The History and Outlook of Animal Drugs Treating Asthma, Chronic Bronchitis, and Haze Episode-induced Respiratory Diseases

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Abstract: Animal drugs have been historically applied in Chinese remedies for more than two thousands. It was reported that Chinese medical animals consisting of 1,590 species took up 12.5% of the total number of all TCM resources. Those animal drugs such as, earthworm, gecko, *periostracum cicadae*, and scorpios, of commonly used in China, are very remarkable and traditional for the treatment of asthma or chronic bronchitis. This review presents research advance of animal drugs possessing significant implications for the development of novel anti-asthma or chronic bronchitis drugs. The experimental studies and clinical efficacies against asthma and chronic bronchitis of animal drugs were summarized herein. Moreover, the potential utilization of animal drugs on inhibiting haze/fog induced respiratory diseases was also discussed.

Keywords: Animal drugs, asthma, chronic bronchitis, medicinal insects, respiratory disease.

INTRODUCTION

Animal drugs used in China has a rather long history. As an example, China began to use bees as early as 3,000 years ago. Farming of pearl and oyster, clinical applications of acutobin antler, musk, gelatin, etc. in China have over 2,000 years of history [1]. As reported in 2,000 years ago, the earliest extant Chinese Pharmacopeia "Shennong Bencao Jing" (Shennong's Herbal Classics) recorded animal medicines for 65 species. "Xinxiu Bencao" (The Newly Revised Materia Medica) appeared in 659 AD described 128 kinds of animal medicines; "Bencao Gangmu" (Compendium of Materia Medica) written in 1590 AD contains 460 kinds of animal medicines. "Medicinal Fauna of China" (1979 edition) collected 1,257 kinds of animal medicines. Publishing in 1979, the "The Dictionary of Traditional Chinese Medicine" containing for 5,767 species of TCM items, whilst 740 kinds of them are animal-oriented drugs [2]. The investigation result of "Traditional Chinese Medicine Resources to China Records" [3] indicated that, China has medicinal animals for 1,590 species, accounting for 12.5% of the total number of all TCM resources. Moreover, western countries also have historically used animal organ to combat disease, but only referred it as the "organ preparations" previously because of its effective components is not quite clear. Since 1820s, researchers begin to gradually understand the effective components in several animal organs, which lead to the discovery of the active substances such as insulin, thyroxine, etc. Between 1840s to 1850s, people subsequently found the important role of adrenal cortical hormone and pituitary hormones on human body, thereafter caused the increasing of drug variety of this kind. Since 1960's, along with the technology matures upon isolation, separation and enzyme purification from organisms, a new era in the application of enzyme preparations in medicine has commenced. This class of drugs has increased to a number of 140 at 1970's, and is still increasing. More and more preparations extracted from animal tissue, organs, glands, body fluids, secretions (toxin) and the skin, bone, horn, armour and placenta have been utilized for treatment of various diseases, which exhibit their effectiveness. This formulation is also often referred to as "animal biochemical drugs". This article mainly aims at the experimental study of animal source drugs to treat asthma and chronic bronchitis disease, while their clinical efficacies were summarized, both are to provide new ideas and methods for the research and development of new anti-asthma drugs. In addition, the description of the potential of animal drugs upon prevention Chinese from haze pollution was also discussed.

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ISSN: 1927-3037/14

1. ANIMAL SOURCE DRUGS TO TREAT ASTHMA

Asthma is a kind of chronic inflammatory airway diseases characterized by the features of airway hyperresponsiveness (AHR), chronic airway inflammation, and airway remodeling, and the patients with cough, wheezing, expiratory dyspnea, chest pain, and cough as the main symptoms [4]. Some patients may be accompanied by reversible airway obstruction, mucus production increase, eosinophil infiltration, and non-specific respiratory hypersensitivity [5]. The global prevalence of asthma was 1% – 18%, and it is estimated that the world has 300 million asthma patients [4]. Currently the front-line drugs for the treatment of asthma are glucocorticoids, which, however, can not thoroughly cure such disease. Many drugs against asthma was not sufficient and most prescription drugs possess side effects [6], thus promoting the development of alternative therapies. The investigations such as western and Asian herbs, acupuncture treatment, all kinds of body control (body manipulation), psychological therapy, homeopathic (homeopathy), research and desensitization treatment have dramatically increased over recent decades [7]. Chinese medical workers has also accomplished series of systematic research for seeking alternative medicines and folk medicines against asthma, during their researches upon the animal medicines traditionally used as traditional Chinese medicines. Researchers have found a number of animal drugs with significant efficacy which is summarized as follows:

1.1. *Periostracum Cicadae*

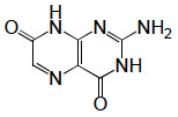
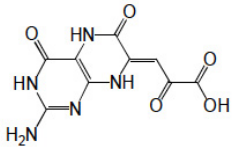
Periostracum Cicadae was initially recorded for clinical utilization in ancient Chinese medical book "Ming Yi Bie Lu" (Transactions of Famous Physicians) (*ca*. 150 AD). In traditional Chinese medicine it indicates the shedding hull of the larvae of the black grasshopper *Crytotympana pustulata* Fabriciousyo (Fabricius) upon feathering off (Figure **1**). It was recorded as an alternative clinical drug upon asthma early at another ancient Chinese medicinal book "Yao Xing Lun" (Treatise on Property of Drug) (Tang dynasty, *ca*. 750 AD) [8]. The description on "Chinese Pharmacopoeia Practical Manual" recounts that *Periostracum Cicadae* demonstrates significant anticonvulsant, antipyretic, analgesic, relieve bronchial smooth muscle spasm, immunosuppressive and anti-allergic effects, as well it plays a protective role the cell membrane of erythrocyte by improving the combining function with oxygen of the erythrocytes [9]. Zhang *et al*. [10] indicated that *Periostracum Cicadae* showed certain protective effect on histamine-induced asthma model. Another investigation confirms that *Periostracum Cicadae* exhibit apparent soothing asthma efficacy on an asthma model induced with histamine [11]. Xu [12] performed a treatment of acute bronchitis and cough for 64 cases by a cough granule made from Periostracum Cicadae. 59 cases were cured, while the cure rate is 92.18%. The total effective rate was 95.31%.

1.2. Scorpio

Traditional Chinese medicine refers the drying whole of Scorpion (*Buthus martensii* Karsch), Buthidae, Scorpiones (Figure **1**). Fresh scorpion contains scorpion venom, trimethylamine, betaine, sulfuric acid, palmitic acid, stearic acid, cholesterol, ammonium salts, lecithin, and picric acid Gai (a kind of column picrate stored in the same poison venom gland with the scorpion venom) [13]. Scorpion venom is mainly composed of protein and non-protein parts [14], the former is actually a kind of protein similar with the snake neurotoxin, which can have an effect on the adrenergic nerve and may inhibit the reduction of airway caliber (bronchoconstriction), thus relieve respiratory spasm [15]. Further pharmacological studies [16] indicated that the "Scorpion-Scolopendra Mixture" can improve the airway inflammation in asthmatic model rats, while reducing the thickness of the bronchial wall and smooth muscle, reducing the proliferation of collagen fibers. Thereof the mixture showed certain improvement or delay effects on airway remodeling. Meanwhile, modern medical research suggests that early suppression of airway remodeling is a new target for bronchial asthma intervention [17], which reveals the outlook for Scorpion utilization upon the treatment of asthma diseases.

1.3. Ants

Ants are a complex group of organisms. Taxomomically these social animals attributed to Insecta, Hymenoptera, Formicidae. In recent years, pharmacological studies confirmed that *Polyrhachis vicina* Roger, PVR, possess clear efficacies of anti-inflammatory, protection of liver, relieving asthma, analgesic, and therefore are clinically used for the treatment of rheumatoid arthritis, hepatitis, spermatorrhea, anemia and other diseases [18,19]. According to the research reports of Zhao *et al*. [20], the alcohol extract of *P. vicina* can antagonize acetylcholine-induced bronchial asthma and intestinal cramps, and against $BeCl_2$-caused intestinal cramps.

Periostracum Cicadae	**Scorpio**
(typical component)	(typical component)
Isoxanthopterin  Erythropterin 	[K^+ ion channel neurotoxin] CTX: FTNVSCTTSKECWSVCQRLHNTSRG KCMNKKCRCYS (4294.1) NTX: IINVKCTSPKQCSKPCKILYGSSAGA KCMNGKCKCYNN* (4195.0) KTX: GVEINVKCSGSPQCLKPCKDAGMRF GKCMNRKCHCTPK (4150.2)

Lumbricus	*Gekko gecko* (**Gekkonidae**)
(typical component)	(typical component)
Lumbritin, lumbrofebin, lumbrukinase, terrestro-lumbrilysin, lumbitin, 1-O-alkyl-2-acyl-sn-lycerophosphocholine, etc.	Carnosine, carnitine, sphingomyelin, phosphatidylethanolamine, phosphatidic acid, phosphatidylcholine, lysolecithin, etc.

Figure 1: Typical TCM animal drugs treating asthma and chronic bronchitis, as well as their characteristic components.

Presumably the mechanism of its relieving asthma or antispasmodic effects are related with anticholinergic and direct inhibition of smooth muscle.

1.4. Snake Bile

Snake bile is a commonly used Chinese medicine, first recorded in "Ming Yi Bie Lu" (Transactions of Famous Physicians) (*ca*. 150 AD), means the gallbladders of Elapidae species such as cobra *Naja naja* Linnaeus, Gold-banded krait *Bungarus fasciatus* Schneider, or Colubridae species squirrel snakes *Ptyas korros* Schlegel. According to reports, an admixture made from snake bile, bezoar, and *Fritillaria cirrhosa* Don. can not only attenuate guinea pig asthma induced by histamine and acetylcholine mixture, but also reduce the number of animals developing asthma [21]. Cai *et al*. [22] compared the pharmacological efficacy of "Shedan Chuanbei Pulvis" (made from 5/6 of snake bile and 1/6 of *Fritillaria unibracteata* Hsiao et K. C. Hsia) and "Shedan Hubei Pulvis" (made from 5/6 of snake bile and 1/6 of *Fritillaria hupehensis* Hsiao et K. C. Hsia) and found both formulation exhibited

strong relieving activity against asthma (P <0.05). Zhang *et al*. [23] treated the bronchitis children with "Shedan Zhuli Mixture" (made from snake bile and bamboo juice etc.) for 82 cases, among which 62 cases were cured, 18 cases improved, 2 cases invalid, while the total efficiency was 97.5%.

1.5. Snake Venom

Ahylysantinfarctase is a new anticoagulant and thrombolytic agents isolated from snake venom with arginase as the main component. Liu *et al*. [24] conduced clinical study on 22 patients with bronchial asthma. The patients were randomly divided into treatment group (12 cases administered with ahylysantinfarctase 0.5U/d intravenous infusion for two weeks) and positive control group (10 cases, inhaled corticosteroid for two weeks) for comparison. The conventional treatments of two groups are the same, including aminophylline, antibiotics treatment for two weeks. The results showed that 9 cases of the treatment group were cured, the average cure days is 5.9 d; 7 cases in the control group were cured with the average cure days of 11.5 d; both groups have 2 cases improved, and 1 case invalid, respectively. The effective rates of the two groups showed no statistical significance, but the number of cure days in the treatment group was significantly shorter than that of the control group, whilst the adverse effects of ahylysantinfarctase group is smaller than corticosteroids group volunteers.

1.6. *Placenta Hominis*

Placenta hominis is dried product of healthy human placents, contained in the ancient Chinese "Supplement to Materia Medica" (Ben Cao Shi Yi) (741 AD). Lü *et al*. [25] reported that the therapeutic use of *placenta hominis* against 34 bronchial asthma patients at the remission period, including 12 cases of bronchial asthma accompanied with chronic bronchitis and 3 cases complicated with of pulmonary heart disease, and the total efficiency is 88.2%. Jiang *et al*. [26] taking traditional therapeutic methods combined treatment with *placenta hominis* upon 64 cases of asthma children, after a 2-year follow-up after treatment observation, the therapy were effective on all treated patients while their improvement rate is 57.15%.

1.7. *Bombyx Batryticatus*

Bombyx batryticatus means death body of insects *Bombyx mori* Linnaeus., Saturniidae, Lepidoptera. After their fourth molt into the domancy state these 4-5 instar larvae were infected or artificial inoculated with *Beauveria bassiana* Bals Vuillant to death before harvest. *Bombyx batryticatus* contain 67.44% of protein, 4.38% of fat, while the protein has a role in stimulating the adrenal cortex [27], which can enhance the body's defense capabilities and regulatory functionalities. In addition, *Bombyx batryticatus* also contain quercetin and kaempferol, whilst quercetin has good effects of expectorant, cease cough, and have certain efficacy of relieving asthma [28]. Li [29] using *Bombyx batryticatus* in compatibility with insects such as scorpion, earthworm, cicada and other drugs upon clinical treatment of cough-variant asthma for 42 cases, and obtained satisfactory results. Among which 17 cases were clinical controlled, 14 cases markedly improved, 8 cases effective, 3 cases ineffective, and the total efficiency of 92.9%; while the positive control group administered 0.025 mg (2 times/d) of procaterol hydrochloride tablets (Otsuka Pharmaceutical Co., Ltd.) on 40 patients, 4 cases were clinical controlled, 12 cases markedly effective, 10 cases improved, 14 cases ineffective, and the total efficiency was 65.0%. The comparison between two groups has a significant difference (P <0.01).

1.8. Bee Venom

Bee venom refers to the defensive venom secreted by *Apis mellifera* Linnaeus, *A. florea* Fabricius, *A. dorsata* Fabricius, *A. cerana* Fabricius, *A. andreniformis* Smith, and *A. laboriosa* Smith. Such secreted venom *via* the poison glands and accessory glands of the worker bees exhibited as a transparent liquid with aromatic odor, usually stored in the poison sac, and was discharged from the stinger upon sting. It has been proved to possess several peptide and proteins, some enzymes, histamines, acids, amino acids, and trace elements [30]. Scientists have performed broad research upon the major component of bee venom [31] such as phospholipase A2, hyaluronidase, melittin, apamin, mast cell degranulation peptides and secapin. It has reported that 280 cases of asthma patients were conducted on bee stings and bee venom injection. The results show a satisfactory therapeutic effect, since the therapy can stop asthma attacks, attenuate breathing difficulties, and all test patients conscious with bee venom has expectorant effect [31,32]. The long-term effective rate of bee stings and bee venom injection therapy attached 80 %. Long-term clinical practice has proved that bee venom treatment of bronchial asthma and other allergic diseases should take a light dosage, and bee venom

therapy is more effective against simple asthma and pediatric asthma than adult patients with complications [30-32].

2. ANIMAL MEDICINE IN TREATING CHRONIC BRONCHITIS

Chronic bronchitis is caused by infectious or non-infectious factors inducing a kind of chronic non-specific inflammation attacking tracheobronchial mucosa and surrounding tissues. As it often occurs in the elderly, therefore is commonly known as the old chronic bronchitis. The pathology is characterized by bronchial wall edema, bronchial gland hyperplasia, increased mucus secretion, and smooth muscle spasm. Because of recurrent respiratory tract infections, the patient suffers long-term hypoxia, declined immune function, leading to recurrent attacks, and therefore hard to be cured whilst has a difficult recovery [33]. According to statistics, in the Chinese elderly over 50 years the incidence rate is of about 15 % to 30 %. As the number of patients with chronic bronchitis increased in recent years, this recurring illness keep bringing a more serious impact on the patient's daily life [34]. This paper also summarized the clinical and pharmacological studies of some animal medicines upon treatment to old chronic bronchitis, in order to provide a broader theoretical foundation for the R&D of new animal drugs against old chronic bronchitis.

2.1. Clamshell

In TCM, clamshell indicated the shell of *Meretrix meretrix* Linnaeus or *Cyclina sinensis* Gmelin (Veneridae) which were harvested and dried as medicine. Deng *et al*. [35] reported that 20 g powder clamshells mixed 10 g of indigo is effective on the treatment of chronic bronchitis, cough and phlegm (per serving 5 g, 2 times a day).

2.2. Pillbugs

Pillbug in TCM indicates dried beetles of *Armadillidium vulgare* Latreille or *Porcellio scaber* Latreille. According to clinical reports [36], 247 cases of chronic bronchitis were taken pillbug as treatment which obtained a good curative effect; recent cured in 24 cases, effective in 71 cases, improved in 107 cases, and 45 cases ineffective, the total effective rate was 81.8 %. For asthmatic old chronic bronchitis the total efficiency was 83.4%, while to the simplex old chronic bronchitis patients the total efficiency was 79.4%. The pillbugs demonstrated better effects for those patients of deficiency of kidney-YANG and cold type, which especially has some effects against their dyspnea, cough, and sputum [36].

2.3. Acutobin

Acutobin is a purified thrombin-like enzyme isolated from the venom of *Agkistrodon acutus* Guenther (Crotalinae, Viperidae) [37]. Qin Rong [38] reported that the application of acutobin injection with antibiotic therapy in 30 cases of patients with acute exacerbation of chronic bronchitis and received satisfactory results: after 5 days' treatment, markedly effective in 20 cases, 8 cases effective, 2 cases ineffective, while 1 case of 80-year-old patient died due to pulmonary heart disease.

3. DRUGS OF ANIMAL ORIGIN POSSESSING CURATIVE EFFECTS BOTH ON ASTHMA AND CHRONIC BRONCHITIS

Many animals have been recorded to be ethnomedicinal drugs to treat both asthma and old chronic bronchitis, such as earthworm, gecko, cantharidin, and pearls. The following are brief introduction of their clinical efficacy and pharmacodynamic study results.

3.1. Lumbricus

3.1.1. Pharmacodynamic Study Overview Upon Lumbricus

Lumbricus (Earthworm) in TCM means the dry bodies of Annelida, Megascolecidae animals such as *Pheretima aspergilum* E. Perrier, *Pheretima vulgaris* Chen, *Pheretima guillelmi* Michaelsen, or *Pheretima pectinifera* Michaelsen, which all above owns a Chinese name of "Di Long" (Figure **1**). Earliest records of clinical use of Lumbricus appeared in the "Shen Nong's Herbal Classic" (Shen Nong Ben Cao Jing) with a broad effectiveness. At Ming dynasty (1578 AD) Li Shi Zhen recorded in the "Compendium of Materia Medica" (Ben Cao Gang Mu) that the earthworms have certain effect against asthma [39]. In the past three decades, pharmacological studies and chemical composition investigations of Lumbricus have made great achievements and significant progress [40-42]. Modern pharmacology studies have shown that the earthworms display various effects such as antibacterial and anti-inflammatory [43], antioxidant [44], anticoagulants [45], anti-tumor [46], cease cough and asthma, and reduce blood pressure, which is therefore popular clinically applied in the treatment of cerebral thrombosis, hypertension, bronchial asthma

burns, and ulcers. In addition, more in-depth research of this animal drug have accomplished in the treatment of respiratory diseases.

3.1.2. Experimental Study of Earthworm in Asthma Treatment and Clinical Efficacy Observation

Zhou *et al*. [47] investigated the anti-inflammatory and anti-allergic effects of the earthworm acidic extract with allergic asthma in mice model, and the results suggested that earthworm acid part can inhibit the levels eosinophil (EOS) in bronchoalveolar lavage fluid (BALF). It can also regulate Th1/Th2 balance which plays an anti-inflammatory and anti-allergic effects in mouse allergic asthma model, while more action mechanisms needs further experimental study. Wu *et al*. [48] reported that the earthworm injections can relieve bronchospasm in asthmatic rats model, reducing airway resistance and improving pulmonary function. Earthworm can reduce the total number of cells, albumin and leukotriene levels in the BALF of allergic asthma guinea model; particular inhibited the increase of eosinophil (EOS), and prevents this cell from activation, since the activated EOS will release variety of toxic proteins which can directly damage epithelial [49]. Yuan *et al*. [50] found the Earthworm capsule ("Dilong Capsule") can improve the expression of C-JUNmRNA in the treatment of asthma; while studies have shown that the expression of C-JUN is an early marker of inflammatory cell activation and was related with inflammatory cell synthesis, and the secretions of cytokines and inflammatory mediators [51]. Ding [52] applied Earthworm Erchen Decoction (a polyjuice potion including earthworm) in treatment of cough variant asthma, the treatment group (40 patients) were cured in 25 cases, effective in 9 cases, 4 cases effective, 2 cases ineffective, while the total efficiency was 95.0%; in the control group (40 patients, administered methoxyphenamine hydrochloride and Noscapine, aminophylline, and brompheniramine maleate complex) were cured 17 cases, markedly effective in 7 cases, effective in 6 cases, 10 cases ineffective, and the total efficiency was 75.0%; the total efficiency of the two groups were significantly different (P <0.05).

3.1.3. Earthworm Treatment of Chronic Bronchitis

Earthworm is not only effective in the treatment of bronchial asthma, but its efficacy upon chronic bronchitis is also quite satisfactory. Pharmacological studies have shown that, earthworm can antagonize histamine and pilocarpine, and is able to enhance the anti-allergic effects. However, in the treatment of chronic bronchitis, earthworm was more often utilized in a compatibility prescription mode. Yang *et al*. [53] used "Huoxue Tongluo Decoction" in the treatment of chronic bronchitis and achieved good results. The researchers found that the earthworm has a significant role in relaxation of bronchial, and can antagonize histamine and pilocarpine contraction of the bronchi. Zhu [54] used "Xiaoqinglong Decoction" adding earthworm in the treatment of 100 cases of acute exacerbation chronic bronchitis patients, the results indicated that 49 cases were markedly improved (wheezing cough and expectoration disappeared), 41 cases improved (wheezing cough and expectoration were apparently relieved), 10 cases ineffective (wheezing cough and expectoration showed no improvement); the total effective rate was 90 %.

3.2. Gecko

In TCM gecko means dry body of *Gekko gecko* Linnaeus (Gekkonidae) with a Chinese name of "Gejie" (Figure **1**), which has curative effects such as anti-tumor, asthma, hormone-like, and anti-inflammatory, etc. Gecko could significantly prolong the incubation period of asthma in guinea pigs, effectively inhibit their asthmatic reaction, thus indicating that Gecko has a significant role in asthma [55]. Li [56] gave Gecko anti-asthma pills (Gejie Fangchuan Pills) to 70 patients with bronchial asthma for treatment, and investigated its clinical efficacy. The results showed that a significant difference existed between the treatment group and the control group, while the Pills can significantly reduce the serum IgE, improving one second forced expiratory gas volume and index of peak expiratory flow rate. Zhang *et al*. [57] using Gecko "Dingchuan Capsule" to treat 150 patients with bronchial asthma, and the clinical observation revealed that this Gecko formulation owns a good efficacy of relieving asthma. Zou *et al*. [58] again reported that Gecko "Dingchuan Capsules" exhibited excellent clinical effect of relieving asthma, expectorant, cease cough, anti-inflammation, immunity enhancement, antibacterial and anti-allergy, etc. while none of the toxic side effects have been found. Luan [59] described a large-scaled clinical investigation of Gecko "Dingchuan Capsules" upon chronic bronchitis and asthma patients for 206 cases, the treatment obtained satisfactory results with the total effective rate of 94.7 %.

3.3. Cantharides

Cantharides used in TCM indicates the dry body of *Mylabris phalerata* Pallas or *Mylabris cichorii* Linnaeus

(Meloidae). TCM physicians often take the acupoint application of cantharidin powder sticking to the patient, make sticking parts congestion, blistering, which may play a similar role like moxibustion, that is the "Tian Zhi" (natural moxibustion), also called vesiculation therapy. This therapy is mainly used for psoriasis, neurodermatitis, joint pain etc.. Guo *et al*. [60] compared the clinical efficacies of Cantharides ointment (compound Mylabris made of cantharidin powder with cloves and cinnamon) and traditional medicine vesiculation treatment on bronchial asthma; 110 patients were randomly divided into Cantharides ointment group (55 cases) and traditional "Tian Zhi" (vesiculation therapy, made from white mustard seed, rhizoma corydalis, asarum, raw kansui) group (55 cases), sticking the corresponding drugs to the testee and to compare the clinical efficacy as well as the quality of life of the testee. The results showed that total effective rate of Cantharides ointment group was 94.55%, higher than that of the traditional "Tian Zhi" (vesiculation therapy) group (82.27%); their score improvements of activity limitation, asthma status, irritants original of reaction etc. are significantly better than those in the control group (P <0.01 or 0.05), which displayed that the Cantharidin ointment treatment of bronchial asthma has a significant effect. Wu *et al*. [61] performed the clinical trial of applicator acupuncture of Cantharidin ointment treatment on 200 cases of asthma and chronic bronchitis patients. The results were satisfactory: in 200 cases were cured 65 cases (32.5%); markedly effective in 63 cases, accounting for 31.5%; improved in 62 cases, accounting for 31%; ineffective in 10 cases, accounting for 5.0%; the total effective rate was 95 %.

3.4. *Nidus Vespae*

In TCM *Nidus vespae* (Chinese name "Feng Chao") means the dry nests of wasp *Polistes olivaceous* (De Geer), *Polistes japonicus* Saussure or *Parapolybia varia* Fabricius [62]. Shen *et al*. [63] using the "Cough Rehabilitation Capsule" (made of ginseng, Placenta, Gecko, dogwood, Honeycomb, Oriental Arborvitae, orange peel, licorice, etc.) on the treatment of patients with chronic bronchitis for 209 cases, the total effective rate was 97.36%. Fan *et al*. [64] using self-made "Hive Shegan Pulvis" (made from *Nidus vespae* and *Belamcanda chinensis* L. Redouté) in the treatment of bronchial asthma for 40 cases, of which 34 cases were markedly effective, 5 cases improved, and 1 case ineffective, the total effective rate was 97.5 %. Jia [65] reported that the application of the drying *Nidus vespae* powdered with a little Gecko powder on the treatment of senile asthma, each administration for 0.5 g, 3 times per day, and received a satisfactory curative effect.

3.5. Pearl

Chinese medicine pearl mainly means the particulate matter formed by stimulation occurred on bivalves mantle of *Pteria martensii* Dunker (Pteriidae), *Hyriopsis cumingii* Lea (Unionidae), *Cristaria plicata* Leach (Anodontidae) etc.. According to Xu's clinical report [66], 275 cases of asthma patients were treated with "Zhubei Dingchuan Wan" (made from pearl and *Fritillaria cirrhosa* D. Don), the effective rate of the testees was 86.5%. In the treatment of 84 cases of chronic bronchitis by "Zhubei Dingchuan Wan", the effective rate was 86.9%, and exhibited a satisfactory long-term late result.

4. DISCUSSION AND OUTLOOK

The pathogenesis of asthma is full of complexity. Some scholars believe that asthma is induced by the balance disorder of body Th1/Th2 (T helper cells called Th cells which can be divided into Th1, Th2, etc.), since normal people take Th1 as the dominant cell, while patients with asthma tends to over-differentiate Th0 to Th2 in the body. This leads to a dominant Th2 cell status, thereof the Th1/Th2 imbalance is an important foundation of asthma [67]. Dong [68] pointed out that the key mechanisms of asthma might be attributed to the imbalance between Th1/Th2 cells, the reduction of the Th1-type cytokines IFN-C, and the increasing secrete of pro-allergic cytokines IL-4, IL-5, IL-13 of Th2 cells. Nevertheless, nowadays more and more scholars tend to present IL-13, IL-4 variation plays an important role in the occurrence of asthma [69-71]. Walsh's studies [72] suggested that among the various cells participated in airway inflammation such as eosinophils (EOS), macrophages, mast cells, T-lymphocytes cells played a key role, which is closely related to the severity of the diseases in both the degree of airway infiltration and the incidence of asthma. Qiu *et al*. [73] showed that the NF-κB system may induce the expression of GATA-3, thereby promoting dominant responses of Th2 cell, leading to airway inflammation.

This review summarizes animal drugs applied for the treatment of asthma or old chronic bronchitis. It could be found that Chinese pharmaceutical scientists has accumulated a wealth of experience in the clinical application, find fact that animal drugs were popularly used in the treatment of asthma or old chronic bronchitis. Not only the single dose of earthworm,

scorpion, silkworm, ants, cantharidin, pillbugs, centipedes etc. can afford a satisfactory curative effect, but also the insect drug compatibility demonstrated significant efficacy [74]. Nevertheless, the experimental study of insect drugs on bronchial asthma intervention mechanism has just started and thereby is rarely reported. Therefore, further systematic pharmacological studies should be accomplished to determine the therapeutic effect of experienced animal drugs or insect drugs, which is urgently expected to provide a reliable basis for clinical trials of these new drug resources of asthma and old chronic bronchitis.

In addition, it is worth to mention that haze wether is a new phenomenon emerged in China in recent years. The possible negative influences arose by several large-scale outbreaks of haze on human health caused widespread concern in the community. The possible main cause of haze might be the high PM2.5 pollution, since PM2.5 pollution and the coerced chemical contaminants have a significant impact in varying degrees upon human and animal respiratory systems, cardiovascular systems, reproductive and nervous systems, while for the human suffering cancer is also associated responsibilities. Prevention of haze-caused respiratory diseases, especially in patients with asthma and chronic bronchitis caused by haze is a new but urgent theme [75].

Chinese National Development and Reform Commission has established National-local Joint Engineering Research Center of Entomoceutics, which recently performed systematic study of more than 1,300 species of extract and effective part of the medicinal insects. They found that a variety of insect extracts or effective parts can significantly inhibit the acute and chronic inflammation, and inhibit edema in rat smooth muscle relaxation in rodent animal experiments. *In vitro* experiments also revealed that more of the active candidates can enhance TNF-α and inhibit IL-2 etc. The research center is now concentrated on directional filtering of innovative drugs for anti-asthma from those which can effectively inhibit inflammation active parts from insects. Moreover, the chronic obstructive pulmonary disease (COPD) model using guinea pigs has been established for further animal experiments. The experimental results of effective parts of medicinal insects on the IL-4, IL-13, and interfere ability of Th1/Th2 ratio, as well as relevant clinical observation will be published soon. Although the international community has different views on alternative medicine and folk medicines, however, in line with internationally accepted standards and pharmacological study of the model, as well as the standard screening test program, the animal medicine in TCM, especially medicinal insects will remarkably promote the R&D progress in the international fight against the chronic asthma and chronic bronchitis. Apparently, to produce such a landmark heavyweight drugs need collaborative innovation from multiple disciplines, multiple departments across multiple industries working together.

ACKNOWLEDGEMENTS

This work was supported by IRTSTYN (2010-ZY-011), the P-MOST Programme for Yunnan Innovative Research Team, Key Projects of Science and Technology Development Plan of Yunnan Province 2012, 2011 Collaborative Innovation Center of Yunnan Province, and Special Funds for the Development of Strategic Emerging Industries Project in Yunnan Province 2013. We thank Prof. Dr. Joachim Stöckigt and Dr. Zhang Jingxin (Sinofi Co., USA) for the helpful discussions. We are in debt to Prof. Dr. Yang Zi-zhong (N-L JERCE) for the help on entomological taxonomy.

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Received on 25-06-2014 Accepted on 25-07-2014 Published on 11-08-2014

DOI: http://dx.doi.org/10.6000/1927-3037.2014.03.02.5