**CHINESE HERBAL MEDICINE IN AUTOIMMUNE DISEASE: CASE REPORTS AND SPECULATED MECHANISMS OF ACTION**

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**Introduction**

Distinguishing between self- and non-self antigens is a vital function of the immune system and serves as a specific defense against invading microorganisms. Failure of this self tolerance leads to "autoimmunity", which literally means immunity against self and is caused by an immune-mediated reaction to self-antigens (1). Susceptibility of the host to pathological autoimmune states has a genetic basis in humans and animals, although numerous viruses, bacteria, chemicals, toxins and drugs have been implicated as the triggering environmental agents (1-4). This mechanism operates by a process of molecular mimicry and/or non-specific inflammation, and is most often mediated by T-cells or their dysfunction (5, 6). The resultant autoimmune diseases reflect the sum of the genetic and environmental factors involved. As stated in a landmark review "perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity" (1).

Autoimmune disease in humans is equal or greater to the incidence of heart disease, the number one cause of death in America. While we don't have exact statistics on the number of clinical cases of diagnosed autoimmune disease in animals, incidence is clearly on the rise. Incidence appears to have increased by five times over the last 20 years. The scale of increase is not able to rationalized by increased awareness or improved diagnostic acumen.
Autoimmune diseases in animals come in many forms, from the mild and manageable to the severe and fatal. They are not generally thought of as curable, with the most severe of them being resource intensive to treat.

Treatments themselves are deliberately “ham-fisted”, suppressing the immune system on a wholesale level rather than providing a nuanced effect consistent with the pathogenesis of the animal’s particular condition. Despite their blunt-force sweeping effects, they are surprisingly inconsistent in controlling disease. Side effects are inevitable, however, varying only in severity. Dissatisfaction with current treatment options has led veterinarians to seek therapeutic alternatives.

This article reviews two cases in which herbal formulas were used to treat two different autoimmune conditions. The same formulas were used in both cases, either in tandem or in sequence. While applied based on Chinese medical theory, ample research exists to explain their efficacy in biomedical terms, revealing new and clinically relevant pathways that might be targeted in the future by pharmaceuticals and other alternative therapies.

**Case 1: Immune-Mediated Hemolytic Anemia (also called Autoimmune Hemolytic Anemia, AIHA)**

**Episode I**

In November of 2012, Lancelot, a 6 year old male neutered Shih-Tzu cross was admitted to a specialty facility in Edmonton, Alberta, Canada with a chief complaint of dyspnea, lethargy and inappetence of a few days duration. Lancelot preferred to be outside in the hours leading up to his admission to hospital, and seemed to crave ice and snow, rather than water.
No cause of the illness was evident. The past medical history included only inactive glaucoma with permanent buphthalmos and an eye that was painless and avissual. No treatment was being provided.

A complete blood count upon admission disclosed a hematocrit of 13%, a very low platelet count, nucleated red blood cells, and spherocytes. Red cells were observed to agglutinate in saline and a diagnosis of Evans syndrome (IMHA + immune-mediated thrombocytopenia, IMTP) was made.

Treatment consisted of a blood transfusion, cyclosporine, immune-suppressive doses of prednisone, famotidine, and maropitant. The hematocrit initially increased to 30% within a few hours of initiating therapy, but then fully declined again over the next three days to pre-treatment levels despite continued drug therapy. Platelet numbers did not respond.

A second transfusion was performed following cross-matching 3 days later. The hematocrit increased again, this time to 38%, but once again began to immediately drop following discontinuation. Despite this, Lancelot was discharged, in the hopes that his medications would take effect before his hematocrit dropped again, but within four days (a week after starting therapy) it had dropped to 21.5%. Platelets at this time were slightly below normal. At this point, Lancelot was referred to one of the authors (SM) for care.

At the time of presentation, in addition to the above-noted findings, Lancelot was vomiting in the early morning hours, had yellow runny stool, was exhibiting high thirst, and was now seeking warmth. Physical examination disclosed rapid prominent superficial and toneless pulses that immediately moderated upon acupuncture to GV 20, GV 3, BL 40, and BL 17. A tonifying treatment was used on all points, which emphasizes the in-thrust of the acupuncture needle.
Lancelot was prescribed a variant of the classical Chinese herbal formula known as Qing Ying Tang, distributed as Cool the Blood Combination (a). The formula is a commonly used alternative treatment for hemolytic anemia, and was dispensed at a dose of 2 ml four times daily. Additionally, Lancelot was prescribed homeopathic China officinalis, 30C strength, to be given four times daily. Meanwhile, at the referring veterinary clinic’s instruction, prednisone was continued at a tapering dose along with famotidine and sulcrate.

Immediately post-acupuncture, Lancelot’s appetite reportedly improved, but was not yet normal. Over the next 48 hours, the stool became darker, vomiting stopped, and lethargy was reduced. The hematocrit increased to 25.5%. After 5 more days, the hematocrit returned to post-transfusion levels, and two weeks following initiation of holistic therapies, the hematocrit was normal. Since the Christmas season was approaching, the owner elected to continue herbal therapy until January 2013.

**Episode II**

Almost exactly six months later, in March 2013, Lancelot re-presented in a state of hemolytic crisis despite having resumed the Qing Ying Tang (a) three weeks earlier because of intermittent restlessness, vomiting, lethargy and inappetance. A CBC at the start of Qing Ying Tang (a) treatment showed a high normal hematocrit.

During the crisis, Lancelot’s hematocrit fell to 10% and his platelets to 58,000 per cu mm. A CBC repeated approximately 2 hours later confirmed these findings. Lancelot had pale gums with a questionably enlarged spleen. He was tachypneic with even slight exertion. His pulse was toned and relatively superficial and forceful. Acupuncture was administered, and the pulse moderated with tonification of GB 25, BL 19 and KI 3.
Despite the severity of the anemia, the owners of Lancelot declined a transfusion and admission to a critical care facility. Instead they requested holistic care only, and a variant of Minor Bupleurum Combination known as Bupleurum, Dragon Bone and Oyster Shell Combination (Chai Hu Jia Long Gu Mu Li Tang; b) was prescribed. The formula was chosen because of its purported abilities in modulating the immune system and promoting splenic contraction. At 22 lbs., Lancelot was given the standard human dose of 1.5 grams at a frequency of three to four times daily. Homeopathic China officinalis was also reinstituted three times daily. No pharmaceuticals were administered.

Within just 18 hours, and in the absence of any transfusion, Lancelot’s hematocrit had risen to 29%, although platelets were still low. Therapy was continued. One day later, the hematocrit and platelet count were not substantially changed and Liu Jun Zi Tang (Six Gentle Pets, c) was instituted at a dose of 2-3 ml three times daily to support appetite, digestion, bone marrow activity and overall vigor. After 5 more days, both counts were within the normal range.

**Case 2: Systemic Lupus Erythematosus**

**History and Physical Examination**

Soffee, a six year old female spayed American Staffordshire terrier presented with a three year history of systemic lupus erythematosus (SLE) that arose following boarding (and possible vaccination) at a kennel facility. Initial signs and symptoms included:

- Fever
- Lameness
- Dermatitis
The condition was initially managed with prednisone (dose not provided), which aided all symptoms at first, but then only the dermatitis with sustained use. Side effects appeared that were unacceptable to the owner, including reverse sneezing and a chronic cough. The drug was subsequently discontinued.

A commercial raw meat diet was instituted, and various homeopathic remedies applied upon the advice of another local veterinarian. Neither these remedies nor the diet particularly aided the condition, but they produced no adverse effects. The owner was then referred to the author’s (SM) clinic.

Examination of Soffee disclosed a highly toned (or ‘wiry’) pulse, and purplish tongue discoloration. Upon scanning of Soffee with an infrared camera, an abrupt thermal gradient was seen in all four limbs at the elbows and knees, with the lower limb and paw being much cooler than the proximal portion of the same limb. Physical examination also revealed:

- Alopecia with associated papules and scabs of the head, ventrum and medial thighs
- Swelling of interphalangeal joints, and of the foot in general, that was worse when stationary

The owner remarked that Soffee was severely itchy, especially in the mornings on waking and again at night. She had also noted apparent hind limb pain that resulted in difficulty sitting down. Soffee also had generally low energy.

**Treatment**

Soffee responded immediately to acupuncture and chiropractic treatment for her hind end discomfort. The owner noted a marked increase in energy level lasting for the next few days.
Additionally, Soffee was prescribed Qing Ying Tang (d) at a dose of 4 g twice daily. Treatment was continued for five months, with Soffee exhibiting dose-dependent improvements. After one month, the owner noted:

- Swollen feet had resolved
- Soffee was itchy when anxious, but not at night
- Hair had regrown in alopecic areas
- Soffee was much more comfortable sitting down
- The cough had resolved

Five months after initiating treatment, Soffee experienced a resurgence of some of her complaints. Stiffness had recurred and she was pruritic along her left side. She had also started licking her toes frequently, as though they were painful. Scabs were noted on the side of her neck and the top of her head, although alopecia was still reduced and the cough remained resolved.

Soffee was prescribed a formula known as Minor Bupleurum Combination (Xiao Chai Hu Tang; e) at a dose of 2 grams BID. Qing Ying Tang (d) was continued.

After an additional five months, Soffee was again re-evaluated. Minor Bupleurum (e) had not been used for the entire period. Qing Ying Tang (d) had been used steadily, but improvements had ceased to accrue. Itch continued to a certain extent. Soffee was still licking her toes, but swelling and alopecia had resolved. Lameness was minimal, and the skin lesions and alopecia were stable. Soffee was prescribed a variant of Minor Bupleurum known as Chai Hu Jia Long Gu Mu Li Tang (Bupleurum, Dragon Bone and Oyster Shell Combination; b). Two weeks later, the owner reported Soffee continued to have good mobility, and was not pruritic. Toe redness
was being seen again, so Qing Ying Tang (d) was resumed. Treatment with the two formulas continues.

**Discussion**

The same two formulas proved effective in the treatment of two different patients, echoing the situation in conventional medicine where a handful of immunosuppressive drugs are applied to a wide array of disorders. We’ll see below, however, that a crucial difference between use of herbs and drugs is their molecular targets.

**Table 1. Qing Ying Tang (Clear the Nutritive Level Combination, d)**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Description</th>
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<tbody>
<tr>
<td>Sheng Di Huang</td>
<td>Rehmannia root</td>
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<tr>
<td>Jin Yin Hua</td>
<td>Honeysuckle flower</td>
</tr>
<tr>
<td>Xuan Shen</td>
<td>Scrophularia root</td>
</tr>
<tr>
<td>Chi Shao Yao</td>
<td>Red Peony root</td>
</tr>
<tr>
<td>Zhi Zi</td>
<td>Gardenia fruit</td>
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<tr>
<td>Da Huang</td>
<td>Rhubarb root and rhizome</td>
</tr>
<tr>
<td>Huang Lian</td>
<td>Coptis rhizome</td>
</tr>
<tr>
<td>Lian Qiao</td>
<td>Forsythia fruit</td>
</tr>
<tr>
<td>Dan Shen</td>
<td>Salvia root</td>
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<td>Dan Zhu Ye</td>
<td>Lophatherum</td>
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Qing Ying Tang was developed to treat septicemia. Despite the advent of antibiotics, the formula is still in use by veterinarians because of its apparent benefits in various autoimmune diseases. Chinese medicine viewed the formula as removing desiccating Heat pathogens from the bloodstream before they could produce bleeding, pathogenic clotting, and circulatory failure. Chinese veterinary herbalists came to realize the presence of Heat and Blood stasis in a range of immune-mediated conditions as well, including IMHA and chronic dermatitis, and applied the formula with equal efficacy.

How can the same formula treat both immune-mediated disease and septicemia? Septicemia, sequestration of blood cells, and chronic inflammation all are driven by one basic pathophysiological mechanism, termed ‘endothelial dysfunction’ (ED). Endothelial dysfunction is characterized by:

- Increased endothelial permeability and edema formation
- Blood vessel attenuation
- Endothelial bud apoptosis
- Reduced tissue vascularity
- Increased adhesion of platelets and white blood cells to the endothelium
- Chronic oxidative stress and free radical accumulation from continued chemotaxis

In septicemia, ED allows vessels become profoundly leaky and prone to wide scale clot formation (DIC). In blood dyscrasias, ED apparently allows cells adhere to the endothelium for

<table>
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<tr>
<th>Mai Men Dong</th>
<th>Ophiopogon root</th>
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easy removal; in chronic inflammation, ED allows continued ingress of white blood cells into the affected area.

ED varies inversely with the amount of nitric oxide present on the endothelium, and thus on the activity of endothelial nitric oxide synthase (eNOS). All pathways that promote development of vascular ED converge on the diminished activity of eNOS and loss of NO bioavailability (7), and most plants that reverse ED promote activity of this enzyme. Increased activity of eNOS is associated with a reduced tendency to autoimmune diseases, including arthritis and vasculitis (8).

There are as yet no commercially available pharmaceuticals that activate eNOS, lending practitioners brave enough to use herbal medicine an important advantage. Within the version of Qing Ying Tang noted above, Rehmannia, Salvia, Peony all promote nitric oxide synthesis through activation of eNOS (9-11).

In general, research has found that the plants Chinese medicine has labeled as Blood movers, Blood tonics, and Yin tonics are most likely to increase eNOS activity and reverse ED. As nitric oxide levels on the endothelium increase and cell adhesion decreases, there is a subsequent recovery of normal function, leading to:

- Increased vascularity and oxygenation
- Reduced vessel permeability
- Heightened vigilance by macrophages within the interstitium
- Draining of edema and free radicals

Plants may also act directly on cell adhesion receptors to reverse aspects of ED, rather than just through eNOS. Other prominent molecular targets for therapy in ED include cell adhesion receptors like VCAM-1. Rhubarb, Rehmannia and Salvia in Qing Ying Tang all directly inhibit
cell adhesion to the endothelium (12) by interfering with cell adhesion receptors. The result appears even further reductions in:

- Movement of all blood cells out of circulation within the spleen and liver sinusoids
- Movement of white blood cells into the interstitium
- Inflammation within the interstitium

**Chai Hu Jia Long Gu Mu Li Tang (Bupleurum, Dragon Bone and Oyster Shell Combination, e)**

There are other means of combating ED. Cytokines elaborated during autoimmune disease drive the development of endothelial dysfunction. An important example is type I interferon, which increases in autoimmune disease and subsequently impairs endothelial nitric oxide synthase (eNOS) activity (7). Bupleurum root is an important ingredient in the second formula used, Chai Hu Jia Long Gu Mu Li Tang (CHJLGMLT), and has been shown to interfere with type I interferon production, as well as the development of lymphadenopathy and other autoimmune cytokines (13).

Radix Bupleuri, is one of the most frequently prescribed crude herbs in the prescriptions of traditional Chinese medicine for the treatment of inflammatory diseases and auto-immune diseases (14). The polysaccharides of Bupleurum have been specifically credited with an ability to reduce autoimmune disease in susceptible animal models (13), including for systemic lupus erythematosus itself (14). They have been shown to protect the kidney from glomerular injury due to circulating immune complexes, reduce autoantibody production, and reduce associated splenomegaly. Some of the arresting effect of Bupleurum on autoimmune disease appears due to an inhibition of the proliferation and activation of T cells via its content of saikosaponins (15).
Bupleurum should not be considered merely an immune suppressive plant, however (13). Rather, its effects appear truly immune modulating and relative to the state of the patient. Bupleurum dampens the immune response in autoimmune disease, for example by interfering with the action of IL-2 on T cells (16), but rallies the immune response in immune suppression. As reviewed by Yen, Lin and Yen (17), studies show that the effects of Bupleurum in immune suppressed mice include:

- An increase in the ratio of helper to suppressor T-cells
- An increase in IL-2
- Increased B cell activity
- Increases in IgA, IgG, and IgM

**Table 2. Minor Bupleurum Combination (b)**

<table>
<thead>
<tr>
<th>Chai Hu</th>
<th>Bupleurum root</th>
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<tbody>
<tr>
<td>Huang Qin</td>
<td>Scutellaria root</td>
</tr>
<tr>
<td>Ban Xia</td>
<td>Pinellia rhizome</td>
</tr>
<tr>
<td>Gan Cao</td>
<td>Licorice root</td>
</tr>
<tr>
<td>Sheng Jiang</td>
<td>Ginger rhizome</td>
</tr>
<tr>
<td>Da Zao</td>
<td>Jujube</td>
</tr>
<tr>
<td>Ren Shen</td>
<td>Ginseng root</td>
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Bupleurum is thus a major consideration in patients over-treated by immune suppressants, and
one of the few truly immune modulating plants in the herbal pharmacopeia.

Bupleurum is seldom used alone in clinical practice, but rather as part of a larger formula. It is often paired with Scutellaria to make the formula called Minor Bupleurum Combination (Table 2).

Scutellaria baicalensis reinforces the immune modulating effects of Bupleurum. It contains Baicalin, a flavone that promotes regulatory T cell differentiation. Whereas helper T cells promote increased activity of cell-mediated and humoral immune reactions, regulatory T cells inhibit autoimmunity and protect cells against injury. The FOXP3 protein specifically promotes differentiation and activation of regulatory T cells. It is inhibited in its expression by pro-inflammatory cytokines, including IL-6, allowing autoimmune conditions to propagate. Baicalin promotes FOXP3 expression in T cells, promoting their differentiation into regulatory cells (18). Presumably this effect would be enhanced when Scutellaria is administered in combination with Bupleurum, since Bupleurum suppresses IL-6 production in inflammatory states (19), thus lifting the shackles on regulatory T cells. Not surprisingly, then, Baicalin from Scutellaria is effective in treating various autoimmune disorders, including encephalitis (20).

While Minor Bupleurum is popular as a treatment for autoimmune disorders by holistic veterinarians, it is additionally modified to target certain symptoms and patient attributes. CHJLGLMT is one such modification. CHJLGLMT has been in consistent use for over 2000 years, and was effectively developed to enhance the calming and cholinergic attributes of Minor Bupleurum. Agitation, constipation, dyspnea, and inhibited urination are listed in the source text as the specific symptom indications calling for use of CHJLGLMT. In the two patients presented
here, CHJLGMLT showed a superior effect in normalizing their immune function, potentially by enhancing cholinergic and parasympathetic activity.

Up until recently, attention has focused on the sympathetic nervous system rather than the parasympathetic nervous system as an immune regulator. Of the two arms of the autonomic nervous system, it is the only one ‘hard-wired’ to immune organs. Recently, however, increasing attention has been paid to the role of the vagus nerve and its origins in immune regulation, via the cholinergic anti-inflammatory reflex (21).

**Table 3. Chai Hu Jia Long Gu Mu Li Tang (Bupleurum, Dragon Bone and Oyster Shell Combination, e)**

<table>
<thead>
<tr>
<th>Chai Hu</th>
<th>Bupleurum root</th>
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<tbody>
<tr>
<td>Fu Ling</td>
<td>Poria</td>
</tr>
<tr>
<td>Gui Zhi</td>
<td>Cinnamon twig</td>
</tr>
<tr>
<td>Huang Qin</td>
<td>Scutellaria root</td>
</tr>
<tr>
<td>Ren Shen</td>
<td>Ginseng root</td>
</tr>
<tr>
<td>Ban Xia</td>
<td>Pinellia rhizome</td>
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<tr>
<td>Da Huang</td>
<td>Rhubarb root and rhizome</td>
</tr>
<tr>
<td>Da Zao</td>
<td>Jujube</td>
</tr>
<tr>
<td>Long Gu</td>
<td>Fossilized Bone</td>
</tr>
<tr>
<td>Mu Li</td>
<td>Oyster Shell</td>
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<tr>
<td>Sheng Jiang</td>
<td>Ginger rhizome</td>
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The afferent arm of the reflex is triggered when the vagal nuclei of the brain detect increased levels of circulating pro-inflammatory cytokines. Heightened vagal nerve output is triggered, causing release of acetylcholine at efferent nerve endings. Acetylcholine then binds to macrophages and other cytokine-producing cells to inhibit further pro-inflammatory cytokine release.

The biologic value of the cholinergic anti-inflammatory reflex appears to be protection of the body from sepsis due to a breach in an epithelial surface following runaway inflammation. The reflex effect is systemic and sweeping, and does not appear to target the specific location where inflammation was incited. Part of the anxiolytic effects of Bupleurum involve protected or enhanced acetylcholine output (22), suggesting that Bupleurum-laden formulas like CHJLGMLT may enhance the cholinergic anti-inflammatory reflex. Additionally, CHJLGMLT contains significant amounts of Rhubarb root, noted for its effects in inhibiting cell adhesion.

Conclusion

Chinese herbal medicine is just one avenue by which holistic veterinarians deal with the challenge of autoimmune disease using means other than immune suppressive drugs. Three of several potential Chinese medical treatments are discussed in this paper, along with two cases that support their clinical efficacy. The formulas appear to work via several novel pathways that might similarly be targeted with other alternative therapies. Currently, no drug approaches yet exist to invoke these effects, which include:

- Active resolution of endothelial dysfunction (ED)
- Enhancement of the cholinergic anti-inflammatory reflex
• Genuine modulation of the immune system in an adaptogenic fashion, where immune suppressive states are boosted and hyper-immune states are attenuated

Use of multiple herbs allows invoking all of these mechanisms simultaneously, raising the potential for synergistic interaction within and among formulas.

Research suggests Chinese herbal formulas are maximally effective when they are appropriate not only from a biomedical perspective but a traditional perspective. Recent practitioner-oriented texts now provide detailed comparisons of the traditional and biomedical indications for these and other formulas, as well as guidance on dosing and responsible clinical use (23).

ENDNOTE:

a. Cool the Blood Combination, Kan Herbs, Santa Cruz, CA. www.kanherbs.com
b. Minor Bupleurum Combination, Natural Path Herb Company, ibid
c. Six Gentle Pets, Kan Herb, ibid
d. Clear the Nutritive, Natural Path Herb Company, Edmonton, AB, Canada, www.nphc.ca
e. Bupleurum, Dragon Bone and Oyster Shell Combination, Natural Path Herb Company, ibid

REFERENCES:


