Treatment and prevention of inflammatory responses and oxidative stress in patients with obstructive sleep apnea hypopnea syndrome using Chinese herbal medicines

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Abstract. The present study aimed to investigate the therapeutic effects of Chinese herbal medicines for the treatment and prevention of inflammatory responses and oxidative stress in obstructive sleep apnea hypopnea syndrome (OSAHS). A total of 60 patients with OSAHS were randomly divided into two groups (n=30/group): The experimental group, who received the conventional treatment + oral administration of the traditional Chinese herbal formula, Jiawei Di Tan Tang; and the control group, who received the conventional treatment only. OSAHS patients were included in the current study if they presented with snoring and had an apnea-hypopnea index (AHI) of >30 in a polysomnography study, without comorbidities. The therapeutic course lasted 12 weeks in both groups. Alterations to the mean clinical symptom score, Epworth sleepiness scale (ESS) and AHI scores, lowest nocturnal blood oxygen saturation (SaO_2) and the serum levels of superoxide dismutase (SOD), malondialdehyde (MDA), interleukin (IL)-6, tumor necrosis factor (TNF)-α and C-reactive protein (CRP) prior to and following treatment were observed. The mean clinical symptom score was significantly decreased in the experimental group post-treatment compared with the control group ($P<0.05$). In addition, the clinical symptoms in the experimental group were significantly improved following treatment compared with pre-treatment symptoms ($P<0.05$). Furthermore, the ESS and AHI scores, lowest nocturnal SaO_2 and serum levels of SOD, MDA, IL-6, TNF-α and CRP were significantly improved in the experimental group post-treatment compared with the control group ($P<0.05$). These parameters in the experimental group were also significantly improved post-treatment compared with those pre-treatment ($P<0.05$). The results of the present study suggested that oral administration of the traditional Chinese herbal formula Jiawei Di Tan Tang was able to attenuate oxidative stress and inflammatory responses in patients with OSAHS, and thus may relieve their clinical symptoms.

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Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a common sleep disorder with potential risks, such as cardio-cerebrovascular events and multiple organ injury. The key clinical manifestations of OSAHS include disturbances in sleep structure and nocturnal hypoxemia and hypercapnia, which may lead to excessive daytime sleepiness, cardio-cerebrovascular events and multiple organ injury that may seriously affect the quality of life (QOL) and life expectancy of OSAHS patients (1). The incidence of OSAHS is ~2-4% in adults worldwide; however, recent epidemiological studies have suggested that the incidence of OSAHS is increasing in the younger members of the population (2-4).

The interest in OSAHS has increased in healthcare settings and society in recent years due to the high incidence and mortality rate of the disorder (5,6). Clinical statistical data have suggested that the 5-year mortality rate of OSAHS patients without treatment is as high as 11-13%, and ~3,000 mortalities per day are associated with OSAHS worldwide (7). In addition, excessive daytime sleepiness decreases the QOL and cognitive and social functions of OSAHS patients (8), and has been associated with a 3-7-fold increase in road traffic accidents (9). However, the main clinical risk associated with OSAHS is severe multi-organ injury, and OSAHS has emerged as an independent risk factor contributing to hypertension, coronary heart disease, cerebrovascular diseases, diabetes and cor pulmonale (10). Previous studies demonstrated that patients with OSAHS experience systemic inflammation and oxidative stress, which are extensively involved in the development, occurrence and progression of OSAHS, resulting in numerous complications (11-14).

At present, OSAHS may be treated using holistic therapies, medical treatment (tricyclic and serotonergic agents),

medical devices, including oral appliances and continuous positive airway pressure (CPAP), and surgery (15). However, no effective drug currently exists for the treatment of OSAHS, and OSAHS patients typically have a poor compliance and tolerance with mechanical treatments (16,17). In addition, surgery has been associated with potential complications, such as profuse bleeding, cardiopathy and hypertension, and uncertainty regarding its long-term therapeutic effect (18,19). Therefore, additional research is required in order to develop more effective therapeutic strategies for the treatment of OSAHS.

Natural Chinese herbal medicines that exert anti-OSAHS activities have emerged as a potential strategy for the treatment of OSAHS (20). In Traditional Chinese Medicine (TCM), the treatment and prevention of the inflammatory responses and oxidative stress associated with OSAHS involves a holistic approach using multi-level and multi-channel control (21). TCM differs from Western medicine in that Western medicine adopts strategies that block a single step in a particular process, whereas TCM uses an overall therapeutic approach to treat and prevent inflammatory responses and oxidative stress with the aim of improving the patient QOL (4). These unique advantages of TCM treatment have attracted the attention of numerous researchers searching for novel ways to combat OSAHS-associated inflammatory responses and oxidative stress (22,23). Among them, Jaiwei Di Tan Tang is a natural Chinese herbal medicine, which may serve a role in anri-OSAHS activities (24,25)

The present study aimed to investigate the potential clinical application of TCM to the treatment of patients with OSAHS, in particular in the prevention of OSAHS inflammatory responses and oxidative stress.

Materials and methods

Study design. A total of 60 outpatients at the Department of Respiratory Diseases of The Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine (Fuzhou, China), complaining of snoring, nocturnal apnea and daytime sleepiness, were enrolled in the present study between October 2013 and July 2014. The patients were diagnosed with OSAHS based on the results of a polysomnography (PSG). Informed consent was obtained from all patients prior to initiation of the study. The present study was approved by the local Ethics Committee of Fujian Medical University (Fuzhou, China). Patients were excluded if they had a history of asthma, bronchiectasis, chronic obstructive pulmonary disease, severe systemic diseases or allergic rhinitis, and if they were active smokers or pregnant. Patients with asthmatic symptoms, including episodic breathlessness, wheezing, coughing and chest tightness, were also excluded. The body mass index (BMI) was calculated for all patients and the sleeping status of the patients was assessed using the Epworth sleepiness scale (ESS). The 60 OSAHS patients that met the inclusion criteria were randomly allocated into experimental or control groups using the Java random number method using SPSS software 16.0 (SPSS, Inc., Chicago, IL, USA).

Treatment. Patients in the control group received the conventional therapeutic strategy, which included lifestyle changes such as quitting smoking, abstaining from alcohol, discontinued use of sedative and hypnotic drugs (as well as any other drugs that may induce or exacerbate OSAHS), alterations to the patient's sleeping position, including adopting side-sleeping positions and avoiding the supine position and limiting overexertion during the daytime. In addition, the patients received instructions on exercise and planned sports programs, as follows: i) Walking had to be the main sports form; ii) the patient had to gradually increase the activity intensity within the range of the target heart rate [target heart rate =(220-age) x (70-85%)]; iii) the patient had to walk ~3,000-4,000 steps per day in ~30 min for 3 months; and iv) the patients had to perform appropriate exercise 4-5 times per week. Appropriate exercise was referred to as a feeling of normal energy following each exercise. The patient was permitted 2-3 breaks during each episode of exercise, with each break not exceeding 5 min. The patients were advised that exercise should be terminated immediately upon experiencing heart palpitations, chest stuffiness or dyspnea.

In addition to the conventional treatment, the patients in the experimental group received oral administration of Jiawei Di Tan Tang, which consisted of 15 g Dangshen, 30 g Huangqi, 15 g Baizhu, 9 g Chenpi, 9 g Fabanxia, 15 g Fuling, 9 g Zhishi, 12 g Zhuru, 15 g Shichangpu, 12 g Dannanxing, 15 g Danshen, 15 g Chuanxiong, 9 g Taoren, 15 g Yujin, 15 g Jiangcan and 15 g Dilong. The herbal components of Jiawei Di Tan Tang were prepared by the TCM pharmacy Kang Ren Tang Medical Hall Pte., Ltd. (Beijing, China) in the form of granules. Jiawei Di Tan Tang was administered orally in two doses (morning and evening), dissolved in boiling water. The patients were monitored weekly by telephone or outpatient visits to record their compliance with their exercise and medical treatments. The treatment course lasted for 12 weeks, and the parameters recorded during the course of treatment were statistically analyzed in order to evaluate the therapeutic effect of Jiawei Di Tan Tang.

Clinical symptoms. Snoring, nocturnal apnea, sleepiness, fatigue and chest congestion were scored by the patients in the two groups prior to and following treatment, as follows: 0 for none of the above, 1 for mild presentation, 2 for moderate presentation and 3 for severe presentation. Clinical syndromes were defined according to 2002 Guidelines for Research on New Chinese Herbal Medicines (26).

ESS. The ESS is a simple eight-item self-administered scale that has been widely used in clinical practice to quantify the level of daytime sleepiness in various situations. This has a score range of 0-24 and scores >10 are indicative of excessive daytime sleepiness (27).

PSG. The patients in both groups underwent a full overnight in-laboratory, diagnostic PSG using the Compumedics E-Series EEG/PSG Recording System (Compumedics USA, Inc., Charlotte, NC, USA) or the Alice 5 Diagnostic Sleep System (Philips Medical Systems, Inc., Bothell, WA, USA), depending on which hospital they were examined in, prior to and following treatment. The electroencephalography (EEG) electrodes were positioned according to the international 10-20 system. Each PSG involved monitoring the sleep status

Table I. Comparison between the control and study groups.

Metric	Control group (n=30)	Study group (n=30)	P-value
Age, years	50.36±14.15	49.87±13.59	0.41
Gender, M/F	20/10	19/11	0.65
Disease course	5.98±4.02	6.32±3.15	0.52
AHI	32.18±15.67	32.66±15.95	0.49
BMI, kg/m^2	24.47±2.65	24.29±2.08	0.28
ESS	13.52±5.17	13.15±4.98	0.58

Data are presented as the mean ± standard deviation. AHI, apnea hypopnea index; BMI, body mass index; ESS, epworth sleepiness scale; M, male; F, female.

of the patient by EEG, electrooculography and electromyography, and an analysis of airflow and respiratory muscle effort by monitoring electrocardiographic rhythms and blood oxygen saturation (SaO_2). The thoracoabdominal plethysmograph (Colsan Company, Guangzhou, China), oronasal temperature thermistor and nasal-cannula pressure transducer systems (Sinochip Electronics Co., Ltd., Nanjing, China) were used to identify apnea and hypopnea. The transcutaneous finger pulse oximeter was used to measure SaO_2. Sleep was recorded and scored according to a standard method (28). The apnoea-hypopnea index (AHI) was defined as the sum of the number of apneas and hypopneas per hour of sleep. OSAHS was defined as an AHI of 5 events/h and the presence of clinical symptoms, including excessive daytime sleepiness, loud snoring, witnessed apneas and nocturnal apnea or an AHI of 5 events/h without any OSAHS symptoms (29). An AHI <5 events/h was considered within the normal limit. No split-night studies were performed.

Biochemical evaluation. Morning fasting venous blood samples (5 ml) were drawn from each patient in the two groups prior to and following treatment, and centrifuged at 1,409 x g for 10 min to separate the serum. The upper-layer supernatant (0.25 ml) containing growth factors was accurately weighed and stored at -70˚C prior to use. Serum levels of C-reactive protein (CRP; cat. no. E02481), interleukin (IL)-6 (cat. no. E03811) and tumor necrosis factor (TNF)-α (cat. no. E037114) were detected using the enzyme-linked immunosorbent assay kits (Shanghai Source Biological Technology Co., Ltd., Shanghai, China), according to the manufacturer's protocol. Serum superoxide dismutase (SOD) levels were detected by the xanthine oxidase method (SOD Assay Kit; cat. no. 19160; Sigma-Aldrich, St. Louis, MO, USA). Serum malondialdehyde (MDA) levels were detected using the thiobarbituric acid colorimetric method (Nanjing JianCheng Bioengineering Institute, Nanjing, China), according to the manufacturer's protocol.

Statistical analysis. Data were analyzed using SPSS software 16.0 and expressed as the mean ± standard deviation. Inter-group comparisons were performed using the Student's t-test for normally distributed data, the Wilcoxon rank-sum test for non-normally distributed data, or a paired t-test. In addition, counted data were analyzed using a χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

Subjects. The control group constituted 20 males and 10 females, who ranged in age from 35-67 years old, with a mean age of 50.36±14.15 years old. The mean disease duration ranged from 2-13 years with a mean disease duration of 5.98±4.02 years. The mean AHI was 32.18±15.67 events/h and the mean BMI was 24.47±2.65 kg/m^2. The mean ESS was 13.52±5.17. The study group consisted of 19 males and 11 females, who ranged in age from 33-65 years old, with a mean age of 49.87±13.59 years old. The disease duration ranged from 3-12 years with a mean disease duration of 6.32±3.15 years. The mean AHI was 32.66±15.95 events/h, the mean BMI of this group was 24.29±2.08 kg/m^2 and the mean ESS was 13.15±4.98. There was no significant difference in age, gender, disease duration, BMI and AHI and ESS scores between the two groups (P>0.05; Table I). The results suggest that the two sets of data are comparable.

Clinical symptom scores. Snoring, nocturnal apnea, daytime sleepiness and chest pain scores were significantly decreased in the experimental group following treatment, compared with those pre-treatment (P<0.05; Table II). Conversely, there was no significant difference in these scores prior to and following treatment in the control group (P>0.05). In addition, the post-treatment clinical symptoms scores were significantly decreased in the experimental group compared with those in the control group (P<0.05; Table II). The results suggest that there are significant differences between the experimental and control group.

Evaluation of ESS and PSG results. The mean ESS score was significantly lower in the experimental group post-treatment compared with that pre-treatment (P<0.05), whereas there was no significant difference in the ESS score prior to and following treatment in the control group (P>0.05). In addition, the mean ESS score in the experimental group post-treatment was significantly decreased compared with that of the control group (P<0.05; Table III).

In the experimental group, the AHI was significantly lower and the lowest nocturnal SaO_2 was significantly higher post-treatment compared with these pre-treatment (P<0.05). Conversely, there was no significant difference in the AHI and the lowest nocturnal SaO_2 prior to and following treatment in

Table II. Clinical symptom scores pre- and post-treatment.

Symptom	Control group (n=30)	Experimental group (n=30)
Snoring		
Pre-treatment	3.25±0.50	3.22±0.47
Post-treatment	3.11±0.48	2.86±0.49[a,b]
Nocturnal apnea		
Pre-treatment	2.86±0.41	2.78±0.39
Post-treatment	2.67±0.45	2.47±0.34[a,b]
Sleepiness		
Pre-treatment	2.91±0.57	2.95±0.61
Post-treatment	2.73±0.62	2.44±0.58[a,b]
Fatigue		
Pre-treatment	3.28±0.48	3.24±0.52
Post-treatment	3.26±0.51	2.89±0.55[a,b]
Chest stuffiness		
Pre-treatment	2.81±0.49	2.76±0.54
Post-treatment	2.67±0.52	2.39±0.59[a,b]

Data are presented as the mean ± standard deviation. [a]P<0.05 vs. pre-treatment; [b]P<0.05 vs. control group.

Table III. ESS and AHI scores and SaO_2 pre- and post-treatment.

Metric	Control group (n=30)	Experimental group (n=30)
ESS		
Pre-treatment	13.52±5.17	13.15±4.98
Post-treatment	11.27±5.26	9.03±4.74[a,b]
AHI		
Pre-treatment	32.18±15.67	32.66±15.95
Post-treatment	26.47±13.71	20.44±13.25[a,b]
Lowest nocturnal SaO_2		
Pre-treatment (%)	84.17±6.49	83.92±6.41
Post-treatment (%)	86.33±7.25	89.53±7.16[a,b]

Data are presented as the mean ± standard deviation. [a]P<0.05 vs. pre-treatment; [b]P<0.05 vs. control group. AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; SaO_2, blood oxygen saturation.

the control group (P>0.05). In addition, the AHI and the lowest nocturnal SaO_2 score in the experimental group post-treatment was significantly decreased compared with the control group (P<0.05) (Table III). The results suggest that there are significantly differences in ESS, PSG, and AHI between the experimental and control group.

Serum biomarkers of oxidative stress. Levels of the oxidative markers SOD and MDA were significantly lower in the experimental group post-treatment compared with those pre-treatment (P<0.05), whereas there was no significant difference in the SOD and MDA levels prior to and following

Table IV. SOD and MDA levels pre- and post-treatment.

Factor	Control group (n=30)	Experimental group (n=30)
SOD, U/ml		
Pre-treatment	87.03±7.62	86.35±8.18
Post-treatment	90.58±8.93	101.24±9.52[a,b]
MDA, nmol/ml		
Pre-treatment	11.35±1.51	11.27±1.24
Post-treatment	10.80±1.46	9.64±1.35[a,b]

Data are presented as the mean ± standard deviation. [a]P<0.05 vs. pre-treatment; [b]P<0.05 vs. control group. SOD, superoxide dismutase; MDA, malondialdehyde.

Table V. Serum levels of inflammatory cytokines pre- and post-treatment.

Serum factor	Control group (n=30)	Experimental group (n=30)
TNF-α, pg/ml		
Pre-treatment	57.86±12.33	58.96±11.59
Post-treatment	53.08±9.85	39.54±10.26[a,b]
IL-6, pg/ml		
Pre-treatment	86.97±16.72	87.32±16.28
Post-treatment	80.15±15.68	73.18±15.15[a,b]
CRP, μg/ml		
Pre-treatment	13.12±5.23	13.25±4.95
Post-treatment	10.96±6.01	7.93±5.16[a,b]

Data are presented as the mean ± standard deviation. [a]P<0.05 vs. pre-treatment; [b]P<0.05 vs. control group. TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein.

treatment in the control group (P>0.05). In addition, the SOD and MDA levels in the experimental group post-treatment were significantly decreased compared with the control group (P<0.05; Table IV). The results suggest that oral administration of the traditional Chinese herbal formula Jiawei Di Tan Tang is able to attenuate serum biomarkers of oxidative stress.

Serum inflammatory cytokines. The levels of the serum inflammatory cytokines TNF-α, IL-6 and CRP following treatment were significantly reduced in the experimental group post-treatment compared with those pre-treatment (P<0.05). Conversely, there was no significant difference in the serum levels of TNF-α, IL-6 and CRP prior to and following treatment in the control group (P>0.05). In addition, the post-treatment levels of these factors were significantly lower in the experimental group compared with those in the control group (P<0.05; Table V). The results suggest that oral administration of the traditional Chinese herbal formula Jiawei Di Tan Tang is able to attenuate inflammatory responses in patients with OSAHS.

Discussion

According to the TCM theory, turbid phlegm and blood stasis are the main factors contributing to the pathogenesis of OSAHS, implying that the disease is predominantly located in the pulmonary tissues (pharynx, larynx and airway) (30,31). Pulmonary, spleen or renal dysfunctions resulting from a congenital abnormality or improper post-birth recuperation may lead to intrinsic production of turbid phlegm, phlegm and blood stagnation, airway roughness, spleen qi deficiency, qi deficiency to attenuate blood stasis and weakness of the pharyngeal muscle due to insufficient qi blood nourishment (32). These factors may result in airway collapse and airway flow resistance (33,34).

Previous studies have implicated systemic inflammation and oxidative stress in the pathogenesis of OSAHS (11-13,18,35), leading to multiple complications, such as cardiovascular disease, cognitive impairment and metabolic syndrome. Therefore, reducing oxidative stress and inflammatory responses may ameliorate the symptoms of OSAHS and improve the QOL of OSAHS patients.

Vgontzas *et al* (36) reported that the levels of pro-inflammatory cytokines, including IL-6 and TNF-α, were elevated in OSAHS patients, and associated them with the clinical manifestation of daytime sleepiness. Similarly, Guven *et al* (37) demonstrated that the levels of CRP and IL-6 were markedly upregulated in OSAHS patients, and were restored to within the normal range following CPAP therapy. Furthermore, Constantinidis *et al* (38) reported that the stimulation of peripheral mononuclear cells with lipopolysaccharides (LPS) resulted in the upregulation of TNF-α and IL-6 in OSAHS patients, which is consistent with the elevation of plasma TNF-α and IL-6 in OSAHS patients (39). In addition, the extent of TNF-α and IL-6 upregulation was associated with the frequency of apnea and the duration of hypopnea.

An imbalance exists between oxidation and antioxidation in OSAHS patients (39). A previous study demonstrated that serum levels of oxidative stress biomarkers were significantly elevated in OSAHS patients compared with a control group, and they were significantly decreased following CPAP therapy (13,37). In addition, Priou *et al* (40) reported that the levels of reactive oxygen species were elevated in OSAHS patients. Furthermore, Chen *et al* (41) demonstrated that the levels of lipid peroxides, including MDA, were significantly elevated, whereas the levels of antioxidants were decreased, in the myocardial tissue of rats exposed to an intermittent hypoxic condition compared with a control group. These results suggested that intermittent hypoxia in patients with OSAHS may induce oxidative stress.

Previous studies have demonstrated that Chinese herbal medicines that tonify qi and inhibit blood stagnation are able to relieve the symptoms of OSAHS and attenuate oxidative stress and inflammatory responses (42-44). In the present study, Jiawei Di Tan Tang, which consists of 16 classic Chinese herbal products, Dangshen, Huangqi, Baizhu, Chenpi, Fabanxia, Fuling, Zhishi, Zhuru, Shichangpu, Dannanxing, Danshen, Chuanxiong, Taoren, Yujin, Jiangcan and Dilong, was used. This has been demonstrated to tonify qi, remove and dissolve phlegm, inhibit stagnation, induce coughing, eliminate dampness, reduce temperature and improve lung function (45). Previous studies reported that Huangqi was able to protect against lipid peroxidation by binding to SOD in the body in order to increase its activity (46-48). Furthermore, *in vitro* studies demonstrated oxygen free radical (OFR) clearing activities for the three extracts of Huangqi (49-51), and Huangqi injection was revealed to reduce the plasma levels of MDA, CRP and IL-6, and increase the levels of SOD in a rat model of chronic bronchitis (43), indicating that Huangqi injection is able to attenuate oxidative stress and the inflammatory response in rats with chronic bronchitis. Dangshen exerts antioxidant, anti-oxidative stress and numerous other biological activities (52,53), and was demonstrated to reduce the TNF-α concentration in insulin resistant rats (54). In addition, Danshen was shown to reduce the content of OFR, increase SOD activity and slightly increase the levels of nitric oxide (55). Tanshinone has been reported to inhibit the production of inflammatory cytokines, protect endothelial cells, exert antioxidant activity and inhibit cell apoptosis (56). Similarly, Ligustrazine was able to attenuate the apoptosis of vascular tissue cells by inhibiting the formation of large quantities of OFR during the oxidative stress response, and ameliorate vascular endothelial injury due to oxidative stress (57). Furthermore, Ligustrazine was reported to reduce the secretion of TNF-α and IL-6 from LPS-induced macrophages (58). In a previous study, Yujin was able to inhibit *Helicobacter pylori*-induced gastritis and reduce the blood level of IL-6 (59), and anti-oxidative activities have been reported for Zhishi, Banxia and Chenpi (60-62). In the present study, the serum levels of SOD, MDA, TNF-α, IL-6 and CRP were significantly decreased in the OSHAS patients of the experimental group following treatment with Jiawei Di Tan Tang compared with those of the control group ($P<0.05$). Conversely, there were no significant changes in the OSHAS patients who received the conventional treatment only ($P>0.05$). In the experimental group, the serum levels of SOD, MDA, TNF-α, IL-6 and CRP significantly decreased post-treatment compared with pre-treatment levels ($P<0.05$). These results suggested that Jiawei Di Tan Tang was able to protect against oxidation and inhibit the production of inflammatory cytokines in patients with OSHAS.

The present study selected OSAHA outpatients whose AHI and ESS scores and BMI were higher than 30, 13 and 26, respectively, in the absence of comorbidities. This was consistent with two previous studies that also included homogenous populations of OSAHS patients without comorbidities (63,64). The results of the present study demonstrated that AHI and ESS scores were significantly decreased in the experimental group following treatment with Jiawei Di Tan Tang, as compared with those pre-treatment ($P<0.05$). Conversely, there were no significant alterations in these parameters in the control group ($P>0.05$). Furthermore, the clinical symptom scores were significantly improved in the experimental group post-treatment compared with pre-treatment scores ($P<0.05$), whereas there was no significant change in the clinical symptom scores of the control group ($P>0.05$). Compared with the control group, the AHI and ESS scores and nocturnal minimum SaO_2, were significantly reduced in the experimental group following treatment with Jiawei Di Tan Tang ($P<0.05$).

In conclusion, the present study demonstrated that Jiawei Di Tan Tang has a protective effect against oxidative stress and inflammatory responses in patients with OSAHS, and that

it attenuates the symptoms of OSHAS. These results suggested that the clinical application of Jiawei Di Tan Tang may improve the QOL of OSHAS patients. Furthermore, the results of the present study may provide an experimental foundation for assessing the use of Chinese herbal medicines in the treatment of OSAHS.

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References

1. Tatsumi K, Kasahara Y, Kurosu K, Tanabe N, Takiguchi Y and Kuriyama T: Sleep oxygen desaturation and circulating leptin in obstructive sleep apnea-hypopnea syndrome. Chest 127: 716-721, 2005.
2. Bounhoure JP, Galinier M, Didier A and Leophonte P: Sleep apnea syndromes and cardiovascular disease. Bull Acad Natl Med 189: 445-459, discussion 460-464, 2005 (In French).
3. Deng HT, Huang Y and Li SL: The epidemiologic survey of OSAHS among children and adolescents in Dongguan district. Zhong Guo Yi Xue Chuang Xin 12: 61-63, 2015 (In Chinese).
4. Hu QL, Yang Y and Zhou H: Epidemiological study on children with obstructive sleep apnea hypopnea syndrome aged from 4 to 7 years in Putuo District of Shanghai. Yan Shi Guang Xue Za Zhi 14: 316-319, 2014 (In Chinese).
5. Ma YL, Wang X and Bao PP: Taiyuan area epidemiological studies of sleep apnea syndrome Zhong Guo Yi Yao Zhi Dao 9: 108-110, 2011 (In Chinese).
6. Ma GQ, Dai G and Li JP: East Inner Mongolia black flag pastoral area population aged over 20 obstructive sleep apnea hypopnea syndrom epidemiological investigation Zhong Hua Lin Chuang Yi Shi Za Zhi 4: 1070-1073, 2010 (In Chinese).
7. Nanduri J, Yuan G, Kumar GK, Semenza GL and Prabhakar NR: Transcriptional responses to intermittent hypoxia. Respir Physiol Neurobiol 164: 277-281, 2008.
8. Takahashi Y, Ganster RW, Gambotto A, Shao L, Kaizu T, Wu T, Yagnik GP, Nakao A, Tsoulfas G, Ishikawa T, *et al*: Role of NF-kappaB on liver cold ischemia-reperfusion injury. Am J Physiol Gastrointest Liver Physiol 283: G1175-G1184, 2002.
9. Baeuerie PA and Baltimore D: NF-kappaB: Ten years after. Cell 87: 13-20, 1996.
10. McNicholas WT and Bonsigore MR; Management Committee of EU COST ACTION B26: Sleep apnoea as an independent risk factor for cardiovascular disease: Current evidence, basic mechanisms and research priorities. Eur Respir J 29: 156-178, 2007.
11. Del Ben M, Loffredo L, Violi F and Angelico F: Strong interplay between metabolic syndrome, obstructive sleep apnoea, oxidative stress and arterial dysfunction. Sleep Breath 18: 223-224, 2014.
12. Wysocka E, Cofta S, Cymerys M, Gozdzik J, Torlinski L and Batura-Gabryel H: The impact of the sleep apnea syndrome on oxidant-antioxidant balance in the blood of overweight and obese patients. J Physiol Pharmacol 59 (Suppl 6): 761-769, 2008.
13. Lavie L, Vishnevsky A and Lavie P: Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 27: 123-128, 2004.
14. Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T and Kimura H: Oxidative stress in obstructive sleep apnea. Chest 127: 1674-1679, 2005.
15. The Chinese Medical Association Respiratory Neurology, Sleep Respiratory Disease Group: Obstructive sleep apnea hypopnea syndrom diagnosis and treatment guidelines (draft). Zhong Hua Jie He he Hu Xi Za Zhi 25: 195-198, 2002 (In Chinese).
16. Platt AB, Kuna ST, Field SH, Chen Z, Gupta R, Roche DF, Christie JD and Asch DA: Adherence to sleep apnea therapy and use of lipid-lowering drugs: A study of the healthy-user effect. Chest 137: 102-108, 2010.
17. Villar I, Izuel M, Carrizo S, Vicente E and Marin JM: Medication adherence and persistence in severe obstructive sleep apnea. Sleep 32: 623-628, 2009.
18. Hobson JC, Robinson S, Antic NA, McEvoy RD, Windler S, Mackay S and Carney AS: What is 'success' following surgery for obstructive sleep apnea? The effect of different polysomnographic scoring systems. Laryngoscope 122: 1878-1881, 2012.
19. Certal V, Nishino N, Camacho M and Capasso R: Reviewing the systematic reviews in OSA surgery. Head Neck Surg 149: 817-829, 2013.
20. Xia R, Chen JZ and Shao GM: Exploration of the correlation between the phlegm dampness constitution and the pathogenesis of OSAHS. Chin J Tradit Chin Med 21: 465-469, 2006.
21. Kang J and Wang ZF: Inflammation, oxidative stress and obstructive sleep apnea hypopnea syndrome. Zhong Hua Jie He He Hu Xi Za Zhi 29: 226-227, 2006 (In Chinese).
22. Liu YH, Wang HY and Yue J: TCM exploration of OSHAS. Liaoning Da Xue Xue Bao 25: 13-15, 2010 (In Chinese).
23. Liu W: TCM syndromes of OSAHAS: Analysis of 300 cases. Zhong Guo Zhong Xi Yao Jie He Za Zhi 29: 2, 2010 (In Chinese).
24. Chua KK, Wong A, Kwan PW, Song JX, Chen LL, Chan AL, Lu JH, Mok V and Li M: The efficacy and safety of the Chinese herbal medicine Di-Tan decoction for treating Alzheimer's disease: Protocol for a randomized controlled trial. Trials 16: 199, 2015.
25. Guo SH and Zhang LJ: Influence of ditan decoction on lipid metabolism, oxidant stress and inflammatory cytokines in atherosclerosis rabbits. Hu Bei Zhong Yi Yao Da Xue Xue Bao 18: 8-11, 2016 (In Chinese).
26. Zheng XY: Chinese Traditional Meditional New Medicine Clinical Research Guiding Principles. 4th Edition. Zhong Guo Yi Yao Ke Ji Chu Ban She, pp42-45, 2002.
27. Johns MW: A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 14: 540-545, 1991.
28. Schulz H: Phasic or transient? Comment on the terminology of the AASM manual for the scoring of sleep and associated events. J Clin Sleep Med 3: 752, 2007.
29. American academy of sleep medicine: International classification of sleep disorders: Diagnostic and coding manual, American academy of sleep medicine, Westchester, Ill, USA, 2005.
30. Meng Y, Zheng WF, Liu WR: Treatment of obstructive sleep apnea hypopnea syndrom. Zhong Guo Shi Yan Fang Ji Xue Za Zhi 17: 281-283, 2011 (In Chinese)
31. Luo XF, Wang HR and Cai YY: Please describe the syndrome differentiation and treatment of sleep apnea syndrome. Zhe Jiang Zhong Yi Za Zhi 38: 490-491, 2003 (In Chinese).
32. Sun GR: The higher colleges and universities of Chinese medicine for teaching. In: Diagnostics of Traditional Chinese Medicine. 5th Edition. Zhong Guo Zhong Yi Yao Chu Ban She, pp33-36, 2007.
33. Zhu WF: The higher colleges and universities of Chinese medicine for teaching. In: Diagnostics of Traditional Chinese Medicine. 5th Edition. Zhong Guo Zhong Xi Yao Jie He Za Zhi, pp37-41, 2007.
34. Zhou ZY: The higher colleges and universities of Chinese medicine for teaching. In: Internal Medicine of Traditional Chinese Medicine. 5th Edition. Zhong Guo Zhong Yi Yao Chu Ban She, 21-25, 2007.
35. Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T and Ouchi Y: Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol 94: 179-184, 2003.
36. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K and Chrousos GP: Elevation of plasma cytokines in disorders of excessive daytime sleepiness: Role of sleep disturbance and obesity. J Clin Endoerinol Metab 82: 1313-1316, 1997.
37. Guven SF, Turkkani MH, Ciftci B, Ciftci TU and Erdogan Y: The relationship between high-sensitivity C-reactive protein levels and the severity of obstructive sleep apnea. Sleep Breath 16: 217-221, 2012.
38. Constantinidis J, Ereliadis S, Angouridakis N, Konstantinidis I, Vital V and Angouridaki C: Cytokine changes after surgical treatment of obstructive sleep apnoea syndrome. Eur Arch Otorhinolaryngol 265: 1275-1279, 2008.
39. Wysocka E, Cofta S, Piorunek T, Dziegielewska-Gesiak S, Bryl W and Torlinski L: Blood antioxidant status, dysglycemia and obstructive sleep apnea. Adv Exp Med Biol 756: 121-129, 2013.
40. Priou P, Gagnadoux F, Tesse A, Mastronardi ML, Agouni A, Meslier N, Racineux JL, Martinez MC, Trzepizur W and Andriantsitohaina R: Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. Am J Pathol 177: 974-983, 2010.

41. Chen L, Einbinder E, Zhang Q, Hasday J, Balke CW and Scharf SM: Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. Am J Respir Crit Care Med 172: 915-920, 2005.
42. Zhang Kun and Xie Chun Guang: Effects of shenqi compound recipe on oxidative stress in GK rats with type II diabetes mellitus macrovascular complications. CJTCMP 4: 1084-1085, 2012.
43. Xu XM, Chen XJ and Chen R: Effect of buyang huanwu decoction on blood viscosity,TXB2 , LPO and SOD in rats. J Shanxi Med Univ 33: 212-214, 2002.
44. Ru J, Chen MQ and Geng YX: Effect of qi benefiting stasis removing method on systemic inflammatory response and coagulation function in MODS patients. Zhong Guo Zhong Xi Yao Jie He Za Zhi 34 34: 365-338, 2014 (In Chinese).
45. Zeng X: Observation of the therapeutic effect of Chinese traditional medicines on OSAHS. Chin Foreign Med Treat 27: 490-491, 2012.
46. Ma X, Zhang K, Li H, Han S, Ma Z and Tu P: Extracts from astragalus membranaceus limit myocardial cell death and improve cardiac function in a rat model of myocardial ischemia. J Ethnopharmacol 149: 720-728, 2013.
47. Song J, Li J, Zheng SR, Jin Y and Huang Y: Anti-inflammatory and immunoregulatory effects of Yupingfeng powder on chronic bronchitis rats. Chin J Integr Med 19: 353-359, 2013.
48. Lv ZK, Liu YZ, Wu Z: Inhibitory effects of different doses of *Astragalus membranaceus* on oxidative stress in the kidneys of diabetic rats. Shang Hai Zhong Yi Yao Za Zhi 49: 68-71, 2015 (In Chinese).
49. Yu DH, Bao YM, Wei CL and An LJ: Studies of chemical constituents and their antioxidant activities from *Astragalus mongholicus* Bunge. Biomed Environ Sci 18: 297-301, 2005.
50. Li J, Han L and Ma YF: Inhibiting effects of three components of Astragalus membranaceus on oxidative stress in Chang Liver cells. Zhong Guo Zhong Yao Za Zhi 40: 318-323, 2015 (In Chinese).
51. Cao LL, Li WZ and Si XL: Astragalus armour glycosides on glomerular mesangial cell protective effect and its mechanism of oxidative stress damage. Zhong Guo Zhong Yao Za Zhi 38: 725-727, 2013 (In Chinese).
52. Gao LS, Zeng FP and Ning LX: Researcheson effects of magnetized codonopsis Pilosula (Franch) nannf. Medicinal solution on carbon expurgatory function of small white rats. Biomagnetism 4: 1-4, 2004.
53. Gao LS, Zeng FP and Ning LX: Researches on effects of magnetized codonopsis Pilosula (Franch) nannf. Medicinal solution on blood function of small rats. Biomagnetism 5: 14-16, 2005.
54. Chen KN, Peng WH, Hou CW, *et al*: Codonopsis javanica root extracts attenuate hyperinsulinemia and lipid peroxidation in fructose-fed insulin resistant rats. Journal of Food and Drug Analysis 4: 347-355, 2013.
55. Zhou GJ, Wang W, Xie XM, Qin MJ, Kuai BK and Zhou TS: Post-harvest induced production of salvianolic acids and significant promotion of antioxidant properties in roots of Salvia miltiorrhiza (Danshen). Molecules 19: 7207-7222, 2014.
56. Wang N, Yang JY, Lu JG, Qiao Q, Wu T, Du X, Bao G and He X: A polysaccharide from Salvia miltiorrhiza Bunge improves immune function in gastric cancer rats. Carbohydr Polym 111: 47-55, 2014.
57. Li CM, Guo YQ, Dong XL, Li H, Wang B, Wu JH, Wong MS and Chan SW: Ethanolic extract of rhizome of ligusticum chuanxiong hort. (chuanxiong) enhances endothelium-dependent vascular reactivity in ovariectomized rats fed with high-fat diet. Food Funct 5: 2475-2485, 2014.
58. Huang J, Lu XQ, Zhang C, Lu J, Li GY, Lin RC and Wang JH: Anti-inflammatory ligustilides from ligusticum chuanxiong hort. Fitoterapia 91: 21-27, 2013.
59. Huang X, Lv B, Zhang S, Dai Q, Chen BB and Meng LN: Effects of radix curcumae-derived diterpenoid C on *Helicobacter pylori*-induced inflammation and nuclear factor kappa B signal pathways. World J Gastroenterol 19: 5085-5093, 2013.
60. Li YY, Wang MR, Zhang QQ, *et al*: Chemical differentiation of Da-Cheng-Qi decoction and its three analogous decoctions using UFLC-ITTOF/MS-based chemomic and chemometric approach. Analytical Methods 6: 1720-1727, 2014.
61. Jin MH, Lu Y, Yang JH, Jo TH, Park YI, Lee CK, Park SJ, Son KH and Chang HW: Anti-inflammatory activity of 6-hydroxy-2,7-di-methoxy-1,4-henanthraquinone from tuberous roots of yam (Dioscorea batatas) through inhibition of prostaglandin D-2 and leukotriene C-4 production in mouse bone marrow-derived mast cells. Arch Pharm Res 34: 1495-1501, 2011.
62. Zeng S, Wang L, Zhang L, Qu H and Gong X: Multi-criteria optimization for ultrasonic-assisted extraction of antioxidants from Pericarpium Citri Reticulataeusing response surface meth-odology, an activity-based approach. J Sep Sci 36: 1861-1868, 2013.
63. Svatikova A, Wolk R, Lerman LO, Juncos LA, Greene EL, McConnell JP and Somers VK: Oxidative stress in obstructive sleep apnoea. Eur Heart J 26: 2435-2439, 2005.
64. Alzoghaibi MA and Bahammam AS: Lipid peroxides, superoxide dismutase and circulating IL-8 and GCP-2 in patients with severe obstructive sleep apnea: A pilot study. Sleep Breath 9: 119-126, 2005.