



Progress in the Treatment of Chronic Cough in Children with Traditional Chinese Medicine Through Anti-inflammatory Action*

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Abstract Chronic cough is a common disease in pediatric respiratory outpatient clinics with diverse etiology and age differences. Modern medicine believes that neurogenic airway inflammation is an important cause of chronic cough. Anti-inflammatory, and anti-allergic drug are used for chronic cough. Traditional Chinese medicine (TCM) treatment of chronic cough in children according to the overall concept and dialectical treatment, mainly from wind, phlegm and deficiency treatment, has a definite effect. Through consulting the literature, this paper summarizes the TCM for the treatment of chronic cough in children, and summarizes its anti-inflammatory mechanism. Clinical studies have found that treating children with chronic cough according to the theory of Fuyang of TCM can obtain good curative effect, so here this is accompanied by a brief description.

Key words traditional Chinese medicine, chronic cough, anti-inflammatory, children

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Cough is the most common reason for treatment in respiratory clinics, and it is also a common symptom that causes clinical visits of children. According to the duration of symptom, children's cough is divided into acute cough (sickness < 2 weeks), prolonged cough (3–4 weeks) and chronic cough (sickness > 4 weeks)^[1], this is different from adult chronic cough, which lasts longer than 8 weeks^[1-2]. Children's chronic cough refers to cough, whose main or only clinical manifestation is cough, course > 4 weeks and chest X-ray film shows no obvious abnormality^[3]. More precise definitions for the duration of the disease can help identifying the causes of chronic cough in children earlier and allow early and effective treatment. Modern medicine for the treatment of chronic cough in children aims mainly to its cause. Usage of bronchodilators, glucocorticoids, anti-inflammatory drugs, or combination therapy is common. However it is easy to relapse after treatment, and recurrent cough affects the quality of life of children seriously. Traditional Chinese medicine (TCM) has a positive effect on the treatment of chronic cough in children. Some studies have found that Chinese medicine can inhibit or

alleviate the symptoms of cough in children through anti-inflammatory effects. This article reviews the anti-inflammatory mechanism of chronic cough in children with TCM, and suppose to provide a literature overview for the application of TCM to chronic cough in children.

1 Understanding and treatment of chronic cough in children in modern medicine

Cough is a kind of defensive nerve reflex of the body. It is aimed at clearing respiratory secretions or foreign bodies. However, too frequent or persistent cough can have adverse effects on people's work and life, and is often a signal of some physical or mental illness. Chronic cough, because of its long duration, is complicated and diverse symptom, has more obvious influence on children. The cause of chronic cough in children is different from that of common chronic

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cough in adults, and shows an age difference. The common chronic cough in infants under 1 year old is due to congenital airway dysplasia, gastroesophageal reflux (GER), pertussis (PT); 1–3 years old children with chronic cough is due to cough post infection (PIC), protracted bacterial bronchitis (PBB), airway foreign body; Common causes of 3–6 years old children with chronic cough, in addition to PIC and PBB, are also upper airway cough syndrome (UACS), bronchiectasis, and cough variant asthma (CVA); UACS, CVA, PIC, and bronchiectasis remain high incidence in adolescent children, some children have a psychogenic cough^[4-5]. In children with chronic cough, the main mechanism of chronic wet cough is inflammatory cell infiltration. The main cause of wet cough is UACS, asthma with UACS, asthma with infection, PBB^[6-7], especially about 75.8% of chronic cough in children under 3 years old was diagnosed as PBB^[8]. Anti-inflammatory treatment is the main treatment for chronic wet cough in children. Especially in young children, PIC and PBB may be the most common and specific cause of chronic cough, which are closely related to chronic inflammation of the airway^[9].

Patients with chronic cough often have high cough sensitivity, while the airway neurogenic inflammation is an important mechanism for increased cough sensitivity. Transient receptor potential cation channel protein family (TRP) can be stimulated by exogenous or endogenous substances to produce various neuropeptides, followed by local tissue vasodilation and increased permeability, inflammatory cell exudation, mucosal congestion and edema, bronchoconstriction and other neurogenic inflammation, which are closely related to the occurrence of cough^[10]. After stimulation of various environmental physicochemical stimuli, the TRP pathway is activated, causing a large amount of Ca^{2+} influx, and resulting in the release of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGMP). Increased SP and CGMP concentrations cause the contraction of smooth muscle, increased vascular permeability, increased epithelial edema and mucus secretion, *etc.* This process is the result of neurogenic inflammation^[11]. In addition, unmyelinated C fibers, which are thought to play an important role in cough reflexes, control the releases of SP, NKA, CGRP, could induce neurogenic inflammation, and lead to increased airway

sensitivity^[12]. Studies have shown that cough models in guinea pig respiratory syncytial virus (RSV) infection, AA metabolism of COX-2 and 5-LOX pathways were activated, COX-2 and 5-LOX protein expression was elevated, suggesting airway inflammation associated with arachidonic acid metabolism network^[13].

Neuropeptides such as SP and CGRP are important mediators of airway neurogenic inflammation, which can increase the sensitivity of cough reflex and play an important role in chronic cough. For example, some exogenous or endogenous substances stimulate certain subtypes of TRP channel proteins, which may lead to the release of neuropeptides, causing changes in airway vascular permeability, inflammatory cell exudation, airway contraction, and coughing^[14]. The important mechanism for increased airway sensitivity of chronic cough is the activation of TRPA1/TRPV1 channels by exogenous stimuli, which leads to the release of neuropeptides such as NGF and SP, and promotes the development and progression of inflammation, especially neurogenic inflammation^[15-16].

Upper airway cough syndrome (UACS) is a chronic cough syndrome associated with various airway diseases such as rhinitis, sinusitis, chronic pharyngitis, chronic tonsillitis, adenoid hypertrophy. UACS, asthma and gastroesophageal reflux constitutes the three main causes of chronic cough in children^[17]. The occurrence of UACS may be related to allergies, infections, local lesions, immunodeficiency, vascular disease and other factors. Airway inflammation and high neurological sensitivity are the most common pathogenesis^[18]. At present, the treatment of UACS is mainly based on the application of antibiotics combined with antiallergic drugs, leukotriene receptor antagonists, expectorants and immunomodulators. Recently, more attention is paid to the joint treatment among disciplines, such as the cooperation between pediatrics, otolaryngology and TCM, and if necessary, surgery can be used, with diversified and individualized treatment methods.

Pulmonary fibrosis (PF) is closely related to chronic cough. Inflammatory response is one of the key pathological mechanisms in the development of PF. Src family kinases play a crucial role in the pathogenesis of PF, making it a promising molecular target for the treatment of these diseases^[19].

According to the studies mentioned above,

chronic cough associated with inflammation may be caused by various factors, such as allergies, infections, immune disorders, *etc.*, and lead to chronic airway inflammation and high airway sensitivity through various routes, thereby inducing repeated and persistent cough. Therefore, the focus of treatment of chronic cough is anti-inflammatory and regulation of the airway neural network.

2 TCM theory related to chronic cough

There is no proper expression for chronic cough in Chinese medicine. According to the symptoms, chronic cough is attributed to the category of "prolonged cough", "stubborn cough" and "internal injury cough". In Chapter of Cough Discussion in Suwen, it was described that "the five zang organs and six fu organs are all coughing, not only the lung". It means that the etiology and pathogenesis of cough is complicated, so it should be carefully distinguished when treatment, clear etiology and pathogenesis, syndrome differentiation and treatment. The Chapter of Cough Discussion in HeJian LiuShu: "Cold, summer-heat, dryness, dampness, wind, fire, six Qi, all can cause cough." According to modern Chinese medicine research, the formation of UACS is closely related to "wind". Cough after infection is related to "heat and deficiency". Prolonged cough is mostly the syndrome of deficiency or the syndrome of deficiency in origin and excess in superficiality.

Wind is good at moving, always vulnerable to lung, and causes cough. The lung is a respiratory organ, reservoir of phlegm, while long time sick, the gas engines of lung can be impeded and phlegm produced. Interaction between phlegm and gas causes airway obstruction, then occurrence recurrent cough and wheezing. So the main factor of chronic cough is "wind evil", "phlegm" is both an important pathological factor and a key pathogenic factor. Hidden wind and phlegm evil are the root of chronic cough. TCM theory holds that infectious diseases are associated with fire, manifested as febrile disease. Heat evil burns body fluid and injures the lung, and causes lung qi and yin deficiency in lung, in the end, causes chronic cough.

It was showed in literature that wind fell lung collaterals and heat phlegm in lung are the most common TCM syndromes of chronic cough in children. CVA and UVCS are mostly wind fell lung

collaterals syndrome, qi deficiency in lung and spleen syndrome, yin deficiency internal heat syndrome, PIC is mostly heat phlegm in lung syndrome and yin deficiency internal heat syndrome, GERC is mostly food-fire attacking lung syndrome^[20-21]. Chronic cough is normally defined in the category of "wind cough" in Chinese medicine, and the hot and cold air, dust and soot that lead to coughing belong to the material basis of "outside wind". After inhalation through the airway, it is activated by TRP channel, conducted by nerve channel, a variety of neuropeptides released, stimulating the release of a variety of inflammatory mediators, including histamine, leukotriene B4 and neutrophil elastase, leading to airway neurogenic inflammation and inducing cough^[22].

Additional, liver and spleen discord, liver and spleen disharmony, liver fire invading lung, spleen deficiency causing phlegm and dampness invading lung, and deficiency of the kidney, all can cause chronic cough. So treatment of chronic cough should pay attention not only to the lungs, and also to liver, spleen, and kidney^[23-24].

3 TCM treatment of chronic cough in children

Chronic cough is mostly attributed to the category of "prolonged cough" in TCM. The incidence is related to the Five Zang, especially the lungs. The main internal factors are "wind evil" and "phlegm", which can be triggered by various external evils such as wind, cold and dampness, then cause chronic cough that is difficult to cure. The treatment of chronic cough with TCM is mainly based on the treatment of lung, strengthening the vital energy and removing pathogenic factors. According to syndrome differentiation, it is supplemented by the treatment of invigorating spleen, regulating liver, benefiting kidney, resolving phlegm, drying dampness expelling wind, and removing blood so as to achieve the purpose of treating both the specimen and preventing recurrence.

Children's zang-fu organs are not complete and strong, with physical deficiency, especially the lung, spleen and kidney function is often inadequate, which closely related to water metabolism disorders and can cause phlegm and dampness. Therefore, for treatment of children chronic cough, can be from the lung,

spleen, stomach, wind, phlegm, blood stasis, pay attention to healthy spleen and stomach, soil and gold, and the nature of medication is mostly peaceful, drug dosage should be light^[25-26].

Chronic cough of children is located in the lung, involving other viscera, so the treatment of chronic cough should be based on lung, as appropriate to consider the dirt of other viscera, chooses Xuanfei, Runfei, clears lung, and converges the lung method. At the same time, you should also consider the dirty factors, from the five viscera treatment, syndrome differentiation using Xuanqing tonifying and convergence, Qi Jianpi phlegm, nourishing yin and kidney and collaterals, clearing liver and purging fire to collect lung or nour^[27]. For example, it is often used in clinic to treat allergic cough by adding and subtracting Ma Xing Shi Gan Tang, San Wu Tang and Xiao Qinglong Tang, and Commonly used drugs are ephedra, bitter almonds, fructus, *Stemona sessilifolia*, licorice and so on^[28]. It is often used in clinic to treat PIC by adding and subtracting Zhisou Powder, Sanren Decoction, Erchen Decoction and Sha Shenmai Dong Decoction with different syndrome^[29-30].

Because the stored sputum is an important factor in recurrent chronic cough in children, so treatment of resolving phlegm and relieving cough drugs are more used in these diseases. For example, professor Wang Shou-chuan, a famous pediatrician of modern Chinese medicine, commonly used *scutellaria baicalensis*, mulberry white skin, mulberry leaves, *polygonum cuspidatum* and other anti-phlegm drugs, such as *peucedani radix*, *eribotryae folium*, grilled ephedra, almonds, *magnoliae flos*, *farfarae flos*, and so on, to treat children cough^[31]. Statistical analysis showed that the traditional Chinese drugs with the highest frequency on PIC are drugs for eliminating phlegm and relieving cough^[32].

In a word, the key point of TCM treatment for chronic cough in children is syndrome differentiation.

4 Fuyang theory for chronic cough

Traditional Chinese medicine theory holds that children are "young yang" bodies, delicate viscera, easy to be invaded by external evil. Disease, drugs or diet injury are vulnerable to damage Yang Qi, and then lead to lingering disease. Professor Zhao Kun believes that children with chronic cough often show Yang deficiency. This phenomenon has the trend, that

the younger the children, Yang Qi more frail. Therefore, the treatment should pay attention to protect its Yang Qi, even by the application of bitter cold drugs a small amount of warm medicine should be assist to neutralize the coldness. On the other hand, it is advocated the usage of heat-clearing drugs should be stopped when disease disappears^[33]. Professor Zhao Kun uses aconite to treat chronic cough and asthma, because the true yang of children belongs to the kidney, and kidney yang is the root of the body yang qi. So once yang qi damaged, we can use aconite to warm kidney yang, help spleen yang, warm body, steam phlegm dampness, and purge the lung. Aconite is particularly applicable for yang deficiency long cough syndrome. A database of 420 prescriptions containing aconite by Professor Zhao Kun was established and data mining was carried out with the help of TCM (V2.5). It was found that the prescriptions of aconite contained by Professor Zhao were often used in the treatment of various pulmonary diseases including occlusive bronchiolitis, lobar pneumonia, interstitial lung disease, pertussis syndrome, asthma and so on, most of which could be classified as chronic cough^[34]. Professor Zhao, on the basis of Zhongjing Jingfang ephedra aconite asarum decoction and small Azure Dragon decoction, self-designed "Wenfeihua decoction", drug composition: aconite, ephedra, cinnamon, Asarum, almond, *radix paeoniae alba*, aster, winter flowers, orange red, orange luo, Chen Pei, *Schisandra chinensis*, licorice, pay attention to Fuyang Gu Ben, treatment of long cough, excellent curative effect, is the representative prescription of Fuyang theory to treat chronic cough. Using 2, 3-butanedione (Diacetyl, DA) intratracheal drip method to construct the rat model of occlusive bronchiolitis, using dexamethasone as positive control, it was found that Wenyangtongbi decoction could improve lung pathology and reduce the deposition of collagen type III in lung tissue in BO rats, which may be one of the mechanisms of the efficacy of this prescription. More studies are still needed^[35].

5 Anti-inflammatory mechanism of Chinese medicine in treating chronic cough in children

Many studies have shown varietal anti-inflammatory effects of TCM. TCM may play an anti-

inflammatory role by regulating the function of HPA axis, affecting the metabolism of arachidonic acid, anti-histamine, 5-hydroxytryptamine, inhibiting the synthesis of leukotriene B₄, immunoregulation, inhibiting leukocyte chemotaxis, activation, oxygen free radicals, *etc*^[36].

Gu *et al.*^[37] used molecular docking and arachidonic acid (AA) metabolic network simulation to analyze the anti-inflammatory function of 28 kinds of Chinese herbal medicines and three groups of Chinese herbal compounds. The results showed that a clear trend in herbal medicines was that they reduced the production of LTB₄, while LTB₄ is associated with cough and asthma. Among them, Licorice showed optimal inhibition effect for PGE₂ and LTB₄, possibly by inhibiting 5-LOX and the production of LTB₄, the latter could inhibit COX-2 producing PGE₂. This study also found that Huang Lian Jie Du Decoction showed significant inhibition effect in the LTB₄ pathway, but only weak inhibition of the PGE₂ pathway, which may be the mechanism for the treatment of symptoms associated with cough or asthma^[37]. The *Belamcanda sinensis* is a common Chinese medicine for treating cough. Its extract can inhibit the expression of COX-2 protein in the lung tissue of model animals and reduce the release of metabolites PGD₂, TXB₂ and 11HETE, also effects release of the enzyme pathways 11, 12-DHET, 14, 15-DHET, slow down the progression of inflammation; it is verified that the anti-airway inflammation mechanism of the *Belamcanda sinensis* extract is related to the cyclooxygenase and arachidonic acid metabolism network^[13,38].

Inflammatory factors can be divided into pro-inflammatory factors and anti-inflammatory factors. TCM for treating chronic cough can achieve anti-inflammatory effects by regulating inflammatory factors.

Wang Mi-Na has observed the curative effect of TCM on children with allergic cough. The control group was given symptomatic treatments such as anti-infection, sucking, oxygen inhalation, antitussive and sedation, and montelukast sodium tablets were taken orally; The experimental group was treated with Sang Xing Zhu Ru Er Chen in addition to the treatments for control group (prescription: Folium mori, Poria, Dark Plum, Fritillaria thunbergii, Honey-fried Flos Farfaraes, Bitter apricot kernel, bamboo shavings, ginger Pinellia, Pericarpium Citri Reticulatae,

Licorice). The course of treatment was 2 months. After treatment, the improvement of inflammatory indexes such as LTS, CRP, IL-6 and IL-8 in the study group were significantly better than that in the control group^[39].

Zhou Chang-Hua divided 76 children with cough variant asthma randomly into two groups, 42 cases in the treatment group and 34 cases in the control group. The control group was given salbutamol sulfate tablets combined with ketotifen fumarate tablets orally; the treatment group was added with Zhi Ke Yi Qi granules (composition: Astragalus membranaceus, Bighead atractylodes rhizome, Cinnamon Twig, Pericarpium Citri Reticulatae, Bitter apricot kernel, Ephedra, Licorice), the course of treatment was 1 month. IL-4, IL-5, IL-6, IL-8 and IgE were decreased in the two groups after treatment ($P < 0.05$), and the treatment group was better than the control group^[40].

Clinical symptoms of children with CAV can be treated with Huangqi granule combined with auricular acupoint, maybe because that the treatment can reduce TNF- α , IL-4, EOS and IgE levels and raise IL-10 levels^[41].

Shufeng Huatan Tongluo Decoction combined with acupoint application, should give a better clinical outcome for CAV children. That maybe May be related to the decrease of serum EOS, IL-4, IL-5^[42].

Modified Liu An Decoction of TCM (composition: Rhizoma Pinelliae, Tangerine, Poria, Bitter apricot kernel, Semen Brassicae, Licorice, bryozoatum, Lepidium seed, Trichosanthes kirilowii Maxim, gallbladder, Fried Radish seed) has a better therapeutic effect on CVA rats. Its mechanism may be to improve cough symptoms and reduce EOS in CVA rats by reducing serum TNF- α and IL-5 levels, to achieve the purpose of treating CVA^[43].

MMP-9 promotes the development of airway inflammation and hyperresponsiveness, while TIMP-1 is an MMP-9 inhibitor that can be secreted by a variety of inflammatory cells. Professor Xu Rongqian's receipt of Jia Wei Xiong Xie Powder (Ligusticum wallichii, Scorpion, Asarum, Peach kernel, Pinellia ternata, Long pepper, Chinses Angelica, Cynanchum glaucescens, Fructus Schisandra chinensis) can improve the pathological damage of lungs in CVA model rats. Infiltration of inflammatory cells can reduce the number of coughs in the model rats, and down-regulate the expression of matrix metalloproteinases-9 (MMP-9) and tissue

inhibitor of metalloproteinase-1 (TIMP-1) in the lungs of model rats^[44]. MMP-9 and TIMP-1 mRNA expression in lung tissue inhibited airway remodeling in CVA model rats^[45].

Xiao Er Fei Ke granules (composition: Astragalus membranaceus, Pericarpium Citri Reticulatae, Ventriculi galli mucosa, Arisaema, Flos Farfaraes, Aster, Trichosanthes kirilowii Maxim, Adenophora stricta, Radix Ophiopogonis, Cortex mori, Fruit of Chinese wolfberry, Turtle shell, Cortex Lycii, Artemisia annua, Chinese rhubarb, Cinnamon Twig, Rhizoma zingiberis) can effectively reduce the degree of cough and shorten the course of cough, facilitate the cure of cough after infection. The disappearance rate of cough and the clinical efficacy of Chinese medicine can significantly improve the quality of life of patients. Its mechanism may be related to down-regulation of serum procalcitonin gene-related peptide (CGRP), cysteinyl leukotriene (Cys LTs), tumor necrosis factor- α (TNF- α), interleukin-8 (IL-8) levels are associated with reduced airway inflammation, reduced airway hyperresponsiveness, and cough reflex sensitivity^[46].

Zhao *et al.*^[47] divided the children into two groups and given different treatments according to their etiology. The children in the control group were treated with Budesonide aerosol inhalation. The experimental group was given the treatment of Hua Tan Qu Yu Decoction besides the treatment in control group (composition: Pinellia ternata, Pericarpium Citri Reticulatae, Poria, Mangnolia officinalis, Bitter apricot kernel, Flos Farfaraes, Asters, Semen Brassicae, Radish seed, Fried Atractylodes rhizome, Licorice). It was observed that after treatment with Hua Tan Qu Yu Decoction, the peripheral blood IFN- γ level was significantly increased, and the levels of TNF- α and IL-4 were significantly decreased. It was proved that drugs of dissipatidissipating phlegm and removing blood stasis can improve cough symptoms by regulating inflammatory cytokines and have anti-inflammatory effects^[47].

Taken the Xuan Shen Sheng Ma Decoction twice in the morning and evening, 14 days course, can significantly lower the levels of TNF- α , IL-6 and IgE to treat chronic cough in children^[48].

It can be seen from the above that the mechanism of TCM in the treatment of chronic cough in children may be related to the inhibition of inflammatory factor expression, then improving chronic airway inflammation

and reducing airway hyperresponsiveness. Western medicine treatment of chronic cough focus on elimination of etiology. Its basis is the treatment of cause, anti-inflammatory, antibacterial, symptomatic treatment^[49]. While TCM treatment focuses on syndrome differentiation. However, the internal molecular mechanism for TCM treatment of chronic cough is not very clear, so it should be studied more deeply.

6 Problems and prospects

Chronic cough is a common disease of children's respiratory system, and its causes are different from those of adults. Chronic airway inflammation and high airway response are important causes of chronic cough in children. Traditional Chinese medicine (TCM) treatment of chronic cough can relieve acute symptoms and regulate overall inflammation. This treatment reduces the sensitivity of the airway, thereby controls the onset of coughing. The anti-inflammatory effect of TCM to treat children's chronic cough is mainly by adjusting the HPA axis to affect the arachidonic acid metabolic network, and ultimately achieve the effect of enhancing anti-inflammatory factors, inhibiting the expression of inflammatory factors, and inhibiting airway remodeling. TCM can reduce airway inflammation through a variety of treatments for chronic cough.

Clinical and experimental studies have shown that Chinese medicine is effective in treating chronic cough in children, but there are still the following problems: a. The understanding of the etiology and pathogenesis of chronic cough is not uniform; b. Lack of clinical multi-center, large sample evidence-based medicine research data; c. For the treatment of chronic cough with TCM, it focuses on clinical efficacy and lacks the detection of related laboratory indicators; d. Lack of research on the effective ingredients of prescriptions; e. The anti-inflammatory mechanism of TCM in the treatment of chronic cough is mostly the detection of one or several inflammatory indicators, and there is a lack of systematic and detailed research. Therefore, we need to screen and summarize the studies of TCM for the treatment of children's chronic cough, find out representative drugs or prescriptions for basic research, and conduct more systematic and in-depth research on the anti-inflammatory mechanism of cells, molecules, genes,

etc. The study on the fangjimic basis of prescription with definite curative effect is helpful for the popularization and application of traditional Chinese medicine prescription in recent years, For example, heat-stable decoctosomes (ELNs) from decoctions may be the main body to exert the clinical curative effect, while sRNAs, such as sRNA-m7 in *rhodiola crenulata* and sRNA-6 in *Taraxacum mongolicum*, exhibit potent anti-fibrosis and anti-inflammatory effects in the ELNs^[50]. So we can study the therapeutic mechanism of Chinese herbal medicine for chronic cough in the direction of omics.

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中药抗炎治疗小儿慢性咳嗽的研究进展*

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摘要 慢性咳嗽是儿童呼吸科门诊的常见疾病, 病因具有多样化和年龄差异. 现代医学认为神经源性气道炎症是慢性咳嗽的重要原因, 多采用抗炎、抗过敏药物治疗. 中药治疗儿童慢性咳嗽遵从整体观念和辨证论治, 主要从风、痰、虚论治, 具有确切疗效. 通过查阅文献, 本文对治疗儿童慢性咳嗽的中药进行了总结, 并对其抗炎机制进行综述. 临床研究发现, 依据中医扶阳理论辨治儿童慢性咳嗽, 可获得良好疗效, 在此一并进行简要阐述.

关键词 中药, 慢性咳嗽, 抗炎, 儿童

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