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ORIGINAL RESEARCH

Modulatory Effects of XIAOPI Formula on CXCL1 and Selected Outcomes in Triple-Negative Breast Cancer: A Randomized Controlled Clinical Trial

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Background: Triple-negative breast cancer (TNBC) is the most aggressive malignancy. Psychological distress and elevated CXCL1 level have been reported to be closely associated with the poor prognosis and quality of life of patients with TNBC. In preclinical studies using xenograft mouse models, XIAOPI formula, a nationally approved drug prescribed to patients at high risk for breast cancer, inhibited CXCL1 expression and improved survival. Traditional Chinese medicine has unique advantages in improving patients' emotional disorders and quality of life. However, the impact of XIAOPI formula on the serum level of CXCL1, psychological distress, and quality of life among patients with TNBC is currently unknown.

Methods: In this study, we designed a randomized, double-blind, placebo-controlled trial. Patients with TNBC were randomly assigned to receive either the XIAOPI formula or a placebo for three months. The primary outcomes include serum CXCL1 expression, Self-Rating Anxiety Scale (SAS), and the Self-Rating Depression Scale (SDS). Secondary outcomes included the Pittsburgh Sleep Quality Index (PSQI) and the Functional Assessment of Cancer Therapy-Breast (FACT-B).

Results: A total of 60 patients with TNBC were enrolled in the investigation. The results showed that the XIAOPI formula significantly decreased CXCL1 expression compared with the control group. Moreover, in comparison to the placebo, the XIAOPI formula increased FACT-B scores while decreasing SDS, SAS, and PSQI scores.

Conclusion: In patients with TNBC, XIAOPI formula may be effective in reducing CXCL1 levels, enhancing psychological well-being, and quality of life. While our research offers a natural alternative therapy that may enhance the prognosis of TNBC, future validation of its therapeutic effects will require large-scale, long-term clinical trials.

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Keywords: anxiety, CXCL1, depression, quality of life, sleep quality, triple-negative breast cancer, XIAOPI formula

Introduction

The most recent international statistics compiled by the International Agency for Research on Cancer (IARC) indicate that breast cancer has the highest incidence rate of all malignancies. Globally, the incidence of breast cancer was estimated to have increased to approximately 2.26 million new cases in 2020, resulting in 0.68 million breast cancer-related deaths.[1]

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Triple-negative breast cancer (TNBC) accounts for 15–20% of all pathological subtypes and is considered to have the most unfavorable clinical outcomes and prognosis.[2] At present, research indicates that the five-year survival rate for triple-negative breast cancer is approximately 77%.[3] This figure is significantly constrained by the slow advancements in targeted drugs. How to improve quality of life and clinical prognosis has emerged as a great challenge for oncologists.

Current research indicates that TNBC is closely associated with human immunity. TNBC is associated with increased tumor mutation burden, T cell infiltration, and PD-L1 expression.[4] Additionally, a poor prognosis and a microenvironment that suppresses the immune system are associated with a high infiltration of tumor-associated macrophages (TAMs) in triple-negative breast cancer.[5] Our previous study has demonstrated that CXCL1 is the highest chemokine secreted by TAMs.[6] In bladder cancer, it has been shown that urinary CXCL1 levels are significantly elevated in patients with invasive phenotypes than in those with noninvasive tumors and normal controls.[7] Whereas, CXCL1 demonstrates predictive power for the survival of patients with gastric cancer as an independent variable,[8] CXCL1 upregulation is significantly correlated with the progression and advanced stage of gastric cancer. Moreover, it was discovered that CXCL1 derived from TAMs recruited $CXCR2^{+}$ myeloid-derived suppressor cells (MDSCs) to form a premetastatic niche, which finally led to liver metastasis in colorectal cancer.[9] In breast cancer, TAM-derived CXCL1 can facilitate metastasis by activating the NF-κB/SOX4 pathway.[6] Meanwhile, bioinformatic analysis and clinical investigation suggest that CXCL1 upregulation is significantly associated with TNBC, lymph node metastasis, and poor overall survival. In addition, a meta-analysis involving 2265 patients with cancer revealed that elevated CXCL1 expression in cancer is a risk factor indicating poor overall survival, an advanced TNM stage, and lymph node metastasis; thus, CXCL1 may be a promising prognostic biomarker for predicting cancer prognosis.[10]

In addition to the immunosuppressive microenvironment, patients with TNBC have a significantly elevated likelihood of developing psychological distress, such as anxiety and depression, when compared to other breast cancer subtypes.[11] Psychological disorders have been demonstrated to adversely affect the adherence to treatment and survival rates of patients with cancer.[12] In addition, psychological disorders may contribute to the recurrence and metastasis of breast cancer through their ability to exacerbate tumor metabolism, immune suppression, oxidative stress, and glucocorticoid secretion, among other mechanisms.

Therefore, TNBC is frequently correlated with a decline in health-related quality of life (HRQoL).[13,14] In addition, poor sleep quality is also prevalent in patients with TNBC due to the cytotoxic therapies and the fear of a poor prognosis.[15] Notably, it has been reported that the economic burden of patients with TNBC is a significant factor influencing their psychological distress and quality of life.[16] Given that TNBC typically occurs in younger individuals, the economic burden on the TNBC population is likely to be even more substantial. Therefore, it is critical and essential to identify an economic and effective way to enhance the psychological well-being and quality of life of patients diagnosed with TNBC.

Traditional Chinese medicine (TCM) is widely recognized for its efficacy and cost-effectiveness in enhancing the clinical prognosis and life quality of patients with cancer. In a prospective cohort study, it was revealed that the implementation of TCM could reduce the disease-related recurrence and metastasis rate by 11%.[17] The 2-year rate of invasive disease-free survival (DFS) in the TCM-exposed group was 88.7%, and in the non-exposed group was 82.5%.[17] At the same time, several TCM formulations have been discovered to inhibit the growth or metastasis of TNBC in mouse xenografts. It has been reported that the Shuganhuazheng formula inhibits TNBC growth by suppressing HIF-1 and Akt expression.[18] Tubeimu extracts were discovered to inhibit TNBC metastasis by decreasing levels of integrin β1, β8, and Rho GTPase activating protein 5.[19] Current evidence regarding the anti-tumor activity of TCM and natural medicine in TNBC is summarized in a literature review.[20] The results demonstrated that TCM formulations and plant medicine inhibited multiple processes of TNBC, including growth, proliferation, migration, invasion, and metastasis. Meanwhile, multiple pathways, such as PI3K/Akt/mTOR, MAPK, and Wnt/β-catenin, are involved in the molecular mechanisms of the anti-tumor activities of TCM. And not only that, TCM has also been proven to have advantages in improving emotional disorders and quality of life in cancer patients. In 2023, a meta-analysis of 9 randomized controlled trials involved 789 participants stated that a therapeutic regimen involving TCM could better improve the depression status and it can be an add-on therapy for postoperative depression in breast cancer patients. The results showed the intervention group was better at decreasing the score of the Hamilton rating scale for depression (HAMD) (mean difference, MD = −4.21, 95% CI −5.54

to −2.88) and SDS (MD = −12.03, 95% CI −15.94 to −8.13).[21] Another meta-analysis showed that TCM, when used in conjunction with the conventional Western medicine, could effectively improve the quality of life of breast cancer patients measured by rating scales (standardized mean difference, SMD = 1.29, *P*=0.01) and ranking scales (relative risk ratio, RR = 1.53, *P*=0.02) compared with the single-used conventional Western medicine treatment.[22]

The XIAOPI formula is an officially approved drug for mammary hyperplasia treatment by the National Medical Products Administration of China. Previous studies demonstrated that the formula is effective in relieving atypical hyperplasia, mastalgia, and lump growth.[23] Meanwhile, the formulation exhibits minimal adverse effects during treatment. Our previous animal study demonstrated that the XIAOPI formula could inhibit TNBC growth and metastasis by suppressing TAMs and CXCL1.[24] Additionally, it was discovered that the XIAOPI formula enhances breast cancer chemosensitivity by inhibiting CXCL1/HMGB1-mediated autophagy.[25] Furthermore, XIAOPI formula can inhibit the pre-metastatic niche formation in TNBC by suppressing TAMs/CXCL1-mediated MDSC accumulation.[24] Intriguingly, the number of cancer stem cells in TNBC was also significantly reduced after XIAOPI administration.[26] These results collectively indicate that the XIAOPI formula could potentially enhance the clinical prognosis and quality of life of patients with TNBC. Further investigation is urgently required to validate its clinical efficacy in enhancing life quality and decreasing CXCL1 levels in patients with TNBC.

A randomized controlled trial was conducted in the current study to investigate the potential clinical effects of the XIAOPI formula on reducing the CXCL1 level and improving selected outcomes, namely anxiety, depression, sleep quality and life quality in patients with TNBC.

Methods

Study Design

This was a preliminary randomized, double-blind, placebo-controlled clinical trial. The Institutional Research Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine granted approval for the study (No. ZF2018-097). The study protocol is registered at the Chinese Clinical Trials Registry (Registration website: www.chictr.org.cn, Registration date: 2018-1-19, Registration number: ChiCTR1800014535). The protocols in this study adhere to the guidelines and regulations of China for good clinical practice as well as the World Medical Association Declaration of Helsinki. All participants provided signed, written informed consent before participating in this research (Supplementary Material - CONSORT 2010 checklist).

Randomization was performed using computer-generated numbers and stratified by center at a ratio of 1:1. An independent statistician with no clinical involvement in the trial prepared the randomization sequence and allocation concealment. The group designations remained unknown to all investigators, staff, participants, pharmacists, and sponsor personnel who were involved in the treatment administration, drug allocation, or clinical evaluation. The XIAOPI medication/placebo was administered in a blinded manner as capsules, which were identically packaged.

Population

The following were the inclusion criteria for the study: (a) Patients included in the study were women aged ≥ 18 years and ≤ 60 years; (b) histologically diagnosed as invasive breast cancer with pathological subtypes as triple negative, including ER-, PR-, and HER2-; (c) complete surgery and chemotherapy and follow up for at least 5 years; (d) absence of dysphagia and ability to take TCM formulas orally; (e) provided written informed consent in accordance with the requirements of the local ethics committee; (f) and an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

The exclusion criteria for this study included the following: (a) metastatic breast cancer; patients with recurrence and metastasis during follow-up; (b) family history of endometrial cancer or any other kind of gynecologic cancer; (c) patients who were pregnant, lactating, menopausal, or had an intention to become pregnant; (d) patients who had received hormone replacement therapy, contraceptives, or androgen treatment within the previous three months; (e) patients who had also been administered other TCM formulas or botanical drugs; (f) individuals who presented with dysphagia, chronic diarrhea, bowel obstruction and other difficulties in taking formulas; (g) allergic to any phytochemical in the formula; (h) severe comorbidity that indicating intolerance to TCM formula treatment; psychiatric disorders or

other diseases leading to noncompliance to the therapy; (i) patients suspected of alcohol or drug abuse; (j) patients with cognitive impairment or limited education who are unable to comprehend and complete the scales.

Intervention and Comparison

Patients with TNBC who completed surgery and chemotherapy were included and randomly assigned (1:1) to either the XIAOPI group (treatment group) or the placebo group (control group). The XIAOPI formula consists of 10 herbs, including Epimedium brevicornum (Chinese name YIN YANG HUO, YYH), Cistanche deserticola (Chinese name ROU CONG RONG, RCR), Leonurus heterophyllus (Chinese name YI MU CAO, YMC), Salvia miltiorrhiza (Chinese name DAN SHEN, DS), Curcuma Aromatica (Chinese name YU JIN, YJ), Rhizoma Curcumae (Chinese name E ZHU, EZ), Ligustrum lucidum (Chinese name NV ZHEN ZI, NZZ), Radix Polygoni Multiflori Praeparata (Chinese name HE SHOU WU, HSW), Crassostrea gigas (Chinese name MU LI, ML), and Carapax Trionycis (Chinese name BIE JIA, BJ). The formulation was manufactured and supplied by Guangdong QIJI Pharmaceutical Company Ltd. (No. 180,101). Placebo was made of maltodextrin and had a taste and appearance similar to XIAOPI formula. All patients were administered either 8.5 g of the XIAOPI formula or placebo treatment three times daily for three months. The dosage used in the current study was compared to that in mammary hyperplasia treatment. The administration of the medication was halted during the menstrual period for the respective patients. The drug treatment was discontinued for patients who experienced severe adverse events during the trial period.

Outcome Measures

The serum level of CXCL1 was detected. CXCL1 concentrations were measured in serum samples collected from the patients both prior to and following the treatment using the Human CXCL1 ELISA Kit (SEA041Hu, USCN Business) in accordance with the ELISA assay protocol.

The anxiety and depression levels of the patients were assessed using the Self-Rating Anxiety Scale (SAS),[27] and the Self-Rating Depression Scale (SDS),[28] respectively, prior to and following the treatment. Each scale consists of 20 parameters, with each item rating from 1 to 4. The scores for each item were then added and multiplied by 1.25 to obtain the final score. In accordance with the Chinese population, a high score (≥ 50) on the SAS or SDS was defined as positive for anxiety or depression, respectively.

The secondary outcomes included life quality improvement and sleep quality in patients with TNBC, which were assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B)[29] and the Pittsburgh Sleep Quality Index (PSQI) questionnaires,[30] respectively. As an instrument for assessing the physiological, emotional, and social functioning of patients with breast cancer, the FACT-B questionnaire is universally utilized. The questionnaire includes the FACT-G, an evaluation of the life quality of patients with general cancer, and a subscale for breast cancer. The FACT-G contains subscales including physical (7 items), functional (7 items), emotional (6 items), and social well-being (7 items). The breast cancer subscale comprises 9 items. The total score of FACT-B is 144. The higher the score, the better the quality of life for the patient.

The PSQI was used to evaluate the sleep quality of patients. PSQI has 7 items, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping pills, and daytime dysfunctions. The aggregate of the individual item scores (from 0 to 3) gives the overall scores, which range from 0 to 21. A score greater than 7 indicated poor sleep quality.

Clinicopathological Information Collection

The clinical information of patients enrolled in the trial was obtained from the electronic medical record system of the Guangdong Provincial Hospital of Chinese Medicine. This information comprised age, menstrual status, body mass index (BMI), ECOG score, and parameters of routine blood tests and biochemical analysis. Pathological sections were diagnosed by two independent pathologists. The parameters included tumor size, lymph node metastasis, histological grade, ER, PR, HER2, and vascular invasion. ER and PR were defined as positive when their expression was $\geq 1\%$. HER2 positive status was confirmed as 3+ by immunohistochemistry or + by fluorescence in situ hybridization (FISH). Breast cancer staging was performed in accordance with the seventh edition of American Joint Committee on Cancer. The previous treatment strategies of each patient were obtained from the database maintained by the multidisciplinary team.

Statistical Analysis

Baseline demographic and clinical characteristics were calculated using *t*-tests for continuous and ordinal variables. Chi-squared tests were used to compare the nominal variables. Comparisons of scale scores at different phases of treatment were performed using analysis of variance tests for paired samples. For the individual time points, between-group analyses were conducted using *t*-tests or Mann–Whitney *U*-tests. Differences were considered statistically significant at $P < 0.05$. All statistical analyses were conducted utilizing version 26.0 of the SPSS software for Windows.

Results

Demographic and Clinical Characteristics of Patients with TNBC

A total of 60 patients with cancer went through the screening process between June 2018 and May 2020. Among these patients, 30 were randomly assigned to the treatment group and the remaining 30 to the control group. The CONSORT flow diagram is presented in Figure 1. Table 1 provides a summary of the demographic characteristics and pathological parameters of the control and treatment groups at baseline. The mean age was 47.1 ± 10.4 years, with 23 women (38.3%) being at least 50 years old; 80% of patients were non-obese (BMI < 25), and the rest were obese (BMI ≥ 25). Thirty-two patients (53.3%) were premenopausal, 26 (43.3%) were postmenopausal, and the remaining 2 (3.3%) were unknown. While implementing randomization, there were no baseline differences observed between the control and treatment groups in terms of age, BMI, menopause status, age at menarche, number of pregnancies, age at first birth, number of births, and lactation time ($P > 0.05$).

Histologically, the pathological grading of breast cancer comprised grade 1 (1.7%), grade 2 (36.7%), and grade 3 (61.7%). Furthermore, an equal distribution was observed between left-side (50.0%) and right-side (50.0%) breast cancer cases. Notably, a majority of patients, accounting for 91.7%, were diagnosed with Stage I or Stage II breast cancer. In

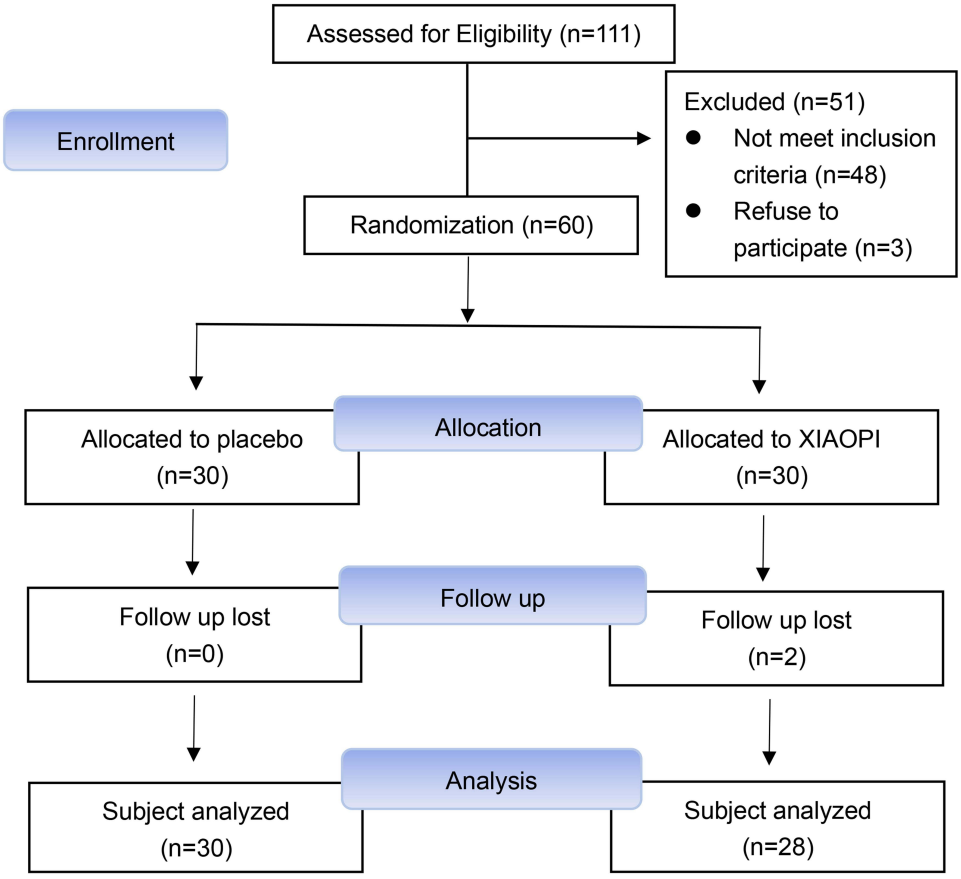

Figure 1 Study flowchart.

Table 1 Demographic and Clinical Characteristics of Enrolled Participants

Characteristic	Total	Control group	XIAOPI group	*P* value
Age, Mean (SD), year	47.1(10.4)	48.6 (9.6)	45.5 (11.1)	0.25
Age				0.18
<50 years	37(61.7%)	16	21	
≥50 years	23(38.3%)	14	9	
BMI				0.52
<25	48(80%)	23	25	
≥25	12(20%)	7	5	
Menopausal status				0.55
Pre-menopausal	32(53.3%)	18	14	
Post-menopausal	26(43.3%)	11	15	
Not known	2(3.3%)	1	1	
Menarche age				0.44
≤13	33(55.0%)	15	18	
>13	27(45.0%)	15	12	
Pregnancy times				0.89
0	3(5%)	2	1	
1–2	32(53.3%)	15	17	
≥3	25(41.7%)	13	12	
Delivery times				0.37
0	4(6.7%)	3	1	
1–2	52(86.7%)	26	26	
≥3	4(6.7%)	1	3	
Age at first reproduction				0.72
20–24 years	17(28.3%)	7	10	
25 −30 years	35(58.3%)	19	16	
>30 years	5(8.3%)	2	3	
Not known	3(5.0%)	2	1	
Duration of lactation				0.72
0–6 months	28(46.7%)	13	15	
7–12 months	21(35.0%)	10	11	
>12 months	7(11.7%)	4	3	
Not known	4(6.7%)	3	1	

(*Continued*)

Table 1 (Continued).

Characteristic	Total	Control group	XIAOPI group	*P* value
Histological grade				0.60
I	1(1.7%)	0	1	
2	22(36.7%)	11	11	
3	37(61.7%)	19	18	
Location of tumor				0.61
Left breast	30 (50.0%)	16	14	
Right breast	30 (50.0%)	14	16	
Cancer stage				0.72
I	24(40.0%)	13	11	
II	31(51.7%)	14	17	
III	5(8.3%)	3	2	
Tumor size				0.79
<2 cm	23(38.3%)	11	12	
≥2 cm	37(61.7%)	19	18	
Number of metastatic lymph nodes				0.78
0	46 (76.7%)	22	24	
1–3	10 (16.7%)	6	4	
≥4	4 (6.7%)	2	2	

relation to tumor size, 61.7% exhibited sizes exceeding 2 cm, while the remaining 38.3% manifested sizes less than 2 cm. Furthermore, a notable observation was made, indicating that 76.7% of the patients did not present with metastatic lymph nodes. Similarly, there were no differences in tumor histological grade, location, stage, tumor size, or lymph node status between the control and treatment groups ($P > 0.05$).

The prevalence of anxiety, depression, and poor sleep quality was balanced between the control and treatment groups at baseline ($P > 0.05$), as shown in Table 2.

Primary Outcomes

XIAOPI Formula Inhibits CXCL1 Expression in Patients with TNBC

To evaluate the effects of the XIAOPI formula on CXCL1 expression in patients with breast cancer, its level was detected in both groups prior to and subsequent to the administration of the drug. There were no statistically significant differences in CXCL1 expression at baseline between the treatment and control groups ($P > 0.05$), as shown in Table 3. However, following 3-month treatment, the downregulation of CXCL1 level (11.28 pg/mL) in the treatment group was significantly higher compared with the control group (0.73 pg/mL).

XIAOPI Formula Decreases the SAS and SDS Scores of Patients with TNBC

To evaluate the effects of the XIAOPI formula on improving patients' emotional well-being, the scores of SAS and SDS were compared before and after treatment. There were no significant differences in anxiety and depression between the treatment and control groups at baseline ($P > 0.05$), as shown in Table 4. However, SAS and SDS scores decreased after

Table 2 Prevalence of Anxiety, Depression, and Sleep Quality in TNBC Patients

Characteristic	Total	Control group	XIAOPI group	*p* value
SAS				0.74
<50	49(81.7%)	25 (83.3%)	24 (80.0%)	
≥50	11(18.3%)	5 (16.7%)	6 (20.0%)	
SDS				0.44
<50	33(55.0%)	15 (50.0%)	18 (60.0%)	
≥50	27(54.0%)	15 (50.0%)	12 (40.0%)	
PSQI				0.60
≤7	24(40.0%)	13 (43.3%)	11 (36.7%)	
>7	36(60.0%)	17 (56.7%)	19 (63.3%)	

Table 3 Comparison of CXCL1 Expression of the Breast Patients Before and After XIAOPI Formula Intervention (`x±s, Pg/Ml)

Variable	Group	Baseline	Postintervention	Mean differences	Statistics (*p*)
CXCL1	Control group	64.23±31.98	57.92±27.43	−0.73±14.04	0.046
	XIAOPI group	67.01±27.32	55.73±19.69	−11.28±22.62	

XIAOPI treatment, while they increased in the control group (Inter-groups comparison, $P = 0.020$ for SAS and $P = 0.031$ for SDS). These findings suggest that anxiety and depression were significantly improved by XIAOPI administration.

Secondary Outcomes

XIAOPI Formula Decreases the PSQI Scores of Patients with TNBC

To evaluate the effects of the XIAOPI formula on enhancing the sleep quality of patients, the scores of PSQI were compared before and after treatment. There were no significant differences in PSQI between the intervention and control groups at baseline ($P > 0.05$), as shown in Table 4. Following XIAOPI administration, PSQI scores decreased by 2.04 points, while they decreased

Table 4 Comparison of the SAS, SDS, PSQI and FACT-B Scores of the Breast Patients Before and After XIAOPI Formula Intervention (`x±s, Scores)

Variable	Group	Baseline	Postintervention	Mean differences	Statistics (*p*)
SAS	Control group	43.57±6.65	45.32±6.56	1.54±3.98	0.020
	XIAOPI group	43.83±8.62	39.48±9.69	−3.78±10.54	
SDS	Control group	48.67±9.80	49.23±8.87	0.57±8.76	0.031
	XIAOPI group	49.53±10.40	43.25±13.29	−6.89±15.50	
PSQI	Control group	9.93±4.71	9.42±4.78	−0.039±2.71	0.019
	XIAOPI group	9.40±4.17	7.37±3.51	−2.04±3.25	

(*Continued*)

Table 4 (Continued).

Variable	Group	Baseline	Postintervention	Mean differences	Statistics (*p*)
Subjective sleep quality	Control group	1.47±0.82	1.54±0.83	0.15±0.83	0.027
	XIAOPI group	1.60±0.77	1.26±0.81	−0.37±0.84	
Sleep latency	Control group	2.30±0.79	2.15±0.78	−0.039±0.72	0.15
	XIAOPI group	2.10±0.80	1.78±0.64	−0.33±0.73	
Sleep duration	Control group	1.33±1.12	1.19±1.13	−0.039±0.66	0.45
	XIAOPI group	1.20±0.92	1.07±0.92	−0.19±0.74	
Sleep efficiency	Control group	1.40±1.25	1.35±1.32	0.039±0.72	0.18
	XIAOPI group	1.23±1.19	0.93±1.11	−0.26±0.86	
Sleep disturbances	Control group	1.37±0.56	1.23±0.51	−0.077±0.48	0.10
	XIAOPI group	1.50±0.57	1.15±0.53	−0.33±0.62	
Sleep medication usage	Control group	0.43±0.94	0.46±1.03	0.077±0.74	0.27
	XIAOPI group	0.20±0.76	0.074±0.27	−0.15±0.72	
Daytime dysfunction	Control group	1.63±0.89	1.57±1.01	−0.15±0.92	0.34
	XIAOPI group	1.50±0.91	1.11±0.85	−0.41±0.97	
Total FACT-B scores	Control group	109.20±17.91	107.63±19.49	−2.00±10.28	0.005
	XIAOPI group	109.54±16.51	115.07±20.19	8.48±15.07	
Physical status	Control group	23.67±3.57	24.15±3.31	0.31±2.31	0.078
	XIAOPI group	22.47±4.33	24.33±3.56	1.89±3.89	
Social/family status	Control group	20.30±6.43	19.12±6.42	−1.92±5.22	0.19
	XIAOPI group	22.33±3.79	21.89±4.70	−0.33±3.37	
Emotional status	Control group	18.43±3.49	19.35±2.70	0.54±2.25	0.54
	XIAOPI group	18.80±4.16	19.63±4.41	1.00±3.14	
Functional status	Control group	20.43±5.32	19.88±5.84	−1.31±4.76	0.11
	XIAOPI group	19.93±6.64	20.67±5.25	1.15±6.24	
Additional attention	Control group	27.67±4.59	27.04±4.78	−2.96±4.78	0.27
	XIAOPI group	25.17±5.90	28.56±5.13	−1.44±5.13	

by 0.039 points in the control group ($P = 0.019$). In addition, patients who received XIAOPI treatment exhibited more substantial enhancements in subjective sleep quality at postintervention when compared to those in the control group ($P = 0.027$).

XIAOPI Formula Increases the FACT-B Scores of Patients with TNBC

Additionally, the life quality of patients with breast cancer in both groups was evaluated prior to and following drug administration. As shown in Table 4, the FACT-B scores at baseline were similar between the treatment and control groups. After the 3-month XIAOPI intervention, the FACT-B total scores of patients in the treatment group improved by 8.48 points, however, there was no difference in the control group. And there was a significant difference between the

two groups ($P = 0.005$). A cumulative effect of XIAOPI treatment on anxiety, depression, sleep disturbances, and quality of life in patients with breast cancer was observed from baseline to three months.

Associations between life quality, sleep disturbances, anxiety, depression, and CXCL1

As illustrated in Figure 2, noteworthy positive correlations were identified among sleep quality, anxiety, and depression in patients, both prior to the commencement of treatment ($P < 0.01$) and following a 3-month intervention ($P < 0.01$). Supplementary analysis was performed to explore associations between SDS, SAS, PSQI, and FACT-B scores before and after treatment. It was observed that SDS, SAS, and PSQI scores exhibited negative correlations with FACT-B scores ($P < 0.01$). Moreover, the level of CXCL1 was also negatively correlated with FACT-B scores prior to treatment ($P < 0.01$).

XIAOPI Formula Can Improve DFS in Patients with TNBC

After a 60-month follow-up period, patients in the XIAOPI group continued to take the XIAOPI formula beyond the conclusion of the trial, for an average duration of 23.6 months. In contrast, patients in the placebo group exhibited poor compliance, with an average post-trial XIAOPI formula intake period of 3.7 months. Disease progression among patients was assessed at 10, 20, 30, 40, 50, and 60 months from the trial's commencement. At the conclusion of the 60-month period, 5 patients in the XIAOPI formula group experienced relapse and metastasis, resulting in zero all-cause deaths. Conversely, 6 patients in the placebo group exhibited relapse and metastasis, with 2 fatalities. Figure 3 illustrates a statistically significant improvement in DFS within the XIAOPI formula group compared to the placebo group ($P < 0.05$).

Discussion

The results of our study demonstrated that the XIAOPI formula could reduce the CXCL1 serum level in patients with TNBC. In a prior study, we also established that the XIAOPI formula could inhibit premetastatic niche formation in breast cancer by decreasing CXCL1.[24] Meanwhile, cancer stem cells were also decreased following XIAOPI treatment,[26] and the formula elevated the chemosensitivity of breast cancer cells, accompanied by a reduction in CXCL1.[25] All of these results however, were derived from mouse xenografts. This is the first clinical study to our knowledge to investigate the effects of the XIAOPI formula on CXCL1 levels. Encouragingly, our findings indicate that XIAOPI can decrease CXCL1 levels following administration for three months, indicating its potential for overcoming cancer metastasis and improving clinical outcomes in patients with TNBC. Notwithstanding these findings, it is imperative to conduct additional clinical trials with larger and more diverse patient cohorts to substantiate and validate the obtained results.

Our results indicated that depression is common in patients with breast cancer (54.0%), which was slightly higher than that found in a previous meta-study (32.2%).[31] However, the current study reveals a reduced prevalence of anxiety

	SAS at baseline	SDS at baseline	PSQI at baseline	FACT-B at baseline	CXCL1 at baseline	SAS-post intervention	SDS-post intervention	PSQI-post intervention	FACT-post intervention	CXCL1-post intervention
SAS at baseline	1									
SDS at baseline	0.59**	1								
PSQI at baseline	0.47**	0.50**	1							
FACT-B at baseline	-0.60**	-0.69**	-0.55**	1						
CXCL1 at baseline	0.16	0.1	-0.03	-0.34**	1					
SAS-post intervention	0.47**	0.28*	0.26	-0.30*	0.11	1				
SDS-post intervention	0.38**	0.29*	0.27*	-0.39**	0.03	0.71**	1			
PSQI-post intervention	0.43**	0.23	0.73**	-0.41**	-0.08	0.39**	0.44**	1		
FACT-post intervention	-0.50**	-0.40**	-0.48**	0.71**	-0.21	-0.63**	-0.60**	-0.57**	1	
CXCL1-post intervention	0.02	-0.17	-0.21	0.05	0.67**	0.05	-0.08	-0.1	-0.06	1

Figure 2 Correlation analysis between SAS, SDS, PSQI, FACT-B, and CXCL1 in patients before and after intervention. The number in the box indicates the Pearson's correlation coefficient, and the color indicates the degree of correlation. **$P < 0.01$, *$P < 0.05$.

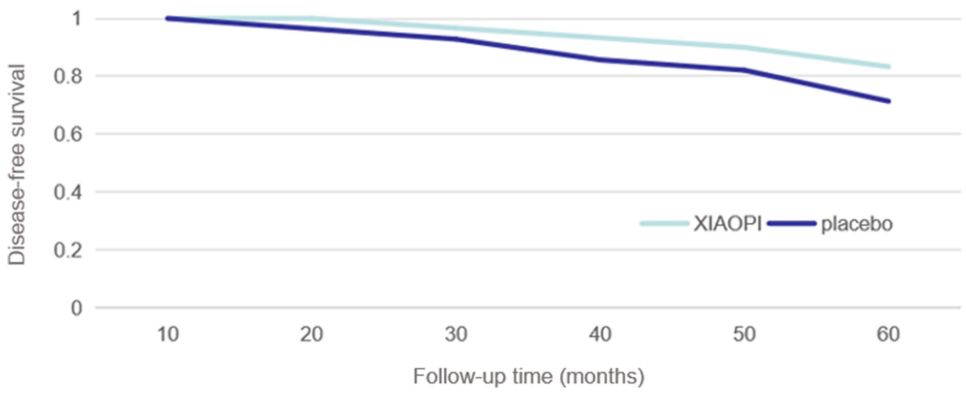

Figure 3 Comparison of DFS between the XIAOPI formula group and the placebo group.

compared to a prior investigation, where it was reported to have reached 41.9%.[32] Interestingly, we found a strong correlation between depression and anxiety before and after treatment, indicating a co-occurrence of these conditions and their negative impacts on the quality of life of patients, which was comparable to the previous report.[33] Patients diagnosed with breast cancer often experience suboptimal sleep quality, including delayed sleep onset, early morning awakening, prolonged nocturnal waking periods, unrefreshing sleep, and daytime sleepiness.[34] Based on our study, the PSQI score was positively correlated with anxiety and depression and negatively correlated with quality of life. In addition to adverse effects, anxiety, depression, pain, the use of opioids, fatigue, and cancer treatment can all contribute to poor sleep quality.[35] In turn, the symptoms of anxiety and depression are likely to be worsened by poor sleep quality.[36] Furthermore, a negative correlation was observed between CXCL1 and FACT-B scores prior to treatment in the current investigation, suggesting that there might exist a feedback loop between high CXCL1 levels and poor life quality. Although a significant difference was not observed in physical status, social or family status, emotional status, functional status, or in terms of additional concerns in the control group compared to those in the treatment group, the XIAOPI formula is effective in enhancing the total FACT-B score of patients with breast cancer. This phenomenon could be ascribed to the limited patient sample size; hence, future studies should involve a larger number of participants. Simultaneously, further research is anticipated to explore the potential benefits of the XIAOPI formula in extending overall survival or DFS in patients with TNBC, given the constraints posed by the limited duration of observation.

Antidepressant agents are preferred for patients with depression in clinical settings. However, drug-drug interactions should be considered when applied to patients with cancer. Antidepressant drugs such as fluoxetine and paroxetine, for instance, may reduce the active metabolite of tamoxifen.[37] Additionally, the common adverse effects of antidepressants,[38] such as constipation, dizziness, or sickness, could reduce compliance with cancer treatment. Therefore, TCMs with low toxicity may be a reasonable choice for patients with breast cancer with depression. The fact that the XIAOPI formula was reported to have few side effects in our study indicates that it may be a viable alternative. Furthermore, compared with antidepressants, TCM formulas work on multiple targets for the treatment of depression, anxiety, sleep quality, and quality of life. Therefore, additional clinical research comparing the XIAOPI formula and antidepressants is warranted for validation. Indeed, increasing evidence indicates that TCM may be helpful for patients with cancer and depression. Chaihu Shugan San, Xiaoyao San, and acupuncture, for instance, are prevalent TCM treatments in the majority of Asian countries. Deng et al demonstrated that Chaihu Shugan San could effectively improve depression in patients with cancer.[39] Jiao et al reported that Xiaoyao San could relieve depression in patients during adjuvant chemotherapy after breast cancer surgery.[40] In their study, Liu et al discovered that needle-warming moxibustion could alleviate edema and improve depression, anxiety, and quality of life for patients with breast cancer after the surgery.[41] Similarly, our findings revealed that anxiety and depression scores also declined significantly by the XIAOPI formula. However, the majority of prior research incorporated nearly every subtype of breast cancer. Considering the impact of tumor heterogeneity on treatment efficacy, our research focused on the most challenging TNBC subtype. Therefore, our results provide greater guidance regarding the precise management of TNBC.

Meanwhile, prior research has demonstrated that psychological disturbances usually occur during periods of diagnosis, surgery, and adjuvant therapies.[42,43] It is common for patients breast cancer to experience symptoms of anxiety and stress-related disorders shortly after diagnosis. This is an overwhelming response to a potentially life-threatening disease and the uncertainty surrounding the future.[44] Although most patients with breast cancer may adapt to the diagnosis over time, psychological stress may persist in specific subgroups, such as young women who have concerns about fertility or weight gain.[45] It has been reported that psychological disorders and low quality of life occur more frequently during periods of surgery, chemotherapy, and radiotherapy.[46–48] A study has identified a positive correlation between depression status and chemotherapy-induced myelosuppression in patients with breast cancer. This finding implies that monitoring depression status before chemotherapy may facilitate better management of adverse events.[49] Notably, patients diagnosed with breast cancer frequently turn to complementary and alternative therapies, primarily motivated by the anticipated benefits or a perceived inadequacy of conventional medicine in addressing their psychosocial needs.[50,51] Our results revealed that the XIAOPI formula may enhance the psychological well-being and quality of life of patients with breast cancer during their recuperation periods. Furthermore, further investigation is warranted into the potential therapeutic value of the XIAOPI formula during the phases of diagnosis, surgery, and adjuvant therapies. Moreover, there is a need to determine the optimal dosage and duration of the XIAOPI formula interventions. A three-month treatment period of 8.5 g of XIAOPI formula was utilized in this investigation to evaluate its efficacy. However, existing literature suggests that the effectiveness of TCM formulas may vary based on varied dosages or extended intervention times.[52,53] Furthermore, the therapeutic effectiveness of the XIAOPI formula in treating different levels or types of mental disorders remains unclear. It is significant to determine the best therapeutic dose and duration of the XIAOPI formula by conducting real-world and multi-center clinical trials. In addition, depressive symptoms are observed to be exceedingly prevalent among patients diagnosed with breast cancer; however, they are frequently disregarded. Therefore, early identification and management of emotional disorders in patients with breast cancer are critical for enhancing the quality of life and clinical outcomes.

As an observational metric, DFS within the XIAOPI formula group exhibited a notable and statistically significant superiority over that observed in the placebo group. This difference may be attributed to the prolonged adherence of patients in the XIAOPI formula group, who continued to diligently consume the XIAOPI formula well beyond the trial's conclusion. The sustained commitment to the XIAOPI formula was contingent upon the patients' perceptions of the drug's efficacy and their willingness to persist in the intake of the TCM formula.

This study impressively demonstrated that in the XIAOPI group, not only are CXCL1 levels effectively reduced, but also mental well-being, sleep quality, quality of life and even patient survival appear to be superior. The clinical results are novel and consistent with previous preclinical animal studies, which will be likely to make a meaningful contribution to the advancement of the management of TNBC. The present study also has some limitations. It is important to note that this study was conducted at a single center, the sample size was small. Therefore, the conclusions drawn from this study should be further confirmed through larger-scale, multi-center, double-blind studies with more diverse patient cohorts. Additionally, assessment of psychological well-being and quality of life was only conducted through patient-reported outcome measures which could be quite subjective sometimes. Furthermore, the therapeutic effects of the XIAOPI formula in treating different levels or types of mental disorders was not explored due to the sample size limitation.

Conclusion

In summary, our results suggest that the XIAOPI formula not only reduces CXCL1 levels effectively but also enhances psychological well-being, sleep quality, and overall quality of life for patients with TNBC. Therefore, it exhibits potential as a natural alternative therapy for improving the prognosis of TNBC. Moving forward, it is anticipated that the validation of therapeutic effects attributed to the XIAOPI formula will be established through large-scale and long-term clinical trials.

Abbreviations

TNBC, Triple-negative breast cancer; TAMs, Tumor-associated macrophages; CXCL1, C-X-C Motif Chemokine Ligand 1; TCM, Traditional Chinese medicine; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; PSQI,

Pittsburgh sleep Quality Index; FACT-B, Functional Assessment of Cancer Therapy–Breast; CONSORT, Consolidated Standards of Reporting Trials.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. All participants provided written informed consent and the protocol was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (ZF2018-097-01).

Consent for Publication

All authors have consented to the publication of the manuscript.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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