

# *Lycium barbarum* Polysaccharide Inhibited Hypoxia-Inducible Factor 1 in COPD Patients

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**Background:** Chronic obstructive pulmonary disease (COPD) is a chronic airway inflammatory disease characterized by irreversible airflow obstruction. Pathogenic mechanisms underlying COPD remain largely unknown.

**Objective:** The current study was designed to explore serum concentration of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) in stable COPD patients and the potential effect of *Lycium barbarum* polysaccharides (LBP) on HIF-1 $\alpha$  protein expression.

**Methods:** Serum HIF-1 $\alpha$  was quantified by ELISA in 102 stable COPD patients before and after 2-week orally taken LBP (100 mL/time, twice daily, 5–15 mg/mL). Correlation of serum LBP and lung function (FEV1%) or blood gas (PO<sub>2</sub> and PCO<sub>2</sub>) was also analyzed. As a control, 105 healthy subjects were also enrolled into this study.

**Results:** Serum concentration of HIF-1 $\alpha$  was significantly higher in the stable COPD patients (37.34  $\pm$  7.20 pg/mL) than that in the healthy subjects (29.55  $\pm$  9.66 pg/mL,  $P < 0.001$ ). Oral administration of LBP (5 mg/mL, 100 mL, twice daily for 2 weeks) not only relieved COPD symptoms but also significantly reduced serum HIF-1 $\alpha$  concentration (36.94  $\pm$  9.23 vs 30.49  $\pm$  6.42 pg/mL,  $P < 0.05$ ). In addition, level of serum HIF-1 $\alpha$  concentration was significantly correlated with PCO<sub>2</sub> ( $r = 0.283$ ,  $P < 0.001$ ), but negatively and significantly correlated with PO<sub>2</sub> ( $r = -0.490$ ,  $P = 0.005$ ) or FEV1% ( $r = -0.420$ ,  $P = 0.018$ ).

**Conclusion:** These findings suggested that activation of HIF-1 signaling pathway may be involved in the pathophysiology of COPD and that stabilization of serum HIF-1 $\alpha$  concentration by LBP might benefit the stable COPD patients.

**Keywords:** chronic obstructive pulmonary disease, COPD, hypoxia-induced factor 1, HIF-1, *Lycium barbarum* polysaccharides, LBP

## Background

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease characterized by progressive and irreversible obstruction of airflow.<sup>1</sup> Cigarette smoking is the most common risk factor for COPD.<sup>2</sup> However, only 25% of smokers suffer from COPD, which indicates that other risk factors or molecular factors may be involved in the pathogenesis and progression of COPD.<sup>3</sup>

Hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor composed of HIF-1 $\alpha$  and HIF-1 $\beta$  subunits, is induced by hypoxia under physiological as well as pathological conditions such as COPD. HIF-1 modulates oxygen homeostasis and physiological responses through its effects on vascular remodeling and oxygen utilization through involvement in redox homeostasis and glucose metabolism.<sup>4–6</sup> HIF-1 also regulates genes related to angiogenesis, energy metabolism, cell proliferation, and

apoptosis.<sup>7</sup> Recently, studies indicated that the HIF-1 signaling pathway may be involved in the pathogenesis of COPD.<sup>8,9</sup>

*Lycium barbarum* polysaccharide (LBP) is isolated from the Chinese herbal *Lycium barbarum*. LBP consists of six monosaccharides, namely, glucose, arabinose, galactose, mannose, rhamnose, and xylose.<sup>10</sup> They are popular and taken as health supplements in China owing to a number of therapeutic effects, including anti-aging,<sup>11</sup> anti-oxidizing properties and metabolic effects,<sup>12</sup> and even improving male fertility.<sup>13</sup> LBP has also been used in the treatment and/or prevention of various diseases<sup>14,15</sup> in that LBP has multiple biological effects including anti-tumor activity,<sup>16,17</sup> immune-regulation,<sup>18,19</sup> neuro-protective effect,<sup>20</sup> and cardio-protective activity.<sup>21</sup>

The current study was, therefore, designed to explore serum concentrations of HIF-1 signaling pathway-related protein (HIF-1 $\alpha$ ) in stable COPD patients in comparison to healthy subjects, and their association with the clinic-pathological characteristics of COPD patients including lung function and blood gas analysis. In addition, the effect of LBP on the alteration of serum HIF-1 $\alpha$  was explored.

## Methods

### Participants

A total of 102 stable COPD patients, who visited The Second Affiliated Hospital of Ningxia Medical University from March 2016 through January 2018, were enrolled into this study. For the control, 105 healthy volunteers were also enrolled.

### Patient Inclusion Criteria

Patients who met the following criteria were enrolled: 1) Met the diagnostic criteria of “Diagnostic and Therapeutic Guidelines of Chronic Obstructive Pulmonary Disease (2018)” defined by The Respiratory Branch, Chinese Thoracic Society.<sup>22</sup> 2) Stable COPD patients with mild symptoms including cough, expectoration, shortness of breath, and wheezing. 3) FEV1/FVC < 70%; FEV1 reversibility within 15 minute of inhaling  $\beta_2$ -agonist was < 15%; and PO<sub>2</sub> < 80%. 4) In order to stabilize COPD symptoms during this study, patients were allowed to use their daily medicines including inhaled corticosteroid (ICS), long acting beta-agonist (LABA), and long acting muscarinic antagonist (LAMA).

### Patient Exclusion Criteria

1) Patients complicated with other respiratory system diseases. 2) Patients complicated with malignancy, metabolic

disease, autoimmunity disease, thyroid disease, tuberculosis, severe heart failure, or cerebrovascular disease. 3) Patients had used antibiotics within 1 month before the enrollment. 4) Patients who had an acute exacerbation of COPD within 1 month before enrollment.

Healthy control subjects were enrolled from the volunteers who visited the hospital for a preventive physical check. All patients and control subjects were informed about the study plan and a signed consent form was obtained from each participant. The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital, Ningxia Medical University, Ningxia Hui Autonomous Region, People's Republic of China (#: 2016–231).

### LBP Treatment

Oral LBP was provided by the Ningxia Kaiyuan Biotechnology Inc. Patients and normal subjects were randomly assigned to the following three groups: low dose group: 5 mg/mL, 100 mL/time, twice daily; medium dose group: 10 mg/mL, 100 mL/time, twice daily; high dose group: 15 mg/mL, 100 mL/time, twice daily. Before and after 2 weeks of LBP administration, blood samples (5 mL) were collected from each participant and serum was stored at –20° C until HIF-1 $\alpha$  quantification by ELISA as described below.

### HIF-1 $\alpha$ Quantification by ELISA

HIF-1 $\alpha$  was quantified using an ELISA kit following the manufacturer's instruction (Shanghai ELISA Biotech, Shanghai, People's Republic of China).

### Artery Blood Gas Analysis

Artery blood sample was collected from each participant before and after 2 weeks of treatment with LBP. Blood gas analyses including PO<sub>2</sub> and PCO<sub>2</sub> were performed using Blood Gas Analysis equipment (RAPIDPoint500, Siemens Healthcare Diagnostics, Germany).

### Pulmonary Function Test

Pulmonary function tests including FEV1%, FEV1/FVC% were performed using a spirometer (CHEST HI-101, Japan).

### Statistical Analysis

Data were presented as mean  $\pm$  standard derivation from three independent replications. Statistical differences between the two groups were analyzed using the Student's *t*-test, and between three or more groups were analyzed with the one-way analysis of variance (ANOVA). Correlation was analyzed by Spearman correlation analysis method. The

SPSS version 22.0 software (SPSS Inc., IBM Corporation, Armonk, NY, USA) was used to perform all the statistical analysis. A *P*-value of < 0.05 was considered to indicate a statistically significant result.

## Results

As shown in Table 1, a total of 105 healthy control subjects and 102 stable COPD patients were enrolled into the current study. There were no significant differences in age, height, weight, and gender ratio between the control and COPD groups. However, baseline FEV1, FVC and CAT score were significantly different between the two groups (Table 1). In addition, blood HIF-1 $\alpha$  and PCO<sub>2</sub> were significantly higher in the COPD patients (HIF-1 $\alpha$ : 37.34  $\pm$  7.20 pg/mL; PCO<sub>2</sub>: 43.06  $\pm$  10.44 mmHg) than that in the healthy control subjects (29.55  $\pm$  9.66 pg/mL and 35.70  $\pm$  5.36 mmHg, respectively, *P*<0.001, Table 1). In contrast, PO<sub>2</sub> was significantly lower in the COPD patients (66.05  $\pm$  10.82 mmHg) compared to that in control group (85.34  $\pm$  4.64 mmHg, *P*<0.001, Table 1).

Correlation analyses between HIF-1 $\alpha$  and blood gas parameters or lung function tests in stable COPD patients were performed. As shown in Table 2 and Figure 1, HIF-1 $\alpha$  was significantly and negatively correlated with PO<sub>2</sub> (*r* = -0.490, *P*=0.005, Figure 1A), but significantly correlated with PCO<sub>2</sub> (*r* = 0.283, *P*<0.001, Figure 1B). HIF-1 $\alpha$  was significantly and negatively correlated with FEV1% (*r* = -0.420, *P*=0.018, Figure 1C) and with FEV1/FVC% (*r* = -0.540, *P*=0.002, Figure 1D).

Stable COPD patients were randomly assigned into the following three groups: a low dose LBP group (34 patients), a medium dose group (34 patients), and a high dose group (34 patients). As shown in Table 3, HIF-1 $\alpha$  concentrations before LBP treatment were 36.94  $\pm$  9.23 pg/mL (low), 39.07  $\pm$  7.20 pg/mL (medium), 36.00  $\pm$  4.44 pg/mL (high),

**Table 1** Comparison of Basic and Clinical Parameters in the Two Groups

	Control (n=105)	Stable COPD (n=102)	<i>p</i> -value
Age (years)	67.46 $\pm$ 12.01	68.63 $\pm$ 11.48	0.619
Height (cm)	164.48 $\pm$ 7.93	166.08 $\pm$ 7.86	0.312
Weight (kg)	65.69 $\pm$ 12.27	66.13 $\pm$ 10.92	0.850
Gender (M/F)	63/42	66/36	0.490
FEV1 (L)	2.84 $\pm$ 0.12	1.64 $\pm$ 0.56	< 0.05
FVC (L)	3.12 $\pm$ 0.34	2.81 $\pm$ 0.77	< 0.05
CAT score	4.12 $\pm$ 1.56	10.55 $\pm$ 3.45	< 0.05
HIF-1 $\alpha$ (pg/mL)	29.55 $\pm$ 9.66	37.34 $\pm$ 7.20	< 0.001
PO <sub>2</sub> (mmHg)	85.34 $\pm$ 4.64	66.05 $\pm$ 10.82	< 0.001
PCO <sub>2</sub> (mmHg)	35.70 $\pm$ 5.36	43.06 $\pm$ 10.44	< 0.001

**Table 2** Correlation Between HIF-1 $\alpha$  and Blood Gas Analysis or Lung Function Test

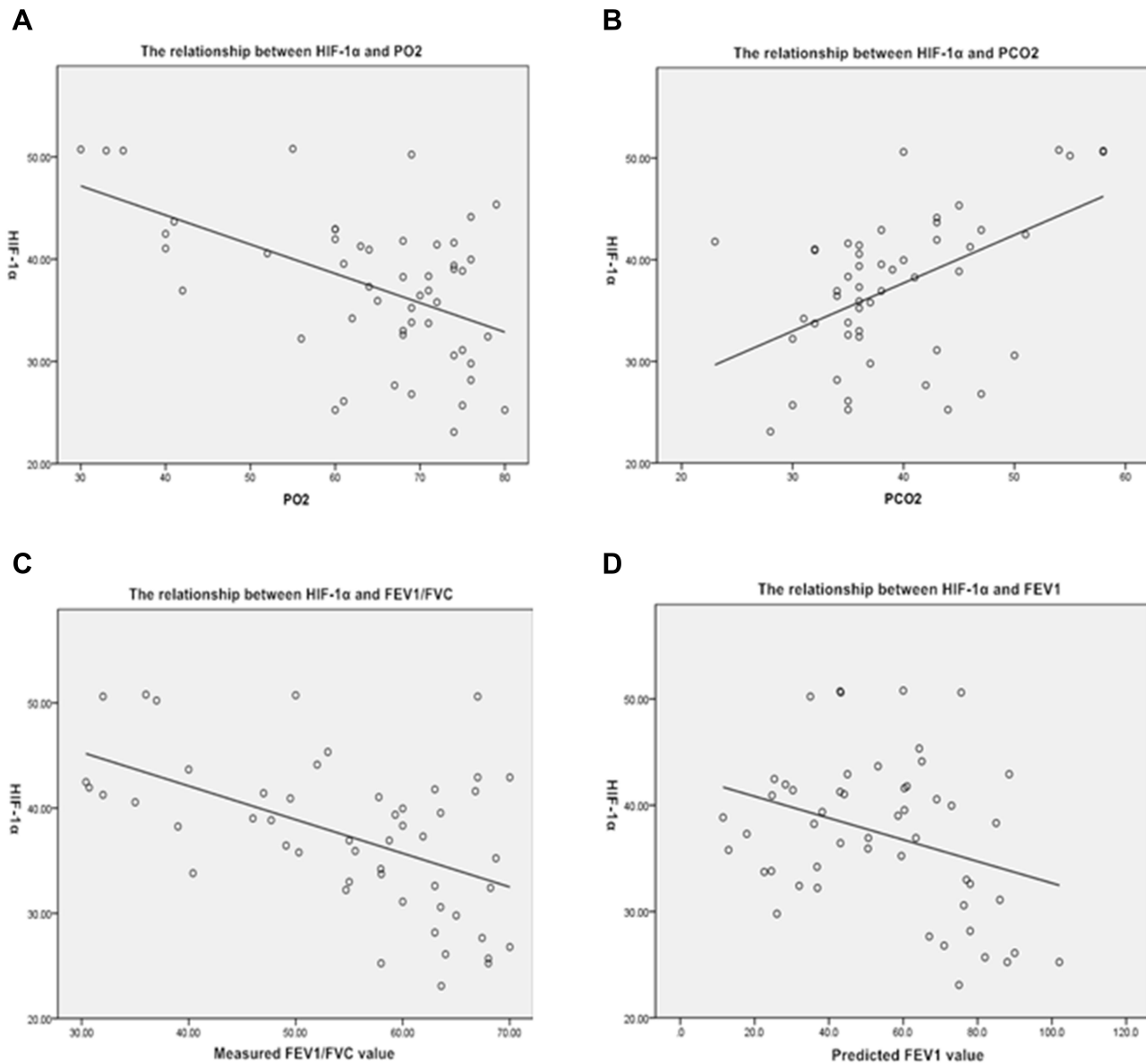
	HIF-1 $\alpha$	
	<i>r</i>	<i>p</i> -value
PO <sub>2</sub>	-0.490	0.005
PCO <sub>2</sub>	0.283	<0.001
FEV1%	-0.420	0.018
FEV1/FVC%	-0.540	0.002

respectively. There was no significant difference in the HIF-1 $\alpha$  between the three dose groups before LBP treatment. After 2 weeks of treatment with 5 mg/mL (low), 10 mg/mL (medium), and 15 mg/mL (high) LBP, HIF-1 $\alpha$  concentration was significantly reduced (low dose: 30.49  $\pm$  6.42; medium dose: 36.62  $\pm$  6.37; high dose: 32.21  $\pm$  6.67, Table 3), which were significantly different between the groups of LBP doses as analyzed by variance analysis (*F*<sub>dose</sub> = 5.358, *P*<0.01, Table 3), as well as at different time points (*F*<sub>time</sub> = 7.438, *P*<0.01, Table 3). However, there was no interaction between different doses of LBP and examination time (*F* = 0.571, *P*>0.05).

After 2 weeks of treatment with LBP, the CAT score was evaluated in the COPD patients. As shown in Table 4, after LBP treatment, 13 out of 43 patients (30.23%) had significant relief in chest tightness and shortness of breath; 7 out of 27 patients (25.92%) had significant improvement in sputum expectoration; 7 out of 39 patients (17.95%) had significant improvement in immunity and reduction in suffering from common cold; and 2 out of 11 patients (18.18%) had significant improvement in vitality. However, as shown in Table 5, after LBP treatment, 4 out of 51 patients (7.84%) had constipation and dry mouth; 1 out of 51 patients (1.96%) had gingival swelling; and 1 out of 51 patients (1.96%) had stomach ache. All of the aforementioned adverse effects disappeared after stopping LBP treatment (100% recovery).

## Discussion

COPD is a progressive and chronic lung disease associated with inflammation. Hypoxia is one of the pathologic outcomes of chronic airway obstruction. Hypoxia-inducible factor is known to be involved in the pathogenesis of various diseases including COPD.<sup>9,23,24</sup> Here, we reported the effect of LBP administration on the level of serum HIF-1 $\alpha$  in the stable COPD patients and normal healthy subjects. It was found that serum HIF-1 $\alpha$  was significantly higher in the stable COPD patients compared to that of



**Figure 1** Correlation between HIF-1 $\alpha$  and blood gas PO<sub>2</sub>, PCO<sub>2</sub>, and lung function in stable COPD patients. **(A)** Correlation between HIF-1 $\alpha$  and PO<sub>2</sub>. **(B)** Correlation between HIF-1 $\alpha$  and PCO<sub>2</sub>. **(C)** Correlation between HIF-1 $\alpha$  and FEV<sub>1</sub>. **(D)** Correlation between HIF-1 $\alpha$  and FEV<sub>1</sub>/FVC.

healthy control subjects; that HIF-1 $\alpha$  was significantly and negatively correlated with PO<sub>2</sub> or FEV<sub>1</sub>%, but significantly correlated with PCO<sub>2</sub>; and that serum HIF-1 $\alpha$  was significantly reduced after 2 weeks administration of LBP in the stable COPD patients.

COPD is a progressive obstructive lung disease with wheezing and productive cough in clinic. Emphysema and airflow limitation caused by the remodeling of lung structure in COPD result in ventilation/perfusion mismatch, leading to hypoxic conditions, which activates the hypoxia signaling pathway through hypoxia-inducible factors. Hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) is a vital transcription factor

that regulates hypoxic responses.<sup>25</sup> HIF-1 is widely expressed in many mammalian and human tissue cells, which are composed of  $\alpha$  and  $\beta$  subunits. The independent transactivation domain and an oxygen-dependent degradation domain in carboxyl-terminal determine the HIF-1 activity.<sup>25</sup> Typically, oxygen-independent pathways regulate HIF-1 protein expression, while oxygen-dependent pathways regulate HIF-1 degradation.<sup>26</sup> Li et al<sup>27</sup> reported that HIF-1 $\alpha$  regulates the oxygen balance, hypoxia adaptation, inflammatory response, and tumor development. In addition, the role of HIF-1 $\alpha$  in allergic inflammation has also been reported.<sup>28–30</sup> Here, we have reported that serum HIF-1 $\alpha$  was significantly increased

**Table 3** Effect of Various Doses of LBP on HIF-1 $\alpha$ 

LBP	Number	HIF-1 $\alpha$ (pg/mL)		$F_{groups}$	p-value
		Before Treatment	2 Weeks After Treatment		
Low dose	34	36.94 $\pm$ 9.23	30.49 $\pm$ 6.42*	5.358	0.008
Medium dose	34	39.07 $\pm$ 7.20	36.62 $\pm$ 6.37		
High dose	34	36.00 $\pm$ 4.44	32.21 $\pm$ 6.67*		
$F_{time}$		7.438			
$P$		0.009			

Note: \* indicates the difference compared with the medium dose group is statistically significant.

**Table 4** Effect of LBP on COPD Patients' Symptom Improvement

Symptoms	Before Treatment	2 Weeks After LBP Treatment		
		Effective	No Effect	Effective Rate
Chest tightness or short of breath	43	13	30	30.23%
Sputum expectoration	27	7	20	25.92%
Cold resistance	39	7	30	17.95%
Poor vitality	11	2	9	18.18%

in the stable COPD patients even if average PO<sub>2</sub> was 66% in these patients, suggesting HIF-1 $\alpha$  protein may be up-regulated through oxygen-independent pathway in the stable COPD patients. Furthermore, level of HIF-1 $\alpha$  was negatively correlated with PO<sub>2</sub> and FEV1%, suggesting HIF-1 $\alpha$  might be involved in the pathogenesis of COPD.

Following hypoxia activation of the hypoxia signaling pathway, HIF stabilization plays a key role in the tissue oxygen balance and tissue repair. Numerous studies have demonstrated that stabilization of HIF can reduce tissue inflammation and promote its repair.<sup>31–34</sup> In this regard, HIF-1 $\alpha$  can render the tissue to metabolically adapt to oxygen deprivation and anaerobic ATP synthesis through up-regulation of glycolytic genes such as phosphoglycerate kinase (PGK) and lactate dehydrogenase A (LDHA).<sup>35</sup> Stabilization of HIF by pharmacologic intervention displays a universally protective phenotype across all organs. Accordingly, HIF and its downstream targets are emerging as novel therapeutic options to treat various organ injuries, including the heart, lung, liver, and kidney.<sup>15</sup> In the current study, therefore, the effect of LBP intervention on HIF-1 $\alpha$  has been investigated. We found that oral administration of

LBP could significantly reduce serum HIF-1 $\alpha$  in the stable COPD patients. In addition, we found that serum level of HIF-1 $\alpha$  was negatively associated with blood PO<sub>2</sub> and FEV1%, while HIF-1 $\alpha$  was significantly associated with PCO<sub>2</sub>. Consistently, Sheng and Fan<sup>36</sup> reported that LBP increased mice tolerance ability to hypoxia and fatigue, and Li et al<sup>37</sup> reported that LBP improved tissue oxygen availability in mice and thus prolonged mice life spans. In addition, it has also reported that LBP significantly suppressed hypoxia-induced up-regulation of HIF-1 $\alpha$  mRNA and protein.<sup>38</sup> These findings suggested that targeting the HIF signaling pathway in chronic lung disease might be a promising intervention in delaying the progression of disease.

LBP, scopoletin, and 2-O- $\beta$ -D- glucopyranosyl-L-ascorbic acid (AA-2 $\beta$ G) are the major constituents of the Chinese herbal *Lycium barbarum* or wolfberry.<sup>39</sup> Of them, LBP is the key bioactive ingredient in wolfberry.<sup>40</sup> LBP is a popular health supplement due to its wide range of health benefits. LBP has multiple biological activities and functions including anti-aging associated with their anti-oxidizing properties, metabolic effects,<sup>11,12</sup> neuro-protective

**Table 5** Adverse Effect of LBP in the Stable COPD Patients

	Before LBP Treatment	After LBP Treatment	Relieved After Withdraw LBP	Incidence Rate (%)	Recovery Rate (%)
Constipation	0	4	4	7.84%	100%
Gingival swell	0	1	1	1.96%	100%
Stomach	0	1	1	1.96%	100%



effects in neuro-degeneration and neurotoxicity,<sup>41–43</sup> improving male fertility,<sup>13</sup> antitumor activity,<sup>16,17,44</sup> immune-regulation,<sup>18,19,45</sup> and cardio-protective activity.<sup>21</sup> Furthermore, LBP could enhance immunity by improving lymphocyte proliferation, and by increasing macrophage phagocytosis and cytotoxic T lymphocyte (CTL) activity.<sup>16,44</sup> However, the effect of LBP in chronic lung disease has not been extensively investigated. In this regard, it has been reported that, after orally taking LBP for 4–8 weeks, 85% of the aged population had improvement in sleep and appetite, and 29–85% of the aged population had enhanced immunity and reduced frequency of suffering from the common cold.<sup>46</sup> Consistently, here, we have reported that oral administration of LBP could relieve COPD symptoms such as chest tightness and shortness of breath, and reduced frequency of suffering from the common cold in the COPD patients. These findings suggested that LBP might benefit the COPD by enhancing immunity and relieving respiratory symptoms. Interestingly, however, lower dose of LBP had the most significant effect on suppression of HIF-1 $\alpha$ . While the mechanism remains to be defined, the lower dose (5 mg/mL) is sufficient and can be used in future studies.

While no documented adverse reactions related to LBP usage have been reported in clinic, there is a lack of awareness amongst the medical and scientific community regarding the safety profile on the use of LBP as a therapeutic agent. In this regard, animal studies found that LBP had no toxicity or sperm deformity effect.<sup>47,48</sup> However, the current study demonstrated that oral administration of LBP could result in mild adverse effects including constipation or dry mouth, gingival swelling, and gastric reaction. Nevertheless, the aforementioned adverse effects in response to LBP intake disappeared when the patients stopped taking LBP, suggesting LBP-associated side effects are transient and reversible.

There were limitations in the current study. First, COPD patients enrolled into this study were at a stable stage and allowed to continue using their daily medicines including ICS, LABA, and LAMA, which might interact with LBP. Second, clinical symptoms and CAT scores were compared before and after LBP treatment, but not between the three-dose treatment groups due to the limited number of cases. Third, HIF-1 $\alpha$  is a transcription factor that may be involved in mediating COPD pathogenesis. While the primary finding of the current study was that LBP significantly suppressed HIF-1 $\alpha$  protein, the biological impact of LBP suppression on HIF-1 $\alpha$  in COPD remains to be further investigated.

Taken together, the current study demonstrated that serum HIF-1 $\alpha$  was significantly higher in the stable COPD patients compared to that in the normal subject. The level of HIF-1 $\alpha$  was significantly correlated with the PCO<sub>2</sub> level, but negatively correlated with PO<sub>2</sub> or FEV1% in COPD patients. Oral administration of LBP could significantly reduce serum HIF-1 $\alpha$  concentration in the stable COPD patients. These findings suggest that HIF-1 $\alpha$  may be involved in the pathophysiology of COPD and LBP may benefit stable COPD patients through reducing serum HIF-1 $\alpha$ .

## Abbreviations

COPD, chronic obstructive pulmonary disease; HIF-1, hypoxia-inducible factor 1; LBP, *Lycium barbarum* polysaccharides.

## Data Sharing Statement

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

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Ningxia Medical University. Written informed consent was obtained from all study subjects before enrollment.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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