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Review

Management of Equine Dermatological Allergies: A Review of Conventional and Complementary Therapies

Sarah Eaton*

ABSTRACT

Dermatological allergies in horses are common and frustrating problems. The three main types of allergies are insect bite hypersensitivity (IBH), atopic dermatitis (AD), and chronic urticaria (CU), with some horses presenting with more than one allergy type at the same time. These diseases run the gamut of hypersensitivity reactions, with IBH due to type I (acute) and type IVb (chronic) reactions. Both AD and CU are also caused by type I hypersensitivity, with CU additionally mediated via type II and III hypersensitivities. Stress, physical stimuli, and exercise also complicate CU. Specific diagnostic tools are limited; therefore, allergens are often diagnosed based on clinical signs, history, and response to treatment. The key to treatment of equine dermatological disease is environmental management, however this may not be possible based on the horse's lifestyle. Conventional medications have focused on antihistamine and immunosuppressive medications, which can have undesirable side effects. Integrating traditional Chinese veterinary medicine (TCVM) provides alternative or ancillary therapy for skin allergies in horses, and offers a variety of modalities (acupuncture, Chinese herbal medicine, food therapy) which can be targeted to patient need and temperament. Combining conventional and TCVM therapies through an integrated medicine approach provides improved management of this complex disease for equine clinicians. A review of the immune mechanisms associated with dermatological allergic disease in horses is presented along with conventional and TCVM treatment options. A case study provides an example of how to organize and institute an integrated protocol for optimal management of equine allergic skin disease.

Keywords: acupuncture, allergies, atopy, Chinese herbal medicine, dermatitis, equine, hives, itch, TCVM, Wind

ABBREVIATIONS: AD: atopic dermatitis; AP: acupuncture; ASIT: allergen specific immunotherapy; CHM: Chinese herbal medicine; COX: cyclooxygenase; Cs: corticosteroids; CU: chronic urticaria; EAP: electroacupuncture; h: hour; IBH: insect bite hypersensitivity; Ig: immunoglobulin; IL: interleukin; IM: intramuscular; IV: intravenous; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PO: per Os; PPID: proximal pars intermedia dysfunction; q: each; TCVM: traditional Chinese veterinary medicine; Th1: T-helper type 1 cell; Th2: T-helper type 2 cell; TNF-α: tumor necrosis factor-alpha

Dermatological allergies in horses present in three main categories: insect bite hypersensitivity, atopic dermatitis, and chronic urticaria.[1,2] Insect bite hypersensitivity (IBH) is the most common allergic skin disease in horses and colloquially known as "sweet itch".[2,3] The incidence of IBH in horses ranges from 2.8 to >50% within a population, depending on factors including age of first insect exposure, location and breed, with some breeds (and lines within breeds) showing a polygenic predisposition towards IBH.[2,4]

Atopic dermatitis (AD) can exist by itself but is also commonly seen in patients with IBH. Patients with AD present similarly to IBH but are differentiated in that insects are not the inciting cause, changing the seasonality of the presentation. There is a genetic predisposition, but age and breed have not been shown to be factors in AD.[2]

Chronic urticaria (CU) can have many triggers and be very frustrating for owners due to the difficulty in definitive diagnosis. There are other, less common, allergic, or autoimmune dermatologic conditions in horses, however IBH, AD, and CU will be the focus of this article. The diagnosis and treatment of dermatological allergies is often protracted and multi-faceted due to various environmental stimuli.[2]

PATHOPHYSIOLOGY

Hypersensitivity Reactions

Most horse owners are aware of allergic skin diseases, whether from their horses or a family member (human or canine). In clinical practice, dermatologic allergies can be refractory cases for veterinarians and disfiguring for horses. Clinical signs are often the result of

Author Professional Degrees and Certifications: DVM, DACT, DABVP-Equine, CVA; **From:** University of Arizona College of Veterinary Medicine, Oro Valley, Arizona, USA; ***Address correspondence to** Dr Eaton (SarahEaton@arizona.edu).

self-trauma in response to the "itch" sensation by a patient. These allergies occur due to one or more of four different types of immune reactions: type I (IgE-mediated, immediate or anaphylactic response), type II (IgM and IgG), type III (soluble antigens), and type IV (cell-mediated response with delayed hypersensitivity).[5] The type IV allergic response is further subdivided based on the underlying pathogenesis into types a through d.[5] Insect hypersensitivity is caused by both type I and type IVb hypersensitivities, depending on the rate of onset and subsequent chronicity of inflammation.[2]

Both atopic dermatitis and chronic urticaria are also caused by type I hypersensitivity, with CU additionally mediated via type II and III hypersensitivities. Stress, physical stimuli, and exercise also complicate CU which makes diagnosis and treatment difficult.[2] To further confound matters, patients may have more than one allergic disease within the same period.

Horses are exposed to allergens via inspiration, contact, or less commonly, through ingestion. The allergen can activate the cellular and/or humoral response. In addition, allergens can either be surface stimulants of the dermis, or injected as intradermal stimuli. The allergens (i.e. antigens), are presented to lymphocytes by macrophages and dermal dendritic cells (dermis) or Langerhans cells and keratinocytes (epidermis). These cells in turn produce cytokines, leading to a cascade of cellular stimulation resulting in the release of additional cytokines, interleukins (IL), and development of specialized T and B lymphocytes. These resulting T and B cells also secrete specific cytokines to modulate the immune response. The activated B cells translocate NF-κB into the promoter region of genes that encode for pro-inflammatory cytokines, increasing production of those molecules, especially TNF-α.[6] Mast cells combine characteristics of the innate and humoral immune systems with release of histamine when stimulated by certain cytokines, allergens, hormones, and IgE molecules. Histamine then acts throughout the body on the nervous system, cardiovascular system, and skin causing clinical signs of allergies.

Insect Bite Hypersensitivity

Patients with IBH are allergic to the bites of blood-feeding insects including midges (genus *Culicoides*), and black flies (genus *Simulium*). *Culicoides* insects are present around the world and various species have predilection for different parts of the horse's body. Horses are bitten by hundreds to thousands of insects throughout their lifetime, creating a sustained antigenic challenge leading to hypersensitization of some animals. This hypersensitization is termed IBH. Anaphylaxis is rare but has been reported in horses and cattle from severe *Simulium* bites.[2]

In general, the response of horses with IBH is two phased. The initial phase (type I hypersensitivity) causes differences in the Th2 (increased) and Th1 (decreased) cell ratio. Initially, this different response leads to an increased secretion of IL-4 and IL-13 from Th2 cells.[4] Both interleukins are important in the recruitment of inflammatory cells. Secretion of IgE can indirectly alter the skin microbiome and decrease the function of the epidermal barrier.[2] Acute clinical signs are caused by the inrush of inflammatory cells to the skin surface, as well as mucous membranes, and the systemic IgE response. The IgE modulation of basophils is also different in IBH horses compared to controls, and studies are ongoing to identify how this difference leads to the commonly seen clinical signs.[2]

Chronic exposure to insect antigens leads to a type IVb response, in which conventional Th2 cells differentiate into pathogenic effector Th2 cells.[4] These pathogenic Th2 cells secrete IL-5, which leads to eosinophilia and increased mast cells in the tissues. Dermal mast cells and eosinophils play a role in chronic, but not acute IBH and blood levels of eosinophils correlate with IBH severity.[2] Histamine granules, synthesized and released from mast cells, stimulate H1 and H4 receptors in sensory nerve endings. This in turn leads to the "itch" sensation that horses attempt to soothe by scratching.[2] Inflamed skin also releases histamine from keratinocytes.[2]

In addition to an animal's own histamine, some insects inject histamine or its analogues while feeding, which promotes vasodilation and increases blood availability.[2] Other stimulators of itch include the release of proteolytic enzymes by mast cells, IL-33 receptors, IL-31, and IL-5.[2] IL-31 binds directly with sensory neurons stimulating the itch response.[4]

Atopic Dermatitis and Chronic Urticaria

Atopic dermatitis is an abnormal immunological response to environmental allergens. Similar to IBH, horses with AD have a relative increase in Th2 and allergen specific IgE compared to non-AD horses. This type I immune response leads to changes in cytokines IL-4, IL-5, IL-6, IL-13, and IL-31.[2] As previously mentioned, IL-5, IL-13, and IL-31 are components of the allergic inflammatory cascade. IL-6 aids in terminal cell differentiation, enhances the activity of IL-4, and promotes T-cell growth.[7] Changes in serum phospholipids are also seen in horses with AD.[2] Certain phospholipids are the precursors of arachidonic acid, which plays an important role in the humoral inflammatory cascade.[7]

The pathogenesis of CU in horses is not completely understood and can be caused by a variety of immune responses and environmental stimuli. Eosinophils and mast cells are present at increased amounts in the dermis of CU horses versus controls.[2] Other involved cells include Th2 cells and macrophages.

CLINICAL SIGNS AND DIAGNOSIS

Insect Bite Hypersensitivity

Non-specific clinical signs of IBH include an agitated horse anticipating the discomfort associated with fly bites characterized by head shaking, tail swatting, stomping, and skin-twitching. The main specific clinical sign is pruritus with subsequent crusting around the tail head, mane, and dorsal or ventral midlines. Less commonly the face, neck and exterior portion of the ears can be affected.[3] The pruritus is typically progressive and seasonal based on

insect life patterns. In addition to crusts, horses may develop wheals or papules that can become secondarily infected and present as bacterial folliculitis.[2] Long term sufferers of IBH can progress to hair loss and secondary lichenification due to chronic self-trauma. Presumptive diagnosis is based on history, physical examination, ruling out of other causes of pruritus, and response to environmental management. Serum and intradermal allergy testing is of limited use in horses with IBH.[2] Skin histopathology shows non-specific superficial to deep perivascular to interstitial dermatitis with eosinophils as the dominant inflammatory cell.[7]

Atopic Dermatitis

Clinical signs of AD include pruritus of the face, distal legs, or trunk, with or without urticaria, or hives. Depending on the allergen, AD may occur seasonally or year round.[3] In horses, summer allergies are associated with pollen or insects. Winter or year-round allergies are most associated with mold, dust, or mites but specific timing can vary based on the animal's housing.[2] The role of food in AD is unclear currently. Allergies can worsen over time and progress from seasonal to year-round. Presumptive diagnosis of AD is based on clinical signs, history, and exclusion of other causes.

Definitive diagnosis for AD is via allergy testing, either intradermal or serum, but some horses without AD will have positive results to antigens on allergy testing.[2] The most common allergens diagnosed via serological testing in horses include insects and mites, with pollens and molds less frequent.[3] It is important to remember that horses may have more than one dermatological disease and should be evaluated in a systematic fashion. Prior to performing serological diagnostics, corticosteroids and antihistamines should be withheld for 14 and 7 days, respectively.[2] The author has found no information on withdrawal times for acupuncture or herbal supplements when performing allergy testing. As with IBH, AD patients with chronic pruritus can develop skin trauma, erosions, hair loss, lichenification, and subsequent pigment changes.[3]

Chronic Urticaria

Chronic urticaria presents as hives or wheals anywhere on the body that can be small or coalesce into large areas. The lesions start soft but become firmer over time and may leak serum ventrally. Presumptive diagnosis is based on clinical signs and an accurate history can help identify possible causes. Histopathology of the lesions is often unrewarding for the diagnosis of CU but can be useful to rule out other dermatological lesions.

TRADITIONAL CHINESE VETERINARY MEDICINE

History

Dermatological disorders have been recognized and treated in traditional Chinese medicine since before 1100 BC. Clinicians during the Zhou Dynasty (1100-221 BC) recognized skin diseases and their seasonal variation.[8] Originally in Chinese medical theory, the skin was classified with the muscles, sinews and tendons; but as Chinese medicine developed, skin gradually began to be studied and treated as its own entity.[8] The skin is the largest organ of the body and protects the Interior *Zang-fu* organs from invasion by Exterior Pathogens. These can attack at any time but are most invasive when the body is in a weakened state. Common treatment modalities for skin disease used in TCVM include acupuncture (AP), Chinese herbal medicine (CHM), and diet modification.

***Zang-fu* Physiology**

Dermatological disease, from a TCVM perspective, is associated with the Metal element, whose *Zang-fu* organs are Lung and Large Intestine. In the body, the Lung occupies the uppermost position and is known as the "canopy" which protects and shelters all other *Zang-fu* organs. In the upper position, Lung has descending/dispersing function and sends Fluids received from the Spleen and *Qi* down to the Kidney which grasps the *Qi* and evaporates some of the Fluids. Then through ascending function, the Kidney sends clear fluid vapor back to the Lungs to moisten them. The Lung, in turn, sends Fluids to moisten the skin. Additionally, Lung with assistance of the Kidney, causes a downward flow of energy providing the ability to sustain a deep breath. The Lung, therefore, dominates *Qi*, respiration, and the body surface.[9,10]

Pathology

Despite its governing and protective role, the Lung is the most delicate organ in the body and most vulnerable to attack by Pathogens, particularly Heat and Dryness. It is vulnerable to invasion of the many Exterior Pathogens which can be carried into the Lung by the master Pathogen "Wind" as it pummels the nostrils and skin.[9,10] Skin diseases are often classified by the type of Pathogen invasion and Exterior/Interior factors promoting loss of *Zang-fu* organ balance. External Pathogenic factors include Wind, Heat, Damp, Dry, parasites and allergies.[8] The Wind can enter at the skin level if the *Wei Qi* (immune *Qi*) is weak and is characterized by itching, papules, and wheals. Heat makes the body itchy, hot-dry and is associated with wheals or blisters, while parasites can cause a local reaction and itching. Damp invades the body and is associated with oozing, erosive, pruritic lesions of the lower body. Allergies to food or drugs is a *Ying-Wei* disharmony which can occur quickly and be associated with erythema, pruritis and pain.[8] Internal factors include Stagnation (Liver *Qi*, Blood), Blood-Heat (Heat-Toxin, *Qi* Stagnation), Blood Deficiency with Wind and Dryness, *Jing* Deficiency (geriatric Kidney *Qi* Deficiency), Liver and Kidney *Yin* Deficiency (chronic illness, dry-flaky skin).[8]

Patterns

When evaluating patients using TCVM for dermatological conditions, it is important to assess the entire patient including history, clinical signs, tongue/pulse diagnosis, regions of body temperature change, and sensitivity at acupoints. This complete evaluation allows

for identification of the TCVM Pattern to then determine the correct treatment plan with the goal of returning the patient to the correct balanced state. Patients with skin allergies can present with different clinical signs but often have a similar TCVM Pattern. The clinical TCVM exam will reflect the pattern to be treated (Table 1). For example, Cold or Deficient Patterns cause the tongue to be wet and pale or dusky purple, while Excess Patterns have a pinker/red dry tongue that may be small. The pulses also reflect the pattern (often fast and shallow due to Excess Patterns) although in chronic conditions may be deep and difficult to feel due to deficiencies. Common TCVM Patterns associated with pruritis and skin allergies include Excess Patterns such as Wind-Heat, Damp-Heat, and Blood-Heat. Deficiency Patterns are often more chronic and tend to be in middle-aged to older animals. These patterns include Blood Deficiency, and Deficiency of Kidney/Liver *Yin* or mixed patterns.[8,11]

- Wind, Wind-Heat TCVM Patterns:

When considering allergic skin disease in horses, the Pathogens Wind or Wind-Heat create most of the clinical signs seen, with few exceptions. Classically, Wind moves around the body and is associated with itching, so when a patient is clinically pruritic, which is generally the most worrisome and annoying problem for the horse, there is some component of a Wind TCVM Pattern. Wind can enter the body at the skin level if the *Wei Qi* fails to protect the body. It can stay in the body at the muscle layer creating itching, papules, or wheals.[8] Wind then transports additional Pathogens such as Heat or Damp throughout the body. Chronic Wind-Heat can lead to depletion of Lung *Qi* culminating in a Lung *Qi* Deficiency which then allows Damp to invade as a secondary Pathogen progressing then to chronic Damp-Heat with secondary skin infections.

Wind and Wind-Heat TCVM Patterns are commonly associated with allergies, particularly seasonal allergies due to invasion of the body surface by these Pathogens. Clinical signs of Wind include marked pruritis commonly in spring and summer with wiry/fast pulses and red tongues. These patients may present with no secondary pattern. The tongue seen with Wind-Heat is red and slightly dry. The pulse will be fast.

- Damp-Heat TCVM Pattern:

As Wind attacks the body surface and combines with Heat, these Pathogens may then be joined by the Damp Pathogen, to form Damp-Heat. This pattern is associated with oozing, erosive, pruritic lesions, most commonly of the lower body. The patient will usually have a forceful, rapid pulse with a red tongue typical of an Excess Pattern.

- Blood-Heat TCVM Pattern:

This Excess Pattern is less common than the other two patterns and is often seen in patients with biopsies showing immune-mediated dermatologic disorders. This pattern can be caused by Stagnation (Blood, Liver *Qi*), Heat-Toxins, or severe *Qi*-Stagnation.[8] Additionally, chronic *Yin* Deficiency, specifically affecting the Liver and Kidney, can cause Blood-Heat.[9,11,12] The Heat-Toxins often include environmental pathogens/allergens (e.g. dry-dusty environment, mold spores in hay).[11,6] They are expelled through skin, damaging it and the blood vessels.[13] These patients have chronic inflammation leading to Excess Fire (forcing Blood from vessels into the insterstitium) and appearance consistent with traditional clinical signs of a chronic dermatitis. Over time, as the body's *Qi* and Blood are consumed, the condition will slowly evolve into a Deficiency Pattern, particularly Blood Deficiency.[9,11,12] The TCVM clinical signs include red or purple tongue, with a fast/forceful pulse.

Table 1: Summary comparison of conventional equine allergy diagnoses with TCVM Pattern diagnosis

Conventional Diagnosis	TCVM Clinical Signs	TCVM Pattern Diagnosis / Pathogen
Insect Bite Hypersensitivity	Acute Tongue: Red and slightly dry Pulse: Wiry, fast Chronic Tongue: Red and dry Pulse: Thready, deep, and fast	Wind or Wind-Heat *Yin* Deficiency (if chronic)
Atopic Dermatitis	Acute Tongue: Pale and dry OR red Pulse: Deep, thready, weak, OR forceful, rapid, OR wiry, fast Chronic Tongue: Red and dry Pulse: Thready, deep, and fast	Wind or Wind-Heat Damp-Heat* Blood Deficiency *Yin* Deficiency (Liver and/or Kidney)**
Chronic Urticaria	Acute Tongue: Bright red Pulse: Surging and rapid Chronic Tongue: Red and dry Pulse: Thready, deep, and fast	Lung Wind *Yin* Deficiency (Liver and/or Kidney)**

* Damp-Heat can present as a sequela to chronic inflammation; ** Associated with chronicity

- Lung Wind TCVM Pattern:

Patients with the Excess Pattern, Lung Wind/Wind-Heat in the Lung, present with sudden wheals/urticaria (head, neck, thorax, abdomen, croup), pruritus, and possible swelling of eyelids/lips. This pattern occurs due to an accumulation of the Pathogens, Wind and Heat.[12] The Lung Wind Pattern of clinical signs occurs extremely rapidly due to the rapid invasion of Wind in the Lung.[9] The pulse is surging-rapid and the tongue is red.

- Blood Deficiency TCVM Pattern:

This pattern is frequently combined with Wind and Dryness and usually has an underlying Spleen *Qi* Deficiency, with or without chronic disease.[8] The skin and muscles are not nourished properly creating dry-flaky skin, and cracked hooves. These patients will have pruritis with pale-dry tongues and thin-weak pulses.[8]

- Liver and Kidney *Yin* Deficiency TCVM Pattern:

This pattern is associated with older animals and chronic illness. Patients have pruritis, dry-flaky skin with alopecia, crusting lesions and a red-dry tongue with a thin-deep, fast pulse.

TREATMENT – CONVENTIONAL THERAPY

Pharmaceuticals

Skin allergies are often initially treated via corticosteroid (Cs) administration (prednisolone 2-4.4 mg/kg PO q24h or dexamethasone 0.04-0.2 mg/kg PO, IM, or IV q24h).[14] They are started at a high dose then quickly weaned to the lowest effective dose. Prednisone is not useful in clinical equine practice due to poor bioavailability.[2] In some cases, such as one-time insect bites, a single dose of a Cs is all that is necessary. Long term administration of Cs has been associated with negative side effects such as laminitis (anecdotal), decrease in insulin sensitivity, immunosuppression, and down-regulation of the hypothalamic-pituitary-adrenal axis.[15]

For long-term use, antihistamines are often the drug of choice when environmental allergens are the cause of dermatological issues but are not very effective for controlling IBH as a sole therapeutic agent.[2] It is important to realize that antihistamines are not as effective in halting an ongoing allergic reaction as they are in preventing one from occurring.[7] Hydroxyzine (1-2 mg/kg PO q8-12h) and cetirizine (0.2-0.4 mg/kg PO q12h) are the common medications used and may have rare side effects of drowsiness or irritability.[7] Not all horses respond in the same manner to each antihistamine, so owners should be counseled that it may be an ongoing trial and error process in which each medication should be tried for at least two weeks. A well-marketed pyrilamine maleate and pseudoephedrine hydrochloride powder[a] (0.66 mg/kg PO q12h) is often requested by clients but has been shown to have poor bioavailability and a long withdrawal time for competition.[14] Recent concerns about the use of pyrilamine maleate in illegal drug manufacture of methamphetamines or abuse by humans has led to more caution in its prescription for equine patients.[14]

Severe, acute systemic allergic reactions can be life threatening due to edema of the airways and may require rapid treatment with epinephrine (1:1000 at 5-10 mL/450 kg SQ or IM**)** or a high dose glucocorticoid (prednisolone 2 mg/kg PO, IM, or IV; or dexamethasone 0.04 mg/kg IV).[7] Non-steroidal anti-inflammatory drugs are not effective for allergic disease.[7] A summary of the commonly used conventional medications for allergies in the horse are listed in Table 2.

Immune Mediators

In addition to the administration of common medications, allergen specific immunotherapy (ASIT) for horses has been developed for dermatological allergies with the goal of reducing or normalizing the horse's inflammatory allergic response. The treatment plan involves serum or intra-dermal testing of each animal against a variety of region-specific allergens, evaluation of the allergic response to each allergen, and then the creation of a custom compounded immunotherapy regime for desensitization. The immunotherapy agent is often administered via a slowly increasing concentrated dose to induce tolerance to specific allergens and can take over six months for maximal (if any) results.[3,5] The goal of ASIT is to stimulate the body to produce allergen specific IgG that binds with the receptor sites for IgE but does not stimulate the cytokine cascade or mast cell degranulation and thus shift the allergic response from Th2 to Th1 and regulatory T cells. This cascade reduces the release of interleukins that would stimulate histamine release.[5]

The response of horses to ASIT is vast and depends on the type of skin allergy. Horses with AD and CU have shown an increased positive response to ASIT over IBH horses.[2] Overall, approximately 70% of horses with dermatological allergies improve, and some can discontinue long term immunotherapy after the initial treatment series.[16] This wide range of responses may be due to differences in compounded medication production (currently the only method available), different IgE responses when compared to humans, different levels of total IgE compared to other species, and the specific type of dermatological allergy.[5]

It is important to remember that when a horse is moved to a new environment, allergen specific immunotherapy may have to be re-evaluated and a new protocol started due to changes in plants, insects, and feed materials that are location specific. Doxepin (0.5-0.75 mg/kg PO q12h) and amitriptyline (1 mg/kg PO q12h) are antidepressants which have shown some anecdotal promise in the treatment of hypersensitivity due to their histamine receptor blocking abilities.[7] Pentoxifylline (starting dose 10-15 mg/kg PO q12h then increase up to 30 mg/kg PO q8-12h) has been shown to modulate B and T-cell activation and proliferation, affect leukocyte function, and modulate interleukin production and effects.[2]

Ancillary Therapy

A Janus kinase inhibitor that is common in the canine market for allergic and atopic dermatitis (oclacitinib maleate[b]) has recently been evaluated for use in horses. Horses given 0.25 mg/kg by mouth once a day for 28 days showed a decrease of 63% of dermatological clinical signs

Table 2: Conventional medications used for allergic dermatitis[2,7,14,17]

Drug		Dose
Systemic Corticosteroids	Dexamethasone	0.04 – 0.2 mg/kg PO, IV or IM q24h then tapered
	Prednisolone	2.0 – 4.4 mg/kg PO q24h then tapered
Antihistamines	Hydroxyzine	1 – 2 mg/kg PO q8-12h
	Cetirizine	0.2 – 0.4 mg/kg PO q12h
	Pyrilamine maleate and pseudoephedrine hydrochloride (Tri-Hist[a])	0.66 mg/kg PO q12h
Anti-depressants (histamine receptor blockers)	Doxepin	0.5 – 0.75 mg/kg PO q12h
	Amitriptyline	1 mg/kg PO q12h
Other Medications	Pentoxifylline (immunomodulator)	10 – 30 mg/kg PO q8-12h
	Oclacitinib maleate (Janus kinase inhibitor)	0.25 mg/kg PO q24h × 28d
Emergency Medications	Epinephrine 1:1000	5 – 10 mL/450 kg SQ or IM
	Prednisolone	2 mg/kg PO, IM, or IV
	Dexamethasone	0.04 mg/kg IV

compared to control.[17] Research is ongoing, but this drug may prove beneficial for animals non-responsive to other therapies. In addition, the once a day dosing (versus twice a day in dogs) makes the product more convenient, albeit expensive.[18]

Nutritional management for dermatological allergies has been attempted by modifying the fatty acid ratios and levels in feed. Specifically, high doses of n-3 fatty acids (omega-3 fatty acids) from flaxseed but not linseed was shown to reduce pruritus, indicating the source of the fatty acids is important in addition to the type.[2]

Topical therapies for pruritic horses have been explored. For IBH, an Australian spray containing essential oils reported to aid in mast cell stabilization, reduction of itch, and repel insects was shown to be effective in 95% of horses.[4]

Environmental

Specific treatment for IBH includes environmental management and insect control. Environmental management includes stabling as needed, fans, reduction in brush within a pasture, and moving horses away from standing water. Insect control relies on topical insecticides, physical protection (fly sheets or masks), and manure management. The topical insecticides shown to be effective against *Culicoides* include permethrin, diethyltoluamide (commonly known as DEET), and cypermethrin whereas citronella and lemon eucalyptus oil were not shown to be effective.[2] Cytokine vaccinations are currently being explored to reduce the circulating IL-5 and IL-31 levels in IBH horses.[2,4] Similarly, control of AD includes reduction of environmental triggers when possible. Allergen specific IgE testing can be useful in horses with CU to help identify possible allergens for management changes.[2]

TCVM TREATMENT – ACUPUNCTURE THERAPY

Evidence Based Studies

Acupuncture is a system of medical therapy used in traditional Chinese medicine for humans and animals for more than 2500 years.[19] Although acupuncture is best known and widely studied for its use in pain conditions, there is a growing body of evidence that it can be effective for dermatologic disease.[19] Clinical trials and case reports of human patients have reported the successful use of acupuncture to treat AD and itch, urticaria, herpes zoster, psoriasis, acne, melasma and to promote wound healing.[19] Investigational studies of acupuncture's mechanisms of action indicate it is mediated through stimulation of sensory/neural pathways and can modulate the immune system via interaction between the neural and endocrine systems.[19-22] Beneficial to the treatment of skin disease is AP's ability to modify mast cell response, pro-inflammatory cytokines, and receptor regulation.[23,24] Acupuncture's parasympathetic effect on vagus nerve stimulation is thought to produce potent anti-inflammatory effects.[20,22,25-27] A 2013 review outlined the effects of various neuropeptides and hormones associated with acupuncture treatment which resulted in immunomodulation, anti-inflammatory and autonomic nerve activity.[19]

Acupuncture has been shown to have a significant effect on experimental itch. Pfab and colleagues through a number of investigations, have done extensive research on itch, noting its significance in allergic skin disease in humans.[28-31] Two randomized clinical trials comparing placebo to real acupoint stimulation demonstrated reduced histamine-induced itch in healthy volunteers. Of note, they found LI-11 (*Qu-chi*) was particularly useful for treating itch when combined with other acupoints and regions.[19,29,30] Pfab's group then looked at patients with atopic dermatitis and found that AP was as effective as cetirizine for preventative intervention, and superior to cetirizine as an abortive intervention (AP applied during itch induction) for reducing itch perception after skin prick of an allergen solution.[19,31] Preventative AP (applied prior to itch induction) was the only therapy found to reduce skin reactions (flare sizes). It was concluded that AP could be valuable as a complimentary therapy for atopic patients.

Traditional Chinese medicine has used AP to treat urticaria for centuries. The Chinese physician, Sun Simiao, as early as 7th century AD, described treating urticaria in his treatise *Qian Jin Yao Fang* (Thousand Ducat Important Prescriptions).[19] A review of a number of case series was published by Chen and Yu describing various AP approaches to useful management of acute and chronic urticaria in humans.[32] They reported a clinically relevant reduction in 50-83% of patients. In a different study, Iraji and colleagues demonstrated a ≥50% reduction by the 3rd week of AP treatment (compared to placebo), in episode duration and frequency for patients with chronic idiopathic urticaria refractory to conventional treatment.[33]

Manipulation of the nervous system using AP can have downstream effects on the immune system. Brain imaging has shown that AP activates the hypothalamus, changes levels of circulating and tissue opioids/non-opioids which can affect type IV hypersensitivity.[20] Additionally, certain acupoints have specific activities. The acupoint ST-36 has been shown to modulate the inflammatory response significantly via changes in Th1:Th2 ratios and modulation of the hypothalamus, as well as decreasing levels of IgE/mast cell infiltration and histamine release.[34] Interestingly, the changes seen were acupoint specific, indicating that the point selection, not just action of needle insertion, is important. Further AP benefits have been demonstrated in studies that have shown an immunomodulatory effect on immune conditions regardless of Th1 or Th2 skewed ratios, suggesting AP treatment helps the patient return to normal, rather than directing the immune response towards one specific T-cell type.[20] Although there has been increasing human clinical trials and laboratory-based research demonstrating AP's usefulness for treating dermatological disorders, as yet there is a lack of evidence-based work in veterinary medicine other than case reports noting its benefits in small animals.[13,35-37]

Acupuncture Treatment

Acupuncture can be beneficial in treating skin disease in horses and in human/mouse studies has been shown to modulate induced and disease-caused itch.[8,28,38] The technique and protocol used will vary depending on patient presentation, patient temperament/personality, practitioner comfort level and TCVM Pattern diagnosis. Some horses with dermatological conditions are sensitive to physical contact, and initial treatment may focus on herbal and nutritional recommendations until the patient is comfortable with acupuncture treatment.

The elimination of External Pathogens (e.g. Wind, Damp, Heat/Heat-Toxins, parasites, allergies) creating Excess Patterns, if identified, should be tackled first followed by strengthening the *Zang-fu* organs and Channels that are identified as Deficient. Tonification of the Lung can be affected by treating the organ itself or supporting the mother-child relationship (supporting Spleen to tonify Lung). The tonification will also target improving *Qi*-Blood flow. Lung Heat, Kidney/Liver *Yin* Deficiency and Blood Deficiencies are the main targeted anomalies in chronic dermatological disease, although secondary Damp may also occur (Tables 3 and 4).

Clearing Heat and Wind, the two most concerning Pathogens, particularly in the Heart and Lung, is via stimulation at BL-10, BL-12, BL-17, GB-20, BL-40, *Er-jian*, and *Wei-jian*. Hemo-acupuncture has been shown to be the most effective method for clearing Excess Heat.[38] Placement of needles in *Er-jian* and/or *Wei-jian* is particularly effective to drain Heat and may provide a clearer evaluation of the underlying pattern. A secondary concern seen with chronic Wind or Heat is the depletion of Blood or Liver/Kidney *Qi*. In these Deficient cases, specific nourishing of Blood and *Yin* with acupoints such as BL-17, BL-23, BL-26, *Bai-hui*, SP-6, SP-9, and SP-10 can help resolve the condition.

For Deficient conditions, electro-acupuncture (EAP) has been shown to be effective at low frequency with high intensity (5-20 Hz oscillating frequency), especially if repeated.[39] Treatment using *Qi* tonic acupoints SP-6 or ST-36 can be beneficial but should be used with care in aged or poor condition animals.[9,10] Moxibustion can also be used for the treatment of chronic Deficiency or Damp, however caution should be followed, as depending on the allergens, it can worsen a patient's skin condition.

Table 3: Treatment recommendations for equine dermatological conditions using TCVM[40]

TCVM Pattern Diagnosis	Acupuncture	Chinese Herbal Medicine[c]
Wind or Wind-Heat	GB-20, BL-10, BL-12, BL-17, SP-10, *Er-jian, Wei-jian*	Wind Toxin External Wind
Yin Deficiency (Liver and Kidney)	KID-3, BL-23, SP-6, SP-9, SP-10, HT-7, GB-20, BL-10, *An-shen*	*Yang Yin Zhi Yang*
Blood Deficiency	SP-10, BL-17, ST-36, SP-6, HT-7, GB-20, BL-10, *An-shen*	*Si Wu Xiao Feng*
Damp-Heat	SP-6, SP-9, ST-40, BL-17, SP-10, *Er-jian, Wei-jian*	Damp Heat Skin
Blood-Heat	GB-20, LIV-3, GB-34, BL-17, SP-10, GV-14, LI-4, LI-11, *Er-jian, Wei-jian*	Blood Heat Formula
Lung Wind	LI-11, LI-4, SP-10, BL-40, BL-17, TH-10, GB-20, BL-10	Lung Wind *Huang*

Table 4: Acupuncture points used for equine dermatological allergies; the most commonly used points are in **BOLD**

Acupuncture Point	Main Goal	Ancillary Goal(s)	Additional Notes
BL-10	Clears Wind	Stops itching	—
BL-11	Resolves cough and asthma	—	—
BL-12	Clears Wind	Affects Wind-Heat; stops itching	Classical name is *Feng-men*
BL-17	Moves Blood and clears Wind	Clears Heat	Back-*shu* point for diaphragm
BL-23	Back-*shu* point for Kidney	—	Kidney association point
BL-40	Clears Wind and Heat	Stops itching	—
GB-20	Clears Wind	Stops itching	—
GB-34	Soothes Liver *Qi*	—	—
SP-6	Tonifies *Qi* and Blood; nourishes *Yin*	Strengthens Spleen and generates Blood	—
SP-9	Nourishes *Yin*; nourishes Blood	—	—
SP-10	Clears Heat in Blood; nourishes *Yin*	Moves Blood and ends Wind	—
LI-4	Clears Wind	Regulates immune function	—
LI-11	Clears Heat and Wind	Regulates immune function	—
TH-10	Clears Heat	—	—
LIV-3	Soothes Liver *Qi*	Resolves Liver *Qi* Stagnation	*Yuan*-source point
ST-36	Strengthens Spleen to generate Blood	—	—
ST-40	Drains Damp and Phlegm	—	Influential point for Phlegm
HT-7	Nourishes Heart	Calms the mind	*Yuan*-source point
KID-3	Tonifies Kidney	Nourishes *Yin*	*Yuan*-source point
Er-jian	Clears Heat	—	—
Wei-jian	Clears Heat	—	—
An-shen	Nourishes Heart	Calms the mind	—

TCVM TREATMENT – CHINESE HERBAL MEDICINE

Evidence Based Studies and Therapeutic Use

The most common dermatological conditions in horses often require lifetime therapy, especially if the environmental causes (insects, pollens, dust) cannot be eradicated. Chinese herbal medications provide an alternative to long-term conventional medications without many of the undesirable side effects (e.g. immunosuppression, altered endogenous adrenocorticoid production). The classic CHMs used for treatment of dermatological allergies are composed of herbs that are immunomodulatory, anti-inflammatory, modulate pain/discomfort, and act as anti-histamine/anti-oxidant compounds.[40,41] The plants within these CHMs contain phytochemicals, iridoids, and flavonoids that are effective on the immune and healing pathways of the body. In human medicine over the past several decades, many of the contents of these herbal combinations have been evaluated for their individual therapeutic actions, along with mechanisms of actions, using traditional research methods (*in vivo*, *in vitro*), primarily in laboratory animal studies.[40]

Herbal Medicine Formulas for Excess Patterns

- Wind, Wind-Heat

Wind attack of the exterior, presenting with an Excess Pattern and pruritis, but without progression to Heat, is commonly treated with *Qu Feng Zhi Yang* (External Wind[c]), which is derived from the classical Chinese herbal medicine formula, Allergy Formula I (Table 5).[40] This formula contains herbs that modulate the immune response by inhibiting production of IgE and release of contents by mast cells, thereby reducing the inflammatory cascade.[40]

One of its herbs, *Bai Xian Pi* (Dictamnus) is a well-known dermal anti-inflammatory agent and has been shown *in vitro* to suppress nitric oxide and pro-inflammatory cytokine production as well as modulate the NF-κB pathway in keratinocytes.[42,43] The effects of *Cang Er Zi* (Xanthium) on mice with induced asthma showed improvement of the Th1:Th2 ratio towards reducing inflammation and cytokine modulation compared to control mice.[44] Human and mouse dermatological models were used to show that extracts from *Mu Dan Pi* (Moutan) inhibited acute anaphylaxis (modulated via IgE) and histamine release via the NF-κB signaling pathway.[45] The fruit, *Di Fu Zi* (Kochia scoparia), in contrast to its

allergenic relative, ragweed (Bassia scoporia), is used for treatment of inflammatory skin disease. Topical application of a *K. scoparia* extract to treat contact dermatitis in a murine study, decreased epidermal hyperplasia, spongiosis and immune cell infiltration, similar to corticosteroid treatment but without the general immune suppression.[46] Finally, both powdered *Jiang Can* (Bombyx) larvae and silkworm droppings extract have been shown to inhibit NF-κB nuclear translocation, MAPK signaling, and Th2 cell-related cytokines in gastrointestinal and dermatologic allergic models in mice.[47,48]

As the master Pathogen, Wind, attacks the body surface; the most *Yang* Pathogen, Heat, joins to then present the TCVM Pattern of Wind-Heat. The Chinese herbal medicine commonly used for this pattern, Wind Toxin[c], is a modification of *Xiao Feng San* (Eliminate Wind Powder). Wind Toxin contains compounds targeted at clearing Heat, Wind, and Damp while at the same time cooling and invigorating Blood and relieving pruritus (Table 6).

Some of the herbal components of External Wind are also found in this formula such as *Jing Jie*, *Bai Xian Pi*, and *Chi Shao* and have similar medicinal properties. One of these, *Jing Jie* (Schizonepeta), similar to many of the other herbs, has been shown to modulate the allergic inflammatory response (*in vivo* and *in vitro* models) at the cellular level via cytokine down regulation, cell receptor level modulation, suppression of NF-κB and MAPK activation.[49]

A different herb used in this formula, *Fu Ling* (Poria) when tested in rats showed anti-oxidant effects, anti-inflammatory effects (gene transcription level), and ameliorated the clinical signs of atopic dermatitis via immunosuppression in cell models with no evidence of toxicity.[50] Evaluation of *Fang Feng* (Ledebouriela) for allergies in mouse studies for an allergic dermatitis model showed the herb extract modulated the tight junctions and subsequently reduced the pro-inflammatory cytokines, especially when administered early in the allergic response.[51] The polysaccharides from the *Bai Zhu* (Atractylodes) have been shown in a number of studies to modulate the immune function via changes in natural killer, B and T cells, TLR4/toll-like receptor-4, and the cyclic AMP pathway in studies in mice, geese, rats, and oxen. Other functions of *Bai Zhu* include antioxidation and neuroprotection.[52]

Jin Yin Hua (Lonicera) also has potent anti-inflammatory effects which include: acting upon cytokines, the T cell differentiation pathway, protein expression pathways (TLR4 and NF-κB), the pro-inflammatory Janus kinase 1 molecule, as a free radical scavenger, and reducing IgE serum levels in mice with experimentally induced allergic rhinitis.[53]

In mice, extract from *Xuan Shen* (Scrophularia) inhibited induced itch.[54] Using an induced respiratory model in mice, *He Shou Wu* (Polygonum) was shown to decrease clinical signs, eosinophil infiltrate, and reduce pro-inflammatory cytokines compared to control mice, all which are mediated by Th2 cell activation.[55] Finally, a mouse model showed that *Ku Shen* (Sophora) reduced mast cell mediated histamine release, thereby reducing itch.[56]

Table 5: Ingredients of the Chinese herbal medicine, External Wind[c], and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Jing Jie	Schizonepeta	Clears Wind-Cold, relieves itching
Cang Er Zi	Xanthium	Clears Wind, opens the Lung
Mu Dan Pi	Tree Peony	Cools Blood and activates Blood
Bai Xian Pi	Dense-fruit Dittany	Kills scabies
Di Fu Zi	Summer Cypress	Clears Wind and benefits skin
Chi Shao	Chinese Peony	Cools Blood and clears Heat
Jiang Can	Bombyx	Clears Wind, detoxifies

Table 6: Ingredients of the Chinese herbal medicine, Wind Toxin[c], and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Bai Xian Pi	Dense-fruit Dittany	Clears Damp-Heat and kills scabies
Fu Ling	Poria	Eliminates Damp and strengthens Spleen
Jing Jie	Schizonepeta	Clears Wind, opens the skin, alleviates itching
Fang Feng	Siler	Clears Wind
Bai Zhu	Atractylodes	Strengthens Spleen
Jin Yin Hua	Honeysuckle	Detoxifies, alleviates itching
Ju Hua	Chrysanthemum	Clears Heat, detoxifies, relieves swollen glands
Xuan Shen	Scrophularia	Clears Damp-Heat, relieves swollen glands
Zhi Zi	Gardenia	Clears Damp-Heat, detoxifies
Bai Ji Li	Tribulus	Clears Wind, alleviates itching
Chi Shao	Chinese Peony	Cools down Blood
Dang Gui	Dong Quai	Invigorates Blood
He Shou Wu	Fo-ti	Tonifies Blood and *Yin*
Ku Shen	Shrubby Sophora	Detoxifies, alleviates itching

- Damp-Heat

Damp Heat Skin[c], which is a modification of *Qing Shi Re Tang*, is indicated for the resolution of Damp-Heat, which often follows Wind-Heat invasion (Table 7). Herbs contained in this formula also have a wealth of anti-inflammatory and immunomodulatory activities. *Tu Fu Ling* (Smilax) has been shown *in vitro* and *in vivo* to have anti-inflammatory and immunomodulatory effects by suppressing the production of pro-inflammatory cytokines and nitric oxide.[57,58] Evaluation of *Huang Bai* (Phellodendron) in mouse studies of immunity showed that it inhibited delayed type hypersensitivity but not the acute phase of the cellular response.[59,60] *Huang Qin* (Skullcap) has been shown to significantly affect the immune system of *in vivo*

and *in vitro* models including reduction in histamine and IgE release, regulation of cytokine production, and may prevent Th2 or mast cell mediated asthma.[61,62] The compounds in *Ban Lan Gen* (Isatis) have been shown to have immunomodulatory and anti-inflammatory effects, including inhibition of TNF-α release and inhibited activation and proliferation of T cells.[63,64] Extracts from the seeds of the *Che Qian Zi* (Plantain), were evaluated in mice and showed improved function of dendritic cells, key cells in proliferation of T cells.[65] Some of the components (*Ku Shen*, *Di Fu Zi*) have been previously discussed and *Sheng Di Huang* (Rehmannia) will be presented later.

- Blood-Heat

Blood Heat Formula[c] which is a modification of *Liang Xue Jie Du Tang* is targeted at helping eliminate excess Blood-Heat, as the name implies (Table 8). *Yu Jin* (Curcuma Longa), also known as turmeric, is a cooking ingredient that has been shown to have immunomodulatory actions, including for allergic diseases. The turmeric compounds interact with many cells of the immune system and have been demonstrated *in vivo* and *in vitro* to suppress the production of pro-inflammatory cytokines, the activation of mast cells, and the production of TNF-α.[66] In addition, immunomodulatory effects on Th1 and Th2 were noted in humans and clinical signs of dermatitis improved with treatment using Curcuma Longa.[66]

Mai Men Dong (Ophiopogon) has been evaluated in human, mouse, and *in vitro* studies for use in allergic conditions. It has been shown in mice to correct Th1/Th2 imbalance in AD disease models and decrease pro-inflammatory cytokines.[67,68] In humans, topical administration reduced the clinical signs of itch and erythema in patients with AD as well as improving the skin barrier compared to controls.[67] The ingredients *Chi Shao*, *Dan Shen*, *Di Fu Zi*, *Huang Bai*, *Mu Dan Pi*, *Sheng Di Huang*, *Xuan Shen*, and their functions are presented with other CHM formulas.

- Lung Wind

The Chinese herbal medicine, Lung Wind *Huang*[c], which is modified *Xiao Huang San*, addresses this TCVM Pattern (Table 9). The formula contains *Huang Qin*, *Yu Jin*, *Fang Feng*, *Huang Bai*, *Jing Jie*, and *Gan Cao*, which are discussed with other formulas. An interesting herb in the formula, *Yin Chen Hao* (Artemisia), has been investigated and shown in mice to modify the adaptive immune cell activation and to inhibit NF-κB activity (*in vitro* studies), leading to a down-regulation in pro-inflammatory cytokines.[69,70]

Da Huang (Rhubarb) is a common herb in CHM and helps to clear Heat and move Blood. *In vitro* and *in vivo* models using the compound in a psoriasis mouse model showed a decrease in clinical signs, inflammatory cytokine levels, and inflammatory cells.[71,72] Additional studies showed the anti-inflammatory effects were mediated via the NF-κB pathway and by reduction in free radicals through scavenging.[72,73] Menthol, one of the components of *Bo He* (Mentha), has been shown to also have anti-inflammatory activities by suppressing the production of inflammatory mediators produced by monocytes.[74]

Table 7: Ingredients of the Chinese herbal medicine, Damp Heat Skin[c] and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Tu Fu Ling	Chinese Smilax	Eliminates Damp, kills fungi
Ku Shen	Shrubby Sophora	Clears Damp-Heat, relieves itching
Sheng Di Huang	Rehmannia	Cools Blood and nourishes *Yin*
Huang Bai	Phellodendron	Clears Damp-Heat, detoxifies
Huang Qin	Chinese Skullcap	Clears Damp-Heat, detoxifies
Ban Lan Gen	Isatis	Clears Heat, detoxifies
Che Qian Zi	Plantain	Clears Damp-Heat, benefits urination
Di Fu Zi	Summer Cypress	Clears Damp-Heat and benefits skin

Table 8: Ingredients of the Chinese herbal medicine, Blood Heat Formula[c], and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Yu Jin	Turmeric	Cools Blood, clears Heat, detoxifies
Chi Shao	Chinese Peony	Cools Blood, clears Heat
Dan Shen	Chinese Salvia	Cools Blood, activates Blood
Di Fu Zi	Summer Cypress	Clears Heat, detoxifies
Huang Bai	Phellodendron	Clears Heat, detoxifies
Mai Men Dong	Ophiopogon	Nourishes *Yin*
Mu Dan Pi	Tree Peony	Cools and moves Blood, eliminates Stagnation
Sheng Di Huang	Rehmannia	Cools Blood, nourishes *Yin*
Xuan Shen	Scrophularia	Cools Blood, clears Heat, resolves nodules

Table 9: Ingredients of the Chinese herbal medicine, Lung Wind *Huang*[c] and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Yin Chen Hao	Yin-chen Wormwood	Clears Heat
Da Huang	Chinese Rhubarb	Clears Heat, Purges LI
Huang Qin	Chinese Skullcap	Clears Heat, detoxifies
Yu Jin	Turmeric	Cools Blood
Bo He	Chinese Mint	Clears Wind-Heat
Fang Feng	Siler	Clears Wind-Cold
Huang Bai	Phellodendron	Clears Heat, detoxifies
Huang Lian	Coptis	Clears Heat, detoxifies
Jing Jie	Schizonepeta	Clears Wind-Cold
Lian Qiao	Forsythia	Clears Heat, detoxifies
Zhe Bei Mu	Zhejiang Fritillary	Transforms Phlegm, clears Heat
Zhi Mu	Anemarrhena	Clears Heat, nourishes *Yin*
Zhi Zi	Gardenia	Clears Heat, detoxifies
Gan Cao	Chinese Licorice	Harmonizes
Chan Tui	Cicada	Clears Wind-Heat

The rhizome of *Huang Lian* (Coptis), modulates the immune system by activating Th1 cells via the MAPK signaling pathway, blocking the NF-κB dependent pathway, and modifying pro and anti-inflammatory secretions, thus altering the immune response.[75,76]

Lian Qiao (Forsythia), has demonstrated anti-inflammatory and anti-allergic capabilities by decreasing mast cell degranulation, histamine release, pro-inflammatory cytokine expression, and the production of nitric oxide.[76] A study in piglets with induced food allergies demonstrated the use of Forythia Suspensa to alleviate anaphylactic symptoms via the reduction of mast cell degranulation, histamine release, and modulation of the innate and acquired immune systems.[77]

The effects of *Zhe Bei Mu* (Fritillary) are antioxidant and anti-inflammatory via multiple pathways including a decrease in the NF-κB mediated transcription of proinflammatory cytokines.[78] The many molecular compounds in *Zhi Mu* (Anemarrhena) have been evaluated and some are shown to be effective against mast-cell mediated allergic reactions via inhibition of histamine release and pro-inflammatory cytokine secretion as well as inhibiting COX-2 expression, a potent enzyme in the pro-inflammatory pathway.[79,80] *Chan Tui* (Cicada) slough used for the treatment of AD in mice demonstrated a decrease in mast cell infiltration, IgE concentration, histamine, and pro-inflammatory cytokines.[81] In an induced lung inflammation model Cicada-treated mice showed a decrease in pro-inflammatory mediators including NF-κB and MAPK.[81,82]

Herbal Medicine Formulas for Deficiency Patterns

Patterns that include Deficiency can occur secondary to chronic Excess Wind or Wind-Heat in the body. Patients with these patterns can be treated with *Yang Yin Zhi Yang*[c] (Kidney or Liver *Yin* Deficiency) or *Si Wu Xiao Feng*[c] for Blood Deficiency.

➢ Kidney and/or Liver *Yin* Deficiency

Yang Yin Zhi Yang herbal medicine formula is used to treat patients with Kidney/Liver *Yin* Deficiency (Table 10). It contains the herbs *Jing Jie* and *Xuan Shen*, which are discussed in other herbal formulas. In addition to the herbs listed, the herbal formula contains a plant commonly used in CHM, *Sheng Di Huang* (Rehmannia), which has been shown to modulate the allergic immune response in mice with induced atopic dermatitis after topical application and in type I allergic reactions induced in rats. The changes seen include down-regulation of pro-inflammatory cytokines such as IL-4 and TNF-α and reduction in histamine.[83,84] Another component of the mixture, *Dan Shen* (Salvia), has been evaluated in allergic models in mice for atopic dermatitis and allergen-induced asthma. In the studies, extracts inhibited the production of pro-inflammatory cytokines and inflammatory cell infiltration, modulated Th1/Th2 cell responses, and modulated the NF-κB pathway.[85-87] Multiple models using *Gan Cao* (Glycyrrhiza), from both naturally grown plants and hydroponic cultivation, showed that oral administration of the active compound (glycyrrhizic acid) inhibited the clinical signs of contact allergy in mice.[88,89] Additional *in vitro* and *in vivo* molecular studies in mice showed that the mechanisms of action include inhibition of mast cell degranulation, modulation of cytokines released, and effects on transcription factors such as NF-κB.[90,91]

➢ Blood Deficiency

Si Wu Xiao Feng (*Si Wu Tang* modification) contains a large number of herbs indicated for the resolution of Blood Deficiency and to resolve Wind which have previously been discussed (*Sheng Di Huang*, *Jing Jie*, *Mu Dan Pi*, *Bai Xian Pi*, *Di Fu Zi*, *Jiang Can*) (Table 11). An additional herb of interest in this formula, Paeonia Lactiflora (*Bai Shao Yao*, root without bark; *Chi Shao*, root with bark) has been shown to have anti-allergic activity through reduction of type I allergy, based on network pharmacology analysis. This approach systematically analyzed the active ingredients of Paeonia to identify allergy-related targets and pharmacological mechanisms related to its medicinal value.[92] Additionally, mouse studies have demonstrated atopic dermatitis symptom reduction (e.g. regulation of white blood cell levels, interleukin expression, mast cell degranulation).[93,94] Extracts of *Chuan Xiong* (Ligusticum) investigated in mouse models (*in vitro* and *in vivo*), have shown anti-inflammatory, anti-oxidant, and analgesic effects.[95] The anti-inflammatory models showed modulation of the cyclooxygenase (COX) and NF-κB pathways resulting in decreased pro-inflammatory cytokine expression.

Table 10: Ingredients of the Chinese herbal medicine, *Yang Yin Zhi Yang*[c], and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Sheng Di Huang	Rehmannia	Cools Blood and nourishes *Yin*
Dan Shen	Chinese Salvia	Cools Blood and activates Blood
Dang Gui	Dong Quai	Nourishes Blood
Jing Jie	Schizonepeta	Clears Wind, relieves itching
Mu Li (*Sheng*)	Oyster Shell	Calms *Shen*, subdues Liver *Yang*
Xuan Shen	Scrophularia	Cools Blood and nourishes *Yin*
Gan Cao	Chinese Licorice	Harmonizes

Table 11: Ingredients of the Chinese herbal medicine, *Si Wu Xiao Feng*[c] and their actions[40]

***Pin Yin* Name**	**Common Name**	**Actions**
Shu Di Huang	Rehmannia	Nourishes Blood and *Jing*
Bai Shao Yao	Chinese Peony (without bark)	Nourishes Blood
Dang Gui	Dong Quai	Nourishes Blood
Jing Jie	Schizonepeta	Clears Wind-Cold, relieves itching
Cang Er Zi	Xanthium	Clears Wind, opens the Lung
Chuan Xiong	Sichuan Lovage	Moves Blood, resolves Stagnation
Mu Dan Pi	Tree Peony	Cools Blood and activates Blood
Bai Xian Pi	Dense-fruit Dittany	Kills scabies
Di Fu Zi	Summer Cypress	Clears Wind and benefits skin
Chi Shao	Chinese Peony (with bark)	Cools Blood and clears Heat
Jiang Can	Bombyx	Clears Wind, detoxifies

TCVM TREATMENT – FOOD THERAPY

Wind and Wind-Heat should be treated by removing hot or warming foods in the diet and adding cooling foods. This can be difficult in horses due to their specific nutritional needs and tastes but may be possible by identifying complete pelleted feeds that avoid certain ingredients. Larger components of the diet that can be modified include removing the hot foods oats and molasses.[10] These can be replaced with millet, alfalfa, flax, soybean oil (which has been shown to specifically modulate the inflammatory response due to its high level of n-3 fatty acids), grass hays, and barley.[96,97] Trial and error or the rotation of food additives is often an effective option. Horse owners should read the feed bag labels of their commercially produced grains and treats to reduce heat producing components (such as oats or molasses) and realize that the processing itself puts heat into the diet. Adding cucumber, peppermint, watermelon (especially the rind), pear, or banana (the skin is especially helpful for pruritus) can be done as a treat or a nutritional additive to the current feed.[10] Unfortunately, carrots and sugar cubes, both common treats for horses, are hot foods and should be removed from the diet.

INTEGRATIVE MEDICAL TREATMENT

Dermatological allergies are frustrating for owners to manage. A combination approach (conventional medicine and TCVM) provides more rapid case improvement, minimization of medications, and may reduce the need for some of the environmental changes which can be difficult to institute. With IBH, a mainstay of the treatment is reduction of insects; which, depending on the owner and husbandry, may not be feasible. Alternatively, barrier protections such as fly sheets, fans, or repellent sprays can reduce the insect-to-horse contact level. When insect avoidance is not possible or complete, treatment is then aimed at reducing the body's response to the insects. Initially, conventional medications reduce the frantic itching and the patient's (and owner) discomfort. Treatment modalities such as AP and CHM can then be added to help modify the immune system dysfunction and reduce the dosage/duration of pharmaceuticals, particularly those with side effects.

The treatment of AD lends itself very well to integrative therapy as it is often a year-round problem due to environmental stimuli that cannot be eliminated. Similarly, the source of CU is often unknown, and the clinical signs of wheals/hives covering the body are unsightly, especially for competition horses. Long term year-round treatment of dermatological allergies with conventional medications can be difficult, especially during competitions which regulate dosage and frequency of both steroids and antihistamines.

The effects of AP on ASIT, or vice versa, are largely unknown. One retrospective study investigated treatment of allergic rhinitis in humans with a combination of AP and sublingual ASIT and showed improved outcome relative to ASIT alone. The study did not evaluate molecular markers to verify and confirm the mechanism for improvement, however, the results are interesting and suggest further investigation.[97]

Integrative Protocol for Skin Disease

- Diagnosis:

Begin with a thorough history, conventional examination, followed by a TCVM examination with TCVM Pattern diagnosis. Key components to determine include the client's main concern, previous and current environments, previous treatments, and current management options. Perform any diagnostics necessary to rule out ancillary dermatologic lesions or secondary bacterial/ fungal infections that might need additional therapy. If serum allergy or intradermal testing is to be performed, it should be done after the TCVM examination and appropriate withdrawal from antihistamines/corticosteroids.

- Treatment:

Use the examinations, historical, and advanced testing information to create two treatment protocols to run concurrently: a conventional plan and a complementary therapy plan. Additionally, review the diet and environment to reduce potential allergens.

- Maintenance:

Determine the recheck schedule. In patients with dermatological allergies, the patient's response to treatment can be monitored by the owner and communicated to the veterinary practitioner via telehealth as a complement to in-person veterinary examinations. The target with AP is to perform the subsequent treatment prior to the allergic signs returning or worsening. Treatment can initially be repeated every 5-7 days, then the interval slowly increased. Monitor resolution of dermatological lesions and pattern of hair regrowth over the subsequent 2-3 months. It is important to note that patients with IBH, AD, or CU may worsen at different times of the year, depending on the insect and environmental allergens, and treatment intervals should be monitored. Many of these patients will need to maintain consistent schedules of AP to continue to modify the immune response.

CLINICAL CASE REPORT

A 16-year old Haflinger mare presented for chronic itching in March. She had been diagnosed with IBH and AD approximately 8 years prior to current presentation and had become progressively more pruritic over time. The horse had been recently moved to Arizona where fly sheets were not feasible due to the ambient summer temperatures. Prior to her move she was managed with antihistamines, fly sheets/masks, and fly repellents and was not currently on allergy medications. In addition to the pruritus, she had a history of proximal pars intermedia dysfunction (PPID, equine Cushing's syndrome) which was controlled with 0.5 mg pergolide[d] by mouth once daily. Most recently she had become so pruritic she lost the hair at the top of her

tail, most of her mane, and had lesions on her ventral midline and legs due to self-mutilation. The mare was used as a companion horse and also provided occasional walking rides for small children. She was the submissive horse in a three-horse herd and had no additional significant medical conditions. The owner's main goal was to make her comfortable and reduce property destruction from itching. Given the patient's history of PPID, corticosteroids were contraindicated.

Diagnosis

➢ History:

Serum allergy testing had been performed four years prior and the horse was treated with ASIT (based on previous environment) for 2 years. A minimal response was noted to the ASIT, so it was discontinued.

➢ Conventional Physical Examination:

Body condition score of 6/9 (weight estimated at 400 kg) and observed to be tail and mane rubbing prior to examination. The horse appeared to be sweating normally and had a bright, interactive demeanor. Abnormalities of the exam included missing portions of the mane and tail hairs to the level of the base with lichenification and hyperpigmentation in approximately 30% of the regions. Additional areas of hair loss included the midpoint of the chest, ventral aspect of the abdomen, and caudal aspect of the pasterns. The patient was pruritic when stimulated by scratching. No secondary infections were noted on examination. Conventional suspected diagnosis: Atopic Dermatitis +/- Insect Bite Hypersensitivity

➢ TCVM Examination:

The ears and dorsal aspect of the body were warm, the tongue was red, small, and dry with deep and thready pulses. No sensitivity to any acupuncture sites noted and the patient was deemed to have an Earth constitution. TCVM Diagnosis: External Wind with Kidney *Yin* and Blood Deficiency.

Treatment

➢ Conventional Plan:

Medical management included starting cetirizine 0.4 mg/kg by mouth twice a day to be continued for one month then recheck.

➢ Complementary Plan:

Treatment included the initial AP treatment as well as CHM to address the TCVM Pattern (External Wind with Kidney *Yin* and Blood Deficiency).

- Acupuncture:
  Dry needle (bilateral): BL-10, BL-12, BL-17, BL-23, GB-20, SP-6, SP-10, KID-3;
  Dry needle (unilateral): LI-11, ST-36 (see Tables 3 and 4)
- Hemo-acupuncture: *Er-jian, Wei-jian*
- Chinese Herbal Medicine: 1) External Wind (10 grams twice daily) for 2 months (clear Heat); 2) *Yang Yin Zhi Yang* (10 grams twice daily) for 3 months (nourish Lung and Kidney *Yin*, nourish Blood) – Note the slight decrease in total dose given the patient's smaller stature
- Food Therapy: Addition of watermelon rind as treats to help reduce Heat. Given her history of insulin dysregulation and PPID, care was taken to choose treats that were low in carbohydrates. The main diet was not modified as she was well managed for her other health concerns.
- Environmental Management Recommendations: The owner was advised to install fans in the stalls and limit the horse to her stall during times of peak insect activity. Topical spray or ointment insect repellent was to be applied daily with focus on the face, legs, and abdomen. A fly mask with good ventilation was placed covering the eyes, ears, and under the jowls.

Case Outcome

Initially, the patient was managed with weekly acupuncture due to the severity of the pruritus and self-trauma. After the initial month, her clinical signs had significantly improved and the acupuncture was reduced to every other week for 1 month, then to monthly, based on owner reported response to therapy. The antihistamines were tapered down starting in the second month, but the clinical signs worsened when the dose was below 0.3 mg/kg, so she was maintained on that dose during peak insect season and stopped after the season. Throughout the subsequent year, clinical signs were seen to worsen when plants were flowering, so acupuncture was increased to every other week during that time and maintained at every 4-8 weeks in the non-flowering season. Clinical signs that were evaluated by the owner included pruritus, hair regrowth, general discomfort (head shaking, trail wringing and foot stomping), and body trauma. Improvement in all areas of clinical concern was noted by the owner.

SUMMARY

Integrative veterinary medicine where both Eastern and Western therapies are combined to provide individualized patient care, can result in a more comfortable equine patient and satisfied owner. The integration of therapies allows for a rapid response to treatment, as commonly seen with conventional therapies but with the added benefit of a reduction in the pharmacologics needed for symptom control over the long term. Successful response to treatment requires committed owner involvement, correct identification of the disease and TCVM Pattern, rapid control of the clinical disease, and long-term therapy including environmental management.

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FOOTNOTES

[a] Tri-Hist, Neogen Corporation, Lansing, MI, USA
[b] Apoquel, Zoetis, Parsipanny, NJ, USA
[c] Chinese herbal medicine formulas, Dr Xie's Jing Tang Herbal, Inc., Ocala, FL, USA
[d] Prascend®, Boehringer Ingelheim Animal Health USA, Inc., Duluth, GA, USA

REFERENCES

1. Verdon M, Lanz S, Rhyner C et al. Allergen-specific immunoglobulin E in sera of horses affected with insect bite hypersensitivity, severe equine asthma or both conditions. J Vet Intern Med 2019; 33(1):266-274. https://doi.org/10.1111/jvim.15355
2. Marsella R, White S, Fadok V et al. Equine allergic skin diseases: Clinical consensus guidelines of the World Association for Veterinary Dermatology. Vet Dermatol 2023; 34(3):175-208. https://doi.org/10.1111/vde.13168
3. Ginel P, Hernández E, Lucena R et al. Allergen-specific immunotherapy in horses with insect bite hypersensitivity: A double-blind, randomized, placebo-controlled study. Vet Dermatol 2014; 25(1):29-e10. https://doi.org/10.1111/vde.12092
4. Cox A, Stewart A. Insect bite hypersensitivity in horses: Causes, diagnosis, scoring and new therapies. Animals (Basel) 2023; 13(15):2514. https://doi.org/10.3390/ani13152514
5. Fettelschoss-Gabriel A, Birkmann K, Pantelyushin S et al. Molecular mechanisms and treatment modalities in equine Culicoides hypersensitivity. Vet J 2021; 276:105741. https://doi.org/10.1016/j.tvjl.2021.105741
6. Felippe M. Equine Clinical Immunology. Ames, IA: Wiley-Blackwell 2016:39-46.
7. Scott D, Miller W. Equine Dermatology. Maryland Heights, MO: Saunders 2011:263-313.
8. Holland C. TCVM for equine skin diseases. Practical Guide to Traditional Chinese Veterinary Medicine, Equine Practice. Xie H, Wedemeyer L, Chrisman C et al (eds). Reddick, FL: Chi Institute Press 2014:387-412.
9. Xie H, Preast V. Traditional Chinese Veterinary Medicine, Fundamental Principles 1st Ed. Reddick, FL: Chi Institute 2005: 105-148, 452.
10. Xie H, Preast V. Traditional Chinese Veterinary Medicine, Fundamental Principles 2nd Ed. Reddick, FL: Chi Institute 2013:96-97, 295-304, 85-110.
11. Xie H, Preast V. Xie's Veterinary Acupuncture. Ames, IA: Blackwell Publishing 2007:316-319.
12. Xie H, Ma A. TCVM for the treatment of pruritus and atopy in dogs. Am J Trad Chin Vet Med 2015; 10(2):75-80. https://doi.org/10.59565/JPSQ9532
13. Park H, Ahn S, Lee H et al. Acupuncture ameliorates not only atopic dermatitis-like skin inflammation but also acute and chronic serotonergic itch possibly through blockade of 5-HT2 and 5-HT7 receptors in mice. Brain Behav Immun 2021; 93:399-408. https://doi.org/10.1016/j.bbi.2021.01.027
14. Plumb D. Plumb's Veterinary Drug Handbook 9th Ed. Ames, IA: Wiley-Blackwell 2018:868-870.
15. Mainguy-Seers S, Lavoie J. Glucocorticoid treatment in horses with asthma: A narrative review. J Vet Intern Med 2021; 35(4):2045-2057. https://doi.org/10.1111/jvim.16189
16. White S. A diagnostic approach to the pruritic horse. BEVA 2015; 27(3):156-166. https://doi.org/10.1111/eve.12278
17. Visser M, Cleaver D, Cundiff B et al. Oclacitinib maleate (Apoquel) dose determination inhorses with naturally occurring allergic dermatitis. In Proceedings from the 2020 ACVIM Forum On Demand: virtual. https://doi.org/10.1111/jvim.15904
18. Collard W, Thorn J, Smith S et al. Pharmacokinetics of oclacitinib following oral and intravenous administration to horses. In Proceedings from the 2020 ACVIM Forum On Demand: virtual. https://doi.org/10.1111/jvim.15904
19. van den Berg-Wolf M, Burgoon T. Acupuncture and cutaneous medicine: Is it effective? Med Acupunct 2017; 29(5):269-275. https://doi.org/10.1089/acu.2017.1227
20. Kim S, Bae H. Acupuncture and immune modulation. Auton Neurosci 2010; 157(1-2):38-41. https://doi.org/10.1016/j.autneu.2010.03.010
21. Wang J, Zhu F, Huang W et al. Therapeutic effect and mechanism of acupuncture in autoimmune diseases. Am J Chin Med 2022; 50(3):639-652. https://doi.org/10.1142/S0192415X22500252
22. Pan W, Fan A, Chen S et al. Acupuncture modulates immunity in sepsis: Toward a science-based protocol. Auton Neurosci 2021; 232:102793. https://doi.org/10.1016/j.autneu.2021.102793
23. Zhang B, Shi H, Cao S et al. Revealing the magic of acupuncture based on biological mechanisms: A literature review. Biosci Trends 2022; 16(1):73-90. https://doi.org/10.5582/bst.2022.01039
24. Wang M, Liu W, Ge J et al. The immunomodulatory mechanisms for acupuncture practice. Front Immunol 2023; 14:1147718. https://doi.org/10.3389/fimmu.2023.1147718
25. Ma C, Sivamani R. Acupuncture as a treatment modality in dermatology: A systematic review. J Altern Complement Med 2015; 21(9):520-529. https://doi.org/10.1089/acm.2014.0274
26. Lim H, Kim M, Lee C et al. Anti-inflammatory effects of acupuncture stimulation via the vagus nerve. PLoS One 2016; 11(3):e0151882. https://doi.org/10.1371/journal.pone.0151882
27. Yang E, Sekhon S, Beck K et al. Neuromodulation in inflammatory skin disease. Dermatol Ther (Heidelb) 2018; 8(1):1-4. https://doi.org/10.1007/s13555-018-0227-4
28. Pfab F, Hammes M, Bäcker M et al. Preventive effect of acupuncture on histamine-induced itch: A blinded, randomized, placebo-controlled, crossover trial. J Allergy Clin Immunol 2005; 116(6):1386-1388. https://doi.org/10.1016/j.jaci.2005.08.055
29. Pfab F, Huss-Marp J, Gatti A et al. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema - a blinded, randomized, placebo-controlled, crossover trial. Allergy 2010; 65(7):903-910. https://doi.org/10.1111/j.1398-9995.2009.02284.x
30. Pfab F, Kirchner M, Huss-Marp J et al. Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis – a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. Allergy 2012; 67(4):566-573. https://doi.org/10.1111/j.1398-9995.2012.02789.x
31. Pfab F, Athanasiadis G, Huss-Marp J et al. Effect of acupuncture on allergen-induced basophil activation in patients with atopic eczema: A pilot trial. J Altern Complement Med 2011; 17(4):309-314. https://doi.org/10.1089/acm.2009.0684
32. Chen C, Yu H. Acupuncture treatment of urticaria. Arch Dermatol 1998; 134(11):1397-1399. https://doi.org/10.1001/archderm.134.11.1397
33. Iraji F, Saghayi M, Mokhtari H et al. Acupuncture in the treatment of chronic urticaria: A double blind study. Internet J Dermatol 2005; 3(2). https://www.academia.edu/78300646/Acupuncture_In_The_Treatment_Of_Chronic_Urticaria_A_Double_Blind_Study
34. Oh J, Kim S. Anti-inflammatory effects of acupuncture at ST36 point: A literature review in animal studies. Front Immunol 2022; 12:813748. https://doi.org/10.3389/fimmu.2021.813748
35. Koh R. TCVM for treating autoimmune skin diseases. TVP 2020; 10(3):74-77. https://todaysveterinarypractice.com/integrative-alternative-medicine/tcvm-for-treating-autoimmune-skin-diseases/
36. Craige J. Acupuncture for fleabite allergic dermatitis. J Am Vet Med Assoc 1985; 187(2):127.
37. Xie H. Acupuncture for dermatologic disorders. In Proceedings from the 34th WSAVA Congress. São Paulo, Brazil: World Small Animal Veterinary Association 2009. https://www.vin.com/doc/?id=4252638&pid=11290
38. Xie H, Holyoak G. Ways to improve acupuncture outcomes in equine practice. Am J Trad Chin Vet Med 2020; 15(2):53-60. https://doi.org/10.59565/001c.83750
39. Pellegrini D, Müller T, Fonteque J et al. Equine acupuncture methods and applications: A review. BEVA 2020; 32(5):268-277. https://doi.org/10.1111/eve.12928
40. Ma A. Clinical Manual of Chinese Veterinary Herbal Medicine 5th Ed. Gainesville, FL: Ancient Art Press 2020:36-37, 88-89, 130-131, 286-293, 301-302, 318-319.
41. Shmalberg J, Xie H. Acupuncture and Chinese herbal medicine for treating horses. Compend Contin Educ Vet 2011; 33(5):E1-E11.
42. Gao P, Wang L, Zhao L et al. Anti-inflammatory quinoline alkaloids from the root bark of Dictamnus dasycarpus. Phytochemistry 2020; 172:112260. https://doi.org/10.1016/j.phytochem.2020.112260
43. Kim H, Han H, Ryu M. Effects of root bark extracts from Dictamnus dasycarpus on ICAM-1 expression and immune cell infiltration in

human keratinocytes. Planta Med 2015; 81(16):PW_88. https://doi.org/10.1055/s-0035-1565712
44. Han J, Zhang S, Jiang B et al. Sesquiterpene lactones from Xanthium sibiricum Patrin alleviate asthma by modulating the Th1/Th2 balance in a murine model. Phytomedicine 2022; 99:154032. https://doi.org/10.1016/j.phymed.2022.154032
45. Hong M, Kim J, Na S et al. Inhibitory effects of Paeonia suffruticosa on allergic reactions by inhibiting the NF-kappaB/I kappaB-alpha signaling pathway and phosphorylation of ERK in an animal model and human mast cells. Biosci Biotechnol Biochem 2010; 74(6):1152-1156. https://doi.org/10.1271/bbb.90676
46. Jo S, Ryu J, Han H et al. Anti-inflammatory activity of Kochia scoparia fruit on contact dermatitis in mice. Mol Med Rep 2016; 13(2):1695-1700. https://doi.org/10.3892/mmr.2015.4698
47. Fan M, Choi Y, Wedamulla N et al. Use of a silkworm (*Bombyx mori*) larvae by-product for the treatment of atopic dermatitis: Inhibition of NF-κB nuclear translocation and MAPK signaling. Nutrients 2023; 15(7):1775. https://doi.org/10.3390/nu15071775
48. Jung S, See H, Kwon D et al. Silkworm dropping extract regulates food allergy symptoms via inhibition of Th2-related responses in an ovalbumin-induced food allergy model. J Sci Food Agric 2019; 99(15):7008-7015. https://doi.org/10.1002/jsfa.9993
49. Shan M, Jiang Y, Fu Y et al. A review of the botany, traditional uses, phytochemistry and pharmacology of *Nepeta tenuifolia* Briq. Phytochem Rev 2021; 20(5):991-1012. https://doi.org/10.1007/s11101-020-09729-x
50. Nie A, Chao Y, Zhang X et al. Phytochemistry and pharmacological activities of Wolfiporia cocos (F.A. Wolf) Ryvarden & Gilb. Front Pharmacol 2020; 11:505249. https://doi.org/10.3389/fphar.2020.505249
51. Wang X, Jiang X, Yu X et al. Cimifugin suppresses allergic inflammation by reducing epithelial derived initiative key factors via regulating tight junctions. J Cell Mol Med 2017; 21(11):2926-2936. https://doi.org/10.1111/jcmm.13204
52. Liu C, Wang S, Xiang Z et al. The chemistry and efficacy benefits of polysaccharides from *Atractylodes macrocephala* Koidz. Front Pharmacol 2022; 13:952061. https://doi.org/10.3389/fphar.2022.952061
53. Zheng S, Liu S, Hou A et al. Systematic review of Lonicerae Japonicae Flos: A significant food and traditional Chinese medicine. Front Pharmacol 2022; 13:1013992. https://doi.org/10.3389/fphar.2022.1013992
54. Tohda C, Kakihara Y, Komatsu K et al. Inhibitory effects of methanol extracts of herbal medicines on substance P-induced itch-scratch response. Biol Pharm Bull 2000; 23(5):599-601. https://doi.org/10.1248/bpb.23.599
55. Lee C, Lee Y, Wang C et al. Polygonum multiflorum decreases airway allergic symptoms in a murine model of asthma. Am J Chin Med 2016; 44(1):133-147. https://doi.org/10.1142/S0192415X16500099
56. Yamaguchi-Miyamoto T, Kawasuji T, Kuraishi Y et al. Antipruritic effects of Sophora flavescens on acute and chronic itch-related responses in mice. Biol Pharm Bull 2003; 26(5):722-724. https://doi.org/10.1248/bpb.26.722
57. Hua S, Zhang Y, Liu J et al. Ethnomedicine, phytochemistry and pharmacology of Smilax glabra: An important traditional Chinese medicine. Am J Chin Med 2018; 46(2):261-297. https://doi.org/10.1142/S0192415X18500143
58. Wang M, Yang X, Zhao J et al. Structural characterization and macrophage immunomodulatory activity of a novel polysaccharide from Smilax glabra Roxb. Carbohydr Polym 2017; 156:390-402. https://doi.org/10.1016/j.carbpol.2016.09.033
59. Mori H, Fuchigami M, Inoue N et al. Principle of the bark of Phellodendron amurense to suppress the cellular immune response: Effect of phellodendrine on cellular and humoral immune responses. Planta Med 1995; 61(1):45-49. https://doi.org/10.1055/s-2006-957997
60. Mori H, Fuchigami M, Inoue N et al. Principle of the bark of Phellodendron amurense to suppress the cellular immune response. Planta Med 1994; 60(5):445-449. https://doi.org/10.1055/s-2006-959529
61. Zhao T, Tang H, Xie L et al. Scutellaria baicalensis Georgi. (Lamiaceae): A review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. J Pharm Pharmacol 2019; 71(9):1353-1369. https://doi.org/10.1111/jphp.13129
62. Jung H, Kim M, Gwak N et al. Antiallergic effects of Scutellaria baicalensis on inflammation *in vivo* and *in vitro*. J Ethnopharmacol 2012; 141(1):345-349. https://doi.org/10.1016/j.jep.2012.02.044
63. Chen Q, Lan H, Peng W et al. Isatis indigotica: A review of phytochemistry, pharmacological activities and clinical applications. J Pharm Pharmacol 2021; 73(9):1137-1150. https://doi.org/10.1093/jpp/rgab014
64. Chen C, Fan N, Xu C et al. A synthetic derivative of bioactive constituents from Isatis indigotica ameliorates hypersensitivity and arthritis by inhibiting JAK2-STAT3 pathway in mice. Int Immunopharmacol 2023; 124(Pt A):110884. https://doi.org/10.1016/j.intimp.2023.110884
65. Huang D, Xie M, Yin J et al. Immunomodulatory activity of the seeds of Plantago asiatica L. J Ethnopharmacol 2009; 124(3):493-498. https://doi.org/10.1016/j.jep.2009.05.017
66. Haftcheshmeh S, Mirhafez S, Abedi M et al. Therapeutic potency of curcumin for allergic diseases: A focus on immunomodulatory actions. Biomed Pharmacother 2022; 154:113646. https://doi.org/10.1016/j.biopha.2022.113646
67. Mainzer C, Le Guillou M, Vyumvuhore R et al. Clinical efficacy of oligofructans from ophiopogon japonicus in reducing atopic dermatitis flare-ups in caucasian patients. Acta Derm Venereol 2019; 99(10):858-864. https://doi.org/10.2340/00015555-3224
68. An E, Kim Y, Lee S et al. Ophiopogonin D ameliorates DNCB-induced atopic dermatitis-like lesions in BALB/c mice and TNF-α-inflamed HaCaT cell. Biochem Biophys Res Commun 2020; 522(1):40-46. https://doi.org/10.1016/j.bbrc.2019.10.190
69. Lee H, Yang G, Choi J et al. Suppression of primary splenocyte proliferation by Artemisia capillaris and its components. Toxicol Res 2017; 33(4):283-290. https://doi.org/10.5487/TR.2017.33.4.283
70. Gao X, Lin X, Wang Q et al. Artemisinins: Promising drug candidates for the treatment of autoimmune diseases. Med Res Rev 2024; 44(2):867-891. https://doi.org/10.1002/med.22001
71. Nguyen L, Ahn S, Shin H et al. Anti-psoriatic effect of Rheum palmatum L. and its underlying molecular mechanisms. Int J Mol Sci 2022; 23(24):16000. https://doi.org/10.3390/ijms232416000
72. Shang X, Dai L, He J et al. A high-value-added application of the stems of Rheum palmatum L. as a healthy food: The nutritional value, chemical composition, and anti-inflammatory and antioxidant activities. Food Funct 2022; 13(9):4901-4913. https://doi.org/10.1039/d1fo04214a
73. Keshavarzi Z, Shakeri F, Maghool F et al. A review on the phytochemistry, pharmacology, and therapeutic effects of rheum ribes. Adv Exp Med Biol 2021; 1328:447-461. https://doi.org/10.1007/978-3-030-73234-9_30
74. Kamatou G, Vermaak I, Viljoen A et al. Menthol: A simple monoterpene with remarkable biological properties. Phytochemistry 2013; 96:15-25. https://doi.org/10.1016/j.phytochem.2013.08.005
75. Kim E, Ahn S, Rhee H et al. Coptis chinensis Franch. extract up-regulate type I helper T-cell cytokine through MAPK activation in MOLT-4 T cell. J Ethnopharmacol 2016; 189:126-131. https://doi.org/10.1016/j.jep.2016.05.046
76. Muluye R, Bian Y, Alemu P. Anti-inflammatory and antimicrobial effects of heat-clearing Chinese herbs: A current review. J Tradit Complement Med 2014; 4(2):93-98. https://doi.org/10.4103/2225-4110.126635
77. Hao Y, Li D, Piao X et al. Forsythia suspensa extract alleviates hypersensitivity induced by soybean β-conglycinin in weaned piglets. J Ethnopharmacol 2010; 128(2):412-418. https://doi.org/10.1016/j.jep.2010.01.035
78. Nile S, Su J, Wu D et al. Fritillaria thunbergii Miq. (*Zhe Beimu*): A review on its traditional uses, phytochemical profile and pharmacological properties. Food Chem Toxicol 2021; 153:112289. https://doi.org/10.1016/j.fct.2021.112289
79. Chai O, Shon D, Han E et al. Effects of Anemarrhena asphodeloides on IgE-mediated passive cutaneous anaphylaxis, compound 48/80-induced systemic anaphylaxis and mast cell activation. Exp Toxicol Pathol 2013; 65(4):419-426. https://doi.org/10.1016/j.etp.2011.12.006
80. Liu C, Cong Z, Wang S et al. A review of the botany, ethnopharmacology, phytochemistry, pharmacology, toxicology and quality of Anemarrhena asphodeloides Bunge. J Ethnopharmacol 2023; 302(Pt A):115857. https://doi.org/10.1016/j.jep.2022.115857

81. Park G, Moon B, Ryu S et al. Cicadidae periostracum attenuates atopic dermatitis symptoms and pathology via the regulation of NLRP3 inflammasome activation. Oxid Med Cell Longev 2021; 2021:8878153. https://doi.org/10.1155/2021/8878153
82. Hong J, Lee Y. Anti-inflammatory effects of cicadidae periostracum extract and oleic acid through inhibiting inflammatory chemokines using PCR arrays in LPS-induced lung inflammation *in vitro*. Life (Basel) 2022; 12(6):857. https://doi.org/10.3390/life12060857
83. Sung Y, Yoon T, Jang J et al. Topical application of Rehmannia glutinosa extract inhibits mite allergen-induced atopic dermatitis in NC/Nga mice. J Ethnopharmacol 2011; 134(1):37-44. https://doi.org/10.1016/j.jep.2010.11.050
84. Kim H, Lee E, Lee S et al. Effect of Rehmannia glutinosa on immediate type allergic reaction. Int J Immunopharmacol 1998; 20(4-5):231-240. https://doi.org/10.1016/s0192-0561(98)00037-x
85. Choi J, Oh H, Lee S et al. Salvia plebeia suppresses atopic dermatitis-like skin lesions. Am J Chin Med 2014; 42(4):967-985. https://doi.org/10.1142/S0192415X1450061X
86. Jang H, Cho S, Kim M et al. Anti-inflammatory effects of Salvia plebeia R. Br extract *in vitro* and in ovalbumin-induced mouse model. Biol Res 2016; 49(1):41. https://doi.org/10.1186/s40659-016-0102-7
87. Luo J, Zhang L, Zhang X et al. Protective effects and active ingredients of Salvia miltiorrhiza Bunge extracts on airway responsiveness, inflammation and remodeling in mice with ovalbumin-induced allergic asthma. Phytomedicine 2019; 52:168-177. https://doi.org/10.1016/j.phymed.2018.09.170
88. Nose M, Tsutsui R, Hisaka S et al. Evaluation of the safety and efficacy of Glycyrrhiza uralensis root extracts produced using artificial hydroponic and artificial hydroponic-field hybrid cultivation systems III: anti-allergic effects of hot water extracts on IgE-mediated immediate hypersensitivity in mice. J Nat Med 2020; 74(2):463-466. https://doi.org/10.1007/s11418-019-01378-5
89. Tsuge A, Hisaka S, Hayashi H et al. Effect of hot water extract of a glycyrrhizin-deficient strain of Glycyrrhiza uralensis on contact hypersensitivity in mice. J Nat Med 2020; 74(2):415-420. https://doi.org/10.1007/s11418-019-01386-5
90. Wang L, Hu G, Lu Y et al. Anti-pseudo-allergic components in licorice extract inhibit mast cell degranulation and calcium influx. Chin J Nat Med 2022; 20(6):421-431. https://doi.org/10.1016/S1875-5364(22)60148-1
91. Fouladi S, Masjedi M, Ganjalikhani Hakemi M et al. The review of *in vitro* and *in vivo* studies over the glycyrrhizic acid as natural remedy option for treatment of allergic asthma. Iran J Allergy Asthma Immunol 2019; 18(1):1-11.
92. Zhao Y, Li H, Li X et al. Network pharmacology-based analysis and experimental *in vitro* validation on the mechanism of Paeonia lactiflora Pall. in the treatment for type I allergy. BMC Complement Med Ther 2022; 22(1):199. https://doi.org/10.1186/s12906-022-03677-z
93. Lee B, Shin Y, Bae E et al. Antiallergic effect of the root of Paeonia lactiflora and its constituents paeoniflorin and paeonol. Arch Pharm Res 2008; 31(4):445-450. https://doi.org/10.1007/s12272-001-1177-6
94. Lee S, Hong S, Kim H et al. Paeonia lactiflora Pallas extract alleviates antibiotics and DNCB-induced atopic dermatitis symptoms by suppressing inflammation and changing the gut microbiota composition in mice. Biomed Pharmacother 2022; 154:113574. https://doi.org/10.1016/j.biopha.2022.113574
95. Liu Y, Meng X, Jin X et al. A comprehensive review of the botany, ethnopharmacology, phytochemistry, pharmacology, quality control and other applications of Ligustici Rhizoma et Radix. J Ethnopharmacol 2024; 323:117687. https://doi.org/10.1016/j.jep.2023.117687
96. Basson A, Ahmed S, Almutairi R et al. Regulation of intestinal inflammation by soybean and soy-derived compounds. Foods 2021; 10(4):774. https://doi.org/10.3390/foods10040774
97. Li J, Yang L, Chen Y et al. Acupuncture as an add-on therapy to sublingual allergen-specific immunotherapy for patients with allergic rhinitis. Medicine (Baltimore) 2019; 98(1):e13945. https://doi.org/10.1097/MD.0000000000013945