

Review

The Therapeutic Actions of Traditional Chinese Herbal Medicine Used for the Treatment of Equine Respiratory Diseases

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ABSTRACT

Equine recurrent airway obstruction and summer pasture-associated obstructive pulmonary disease are the major causes of chronic poor performance and exercise intolerance in athletic horses. Conventional treatment includes administration of a bronchodilator, an anti-inflammatory agent, and elimination of the inciting environment. Affected horses usually require life-long medication. If a corticosteroid is being used as the anti-inflammatory agent, an iatrogenic immune suppression and repression of the endogenous adrenocorticosteroid production are the most common side effects. Chinese veterinary herbal medicine provides an alternative long-term therapy with minimal side effects. Four common Chinese herbal formulas, Schisandra 5, Lily Combination, *Bu Fei San*, and Breath Easer have been shown to be useful for treating chronic respiratory disease. The pharmacological mechanisms of the phytochemical compounds present in 23 herbs found in these formulas are reviewed in this article. Active phytochemical compounds in the herbs are found in the form of primary and secondary metabolites. They may possess antimicrobial, antioxidant, anti-inflammatory, antihistamine, or antitussive properties alone or in combination. The evidence for a relevant pharmacological mechanism of the active phytochemical compounds in each herb validates the use of Chinese herbal supplements for treating chronic respiratory problems. These findings emphasize that the development of herbal formulas by ancient Chinese herbalists was conducted cautiously and based on a unique knowledge of pharmacology and toxicology.

Key words: Veterinary medicine; Chronic respiratory diseases; Horses; Herbal medicine; Active phytochemicals; Secondary metabolites.

Equine recurrent airway obstruction (RAO) and summer pasture-associated obstructive pulmonary disease (SPAOPD) are major causes of chronic poor performance and exercise intolerance in athletic horses. Conventional treatment includes administration of a bronchodilator, an anti-inflammatory agent, and elimination of the inciting environment. Affected horses usually require life-long medication. If a corticosteroid is being used as the anti-inflammatory agent, an iatrogenic immune suppression and repression of the endogenous adrenocorticosteroid production are the most common side effects. Chinese veterinary herbal medicine provides an alternative long-term therapy

with minimal side effects.

A significant worldwide increase in the use of natural products has occurred.¹ Consumers who want to be environmentally friendly and health conscious seem to be looking for products obtained from nature. Phytochemicals and herbal supplements are available for a wide range of uses from weight loss to aphrodisiacs. The estimated total sale of herbal products in the United States was over four billion dollars in 2005 with a steady growth trend.¹ Most of the currently available products are formulated for human consumption. There are a limited number of veterinary herbal supplements available.

Herbal medicine is associated with several traditional medicines such as Chinese Medicine, Ayurveda Medicine of India, and folk medicines around the world. It is understandable that animal

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owners who have gained a personal health benefit from herbal supplementation are seeking the same benefit for their pets and performance animals. Therefore, a better understanding of the chemistry, pharmacology, and toxicology of the active phytochemical compounds present in the herbal supplements being used in veterinary medicine is important to both veterinarians and animal owners.

In traditional Chinese veterinary medicine (TCVM), clinical disorders of the respiratory system can be classified into four major patterns (*Bian Zheng*): Allergy Heat, Lung *Yin* deficiency, Lung *Qi* deficiency, and Lung/Kidney *Qi* deficiency. The differences in clinical manifestations of each pattern can be found elsewhere and will not be reviewed here.²

In TCVM herbal medicine, there are four major herbal formulas commonly used to treat equine chronic respiratory diseases: Schisandra 5, Lily Combination, *Bu Fei San*, and Breath Easer (Table 1).² Schisandra 5 is the most recently developed formula. Its TCVM indication includes heaves, Heat-associated allergy, general allergies, and chronic cough due to Lung Heat with *Yin* deficiency.^{2,3}

Lily Combination is modified from the classical antecedent “*Bai He Gu Jin Tang*” from *Yi Fang Ji Jie (Analytic Collection of Medical Formulas)*, written by Wang Ang in 1682).² The TCVM indications for Lily combination include dry cough without phlegm, cough due to Lung/Kidney *Yin* deficiency, red tongue without coating, and a fast thin pulse, while indications for its use in conventional veterinary medicine includes dry cough, chronic bronchitis, and RAO.

Bu Fei San is modified from the classical antecedent “*Bu Fei Tang*” from *Yong Lei Qian Fang (Everlasting Categorization of Seal Formulas)*, written by Li Zhong Nan in 1331).² Its TCVM indication includes Lung *Qi* deficiency, shortness of breath, chronic cough or asthma, pale and wet tongue, deep and weak pulse, and exercise intolerance, while indication for conventional veterinary medicine includes chronic cough or asthma.

Breath Easer is modified from the classical antecedent “*Ge Jie San*” from *Yuan Heng Liao Ma Ji (Yuan Heng's Therapeutic Treatise of Horses)*, written by Yuan Heng in 1608).² Its TCVM indication includes dyspnea/asthma/cough due to

Lung/Kidney *Qi* deficiency, pale and swollen tongue, and weak deep pulse, while the indication for contemporary veterinary medicine includes RAO and dyspnea. A list of the herbal ingredients contained in each formula is found in Table 1.

Pharmacologically active compounds in herbal medicine usually are in the form of primary and secondary metabolites. Primary metabolites include carbohydrates, amino acids, sterols, and nucleotides. They are essential for maintaining general metabolism and normal plant physiology. The primary metabolites are synthesized via diverse enzymatic pathways, which can be found in almost every plant. They possess little or no significant medicinal properties.

In contrast, secondary metabolites are distinctive in each group of plants. They include alkaloids, terpenoids, glycosides, phenolic compounds, phenazines, polyketides, fatty acids, and non-ribosomal peptides. Occurrence of a specific secondary metabolite requires unique biochemical pathways in each group of plants. Until recently the precise physiological function of many of the secondary metabolites has not been identified. It is obvious that both primary and secondary metabolites are essential for plant survival. For humans, the secondary metabolites provide nutrients, natural colors, spices and medicines. Below is a review of the major pharmacologically active secondary metabolites found in 23 Chinese herbs commonly used for treating equine chronic respiratory diseases. Information about the mechanism of the actions of the most important secondary metabolites is also presented. A list of the herbs to be reviewed and their actions are outlined in Tables 1 and 2.^{2,3}

***Bai Guo* (Ginkgo nut), or Ginkgo Semen**

Bai Guo (Ginkgo nut) or Ginkgo Semen, refers to the nut of *Ginkgo biloba*. It is one of the most studied and marketed Chinese herbs around the world. The neuroprotective and anticoagulation properties of *Bai Guo* supplementation are well recognized. The extract from *Bai Guo* contains flavonoid glycosides and terpenoids such as ginkgolides and bilobalides.⁴ Pharmacological tests in humans indicated that *Bai Guo* extract possesses three major physiological properties: improved blood circulation in most tissues and organs, anti-inflammatory and reduced oxidative damage of

Table 1: Herbal ingredients used in 4 common formulas used for treating horses with respiratory diseases

| Pin Yin name | Common name | Scientific name | Formula* | | | |
|-----------------------|-----------------------|--|----------|----|-----|----|
| | | | I | II | III | IV |
| <i>Bai Guo</i> | Ginkgo | <i>Ginkgo biloba</i> . | | | + | |
| <i>Bai He</i> | Lily bulb | <i>Lilium lancifolium</i> , <i>L. brownii</i> , or <i>L. pumilum</i> . | | + | | + |
| <i>Bai Shao Yao</i> | White paeonia | <i>Paeonia lactiflora</i> . | | + | | |
| <i>Chai Hu</i> | Bupleurum | <i>Bupleurum chinense</i> or <i>B. scorzonrifolium</i> . | + | | | |
| <i>Chuan Bei Mu</i> | Tendrilled fritillary | <i>Fritillaria cirrhosa</i> , <i>F. unibracteata</i> , <i>F. przewalskii</i> , or <i>F. delavayi</i> Franch | | + | | + |
| <i>Dang Gui</i> | Angelica | <i>Angelica sinensis</i> . | | + | | |
| <i>Dang Shen</i> | Codonopsis | <i>Codonopsis pilosula</i> or <i>C tangshen</i> . | | | + | |
| <i>Di Long</i> | Lumbricus | <i>Pheretima aspergillum</i> , <i>P. vulgaris</i> , <i>P. guillelmi</i> , or <i>P. pectinifera</i> . | | | + | + |
| <i>Fang Feng</i> | Ledebouriella | <i>Saposhnikovia divaricata</i> . | + | | | |
| <i>Gan Cao</i> | Licorice | <i>Glycyrrhiza glabra</i> . <i>G. uralensis</i> , or <i>G. inflata</i> . | + | + | + | |
| <i>Huang Qi</i> | Astragalus | <i>Astragalus membranaceus</i> . | | | + | |
| <i>Jie Geng</i> | Platycodon | <i>Platycodon grandiflorus</i> . | | + | + | + |
| <i>Mai Men Dong</i> | Ophiopogon | <i>Ophiopogon japonicus</i> . | | + | | + |
| <i>Ren Shen</i> | Ginseng | <i>Panax ginseng</i> . | | | + | + |
| <i>Sang Bai Pi</i> | Mulberry root bark | <i>Morus alba</i> . | | | + | |
| <i>Sheng Di Huang</i> | Rhemanina (raw) | <i>Rehmannia glutinosa</i> . | | + | | |
| <i>Shu Di Huang</i> | Rhemanina (cooked) | <i>Rehmannia glutinosa</i> . | | + | + | |
| <i>Wu Mei</i> | Mume | <i>Prunus mume</i> . | + | | | |
| <i>Wu Wei Zi</i> | Schisandra | <i>Schisandra chinensis</i> or <i>S. sphenanthera</i> . | + | | + | + |
| <i>Xuan Shen</i> | Scrophularia | <i>Scrophularia ningpoensis</i> . | | + | | |
| <i>Zhe Bei Mu</i> | Thunberg Fritillaria | <i>Fritillaria thunbergii</i> . | | + | | + |
| <i>Zi Su Zi</i> | Perillae | <i>Perillae frutescens</i> . | | | + | |
| <i>Zi Wan</i> | Purple aster | <i>Aster tataricus</i> . | | | + | |

*Formula: I = Schisandra 5, II = Lilly Combination, III = *Bu Fei San*, IV = Breath Easer.

Table 2: Therapeutic actions of Chinese herbs used in TCVM for equine respiratory disorders

| Therapeutic action | Chinese herbs |
|--|---|
| Expectorant | <i>Bai He, Jie Geng, Gan Cao.</i> |
| Reduce smooth muscle contraction and spasmolytic | <i>Zhe Bei Mu, Gan Cao, Chuan Bei Mu, Di Long.</i> |
| Antitussive | <i>Zhe Bei Mu, Chuan Bei Mu, Di Long, Gan Cao.</i> |
| Anti-histamine/inhibit histamine release | <i>Ren Shen, Chi Hu, Sang Bai Pi.</i> |
| Anti-inflammatory | <i>Mai Men Dong, Bai Shao Yao, Xuan Shen, Jie Geng, Gan Cao, Chuan Bei Mu, Huang Qi, Bai Guo, Zi Su Zi, Chi Hu, Di Huang, Fang Feng, Zi Wan, Dang Gui, Wu Wei Zi, Sang Bai Pi, Di Long.</i> |
| Anti-oxidative | <i>Bai Shao Yao, Dan Gui, Fang Feng, Bai Guo, Zi Wan, Sang Bai Pi.</i> |
| Reduction of inflammatory cytokines | <i>Sheng Di Huang, Bai Shao Yao, Jie Geng, Gan Cao, Chuan Bei Mu, Dang Gui, Dang Shen, Bai Guo, Wu Wei Zi, Zi Su Zi, Ren Shen, Bai He, Huang Qi, Xuan Shen.</i> |
| Increase macrophage activity | <i>Dang Gui, Huang Qi.</i> |
| Reduction of lymphocyte proliferation | <i>Mai Men Dong, Bai Guo.</i> |
| Modulation of TH1/TH2 immune system | <i>Bai He, Gan Cao, Chuan Bei Mu, Dang Gui, Huang Qi, Ren Shen.</i> |
| Antimicrobial | <i>Xuan Shen, Di Long.</i> |

body tissue from free radicals, and anti-platelet and antithrombotic activities.⁵⁻⁸

The extract of *Bai Guo* significantly decreases the infiltration of eosinophils and lymphocytes in humans suffering from asthma. This is thought to be a result of a reduction of the level of eosinophil chemotactic cytokine, IL-5, in the airway secretion.⁹ The extract also markedly improves the mean arterial pressure and attenuated injury of the lung, which is manifested by the improvement of histological changes, significant decreases in the pulmonary wet/dry ratio and pulmonary permeability index.¹⁰ It markedly increases superoxide dismutase activity, reduces myeloperoxidase activity, and suppresses nitric oxide (NO) generation accompanied by down-regulation of inducible nitric oxide synthase (iNOS) expression. These findings indicate that the extract possesses a pulmonary protective effect by reducing oxidative tissue injury.

Ginkgolides inhibit the in-vitro proliferation and apoptotic rate of circulating lymphocytes in both the normal and asthma induced rat.¹¹ They also significantly inhibit platelet activating factor (PAF) induced adhesion, chemotaxis and degranulation of rat polymorphonuclear leukocytes.¹² Liquor extract of

the leaves contains bilobalides, which are terpenoids that significantly reduce airway hyperreactivity and improve clinical symptoms and pulmonary function parameters of the asthmatic patients.¹³ Ginkgolide B is also capable of activating the intracellular signaling pathway such as tyrosine phosphorylation and phospholipase D of the neutrophils that has a potential to prime the neutrophils defense activity.¹⁴ Although most of the studies of *Bai Guo* have been performed with phytochemical extracts obtained from leaves, there is also evidence that *Bai Guo* (Ginkgo nut) is useful in treating respiratory diseases.

Bai He* (Lily bulb), or *Lilii Bulbus

Bai He (Lily bulb), or *Lilii Bulbus*, is the dried scale obtained from the bulb of *Lilium lancifolium*, *L. brownii*, or *L. pumilum*. Several chemical compounds have been isolated from *Bai He* including regaloside A, regaloside C, daucosterol, adenoside, berberine and polysaccharides.¹⁵ Berberine is an isoquinoline alkaloid that can inhibit in vitro release of IL-1b and TNF- α from human lung cells.¹⁶ It also increases the production of IL-12 from the mouse macrophage. IL-12 is the cytokine that plays an important role in the development of the naïve T-cell into the TH-1 cell.¹⁷ Berberine

increases mucin release in hamster tracheal epithelial cell cultures. Its mechanism is still unknown, but some results indicated that berberine may have an expectorant effect and facilitate the clearing of the respiratory secretion.¹⁸ Down regulation of the production of inflammatory cytokines and the immune modulation capabilities of berberine may explain why *Bai He* is beneficial for the treatment of heaves and asthma as these are thought to be caused by a disorder of TH-1 and TH-2 cytokines immune regulation.¹⁹

Bai Shao Yao* (White paeonia), or *Paeoniae Radix Alba

Bai Shao Yao (White paeonia), or *Paeoniae Radix Alba*, is obtained from the root of *Paeonia lactiflora*. Glycosides are the most important phytochemicals and include paeoniflorin, paeonol, albiflorin, 6'-O-beta-D-glucopyranosylalbiflorin, and 6'-O-benzoylalbiflorin.^{20,21} Besides the neuro-protective and anti-nociceptive action of paeoniflorin, its anti-inflammatory properties also have been demonstrated.²² Paeoniflorin down regulates the expression of TNF- α and IL-6 mRNA in the induced hepatic injury experimental model.²³ Paeonol also possesses anti-inflammatory, antioxidant, and cardiovascular protective activities.²⁴ It reduces TNF- α induced production of the intercellular adhesion molecule-1 (ICAM-1) in a dose dependent manner. ICAM-1 is an important adhesion molecule expressed in white blood cells such as monocytes. It is essential for the monocytes to adhere to the endothelium prior to migration to the inflammatory site. The mechanism of ICAM-1 down regulation is thought to be mediated by the inhibition of the transcription factors p38 ERK and NF-kB signaling pathways. The extract of *Bai Sao Yao* significantly inhibits the production of monocyte chemotactic protein 1 and 3 in human nasal fibroblast.²⁵ Therefore it is possible that the effect of *Bai Sao Yao* is partly due to the modulation of the local respiratory epithelium immunity.

Chai Hu* (Bupleurum), or *Bupleuri Radix

Chai Hu (Bupleurum), or *Bupleuri Radix*, refers to the root of *Bupleurum chinense* or *B. scorzonnerifolium*. Saikosaponins, the triterpenoid saponins, are the major active phytochemical compounds found in a high concentration in the

root.²⁶ Other secondary metabolites such as flavonoids and fatty acids also have been identified.^{27,28} The antibronchoconstriction property of saikosaponin has been demonstrated.²⁹ In a dose dependent manner, it significantly reduced airway resistance induced by ovalbumin stimulation in the guinea pigs. Its in-vitro inhibition of histamine release by peritoneal mast cells infers that antibronchoconstriction following saikosaponin administration is associated with the attenuation of histamine release from the pulmonary mast cell. Moreover, saikosaponin possesses anti-inflammatory activity. It attenuates the increase of the vascular permeability by inhibiting the inflammatory cytokines such as prostaglandin E2 (PGE2), thromboxane B2 (TXB2), and leukotriene E4 (LTC4) generation.³⁰

Chuan Bei Mu* (Tendrilled fritillary), or *Fritillariae cirrhosae Bulbus

Chuan Bei Mu (Tendrilled fritillary), or *Fritillariae cirrhosae Bulbus*, refers to the bulb of *Fritillaria cirrhosa*, *F. unibracteata*, *F. przewalskii*, or *F. delavayi* which contains several alkaloids such as imperialine and speimine.^{31,32} Other steroidal alkaloids such as verticine, verticinone, isovericine, ebeiedine, and ebeiedinone, also have been identified in plants within the same genus.³³ Supplementation of *Chuan Bei Mu* reduces eosinophil infiltration in the ovalbumin-induced asthma in mice.³⁴ This result was concurrent with a reduction of the TH-2 inflammatory cytokines (IL-5, IL-13, and IL-4), but with an increase of the TH-1 cytokine, IFN-g, in the bronchoalveolar lavage. Imperialine alone possesses spasmolytic and antitussive activities.³¹ Imperialine is also an anticholinergic agent that is antagonist to muscarinic receptors.³⁵

Dang Gui* (Chinese angelica), or *Angelicae sinensis Radix

Dang Gui (Chinese angelica), or *Angelicae sinensis Radix*, is obtained from the root of *Angelica sinensis*. It is commonly used in Chinese medicine to treat gynecological ailments, fatigue, mild anemia, and high blood pressure. It is one of the most studied Chinese herbs. Phytochemical analysis has revealed that it contains several volatile oils, organic acids, polysaccharides, sterols, and amino acids.³⁶⁻³⁸ Pharmacologically important

phytochemicals include ferulic acid, phthalide, ligustilide, and senkyunolides.^{39,40} Ferulic acid possesses anti-inflammatory and analgesic properties.⁴¹ *Dang Gui*'s polysaccharides increase the proliferation of macrophages and T-cell lymphocytes.^{42,43} They increase the mRNA expression of TH-1 cytokines (IL-2 and IFN γ) and down-regulate the mRNA expression of TH-2 cytokine (IL-4).⁴² They also inhibit the NO release and reactive oxygen species production by the macrophages.⁴⁴ Pulmonary smooth muscle hyperplasia and fibrosis are some of the major consequences of chronic airway inflammation. Hyperplasia of airway smooth muscle and metaplasia of the mucus-producing cells elevate the total airway resistance. *Dang Gui* supplementation significantly reduces the mRNA expression of TNF- α and TGF- β 1 in the lung tissue in the radiation-induced pulmonary fibrosis model.⁴⁵ This indicates that *Dang Gui* not only possesses an anti-inflammatory property, but also possesses pulmonary protective benefits against oxidative injury of the lung tissue.

***Dang Shen* (Codonopsis), or Codonopsis Radix**

Dang Shen (Codonopsis), or Codonopsis Radix, can be obtained from the root of *Codonopsis pilosula*, or *C. tangshen*. Secondary metabolites found in *Dang Shen* include several alkaloids and saponins such as tangshenoside, friedelin, taraxerol, and alpha-spinasterol.^{46,47} Supplementation with the crude herb has been demonstrated to significantly reduce the plasma level of thromboxane A2 and prostacyclin level in patients with angina pectoris.⁴⁸ Its extract enhances activity of cytotoxic T-lymphocytes, increases immunoglobulin production by B cells, and increases IL-1 production by the monocytes.⁴⁹

***Di Long* (Lumbricus), or Pheretima**

Di Long (Lumbricus), or Pheretima, can be obtained from *Pheretima aspergillum*, *P. vulgaris*, *P. guillelmi*, or *P. pectinifera*. Major chemical compounds found in *Di Long* include volatile oils, lipids, fatty acids, and amino acids.⁵⁰ Lumbricin, a proline rich amino acid found in several species of *Di Long* possesses antimicrobial activity against several bacterial species.⁵¹ *Di Long* decoction has been demonstrated to reduce the number of eosinophils, neutrophils, and total cell counts in the

bronchoalveolar lavage fluid of an experimental bronchial asthma model in guinea pigs.⁵² At a large dose, it reduces bronchial epithelial damage following an antigen challenge. Its acidic fraction is a potent spasmolytic agent against histamine induced tracheal smooth muscle contraction, and it has been shown to significantly decrease the frequency of cough.⁵³ This bronchodilatation and spasmolytic effect is thought to be associated with the antihistamine property of *Di Long*.⁵⁴

***Fang Feng* (Ledebouriella or Saposhnikovia), or Saposhnikovia Radix**

Fang Feng (Ledebouriella or Saposhnikovia), or Saposhnikovia Radix, refers to the root of *Saposhnikovia divaricata*. Reported active phytochemical compounds include coumarins (psoralen, bergapten, imperatoin, phellopterin, deltoin, xanthoin, and scopoletin), polysaccharides (saposhnikovans), polyacetylenes (faltarinone, panaxynol, faltarindiol, panaxydol, and panaxytriol), fangfengalpyrimidine, clemiscosin, 5-hydroxy-8-methoxypsoralen, hamaudol, nodakenetin, cimifugin, 5-O-methylvisaminol, marmesin, adenosine, and beta-sitosterol.⁵⁵⁻⁵⁷ It has been demonstrated that the ethanol extract of *Fang Feng* possesses antioxidative and anti-inflammatory effects.⁵⁸ Later studies demonstrated that polyacetylene, imperatoin, and deltoin are potent iNOS inhibitors, they inhibit NO production which plays a major role in the early inflammatory cascade triggered by oxidative tissue injury.^{56,59}

***Gan Cao* (Licorice), or Glycyrrhizae Radix**

Gan Cao (Licorice), or Glycyrrhizae Radix, refers to the root of *Glycyrrhiza glabra*, *G. uralensis*, or *G. inflata*. The most important active phytochemical compound found in *Gan Cao* is glycyrrhizin.⁶⁰ Oral supplementation of glycyrrhizin in the ovalbumin induced asthma model in mice reduces the concentration of TH-2 cytokines (IL-4, IL-5) and maintains the level of the TH-1 cytokines (IFN- γ) in bronchoalveolar lavage. It markedly alleviates airway constriction and reduces infiltration of eosinophils into the peribronchial and perivascular areas.⁶¹ Liquiritin apioside obtained from the water extract of *Gan Cao* possesses antitussive activity in the capsaicin induced cough reflex in experimental animals.⁶²

This antitussive action was hypothesized to be associated with both peripheral and central nervous system mechanisms. Glycyrrhizin and other secondary metabolites, 18 beta-glycyrrhetic acid and liquiritigenin, possess anti-allergic properties mediated via inhibition of IgE production.⁶³

Huang Qi (Astragalus), or Astagali Radix

Huang Qi (Astragalus), or Astagali Radix, can be obtained from the root of *Astragalus membranaceus*. Several secondary metabolites, including saponins and flavonoids, have been identified. These include astragalosides, alexandroside, isoquercitrin, calycosin, ononin, calycosin, formononetin, and odoratin.⁶⁴ *Huang Qi* supplementation increases the expression of IFN- γ and reduces IL-4 in peripheral blood mononuclear cells. This suggests that *Huang Qi* is capable of reversing the TH-2 cytokine predominate status found in asthmatic patients.⁶⁵ Supplementation of *Huang Qi* polysaccharide extract in the ovalbumin induced asthma model prevents eosinophil infiltration into the airways and inhibits lymphocyte proliferation, and IL-2 production.⁶⁶ In human asthma, *Huang Qi* supplementation was found to reduce the hyper-responsiveness of the airway to a methacholine challenge and improve the forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), and peak expiratory flow (PEF).⁶⁷ It also enhanced the phagocytic activity of the mouse peritoneal macrophage against *M. tuberculosis*.⁶⁸ Astragaloside alone inhibited NO production, enhanced the phagocytic activity of the peritoneal macrophage and increased inflammatory cytokine secretion by the macrophages.^{68,69}

Jie Geng (Platycodon), or Platycodi Radix

Jie Geng (Platycodon), or Platycodi Radix, can be obtained from the root of *Platycodon grandiflorus*. Secondary metabolites found in *Jie Geng* include triterpenoids saponins, tangeritin, 3-O-beta-D-glucopyranosylplatycodigenin methyl ester, 3-O-beta-D-glucopyranosylplatycogenic acid A lactone, 3-O-beta-D-glucopyranosylplatycodigenin, deapio-platyconic acid A lactone, deapio-platycodin-D, platycoside-G1, and platycoside-E.^{70,71} *Jie Geng* derived glycosides exhibit anti-inflammatory activity that is mediated by inhibition of the NOS and cyclooxygenase II production.⁷² This inhibition is governed by blocking the

translocation of the transcription factor, nuclear factor kappa B (NF- κ B).⁷³ Its glycosides have been found to increase the secretion of mucin from both rat and hamster tracheal epithelium. Therefore *Jie Geng* supplementation is capable of reducing the airway inflammation, increasing the mucociliary clearance, and alleviating the accumulation of respiratory secretion.

Mai Men Dong (Ophiopogon), or Ophiopogonis Radix

Mai Men Dong (Ophiopogon), or Ophiopogonis Radix, can be obtained from the root of *Ophiopogon japonicus*. The plant is native to Japan and is also known as mondo grass. It is commonly used as an ornamental plant in the United States. Active phytochemical compounds include ophiogonins, ophiopogonin, ophiopogonin-D, ruscogenin, fructan, and opaw-2.⁷⁴⁻⁷⁷ Opaw-2 significantly stimulates the proliferation of lymphocytes in a dose-dependent manner.⁷⁷ Ruscogenin and ophiopogonin have anti-inflammatory activity. They reduce the zymosan-induced migration of peritoneal leukocytes.⁷⁶ Mucociliary protective activity of *Mai Men Dong* extract also has been demonstrated.⁷⁸

Ren Shen (Ginseng), or Ginseng Radix

Ren Shen (Ginseng), or Ginseng Radix, can be obtained from the root of *Panax ginseng*. It is widely used in several herbal formulations and is probably one of the most studied Chinese herbs. The major pharmacologically active secondary metabolites are ginsenoside saponins.⁷⁹ Its neuroprotective, immune modulation, anti-inflammatory, and anti-oxidative properties are all well recognized.⁸⁰⁻⁸⁵ Ginsenosides inhibit histamine release from rat peritoneal mast cell and inhibit the IgE induced passive cutaneous anaphylaxis reaction.⁸⁶ Its immune modulation properties are partly due to an inhibition of the production of pro-inflammatory cytokines such as NO and PGE2.⁸⁷ Its TH-1/TH-2 immune balancing properties also have been demonstrated.⁸⁸ Therefore the mechanism of *Ren Shen* in treating allergic respiratory disease may be due to its anti-inflammatory, anti-histamine, and immune modulating properties.

Sang Bai Pi* (Mulberry root bark), or *Mori Cortex

Sang Bai Pi (Mulberry root bark), or *Mori Cortex*, is obtained from *Morus alba*. Extract of the herb contains stilbene glucosides, mulberroside A, cis-mulberroside A, and oxyresveratrol.⁸⁹ Extract of *Sang Bai Pi* inhibits the histamine release from the rat peritoneal mast cell and inhibits a cutaneous anaphylaxis reaction activated by the IgG.⁹⁰ Both mulberroside and oxyresveratrol are potent anti-oxidative and anti-inflammatory agents.⁹¹ Oxyresveratrol inhibits the LPS-induced increase of iNOS expression in a concentration-dependent manner. It also significantly inhibits LPS-induced nuclear translocation of NF- κ B and COX-2 activity.

Di Huang* (Rehmannia), or *Rehmanniae Radix

Di Huang (Rehmannia), or *Rehmanniae Radix*, is obtained from the tuber of *Rehmannia glutinosa*. Two forms have been used in herbal medicine, *Sheng Di Huang* (uncooked) and *Shu Di Huang* (cooked). The most important phytochemical compound is catalpol.⁹² *Di Huang* extract possesses anti-inflammatory action via down regulation of cyclooxygenase activity and suppresses TNF- α production.^{93,94} The neuroprotective effect of the extract is also well established.⁹⁵⁻⁹⁷

Wu Mei* (Mume), or *Mume Fructus

Wu Mei (Mume), or *Mume Fructus*, refers to the fruit of *Prunus mume*. It is also known as Japanese apricot. *Wu Mei* is rich in organic acids. These include ascorbic acid, oxalic acid, tartaric acid, malic acid, lactic acid, acetic acid, citric acid, and succinic acid.⁹⁸ There are limited scientific studies of the secondary metabolites from the fruit of *Wu Mei*. However, the anti-oxidative benefit of ascorbic acid is well recognized. Several studies have shown that the human asthmatic patient might benefit from a long term supplementation of vitamin C, which reduces the exercise induced bronchoconstriction, exhaled NO, and urinary leukotriene and prostaglandin.⁹⁹ In the guinea pigs, 30 days of oral supplementation reduced airway hyper-responsiveness induced by both ovalbumin and methacholine.¹⁰⁰ Despite persuasive evidence that ascorbic acid possesses health benefits, the true value of *Wu Mei* in treating respiratory disease is still uncertain.

Wu Wei Zi* (Schisandra), or *Schisandrae Fructus

Wu Wei Zi (Schisandra), or *Schisandrae Fructus*, is the dry fruit of *Schisandra chinensis* or *S. sphenanthera*. Pharmacologically active compounds include dibenzocyclooctadiene, octadecanoic acid, schizandrin, deoxyschizandrin, and gomisins.¹⁰¹⁻¹⁰³ Water extract of *Wu Wei Zi* suppresses phorbol-12 myristate 13 acetate (PMA) and calcium ionophore induced TNF- α , IL-6, and granulocyte-macrophage colony stimulating factor production from human mast cell in a dose dependent manner.¹⁰⁴ More specifically schizandrin reduces in vitro expressions of TNF- α and IL-4 in IgE-induced RBL2H3 cells.¹⁰⁵ These findings indicated that *Wu Wei Zi* contains pharmacologically active compounds that possess immune modulatory and anti-inflammatory activities.

Xuan Shen* (Scrophularia), or *Scrophulariae Radix

Xuan Shen (Scrophularia), or *Scrophulariae Radix*, is also known as Chinese figwort. It can be obtained from the root of *Scrophularia ningpoensis*. Major pharmacologically active compounds include harpagoside, harpagide, E-cinnamic acid, and E-p-methoxycinnamic acid.¹⁰⁶ Harpagoside is a strong anti-inflammatory agent, and possesses antimicrobial activity against several microorganisms.^{107,108} It inhibits macrophage expression of COX-2 and inducible NO by preventing the translocation of NF- κ B(p65) into the nucleus.¹⁰⁹

Zhe Bei Mu* (Thunberg fritillaria), or *Fritillariae thunbergii Bulbus

Zhe Bei Mu (Thunberg fritillaria), or *Fritillariae thunbergii Bulbus*, refers to the bulb of *Fritillaria thunbergii*. Important phytochemical compounds include verticine, verticinone, ebeiedine, ebeiedione, peimine, peiminine, zhebeinine, and steroidal alkaloids.^{33,110,111} Verticinone possesses antitussive effects that may be modulated via opioid and non-opioid mechanism.¹¹² The antimuscarinic activity of fritillaria's alkaloids (verticine/verticinone/imperialine/imperialine-3b-D-glucoside/puqietinone) have been demonstrated in M2-receptor transfected human embryonic kidney cells.¹¹³ This property may reduce airway smooth muscle cell contraction,

and it can be used to explain the antitussive effect of the herb. Moreover, an acid salt form of verticinone (verticinone-cholic acid salt) found in a bile acid containing formula possesses a stronger antitussive action than that of the original alkaloids.¹¹²

Zi Su Zi (Perilla), or Perillae Fructus

Zi Su Zi (Perilla), or *Perillae Fructus*, refers to the seed of *Perilla frutescens*. It is commonly known as Chinese basil seed. Its major phytochemical compounds include octacosanol, hexacosanol, and triacontanol.¹¹⁴ The seed also contains a high level of omega-3 fatty acid and alpha linolenic acid.¹¹⁵ Oral supplementation of *Zi Su Zi* oil alleviates increased airway resistance and the decrease in the dynamic compliance of the lung in the asthmatic induced guinea pig model. *Zi Su Zi* also inhibits the infiltration of inflammatory cells following antigen stimulation and down regulated calcium ionophore induced leukotriene release from the lung tissue.¹¹⁶ Long term oral supplementation of *Zi Su Zi* oil in humans suffering from asthma was found to suppress the production of LTC-4 by leukocytes and to improve pulmonary function parameters.¹¹⁷

Zi Wan (Purple aster), or Asteris Radix

Zi Wan (Purple aster), or *Asteris Radix*, can be obtained from the root of *Aster tartaricus*. It contains several phytochemicals such as shionosides, quercetin, kaemferol, emodin, chrysophanol, physcion, benzoic acid, E-caffeic acid, scopoletin, arantiamide acetate, and 1,7-dihydroxy-6-methyl anthraquinone.¹¹⁸⁻¹²⁰ Of all of these compounds, quercetin and kaempferol are the most potent anti-hemolysis and anti-superoxide radical generation agents.¹²⁰ Quercetin is a potent lipoxygenase inhibitor. It inhibits the 15-lipoxygenase and endogenous pro-oxidant which may contributes to the universal antioxidative and anti-inflammatory activities of *Zi Wan*.¹²¹ The smooth muscle relaxant and spasmolytic properties of quercetin have been demonstrated in intestinal smooth muscle.¹²² However, its spasmolytic benefit to the smooth muscle of the airway is still inconclusive.

CONCLUSION

The ability of ancient Chinese herbalists to

accurately identify pharmacological actions of herbs is a remarkable achievement given the fact that the development of Chinese herbal medicine was based solely on the ancient Chinese philosophies *Ying/Yang* and Five Elements. Modern pharmacochemistry has confirmed the presence of pharmacologically active phytochemicals in plants. As previously stated, these phytochemicals are mostly secondary metabolites, including alkaloids, terpenoids, glycosides, phenolic compounds, phenazines, polyketides, fatty acids, and non-ribosomal peptides. It seems apparent that the development of Chinese herbal formulas must have been based on some ancient knowledge of pharmacotoxicology.

Evidence of the pharmacologically active compounds in herbal formulas used for treating equine chronic respiratory disorders validates their use in clinical applications. Therapeutic mechanisms of action depend on the existing pharmacologically active phytochemicals and include anti-inflammatory, antimicrobial, antitussive, antihistamine, antioxidative, expectorant, and spasmolytic effects. As well the Chinese herbs described inhibit inflammatory cytokine production, and modulate activity of the immune system alone or in combination. Further biochemical study of pharmacologically active secondary metabolites will increase our knowledge of the effects of phytochemicals and their mechanisms of action. Additional scientific inquiry will bring more of the wisdom from ancient herbology to modern science. With more information on herbal pharmacotoxicology, further modification of the formulas will lead to even better therapeutic action with minimal toxic side effects. Lastly, detailed studies of pharmacologically active phytochemicals may lead to the discovery of novel drugs for treating other diseases such as immune-mediated disorders and cancers.

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ABSTRACT

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Electroencephalographic Evaluation of Gold Wire Implants Inserted in Acupuncture Points in Dogs with Epileptic Seizures. *Res Vet Sci.* 2008 Jul 11. [Epub ahead of print]

The purpose of this study was to evaluate both, clinically and with electroencephalographic (EEG) recordings, the effect of gold wire implants in acupuncture points in dogs with uncontrolled idiopathic epileptic seizures. Fifteen dogs with such diagnosis were enrolled in the study. A first EEG recording was performed in all dogs under anaesthesia with xylazine (1mg/kg) and propofol (6mg/kg) before the treatment protocol, and a second EEG was performed 15 weeks later. Relative frequency power, intrahemispheric coherence available through EEG, number of seizures and seizure severity were compared before and after treatment using a Wilcoxon signed-rank test. There were no significant statistical differences before and after treatment in relative power or in intrahemispheric coherence in the EEG recording. However, there was a significant mean difference in seizure frequency and seizure severity between control and treatment periods. After treatment, nine of the 15 dogs (60%) had at least a 50% reduction in seizures frequency during the 15 weeks established as follow-up of this treatment.