JTCM 中医杂志

Online Submissions: http://www.journaltcm.com
info@journaltcm.com

J Tradit Chin Med 2016 August 15; 36(4): 418-426
ISSN 0255-2922

CLINICAL STUDY

Sugarcane bagasse dietary fiber as an adjuvant therapy for stable chronic obstructive pulmonary disease: a four-center, randomized, double-blind, placebo-controlled study

Liu Miao, Zheng Fengjie, Ni Lei, Sun Yan, Wu Ruohan, Zhang Tianyu, Zhang Jinchao, Zhong Xianggen, Li Yuhang

Liu Miao, Zheng Fengjie, Ni Lei, Sun Yan, Wu Ruohan, Zhang Tianyu, Zhang Jinchao, Zhong Xianggen, Li Yuhang, School of Preclinical Medicine, Beijing University of Chinese Medicine, Beijing 100029, China
Supported by the National Basic Research Program of China: Study on Mechanism of Lung-Intestine Communication in View of the Theory of COPD Treatment Based on Intestine (No. 2009CB522704)
Correspondence to: Prof. Li Yuhang, School of Preclinical Medicine, Beijing University of Chinese Medicine, Beijing 100029, China. liyuhang@bucm.edu.cn
Telephone: +86-10-64287503; +86-15210694921
Accepted: September 21, 2015

Abstract

OBJECTIVE: To evaluate the efficacy and safety of sugarcane bagasse dietary fiber as an adjuvant therapy for improving quality of life in patients with stable chronic obstructive pulmonary disease (COPD).

METHODS: This was a multicenter, randomized, double-blind, placebo-controlled trial. A total of 196 participants were randomized into a trial group (treated with 6 g/day sugarcane bagasse plus conventional treatment, n = 98) and a control group (treated with placebo plus conventional treatment, n = 98). All efficacy analyses were performed according to the intention-to-treat (ITT) principle. A per-protocol analysis set (PPS) was used to analyze the cases that completed the clinical trial with good compliance. The trial period was 30 days, with a 6-month follow-up. Pre- and post-treatment pulmonary symptom scores (cough, sputum, wheezing, and dyspnea) were recorded for both groups. The St. George's Respiratory Questionnaire (SGRQ) and the modified Medical Research Council (mMRC) dyspnea scale were assessed before treatment and at the end of the 6-month follow-up.

RESULTS: The ITT population was 178 and the PPS population was 166. Post-treatment pulmonary clinical symptoms and severity of dyspnea (mMRC and SGRQ evaluation) were significantly improved in both the trial group and the control group (ITT and PPS: $P < 0.05$). However, there was no statistical difference between the two groups in post-treatment pulmonary symptoms and mMRC. There was a greater reduction in the SGRQ subscales of activity, effect and total score in the trial group compared with the control group (ITT and PPS: $P < 0.01$). There was no statistical difference in pre- and post-treatment safety variables in either group.

CONCLUSION: Sugarcane bagasse combined with conventional treatment improved quality of life in patients with stable COPD. Sugarcane bagasse appears to be a safe herbal medicine with potential for treating patients with stable COPD when taken orally as an adjuvant therapy.

Key words: Saccharum; Pulmonary disease, chronic obstructive; Randomized clinical trial; Medicine, Chinese Traditional

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by constant disruption of airflow into and out of the lungs. COPD induces morbidity and mortality and places a tremendous burden on patients, health-care systems and society.[1] COPD not only disrupts psychological, emotional and social function, but also imposes restrictions on daily activities, and seriously influences patients' health-related quality of life (HRQoL).[2] Based on current trends, COPD is predicted to become the fifth top burden in the world by 2020.[3] Zhong *et al* [4] reported that the prevalence of COPD in China in people 40 years or older was 8.2%, or 43 million based on China's population in 2002-2004.

COPD management is aimed at relieving symptoms, preventing disease progression, treating complications and exacerbations, improving exercise tolerance and health status, and reducing mortality.[5] Therapeutic modalities encompass pharmacologic and non-pharmacologic therapies including oxygen therapy, ventilator support, surgery, and lifestyle changes. Pharmacologic therapy can relieve COPD symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status; however, these medications can also cause side effects. For example, anticholinergics can lead to dry mouth, methylxanthines are associated with cardiac arrhythmias,[6] and long-term use of inhaled corticosteroids is related to higher prevalence of hoarseness, oral candidiasis, and skin bruising.[7] Thus, new COPD therapies are needed.

In China, Traditional Chinese Medicine (TCM) is commonly used to treat COPD. The TCM treatment approach is founded on the concept put forth in the ancient classic *Huang Di Nei Jing* that each internal organ has an interrelated organ.[8] Based on this concept, the large intestine is the paired organ of the lung. Thus, one TCM approach widely used in treating lung diseases such as COPD is to promote bowel regularity.

Chinese sugarcane (Saccharum sinense Roxb.) has been used in China as both food and medicine for more than 2000 years. *Ben Cao Gang Mu*, one of the most complete tomes on TCM theory and treatment, reports that sugarcane relaxes the large intestine.[9] Inspired by this, our previous research found that a dietary fiber preparation made from sugarcane bagasse prevented and treated the rat model of COPD.[10]

To verify this new treatment in humans, we undertook a multicenter, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of sugarcane bagasse dietary fiber as an adjuvant therapy in patients with stable COPD.

METERIALS AND METHODS

Ethics and trial registration

This trial was conducted according to the guidelines of the Declaration of Helsinki.[11] This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-09003117), and was approved by the Ethical Research Committee of the Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (DZMSP20090302). All participants signed informed consent forms, which are on file at the Department of Preclinical Medicine, Beijing University of Chinese Medicine, Beijing, China.

Participants

In this study, 196 out- and in-patients with stable COPD were recruited from November 2009 to February 2013 from four hospitals in China: 58 cases from the Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine (Beijing, 29.6%), 78 cases from Hebei Provincial Hospital of Traditional Chinese Medicine (Shijiazhuang, 39.8%), 40 cases from the Affiliated Hospital of Gansu University of Traditional Chinese Medicine (Lanzhou, 20.4%), and 20 cases from the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine (Shenyang, 10.2%).

Patients were considered eligible if they met all of the following inclusion criteria: (a) diagnosis of COPD (post-bronchodilator FEV_1/FVC less than 70%) based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD; 2007)12 and Chinese Society of Respiratory Diseases;[13] (b) stable COPD; (c) < 80 years old at the time of study commencement; and (d) participating of their own free will after signing an informed consent form. Patients meeting any of the following criteria were excluded from the study: (a) chronic enteritis or diarrhea (> three times/day) with concurrent dizziness and fatigue; (b) intractable constipation and use of stimulant laxatives such as Dahuang (*Radix Et Rhizoma Rhei Palmati*), Fanxieye (*Folium Sennae*), castor oil, or phenolphthalein; (c) severe comorbid disease such as peritonitis, mechanical intestinal obstruction, intestinal stenosis, severe hemorrhoids, hernia, post-colorectal surgery, anal mucosal inflammatory edema, severe anemia, aneurysms, intestinal bleeding or perforation, colorectal cancer, liver cirrhosis, anal fistula, acute cerebral hemorrhage, acute left heart failure, gastrointestinal hemorrhage, acute renal failure, or aplastic anemia; (d) airflow limitation because of bronchiectasis, cystic pulmonary fibrosis, lung cancer, active tuberculosis or other disorders; (e) serious heart, hepatic, renal or hematopoietic diseases; (f) having recently taken immunosuppressant medication; (g) pregnant or breast-feeding; (h) psychiatric or any type of neurological deficit (cognitive impairment or aphasia) that rendered patients unable to understand the nature, scope and possible consequences of the study; (i) digestive obstacles, malnutrition, physical weakness or dehydration; and (j) allergy to the experimental drug.

Participants could withdraw from the study at any time for any reason. Researchers recorded the reasons for withdrawal or early discontinuation, although every

effort was made to ensure adherence during the trial. If adverse events (AEs) occurred, researchers discussed whether the symptoms were severe enough to warrant termination of the participant from the trial. In general, termination criteria were: (a) non-adherence to the treatment or follow-up protocols; (b) using other medications during the trial that might impact the results or cause adverse effects; (c) adverse effects that precluded continuation in the trial; and (d) not meeting the entry criteria.

Sample size

As this was an exploratory study, there were no existing clinical data on the use of sugarcane bagasse for the treatment of stable COPD available as a reference for our trial. Therefore, we referred to literature on analog medicines used for stable COPD and hypothesized the effect rate for calculating sample size.[14,15] The effect rate was hypothesized to be 70% for conventional medicine plus placebo and 90% for conventional medicine plus sugarcane bagasse. A 1∶1 parallel design was used for the control group and the trial group. With a one-sided significance level of 5%, a statistical power of 90%, and an assumed drop-out rate of approximately 20%, we needed to randomly assign 98 participants to each group.

Medicine preparation

Fresh sugarcane was purchased from the Sugarcane Quality Supervision, Inspection and Test Center, Ministry of Agriculture of the People's Republic of China, Beijing, China. Sugarcane bagasse was made from fresh sugarcane into pills (a standard 1-g pill contained 0.5 g sugarcane bagasse/pill, plus the same other ingredients as in the placebo pill) as described by Beijing Zheng Yuan Ju Xin Health Food Technology Development Co., Ltd., Beijing, China (batch numbers: 20090501, 20090502, 20090503).[16] This supplier was also commissioned to prepare the placebo tablet, which was made of skim milk powder with a sugar and dextrin coating, and was designed to have a similar taste, smell, and appearance to the sugarcane bagasse pills.

Randomization and blinding

Randomization was generated by SAS 8.0 software (SAS Institute Inc., Cary, NC, USA). To ensure allocation concealment, the drugs were packaged by an independent clinical statistician. Participants were randomized into one of the two groups when they met the inclusion criteria and signed the informed consent form. Participants and investigators were blinded until the end of the trial. In addition, opaque and sealed emergency letters were printed in accord with the randomized list. In the event of a clinical emergency, the participant's randomization code and group allocation could be identified using the emergency envelope. A single investigator was assigned at each center to record and secure randomization information; this individual did not have contact with other trial investigators, thus ensuring that there was no investigator effect on enrollment and randomization. An independent clinical statistician completed the outcome assessments; this individual was blinded to randomization and did not participate in any other part of the trial.

Interventions

All participants in both groups were given conventional medication based on GOLD[12] and Chinese Society of Respiratory Diseases[13] recommendations (Table 1).

The trial group was given conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days). The control group was given conventional medication plus placebo (six pills twice daily for 30 days). Participants did not receive any intervention during the 6-month follow-up period. A telephone hotline was established to address participant queries or issues.

Outcome measures

Based on previous nationwide research (Symptom Standardization of Traditional Chinese Medicine, No. 2003CB517100, supported by the National Basic Research Program of China), a case report form was developed based on literature research,[17] a pilot survey, and expert opinions. The details were as follows:

Symptom scores: this was the primary measure in the study. Based on the Likert response scale[18] as well as symptom quantification and classification from the Guide to New Traditional Chinese Medicine Research,[19] values of 0, 2, 4, and 6 respectively were assigned to

Table 1 Therapy given according to stage of chronic obstructive pulmonary disease

COPD stage	Lung function	Therapy[a]
Ⅰ: mild	FEV_1/FVC < 70%; FEV_1 ≥ 80% of predicted value	Initiate risk factor reduction; use short-acting bronchodilator as needed, i.e., salbutamol, albuterol
Ⅱ: moderate	FEV_1/FVC < 70%; FEV_1 50% - < 80% of predicted value	Add one or more long-acting bronchodilators as needed, i.e., formoterol; add rehabilitation
Ⅲ: severe	FEV_1/FVC < 70%; FEV_1 30% - < 50% of predicted value	Add inhaled glucocorticoids for repeated exacerbations, i.e. salmeterol or formoterol dry powder
Ⅳ: very severe	FEV_1/FVC < 70%; FEV_1 < 30% of predicted value, or FEV_1 < 50% of predicted value plus chronic respiratory failure	Add long-term oxygen for chronic respiratory failure; consider surgery

Notes: [a]based on recommendations by the Global Initiative for Chronic Obstructive Lung Disease.[12] COPD: chronic obstructive pulmonary disease; FEV_1/FVC: the ratio of forced expiratory volume in 1 second to forced vital capacity; FEV_1%: FEV_1 percentage of the predicted value.

the four symptom grades of none, mild, moderate, and severe. Major pulmonary symptoms (cough, sputum, wheezing, and dyspnea) were then evaluated and reported by patients. Pre- and post-treatment symptom scores were recorded.

Health-related quality of life: HRQoL was evaluated using the Chinese translation of the St. George's Respiratory Questionnaire (SGRQ).[20] The SGRQ is composed of symptoms, activity, impact of disease, and total score, and was designed to quantify and measure the impact of chronic respiratory disease on patients' quality of life. Health status as measured by the SGRQ was therefore used as a co-primary endpoint in the trial. SGRQ scores were recorded pre-treatment and at the 6-month follow-up visit.

Modified Medical Research Council (mMRC) dyspnea scale: the mMRC dyspnea questionnaire is related to other measures of health status[21] and predicts future mortality risk.[22] Assessment of the degree of breathing difficulty is crucial to understanding the severity of the disease, patients' health status, and to evaluate the effects of intervention. For all participants, dyspnea severity was assessed according to the mMRC scale pre-treatment and at the sixth follow-up visit.[23]

Safety assessments: pre- and post-treatment safety assessments were performed. Routine blood, urine, and stool samples were collected. Liver and kidney function tests as well as electrocardiography (ECG) were carried out. All AEs that occurred during the study, including the treatment and follow-up periods, were assessed and recorded.

Data entry and statistical analysis

Data were entered by two independent researchers using EpiData 3.0 software (The EpiData Association, Odense, Denmark). All efficacy analyses were performed on the intention-to-treat (ITT) population, which included all patients who were randomized and received treatment. Partially missing data of the clinical evaluation were resolved with the principle of the last observation carried forward. A per-protocol analysis set (PPS) was adopted to analyze the cases that completed the clinical trial with good compliance. All statistical tests were two-tailed, and $P < 0.05$ was taken to be statistically significant. Enumeration data were represented as a percentage and evaluated by the chi-square test. Between-group difference after treatment was assessed by analysis of variance and/or analysis of covariance represented by the mean ± standard deviation ($\bar{x} \pm s$). Within-group difference between pre- and post-treatment values was assessed using the paired *t*-test. Statistical analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Study population

A total of 219 patients were screened for entry into the study, with 23 deemed ineligible. Of the remaining 196 patients, one dropped out because of heartburn and six were lost to follow-up. Therefore, 189 patients completed the entire 30-day treatment and 6-month follow-up. Five participants did not adhere to protocols, with less than 240 (2/3) of 360 pills taken (compliance < 80%), and 18 were excluded from the efficacy analysis because they failed to meet the inclusion criteria. Therefore, the final number in the PPS was 166, with 84 patients in the trial group and 82 patients in the control group. The final ITT population was 178, with 91 in the trial group and 87 in the control group (Figure 1).

There was no significant pre-treatment difference between the trial group and the control group in age, sex, body mass index, educational status, smoking status, GOLD classification of lung function, course of disease, symptom exacerbations, or whether the participants had received the influenza vaccine (Table 2).

Symptoms

Within the trial and the control group, the mean post-treatment pulmonary symptom values were significantly decreased compared with pre-treatment values ($P < 0.001$). However, there was no significant difference between the two groups (ITT: − 0.42, 95% *CI*: − 1.66 to 0.82, $P = 0.506$; PPS: − 0.45, 95% *CI*: − 1.74 to 0.84, $P = 0.490$) (Table 3).

Health-related quality of life

The four subscale scores of the SGRQ (symptoms, activity, impact of disease, and total score) were significantly reduced in both the trial and the control group compared with pre-treatment values (ITT and PPS: $P < 0.05$). After the 30-day treatment period, three SGRQ subscale scores (activity, impact of disease, and total score) were significantly lower in the trial group compared with the control group (activity: ITT: $P < 0.001$ and PPS: $P = 0.001$; impact of disease: ITT: $P = 0.002$ and PPS: $P = 0.002$; total score: ITT: $P = 0.001$ and PPS: $P < 0.001$). The subscale score of symptoms was more obviously reduced in the trial group than in the control group, but this difference was not statistically significant (ITT: − 6.20, 95% *CI*: − 12.54 to 0.14, $P = 0.055$; PPS: − 5.94, 95% *CI*: − 12.19 to 0.31, $P = 0.062$; Table 4).

Dyspnea grade

Compared with pre-treatment, dyspnea improved significantly in both the trial group (ITT: $P = 0.006$, PPS: $P = 0.005$) and the control group (ITT: $P = 0.019$; PPS: $P = 0.021$); however, there was no significant difference between the two groups after treatment (ITT: $P = 0.779$, PPS: $P = 0.627$, Table 5).

Safety

Treatment was discontinued because of an AE (heartburn) in one of 91 (1%) patients in the trial group versus no patients in the control group ($P = 0.327$). There

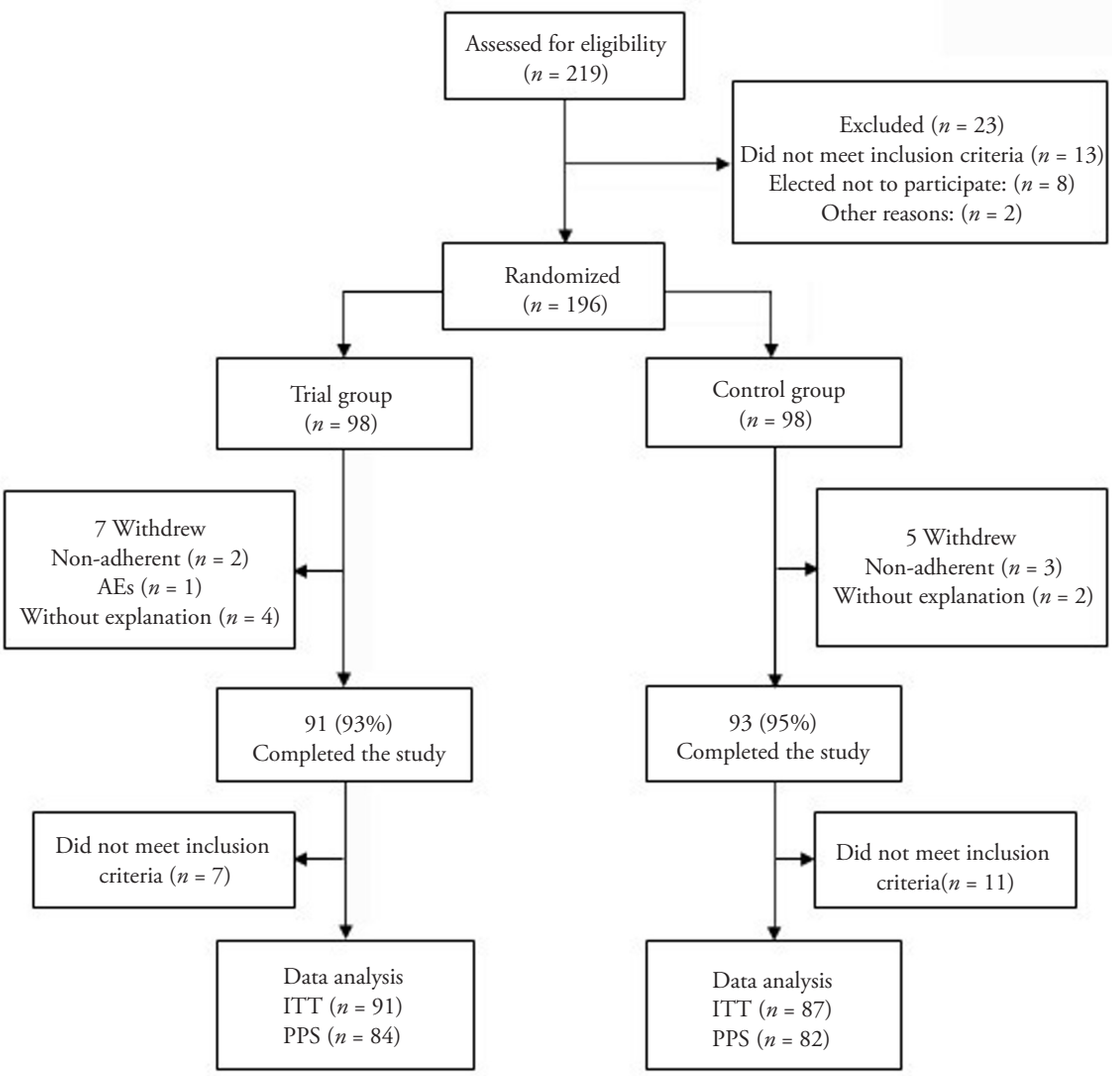

Figure 1 Flowchart of study
ITT: intention-to-treat; PPS: per protocol set.

was no statistical difference in routine blood, urine, and stool testing, liver and kidney function, or ECG in both groups before and after treatment (Table 6).

DISCUSSION

To our knowledge, this is the first trial to investigate sugarcane bagasse dietary fiber as an adjuvant therapy for stable COPD. The overall clinical interventions were effective; pulmonary clinical symptom scores and severity of dyspnea grade on mMRC and SGRQ evaluation were significantly improved after treatment in both the sugarcane bagasse trial group and the placebo control group. Compared with those of the control group, the symptom scores and mMRC of the trial group appeared slightly improved; however, there was no statistical difference between the two groups after treatment. The post-treatment SGRQ subscales of activity, impact of disease and total score were significantly more reduced in the trial group than in the control group, demonstrating that sugarcane bagasse dietary fiber was an effective adjuvant therapy to conventional COPD medication in improving HRQoL.

Quality of life has emerged as a significant consideration in disease treatment and prevention in recent decades.[24,25] COPD has a considerable influence on patients' physical and emotional well-being, social activity, and work. Health status is closely related to mortality and is independent of airflow limitation or age.[26] Improving quality of life is a desirable indicator in managing patients with COPD. The SGRQ measures the effect of chronic respiratory disease on patients' HRQoL.[27] We found no significant difference between the trial and the control group in post-treatment SGRQ pulmonary symptom scores; however, the SGRQ subscales of activity, impact of disease and total score, which were concerned with physical activities that either cause or are limited by breathlessness and expectations for health and disturbance of daily life, were significantly more reduced in the trial group compared with the control group. Adjunctive therapy with sugarcane bagasse had a better effect than conventional medicine alone in mitigating quality of life.

Several lines of evidence have independently suggested that higher fiber intake is related to better lung function and lower risk of developing COPD.[28,29] However,

Table 2 Baseline characteristics of participants ($\bar{x} \pm s$)

Item	Variable	Trial group (n = 91)	Control group (n = 87)
Age (years)		62.89±9.53	63.77±9.58
Male/Female (n)		64/27	58/29
BMI (kg/m^2)		23.60±2.71	23.21±2.71
Body temperature (℃),		36.47±0.44	36.38±0.24
Frequency of exacerbation		2.18±0.68	2.24±0.59
Tobacco history	Currently smoking [n (%)]	12 (13.1)	10 (11.5)
	Never smoked [n (%)]	40 (44.0)	33 (37.9)
	Ever smoked [n (%)]	39 (42.9)	44 (50.6)
	No. of packs/year	186.91±230.72	155.65±189.84
	FEV_1/FVC	59.18±10.14	58.02±11.61
Disease severity	GOLD stage Ⅰ [n (%)]	5 (5.5)	7 (8.0)
	GOLD stage Ⅱ [n (%)]	60 (65.9)	53 (60.9)
	GOLD stage Ⅲ [n (%)]	21 (23.1)	20 (23.1)
	GOLD stage Ⅳ [n (%)]	5 (5.5)	7 (8.0)
Course of disease	> 5 years	78 (85.7)	80 (92.0)
	≤ 5 years	13 (14.3)	7 (8.0)
	Influenza vaccinations (n)	47/44	49/38

Notes: trial group was treated with conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days); control group was treated with conventional medication plus placebo (six pills twice daily for 30 days). BMI: body mass index; FEV_1/FVC: the ratio of forced expiratory volume in 1 second to forced vital capacity; GOLD: global initiative for chronic obstructive lung disease.

Table 3 Comparison of pre- and post-treatment symptom scores between the trial and the control group ($\bar{x} \pm s$)

Pulmonary symptoms [a]	Trial group			Control group			Treatment effect[b] (95% *CI*; *P* value)
	Pre	Post	Mean D[b]	Pre	Post	Mean D[c]	
ITT	10.40 (4.52)	5.30 (3.96)	− 5.10 (5.64)	10.74 (4.10)	5.86 (4.38)	− 4.87 (5.27)	− 0.42 (− 1.66, 0.82; 0.506)
PPS	10.48 (4.58)	5.29 (3.98)	− 5.19 (5.82)	10.76 (4.21)	5.78 (4.48)	− 4.98 (5.39)	− 0.45 (− 1.74, 0.84; 0.490)

Notes: trial group was treated with conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days); control group was treated with conventional medication plus placebo (six pills twice daily for 30 days). Mean D: mean difference; *CI*: confidence interval; ITT: intention-to-treat; PPS: per protocol set. Data are presented as mean (*SD*). [a]The ITT population was 91 in the trial group and 87 in the control group; the PPS population was 84 in the trial group and 82 in the control group. [b]Covariance analysis estimate with 95% *CI* for the difference. [c]$P < 0.001$ for change between pre- and post-treatment value (within-group difference analyzed by the paired *t*-test).

the exact mechanism between COPD and dietary fiber is still unclear. Our study was designed to evaluate the hypothesis that sugarcane bagasse, which is used as dietary fiber and a laxative, could improve COPD symptoms. Our hypothesis was based on a fundamental TCM theory in which the lung and large intestine interact with one another physiologically and pathologically. This phenomenon appears to also occur in Western (conventional) Medicine.[30,31] Sugarcane bagasse is the fibrous byproduct that remains after sugar cane stalks are crushed to extract juice. The fibrous portion of bagasse is composed mainly of cellulose, hemicellulose, and lignin. Such types of soluble fiber are not assimilated by the intestine, and when ingested they increase stool bulk and keep the stool moist, improving stool transit time to prevent and treat constipation.[32-34] Our trial indicates that the beneficial effect of sugarcane bagasse dietary fiber in improving quality of life in patients with stable COPD could be achieved through regulation of the intestinal environment.

The anti-inflammatory and antioxidant properties of fiber are another potential mechanism for the efficacy of sugarcane bagasse in improving quality of life in patients with stable COPD.[35] Airway inflammation is the primary pathogenic factor for both parenchymal destruction and airway remodeling in COPD.[36] Previous research has demonstrated that increased intake of total dietary fiber decreased the concentration of interleukin-6, interleukin-18 and C-reactive protein.[37-40] King indicated that dietary fiber reduced lipid oxidation, which in turn is associated with decreased inflammation.[41] Our previous research found that sugarcane ba-

Table 4 Comparison of St. George's Respiratory Questionnaire scores in the trial and the control group ($\bar{x} \pm s$)

SGRQ[1]		Trial group			Control group			Treatment effect (95% *CI*; *P* value)[2]
		Pre	Post	Mean D	Pre	Post	Mean D	
Symptom	ITT	57.00 (22.56)	41.11 (21.94)	− 15.89 (30.51)[a]	54.42 (21.56)	47.41 (20.76)	− 7.01 (31.94)[b]	− 6.20 (− 12.54, 0.14; 0.055)
	PPS	56.11 (22.87)	39.18 (21.20)	− 16.93 (31.93)[a]	53.31 (21.60)	45.50 (19.79)	− 7.81 (32.68)[b]	− 5.94 (− 12.19, 0.31; 0.062)
Activity	ITT	47.21 (20.64)	30.98 (17.17)	− 16.23 (22.99)[a]	48.25 (21.53)	46.07 (21.97)	− 6.18 (28.73)[b]	− 10.96 (− 16.77, − 5.16; <0.001)
	PPS	47.18 (20.79)	31.17 (16.78)	− 17.01 (25.62)[a]	47.89 (21.97)	40.79 (21.84)	− 7.10 (29.21)[b]	− 10.56 (− 16.53, − 4.60; 0.001)
Impact	ITT	36.24 (22.18)	19.49 (16.28)	− 16.75 (25.95)[a]	37.60 (20.72)	28.46 (20.32)	− 9.14 (25.58)[a]	− 8.76 (− 14.13, − 3.39; 0.002)
	PPS	36.26 (22.47)	18.23 (15.17)	− 18.23 (26.46)[a]	36.83 (20.80)	26.60 (19.29)	− 10.23 (25.68)[a]	− 8.52 (− 13.80, − 3.23; 0.002)
Total	ITT	44.13 (19.48)	26.39 (16.41)	− 17.10 (23.68)[a]	45.23 (18.92)	36.52 (20.10)	− 7.95 (25.59)[a]	− 9.15 (− 14.43, − 3.87; 0.001)
	PPS	42.80 (19.96)	24.43 (14.47)	− 18.37 (24.15)[a]	42.84 (18.87)	33.88 (18.75)	− 8.96 (25.86)[a]	− 9.45 (− 14.60, − 4.30; < 0.001)

Notes: trial group was treated with conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days); control group was treated with conventional medication plus placebo (six pills twice daily for 30 days). SGRQ: St. George's Respiratory Questionnaire; Mean D: mean difference; *CI*: confidence interval; ITT: intention-to-treat; PPS: per protocol set. Data are presented as mean (*SD*). [a]$P < 0.001$, [b]$P < 0.05$, for the change between pre- and post-treatment (within-group difference analyzed by the paired *t*-test). [1]The ITT population was 91 in the trial group and 87 in the control group; the PPS population was 84 in the trial group and 82 in the control group. [2]Covariance analysis estimate with 95% *CI* for the difference.

Table 5 Comparison of the dyspnea grades in the trial and the control group [*n* (%)]

Modified Medical Research Council (mMRC) scale[a]	Intend to treat			Per protocol set		
	Trial group (*n* = 91)	Control group (*n* = 87)	*P* value[b]	Trial group (*n* = 84)	Control group (*n* = 82)	*P* value[b]
Pre-treatment			0.733			0.640
0	19 (20.88)	19 (21.84)		18 (21.69)	18 (21.95)	
1	34 (37.36)	34 (39.08)		31 (37.35)	33 (40.24)	
2	20 (21.98)	18 (20.69)		17 (20.48)	15 (18.29)	
3	16 (17.58)	16 (6.90)		16 (19.28)	16 (19.51)	
4	2 (2.20)	0 (0)		2 (2.41)	0 (0)	
Post-treatment			0.779			0.627
0	29 (31.87)	30 (34.48)		28 (33.73)	29 (35.37)	
1	45 (49.45)	40 (45.98)		42 (50.60)	38 (46.34)	
2	13 (14.29)	12 (13.79)		10 (12.05)	10 (12.20)	
3	3 (3.30)	5 (5.75)		3 (3.61)	5 (6.10)	
4	1 (1.10)	0 (0)		1 (1.20)	0 (0)	
P value[c]	0.006	0.019		0.005	0.021	

Notes: trial group was treated with conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days); control group was treated with conventional medication plus placebo (six pills twice daily for 30 days). Rank-sum test for two independent samples was used for comparison of dyspnea grade pre- and post-treatment. Values are presented as *n* (%). [a]Modified Medical Research Council scale:[19] 0: not troubled by breathlessness except with strenuous exercise; 1: short of breath when walking quickly on level ground or walking up a slight hill; 2: walks slower than others of the same age because of breathlessness or has to stop to catch breath when walking on level ground; 3: stops to catch breath after walking about 100 meters/yards or after a few minutes on level ground; 4: too breathless to leave the house or breathless when dressing or undressing. [b]*P* values for the comparison of the pre- and post-treatment values in the trial group with those of the control group. [c]*P* values for the comparison of the pre-treatment values with the post-treatment values in the trial and control groups.

gasse had beneficial effects for COPD rats in reducing malondialdehyde, increasing superoxide dismutase activity, and improving airflow limitation.[10] Taken together, these findings suggest that anti-inflammatory and antioxidant properties might be the potential mechanism for the effect of sugarcane bagasse on improving HRQoL in patients with COPD.

Our study found that sugarcane bagasse pills were a

Table 6 Safety profile [*n* (%)]

Variable[a]	Trial group (*n* = 91)		Control group (*n* = 87)		*P* value[a]
	Day 1 (Baseline)	Day 10 (End)	Day 1 (Baseline)	Day 10 (End)	
WBC	7.61 (2.29)	7.44 (1.91)	7.63 (2.41)	7.46 (2.22)	0.811
HB	150.7 (36.7)	163.8 (39.9)	146.4 (36.7)	150.3 (31.5)	0.252
RBC	4.62 (0.62)	4.62 (0.59)	4.57 (0.47)	4.51 (0.45)	0.276
PLT	205.8 (69.3)	206.6 (69.4)	204.1 (63.7)	201.8 (54.2)	0.635
NEUT	58.2 (14.0)	56.5 (12.7)	59.9 (12.8)	57.9 (9.7)	0.573
ALT	24.7 (11.0)	25.4 (9.6)	26.0 (13.6)	25.9 (11.5)	0.571
BUN	5.0 (1.5)	4.9 (1.4)	5.3 (1.4)	5.1 (1.4)	0.360
Cr	71.9 (14.7)	71.6 (14.3)	74.0 (14.1)	74.2 (13.6)	0.424
ECG[b]	27 (91)	23 (91)	24 (87)	21 (87)	0.860

Notes: trial group was treated with conventional medication plus sugarcane bagasse pills orally (six pills twice daily for 30 days); control group was treated with conventional medication plus placebo (six pills twice daily for 30 days). WBC: white blood cells; HB: hemoglobin; RBC: red blood cells; PLT: platelets; NEUT: neutrophilic granulocyte; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; ECG: electrocardiogram. Data are presented as mean ± standard deviation. [a]Covariance analysis for between-group values after treatment. [b]*Chi*-square test for between-group values after treatment.

well-tolerated addition to pharmacotherapy for stable COPD. This may be because sugarcane bagasse pills are easier to take compared with drinking a decoction. Furthermore, since sugarcane bagasse is a byproduct of sugarcane processing, it is less expensive than other TCM medicines. Therefore, sugarcane bagasse taken orally as an adjuvant therapy has potential value in improving HRQoL of patients with stable COPD.

Lung function testing was not used as an assessment in our study. Although lung function test is an objective indicator of airway limitation with FEV_1 as a marker for some pathophysiological changes in COPD, it still correlates only poorly with the severity of dyspnea and other symptoms.[42] In addition, patients in this trial were in the stable phase of COPD, so their lung function would not have obviously changed except under acute exacerbation.

A limitation of our study is the relatively short treatment period (30 days) and follow-up time (6 months), which is not long enough to account for the frequency and duration of acute exacerbations of COPD. Further studies are required to confirm the long-term effects of sugarcane bagasse on stable COPD.

In conclusion, sugarcane bagasse dietary fiber appears to be a safe and effective adjuvant therapy that improved quality of life in patients with stable COPD during 6 months of follow-up. Although this study demonstrates that sugarcane bagasse is an effective adjuvant treatment for patients with stable COPD, further studies are required to elucidate the mechanism of sugarcane bagasse for treating stable COPD.

ACKNOWLEDGMENTS

The authors are grateful to the Ministry of Science and Technology of the People's Republic of China for funding this study.

The authors appreciate assistance and support received from the following individuals during patient recruitment: Dr. Su Huiping (Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine), Dr. Geng Limei (Hebei Provincial Hospital of Traditional Chinese Medicine), Dr. Xu Yanling (Affiliated Hospital of Liaoning University of Traditional Chinese Medicine), Dr. Li Hong (Affiliated Hospital of Gansu University of Traditional Chinese Medicine), and all medical staff involved in this study.

The authors also thank Nissi S. Wang, MSc for reviewing and editing the manuscript.

REFERENCES

1 **Skrepnek GH**, Skrepnek SV. Epidemiology, clinical and economic burden, and natural history of chronic obstructive pulmonary disease and asthma. Am J Manage Care 2004; 10(Suppl S): S129-S138.

2 **Agh T**, Domotor P, Bartfai Z, Inotai A, Fujsz E, Meszaros A. Relationship between medication adherence and health-related quality of life in subjects with copd: a systematic review. Resp Care 2015; 60(2): 297-303.

3 **Lopez AD**, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998; 4(11): 1241-1243.

4 **Zhong NS**, Wang C, Yao WZ, et al. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med 2007; 176 (8): 753-760.

5 **Metzger NL**, Lundquist LM. A review of the advances in chronic obstructive pulmonary disease treatment. J Pharm Pract 2012; 25(6): 576-582.

6 Global strategy for diagnosis, management, and prevention of Chronic Obstructive Lung Disease. 2015-12, cited 2016-4-19. Available from URL: http://www.goldcopd.org/Guidelines/guidelines-global-strategy-for-diagnosismanagement.html.

7 **Pauwels RA**, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 1999; 340(25): 1948-1953.

8 **Tian DH**, Liu GS. Huang Di Nei Jing Su Wen (Warring States Period to Western Han Dynasty). Beijing: People's Medical Publishing House, 2013: 8.

9 **LI SZ** (Qing dynasty). Ben Cao Gang Mu. Beijing: People's Medical Publishing House, 1981: 1889.

10 **Li YH**, Zhong XG, Jia X, et al. Influences of relaxing large intestine therapy on lung function and blood gas in rat model of chronic obstructive pulmonary disease. Beijing Zhong Yi Yao Da Xue Xue Bao 2010; 33(7): 452-455.

11 **Puri KS**, Suresh KR, Gogtay NJ, Thatte UM. Declaration of Helsinki, 2008: implications for stakeholders in research. J Postgrad Med 2009; 55(2): 131.

12 Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2007-12, cited 2016-4-19. Available from URL: http://www.goldcopd.org/Guidelines/guidelines-global-strategy-for-diagnosis-management-2007.html.

13 Treatment guidelines of chronic obstructive pulmonary disease (revised 2007). Zhong Hua Jie He He Hu Xi Za Zhi 2007; 30(1): 8-17.

14 **Peng WB**, Li SF. Clinical observation of lung-purging, blood-activating and fu-unblocking herbs with Western Medicine in treating acute exacerbation of chronic obstructive pulmonary disease. Shanghai Zhong Yi Yao Za Zhi 2009; 7(43): 28-30.

15 **Chen H**, Zhi KY, Feng WJ. Clinical observation of fu-unblocking, clearing-heat in treating 128 patients with acute exacerbation of chronic obstructive pulmonary disease. Shanxi Zhong Yi 2008; 6(24): 29-30.

16 **Sangeetha AV**, Mahadevamma S, Begum K, Sudha ML. Influence of processed sugarcane bagasse on the microbial, nutritional, rheological and quality characteristics of biscuits. Int J Food Sci Nutr 2011; 62(5): 457-464.

17 **Xu WJ**, Wang TF, Wang ZY, Yu LL, Lü JC, Wang QG. Analysis of characteristics of traditional Chinese symptoms of COPD based on recent literature. Shanghai Zhong Yi Yao Za Zhi 2008; 42(2): 20-22.

18 **Jamieson S**. Likert scales: how to (ab)use them. Med Educ 2004; 38(12): 1217-1218.

19 **Zheng XY**. Respiratory disease. Clinical guidelines of Traditional Chinese Medicine new drug. Volume 1. Beijing: China Medical Science Press, 2002: 53-58.

20 **Liu T**, Cai BQ. Assessment methods and significance of Quality of Life for patients with chronic obstructive pulmonary disease. Zhong Guo Hu Xi Yu Wei Zhong Jian Hu Za Zhi 2003; 4(2): 8-9.

21 **Jones PW**. Health status measurement in chronic obstructive pulmonary disease. Thorax 2001; 56(11): 880-887.

22 **Nishmura K**, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002; 121(5): 1434-1440.

23 **Mahler DA**, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3): 580-586.

24 **Sanders C**, Egger M, Donovan J, Tallon D, Frankel S. Reporting on quality of life in randomised controlled trials: Bibliographic study. Brit Med J 1998; 317(7176): 1191-1194.

25 **Gill TM**, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. J Am Med Asso 1994; 272 (8): 619-626.

26 **Oga T**, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 2003; 167(4): 544-549.

27 **Jones PW**, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145(6): 1321-1327.

28 **Kan H**, Stevens J, Heiss G, Rose KM, London SJ. Dietary fiber, lung function, and chronic obstructive pulmonary disease in the atherosclerosis risk in communities study. Am J Epidemiol 2008; 167(5): 570-578.

29 **Varraso R**, Willett WC, Camargo CA. Prospective study of dietary fiber and risk of chronic obstructive pulmonary disease among US women and men. Am J Epidemiol 2010; 171(7): 776-784.

30 **Powell N**, Huntley B, Beech T, Knight W, Knight, Corrigan CJ. Increased prevalence of gastrointestinal symptoms in patients with allergic disease. Postgrad Med J 2007; 83 (977): 182-186.

31 **Ceyhan BB**, Karakurt S, Cevik H, Sungur M. Bronchial hyperreactivity and allergic status in inflammatory bowel disease. Respiration 2003; 70(1): 60-66.

32 **Lembo A**, Camilleri M. Chronic constipation. N Engl J Med 2003; 349(14): 1360-1368.

33 **Yang J**, Wang HP, Zhou L, Xu CF. Effect of dietary fiber on constipation: a Meta analysis. World J Gastroenterol 2012; 18(48): 7378-7383.

34 **Slavin JL**. Position of the American Dietetic Association: health implications of dietary fiber. J Am Diet Assoc 2008; 108(10): 1716-1731.

35 **Galisteo M**, Duarte J, Zarzuelo A. Effects of dietary fibers on disturbances clustered in the metabolic syndrome. J Nutr Biochem 2008; 19(2): 71-84.

36 **O'Donnell R**, Breen D, Wilson S, Djukanovic R. Inflammatory cells in the airways in COPD. Thorax 2006; 61 (5): 448-454.

37 **Esposito K**, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women. JAMA 2003; 289(14): 1799-1804.

38 **King DE**, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol 2003; 92(11): 1335-1339.

39 **Ajani UA**, Ford ES, Mokdad AH. Dietary fiber and C-reactive protein: findings from national health and nutrition examination survey data. J Nutr 2004; 134(5): 1181-1185.

40 **Ma Y**, Griffith JA, Chasan-Taber L, et al. Association between dietary fiber and serum C-reactive protein. Am J Clinl Nutr 2006; 83(4): 760-766.

41 **King DE**. Dietary fiber, inflammation, and cardiovascular disease. Mol Nutr Food Res 2005; 49(6): 594-600.

42 **Nishmura K**, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002; 121(5): 1434-1440.