, the third cycle after adjuvant chemotherapy; T₄, the fourth cycle after adjuvant chemotherapy. *, a HADS-D score greater than 7 was defined as depression.

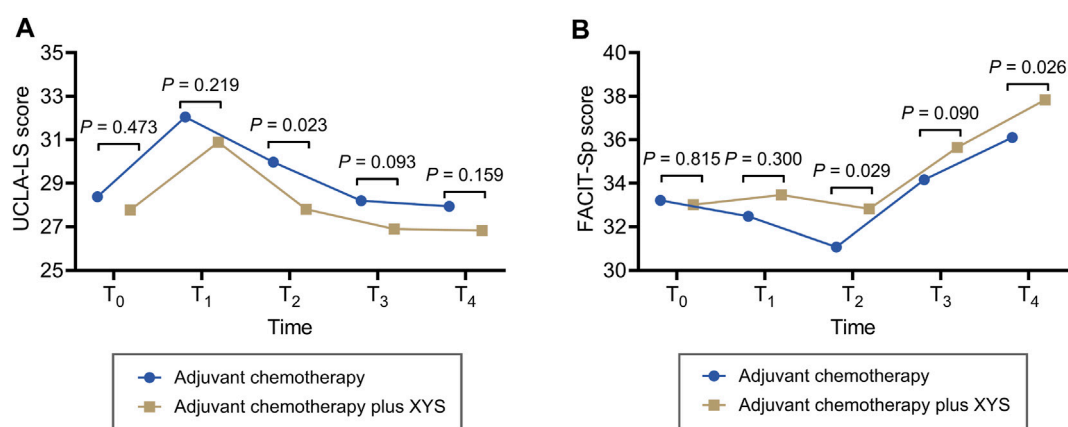


FIGURE 2
YYS attenuated loneliness and improved spiritual well-being. Comparisons of the UCLA-LS score (A) and FACIT-Sp score (B) at T₀, T₁, T₂, T₃, and T₄ between the adjuvant chemotherapy plus YYS group and the adjuvant chemotherapy group.

chemotherapy group (Table 5). Furthermore, no liver- or kidney-related adverse events occurred in this study.

3.7 Subgroup analysis

The subgroup analysis was carried out based on the TNM stage. These findings indicated that most outcomes were not statistically significant in the subgroup analysis, even though a tendency still existed. Specifically, the QLQ-C30 global health status score, QLQ-C30 functional scale score, and FACIT-Sp score were numerically greater, while the QLQ-C30 symptom scale score, HADS-A score, anxiety rate, HADS-D score, depression rate, and UCLA-LS score were numerically lower at T₄ in the adjuvant chemotherapy plus YYS subgroup than in the adjuvant chemotherapy subgroup in the TNM stage I, II, and III subgroups (Supplementary Table S1).

4 Discussion

Previous studies have focused mainly on the ability of YYS to alleviate anxiety or depression, and some studies have explored its potential mechanism (Wang et al., 2024; Wu et al., 2024). For instance, one study indicated that YYS might inhibit neuroinflammation to treat depression by regulating the TRIM31/NLRP3 inflammasome (Wang et al., 2024). However, the effect of YYS on QoL in breast cancer patients has seldom been reported. In this study, the addition of YYS to chemotherapy might improve the QLQ-C30 global health and symptom scores. These findings were similar to those of the previous studies, which also reported that YYS might alleviate depression symptoms in patients with depression (Hu et al., 2021; Liu et al., 2021). Even though this study did not carry out any mechanistic experiment, the mechanism of YYS on improving the QLQ-C30 global health and symptom scores might be explained by referring to the previous study, which reported

that YYS could relieve depression and anxiety through several mechanisms, such as participating in the autophagy of hypothalamic neurons (Peterman et al., 2002; Zeng et al., 2022; Wang et al., 2024), regulating synapses or synaptic-associated signals (Wu et al., 2024), regulating neurotransmitters (Hagiwara et al., 2023; Javan Biparva et al., 2023; Gudhoor et al., 2024), and regulating the brain-gut axis (Chen et al., 2022), thereby alleviating mental disorders to further improve the global health status and reduce the symptoms of breast cancer patients. However, these hypotheses about the mechanism still need further exploration. However, the functional score of the QLQ-C30 improved relatively little, which was mainly because the QLQ-C30 functional score mainly consisted of the physical function, role function, emotional function, cognitive function, and social function ((Hagiwara et al., 2023; Biparva et al., 2023)); YYS could only have a specific effect on emotional function and social function but had little impact on physical function, role function, or cognitive function. Therefore, chemotherapy plus YYS improved the QLQ-C30 functional score only to a certain degree (the significance of the difference between the two groups was observed only at T₄).

Mental disorders, including anxiety and depression, are frequently reported in cancer patients, especially in breast cancer patients undergoing adjuvant chemotherapy, who might suffer from adverse reactions to mastectomy and chemotherapy (Hashemi et al., 2020; Biparva et al., 2023). It has been reported that the depression and anxiety rates in breast cancer patients are as high as 30.2% and 41.9%, respectively (Hashemi et al., 2020; Biparva et al., 2023). These mental disorders further induce low compliance with subsequent therapy and even lead to suicide (Bui and Fava, 2017). Hence, it is essential to relieve mental illness in patients with breast cancer. YYS is a traditional Chinese medicine consisting of *Angelicae Sinensis* Radix, *Bupleuri* Radix, *Paeoniae* Radix Alba, *Atractylodis Macrocephalae* Rhizoma, *Poria*, *Zingiberis* Rhizoma Recens, *Glycyrrhizae* Radix et Rhizoma, and

TABLE 4 Clinical characteristics of breast cancer patients after adjustment via propensity score analysis.

Characteristic	Adjuvant chemotherapy ^{ad} (N = 73)	Adjuvant chemotherapy plus XYS ^{ad} (N = 73)	<i>P</i> ^{ad} value
Age (years), mean ± SD	52.9 ± 10.5	50.9 ± 10.4	0.253
Married, No. (%)	64 (87.7)	63 (86.3)	0.806
Employed, No. (%)	34 (46.6)	40 (54.8)	0.321
Level of education, No. (%)			0.299
Primary school	5 (6.8)	2 (2.7)	
Middle school	20 (27.4)	13 (17.8)	
High school	31 (42.5)	43 (58.9)	
Undergraduate or above	17 (23.3)	15 (20.5)	
Residence, No. (%)			0.574
Rural	8 (11.0)	6 (8.2)	
Urban	65 (89.0)	67 (91.8)	
Lesion site, No. (%)			0.796
Unilateral	65 (89.0)	64 (87.7)	
Bilateral	8 (11.0)	9 (12.3)	
Histologic grading, No. (%)			0.577
Grade I	16 (21.9)	12 (16.4)	
Grade II	35 (47.9)	38 (52.1)	
Grade III	22 (30.1)	23 (31.5)	
T-stage, No. (%)			0.291
1	19 (26.0)	11 (15.1)	
2	44 (60.3)	53 (72.6)	
3	10 (13.7)	9 (12.3)	
N-stage, No. (%)			0.178
0	39 (53.4)	47 (64.4)	
1	17 (23.3)	14 (19.2)	
2	15 (20.5)	10 (13.7)	
3	2 (2.7)	2 (2.7)	
M-stage, No. (%)			1.000
0	73 (100.0)	73 (100.0)	
TNM stage, No. (%)			0.442
I	9 (12.3)	8 (11.0)	
II	44 (60.3)	51 (69.9)	
III	20 (27.4)	14 (19.2)	
ER positive, No. (%)	42 (57.5)	41 (56.2)	0.867
PR positive, No. (%)	39 (53.4)	38 (52.1)	0.868
HER-2 positive, No. (%)	22 (30.1)	24 (32.9)	0.722
Ki67 ≥ 30%, No. (%)	24 (32.9)	28 (38.4)	0.489

(Continued on following page)

TABLE 4 (Continued) Clinical characteristics of breast cancer patients after adjustment via propensity score analysis.

Characteristic	Adjuvant chemotherapy ^{ad} (N = 73)	Adjuvant chemotherapy plus YYS ^{ad} (N = 73)	P ^{ad} value
Adjuvant chemotherapy regimen, No. (%)			0.754
AC-T	46 (63.0)	41 (56.2)	
AC-TH	15 (20.5)	19 (26.0)	
AC	5 (6.8)	8 (11.0)	
AC-THP	5 (6.8)	4 (5.5)	
AC + H	2 (2.7)	1 (1.4)	

YYS, Xiaoyaosan; SD, standard deviation; TNM, tumor–node–metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; T₀, before adjuvant chemotherapy; T₁, the first cycle after adjuvant chemotherapy; T₂, the second cycle after adjuvant chemotherapy; T₃, the third cycle after adjuvant chemotherapy; T₄, the fourth cycle after adjuvant chemotherapy. 'ad' indicates that the data were adjusted via propensity score analysis.

Menthae Haplocalycis Herba, which can alleviate depression-like behavior by regulating necroptosis-related cellular senescence in the hypothalamus in a mouse model (Jiao et al., 2023). However, its clinical application for relieving mental disorders in breast cancer patients is scarce. In this study, treatment with adjuvant chemotherapy plus YYS decreased the depression rate from 34.6% to 24.6% and the anxiety rate from 39.5% to 26.1% in breast cancer patients, which was more satisfactory than that of adjuvant chemotherapy monotherapy. These findings could be explained as follows: (Sung et al., 2021): YYS might have an antidepressant effect through various mechanisms, such as downregulating A2AR signaling, participating in the autophagy of hypothalamic neurons by regulating GLUT4 expression, and promoting hippocampal neurogenesis (Yang FR. et al., 2022; Zeng et al., 2022; Zhu et al., 2022; Ren et al., 2022). YYS can also regulate synapse- or synaptic-associated signaling pathways, including the neurotrophin signaling and PI3K/AKT signaling pathways, thereby alleviating depression (Meng et al., 2023; Yang S. et al., 2022). YYS has a specific effect on regulating neurotransmitters such as dopamine, 5-hydroxytryptophan, and thyroid hormone; the latter plays an essential role in the pathogenesis of depression and anxiety (Kong et al., 2010; Ding et al., 2014; Zhang et al., 2021; Alkabban and Ferguson, 2023). YYS can also regulate the brain–gut axis, neuroinflammation, and the neuroendocrine axis, thus further acting on its antidepressant effect (Chen et al., 2022). Hence, YYS might play an antidepressant role in breast cancer patients in this study.

Additionally, YYS improved loneliness (as reflected by the UCLA-LS score) and spiritual well-being (as reflected by the FACIT-Sp score) in this study. These findings could be explained as follows: loneliness was positively associated with depression symptoms (Friedman-Ezra et al., 2024). YYS might alleviate depression symptoms through several mechanisms, as mentioned above; therefore, feelings of loneliness are relieved accordingly. Therefore, spiritual well-being is a subjective feeling based on comprehensive assessments of the overall status of the patients themselves. When the QoL improved, anxiety and depression were relieved, and their spiritual well-being improved accordingly.

There was an imbalance in the baseline (T₀) characteristics between the two groups. Hence, the adjustment of the baseline characteristics via propensity score methods was carried out to eliminate this potential confounder (D'Agostino, 1998). After the adjustment, there was no difference in the baseline characteristics between the two groups, and the difference in primary outcomes, including anxiety, depression, QoL, loneliness, and spiritual well-being, did not change between the two groups. These findings further validated the effectiveness of chemotherapy plus YYS in breast cancer patients.

Although some methods, such as the propensity score method, have been used for remedying methodological deficiencies, our study has several limitations (Sung et al., 2021). The sample size was small, and this limitation was aggravated after adjustment by the propensity score method. Hence, further studies with larger sample sizes are needed (Ren et al., 2022). The follow-up period should be prolonged due to the short follow-up period in this study (Yang S. et al., 2022). The TNM stage was mainly I–II in most patients (approximately 70%) in this study, indicating a relatively low disease burden. However, treatment strategies differ between early-stage and advanced-stage breast cancer patients, which means that the outcomes and treatment-related side effects also differ. Hence, further studies should be conducted to determine the efficacy of chemotherapy plus YYS in breast cancer patients with greater disease burdens, such as those with advanced breast cancer (Alkabban and Ferguson, 2023). When we would like to apply YYS in treating breast cancer patients, some research gaps needed to be solved, such as the detailed mechanism, its efficacy and safety, how to be involved in the current treatment strategy, treatment timing, dosage, and individualized treatment. Our study only preliminarily explored its efficacy and safety. However, more studies are needed to resolve other research gaps before extensively applying YYS in treating breast cancer patients.

In conclusion, adding YYS to adjuvant chemotherapy improved QoL, psychological pressure, and spiritual well-being in postoperative patients with breast cancer, and these advancements remained even after adjustment via propensity score analysis.

TABLE 5 Comparisons of the QLQ-C30 scores, HADS-A scores, anxiety rates, HADS-D scores, depression rates, UCLA-LS scores, and FACIT-Sp scores between the two groups after adjustment.

Item	Adjuvant chemotherapy ^{ad}	Adjuvant chemotherapy plus XYS ^{ad}	<i>P</i> ^{ad} value
QLQ-C30 global health status, mean ± SD			
T ₀	67.3 ± 13.6	67.3 ± 15.9	0.991
T ₄	67.9 ± 14.8	74.5 ± 15.3	0.013
QLQ-C30 functional scale, mean ± SD			
T ₀	65.5 ± 16.1	65.8 ± 15.7	0.909
T ₄	68.2 ± 13.7	74.3 ± 12.9	0.010
QLQ-C30 symptom scale, mean ± SD			
T ₀	29.4 ± 15.8	30.6 ± 16.5	0.645
T ₄	27.8 ± 13.0	23.7 ± 11.9	0.066
HADS-A score, mean ± SD			
T ₀	7.4 ± 3.7	7.6 ± 3.1	0.700
T ₄	7.7 ± 3.4	6.8 ± 2.6	0.077
Anxiety rate, %			
T ₀	32.9	39.7	0.389
T ₄	39.7	29.0	0.201
HADS-D score, mean ± SD			
T ₀	7.5 ± 2.9	7.3 ± 2.8	0.749
T ₄	7.8 ± 2.8	6.4 ± 2.4	0.002
Depression rate, %			
T ₀	35.6	35.6	1.000
T ₄	44.1	22.6	0.010
UCLA-LS score, mean ± SD			
T ₀	28.3 ± 6.3	27.7 ± 4.9	0.570
T ₄	27.7 ± 5.6	26.8 ± 3.5	0.271
FACIT-Sp score, mean ± SD			
T ₀	32.8 ± 5.3	33.4 ± 5.7	0.558
T ₄	36.1 ± 4.4	37.9 ± 5.0	0.035

QLQ-C30, Quality of Life Questionnaire Core 30; HADS-A, Hospital Anxiety and Depression Scale for anxiety; HADS-D, Hospital Anxiety and Depression Scale for depression; UCLA-LS, University of California Los Angeles Loneliness Scale; FACIT-Sp, Functional Assessment of Chronic Illness Therapy–Spiritual Well-being; XYS, Xiaoyaosan; SD, standard deviation; T₀, before adjuvant chemotherapy; T₄, the fourth cycle after adjuvant chemotherapy. 'ad' indicates that the data were adjusted via propensity score analysis. Anxiety was defined as a HADS-A score greater than 7, and depression was defined as a HADS-D score greater than 7.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of The First Affiliated Hospital of Bengbu Medical University. The studies were conducted in accordance with the

local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CW: conceptualization, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing. LY: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing–original draft, and writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2024.1388646/full#supplementary-material>

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