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Editorial

Chinese Veterinary Herbal Medicine: History, Scientific Validation and Regulations

Huisheng Xie DVM, MS, PhD

Shen Nong was the ruler of China about 5,000 years ago (approximately 2800 BC) and he taught the ancient Chinese people agricultural practices and herbal medicine. Shen Nong literally means "Divine Farmer" and he has become known as the father of Chinese agriculture and the "Emperor of the Five Grains".^{1,2} Chinese healers of that era began tasting herbs, testing their medicinal properties and explored the effects of different plants on disease. Between 145-90 BC, Sima Qian wrote the first systematic Chinese historical book *Shi Ji* (The Records of the Grand Historian). Sima Qian recounted Chinese history from the time of the Yellow Emperor (traditionally dated around 2600 BC) to his time and became known as the father of Chinese historiography. In the *Shi Ji*, Sima Qian stated that "Shen Nong tasted hundreds of herbs and was the originator of Chinese herbal medicine." Between 100 BC and 100 AD, information on 365 medicinal herbs was compiled into the textbook *Shen Nong Ben Cao Jing* (Shen Nong's Book of Medical Herbs) named to honor the contributions of Shen Nong to Chinese herbal medicine and this text became the first Chinese herbal material medica. These 365 herbs are still commonly used in current Traditional Chinese Medicine (TCM) and Traditional Chinese Veterinary Medicine (TCVM) practices.

The majority of Chinese herbal medicines are roots,

leaves, flowers, seeds and bark of plants. For example, the root of *Angelica sinensis* is called *Dang Gui* and was described approximately 2000 years ago in *Shen Nong Ben Cao Jing* as a warm, sweet and pungent herb with no toxicity. *Dang Gui* (*Angelica*) tonifies and invigorates Blood and regulates the estrous cycle and is commonly and widely used in both human and veterinary herbal medicines for the treatment of lipid, endocrine and cardiac disorders, anemia and pain.³ Information regarding the best locations for production, optimum harvesting and processing techniques, basic natures and flavors, pharmacological properties, safety and toxicity, synergistic combinations, indications, cautions and contraindications, dispensing, dosages and forms of administration of Chinese herbs have been recorded and revised over the past 2,000 years and evolved into the detailed Chinese herbal materia medica and formula descriptions used today.^{3,4}

Scientific Validation of Efficacy and Actions

The quantity and quality of scientific research on the basic mechanisms and clinical applications of many different Chinese herbal medicines has been increasing yearly as can be evidenced by the accumulation of references in the United States National Library of Medicine database (searched through PubMed). For example, as of August 2011, a PubMed database search

using the keyword “Angelica” produced over 1,000 references to various forms of the Chinese herb, most of which have been published in the past 15 years.⁵ There are many other articles in the Chinese data bases in China. Among the PubMed references, eleven articles are specific to veterinary medicine and provide evidence to validate the theories and effectiveness of this Chinese herbal medicine.^{4,5} Examples of a few studies on *Dang Gui* (Angelica) that illustrate the diversity of effects are:

1. *Dang-Gui-Bu-Xue* decoction (Angelica is the main ingredient) increased the quantity of RBC, WBC and bone marrow nucleated cells (BMNC), and promoted the proliferation of BMNC and increased the quantity of colony-forming units (CFU)-Mix (progenitor cells). The most potent component was a polysaccharide of Angelica.⁶
2. *Dang Gui* (Angelica) attenuated visceral fat accumulation and improved hyperlipidemia in high-fat diet (HFD)-induced obesity by increasing lipid metabolism.⁷
3. *Dang Gui* (Angelica) alleviated the disordered blood glucose and lipids and protected against the progression of renal nephropathy in diabetic rats.⁸
4. *Dang Gui* (Angelica) was shown to have distinct antioxidant properties and be useful to rescue neuronal oxidative stress, by blocking lipid peroxidation and restoring the endogenous antioxidant system.⁹
5. For arthritis treatment, one of the mechanisms of action of chondroprotective effects of *Dang Gui* (Angelica) was shown to be due to a decrease in the hydrogen peroxide-induced interleukin-1beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha).¹⁰
6. Angelica was a potential chemopreventive agent through induction of detoxification enzymes.¹¹
7. *Dang Gui* (Angelica) combined with *Astragalus* (*Huang Qi*) protected against myocardial ischemia-reperfusion (IR) injury in a dose-dependent manner by enhancing myocardial mitochondrial as well as red blood cell (RBC) glutathione status, thereby increasing resistance to oxidative stress-induced injury in rats.¹²
8. *Dang Gui* (Angelica) contains water-soluble components that exerted protective effects against lethal endotoxemia and experimental sepsis in part by attenuating systemic accumulation of a late pro-inflammatory cytokine.¹³

One of the missions of the AJTCVM is to publish TCVM research and several original scientific studies of Chinese herbs as well as clinical studies and research reviews have been published over the past 6 years. In a bovine mastitis study by Wang et al the Chinese herbal extract pyrolacin compared favorably with four antibiotics and was suggested as a sole or integrated therapy to reduce expense and antibiotic resistance and

resides in milk.¹⁴ In another clinical trial, the Chinese herbal formula *Hai Zao Yu Hu Tang* was administered to 14 cats with hyperthyroidism and resulted in a significant reduction of heart and respiratory rates, hyperactive and aggressive behavior, polyphagia, vomiting, polyuria, and polydipsia. As well there was a significant weight gain and overall improvement of life quality even though thyroxin levels remained elevated.¹⁵

The classical Chinese herbal formula *Shen Qi Yi Mu Tang* is often used for postpartum complications in horses and cattle.¹⁶ A randomized controlled trial at a dairy farm was used to evaluate the effects of *Shen Qi Yi Mu Tang* on the antioxidant status of postpartum dairy cows. Twenty postpartum dairy cows, from the same farm, were randomly divided into control and treatment groups (n=10 in each group). Serum superoxide dismutase (SOD) activity, glutathione peroxidase (GSH-Px) activity, total antioxidant capacity (T-AOC) and malondialdehyde (MDA) concentrations were analyzed. The SOD activity, GSH-Px activity and T-AOC of dairy cows in the treatment group were elevated significantly compared to the control group ($p<0.01$ or $p<0.05$). The MDA levels declined significantly compared to the control group ($p<0.01$). From these findings it was concluded that *Shen Qi Yi Mu Tang* enhanced the antioxidant capacity of postpartum dairy cows.¹⁶

In an experimental randomized controlled trial in mice, the effects of the oral administration of eight Chinese herbs at three different doses on humoral immune responses were evaluated.¹⁷ Oral administration of *Bai Zhu* (*Atractylodes*) at all three doses and *Mai Men Dong* (*Ophiopogon*) and *Xuan Shen* (*Scrophularia*) at high doses significantly enhanced the serum ovalbumin-specific IgG, IgG2a, IgG2b and IgG3 responses and therefore potentiated the humoral immune response.¹⁷

In a clinical randomized controlled trial in nineteen horses that were diagnosed with acute necrotic hepatitis, twelve horses received the Chinese herbal medicine *Yin Chen Hu Gan San* and seven horses received conventional treatment. After 5 consecutive days of treatment, the icterus in horses of both groups had resolved and liver test parameters (serum icteric index, thymol turbidity, zinc sulfate turbidity, glutamate pyruvate transaminase activity and glutamic oxalacetic transaminase activity) had returned to the normal range. However, horses in the control group had residual weakness, reduced appetites and incomplete digestion as compared to those in the *Yin Chen Hu Gan San* group. Although liver test parameters had returned to the normal range in both groups, the mean values were also significantly lower ($p<0.01$) in the *Yin Chen Hu Gan San* group. It was concluded from this study that *Yin Chen Hu Gan San* could be an effective treatment for acute non-infectious hepatitis.

In another experimental randomized controlled trial, the antibacterial and antiviral effects of two different concentrations of a combination of nine Chinese herbs were evaluated in shrimp aquacultures. After being fed

the herbs for 60 days, groups of shrimp were exposed to *Vibrio alginolyticus* or white Spot syndrome virus. There was a significant reduction of shrimp deaths in the herbal groups compared to the non-treated control group for both common infectious disease.¹⁹ The long term follow-up of eight dogs with mammary neoplasia treated with surgical excision plus a proprietary blend of 28 Chinese herbs was reported and survival rates were significantly higher than previously published reports for dogs treated with surgical excision and conventional chemotherapy.²⁰

Review articles on the clinical applications and research on the commonly used Chinese herbal formulas *Si Wu Tang*, *Shi Quan Da Bu Tang*, *Si Jun Zi Tang* and Chinese herbal medicines for equine respiratory diseases and the prevention and treatment of cancer have also been published in AJTCVM.²¹⁻²⁵ In this issue of AJTCVM an experimental randomized controlled study of *Ren Shen* (Ginseng) in mice showed that two saponins, ginsenoside Rg1 and Rb1 enhanced several immune parameters and had adjuvant properties via estrogen receptors that enhance the effectiveness of the antibody response to vaccinations.²⁶ Also in this issue an experimental randomized controlled study showed that the addition of a proprietary blend of eight Chinese herbs added to the feed of hens had a significant positive effects on egg production, immune function and oxidative stress indicators compared to controls and may be an effective replacement for conventional drugs in poultry production.²⁷

Endangered Species Are Not Used in Veterinary Chinese Herbal Formulas

The Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) is an international agreement between governments.²⁸ Its aim is to ensure that the international trade in specimens of wild animals and plants does not threaten their survival. Detailed information can be found at <http://www.cites.org/>. The CITES was drafted as a result of a resolution adopted in 1963 at a meeting of members of the World Conservation Union. The text of the CITES was ratified at a meeting of representatives from eighty countries on March 3, 1973. The CITES agreement has been a mandatory regulation in China since September 1, 2006, when the agreement was signed by Wen Jiabao, the Prime Minister of China.²⁹

The CITES protects approximately 5,000 species of animals and 28,000 species of plants against over-exploitation through international trade. There are three levels of endangerment and the species are listed in the three appendices of the CITES documents.²⁸ Appendix I lists species that are the most endangered among CITES-listed animals and plants. They are threatened with extinction and CITES prohibits international trade. Appendix II lists species that are not threatened with extinction now, but that may become so unless trade is closely controlled. Appendix III is a list of species

included at the request of a group that already regulates trade in the species and that needs the cooperation of other countries to prevent unsustainable or illegal exploitation. International trade in specimens of species listed in this appendix is allowed only on presentation of the appropriate permits or certificates.

When an herbal manufacturer in China wishes to export its herbal product, it must apply for an export permission certificate from the General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China (AQSIQ) in Beijing.³⁰ A complete list of all herbal ingredients must be supplied to AQSIQ and if any ingredient of a herbal product is listed as an endangered species by the CITES then permission for export will be denied. Endangered species are not part of Chinese herbal formulas for humans or animals today.

Regulations for Importation of Chinese Herbal Medicine to the United States

Also when applying for export permission from AQSIQ, an herbal manufacturer in China must provide documents containing the results of screening tests for heavy metals, pesticide residues, moisture and bacteria as requested by an importing company in the USA.³⁰ If any ingredient of a herbal product does not meet the testing requirements, then appropriate permissions will not be granted and thereby, the herbal product cannot be sent to the United States (US). When an herbal product arrives at the US border, it must go through customs and quarantine processes including US Federal Drug Administration (FDA) and the US Department of Agriculture (USDA) inspections. The USDA inspections focus on infectious pathogens related to plants and animals and also on CITES compliance. The FDA inspections also focus on the safety of the herbs. If an herbal product fails inspection by USDA or the FDA, it will be destroyed or returned to China with the costs paid by the importing company.

The United States Food and Drug Administration (FDA) has established current Good Manufacturing Practices (cGMP) guidelines for all dietary supplements, which includes herbal supplements.³¹ The cGMP standard is a basic requirement for the manufacture of all Chinese herbal products and is the same for both herbal and pharmaceutical drugs in China. All reputable Chinese herbal companies in the United States comply with both the US cGMP and Chinese GMP regulations and standards to ensure purity, consistent composition, safety, efficacy and quality of all finished products. A rigorous compliance process evaluates the facility, including materials used in its construction and the grounds surrounding the facility, production and testing equipment, calibration of equipment, personnel and training, sanitation and hygiene, air and water purification, environmental conditions for both storage and manufacturing, the manufacturing process, receiving

and testing of all raw components, product testing for identity, purity, strength and composition and the traceability of all ingredients and components used in each batch produced. These standards also provide documentation that correct, consistent procedures are followed at each step of the manufacturing process.

Chinese Herbal Medicine Safety

The FDA is continuously updating its toxicological data on herbs in an effort to enhance screening and reduce safety issues. The American Association of Traditional Chinese Veterinary Medicine (AATCVM) in its Case Discussion Forum is adding a section on Herbal Guidelines and Safety where suspected adverse reactions to specific Chinese herbal medicines may be posted. The toxicity of Chinese herbal medicines was also the subject of a recent AJTCVM review article.¹ In this article it stated “Adverse reactions are due to the use of known toxic herbs, mistaken herbal substitutions, inappropriate use of herbs, processing mistakes, herb overdose, inappropriate herbal combinations, drug interactions with conventional pharmaceutical drugs, individual patient sensitivity and misdiagnosis and mistreatment of the traditional Chinese veterinarian medicine pattern diagnosis”.¹

Veterinarians practicing conventional medicine may want to know “the best” Chinese herbal medicine to treat a specific conventional diagnosis, but the “one size fits all” therapy model does not apply to TCVM and especially when using Chinese herbs. Since there are usually several different TCVM patterns associated with one conventional diagnosis, the most effective Chinese herbal medicine will vary depending on the TCVM pattern. To avoid adverse reactions and ensure the optimum efficacy, the correct Chinese herbal prescription must be based on a correct TCVM disease pattern identification. For example, treatment of chronic renal failure due to Kidney *Yin* Deficiency with a hot herbal formula such as *You Gui Wan* can worsen the Kidney *Yin* Deficiency and the clinical signs, adversely affecting the patient. *You Gui Wan* is designed for Kidney *Yang* Deficiency but contraindicated for any Kidney *Yin* Deficiency Pattern. To ensure safety and proper use of Chinese herbs, conventionally trained veterinarians must receive further training and study in TCVM and Chinese herbal medicine. Increasing scientific evidence for the efficacy and safety of many Chinese herbal medicines, more stringent regulations of the herbal industry and improved continuing education programs for veterinarians ensure Chinese herbs are used appropriately and safely. Further investigations of traditional Chinese veterinary herbal medicine integrated with conventional treatments or as sole therapy are warranted.

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ABSTRACT

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Ancient Chinese medicine and mechanistic evidence of acupuncture physiology.

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Acupuncture has been widely used in China for three millennia as an art of healing. Yet, its physiology is not yet understood. The current interest in acupuncture started in 1971. Soon afterward, extensive research led to the concept of neural signaling with possible involvement of opioid peptides, glutamate, adenosine and identifying responsive parts in the central nervous system. In the last decade scientists began investigating the subject with anatomical and molecular imaging. It was found that mechanical movements of the needle, ignored in the past, appear to be central to the method and intracellular calcium ions may play a pivotal role. In this review, we trace the technique of clinical treatment from the first written record about 2,200 years ago to the modern time. The ancient texts have been used to introduce the concepts of yin, yang, qi, de qi, and meridians, the traditional foundation of acupuncture. We explore the sequence of the physiological process, from the turning of the needle, the mechanical wave activation of calcium ion channel to beta-endorphin secretion. By using modern terminology to re-interpret the ancient texts, we have found that the 2nd century B.C.: physiologists were meticulous investigators and their explanation fits well with the mechanistic model derived from magnetic resonance imaging (MRI) and confocal microscopy. In conclusion, the ancient model appears to have withstood the test of time surprisingly well confirming the popular axiom that the old wine is better than the new.