doi.org/10.36721/PJPS.2023.36.3.SP.1001-1007.1

Clinical efficacy and safety of fluticasone/salmeterol inhalation powder combined with huaiqihuang granules in the treatment of children with cough variant asthma

Junting Liu[1], Jing Yang[2], Shiyu Du[3], Run Guo[2], Yuanyuan Guo[4], Chao Gao[1], Ruiqian Xi[1] and Chao Chen[2]*

[1]Child Health Department, CangZhou Central Hospital, Cangzhou, Hebei, China
[2]Department of Cardiology, CangZhou Central Hospital, Cangzhou, Hebei, China
[3]Medical Insurance Division Fee Section, CangZhou Central Hospital, Cangzhou, Hebei, China
[4]Children's Rehabilitation Department, CangZhou Central Hospital, Cangzhou, Hebei, China

Abstract: This study was to evaluate the clinical efficacy and safety of fluticasone/ salmeterol inhalation powder plus Huaiqihuang Granules for children with cough variant asthma (CVA). From June 2019 to May 2021, 60 children with CVA were hospitalized to the Pediatrics Department of Cangzhou Central Hospital and randomized to the observation (fluticasone/salmeterol inhalation powder plus huaiqihuang granules) and control group (fluticasone/salmeterol inhalation powder) using the random number table method. The outcome measures include clinical efficacy, forced vital capacity (FVC), forced expiratory volume per second (FEV1), peak expiratory flow (PEF), FeNO, high-sensitivity C-reactive protein (hs-CRP), interleukin-17 (IL-17) and IL-23, airway anatomical indicators, and T lymphocyte subsets levels. Both groups exhibited remarkable improvements in FVC, FEV1, PEF and FeNO and hs-CRP, IL-17 and IL-23, with higher FVC, FEV1 and PEF and lower FeNO, hs-CRP, IL-17 and IL-23 in the observation group (all $P<0.05$). Significantly higher levels of CD4+ and CD4+/CD8+ were observed in the observation group versus control group, but lower airway wall thickness, basement membrane thickness, total airway wall area, and CD8+ in the observation group (all $P<0.05$). Fluticasone/salmeterol inhalation powder plus Huaiqihuang Granules improves lung function, FeNO and airway inflammation in children with CVA, and boosts cellular and humoral immune function.

Keywords: Cough variant asthma, inflammatory factors, immune system, fluticasone/salmeterol inhalation powder, huaiqihuang granules.

INTRODUCTION

Cough variant asthma (CVA) is one of the common causes of chronic cough in children in China and its triggers include cold, fog and smoke. It mainly presents as an irritating cough in children in the morning or at night that lasts for more than one month (Anderson *et al*., 2018). Due to the poor efficacy of antibiotics and recovery, it has an impact on the quality of life of patients. CVA accounts for 17.0%-40.1% of chronic isolated cough in children and severely hampers the daily life of patients with a long duration of illness (Rocha *et al*., 2019). A recent study found a link between the pathogenesis of CVA and airway hyper responsiveness, as well as similarities between the pathogenesis of CVA and that of typical asthma and also found that chronic inflammation of the airways and airway remodelling promote its development (Weers *et al*., 2019). Statistics show that approximately 30% of patients with CVA develop wheezing symptoms and eventually develop typical asthma, with 40%-75% of these patients having documented wheezing within 6 months to 8 years of follow-up (Preston *et al*., 2021), highlighting the importance of timely and appropriate intervention for CVA to prevent its development into asthma. Furthermore, given the long-term course of CVA and its propensity for poor recovery, one of the most critical clinical issues is the adoption of effective and correct treatments to combat it (Sobieraj *et al*., 2018).

Currently, the main management for CVA is the implementation of anti-inflammatory, release of smooth muscle spasm and anti-allergy. Salmeterol and ficapone are majorly used for the treatment of CVA and are more effective in a short period of time. However, with the prolongation of the course of treatment, the overall efficacy does not meet clinical expectations due to poor compliance and adverse drug reactions (Zheng *et al*., 2021). Cough variant asthma belongs to the categories of “wheezing cough” and “wind cough” in traditional Chinese medicine. Exogenous pathogens such as damp pathogens lead to the dysfunction of lungs, the convulsions of the airways and the upward reversion of lung qi, which leads to frequent coughing (Zhong *et al*., 2022). Although there are many treatments available for CVA, the results remain unsatisfactory. In clinical practice, fluticasone/salmeterol inhalation powder is a common drug used to treat CVA. The Huaiqihuang Granules are also effective in the treatment of CVA patients in our hospital. Therefore, the aim of this study

**Corresponding author:* e-mail: chaocangdanwei3209@163.com

was to evaluate the clinical effectiveness and safety of fluticasone/ salmeterol inhalation powder plus Huaiqihuang Granules in the treatment of CVA in children.

MATERIALS AND METHODS

Participants

A total of 60 children with CVA admitted to the Department of Pediatrics of Cangzhou Central Hospital from June 2019 to May 2020 were enrolled for the study.

The children were randomized (1:1) into the observation group and the control group using the random number table method. The baseline characteristics were similar in the two groups (p>0.05, table 1). This study was ratified by the ethics committee of our hospital (NO. CZ19-032-010), and all enrolled patients and their family members signed informed consent forms after being informed of the purpose and process of the study.

Inclusion criteria (Mukhopadhyay *et al*., 2020): (1) patients who were confirmed by bronchodilator consultation and bronchial excitation test to meet the diagnostic criteria for CVA as per the Chinese Guidelines for the Diagnosis and Management of Chronic Cough in Children (revised 2013); (2) patients who had a good compliance with the test; (3) patients who had no allergic reaction to the drugs used in this study; (4) patients who had no other lung diseases.

Exclusion criteria: (1) Patients with chronic cough symptoms caused by other factors, such as chronic pharyngitis, sinusitis, tonsillitis, airway foreign bodies, etc.; (2) Patients who have received theophylline, glucocorticoids, β2 agonists or other related drugs within the past 2 months; (3) Patients with liver, kidney, heart or other vital organ dysfunction; (4) Patients with malignancy; (5) Patients with psychiatric disorders; (6) Patients with contraindications to the drugs used in the study.

Methods

Both groups of children were given conventional treatment. In addition, children in the control group were treated with fluticasone/salmeterol inhalation powder (specification: 50μg:100μg), twice a day, and the dose was increased to 3 times a day according to the severity of asthma. While those in the observation group were additionally given oral administration of Huaiqihuang Granules (Qidong Gaitianli Pharmaceutical Co., Ltd., NMPA Approval Number B20020074) orally for 8 weeks at 10g each time (10g per sachet), twice a day in the morning and evening.

Outcome measures

(1) The lung function indexes of the two groups of children before and after treatment were compared (tested by German Gretel pulmonary function tester). A lung function detector was used to determine the children's forced vital capacity (FVC), forced expiratory volume in 1s (FEV1), and peak expiratory flow (PEF).

(2) The airway anatomy indicators of the two groups of children before and after treatment were compared. The CT detection method was utilized to measure the children's airway wall thickness and total airway wall area before and after therapy and the hematoxylin-eosin (HE) staining method was employed to determine their basement membrane thickness.

(3) The levels of T lymphocyte subsets before and after treatment were compared between the two groups. 10 ml fasting peripheral venous blood was secured from each patient in the morning, followed by determination of T lymphocyte subsets (CD4+, CD8+) and CD4+/CD8+ using flow cytometer (Louati *et al*., 2019).

(4) Inflammatory factors in the two groups before and after treatment were compared. 10 ml fasting peripheral venous blood was secured in the morning, followed by detection of the levels of serum hypersensitive C-reactive protein (hs-CRP), interleukin-17 (IL-17), and IL-23. The kits were purchased from Shanghai Kexing Technology, and the batch numbers were B19047, A80220, A196079, C20508, and B80205.

(5) FeNO: A nitric oxide analyzer produced by Wuxi Sunwo Biotechnology Co., Ltd. was used to detect the FeNO levels. During this time, the patient is instructed to exhale air from the lungs and continue breathing for more than 10 seconds with even breaths, with the results expressed as ppb.

(6) Adverse reactions during treatment were recorded.

(7) Clinical efficacy was assessed after 8 weeks of treatment. Cured was defined if there was no recurrence, with complete disappearance of cough symptoms and return of the lung function to normal; Effective was considered if the cough symptoms were relieved, and the lung function was partially improved; whereas ineffective was deemed if there was no significant alleviation in the symptoms, or worsening of the condition; Total effective rate = (the number of cured patients + the number of effectively treated patients)/the total number of cases × 100%.

Sample size

With the test level of 0.05 on both sides and 80% test efficacy, the sample size estimation method was used for each group's measurement data. When the sample number of each group was equal, at least 21 cases were needed in each group. According to the estimation of 15% dropout rate in the study, at least 28 cases were needed in each group, and at least 56 cases were included in the sample size. The final sample size was 60.

STATISTICAL ANALYSIS

The counting data were analyzed by the x2 test and expressed by [n(%)], and the measurement data were expressed by (x±s) and analyzed by the t-test. For all the tests, statistical significance was set at $p<.05$ (two-tailed). All data were analyzed using SPSS (version 24; IBM, Armonk, NY).

RESULTS

Clinical efficacy
The observation group exhibited higher clinical efficacy versus the control group (93.33% *vs.* 63.33%, $p<0.05$) (table 2).

Lung function indices
Both groups witnessed improvement in FVC, FEV1, and PEF after treatment, with significantly higher FVC, FEV1, and PEF in the observation group versus the control group ($p<0.05$) (table 3).

FeNO levels
Significant declines were observed in the FeNO levels in the two groups after treatment, with lower values in the observation group versus the control group ($p<0.05$) (table 4).

Airway inflammation indices
After treatment, the airway inflammation index in both groups demonstrated significant improvements, with significantly lower levels of hs-CRP, IL-17 and IL-23 in the observation group versus the control group ($p<0.05$) (table 5).

T lymphocyte subsets
After treatment, the observation group exhibited a remarkably higher CD4+ and CD4+/CD8+ values and a lower CD8+ than the control group ($p<0.05$) (table 6).

Airway anatomy indexes
Prior to treatment, the two groups showed similar airway morphology; after treatment, airway wall thickness, basement membrane thickness, and total airway wall area in both groups reduced dramatically, with lower results in the observation group versus the control group ($p<0.05$) (table 7).

Cough degree and frequency score
Before treatment, the difference in the cough degree and frequency scores did not come up to statistical standards in the two groups, whereas after treatment the cough degree and frequency scores of the two groups decreased significantly, with more favorable outcomes in the observation group versus the control group ($p<0.05$) (table 8).

Safety profiles
There were 2 cases of stomach discomfort and 1case of hoarse voice in the observation group and 1 case of abdominal pain and 3 cases of hoarse voice in the control group. Overall, the incidence of adverse responses did not statistically differ between the two groups (10.00% *vs.* 13.33%, $p>0.05$) (table 9).

DISCUSSION

As human society continues to develop, industrialisation has led to increasing environmental pollution (Li *et al*., 2019), resulting in a rising trend in the incidence of CVA in children. Recurrent chronic cough is a symptom that impairs the physical and mental health of children (Portincasa *et al*., 2020). CVA is a chronic non-specific airway inflammation secondary to inflammatory cells affecting the release of allergens and inflammatory cells such as eosinophils, basophils and mast cells, for which the reduced immune function of children can lead to recurrent respiratory infections and severe CVA recurrence (Han *et al*., 2020). Currently, bronchodilators and glucocorticoids are widely used in Western medicine. However, corticosteroids can induce rapid contraction of bronchial smooth muscle in children, thereby accelerating mucus secretion, and increased vascular permeability can cause mucosal oedema and impede respiratory function (Hong *et al*., 2020). Therefore, immunity enhancement in children without affecting their bronchi plays a critical role in improving the efficacy of CVA.

CVA belongs to the category of "cough" in traditional Chinese medicine. Chinese medicine believes that whether it is the six evils and external pathogens invading the lungs, or the dysfunction of the viscera, and the internal pathogens invading the lungs, all can cause the lungs to disperse and descend and cause the lung to lose its function and cause a cough. In children, the lungs are often underdeveloped that cannot be self-regulated and they are most susceptible to evils. After entering into the interior, it turns heat, causing the interior heat to flourish, and the heat burns the body fluid to form phlegm, resulting in the syndrome of phlegm-heat. The main treatment is to clear away heat and resolve phlegm, relieve cough and asthma (Kroes *et al*., 2019). Accordingly, this study adopted Huaiqihuang Granules with main functions of strengthening the body, invigorating the lungs, and replenishing Qi for treatment to strengthen the lungs and qi to consolidate the foundation. Huaiqihuang Granules are traditional Chinese medicine granules made from the fermented extracts of *Sophora japonica mycelium, wolfberry* and *Huangjing*.
They have been clinically used in pediatrics for many diseases as an immunomodulator (Yao *et al*., 2020) and demonstrated promising outcomes on children's autoimmune diseases, allergic diseases, and infectious diseases (Santus *et al*., 2020). With Sophora japonicus as

Table 1: Comparison of general clinical information of the two groups of patients

Groups	N	Gender		Age (year)	Weight (kg)	Course of disease (month)
		Male	Female			
Observation group	30	17	13	8.04±3.21	26.16±3.22	3.57±0.63
Control group	30	18	12	8.23±3.32	26.35±3.27	3.45±0.72
t/χ^2		0.069		0.225	0.235	0.723
P-value		0.793		0.823	0.815	0.472

Table 2: Comparison of clinical efficacy between the two groups of patients

Groups	N	Cured	Effective	Ineffective	Total effective rate
Observation group	30	13	15	2	28 (93.33%)
Control group	30	8	11	11	19 (63.33%)
χ^2					7.954
P-value					0.005

Table 3: Comparison of lung function indexes before and after treatment in the two groups

Groups	N	FVC (L)		FEV1/FVC (%)		PEF (L/min)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	1.79±0.22	2.85±0.34#	1.45±0.72	1.71±0.28#	1.53±0.24#	1.91±0.31#
Control group	30	1.80±0.34	2.33±0.23#	1.40±0.39	1.52±0.36#	1.59±0.29#	1.73±0.24#
T		0.135	6.869	0.334	2.194	0.808	2.582
P-value		0.893	0.000	0.740	0.032	0.422	0.012

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

Table 4: Comparison of FeNO levels before and after treatment in the two groups

Groups	N	FeNO (ppb)	
		Before treatment	After treatment
Observation group	30	25.13±2.61	16.19±2.18#
Control group	30	25.29±2.73	19.92±2.22#
T		0.232	6.569
P-value		0.817	0.000

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

Table 5: Comparison of airway inflammation indexes before and after treatment in the two groups

Groups	N	IL-17 (ng/mL)		IL-23 (ng/mL)		hs-CRP (mg /L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	132.21±32.14	60.57±17.32#	35.68±3.78	21.26±2.78#	20.71±2.27	11.75±3.73#
Control group	30	134.31±33.29	85.39±20.45#	35.49±4.10	27.32±2.69#	20.65±2.38	6.81±3.91#
T		0.249	5.072	0.196	8.565	0.100	4.998
P-value		0.805	0.000	0.845	0.000	0.920	0.000

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

the monarch drug and Lycium barbarum and Polygonatum as the ministerial drug, Huaiqihuang Granules are considered as an ideal immunomodulator for their ability to promote the immune balance of the body and non-specific immune function and their regulation in humoral immunity and cellular immunity (Sharma *et al*., 2021). Sophora japonica contains fungal polysaccharide that can contribute to the activation of neutrophils, macrophages, and natural killer (NK) cells in the body's immune system, promote the activity of NK cells and division, proliferation, maturation, and activation of T cells, and adjust the ratio of T-helper cells (Th) and

Table 6: Comparison of the levels of T lymphocyte subsets of the two groups of children before and after treatment

Groups	N	CD4+ (%)		CD8+ (%)		CD4+/CD8+	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	30.16±2.42	39.84±3.24#	30.71±2.56	22.71±2.23#	1.03±0.17	1.78±0.11#
Control group	30	30.13±2.38	35.73±3.32#	30.93±2.54	26.87±2.34#	1.02±0.15	1.39±0.12#
T		0.033	4.860	0.319	7.032	0.008	13.454
P-value		0.974	0.000	0.751	0.000	0.994	0.000

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

Table 7: Comparison of airway anatomy indicators between the two groups of children before and after treatment

Groups	N	Airway wall thickness (mm)		Basement membrane thickness (mm)		Total airway wall area (mm2)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	2.23±0.31	0.85±0.18#	8.52±1.06	5.28±0.81#	7.14±1.34	3.74±1.35#
Control group	30	2.14±0.33	1.29±0.14#	8.48±1.08	6.37±1.13#	7.21±1.29	5.69±1.26#
T		0.968	10.409	0.108	4.330	0.235	5.737
P-value		0.337	0.000	0.914	0.000	0.815	0.000

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

Table 8: Comparison of cough degree and frequency score before and after treatment between the two groups

Groups	N	Cough degree		Cough frequency	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	30	4.52±0.63	0.88±0.37#	4.91±0.53	1.06±0.33#
Control group	30	4.49±0.72	2.24±0.45#	4.97±0.54	2.55±0.36#
T		0.227	12.644	0.438	16.827
P-value		0.821	0.000	0.663	0.000

Note: # indicates that a statistical difference was observed within the groups pre and post treatment.

Table 9: Safety evaluation during treatment of the two groups of children

Groups	N	Abdominal pain	Hoarse voice	Total incidence
Observation group	30	2	1	3 (10.00%)
Control group	30	0	3	4 (13.33%)
$\chi 2$				0.753
P-value				0.385

suppressor T cells (Th/Ts), thereby activating relevant immune cells and enhancing the body's cellular immune function (Porcaro *et al*., 2020; Maciag *et al*., 2020).

The results of this study showed that after 8 weeks of treatment, the observation group obtained lower levels of FeNO, hs-CRP, IL-17 and IL-23 and higher levels of CD4+ and CD4+/CD8+ compared to the control group, indicating that Huaiqihuang granules have good inflammatory control and immunomodulatory effects and can repair the body's immune system. In addition, the clinical efficacy of the observation group was higher than that of the control group, indicating that the therapeutic ability of fluticasone/ salmeterol inhalation powder combined with Huaiqihuang granules was higher than that of fluticasone/ salmeterol inhalation powder as a single treatment. Given that the etiology and pathogenesis of CVA disease is similar to that of bronchial asthma, it can be treated according to asthma control guidelines (Papanicolaou *et al*., 2020; Choi *et al*., 2020; Chałubiński *et al*., 2020; Che *et al*., 2021). In a previous study (Shen *et al*., 2021), 43 patients who were first diagnosed with CVA and treated with inhaled corticosteroids (ICS) were randomised to two groups and the timing of ICS tapering was assessed based on lung function and FeNO results, and the results showed that FeNO demonstrated potential as a monitoring indicator during glucocorticoid therapy for CVA and guided the reduction of glucocorticoid therapy. Similar results were obtained in this study that FeNO levels in the observation group were significantly

lower than those in the control group, suggesting the potential of FeNO as an indicator for efficacy testing. Possibly, salmeterol and fexcarbazone inhalation powder inhaler is a combination of the long-acting sting the potential of FeNO as an indicator fond fluticasone propionate, which promotes the synthesis of cyclic adenosine monophosphate in human cells by effectively stimulating β2 receptors *in vivo* and activating adenylate cyclase, resulting in stabilization of mast cell membranes and relaxation of bronchial smooth muscle *in vivo* (Wang *et al*., 2021). CVA can fall under the category of wind cough in TCM, presenting with cough, sore throat, shortness of breath and suddenness. The dysfunction of the lungs caused by the invasion of evil qi, together with the patient's deficiency of yang qi, leads to the onset of the disease (He *et al*., 2021). Huaiqihuang Granules can invigorate the righteousness and improve the function of protection against external factors and prevent the invasion of evil Qi.

However, although our study leads the way in treating children with CVA, limitations merit attention. The small sample size would possibly bias our results toward the null; Our study was unable to examine the patient's history of possible triggers, such as dietary habits, home environment or family history, which may have influenced our findings. Hence the finding of the present study needs to be interpreted with caution.

CONCLUSION

In conclusion, fluticasone/ salmeterol inhalation powder combined with Huaiqihuang Granules might be a feasible management strategy for children with CVA given its potential in effectively improving the lung function, FeNO levels, attenuating airway inflammation and boosting cellular and humoral immune function. There for, it merits promotion and application in clinic setting.

REFERENCES

Anderson SD, Daviskas E, Brannan JD and Chan HK (2018). Repurposing excipients as active inhalation agents: The mannitol story. *Adv. Drug Deliv. Rev.,* **133**: 45-56.

Chałubiński M, Gajewski A and Kowalski ML (2020). The relationship between human corona viruses, asthma and allergy-An unresolved dilemma. *Clin. Exp. Allergy,* **50**(10): 1122-1126.

Che KF, Tengvall S and Linden A (2021). Interleukin-26 in host defense and inflammatory disorders of the airways. *Cytokine Growth Factor Rev.,* **57**: 1-10.

Choi Y, Jang J and Park HS (2020). Pulmonary surfactants: A new therapeutic target in asthma. *Curr. Allergy Asthma Rep.,* **20**(11): 70.

Han X, Krempski JW and Nadeau K (2020). Advances and novel developments in mechanisms of allergic inflammation. *Allergy,* **75**(12): 3100-3111.

He Long (2021). Clinical analysis of self-made Yiqi Qutan prescription in the treatment of variant bronchial asthma with Qi deficiency and phlegm stasis. Chin *Med Guid.,* **19**(20): 84-85.

Hong H, Liao S, Chen F, Yang Q and Wang DY (2020). Role of IL-25, IL-33 and TSLP in triggering united airway diseases toward type 2 inflammation. *Allergy,* **75**(11): 2794-2804.

Kroes JA, Zielhuis SW, van Roon EN and Ten Brinke A (2020). Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochem Pharmacol.,* **179**: 113978.

Li E, Knight JM and Wu Y (2019). Airway mycosis in allergic airway disease. *Adv. Immunol.,* **142**: 85-140.

Louati N, Rekik T, Menif H and Gargouri J (2019). Blood lymphocyte T subsets reference values in blood donors by flow cytometry. *Tunis Med.,* **97**(2): 327-334.

Maciag MC and Phipatanakul W (2022). Prevention of asthma: Targets for intervention. *Chest,* **158**(3): 913-922.

Mukhopadhyay A, Waked M, Gogtay J and Gaur V (2020). Comparing the efficacy and safety of formoterol/budesonide pMDI versus its mono-components and other LABA/ICS in patients with asthma. *Respir. Med.,* **170**: 106055.

Papanicolaou A, Wang H, Satzke C, Vlahos R, Wilson N and Bozinovski S (2020). Novel therapies for pneumonia-associated severe asthma phenotypes. *Trends Mol. Med.,* **26**(11): 1047-1058.

Portincasa P, Krawczyk M, Smyk W, Lammert F and Di Ciaula A (2020). COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics. *Eur. J. Clin. Invest,* **50**(10): e13338.

Porcaro F, Ullmann N, Allegorico A, Di Marco A and Cutrera R (2020). Difficult and severe asthma in children. *Children* (Basel). **7**(12): 286.

Preston KB and Randolph TW (2021). Stability of lyophilized and spray dried vaccine formulations. *Adv. Drug Deliv. Rev.,* **171**: 50-61.

Rocha DMUP, Caldas APS, da Silva BP, Hermsdorff HHM and Alfenas RCG (2019). Effects of blueberry and cranberry consumption on type 2 diabetes glycemic control: A systematic review. *Crit. Rev. Food Sci, Nutr.,* **59**(11): 1816-1828.

Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE and Baker WL (2018). Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and meta-analysis. *JAMA,* **319**(14): 1485-1496.

Santus P, Radovanovic D, Pecchiari M, Ferrando M, Tursi F, Patella V and Braido F (2020). The relevance of targeting treatment to small airways in asthma and COPD. *Respir. Care,* **65**(9): 1392-1412.

Sharma S, Hashmi MF and Chakraborty RK (2021).

Asthma medications. *In*: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. PMID: 30285350.

Shen WF, Liu MX and Cao J (2022). Clinical study on the adjuvant treatment of cough variant asthma with Fengsheng contracture and acute syndrome with Qufengzhike recipe. *Inter. J. Tradit Chin. Med.,* **43**(12): 1179-1183.

Wang Y and Yang YM (2021). Research overview of Sanao decoction in the treatment of children with cough variant asthma. *Chin. Ethnic. Folk Med.,* **30**(24): 62-65.

Weers JG, Miller DP and Tarara TE (2019). Spray-dried pulmosphere™ formulations for inhalation comprising crystalline drug particles. *AAPS Pharm. Sci. Tech.,* **20**(3): 103.

Yao Y, Wang H and Liu Z (2020). Expression of ACE2 in airways: Implication for COVID-19 risk and disease management in patients with chronic inflammatory respiratory diseases. *Clin. Exp. Allergy,* **50**(12): 1313-1324.

Zheng YF, Wu Y and Mao WP (2021). Qufeng Sanhanzhisou prescription combined with western medicine in the treatment of 49 cases of cough variant asthma in children. *Chin. Sci. Tech Tradit. Chin. Med.,* **28**(06): 997-999.

Zhong Y, Cai HJ and Cao JB (2022). Clinical study on the treatment of cough variant asthma with Kangmin Zhenke Decoction. *Henan. Chin Med.,* **42**(06): 923-927.