

Review of Traditional Chinese Herbs Used in the Clinical Treatment of Canine Parvovirus Infection

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ABSTRACT

Chinese medicinal herbs that have appeared useful for prevention and treatment of viral diseases and in particular, canine viruses, have attracted research attention in recent years. Canine parvovirus infection which can be associated with high morbidity and mortality continues to cause disease outbreaks due to lack of efficacy of preventative procedures and immunity failure of susceptible animals. Increasingly researchers have been evaluating herbs ranging from traditional formulas to self-made prescriptions that have anti-viral activity to improve treatment and control of canine parvovirus infection. In this review, Chinese herbal medicines that appear to provide both effective treatment and a complimentary adjunct to traditional Western methods of treatment are presented.

Key words: Traditional Chinese herbs, canine parvovirus, traditional Chinese veterinary medicine

ABBREVIATIONS

CPV	Canine Parvovirus
TCVM	Traditional Chinese Veterinary Medicine
TCM	Traditional Chinese Medicine

Traditional Chinese medicine (TCM) which originated in ancient China has evolved over thousands of years. The Yellow Emperor's Inner Canon, the oldest recorded work of Chinese medical theory, was compiled around the first century BCE and was based on shorter texts from different medical lineages.^{1,2} Based on these early principles, TCM practitioners use various forms of herbal medicine, acupuncture, massage (Tui-na), exercise (Qi-gong) and dietary therapy to treat a wide range of disease syndromes.^{3,4} Although TCM has a long history and has been used for thousands of years, it was not widely used or recognized by western countries until approximately 20 years ago.^{5,6} It is gradually gaining acceptance as some TCM methods and herbs to prevent or treat disease demonstrate efficacy in both clinical and mechanistic research.^{7,8}

In 1970, Binn and coworkers first reported the isolation of a parvovirus from asymptomatic dogs.^{9,10} Many veterinary clinicians and researchers throughout the

world sensed the presence of a new disease when canine parvovirus type 2 (CPV-2) was first confirmed in 1978 and then, within 1-2 years, spread worldwide.¹¹⁻¹⁵ Since then CPV-2 has continued to genetically evolve, with CPV 2a, 2b and 2c gradually replacing earlier strains.¹⁶⁻¹⁸ Since 1979, nearly 108,000 articles, papers, numerous text chapters and monographs have been published on the subject of canine parvovirus. At present, canine parvovirus (CPV) infection is primarily caused by CPV-2 with clinical signs including severe vomiting, leukopenia, myocarditis and hemorrhagic gastroenteritis. Its infection rate is as high as 100%, while the case fatality ratio ranges from 10%-50%.^{19,20} In recent years, researchers have proposed a variety of methods for prevention of canine parvovirus, such as a canine parvovirus DNA vaccine (pVCPV-VP2), CPV recombinant live vector vaccine (CAV2 / CPV), canine parvovirus enteritis attenuated vaccine (M-CPV) and canine parvovirus monoclonal antibodies (CPV McAb).²¹⁻²⁵ Vaccination failure, however, is common and predominately associated with interference by maternally derived immunity, antigenic drift, secondary infections and environmental factors; therefore, effective treatment of the disease continues to be important.²⁶⁻²⁸ In this review, Chinese herbal medicines that appear to provide both effective treatment and a complimentary adjunct to traditional Western methods of treatment will be presented. It is hoped this review will contribute to an understanding of Chinese herbal medicines as an effective treatment for CPV and provide useful information for the development of more effective antiviral drugs.

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CHINESE HERBAL FORMULAS WITH ANTI-CPV ACTIVITY

Traditional Chinese veterinary herbal formulas are a combination of compatible herbs in fixed dosages guided by TCM principles, and are usually derived from classical or well-known Chinese textbooks of medicine (e.g., *Yuan Heng Liao Ma Ji*, the first traditional Chinese veterinary medicine book).²⁹ Currently, several traditional Chinese herbal formulas have been found to have a potentially beneficial effect for treating CPV. A brief outline of the antiviral pharmacology of the most commonly used Chinese herbal formulas is discussed below and summarized in Table 1.

Yu Jin San

Yu Jin San is a traditional Chinese herbal formula, originally recorded in *Yuan Heng Liao Ma Ji* written by Yu Benyuan and Yu Benheng in 1608 C.E. This formula clears Heat and detoxifies the large and small intestine and has been used to treat CPV.³⁰ It is a mixture of ten herbs: *Jiang Huang* (Curcuma), *He Zi* (Chebula), *Huang Qin* (Scutellaria), *Da Huang* (Rheum), *Huang Lian* (Coptis), *Zhi Zi* (Gardenia), *Bai Shao* (Niae Alba), *Huang Bo* (Phellodendron) and *Gui Pi* (Cinnamomum verum). Some researchers have added Yunnan Bai Yao (to control hemorrhage), along with 40% *San Qi* (Notoginseng), 13.3% *Shan Yao* (Dioscorea), 6% *Di Yu* (Dioscorea Parviflora), 11.5% *Ye Shan Yao* (Dioscorea Nipponica), 5% *Bai Niu Dan* (Inulae Cappae), 17% *Li Zhi Hao* (*Ajuga Forrestii*) and 7.2% *Lao Guan Cao* (*Geranii*), to the *Yu Jin San* formula for treating CPV disease.³¹

Shao Yao Tang

This formula combines herbs with known antibacterial and antiviral properties and acts to drain Heat and Damp. The source of this herbal formula is *Suo Wen Bing Ji Qi Yi Bao Ming Ji*, written by Liu Yuan Su in the Song and Jin periods.³² It is a mixture of ten herbs: *Shao Yao* (Paeonia), *Gan Cao* (Glycyrrhiza), *Huang Lian* (Coptis), *Huang Qin* (Scutellaria), *Mu Xiang* (Saussurea), *Bing Lang* (Areca), *Dang Gui* (Angelica), *Guan Gui* (Cinnamomum) and *Da Huang* (Rheum). This formula combines herbs that resolve Phlegm, tonify the Spleen, and resolve Stagnation (*Qi* Stagnation and/or Blood Stagnation secondary to a toxin such as Heat).³⁰

NOVEL CLINICAL CHINESE HERBAL MEDICINE PRESCRIPTIONS WITH ANTI-CPV ACTIVITY

Prescription 1:

This prescription created by the sixty-sixth Regiment of the Fourth Agricultural Division's Veterinary Station located in Xinjiang province and Boxing County's Animal Husbandry Bureau located in Shandong province contains *Huang Lian* (Coptis) 15 g, *Huang Qin* (Scutellaria) 15g, *Ge Gen* (Pueraria) 8g, *Fu Ling* (Poria) 10g, *Che Qian Zi*

(*Plantago*) 6g, *Di Yu* (Sanguisorba) 8g, *Hou Pu* (Magnolia) 8g, *Huo Xiang* (Pogostemon) 6g, *Zi Jin* (Corydalis) 5g, *Huang Qi* (Astragalus) 12g, and *Gan Cao* (Glycyrrhiza) 8g. According to Ge *Gen Huang Qin Huang Lian Tang's* research, the cure rate of canine parvovirus disease with this formula approaches 96%.³³ If the affected animal was treated early and the disease syndrome was mild, the cure rate among puppies 3-12 weeks old and adults extending in age to more than 5 years old was 100%. In contrast, treatment failure occurred when a dog presented with a dry and cracked nose, oral ulcers, no appetite, poor anal tone, and body temperature less than 102 degrees F°. ³³ In particular, there was high mortality in dogs with severe hematochezia and vomiting; most likely associated with poor absorption of the active ingredient of the formula due to vomiting.

Prescription 2:

The Shenqin compound consisting of *Ku Shen* (Sophora), *Ban Lan Gen* (Isatis), *Jin Yin Hua* (Lonicera), *Lian Qiao* (Forsythia), *Huang Qi* (Astragalus), *Bai Zhu* (Atractylodes), and *Dan Shen* (Salvia) was developed by the Animal Medicine Department of Southwest University (Chongqing, China). The formula is based on the Eight Principles theory and is designed to treat affected animals by moving Blood, clearing Heat Toxin, and removing Damp. Liu Junwei et al. reported that Shenqin compound could up-regulate the expression of Bcl-2 mRNA (anti-apoptotic protein expression) and down-regulate the Bax mRNA (apoptotic activator protein). As an apoptotic activator, this protein forms a heterodimer with Bcl-2 to inhibit myocardial apoptosis and protect canine myocardium from canine parvovirus damage.^{34, 35.}

Prescription 3:

Compound Kuqin, based on Eight Principles and *Zang Fu* patterns, contains *Ku Shen* (Sophora), *Huang Qin* (Scutellaria), *Huang Qi* (Astragalus), *Jin Yin Hua* (Lonicera), *Guang Huo Xiang* (Pogostemon), *Bai Tou Weng* (Pulsatilla), *Zhi Zi* (Gardenia) and *Bai Zhu* (Atractylodes). Formula characteristics include Heat-clearing and treating diarrhea (astringent qualities of Sophora and Scutellariae); and tonifying the Spleen by Astragalus and Rhizoma Atractylodes.^{36, 37} Compound Kuqin demonstrated a protective function against canine parvovirus in dogs receiving injections (0.5mL/kg body weight, three times per a day for 3 consecutive days) of the compound. Zhu Zhaorong reported survival rate reached 90% in dogs dosed with Compound Kuqin and then injected with CPV and recovery of the Compound Kuqin treatment group when clinically sick which reached 70%. This study also demonstrated that compound Kuqin had an immune modulating activity characterized by increased serum gamma globulin, total white blood cell count, and macrophage phagocytosis in the mouse abdominal cavity.^{38.}

Table 1: Traditional Chinese herbal formulas with anti-CPV activities

Common Name	Source	Composition	Biological activity	Ref.
<i>Yu Jin San</i>	Yuan Heng Liao Ma Ji the Ming dynasty (1608 C.E.)	Includes 9 herbs: <i>Jiang Huang</i> (Curcuma), <i>He Zi</i> (Chebula), <i>Huang Qin</i> (Scutellaria), <i>Da Huang</i> (Rheum), <i>Huang Lian</i> (Coptis), <i>Zhi Zi</i> (Gardenia), <i>Bai Shao</i> (Niae Alba), <i>Huang Bo</i> (Phellodendron), <i>Gui Pi</i> (Cinnamomum verum)	Anti-inflammatory, anti-bacterial (<i>Pseudomonas aeruginosa</i>), treats canine hemorrhagic enterocolitis and CPV disease	[28, 32, 62-65]
<i>Shao Yao Tang</i>	<i>Suo Wen Bing Ji Qi Yi Bao Ming Ji</i> Song and Jin periods (1186 A.D.)	Includes 9 herbs: <i>Shao Yao</i> (Paeonia), <i>Gan Cao</i> (Glycyrrhiza), <i>Huang Lian</i> (Coptis), <i>Huang Qin</i> (Scutellaria), <i>Mu Xiang</i> (Saussurea), <i>Bing Lang</i> (Areca), <i>Dang Gui</i> (Angelica), <i>Guan Gui</i> (Cinnamomum) and <i>Da Huang</i> (Rheum)	Immunomodulation, treat canine hemorrhagic enterocolitis, ulcerative colitis and acute radiation proctitis	[30, 66-70]
Novel Clinical Chinese herbal medicine prescription I	Sixty-six Regiment Veterinary Station, Agricultural Fourth Division, Production and Construction Corps (Xinjiang, China)	Includes 11 herbs: <i>Huang Lian</i> (Coptis), <i>Huang Qin</i> (Scutellaria), <i>Ge Gen</i> (Pueraria), <i>Fu Ling</i> (Poria), <i>Che Qian Zi</i> (Plantago), <i>Di Yu</i> (Sanguisorba), <i>Hou Pu</i> (Magnolia), <i>Huo Xiang</i> (Pogostemon), <i>Zi Jin</i> (Corydalis), <i>Huang Qi</i> (Astragalus), and <i>Gan Cao</i> (Glycyrrhiza)	Treat CPV disease	[33]
Novel Clinical Chinese herbal medicine prescription II (Shenqin compound)	Animal Medicine Department of Southwest University (Chongqing, China)	Includes 7 herbs: <i>Ku Shen</i> (Sophora), <i>Ban Lan Gen</i> (Isatis), <i>Jin Yin Hua</i> (Lonicera), <i>Lian Qiao</i> (Forsythia), <i>Huang Qi</i> (Astragalus), <i>Bai Zhu</i> (Atractylodes), and <i>Dan Shen</i> (Salvia)	Treat CPV disease	[34, 35]
Novel Clinical Chinese herbal medicine prescription III (Compound Kuqin)	Animal Medicine Department of Southwest University (Chongqing, China)	Includes 8 herbs: <i>Ku Shen</i> (Sophora), <i>Huang Qin</i> (Scutellaria), <i>Huang Qi</i> (Astragalus), <i>Jin Yin Hua</i> (Lonicera), <i>Guang Huo Xiang</i> (Pogostemon), <i>Bai Tou Weng</i> (Pulsatilla), <i>Zhi Zi</i> (Gardenia) and <i>Bai Zhu</i> (Atractylodes)	Heat-clearing, tonify the Spleen	[26, 36, 37]
Novel Clinical Chinese herbal medicine prescription IV	Animal Center of PLA General Hospital Medical Laboratory	Mainly composed of 2 herbs: <i>Shan Cha</i> (Camellia japonica L.) and <i>Huang Qi</i> (Astragalus) Chinese Patent Formula	Anti-bacterial and anti-viral	[39]

Prescription 4:

In a survey on the antiviral effects of *Cass nomame* (sieb) Honda, it was superior to other anti-viral extracts applied to F81 cells with a 63.04% inhibition rate of its composite. Gou Peng et al. (Medical Laboratory Animal Center of PLA General Hospital) reported this formula was mainly composed of *Shan Cha* (*Camellia japonica* L.) and *Huang Qi* (*Astragalus*).³⁹ The IC₅₀ against CPV was 1:587.5. In addition, the formula had an inhibitory effect against *Escherichia coli*, salmonella and staphylococcus aureus with 6.25 mg, 25 mg and 12.5 mg, respectively, in MIC assays. It has yet to be used in clinical cases but shows promise.

SINGLE CHINESE HERBS WITH ANTI-CPV ACTIVITY**Lysimachia**

Lysimachia, (known as *Jin Qian Cao* or *Ma Ti Xiang*) affects gastrointestinal movement, is a sedative, provides analgesia, and has anti-cancer and antiviral activity.⁴⁰⁻⁴² Research at Shaoxing People's Hospital (in Shaoxing, Zhejiang Province) demonstrated that *Ma Ti Xiang* could suppress peristalsis and shorten the time of diarrhea secondary to severe enteritis.⁴³ It was also reported that *Ma Ti Xiang* was curative for CPV disease with resolution of intestinal mucosal lesions.⁴⁴

CHINESE HERBAL EXTRACTS WITH ANTI-CPV ACTIVITY

In recent years, active research centered on producing anti-viral medications from biologically active components of Chinese herbal medicines has increased. The most popular extractions are polysaccharides, alkaloids and flavonoids, which are being evaluated for their anti-viral activity.

Polysaccharides

Polysaccharides are polymeric carbohydrate molecules composed of long chains of monosaccharide units bound together by glycosidic linkages. It is the form in which most natural carbohydrates occur and hydrolysis will break them into constituent monosaccharides or oligosaccharides. Examples include starch, glycogen, cellulose, and chitin. Current research has demonstrated that polysaccharides have anti-viral and anti-cancer effects along with immunomodulation, which stimulates protective immunity.

Feng et al. reported that *Astragalus* polysaccharides (APS), *Rhizoma Atractylodes* polysaccharides (RAPS), root of *Baikal skullcap* polysaccharide (BSPS) and *Flos Lonicerae* polysaccharide (FLPS) are biologically active polysaccharide ingredients of compound Kuqin. Resistance to canine parvovirus was demonstrated by CPV infected F81 (cat fetal kidney cells) cell line studies receiving the compound.^{45, 46, 47.}

Additional work reported by Gou Peng, demonstrated the alcohol extract precipitation of *Cass nomame* (sieb) *honda*, which is a polysaccharide, resisted canine parvovirus infection in-vitro with an inhibition rate of 55.24%.³⁹ The inhibition rate of its composite consisting of *Cass nomame* (sieb) *honda*, *Astragalus* and *Coptis* was 63.04% and the composite could inhibit drug-resistant strains of *Escherichia coli* and *S. cholera* along with enhancement of effective lymphocyte transformation.³⁹

In a review of anti-viral activities of the pinon shell polysaccharide (PSP), which is extracted from Korean pine in China, it was noted that this polysaccharide displayed a distinct antiviral effect at different concentrations on two viruses, one of which was CPV. At the lowest concentration (31.2 mg/liter), cell survival rates were above 49.08% for all three methods used (pretreatment, pretreatment/ posttreatment, posttreatment).⁴⁸

Flavonoids

Flavonoids are widely distributed in plants, fulfilling many functions. They are the most important plant pigments for flower coloration as well as producing yellow or red/blue pigmentation in petals designed to attract pollinators.^{49, 50} In higher plants, flavonoids are involved in UV filtration, symbiotic nitrogen fixation and floral pigmentation. Their dietary intake is quite high compared to other dietary antioxidants like vitamins C and E.^{51, 52}

Studies evaluating flavonoid activity have been plentiful in recent years.⁵³ Feng et al. demonstrated that the *Flos Lonicerae* flavone (FLF) from Compound Kuqin, at a dose of 15.625-7.813mg/L can inhibit CPV proliferation in F81 fetal cell lines.⁴⁷ Carvalho et al evaluated the effect of the flavonoid, quercetin, on canine parvovirus replication in-vitro through a series of assays. Test 1 determined its viracidal activity, Test 2 looked at activity on the cell and test three, its effect (time assay) on steps of the viral replication cycle. Quercetin showed significant antiviral activity, with maximum values of 96.3% virus reduction in test 1, and 90% for tests 2 and 3. The most significant effects occurred in adhesion and viral penetration.⁵⁴

Alkaloids

Alkaloids are a group of naturally occurring chemicals that are made by plants and are organic nitrogen containing bases. Many *alkaloids* possess potent pharmacologic effects on humans and other animals and include such well-known substances as morphine, strychnine, quinine and nicotine.⁵⁵⁻⁵⁸

Alkaloids from northern Nigeria plants with a history of use in both human and veterinary traditional medicine were tested for viracidal activity against poliovirus, astrovirus, herpes simplex viruses and parvovirus, using microtitre plate inhibition tests at a dose rate between 100 and 400 µg/100 µl.⁵⁹ Wang et al. reported that the alkaloids from *Corydalis* were able to inhibit HIV-1 reverse transcriptase.⁶⁰

Rymerson et al. reported that *N. tabacum* cultivars (containing 81V9 alkaloid) derived from the upper leaves enhances the ability of serum antibodies to neutralize the infectivity of porcine parvovirus as demonstrated by a serum neutralization assay (1:2700–1:3900). This suggests the alkaloid (81V9) associated with the *N. tabacum* leaves may mimic VP2 (major protective surface antigen of porcine parvovirus) and has potential to improve the efficacy of a vaccine against this virus.⁶¹

CONCLUSION

Based upon review of current scientific literature and upon prior knowledge and experience of the author, Chinese herbal medicines (including Chinese herbal formulas, single herbs and related biologically-active compounds) that appear effective and worthy of additional in-depth study in treating CPV were selected for presentation. Experimental results from both mechanistic and clinical studies demonstrate that there is mounting evidence that some Chinese herbal medicines (e.g. *Yu Jin San*, *Shao Yao Tang* and Compound Kuqin) can be an effective treatment for clinical cases of canine parvovirus. Further investigation in well-designed clinical trials will yield a better understanding of mechanisms, therapeutic effects, and the safety profile of Chinese herbal medicine used to treat canine parvovirus disease and will give clinicians another tool to combat this serious canine disease.

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