

## Exhalta™

### Control Snoring

### Product Information Sheet



**Exhalta™ Snoring Control Extract** is a Phytotherapeutic extraction of ***Gastrodia elata***, ***Angelica sinensis***, ***Radix bupleuri***, ***Zingiber officinale*** and ***Cinnamomum verum***. Using advanced laboratory extraction apparatus & proprietary production protocols, these phytochemicals are known for their snoring control properties.

Sleep disordered breathing such as serious snoring and sleep apnea is common in aging. Snoring is a sign of resistance to the passage of air into the lungs and also a sign of breathing problems. Many studies have reported that sleep disordered breathing, such as snoring, was connected with many causes of death such as hypertension, myocardial infarction, and stroke. Obstructive sleep apnea hypopnea syndrome (OSAHS) is a common and potentially dangerous sleep disorder accompanied by cardio cerebrovascular events and multiple organ injury, which is caused by airway occlusion during sleep secondary to pharyngeal collapse and is characterized by repetitive breathing interruptions when sleeping. An herbal composition including *Gastrodia elata* and *Cinnamomum* is a well-known, Chinese herbal formula for patients with sleep disorders to reduce snoring.

***Gastrodia elata*** (Tianma) promotes neuro-regenerative processes by inhibiting stress related proteins and mobilizing neuroprotective genes such as Nxn, Dbnl, Mobk13, Clic4, Mki67 and Bax with various regenerative modalities and capacities related to neuro-synaptic plasticity.

***Radix Bupleuri*** has been widely used for the treatment of several types of chronic inflammatory diseases. The crude polysaccharides isolated from the roots of Bupleurum attenuated lung injury by inhibiting the level of myeloperoxidase (MPO), tumor necrosis factor (TNF), and serum nitric oxide (NO). Chun et al. reported that saikosaponins from *Radix Bupleuri* exhibited anti-inflammatory activity on inflammatory processes including inhibition of inflammatory exudation, capillary permeability, inflammatory mediators release, migration of white cells, connective tissue hyperplasia, and a variety of allergic inflammation.

***Gastrodia elata***, (Tianma) is a traditional Chinese medicine often used for the treatment of headache, convulsions, hypertension, and cardiovascular diseases.

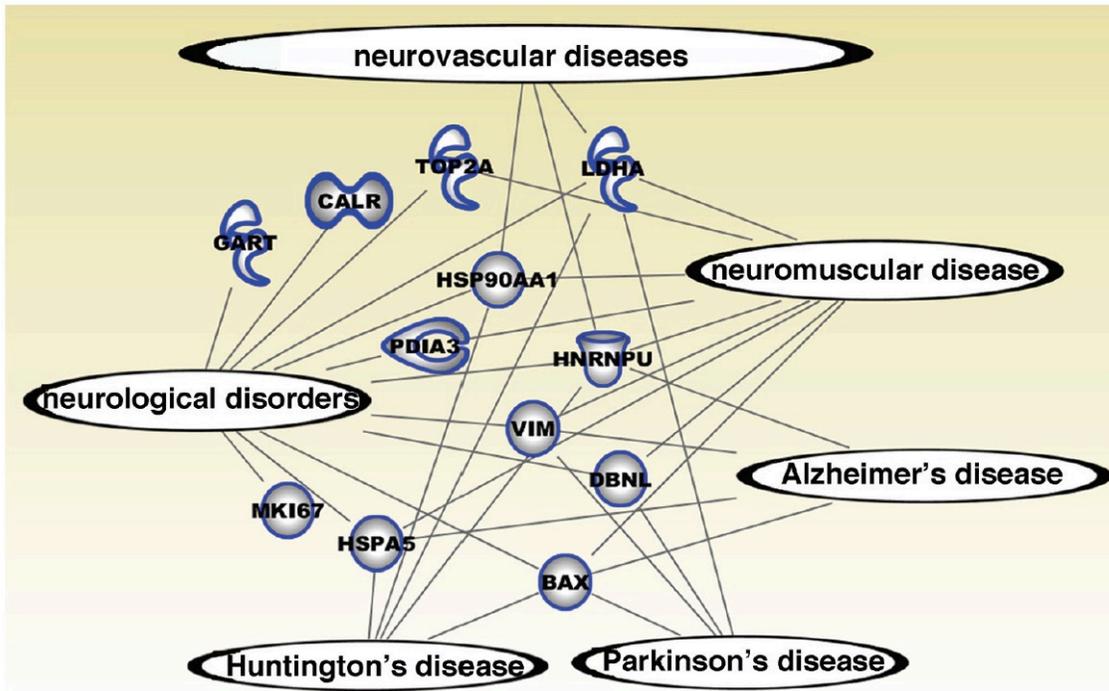
***Angelica sinensis***, known as Dong gui in TCM, has traditionally been used to treat a variety of blood-related ailments including menstrual cramps, blood deficiencies, uterine disorders, as well as ischemias of both the heart and brain. Angelica roots are used for tonifying, replenishing, and invigorating blood.

***Radix bupleuri***, exhibited various biological activities, such as anti-inflammatory, anticancer, antipyretic, antimicrobial, antiviral, hepatoprotective, neuroprotective, and immunomodulatory effects.

***Zingiber officinale*** ginger extract was effective against several strains of drug-resistant bacteria. It may help inhibit the synthesis of certain markers of inflammation. It contains gingerol and other anti-inflammatory compounds like shogaol, paradol and zingerone.

***Cinnamomum verum*** Contains antioxidants, including polyphenols, phenolic acid and flavonoids. These compounds work to fight oxidative stress in the body and aid in the prevention of chronic disease.

**Exhalta™** is uniquely extracted from organic herbs using organic cane alcohol and deep ocean mineral water, as the extraction solvent. Utilizing advanced all-glass apparatus **Exhalta™** undergoes hours of reflux extraction that applies heat and ethanol to enhance the bioavailability of the resultant extraction.



**Figure 10.** Neurodegenerative-diseases-specific network analysis of iTRAQ-based proteomic metabolism in tianma-activated differentiated mouse neuronal N2a cells using IPA. IPA analysis deciphered a group of identified proteins modulated by neural tianma stimulation and their potential interactive link within the context of various neurodegenerative-diseases.

# Traditional Chinese herbal formula relieves snoring by modulating activities of upper airway related nerves in aged rats

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**Aim:** The present study investigated whether intraperitoneal treatment with the herbal formula B210 ([B210]; a herbal composition of *Gastrodia elata* and *Cinnamomum cassia*) can reduce snoring in aged rats. Also, we studied possible neural mechanisms involved in B210 treatment and subsequent reduced snoring in rats.

**Methods and result:** We compared pressure and frequency of snoring, activities of phrenic nerve (PNA), activities of recurrent laryngeal nerve (RLNA) and activities of hypoglossal nerve (HNA), inspiratory time ( $T_i$ ) and expiratory time ( $T_e$ ) of PNA, and pre-inspiratory time (Pre- $T_i$ ) of HNA in aged rats between sham and B210 treatment groups (30 mg/mL dissolved in DMSO). We found that aged rats that received B210 treatment had significantly reduced pressure and frequency of snoring than rats who received sham treatment. Also, we observed that aged rats that received B210 treatment had significantly increased PNA, RLNA, and HNA, extended  $T_i$  and  $T_e$  of PNA, and prolonged Pre- $T_i$  of HNA compared to rats that received sham treatment. In other words, B210 treatment may relieve snoring through modulating activities and breathing time of upper airway related nerves in aged rats.

**Conclusion:** We suggested that the B210 might be a potential herbal formula for snoring remission.

**Keywords:** Chinese herbal medicine, snoring remission, upper airway, phrenic nerve, recurrent laryngeal nerve, hypoglossal nerve

## Introduction

Sleep disordered breathing such as serious snoring and sleep apnea is common in aging.<sup>1</sup> Snoring is a sign of resistance to the passage of air into the lungs and also a sign of breathing problems.<sup>2</sup> Many studies have reported that sleep disordered breathing, such as snoring, was connected with many causes of death such as hypertension, myocardial infarction, and stroke.<sup>3-5</sup> Electrical stimulation of the upper airway dilator muscles to reduce snoring has been used for many years, however, most people do not want intrusive surgery.<sup>6</sup> All over the world, including Taiwan, many patients with serious snoring are unwilling to use continuous positive airway pressure and to undergo surgery. Thus, seeking a potential traditional Chinese medicine as an alternative treatment may be another option for the treatment of serious snoring.<sup>7</sup> In Taiwan, the herbal formula B210 ([B210]; a herbal composition of *Gastrodia elata* and *Cinnamomum cassia*) is a well-known, patented Chinese herbal formula (patent no 361075 issued by Intellectual Property Office of Taiwan; patent owner: Brion Research Institute of Taiwan) for patients with sleep disorders to reduce snoring. However, the possible neural mechanism concerning pharmacological

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# Chinese Herbs Medicine Huatan Huoxue Prescription for obstructive sleep apnea hypopnea syndrome as complementary therapy

## A protocol for a systematic review and meta-analysis

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### Abstract

**Objective:** The aim of this systematic review and meta-analysis is to assess effectiveness and safety of Chinese Herbs Medicine Huatan Huoxue Prescription (HTHXP) as complementary therapy in treating bronchiectasis.

**Methods:** The following databases will be searched: Embase, Cochrane, PubMed, China National Knowledge Infrastructure, Wan Fang, and VIP database from their inception to April 1, 2020. We performed and completed meta-analysis and methodologic evaluation by Review Manager 5.3.3 and stata 12.0 software. Study selection, data extraction, quality assessment, and assessment of risk bias will be performed by 2 reviewers independently. Odds ratios and correlative 95% confidence intervals will be calculated to present the association between the HTHXP and western medicine treatment using Review Manager version 5.3 when there is sufficient available data.

**Results:** The results will be disseminated through a peer-reviewed journal publication.

**Conclusion:** These systematic review findings will summarize up-to-date evidence for that HTHXP is more effective and safe as adjunctive treatment for patients with bronchiectasis.

**Ethics and dissemination:** Ethics approval and patient consent are not required as this study is a systematic review based on published articles.

**PROSPERO registration number:** INPLASY202050079.

**Abbreviations:** CPAP = continuous positive airway pressure, GRADE = Grading of Recommendations Assessment, Development and Evaluation, OSAHS = obstructive sleep apnea hypopnea syndrome, TCM = traditional Chinese medicine.

**Keywords:** Chinese medicine, Huatan Huoxue prescription, meta-analysis, protocol, systematic review

MZ and FX contributed equally to the work.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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### 1. Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a common and potentially dangerous sleep disorder accompanied by cardio-cerebrovascular events and multiple organ injury, which is caused by airway occlusion during sleep secondary to pharyngeal collapse and is characterized by repetitive breathing interruptions when sleeping.<sup>[1,2]</sup> The incidence of OSAHS is ~2% to 4% in adults worldwide; nevertheless, relevant epidemiologic studies have revealed that the incidence of OSAHS is increasing especially in younger, which is more common in men than in women.<sup>[3-5]</sup> In recent years, considering the high incidence and mortality of OSAHS, the focus in OSAHS has increased in medical institutions and society.<sup>[6,7]</sup> Recent statistics have demonstrated that the 5-year mortality rate of untreated OSAHS patients is as high as 11% to 13%, and about 3000 mortalities per day related to OSAHS.<sup>[8]</sup> What is more, excessive daytime sleepiness reduces the quality of life of OSAHS patients. Up to now, advanced scientific treatments on OSAHS have been achieved, including oral drugs and continuous positive airway pressure (CPAP), and surgery.<sup>[9]</sup> Nevertheless, despite the advanced treatment, OSAHS patients typically show a poor tolerance and compliance.<sup>[10]</sup> Furthermore, surgery has been associated with potential complications, such as profuse

## Tianma Modulates Blood Vessel Tonicity

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**Abstract:** Tianma is a traditional Chinese medicine (TCM) often used for the treatment of hypertension and heart diseases. To elucidate the function of tianma at the molecular level, we investigated the effect of tianma on vascular functions and aortic protein metabolism. We found that long-term treatment with tianma (~2.5g/kg/day for three months) in one-year-old rats could enhance acetylcholine (ACh)-induced vasorelaxation in endothelium-intact thoracic aortic rings against both KCl (80 mM)- and phenylephrine (PE)-induced contraction. By using the iTRAQ (isobaric tag for relative and absolute quantification) technique, we confirmed from the functional data at the proteome level that tianma treatment down-regulated the expressions of contractile proteins (e.g. Acta2) and other related structural proteins (e.g. desmin), and up-regulated the expressions of extracellular matrix (ECM) glycoproteins (e.g. Fbln5) and anti-thrombotic proteins (e.g. Anxa2) in aortic tissue. By inductive reasoning, tianma could perform its vasodilatory effect not only by inhibiting vascular smooth muscle contraction, but also by enhancing blood vessel elasticity and stabilizing the arterial structure. Thus, tianma might become a novel therapeutic herbal medicine for cardiovascular diseases by regulating the aortic proteome metabolism.

**Keywords:** Tianma, Vascular disease, Aorta, TCM.

### INTRODUCTION

The research, development and use of natural products as therapeutic agents, especially those derived from higher plants, have been increasing in recent years. Traditional Chinese medicine (TCM) involves thousands of herbs for clinical treatments [1-3]. However, the underlying molecular and cellular mechanisms of most herbal medicines remain obscure.

Tianma is the tuber of an orchid, *Gastrodia elata Blume*, and has been used as an ancient Chinese herbal medicine for treating various cardio- and cerebro-vascular and nervous diseases, including convulsion, headache, epilepsy, hypertension and coronary heart diseases [4-6]. Tianma contains many bioactive components such as vanilline, gastrodin, daucosterol, citric acid, succinct acid, parishin and minerals [7-11]. Besides its well known neuroprotective effects [12], tianma also plays a role in vascular circulation through controlling the functions of vascular smooth muscle cells (VSMCs) and inhibiting platelet aggregation [13]. Cardiovascular remodeling caused by VSMCs overgrowth in the large and medium size vessels contributed to the pathogenesis of hypertension and restenosis after angioplasty [14, 15].

Tianma was found to inhibit VSMCs proliferation through decreasing the expressions of proliferating cell nuclear antigen (PCNA) and c-myc, thus inhibiting cardiovascular remodeling [16]. Tianma could also elicit relaxant effects on smooth muscles in the blood vessels, gastrointestinal tract [17] and bladder [18] directly or through inhibiting neurogenic contraction.

In order to comprehensively understand the potential mechanisms by which tianma regulates vascular functions, we investigated the vasodilatory effects of tianma on vascular smooth muscles by measuring the KCl- and phenylephrine (PE)-induced contractility of rat thoracic aorta *ex vivo* using myography. We then quantitatively analyzed the proteomic changes of arterial smooth muscle cells using iTRAQ (two-dimensional (2D) liquid chromatography coupled with tandem mass spectrometry (2D-LC-MS/MS)-based multidimensional protein identification technology combined with multiplex isobaric tag for relative and absolute quantification [19]) after long-term tianma treatment of one-year-old rats. The selective iTRAQ-detected changed proteins were further confirmed at the protein level by using western blot analyses (Fig. 1). Our experimental results showed for the first time that tianma could dilate blood vessels through regulating the cellular protein metabolism, including contractile/structural proteins as well as extra-cellular matrix glycoproteins and anti-thrombotic proteins.

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## Review Article

# **Radix Bupleuri: A Review of Traditional Uses, Botany, Phytochemistry, Pharmacology, and Toxicology**

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*Radix Bupleuri* (Chaihu) has been used as a traditional medicine for more than 2000 years in China, Japan, Korea, and other Asian countries. Phytochemical studies demonstrated that this plant contains essential oils, triterpenoid saponins, polyacetylenes, flavonoids, lignans, fatty acids, and sterols. Crude extracts and pure compounds isolated from *Radix Bupleuri* exhibited various biological activities, such as anti-inflammatory, anticancer, antipyretic, antimicrobial, antiviral, hepatoprotective, neuroprotective, and immunomodulatory effects. However, *Radix Bupleuri* could also lead to hepatotoxicity, particularly in high doses and with long-term use. Pharmacokinetic studies have demonstrated that the major bioactive compounds (saikosaponins a, b, c, and d) were absorbed rapidly in rats after oral administration of the extract of *Radix Bupleuri*. This review aims to comprehensively summarize the traditional uses, botany, phytochemistry, pharmacology, toxicology, and pharmacokinetics of *Radix Bupleuri* reported to date with an emphasis on its biological properties and mechanisms of action.

## 1. Introduction

*Radix Bupleuri*, also called “Chaihu” in Chinese, is derived from the dried roots of *Bupleurum chinense* DC. and *Bupleurum scorzonerifolium* Willd. [1]. As a traditional herbal medicine, *Radix Bupleuri* has been used widely for the treatments of influenza, fever, inflammation, malaria, menstrual disorders, and hepatitis in China, Japan, Korea, and other Asian countries [2, 3]. According to ancient Chinese medical literatures, *Radix Bupleuri* is capable of regulating the exterior and interior metabolisms, dispersing evil heat from the superficies, soothing the liver, and promoting yang and qi (representing “life energy” or “life force” in TCM theories). In recent decades, investigations of *Radix Bupleuri* have focused on its biological activities, including its anti-inflammatory [4, 5], anticancer [6, 7], antipyretic [8], antimicrobial [9], antiviral [10], hepatoprotective [11], and immunomodulatory effects [12]. In addition, *Radix Bupleuri* also exhibited significant effects on membrane fluidity [13]. These studies have resulted in the isolation of essential oils, triterpenoid saponins, polyacetylenes, flavonoids, lignans, fatty acids, and sterols from this plant [14]. Among them,

triterpenoid saponins are known to be the major bioactive compounds [15, 16]. Saikosaponins a and d are commonly used as chemical standards for quality evaluation of *Radix Bupleuri* in the current Chinese Pharmacopoeia and recent publications. However, an increasing number of recently published studies have reported adverse effects of *Radix Bupleuri*. The purpose of this review is to provide updated, comprehensive information on the traditional uses, botany, phytochemistry, pharmacology, toxicology, and pharmacokinetics of *Radix Bupleuri* based on scientific literatures in the past few decades. This study will facilitate exploring the therapeutic potential of this plant and evaluate future research opportunities.

## 2. Traditional Uses

*Radix Bupleuri*, which is characterized by a wide spectrum of biological and pharmacological effects, has been used as a famous traditional Chinese medicinal herb with a history of medical use in China. According to TCM theory, *Radix Bupleuri* is thought to regulate the exterior and interior

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## Original Article

# *Gastrodia elata* Blume (tianma) mobilizes neuro-protective capacities

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**Abstract:** Tianma (*Gastrodia elata* Blume) is a traditional Chinese medicine (TCM) often used for the treatment of headache, convulsions, hypertension and neurodegenerative diseases. Tianma also modulates the cleavage of the amyloid precursor protein App and cognitive functions in mice. The neuronal actions of tianma thus led us to investigate its specific effects on neuronal signalling. Accordingly, this pilot study was designed to examine the effects of tianma on the proteome metabolism in differentiated mouse neuronal N2a cells using an iTRAQ (isobaric tags for relative and absolute quantitation)-based proteomics research approach. We identified 2178 proteins, out of which 74 were found to be altered upon tianma treatment in differentiated mouse neuronal N2a cells. Based on the observed data obtained, we hypothesize that tianma could promote neuro-regenerative processes by inhibiting stress-related proteins and mobilizing neuroprotective genes such as Nxn, Dbnl, Mobkl3, Clic4, Mki67 and Bax with various regenerative modalities and capacities related to neuro-synaptic plasticity.

**Keywords:** Aging, tianma, neuron, neurodegeneration, metabolism, signalling, TCM

## Introduction

Since recent data show that the number of people affected by Alzheimer's disease (AD) and dementia is increasing at an epidemic pace, there has been an interest in developing novel protective agents because biological aging also represents the major risk factor with respect to the development of AD, vascular dementia (VD) and other cardiovascular diseases (CD). Traditional herbal medicine is especially attractive for disease prevention, health maintenance, and sicknesses that are non-responsive to current Western medicine and thus has potential benefits that attract worldwide attention and interests. The use of medicinal herbs has a long history in Asia and is commonly used to treat various neurological diseases including stroke, epilepsy and VD [1-3]. Orchids and their derivatives have been shown to benefit the improvement of neural functions in clinical studies but the underlying mechanisms are largely unknown which severely hampered the more extensive applica-

tion of such potential drugs as well as the potential of industrial exploitation of it [4-6]. According to ancient Chinese medical literature, tianma (*Gastrodia elata* Blume, Orchidaceae) is a herbal medicine for the control of the internal movement of wind. The dry tuber of tianma has long been officially listed in the Chinese Pharmacopoeia and is used in treating headaches, dizziness, tetanus, epilepsy, infantile convulsions and numbness of the limbs [4, 6-11]. Previously, we could demonstrate *in vivo* the potential neuro-protective action of tianma and its capacity to enhance cognitive functions in mice [12].

Recently, we have successfully applied the two dimensional (2D) liquid chromatography coupled with tandem mass spectrometry-based isobaric tag for relative and absolute quantification (2D-LC-MS/MS-iTRAQ) strategy in the area of neuro-degenerative diseases [13, 14]. Our group has recently reported the facilitating effect of tianma on  $\alpha$ -secretase-mediated cleav-