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Article

Berberine hydrochloride alleviates psychological distress and enhances quality of life in lung cancer patients with comorbid idiopathic pulmonary fibrosis: a randomized controlled trial

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Abstract: Lung cancer frequently involves psychological distress, amplified by comorbid idiopathic pulmonary fibrosis (IPF), and options addressing both are limited. We therefore assessed, in a randomized, double-blind, placebo-controlled trial, whether berberine (BBR), a mood-regulatory, anti-inflammatory alkaloid, improves psychological distress and quality of life in 84 lung cancer patients with comorbid IPF (42 per group). The primary outcomes (Hospital Anxiety and Depression Scale [HADS], HADS-Anxiety and HADS-Depression; St. George's Respiratory Questionnaire [SGRQ], SGRQ-Total) were assessed at baseline, 6 and 12 months; pulmonary function and network pharmacology were secondary. Compared with placebo, BBR was associated with improvements in HADS-Anxiety (10.8 ± 3.3 to 8.3 ± 3.0; $p < 0.01$) and HADS-Depression (9.6 ± 3.7 to 7.6 ± 3.1; $p = 0.02$), and the proportions meeting the HADS-Anxiety (≥ 8) and HADS-Depression (≥ 8) cutoffs fell from 69.0% to 40.5% and 61.9% to 35.7% versus 69.0% to 64.3% and 59.5% to 54.8% ($p = 0.03$ and 0.04). SGRQ-Total improved from 61.8 ± 16.0 to 51.5 ± 15.0 ($p < 0.01$), exceeding the minimum clinically important difference. BBR was also associated with a smaller 12-month decline in forced vital capacity (FVC)% and diffusing capacity for carbon monoxide (DLCO)% ($p = 0.03$ and 0.02), and greater functional preservation correlated with better quality of life and lower anxiety ($r = -0.58$ and -0.50; $p < 0.001$). Bioinformatics identified 29 shared targets enriched in PI3K-Akt, HIF-1, JAK-STAT, TNF and NF-κB signaling. In this exploratory trial, BBR was associated with reduced psychological distress, improved quality of life and parallel pulmonary-function changes.

Keywords: Psychological distress; quality of life; lung cancer; idiopathic pulmonary fibrosis; berberine; psycho-oncology; anxiety; depression

1. Introduction

Lung cancer is one of the most common malignancies worldwide and is a leading cause of cancer-related mortality [1]. Despite advances in diagnosis and treatment, lung cancer patients continue to experience a substantial physical and psychological burden, with elevated symptoms of anxiety and depression (Hospital Anxiety and Depression Scale [HADS] score ≥ 8) affecting approximately 30–50% of this population [2]. These psychological comorbidities are associated with poorer treatment adherence, reduced quality of life, and increased mortality, highlighting the urgent need for integrated psychosocial care within oncology [3]. However, the management of psychological distress in lung cancer patients is frequently

complicated by comorbidities that amplify both physical symptoms and emotional suffering. Among these comorbidities, idiopathic pulmonary fibrosis (IPF) remains particularly significant.

IPF is a progressive, chronic lung disease characterized by irreversible fibrosis and destruction of the lung parenchyma [4]. Importantly, IPF is an established independent risk factor for lung cancer, with reported incidence rates of 3–22% among IPF patients, representing a 3- to 10-fold increased risk compared to the general population [5]. The coexistence of these two conditions poses a unique clinical challenge: patients face the compounded burden of malignancy, progressive respiratory decline, and the psychological impact of two life-limiting diseases simultaneously. Studies indicate that 35–52% of patients with chronic respiratory conditions experience high psychological distress [6,7]. When combined with a cancer diagnosis, this burden is further amplified yet remains inadequately addressed in current psycho-oncology frameworks.

At a biological level, IPF is a chronic fibrotic lung disease driven by persistent inflammation and dysregulated tissue repair [8,9]. These processes engage signaling pathways such as NF-κB and JAK-STAT [10], which also contribute to the neuroinflammation underlying depression and anxiety [11–14]. Beyond idiopathic disease, pulmonary fibrosis also arises as a late complication of thoracic radiation [15–17], adding a further layer of physical and psychological burden for cancer survivors. This overlap between fibrotic and mood-related signaling provides a plausible biological bridge linking respiratory decline with cancer-related psychological distress, thereby clarifying why patients carrying both diagnoses constitute a distinct, high-burden subgroup within psycho-oncology.

The compounded psychosocial impact in lung cancer patients with IPF extends beyond what is observed in either condition alone. The combination of poor prognosis, disease uncertainty, progressive dyspnea, and the psychosocial burden of both cancer and chronic lung disease heavily impacts quality of life [18]. Anxiety and depression in this population negatively affect treatment adherence, healthcare utilization, and overall disease management [19,20]. Currently, therapeutic options for IPF are limited, with existing treatments such as nintedanib and pirfenidone mainly focusing on slowing disease progression [21]. These antifibrotic agents offer limited efficacy in reversing fibrosis, and their adverse effects may exacerbate the psychological burden in patients already coping with cancer treatment [22]. From a psycho-oncology perspective, there is a pressing need for pharmacological strategies that can simultaneously address fibrotic pathology and psychological distress, an integrated approach that aligns with the biopsychosocial model of comprehensive cancer care.

Within this framework, integrative medicine strategies that target both physiological and psychological dimensions are increasingly valued. Berberine hydrochloride (BBR), a natural alkaloid derived from Coptis chinensis, exhibits a wide range of pharmacological activities including anti-inflammatory, antioxidative, and hypoglycemic properties [23]. Its favorable safety profile makes it a promising candidate for adjunctive therapy in complex disease states. Previous research has demonstrated that BBR may have therapeutic effects in various fibrotic diseases, including liver fibrosis, renal fibrosis, and cardiac fibrosis [24], and *in vivo* studies have indicated that BBR may alleviate pulmonary fibrosis by inhibiting fibroblast activation and reducing inflammation [25,26]. However, it remains unknown whether BBR can simultaneously improve pulmonary function and psychological distress,

and whether these dual effects are mediated through shared molecular pathways, particularly in the context of cancer patients with fibrotic lung disease.

In the present study, we enrolled lung cancer patients with comorbid IPF—a population at elevated risk of psychological distress—and evaluated whether BBR alleviates anxiety, depression, and impaired quality of life, the core outcomes of psycho-oncology and supportive cancer care. To contextualize the integrated benefits, we performed an exploratory network pharmacology analysis integrating BBR targets with IPF- and lung cancer-related gene sets to probe potential shared inflammatory pathways linking physical and psychological symptoms. This combined clinical and *in silico* approach was designed not to establish mechanism definitively but to frame BBR's potential as an integrative, psychosocially oriented intervention for patients whose psychological burden is compounded by fibrotic comorbidity, thereby informing comprehensive cancer care.

2. Materials and methods

2.1. Study design and participants

We conducted a randomized, double-blind, placebo-controlled trial in lung cancer patients with comorbid IPF. Lung cancer was confirmed by histopathological examination, and IPF was diagnosed according to the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guidelines. Participants were randomly assigned in a 1:1 ratio to receive BBR (500 mg three times daily) [23], a dose regimen established in prior clinical trials, or a matched placebo for 12 months. Randomization was performed using a computer-generated sequence with stratification according to disease severity, defined as baseline forced vital capacity (FVC) % predicted < 65% versus ≥ 65%. All participants, investigators, and outcome assessors were blinded to group assignment throughout the study period, and all participants provided written informed consent prior to enrollment.

This randomized controlled trial was retrospectively registered in the International Traditional Medicine Clinical Trial Registry (ITMCTR) under the identifier ITMCTR2026002663. The protocol adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine (Approval No. KY2024023). Reporting follows the CONSORT 2010 Statement. A CONSORT flow diagram (**Supplementary Figure S1**) details screening, randomization, allocation, and follow-up, including withdrawals and reasons for exclusion.

The sample size of 84 participants (42 per arm) was determined by feasibility at a single center. With two-sided $\alpha = 0.05$, this sample size would provide 80% power to detect an effect size of $d = 0.62$; the observed between-group effect sizes are reported in the Results. Given the single-center, exploratory nature of this trial, the results should be regarded as hypothesis-generating, and adequately powered confirmatory trials are warranted.

Recruitment took place from March 2024 to March 2025. Key exclusion criteria were: IPF of a known alternative cause (e.g., connective tissue disease or drug-induced); acute IPF exacerbation or severe respiratory insufficiency requiring hospitalization within the preceding 3 months; severe comorbidity, including hepatic or renal dysfunction and severe cardiac disease (New York Heart Association class III–IV); a second malignancy within the preceding 5 years; severe psychiatric or cognitive disorder precluding valid completion of the study questionnaires or informed consent; and pregnancy or lactation, known hypersensitivity to berberine,

or concurrent participation in another interventional trial. A total of 90 patients were screened for eligibility at our center; all 90 met the inclusion criteria, and six declined to participate before randomization and were therefore not enrolled. The remaining 84 participants were randomized. All randomized participants attended follow-up assessments at baseline, 6 months, and 12 months. Safety was monitored at each scheduled visit by clinical evaluation and routine laboratory testing of liver and renal function. Adherence was assessed as continuation of the assigned regimen through the 12-month treatment period; pill counts were not performed. In accordance with the protocol, trial treatment could be discontinued, or a participant could decline to continue, in the event of severe adverse reactions, including liver or kidney function impairment and cardiopulmonary insufficiency. In the present cohort, no participant withdrew, discontinued trial treatment, or was lost to follow-up during the study.

2.2. Psychological and physiological assessments

The primary outcomes were psychological distress (HADS and its HADS-Anxiety and HADS-Depression) and quality of life (St. George's Respiratory Questionnaire [SGRQ]-Total); pulmonary function (FVC% and diffusing capacity for carbon monoxide [DLCO]% predicted) was a secondary outcome.

The HADS is a 14-item questionnaire with distinct anxiety (HADS-A) and depression (HADS-D) subscales, each containing 7 items scored 0–3, with total subscale scores ranging from 0–21. Scores ≥ 8 on either subscale were considered indicative of elevated symptom levels rather than a diagnosis. This instrument was selected for its demonstrated validity in respiratory disease populations and its ability to minimize confounding by somatic symptoms common in chronic respiratory disorders. This threshold is a screening cutoff only and does not establish a psychiatric diagnosis; no structured diagnostic interview was conducted in this trial.

HADS (anxiety and depression subscales) and SGRQ were assessed at baseline, 6 months, and 12 months (**Table 1**). Concomitant psychological and psychiatric care was also recorded: no participant received psychological counseling, psychiatric treatment, antidepressants, anxiolytics, or other psychosocial interventions at any time from baseline through 12 months. Because no such concomitant interventions were used, they cannot have confounded the between-group comparison, and no adjustment for them was required. HADS scores were interpreted as symptom-level outcomes only, not as a basis for establishing or ruling out any psychiatric diagnosis.

Table 1. Timeline of assessments and measurements in the psychosocial evaluation of berberine treatment

Assessment Category	Measure	Baseline	6 Months	12 Months
Psychological Parameters	HADS-Anxiety	√	√	√
	HADS-Depression	√	√	√
Quality of Life Measures	SGRQ-Symptoms	√	√	√
	SGRQ-Activity	√	√	√
	SGRQ-Impacts	√	√	√
	SGRQ-Total	√	√	√
Physiological Parameters	FVC (% predicted)	√	√	√
	DLCO (% predicted)	√	√	√

Continuation Table:

Assessment Category	Measure	Baseline	6 Months	12 Months
Treatment Monitoring	Treatment Adherence	-	√	√
	Adverse Events	-	√	√
	Concomitant Psychological and Psychiatric Care	√	√	√

The SGRQ is a disease-specific instrument measuring health-related quality of life in patients with respiratory disease. This 50-item questionnaire yields scores in three domains (symptoms, activity, and impacts) and a total score ranging from 0–100, with higher scores indicating worse quality of life; the minimum clinically important difference for the total score is approximately 4 points [27]. The SGRQ was selected as the primary quality-of-life outcome because respiratory symptoms and functional impairment dominate quality of life in patients with comorbid IPF, and because it is one of the most extensively validated health-related quality-of-life measures in IPF [28] and is responsive to clinically meaningful change [27].

2.3. Network pharmacology analysis

Network pharmacology analysis was performed as follows. BBR-related targets (n = 98) were obtained from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP; https://tcmsp-e.com/) and SwissTargetPrediction (http://www.swisstargetprediction.ch); the target lists retrieved from the two resources were merged and de-duplicated to yield 98 unique targets. IPF- and lung cancer- related genes were retrieved from the National Center for Biotechnology Information (NCBI) Gene database (https://www.ncbi.nlm.nih.gov/gene) via the E-utilities API (https://www.ncbi.nlm.nih.gov/books/NBK25501/) on 11 July 2026, using the queries “idiopathic pulmonary fibrosis AND human [Organism]” and “lung cancer AND human [Organism]”. These returned 428 and 4,311 gene records, respectively. Because the lung cancer query returned a much larger record set than the other queries, a fixed cap of 1,000 records per gene set was applied so that every gene set was processed under the same rule; records were taken in the order in which they were returned by the query, without additional sorting, ranking or filtering. Only the lung cancer list exceeded this cap, so only that list was truncated. All identifiers were harmonized to official gene symbols converted from Entrez Gene IDs with the E-utilities esummary utility, and duplicates were removed by case-normalized gene symbol. The intersection of the three gene sets yielded 29 targets common to BBR, IPF and lung cancer. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment was assessed for a pre-specified set of 14 pathways related to fibrosis, cancer and inflammation (listed in **Supplementary Table S1**) using a one-sided hypergeometric test, $P(X \geq k)$, with 20,091 Homo sapiens protein-coding genes as background (N; KEGG organism hsa, T01001) and the number of genes annotated to each pathway as K; KEGG data were obtained through the KEGG REST API (https://rest.kegg.jp/) on 11 September 2026. P-values were adjusted for multiple testing using the Benjamini–Hochberg procedure applied to the 14 pre-specified pathways only; no other pathways were tested. Pathways with $q < 0.05$ were considered significantly enriched. Analyses were performed in Python 3.13 with the E-utilities and KEGG REST APIs and matplotlib (v3.11.0). This analysis is exploratory and hypothesis-generating: it was undertaken to generate hypotheses about shared pathways rather than to establish mechanism, and

no inflammatory biomarkers or pathway-activity measurements were obtained from participants.

2.4. Statistical analysis

Statistical analyses were conducted using GraphPad Prism version 8.0 (RRID: SCR_002798). Baseline characteristics were compared between groups using independent t-tests for continuous variables and chi-square tests for categorical variables. Analyses were conducted on both an intention-to-treat (ITT; all randomized, n = 84) and a per-protocol (PP) basis; as no participant withdrew or was lost to follow-up, the two analyses yielded identical results, and no missing-data handling was required. For all continuous outcomes, changes within each group across baseline, 6 and 12 months were assessed using repeated-measures analysis of variance (ANOVA) followed by Bonferroni-corrected post-hoc comparisons between baseline and each follow-up time point, and between-group differences at 12 months were assessed using independent-samples comparisons of the change from baseline. The two binary cutoff outcomes (HADS-A $\geq$ 8 and HADS-D $\geq$ 8) were analyzed as a secondary, exploratory comparison and are reported descriptively; no repeated-measures model for binary data was fitted, and only the between-group comparison of the change in binary status from baseline to 12 months is reported. Pearson correlation analyses were used to explore relationships between changes in pulmonary function parameters and changes in psychological metrics within the BBR group; six comparisons were examined and Bonferroni correction was applied across them ($\alpha = 0.05/6 = 0.0083$). Data distribution was assessed for normality using the Shapiro-Wilk test before parametric testing. Quantitative data are presented as mean ± standard deviation (SD). Effect sizes are reported as Cohen's d, calculated from the between-group difference in change scores from baseline to 12 months and standardized by the pooled standard deviation of the 12-month values—that is, the pooled standard deviation of the outcome at the time point at which the two groups are compared. This standardizer expresses the between-group difference in units of the between-participant variability of the outcome itself, which is the scale on which the conventional benchmarks for d are defined; because the denominator is stated explicitly, the effect size can be recalculated using any alternative standardizer [29]. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and psychological burden

A total of 84 lung cancer patients with comorbid IPF were enrolled in this study (42 in the BBR group and 42 in the placebo group). Baseline demographic and clinical characteristics are summarized in **Table 2**. No statistically significant differences were observed between the two groups in age, sex, histological type, disease stage, prior treatments, or baseline pulmonary function (all $p > 0.05$). Elevated psychological symptom burden (HADS-A or HADS-D $\geq$ 8) was prevalent at baseline, with mean HADS-Anxiety scores of 10.8 ± 3.3 in the BBR group and 10.6 ± 3.5 in the placebo group, and HADS-Depression scores of 9.6 ± 3.7 and 9.4 ± 3.9, respectively. SGRQ-Total scores were also comparable between groups (61.8 ± 16.0 vs. 61.2 ± 16.8), confirming a substantial psychosocial burden in this comorbid population.

Table 2. Baseline characteristics of lung cancer patients with comorbid IPF

Category	Characteristic	Total (n = 84)	BBR (n = 42)	Placebo (n = 42)
Demographics				
	Age (years)	64.8 ± 7.6	65.2 ± 7.4	64.4 ± 7.9
	Sex, male, n (%)	55 (65.5)	28 (66.7)	27 (64.3)
	BMI (kg/m²)	23.5 ± 3.2	23.7 ± 3.0	23.3 ± 3.4
Lung Cancer Characteristics				
	Histological type, n (%)			
	Non-small cell lung cancer, n (%)	67 (79.8)	34 (81.0)	33 (78.6)
	Small cell lung cancer, n (%)	17 (20.2)	8 (19.0)	9 (21.4)
	TNM stage			
	Stage I–II	30 (35.7)	16 (38.1)	14 (33.3)
	Stage III–IV	54 (64.3)	26 (61.9)	28 (66.7)
	Prior cancer treatment			
	Surgery	27 (32.1)	13 (31.0)	14 (33.3)
	Previous chemotherapy, n (%)	47 (56.0)	24 (57.1)	23 (54.8)
	Previous radiation therapy, n (%)	35 (41.7)	18 (42.9)	17 (40.5)
IPF Characteristics				
	Time since IPF diagnosis (years)	3.2 ± 1.8	3.1 ± 1.7	3.3 ± 1.9
	FVC (% predicted)	71.8 ± 11.6	72.3 ± 11.2	71.3 ± 12.0
	DLCO (% predicted)	54.6 ± 9.8	55.0 ± 9.5	54.2 ± 10.1
Psychological Parameters	HADS-Anxiety score	10.7 ± 3.4	10.8 ± 3.3	10.6 ± 3.5
	HADS-A ≥ 8, n (%)	58 (69.0)	29 (69.0)	29 (69.0)
	HADS-Depression score	9.5 ± 3.8	9.6 ± 3.7	9.4 ± 3.9
	HADS-D ≥ 8, n (%)	51 (60.7)	26 (61.9)	25 (59.5)
Quality of Life Measures	SGRQ total score	61.5 ± 16.4	61.8 ± 16.0	61.2 ± 16.8

3.2. Effects of BBR treatment on psychological parameters and quality of life

Compared to baseline, BBR treatment was associated with progressive improvements in psychological parameters and quality of life at both 6 and 12 months (**Table 3**). HADS-Anxiety scores decreased from 10.8 ± 3.3 at baseline to 8.3 ± 3.0 at 12 months in the BBR group ($p < 0.01$), whereas minimal change was observed in the placebo group (10.6 ± 3.5 to 9.8 ± 3.4; between-group $p < 0.01$). Similarly, HADS-Depression scores decreased from 9.6 ± 3.7 to 7.6 ± 3.1 in the BBR group ($p < 0.05$), compared with 9.4 ± 3.9 to 9.0 ± 3.7 in the placebo group (between-group $p = 0.02$). The proportion of participants meeting the HADS-A cutoff (≥ 8) decreased from 69.0% (29/42) at baseline to 40.5% (17/42) at 12 months in the BBR group, compared with a decrease from 69.0% to 64.3% in the placebo group (between-group $p = 0.03$).

The proportion of patients meeting the HADS-D cutoff (≥ 8) decreased from 61.9% (26/42) to 35.7% (15/42) in the BBR group, compared with 59.5% to 54.8% in the placebo group (between-group $p = 0.04$). Quality of life, as measured by SGRQ-Total scores, improved from 61.8 ± 16.0 at baseline to 51.5 ± 15.0 at 12 months in the BBR group ($p < 0.01$), exceeding the minimum clinically important difference. In contrast, the placebo group showed minimal change (61.2 ± 16.8 to 59.5 ± 16.4; between-group $p < 0.01$). The corresponding between-group effect sizes for the change from baseline to 12 months were d = 0.53 (95% confidence interval [CI] 0.09–0.97) for HADS-Anxiety, d = 0.47 (95% CI 0.04–0.90) for HADS-Depression, and d = 0.55 (95% CI 0.11–0.99) for SGRQ-Total.

Table 3. Changes in psychological parameters and quality of life measures following berberine treatment

Parameter	BBR Baseline	BBR 6 Months	BBR 12 Months	Placebo Baseline	Placebo 6 Months	Placebo 12 Months	Between-group *p*
Psychological Measures							
HADS-Anxiety score	10.8 ± 3.3	9.0 ± 3.1[b]	8.3 ± 3.0[b]	10.6 ± 3.5	10.3 ± 3.5	9.8 ± 3.4	<0.01
HADS-Depression score	9.6 ± 3.7	8.3 ± 3.3[a]	7.6 ± 3.1[a]	9.4 ± 3.9	9.2 ± 3.8	9.0 ± 3.7	0.02
HADS-A ≥ 8, n (%)	29 (69.0)	21 (50.0)	17 (40.5)	29 (69.0)	28 (66.7)	27 (64.3)	0.03
HADS-D ≥ 8, n (%)	26 (61.9)	19 (45.2)	15 (35.7)	25 (59.5)	24 (57.1)	23 (54.8)	0.04
Quality of Life Measures							
SGRQ-Symptoms	63.8 ± 17.9	56.5 ± 17.0[a]	53.0 ± 16.5[a]	62.9 ± 18.1	61.8 ± 18.0	61.0 ± 17.8	0.02
SGRQ-Activity	69.9 ± 18.8	64.0 ± 18.0[a]	61.0 ± 17.5[a]	69.1 ± 19.0	68.2 ± 18.8	67.5 ± 18.5	0.04
SGRQ-Impacts	55.7 ± 17.2	50.5 ± 16.0[a]	48.0 ± 15.5[a]	54.9 ± 17.5	54.0 ± 17.5	53.2 ± 17.2	0.03
SGRQ-Total	61.8 ± 16.0	54.5 ± 15.5[a]	51.5 ± 15.0[b]	61.2 ± 16.8	60.2 ± 16.6	59.5 ± 16.4	<0.01
Physiological Measures							
FVC (% predicted)	72.3 ± 11.2	71.0 ± 11.5	70.0 ± 12.0	71.3 ± 12.0	69.0 ± 12.5	66.5 ± 13.0	0.03
DLCO (% predicted)	55.0 ± 9.5	53.5 ± 10.0	51.5 ± 10.5	54.2 ± 10.1	51.0 ± 10.8	48.0 ± 11.5	0.02

Note: [a]$p < 0.05$, [b]$p < 0.01$ for within-group comparison vs. baseline (repeated-measures ANOVA with Bonferroni-corrected post-hoc comparisons); these within-group comparisons apply to the continuous outcomes only; the two binary cutoff outcomes (HADS-A ≥ 8 and HADS-D ≥ 8) were analyzed descriptively as an exploratory comparison. Between-group p-values are shown in the last column: for continuous outcomes (HADS-Anxiety and HADS-Depression scores, SGRQ domains and total, FVC, DLCO), the p-value is the comparison between groups of the change from baseline to 12 months (independent-samples comparison of change scores); for the binary cutoff outcomes, the same between-group comparison was applied to the change in binary status from baseline to 12 months. Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. For SGRQ and HADS scores, lower values indicate improvement. For FVC and DLCO, negative changes indicate pulmonary function decline. Abbreviations: HADS, Hospital Anxiety and Depression Scale; SGRQ, St. George's Respiratory Questionnaire; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.

3.3. Effects of BBR on pulmonary function

Over 12 months, both arms showed a decline in pulmonary function, but the BBR group declined less than placebo. FVC (% predicted) changed from 72.3 ± 11.2 to 70.0 ± 12.0 in the BBR group versus 71.3 ± 12.0 to 66.5 ± 13.0 in placebo (between-group $p = 0.03$); DLCO (% predicted) changed from 55.0 ± 9.5 to 51.5

± 10.5 versus 54.2 ± 10.1 to 48.0 ± 11.5 (between-group $p = 0.02$). These findings indicate that BBR was associated with a smaller decline in pulmonary function relative to placebo.

3.4. Correlation between pulmonary function and psychological improvements

To explore the relationship between physiological and psychological improvements, six correlations were examined in the BBR group: changes in the two pulmonary function parameters (FVC and DLCO) against changes in the three psychological outcomes (HADS-Anxiety, HADS-Depression and SGRQ-Total). Two of the six were statistically significant and both remained significant after Bonferroni correction, namely FVC with SGRQ-Total (r = −0.58) and DLCO with HADS-Anxiety (r = −0.50); the other four were not statistically significant. As shown in **Figure 1A**, change in FVC (% predicted) showed a significant negative correlation with change in SGRQ-Total score (r = −0.58, $p < 0.001$), with greater lung-function improvements accompanying larger gains in quality of life. Similarly, change in DLCO (% predicted) showed a significant negative correlation with change in HADS-Anxiety score (r = −0.50, $p < 0.001$) (**Figure 1B**). These correlations indicate that improvements in pulmonary function and psychological well-being are interrelated in BBR-treated patients. Collectively, these findings indicate that BBR treatment was associated with concurrent improvements in pulmonary function and psychological well-being in this population. These analyses are correlational and do not establish that either improvement caused the other.

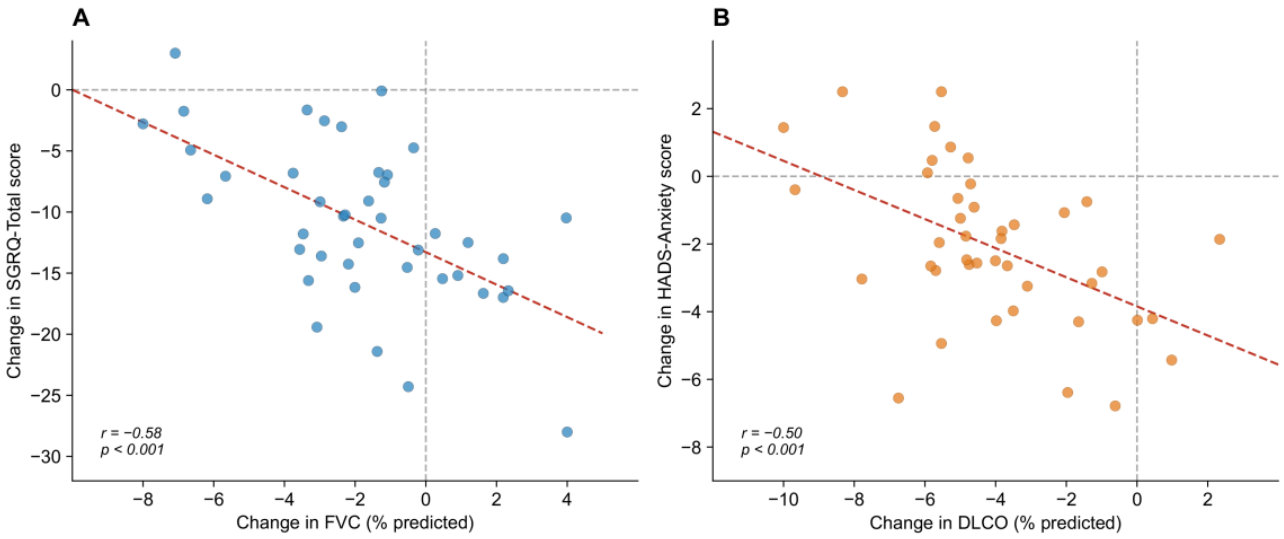


Figure 1. Association between 12-month changes in pulmonary function and improvements in psychological well-being in BBR-treated lung cancer patients with comorbid IPF. Scatter plots show the relationship between changes in pulmonary function and changes in psychological outcomes within the BBR group (n = 42) from baseline to 12 months. (A) Change in FVC (% predicted) was negatively correlated with change in SGRQ-Total score (r = −0.58, $p < 0.001$), indicating that greater improvement in lung function accompanied larger gains in quality of life. (B) Change in DLCO (% predicted) was negatively correlated with change in HADS-Anxiety score (r = −0.50, $p < 0.001$). Dashed red lines represent linear regression fits.

3.5. Safety and adherence

During the 12-month treatment period, no adverse drug reactions or serious adverse events were recorded during scheduled clinical assessments or routine laboratory monitoring in either group, and liver and renal function tests showed no

clinically significant impairment in any participant. All 84 participants (42 BBR, 42 placebo) continued and completed the assigned 12-month regimen; no participant discontinued treatment or was lost to follow-up. Because systematic prospective collection of adverse events and serious adverse events was not pre-specified as an endpoint, these observations indicate the absence of events recorded through scheduled clinical assessments and routine laboratory monitoring rather than a definitive assessment of drug safety, and continuation of the assigned regimen — in the absence of pill counts or drug-level monitoring — should not be interpreted as verified full adherence.

3.6. *In silico* prediction of BBR molecular targets in lung cancer with comorbid IPF

To identify candidate molecular targets of BBR specific to lung cancer patients with comorbid IPF, a three-way network pharmacology analysis was conducted. BBR-related targets (n = 98) were identified using the TCMSP and SwissTargetPrediction databases. IPF-related genes (n = 428) and lung cancer-related genes (n = 4,311 total; the first 1,000 records returned by the database were retained for analysis) were retrieved from the NCBI Gene database. The intersection of these three gene sets yielded 29 overlapping genes, representing BBR targets common to both IPF and lung cancer pathophysiology (**Figure 2**). KEGG pathway enrichment analysis performed on these 29 genes identified significant enrichment of multiple fibrosis-, cancer- and inflammation-related pathways. The largest overlaps were with PI3K-Akt (11 genes), HIF-1 (10 genes), JAK-STAT (9 genes), TNF (8 genes) and IL-17 (7 genes) signaling, followed by NF-κB, Toll-like receptor and MAPK signaling (6 genes each; all $q < 0.001$) (**Figure 3**). These pathways are known to be involved in fibrotic remodeling, oncogenic signaling, and inflammation-associated mood regulation, generating hypotheses about shared pathways that may be consistent with the concurrent improvements observed in the clinical cohort; pathway activity itself was not measured.



Figure 2. Three-way overlap among BBR target genes, IPF-related genes, and lung cancer genes. Venn diagram illustrating the intersection of three gene sets: BBR targets (n = 98, predicted from the TCMSP database and SwissTargetPrediction), IPF-related genes (n = 428), and lung cancer genes (n = 4,311 total; the first 1,000 records returned by the database were retained for analysis), the latter two retrieved from the NCBI Gene database via E-utilities. Numbers within each region indicate the count of overlapping genes. Circles are drawn at equal size for visual clarity; actual set sizes are indicated in parentheses.

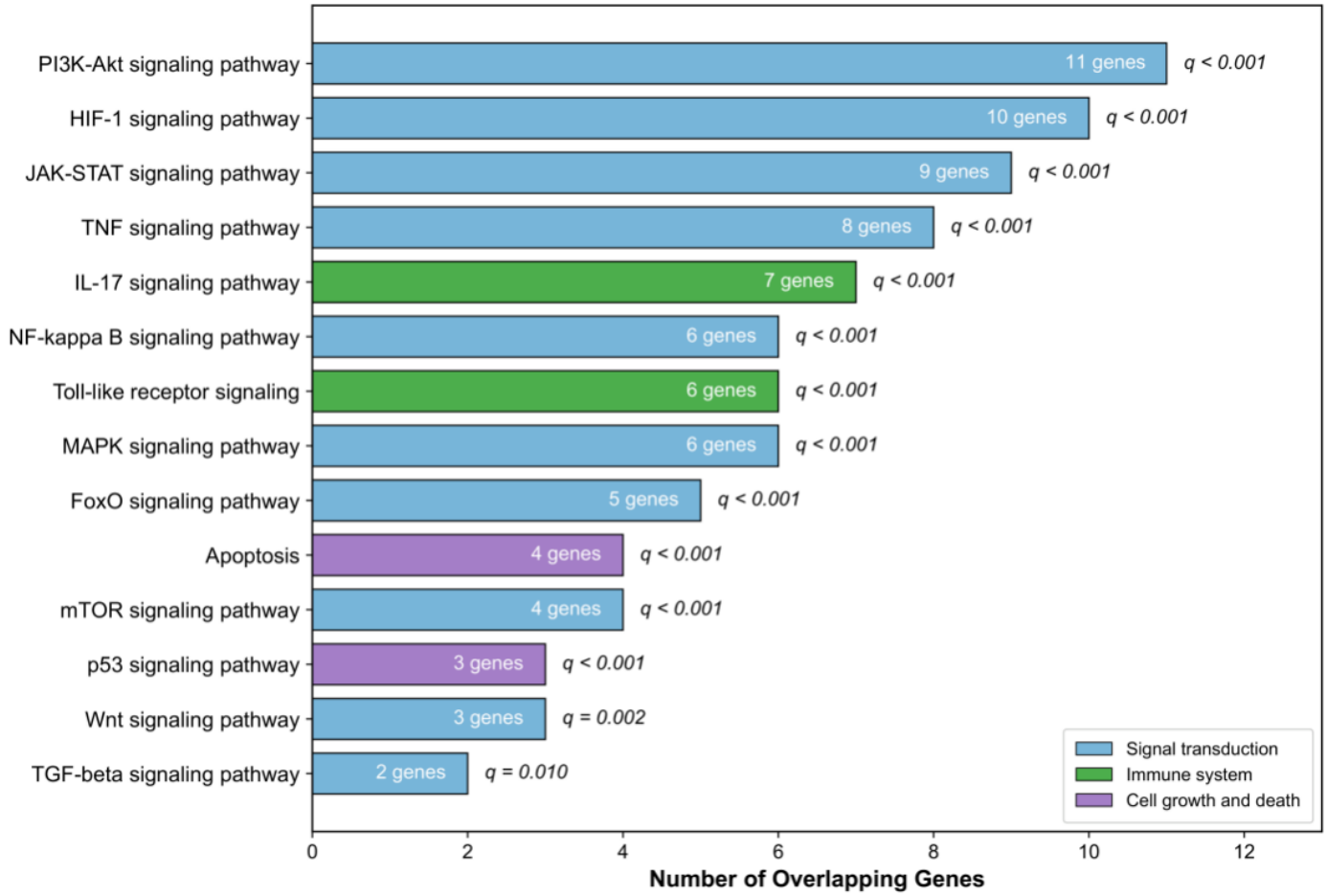


Figure 3. KEGG pathway enrichment of the 29 target genes common to BBR, IPF, and lung cancer. These genes correspond to the 29-gene intersection of BBR targets, IPF-related genes, and lung cancer genes identified in **Figure 2**. Horizontal bars denote significantly enriched KEGG pathways, with bar length proportional to the number of overlapping genes (indicated within each bar). Benjamini–Hochberg adjusted q-values are shown to the right of each bar. All 14 pre-specified pathways remained significantly enriched after correction ($q < 0.05$); the largest adjusted value was $q = 0.010$ (TGF-β signaling). Unadjusted p-values and adjusted q-values for all 14 pathways are provided in **Supplementary Table S1**. Pathways are grouped according to KEGG category (Signal transduction, Immune system, and Cell growth and death).

4. Discussion

Lung cancer is among the most prevalent malignancies worldwide and carries one of the highest rates of psychological comorbidity, with a substantial proportion of patients experiencing elevated anxiety or depressive symptoms (HADS ≥ 8) that profoundly affects treatment adherence, quality of life, and survival [1–3]. When lung cancer is comorbid with IPF—a chronic, progressive fibrotic lung disease that is itself an independent risk factor for lung cancer—the psychosocial burden is amplified substantially [4,5]. These patients must contend with the compounded challenges of malignancy, progressive respiratory decline, prognostic uncertainty arising from two life-limiting diagnoses, and the additive burden of managing two concurrent diseases. Despite the severity of this clinical challenge, these patients remain inadequately addressed in both psycho-oncology and respiratory medicine. In this randomized, double-blind, placebo-controlled trial, we observed that BBR was associated with significant reductions in psychological distress and improvements in quality of life

in lung cancer patients with comorbid IPF. At 12 months, BBR treatment reduced HADS-Anxiety scores from 10.8 ± 3.3 at baseline to 8.3 ± 3.0 ($p < 0.01$) and HADS-Depression scores from 9.6 ± 3.7 to 7.6 ± 3.1 ($p < 0.05$), both reductions exceeded the published minimal clinically important difference of approximately 1.5 points reported for the HADS subscales in patients with chronic respiratory disease [30]. SGRQ-Total improvements (61.8 ± 16.0 to 51.5 ± 15.0; $p < 0.01$) likewise exceeded the established threshold.

Several considerations qualify the interpretation of the psychological improvements. First, HADS scores reflect self-reported symptom severity and do not correspond to a clinical diagnosis. Second, because HADS scores were elevated at baseline in both groups, regression to the mean may have contributed to the within-group improvements; however, the placebo group, whose baseline scores were nearly identical, showed reductions of only 0.8 points on HADS-Anxiety and 0.4 points on HADS-Depression, so the between-group differences of approximately 1.7 and 1.6 points are unlikely to be explained by regression to the mean alone.

BBR was also associated with a smaller 12-month decline in FVC and DLCO relative to placebo ($p = 0.03$ and 0.02, respectively). Within the BBR group, less pulmonary-function loss tracked with better symptom control (**Figure 1A–B**), indicating that physical and psychological improvements occurred in parallel; this association is observational, however, and does not establish that functional preservation directly mediated the symptomatic improvement.

From a psycho-oncology perspective, these findings have implications for symptom management and supportive care in this population. The principal contribution of this trial is to show that a single oral agent can improve patient-reported distress and quality of life in this population, suggesting that pharmacological approaches may have a role in the supportive care of these patients. HADS and SGRQ are patient-reported outcome measures: the gains captured here reflect mood, daily functioning and health-related quality of life as patients themselves experience them, rather than changes confined to spirometric or radiographic measures, and are therefore directly relevant to how supportive care is assessed and delivered. Positioning within existing care pathways requires caution. Collaborative care and structured psychological or pharmacological interventions remain the reference standard for diagnosed depressive and anxiety disorders in lung cancer [31,32], and this trial was not designed to compare BBR with them. BBR should therefore be regarded, if at all, as a possible adjunct to—not a replacement for—guideline-concordant psychological support, pharmacotherapy and specialist referral. Whether this clinical pattern relates to the signaling pathways discussed below remains untested in the absence of pathway-specific measurements.

Complementary network pharmacology analysis identified 29 shared target genes among BBR, IPF, and lung cancer significantly enriched in multiple signaling pathways, among which PI3K-Akt, HIF-1, JAK-STAT, TNF and NF-κB were the most prominently enriched, consistently implicated across fibrotic remodeling, oncogenic signaling, and mood regulation (**Figures 2 and 3**). The NF-κB signaling pathway drives pro-fibrotic gene expression in pulmonary fibroblasts [33], promotes tumor cell survival and proliferation in lung cancer [34], and has been implicated in the neuroinflammatory processes underlying depression and anxiety disorders [11,12]. Similarly, the JAK-STAT pathway plays a well-established role in both pulmonary fibrosis progression and cancer cell proliferation [35], and its dysregulation has been linked to the pathophysiology of depression and anxiety disorders [13,14].

Its upstream activator IL-6 is consistently elevated in these conditions, providing a mechanistic link between pathway activity and inflammation-associated mood disturbance [36,37]. The TNF signaling pathway likewise contributes to both fibrogenesis and tumor microenvironment remodeling [38,39], and TNF-α inhibitors have shown preliminary anxiolytic effects in chronic inflammatory conditions [40,41]. Additional enriched pathways—including HIF-1 [42,43], PI3K-Akt, IL-17 and Toll-like receptor signaling [44–47]—reinforce this pattern through convergent mechanisms. The convergence of these pathways on shared biological processes suggests that BBR may act through multi-target modulation of interconnected networks, consistent with the concurrent improvements in pulmonary function, psychological well-being, and quality of life observed in this study.

BBR, a naturally occurring compound, exhibits anti-fibrotic, anti-tumor and mood-regulatory activities [23,24]. Preclinical studies indicate that BBR attenuates pulmonary fibrosis by inhibiting TGF-β1/Smad signaling and reducing extracellular matrix deposition [48,49], exerts antidepressant-like effects through monoamine regulation and PI3K/Akt/CREB/BDNF activation [23,45], and suppresses lung cancer cell proliferation via PI3K/Akt and MAPK modulation [50,51]. This integrated profile aligns with the multi-pathway enrichment identified in our network pharmacology analysis and provides a pharmacological rationale for the pulmonary and psychological benefits observed. From a clinical perspective, BBR has a well-documented safety record and favorable long-term tolerability [23], consistent with the present trial, in which no adverse drug reactions or serious adverse events were recorded during scheduled clinical assessments or routine laboratory monitoring over 12 months in either group and liver and renal function tests showed no clinically significant impairment in any participant. Its affordability and wide availability are additional considerations for long-term use in patients receiving chemotherapy, immunotherapy or targeted therapy. These attributes do not, however, establish superiority over conventional psychopharmacological agents, which remains untested.

Several limitations should be acknowledged. First, the network pharmacology analysis provides *in silico* predictions that, while consistent with existing literature, require functional validation through cellular assays or biomarker profiling to confirm the proposed multi-pathway explanatory framework in lung cancer patients with comorbid IPF; in addition, because the lung cancer gene set was restricted to the first 1,000 of the 4,311 records returned by the database query, some lung cancer genes were not considered, which may have reduced the number of genes overlapping with the BBR and IPF gene sets and thereby the gene counts and enrichment statistics reported for individual pathways (the pre-specified pathway set itself was unaffected). Second, the absence of longitudinal inflammatory biomarker measurement (e.g., IL-6, CRP, TNF-α), biomarkers that serve as indirect readouts of the enriched NF-κB and JAK-STAT signaling pathways, limited our ability to directly link pathway activity to psychological outcomes in this trial. Third, the sample size (n = 84) was relatively small, and the study was single center; larger multicenter trials are warranted to confirm generalizability. Fourth, although the 12-month follow-up captured the initial treatment response and short-term psychological and clinical benefits, it may be insufficient to establish their long-term durability. Late disease progression or mortality, as well as the persistence of psychological improvement, may only become evident with extended observation; longer follow-up with serial psychological and clinical assessments is therefore needed to confirm the durability of benefits and the natural history of disease. Fifth, this trial was designed primarily to assess

psychological distress and quality of life, and systematic adverse-event (AE) and serious AE (SAE) capture was not pre-specified as an endpoint; safety was assessed by clinical evaluation and routine laboratory testing at scheduled visits. In addition, although concomitant use of agents with pharmacological actions similar to berberine was avoided where clinically appropriate, systematic evaluation of pharmacokinetic interactions with anticancer or antifibrotic therapies was not performed. Baseline antifibrotic use was not recorded, and changes in concomitant anticancer or antifibrotic therapy during the 12-month period were also not systematically captured. The two binary cutoff outcomes (HADS-A ≥ 8 and HADS-D ≥ 8) were analyzed descriptively rather than with a model developed for repeated binary data, such as a generalized estimating equation or a generalized linear mixed model; repeated-measures ANOVA is not appropriate for repeated binary outcomes, and no within-group p-values are therefore reported for these rows, so the proportions meeting each cutoff at each time point should be interpreted descriptively. The between-group comparison of the change in binary status from baseline to 12 months does not rely on a repeated-measures model, and the reported between-group p-values are therefore unaffected by this limitation; these outcomes nevertheless remain exploratory. Adequately powered safety assessment should be prioritized in future berberine trials in this population. Sixth, quality of life was assessed with the SGRQ, an instrument specific to respiratory disease; no cancer-specific instrument such as the EORTC QLQ-C30 or FACT-L was administered. Because the SGRQ focuses on respiratory symptoms and functional limitation—the dimensions that dominate quality of life in patients with comorbid IPF—cancer-related aspects of quality of life, such as the impact of the malignancy and its treatment, may have been incompletely captured. Seventh, the cohort included heterogeneous lung cancer histologies (non-small-cell lung cancer [NSCLC]/small-cell lung cancer [SCLC]) and stages (I–IV). No formal subgroup analyses by histology or stage were performed, as the sample was not adequately powered for them and only descriptive comparisons were possible. Definitive conclusions are precluded by the modest size; tumor-type heterogeneity should be considered in interpretation and addressed in larger, stratified trials.

To address the limitations of this study and fulfill the therapeutic potential of BBR, future research should pursue a coordinated agenda spanning mechanistic validation, biomarker-guided trials, and clinical implementation. Biomarker-embedded clinical trials are needed to test whether patients with elevated baseline inflammatory markers (e.g., IL-6, CRP, TNF-α) show differential responses to BBR, yielding treatment-predictive biomarkers and mechanistic evidence linking pathway engagement to psychological outcomes. Future studies should consider comparative effectiveness research evaluating BBR against standard psychopharmacological interventions in lung cancer patients with comorbid IPF, which would help position BBR within the psycho-oncology treatment landscape. From a translational perspective, mechanistic studies in both pulmonary and neuronal models are warranted to validate the multi-pathway framework proposed herein. Future trials should also incorporate cancer-specific quality-of-life instruments alongside the SGRQ and pre-specified safety endpoints, so that cancer-related quality of life and adverse events are captured directly. Finally, larger multicenter randomized trials with extended, serial follow-up are required to confirm the durability of benefits and to examine whether this integrated profile generalizes to other cancer populations burdened by comorbid fibrotic or chronic inflammatory disease.

In conclusion, this randomized, double-blind, placebo-controlled trial indicates

that BBR was associated with significant reductions in psychological distress and improvements in quality of life in lung cancer patients with comorbid IPF—a population long overlooked in psycho-oncology despite a high symptom burden. Integrating clinical evaluation with network pharmacology generates testable hypotheses about shared inflammatory pathways that may underlie these integrated physical–psychological benefits; because pathway activity was not measured, these mechanistic hypotheses remain exploratory and require validation. These findings nonetheless support BBR's further evaluation as an integrative therapeutic agent within psycho-oncology care.

Supplementary materials: Supplementary Figure S1 (CONSORT flow diagram) and **Supplementary Table S1** (KEGG pathway enrichment of the 29 shared target genes, with unadjusted p-values and Benjamini–Hochberg adjusted q-values) are provided at the end of this file.

Author contributions: Conceptualization, Yichao Zhao and Shufei Wu; methodology, Yichao Zhao and Shufei Wu; investigation, Yichao Zhao, Qi Li and Huihui Zhu; formal analysis, Yichao Zhao, Qi Li and Huihui Zhu; data curation, Yichao Zhao, Qi Li and Huihui Zhu; writing—original draft preparation, Yichao Zhao; writing—review and editing, Deyin Song and Shufei Wu; funding acquisition, Deyin Song; supervision, Shufei Wu. All authors have read and agreed to the published version of the manuscript. Shufei Wu had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical approval: This study was reviewed and approved by the Medical Ethics Committee of Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine (approval number: KY2024023).

Trial registration: International Traditional Medicine Clinical Trial Registry, identifier ITMCTR2026002663. Retrospectively registered.

Informed consent statement: All study participants provided written informed consent before enrollment.

Consent for publication: Not applicable.

Data availability statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request. The gene sets and databases used in the network pharmacology analysis are publicly available (TCMSP, SwissTargetPrediction, NCBI Gene and KEGG); their access dates and versions are given in the Methods. Analysis scripts are available from the corresponding author on reasonable request.

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Conflict of interest: The authors declare no conflict of interest.

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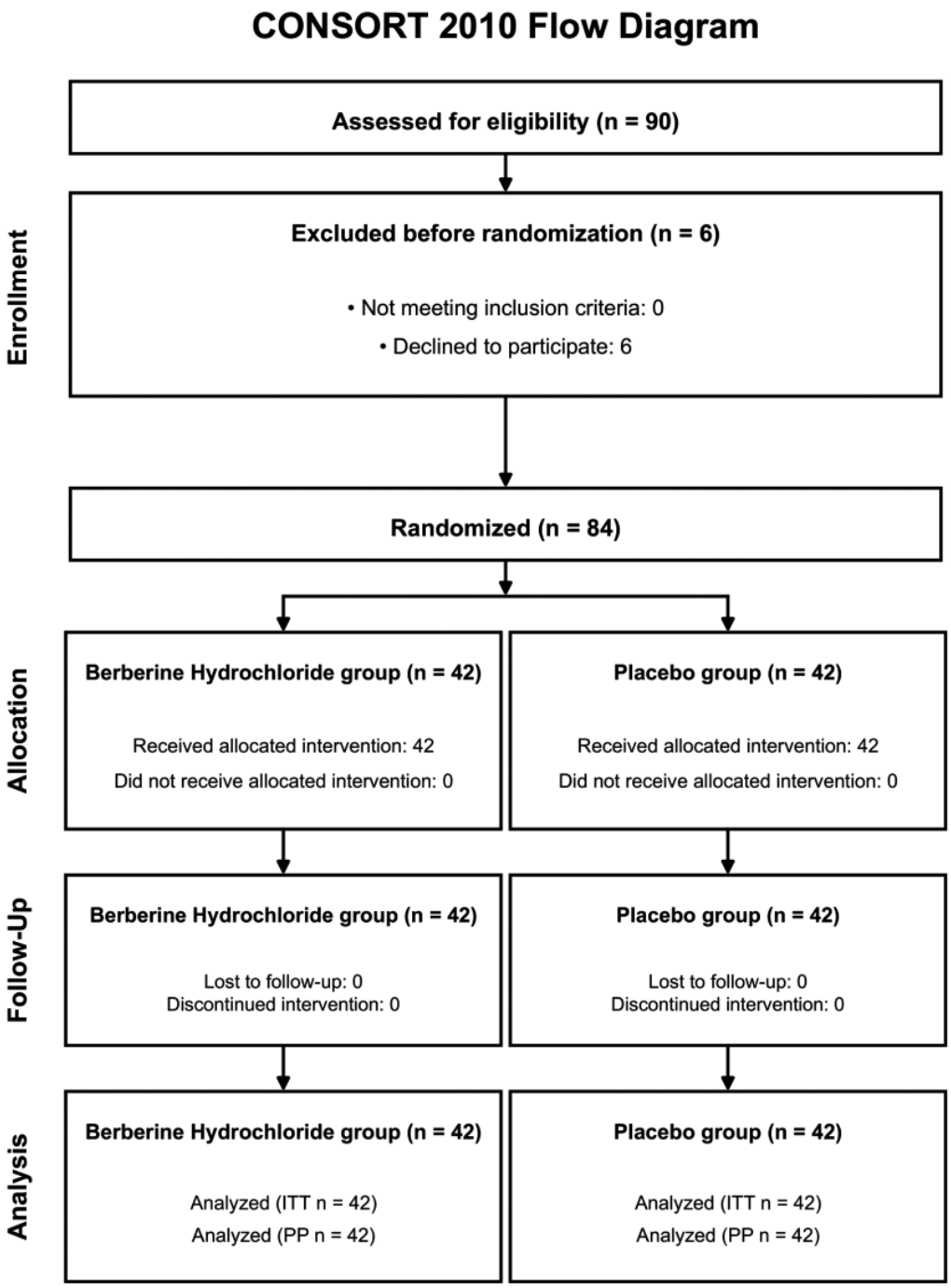
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Supplementary materials



Supplementary Figure S1. CONSORT flow diagram of participant screening, randomization, allocation and follow-up. Of 90 patients assessed for eligibility, 6 declined to participate before randomization, and 84 were randomized 1:1 to berberine hydrochloride (n = 42) or placebo (n = 42). All participants in both groups completed the 12-month follow-up; no participant discontinued the allocated intervention.

Supplementary Table S1. KEGG pathway enrichment of the 29 target genes common to BBR, IPF and lung cancer: unadjusted and Benjamini–Hochberg adjusted results for all 14 pre-specified pathways.

KEGG pathway	Overlapping genes (k)	Pathway size (K)	Unadjusted p	BH-adjusted q	KEGG category
PI3K-Akt signaling pathway	11	360	1.36×10^{-12}	6.35×10^{-12}	Signal transduction

Continuation Table:

KEGG pathway	Overlapping genes (k)	Pathway size (K)	Unadjusted p	BH-adjusted q	KEGG category
HIF-1 signaling pathway	10	109	2.66×10^{-16}	3.73×10^{-15}	Signal transduction
JAK-STAT signaling pathway	9	167	1.32×10^{-12}	6.35×10^{-12}	Signal transduction
TNF signaling pathway	8	118	4.31×10^{-12}	1.51×10^{-11}	Signal transduction
IL-17 signaling pathway	7	93	5.20×10^{-11}	1.46×10^{-10}	Immune system
NF-kappa B signaling pathway	6	104	7.17×10^{-9}	1.67×10^{-8}	Signal transduction
Toll-like receptor signaling pathway	6	108	9.01×10^{-9}	1.80×10^{-8}	Immune system
MAPK signaling pathway	6	300	3.75×10^{-6}	5.83×10^{-6}	Signal transduction
FoxO signaling pathway	5	132	1.19×10^{-6}	2.08×10^{-6}	Signal transduction
Apoptosis	4	135	4.06×10^{-5}	5.69×10^{-5}	Cell growth and death
mTOR signaling pathway	4	157	7.32×10^{-5}	9.32×10^{-5}	Signal transduction
p53 signaling pathway	3	74	1.64×10^{-4}	1.91×10^{-4}	Cell growth and death
Wnt signaling pathway	3	177	2.08×10^{-3}	2.24×10^{-3}	Signal transduction
TGF-beta signaling pathway	2	105	1.00×10^{-2}	1.00×10^{-2}	Signal transduction

Note: k, number of the 29 overlapping genes annotated to the pathway (KEGG organism hsa, T01001); K, total number of Homo sapiens protein-coding genes annotated to the pathway; background N = 20,091. Unadjusted p-values were obtained with a one-sided hypergeometric test, P ($X \geq k$). The Benjamini–Hochberg procedure was applied to the 14 pre-specified pathways only; no other pathways were tested. All 14 pathways remained significant at $q < 0.05$. Abbreviations: BBR, berberine hydrochloride; IPF, idiopathic pulmonary fibrosis; BH, Benjamini–Hochberg; KEGG, Kyoto Encyclopedia of Genes and Genomes.