

Advances in Treating Immune-Mediated Disease: Old Systems Yield New Approaches

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Abstract

The immune system is complicated, but drugs for treating it are not. Medicine relies almost exclusively on immune suppression as a treatment strategy, even as ongoing research identifies a myriad of other mechanisms that could serve as targets for intervention. Ironically, traditional holistic medicine disciplines target many of these mechanisms, even though the words *immune system* do not appear in their paradigms. This article reviews 3 Chinese medical diagnoses and their associated treatments that can bring veterinarians closer to realizing a cure for their immune-mediated disease patients. Generic treatments are suggested that are available at varying costs and quality from a number of manufacturers.

The Need for a Different Perspective

Once a problem is framed as immune-mediated, the majority of veterinarians rely almost exclusively on some form of itch and immune suppression as a treatment strategy. The results are gratifying enough to establish these approaches as a go-to plan, but they are lacking in that clinical signs return and are often worse if the drugs are discontinued, overall efficacy can subside with sustained use, and serious side effects are common. This state of affairs led to the rise in interest in holistic paradigms among veterinarians looking for different treatment approaches. The paradigms of most interest predate immune research and yet apparently

can treat immune-mediated conditions successfully. The explanations within some of these paradigms show clear parallels with biomedicine's newly discovered mechanisms that underpin chronic inflammation and immune sensitization.

Excessive Inflammatory Responses: The Damp Heat Pathogen of Chinese Medicine

Various cytokines mediate inflammation, and immune suppressants are relied upon to suppress their synthesis. Examining the treatments used to address the Damp Heat pathogen of Chinese medicine exposes another potential means of tempering exuberant inflammatory responses. Knowledge of anatomy in China was crude for most of Chinese history because of laws prohibiting human dissection that persisted until the last few hundred years. As a result, the liver was believed to be on the left side of the body instead of the right, and the spleen was believed to be the organ governing digestion since it was visually prominent in the region where digestion was literally felt to occur. Because Chinese medicine did not practice surgery *per se* but just applied a metaphoric model to make hypotheses about the body, these anatomical inaccuracies are inconsequential but helpful to be aware of when studying Chinese medical theories of pathophysiology. In this paper, the first letter of an organ is capitalized when it is being discussed from a Chinese medical perspective.

In Chinese medical theory the Spleen is assigned the role of overseeing the complete transformation and assimilation of food into pure vital substances that the various organs can use to perform their functions. These Fundamental Substances are moist in some way, even so-called Qi, which confers all organs with the ability to function and which is envisioned to guide the movement of Blood within vessels. If the Spleen is compromised in some way, digestion is incomplete and non-usable fluids are produced instead. Chinese medicine terms these fluids *Dampness*. Dampness becomes a pathogen when it accumulates in sufficient amounts to clog tissues and interfere with circulation and the function of various organs. Since the Spleen is a digestive organ, the main avenue by which it is weakened is through the consumption of sub-optimal food. Dampness ensues when an excess of sweet taste (from sugar, fat, or protein) impairs and overwhelms the Spleen with too much food to process. Since none of the body organs can utilize Dampness, it slowly accumulates, manifesting eventually as exudates, excess perspiration, polyuria, mucous, phlegm, and lipid stores. Dampness also enters into and impairs circulation the way sludge accumulates in a river, eventually slowing and redirecting water flow. When the flow of Qi that is in turn driving the circulation of Blood is slowed by accumulating Dampness, a heat of friction is elaborated and the resulting pathogen is now known as *Damp Heat*. Signs of heat and redness appear, along with the other cardinal signs of inflammation.

Medical correlation

The explanation in Chinese medicine of how Damp Heat materializes in the body is an explanation for the empirically observed association of the symptoms of inflammation and weight gain with an immoderate diet. This link has been documented by Western medicine, extensively researched over the past few decades, and found to exist not only in humans but in companion animals as well (1-3). The precise metabolic events leading to obesity in animals as opposed to humans vary somewhat, but once present, the ability to trigger and sustain chronic inflammation is undisputed.

The pathophysiology of the overall dynamic has been most extensively researched in humans and constitutes a self-propagating cycle in which initially rapid and excessive food consumption leads to a high rate of mitochondrial activity that promotes lipid accumulation in cells. This lipid accumulation leads to increased fat stores and obesity that hinder the effects of insulin. Insulin stays elevated as a result of continued induction in the face of this hindrance. Obesity leads to inflammation through the secretion of cytokines by macrophages that are accumulating in the increasingly abundant abdominal fat. Ultimately, the inflammation leads to further insulin resistance.

Although some details may differ regarding the links between overconsumption, obesity, and inflammation in dogs and cats, the mechanisms are apparently similar enough to the human model for the herbal treatments used in humans to also work in animals. The author terms this syndrome *inflammation dysregulation*.

Herbal treatment

An excellent example of an acute-acting anti-inflammatory formula for the treatment of inflammation dysregulation is Four Marvels Combination (*Si Miao San*). It is very commonly used in veterinary Chinese herbal medicine (Table 1).

Table 1: Four Marvels Combination (<i>Si Miao San</i>) ingredients	
Pin Yin herb name	English name (with usual species)
<i>Cang Zhu</i>	<i>Atractylodes lancea</i> rhizome
<i>Huai Niu Xi</i>	<i>Achyranthes bidentata</i> root
<i>Yi Yi Ren</i>	<i>Coix lacryma-jobi</i> seed
<i>Huang Bai</i>	<i>Phellodendron amurense</i> bark

From a Chinese medical perspective, the herbal components of *Si Miao San* treat the entire sequence of steps involved in the generation of Damp Heat. *Atractylodes* strengthens the Spleen, while coix drains the Damp that is elaborated when the Spleen is malfunctioning. *Phellodendron* clears the Heat that is elaborated when Dampness obstructs the circulation. *Achyranthes* helps stir that circulation back into motion.

Given the observation in Chinese medicine that *phellodendron* clears Heat, a logical correlation is that it possesses anti-inflammatory and antioxidant effects. *Phellodendron* has demonstrated antioxidant activity in numerous studies and has an anti-inflammatory effect through its inhibition of the production of inflammatory cytokines and nitric oxide (4). It inhibits both gene expression for, and production of, inducible nitric oxide synthase (iNOS), as well as tumor necrosis factor (TNF-alpha) (5). *Si Miao San* as a formula has been shown to improve insulin sensitization and signaling through the insulin receptor substrate 1(IRS-1)/protein kinase B (AKT)-dependent pathway (6). Berberine, a plant compound present in *phellodendron* in *Si Miao San*,

has been shown through a systematic review of clinical trials to improve multiple aspects of Type II diabetes and insulin resistance, including blood glucose markers such as hemoglobin A1c, hyperlipidemia, and hypertension (7). Both phellodendron root itself and *Si Miao San* as a formula have been shown to directly combat the central mechanism by which insulin resistance is generated by reversing the inhibition by AMP-activated protein kinase (AMPK) of glucose and lipid oxidation, thereby facilitating the removal of adipose stored in hepatocytes (8, 9). The atractylodes constituent in *Si Miao San* has been shown to improve several metrics in diabetic patients (10).

Dietary treatment

From both the Eastern and Western perspectives, dietary therapy is the cornerstone of treatment of inflammation dysregulation or Damp Heat. Chinese medicine observes that real food diets are more slowly transported, giving the Spleen more time to completely transform them into pure Fundamental Substances so that Dampness does not form. Biomedical research supports the Chinese medical contention that an unprocessed diet is more advantageous. Mechanisms by which processed diets contribute to cardiometabolic disease are numerous but include a relatively faster rate of absorption, causing a more rapid rise in insulin levels and more rapid inhibition of AMPK, leading ultimately to insulin resistance, obesity, and inflammation (11).

In the author's experience, freeze-drying seems to be the maximum tolerable level of processing, beyond which mechanisms connecting metabolism and inflammation are invoked. Home-cooked or commercially available real food diets and commercially available raw diets appear to be more anti-inflammatory than freeze-dried diets. Chinese medicine views raw diets as too cold to be used in an already taxed system, explaining why some elderly animals might refuse to eat them. Otherwise, they are well tolerated in carnivores. Unfortunately, raw diets seem to make inflammation in some animals worse or at least allow it to continue recurring, potentially because of the impact of raw diets on the microbiome.

Role of the Microbiome: The Shao Yang Model

Chinese medicine understands the concept of an immune system, even if it is not termed as such. For several thousand years, the writings have acknowledged the reality that pathogens seem to invade the body from outside to cause disease unless the body is successfully defended by its Upright Qi.

Different layers offer resistance in their fights against pathogen invasion. *Wei Qi* accumulates in the outermost or *Tai Yang* layer to present a barrier to invasion. If it is breached, the patient experiences chills and body aches. The appropriate response is to expel the pathogen through the use of herbs containing warming antimicrobial volatile oils that increase the flow of blood and its immune components to the body periphery.

If, on the other hand, a pathogen penetrates deeply into the *Yang Ming*, or body interior, the vigor of the resultant immune and inflammatory response can kill the patient through induction of high fevers, seizures, delirium, and collapse. Warming herbs that enhance peripheral and cerebral circulation are contraindicated for fear of making the patient worse. Treatment emphasis shifts to controlling and countering the systemic immune and inflammatory response through the use of bitter antimicrobial and anti-inflammatory herbs, considered cold. These plants are viewed as precipitating the pathogen out through the GI tract rather than expelling it through the body periphery.

What, then, of a pathogen that manages to penetrate halfway between the interior and exterior? This is the *Shao Yang* layer, and a pathogen lodged here creates a *Shao Yang* disharmony. If efforts are directed solely at expelling the pathogen, ie, provoking an immune response, the patient's signs are often aggravated by accentuated inflammation. If instead the focus is on suppressing the immune response, such as with the use of anti-inflammatories, the patient can be aggravated by hampering the ability to combat the invading pathogen. When managing *Shao Yang* disharmonies, the strategy becomes both expulsion (immune stimulation) and precipitation (use of anti-inflammatories) at the same time.

Medical correlation

Modern-day practitioners often interpret the deeply penetrated pathogens of *Shao Yang* disharmonies to be microorganisms such as those causing leptospirosis, malaria, Lyme disease, or babesiosis. One might question the relevance of the model to the management of immune-mediated diseases like atopic dermatitis or immune thrombocytopenia that do not arise from an infection. New understandings of the central role of the microbiome in the pathogenesis of immune-mediated disease in animals and humans suggest that *Shao Yang* treatments are exactly what the doctor ordered (12).

In both humans and animals, adverse shifts in the microbiome, known as dysbiosis, can cause the synthesis of

metabolites having an epigenetic function in immune dysregulation and a deficiency of other metabolites that play a role in immune modulation. Dysbiosis can increase gut permeability, resulting in what is called *leaky gut* and causing sensitization to antigens in the gut lumen. This sensitization is propagated via cytokines and the systemic immune system, heightening inflammatory responses in the skin from any cause. Finally, this ramping up of systemic immune responses perpetuates inflammation in the gut wall, leading to inflammatory bowel disease that creates persistent gut permeability and sustained antigen sensitization. These latter 2 mechanisms constitute cell-mediated immune reactions. Helper T cells stimulated at the gut level through excessive exposure to microflora circulate, eventually prompting effector T cells on other epithelial surfaces to secrete interleukins that stimulate macrophages and neutrophils to heighten their inflammatory response to local irritants. In other words, inflammation from a shift in the microflora in the gut increases the inflammatory response to entirely different antigens located elsewhere. If the leaky gut and the exposure to local irritants are both ongoing, inflammatory responses on those surfaces persist or continue to grow (13, 14).

Conventional treatment with anti-inflammatory and immunosuppressive therapies often provides relief by suppressing the cell-mediated immune reaction in, for example, the skin but may potentiate increased permeability and dysbiosis by impairing local immunity at the gut wall. Once immune suppressants are removed, the dermatitis often fully recurs or even worsens, since the immune deficiency that caused the dysbiosis has not been addressed or may have even progressed. Stress can amplify the role of the gut in inducing immune-mediated disease. Stress suppresses gut immunity through increased secretion of cortisol, allowing dysbiosis to occur. The proliferation of enteropathogens eventually prods the immune system into a state of hyperactivity, producing the cell-mediated inflammatory response that damages the gut wall and heightens the inflammatory response to irritants at other body surfaces.

Complete protocols to properly resolve this mechanism of immune-mediated disease consist of both immune *suppressants* to reduce the exacerbation of excessive systemic immune stimulation and immune *stimulants* to improve control of enteropathogens, hopefully allowing the gut wall to eventually be sealed. While there are no pharmaceuticals that fill both of these needs, the Chinese herbal formula developed to treat *Shao Yang* disharmony is designed to do just that, by expelling invading pathogens at the gut wall and skin while also clearing the Heat (ie, inflam-

mation and excess immune responses) of pathogens that have penetrated to the interior.

Herbal treatment

Minor Bupleurum (*Xiao Chai Hu Tang*) is another Chinese herbal formula very commonly prescribed by veterinarians (Table 2). It consists of 3 key herbs: *Bupleurum chinense* root (*Chai Hu*), *Scutellaria baicalensis* root (*Huang Qin*), and *Panax ginseng* root (*Ren Shen*), which confer the majority of the formula's apparent efficacy in the management of immune dysregulation caused by leaky gut. All 3 plants function together, reducing the predisposition to, and the adverse effects of, stress on the microflora. The herbs also modulate the immune system to support local immunity while reducing the intensity of cell-mediated immune reactions. Specifically, the formula shows redundant benefits in the treatment of dysbiosis, immune dysregulation, and the brain-gut-skin axis.

Table 2: Minor Bupleurum Combination (<i>Xiao Chai Hu Tang</i>) ingredients	
Pin Yin herb name	English name (with usual species)
<i>Chai Hu</i>	<i>Bupleurum chinense</i> root
<i>Ban Xia</i>	<i>Pinellia ternata</i> rhizome
<i>Gan Cao</i>	Licorice (<i>Glycyrrhiza uralensis</i>) root
<i>Sheng Jiang</i>	Ginger (<i>Zingiber officinale</i>) rhizome
<i>Da Zao</i>	Jujube (<i>Ziziphus jujuba</i>)
<i>Ren Shen</i>	<i>Panax ginseng</i> root
<i>Huang Qin</i>	<i>Scutellaria baicalensis</i> root

Effects on dysbiosis

Bupleurum root was shown in the context of another formula, Bupleurum Soothe the Liver Combination (*Chai Hu Shu Gan San*), to protect gut microflora from pathogenic overgrowth (15). *Scutellaria* (in the formula *Huang Lian Jie Du Tang*) has been shown to help restore normal gut flora in rats by reducing pathogens and increasing the presence of bacteria that do not incite inflammatory responses. The synthesis of short chain fatty acids (SCFA),

which the mucosa relies upon to maintain gut wall integrity, increased accordingly (16). Many studies support the use of ginseng, which is included in Minor Bupleurum, for the correction of dysbiosis secondary to antibiotic use (17).

Brain-gut-skin axis

As mentioned above, stress can aggravate dysbiosis, worsening the bowel wall integrity that can in turn lead to cell-mediated hypersensitivity. This relationship is commonly encapsulated in the term *brain-gut-skin axis*, and the ingredients in Minor Bupleurum have shown efficacy in addressing the problem. Ginseng is widely known as an adaptogenic herb that can normalize and optimize adrenal gland output of cortisol, lessening its secretion in times of repetitive stress, but increasing it when more alertness is required. Normalization of cortisol secretion reduces immune suppression that otherwise allows overgrowth of enteropathogenic bacteria. *Scutellaria* spp likewise have research support for their long history of use in treating anxiety and other CNS organic and mood disorders (18). Bupleurum has been shown to reduce depression and anxiety in animal models of repetitive stress (19).

Immune dysregulation

This paper uses the term *immune dysregulation* to describe the association of systemic cell-mediated hypersensitivity with peripheral immune deficiency that seems to underpin many cases of immune-mediated disease in animals. Minor Bupleurum Combination is unique in that it contains products that bolster local immunity at epithelial surfaces and temper overzealous systemic immune tendencies that aggravate inflammatory responses. Wogonin, a substance found in scutellaria, has been analyzed for its ability to support normal immunity and reduce inflammatory bowel changes in colitis in rats. Levels of protective IgA were increased, while IgE levels associated with hypersensitivity were maintained at low levels. The ability to induce local immunity in the gut was increased in rats given wogonin, but the intensity of the inflammatory response during colitis was reduced, making scutellaria a true immune modulator (20).

A decrease in bowel wall integrity can increase exposure of the immune system to lipopolysaccharide endotoxins, sparking an inflammatory response that can spread to the skin. The administration of bupleurum tempers the pro-inflammatory effects of the exposure while supporting phagocytosis and the removal of offending antigens (21). Bupleurum's tempering effect on an immune response has

been widely studied and demonstrated on other mucosal surfaces as well, including for the reduction of allergic responses at respiratory epithelia (22).

Dietary treatment

In addition to local immune competency, for the optimal microflora to thrive in the digestive tract, correct foods are also required. Animals with *Shao Yang* disharmony appear to not thrive on raw diets, perhaps because they are often lacking in carbohydrates. Studies have shown that the numbers of lactobacilli and other carbohydrate-metabolizing microflora plummet on raw diets, yet these species produce propionate, which may play an important role in regulating the immune response (23). Clinical experience suggests that introduction of fermentable carbohydrates and fiber to affected *Shao Yang* animals helps mitigate immune-mediated disease and hypersensitivities, especially when used in tandem with Minor Bupleurum Combination. The occurrence of immune-mediated and allergic disease in animals while on raw diets suggests that a *Shao Yang* disharmony treatment approach may offer better control of their signs. Even once a healthy diet and herbal formula are in place, inflammation might need to be actively resolved before signs disappear. Active resolution involves normalizing peripheral circulation and is the subject of the next section.

Microcirculation: The Blood Deficiency and Stasis Model

Chinese medicine deserves credit for what began to be discovered by modern medicine just 30 years ago, which is that aberrant microcirculation patterns play a central role in disease pathogenesis. At the time of this writing, there are over 1,700 review articles in the Pubmed database that describe disturbed microcirculation at the core of degenerative, neoplastic, and inflammatory pathologies throughout the body. Chinese medicine's understanding of the importance of circulation in health and disease is implicit in its reliance on pulse diagnosis to guide acupuncture treatments, massage, and prescribed body movement in the treatment of disease. Some of the most important herbal formulas are those that deal with Blood volume and its overall regulation from a Chinese medical perspective.

In Chinese medicine, the Liver is in charge of microcirculation. It is the storehouse of blood, even from a biomedical perspective. Sufficient Blood in the Liver is required to serve peripheral circulatory needs. The Liver does not just store the Blood but oversees its distribution all over the body. It does so by coursing and draining the

Qi, which is the motive force of Blood. If Qi is not flowing, it is reflected in a thin Wiry (ie, vasoconstricted) pulse. If the vasoconstriction persists and congestion becomes physically visible or consequential, the patient is experiencing Blood stasis.

Medical correlation

The Chinese medical model above is easy to relate to the biomedical understanding of hemodynamics. If a patient is volume depleted (ie, Blood deficient), vasoconstriction (considered as Qi stagnation) is the expected response. Circulation to peripheral organs and structures is temporarily reduced, but with no lasting consequences. Problems arise, though, if the peripheral tissue is chronically inflamed. As reviewed by Lawrence and Gilroy, inflammation is initiated and resolved in 2 phases. In the first phase, when it is initiated by resident macrophages and mast cells, the nearby vasculature becomes dilated and leaky, allowing for easy neutrophil and monocyte passage into the interstitium (24). Monocytes become macrophages, engaged in phagocytosis and antigen presentation. Neutrophils activate, degranulate, and escalate the inflammatory response. At the same time inflammation is escalating, by-products of acute inflammation are accumulating that normally bring about its resolution through negative feedback inhibition.

Equally important though in the resolution phase is the behavior of the vasculature. Gaps between endothelial cells seal up. Edema, cellular debris, and free radicals are drained off. Cell adhesion molecules disappear, macrophages and mast cells once again predominate in the interstitium, and new endothelial buds appear that will grow new vessels to help nourish and oxygenate the tissue as it begins the process of repair. If these vascular events do not happen, chronic inflammation can continue to smolder in a state of endothelial dysfunction. Active resolution may not proceed for a number of reasons. Both phases of inflammation are mediated by cyclo-oxygenase. If its activity is repeatedly suppressed with the use of anti-inflammatories, resolution may fail to occur.

Even more important is the role of diet in promoting endothelial dysfunction. Diets that promote oxidative stress and obesity such as calorically-dense processed foods contribute both directly and indirectly to vascular dysfunction (25). This is one more mechanism by which real food diets are able to counter inflammation.

Herbal treatment

Conventional medicine does not yet have drugs to counter endothelial dysfunction, but Chinese medicine has many herbs that do, which is perhaps to be expected given the

emphasis placed by Chinese medicine on the regulation of blood flow. The traditional Chinese medical model may well have been built around the observed effects and successes of folk treatments that improve microcirculation from a biomedical perspective.

An example herb is *Rehmannia glutinosa* root, a key in Four Materials Combination, which is the quintessential Blood-tonifying and moving formula of Chinese herbal medicine (Table 3). It has been shown to significantly reduce dermatitis lesions, ear thickness, and serum histamine levels in laboratory animal models of atopic dermatitis. Histological analysis demonstrated decreased thickening of the dermis and epidermis, along with reduced dermal infiltration by inflammatory cells. Much of the credit for this effect stems from rehmannia’s ability to inhibit not just inflammatory cytokines like interleukin-4 and tumor necrosis factor- α , but also vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (26). As mentioned, an abundance of WBC adhesion molecules is one feature of endothelial dysfunction that prevents the active resolution of inflammation, since it facilitates the egress of circulating WBCs into the interstitium. In addition to reducing the stickiness of the endothelium, rehmannia stimulates the bone marrow to produce more RBCs, serving to address the Blood deficiency aspect of the condition and not just the chronic inflammation or Blood stasis aspect (27).

Table 3: Four Materials Combination (Si Wu Tang) ingredients

Pin Yin herb name	English name (with usual species)
<i>Shu Di Huang</i>	<i>Rehmannia glutinosa</i> root
<i>Dang Gui</i>	<i>Angelica sinensis</i> root
<i>Bai Shao</i>	White peony (<i>Paeonia lactiflora</i>) root
<i>Chuan Xiong</i>	<i>Ligusticum chuanxiong</i> root

Many other plants have been shown to ameliorate different aspects of endothelial dysfunction. When used together in formulas, powerful synergies emerge that can allow the safe resolution of chronic inflammation. For example, the formula Bupleurum and *Dang Gui* Combination is commonly used in veterinary medicine to address chronic active hepatitis in the dog and has been reviewed for its similar benefits in addressing hepatitis B in humans (28).

Si Wu Tang (Four Materials Combination) contains both rehmannia and *dang gui* and is commonly effective in the author's experience when combined with Minor Bupleurum (discussed above) for the resolution of immune-mediated skin disease in dogs. This latter combination can be made by combining 1 part *Si Wu Tang* (Four Materials Combination) formula with 2 parts *Xiao Chai Hu Tang* (Minor Bupleurum Combination) formula. This mixture is available over the counter directly to pet owners (a).

Conclusion

Holistic medical paradigms should not be looked upon as erroneously supplanting medical thinking. Analysis of those systems which appear effective has shed light upon the body processes most important in overcoming problems with the immune system. Holistic medical systems have helped us to see the immune system not as a central problem to be exclusively focused upon, but as a system within a larger ecosystem that can be normalized by targeting that system as a whole. Ironically then, traditional medical systems are a source of inspiration for cutting-edge medical solutions.

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The author has a financial interest in Natural Path Herb Company and is a consultant to Kan Herbs and Gold Standard Herbs. These companies may make versions of the formulas described, which are also made by other manufacturers.

Endnotes

a. Cessorex™. Gold Standard Herbs, 5580 La Jolla Blvd, Ste 160, La Jolla CA 92037

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