Autoimmune Disorders

John K. Chen
Ph.D., Pharm.D., O.M.D., L.Ac.

Lotus Institute of Integrative Medicine
Tel: (626) 780-7182  Fax: (626) 609-2929
Website: www.eLotus.org  Email: info@eLotus.org

Trend of Allergy-related Disorders

Trend of Autoimmune-related Disorders
Etiology

- Cause: UNKNOWN
  - Genetics
  - Sex (more female than male)
  - Others ???

Etiology

"When zheng (upright) qi is present, pathogenic factors cannot attack."

Su Wen (Basic Questions), 2nd century A.D.

Overview

- Pathogens
  - Micro-organisms (bacteria, virus, fungus, parasites)
  - Environmental chemicals and toxins
  - Foods that trigger allergy and autoimmunity
- The immune system
- Autoimmune diseases
  - Connective tissues (skin, joints, glands, blood vessels)
  - Internal organs (thyroid, intestines, heart, lung, CNS)
Microbes associated with autoimmunity

<table>
<thead>
<tr>
<th>Pathogen antigen</th>
<th>Cross-reactive self antigen</th>
<th>Autoimmune Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>Coated antigen</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Croup-like virus</td>
<td>Cardiac myofibril</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Coxsackievirus</td>
<td>Glial fibrillary acidic</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Hemoglobin</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>E. coli</td>
<td>Thrombopoietin</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Salmonella enterica</td>
<td>Endothelial cell</td>
<td>Leukemia</td>
</tr>
<tr>
<td>HPV</td>
<td>Myoglobin</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>Myeloid cell</td>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>E. coli</td>
<td>Glycosyltransferase</td>
<td>Multiple sclerosis</td>
</tr>
</tbody>
</table>

Vaccination

- Diphtheria, tetanus and polio vaccines have a dangerous link with a number of autoimmune disorders.
- Measles, mumps and rubella vaccines linked to rheumatoid arthritis.
- Influenza vaccine linked to type 1 diabetes in children.
- Mercury (thimerosal) is still present in flu vaccines, but has been removed from most other vaccines.
  – JAMA, 1994

Environmental chemicals and toxins

- 287 industrial chemicals were found fetal cord blood collected by American Red Cross from ten newborn infants from around the US.
- Chemicals included pesticides, phthalates, dioxins, flame retardants, by-products of Teflon, and many others.

  – Center of Disease Control (CDC), 2004.
Air pollution

- Car exhaust
- Jet fuel exhaust
- Mining plants
- Coal burning plants
- Brush and forest fire
- Earthquake

Air pollution

- Ozone, carbon monoxide, nitrogen dioxide
- Toxic heavy metals (arsenic, cadmium, lead, mercury, copper, chromium, nickel, zinc)
- Solvents and petrochemicals (acetylaldehyde, benzene, benzopyrene, chloroform, formaldehyde, naphthalene, toluene, trichloroethylene, xylene)

Jet Fuel and Air Travel

- Fatigue from travel and jet lag
- Dehydration from radiation and dry air
- Toxicity from kerosene-based jet fuel exposure
- Increased risk of infection from enclosed environment
## Chemical cleaners
- Chemical cleaners used everyday in household makes indoor air five times more polluted than outdoor air.
- This is true even in New York and Los Angeles.
- Use only white vinegar and baking soda!  
  – EPA

## Water pollution
- 145 total contaminants
- 35 agricultural pesticides
- 31 urban lawn chemicals
- 100 industrial heavy metals and petrochemicals
- 30 water treatment byproducts
- Others  
  – www.ewg.org

## New Carpet
- Acetone
- Bis(2-ethylhexyl) phthalate
- Benzene
- Caprolactam
- Diethylene glycol
- P-dichlorobenzene
- Formaldehyde
- Hexane
- Styrene
- Toluene
- Vinylcyclohexene
- Xylenes
Old Carpet

- Dust and mold that is impossible to remove

Cosmetics

- Skin is the largest organ in human body.
- Avoid cosmetics with parabens, phthalates, sodium laureth, sodium laurel sulfate, petrolatum, cocamide DEA, diazolidinyl urea, toluene, and triethanolamine.
- Avoid synthetic colors and fragrances in cosmetics, perfumes and colognes.

Hair dye and nail polish

- Hair dye causes three times higher risk of lupus for those who use them.
- Nail polish (contains phthalates, formaldehyde or toluene) is toxic when applied, and is also toxic when removed (with solvents).
Polybrominated diphenyl ethers (PBDE)

- PBDE: flame retardant used in just about everything, such as carpet, bedding, chair, fabric, plastic, etc.
- PBDEs are not chemically bound to plastics, foam, fabrics, or other products, making them more likely to leach out of these products.
- Persistent, bioaccumulative, and dangerous neurotoxin to humans, animals, and the environment.
- Babies and toddlers have highest levels of PBDE because they crawl on carpet and chew on everything.
  - EPA

Perfluorooctanoic acid (PFOA)

- PFOA (C8) is a fire-resistant and oil-, stain-, grease-, and water-repellent chemical (i.e., Teflon).
- Used in non-stick cookware; waterproof, breathable membranes for clothing; flooring, carpet guards, grease-resistant french fry boxes, coffee cups, and many industry segments, including the aerospace, automotive, building/construction, chemical processing, electronics, semiconductors, and textile industries.
- Found in the blood of 96% of Americans; and it’s half-life of 4.4 years.
- Increased risks of hypercholesterolemia, thyroid disease, and reduced fertility.
- Increased risks of testicular and kidney cancer
  - American Cancer Society (ACS)

Dioxin

- Dioxin is a by-product formed by burning chlorine-based chemical compounds with hydrocarbons. The major source of dioxin in the environment comes from waste-burning incinerators, factories which use chlorine bleaching in their process and with the production of paper or plastics. It is also present in exhaust fume from diesel trucks and buses.
- Dioxin accumulates in food (mainly meat and dairy products, fish and shellfish), which then accumulates fatty tissue of human.
- Dioxins are highly toxic and can cause reproductive and developmental problems, damage the immune system, interfere with hormones and also cause cancer.
- Dioxin crosses the placenta from mother to babies.
  - World Health Organization (WHO)
Formaldehyde (FA)

- Widely used in industrial and medical settings and as a sterilizing agent, disinfectant, and preservative.
- Found in the polluted atmosphere of cities, domestic air (e.g., paint, insulating materials, chipboard and plywood, fabrics, furniture, paper), and cigarette smoke, diesel and gas exhaust, antiperspirants, cosmetics, hair care, soap, etc.
- Potent carcinogen as it cross-links to DNA

Formaldehyde by-products

- para-formaldehyde
- hexamethylene tetramine
- DMDM hydantoin
- polynoxyline
- dimethylolurea
- preventol D1
- preventol D2
- preventol D3
- quaternium 15
- bakzid
- bakzid P
- parmelot k50
- grotan BK
- imidazolidinyl urea
- diazolidinyl urea
- 2-bromo-2-nitropropane-1,3-diol
- KM 103
- biocide DS 5249 (Proxel T)
- tris hydroxymethyl nitromethane (Tris nitro)
- hydroxymethylglycinate (Suttocide A)

Bisphenol A (BPA)

- BPA is a structural component that protect the food from directly contacting packaging surfaces, such as water bottles and metal can coatings, and has been used since the 1960s.
- It is also used as a plasticizers used in many plastic products, including helmets, dental sealants, eyeglasses, etc.
- It’s in the blood of 90% Americans
  - www.fda.gov
BPA toxicities

• Hormone levels. It acts like a hormone in the body, disrupting normal hormone levels and development in fetuses, babies, and children.
• Other conditions: heart problems, obesity, diabetes, ADHD, and others.
  - www.webmd.com

Phthalates and parabens

• Phthalates and parabens are plasticizers that make cosmetics creamier, plastics more flexible and less brittle, and toys more pliable.
• Easily leech out from products
• Present in almost all Americans
• May cause infertility, testicular dysgenesis, obesity, asthma, and allergies, as well as leiomyomas and breast cancer.

Polyvinyl chloride (PVC)

• Used in plastic pipes, wires, cable coatings, packaging materials
• Acute (short-term) toxicity through inhalation: central nervous system effects (CNS), such as dizziness, drowsiness, and headaches in humans.
• Chronic (long-term) toxicity through inhalation and oral ingestion: liver damage and liver cancer, increased risks of lupus, scleroderma, and rheumatoid arthritis
  - EPA
Trichloroethylene (TCE)

- Cleansing solvent used to wash planes, tanks, trucks, and machinery. Commonly used in dry cleaning. TCE is present in air and in tap water.
- CNS side effect, such as dizziness, headaches, confusion, euphoria, facial numbness, and weakness.
- Liver, kidney, immunological, endocrine, and developmental toxicities.
- Cancer in kidney, liver, cervix, and lymphatic system.
  - EPA

Foods

- Heavy metals
- Pesticide
- Mycotoxins: aflatoxins and ochratoxins
- Processed foods
- GMO foods
- Food allergens
- Gluten
- Coffee
- Leaky gut syndrome

Lead

- Sources: leaded gasoline, water conveyed by lead-pipes, cans, lead-based paint, and improperly glazed ceramics and cookwares.
- Oral ingestion of foods contaminated with lead is the primary source of poisoning.
- Clinical manifestation of lead poisoning include abdominal pain, irritability, lethargy, anorexia, pale face, ataxia, slurred speech, and in severe cases, convulsions and coma. [i] [ii]

Mercury

• Sources: thermometers, batteries, dental amalgams, preservative in vaccines, manufacturing of certain electronics, plastics, fungicides, and germicides. These products may subsequently contaminate the water and soil, and become present in the foods (such as tuna and swordfish which concentrate methyl mercury at high levels).
• Toxic effects of mercury poisoning include sensory impairment (vision, hearing, speech), disturbed coordination, and damage to the internal organs (brain, kidneys, and lungs). [i], [ii]


Arsenic

• Sources: Arsenic pollute the environment via mining, smelting, and burning of coal, and arsenic contaminate the water and soil when it is used to manufacture herbicide and pesticide, or added to feed of poultry and livestocks to promote growth. In turn, as humans are exposed to arsenic via breathing, drinking and eating.
• Clinical manifestations of toxic reactions include muscle weakness, hyperpigmentation of the skin, hyperkeratosis, exfoliative dermatitis, edema, sensory and motor polyneuritis, and inflammation of respiratory mucosa. [i], [ii]


Cadmium

• Cadmium is a valuable metal, and is mined and used in industrial production of many products, such as electroplating and galvanization and its use in plastics, paint pigments (cadmium yellow), and nickel-cadmium batteries. If these products are not properly disposed, cadmium will contaminate water and soil in the environment. In turn, cadmium has been found at high concentration in various types of foods, including grains, cereals, leafy vegetables, shellfish, and liver and kidneys from animals.
• Clinical manifestations of cadmium poisoning include yellow discoloration of the teeth, emphysema, changes in liver functions, anemia, renal disorder, and osteomalacia. [i], [ii]

### Recommended Limits Based on Concentration

<table>
<thead>
<tr>
<th></th>
<th>Daily Intake</th>
<th>WHO</th>
<th>USP</th>
<th>EUP</th>
<th>Swiss</th>
<th>TGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead (Pb)</td>
<td>0.1-0.2 mg</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>5 ppm</td>
<td>5 ppm</td>
<td>5 ppm</td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>n/a</td>
<td>0.3 ppm</td>
<td>5 ppm</td>
<td>0.1 ppm</td>
<td>0.1 ppm</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>300 mcg</td>
<td>n/a</td>
<td>3 ppm</td>
<td>2 ppm</td>
<td>2 ppm</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>50 mcg</td>
<td>0.3 ppm</td>
<td>3 ppm</td>
<td>0.2 ppm</td>
<td>0.2 ppm</td>
<td>3 ppm</td>
</tr>
</tbody>
</table>

[1] The Average Daily Intake for an adult in the United States
[3] United States Pharmacopoeia. These are the heavy limits for many of the botanicals listed in the USP.
[4] European Union Pharmacopoeia. These are heavy metal limits for botanical drugs.
[5] Swissmedic of Switzerland. These are heavy metal limits for botanical drugs.
Pesticide

- Organochlorine
- Organophosphorus
- Pyrithroids
- Toxicities: dyspnea, respiratory depression, pulmonary edema, cyanosis, loss of sphincter control, bradycardia or tachycardia, cardiac ischaemia, cardiac dysrhythmias, seizures, convulsions, and coma

Organochlorines

- Organochlorines are insecticides that contain chlorinated ethane derivatives. There are at least 33 different organochlorine insecticides, including endrin, dieldrin, aldrin, quintozene and dichlorodiphenyltrichloroethane [DDT].

Organophosphorous

- Organophosphorous are insecticides that contain a phosphorus compound. There are over 100 different types of organophosphorous pesticides, including malathion and parathion. As pesticides, organophosphorous may be used by itself, or in conjunction with organochlorines. Organophosphorous pesticides kills insects that adversely affect foods, crops and buildings.
Pyrethrums

- As botanical insecticides, pyrethrums are derived from flowers of a plant called *Chrysanthemum cincereaefolium*. Examples of pyrethrum pesticide include: bifenthrin, cyfluthrin, cyhalothrin, cypermethrin (and isomers), deltamethrin, fenpropathrin, fenvalerat and esfenvalerat (sum of isomers), fluvalinat, flucythrinat, permethrin, phenothrin, resmethrin, and tetramethrin.

Pesticides and Insecticides

- Greater quantities of pesticides and insecticides, such as weed killer atrazine, is applied to suburban area than agricultural land.
- Induces autoimmune disorders
  - Environmental Protection Agency (EPA)
Aflatoxins

- Aflatoxins are toxic metabolites produced by certain strains of fungi, namely *Aspergillus flavus* and *A. parasiticus*.
- Foods and feeds most likely to be affected by aflatoxins include corn and corn products, peanuts and peanut products, cottonseed, grains, tree nuts (Brazil nuts, pecans, pistachio nuts, walnuts, almonds), milk, cheese, figs, and spices.\[i\],[ii]


Aflatoxins B1, B2, G1, G2

- One of the most potent hepatotoxin and carcinogen.
  - National Institute of Health (NIH)

Aflatoxins

- *Bai Zi Ren* (Semen Platycladi)
- *Chen Pi* (Pericarpium Citri Reticulatae)
- *Da Fu Pi* (Pericarpium Arecae)
- *Da Zao* (Fructus Jujubae)
- *Gou Qi Zi* (Fructus Lycii)
- *Gou Teng* (Ramulus Uncariae cum Uncis)
- *He Ye* (Folium Nelumbinis)
- *He Ye* (Folium Nelumbinis)
- *Huang Qi* (Radix Astragali)
- *Ku Xing Ren* (Semen Armeniacae Amarum)

- *Lian Zi* (Semen Nelumbinis)
- *Nu Zhen Zi* (Fructus Ligustri Lucidi)
- *Shan Zha* (Fructus Crataegi)
- *Shan Zhu Yu* (Fructus Corni)
- *Shen Qu* (Massa Fermentata)
- *Suan Zao Ren* (Semen Ziziphi Spinosae)
- *Tao Ren* (Semen Persicae)
- *Yan Hu Suo* (Rhizoma Corydalis)
- *Zhi He Shou Wu* (Radix Polygoni Multiflori Praeparata)
Safety Limits of Aflatoxins

<table>
<thead>
<tr>
<th></th>
<th>US FDA</th>
<th>AHPA</th>
<th>EUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins B1</td>
<td>5 ppb</td>
<td>2 ppb</td>
<td></td>
</tr>
<tr>
<td>Aflatoxins B1, B2, G1, G2</td>
<td>20 ppb</td>
<td>20 ppb</td>
<td>4 ppb</td>
</tr>
</tbody>
</table>

* ppb – parts per billion

### REPORT OF ANALYSIS

**Sample Code:** 460-2012-00258 120  
**Description:** HERB EXTRACT  
**Client Sample Code:** TANING DUO  
**Reference:**  

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Result</th>
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<td>QA31 - ALLOMITREN PROFILE (GC-MS/MS)</td>
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<td>Completion Date: 02/09/2012</td>
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<td>Method: AOAC 991.31</td>
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</tr>
<tr>
<td>AD安倍(80)</td>
<td>&lt;0.5 ppm</td>
</tr>
<tr>
<td>AD安倍(81)</td>
<td>&lt;0.5 ppm</td>
</tr>
<tr>
<td>AD安倍(82)</td>
<td>0.5 ppm</td>
</tr>
</tbody>
</table>

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### REPORT OF ANALYSIS

**Sample Code:** 460-2012-00258 127  
**Description:** HERB EXTRACT  
**Client Sample Code:** TANING DUO  
**Reference:**  

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Result</th>
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<tr>
<td>AD安倍(80)</td>
<td>&lt;0.5 ppm</td>
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<tr>
<td>AD安倍(81)</td>
<td>&lt;0.5 ppm</td>
</tr>
<tr>
<td>AD安倍(82)</td>
<td>0.5 ppm</td>
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</tbody>
</table>

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### REPORT OF ANALYSIS

<table>
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<tr>
<th>Test Results</th>
<th>Result</th>
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<tr>
<td>Completion Date: 02/09/2012</td>
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<td>Method: AOAC 991.31</td>
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<td>AD安倍(80)</td>
<td>&lt;0.5 ppm</td>
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<tr>
<td>AD安倍(81)</td>
<td>&lt;0.5 ppm</td>
</tr>
<tr>
<td>AD安倍(82)</td>
<td>0.5 ppm</td>
</tr>
</tbody>
</table>

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Shall not be copied, duplicated, or distributed in any format or be used for teaching without prior written consent from Lotus Institute.
Ochratoxins

- Ochratoxins are toxic metabolites produced by certain strains of fungi, namely *Aspergillus ochraceus*, *Aspergillus alliaceus* and *Penicillium verrucosum*.[i]
- Ochratoxins are commonly found in foods such as grape juice, coffee, wine, beer, cereals (e.g., wheat, maize, rye, barley, and oats), dried vine fruit (e.g., raisins and currants), corn, peanuts, grains, cottonseeds, rice, and beans.[ii],[iii]

Ochratoxins

- *Gou Qi Zi* (Fructus Lycii),
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae)
- *Zhi Gan Cao* (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle)
Safety Limits of Ochratoxins

<table>
<thead>
<tr>
<th>Ochratoxin</th>
<th>US FDA</th>
<th>AHPA</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>n/a</td>
<td>n/a</td>
<td>3-10 ppb</td>
</tr>
</tbody>
</table>

* ppb – parts per billion


Processed foods

- Processed foods with nitrates, nitrites, benzoates, BHA, BHT, MSG, parabens and sulfites. They are contain excessive salt and are overly acidic.
- Food dye, FD&C yellow no. 5 is linked with allergy and asthma.
- Fast food, TV dinner, microwave food, canned food, and foods with artificial color and flavors, MSG, aspartame, high fructose corn syrup.
GMO foods

- **Corn**
  - 96% of all corn are GMO
  - High fructose corn syrup
  - Cooking oil made from corn
- **Soy**
  - 94% of all soy are GMO
  - Baby formula made from soy
- **Sugar and aspartame**
  - Aspartame turns into formadehyde at 86F
- **Canola oil**
  - GMO oil

Eight Major Groups of Allergens

1. Milk
2. Eggs
3. Fish
4. Peanuts
5. Crustacean shellfish
6. Tree nuts
7. Soybeans
8. Wheat

Major Groups of Allergens (Shellfish)

- Crustacean shellfish: shellfish with a hard shell and no backbone, such as crab, crayfish, lobster, prawns and shrimp
- None in Chinese materia medica
- Possible cross allergy
  - *Mu Li* (Concha Ostreae)
  - *Ge Qiao* (Concha Meretricis seu Cyclinae)
  - *Hai Piao Xiao* (Endococha Sepiae)
  - *Zhen Zhu* (Margarita)
  - *Zhen Zhu Yu* (Concha Margaritiferae)
  - *Shi Jue Ming* (Concha Haliotidis)
  - *We Leng Zi* (Concha Arcae)
Major Groups of Allergens (Tree Nuts)

- Tree nuts (high risk):
  - Bai Guo (Semen Ginkgo)
  - He Tao Ren [Hu Tao Ren] (Semen Juglandis)
  - Song Zi Ren (Semen Pini)
  - Li Zhi He (Semen Litchi)

- Tree nuts (possible cross-allergy):
  - Tao Ren (Semen Persicae)
  - Yu Li Ren (Semen Pruni)
  - Bai Zi Ren (Semen Platycladi)
  - Ku Xing Ren (Semen Armeniacae Amarum)
    - Shen Qu (Massa Fermentata),
    - Jian Shen Qu (Massa Fermentata Praeparata)
    - Ban Xia Qu (Rhizoma Pinelliae Massa Fermentata)

Major Groups of Allergens (Wheat)

- Wheat
  - Xiao Mai (Fructus Triticci)
  - Fu Xiao Mai (Fructus Triticci Levis)

- Herbs that contain wheat
  - Shen Qu (Massa Fermentata)
  - Jian Shen Qu (Massa Fermentata Praeparata)
  - Ban Xia Qu (Rhizoma Pinelliae Massa Fermentata)

- Herb that could be made from wheat
  - Yi Tang (Maltosum): generally made from rice or glutinous rice (other sources could be from barley, wheat, millet or corn.)

Major Groups of Allergens (Soybeans)

- Soybean herbs
  - Dan Dou Chi (Semen Sojae Praeparatum)

- Herbs that may be processed with soybean
  - Zhi He Shou Wu (Radix Polygoni Multiflori Praeparata) - if processed with black soybean
  - E Jiao (Colla Corii Asini) - if soya-bean oil is used to thicken glue
### Gluten

<table>
<thead>
<tr>
<th>Non-GMO wheat</th>
<th>GMO wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 100,000 with allergy</td>
<td>1 in 133 with allergy</td>
</tr>
<tr>
<td></td>
<td>Contains gluten peptide (glia-α9)</td>
</tr>
<tr>
<td></td>
<td>Glyphosate</td>
</tr>
</tbody>
</table>

### Gluten

- Food: Wheat, rye and barley.
- Herbs:
  - *Xiao Mai* (Fructus Triticus) - wheat
  - *Fu Xiao Mai* (Fructus Tritic Levis) - floating wheat
  - *Yi Tang* (Maltosum) - sugar from rice, barley, wheat, millet or corn
  - *Shen Qu* (Massa Fermentata) - contains wheat
  - *Jian Shen Qu* (Massa Fermentata Praeparata) - contains wheat
  - *Ban Xia Qu* (Rhizoma Pinelliae Massa Fermentata) - contains wheat

### Coffee

- There are over 1,000 chemical compounds in roasted [burned] coffee. Of 28 tested, 19 are carcinogenic.
- “One cup of coffee gives you more carcinogen than you get in foods in a year!”
  - Dr. Bruce Aimes, toxicologist, UC Berkeley
Carcinogens

- Cigarette smoking > 30% of all cancer
- Hormones > 30% of all cancer

  - Dr. Bruce Aimes, toxicologist, UC Berkeley

Leaky Gut Syndrome

- Due in part to chemicals, artificial preservatives, dyes, GMO-foods and NSAIDS.
- Flood gate opens for allergen and antigen to enter the body

  Treating Leaky Gut Syndrome in a TCM Practice, Jake Paul Fratkin, OMD, L.Ac.

“The skilled practitioner treats before an illness occurs, not once it has occurred.”

Ling Shu (Divine Pivot), 2nd century A.D.
Solution

• Stop the influx of all pathogens
  – Prevent infection
  – Avoid environmental chemicals and toxins
  – Consume organic and whole foods

• Eliminate the accumulation of pathogens
  – Increase blood circulation
  – Facilitate liver metabolism
  – Enhance kidney elimination

• Treat diseases and restore wellness

The Immune System

• Antigen
• Antibodies
• Complement
• Hypersensitivity
• Tolerance

Antigen

• Definition: any substance that causes the immune system to produce antibodies against it.
  – bacteria,
  – virus,
  – fungus,
  – parasite,
  – allergens,
  – chemicals,
  – toxins,
  – many (any) others
The Immune System

- Innate immunity
  - Skin, mucous
  - Macrophages, natural kills (NK) cells

- Acquired immunity
  - Cell mediated Immunity (T cells, B cells)
  - Humoral immunity (antibodies)

Cell Mediated Immunity

- T cells (thymocytes) originate from stem cells in the bone marrow and mature in thymus.
- T cells help with regulation and communication of the immune system
- Four types of T cells:
  - T helper cells
  - T killer/cytotoxic cells
  - T suppressor/regulatory cells
  - T memory cells

T helper cells

- T helper cells orchestrate the entire immune response
  - Tₕ,1: activates T killer/cytotoxic cells to kill pathogens
  - Tₕ,2: activates B cells to produce antibodies to bind to pathogen
  - Tₕ,17: produces IL-17 and IL-22, and causes excessive inflammation and tissue injury in autoimmune disease
T killer/cytotoxic cells

- They produce cytotoxin to cause cell lysis and apoptosis
- They kill pathogens (bacteria, virus, fungus, others)
- They kill damaged or dysfunctional cells

T suppressor/regulatory cells

- They suppress the continued or excessive immune system activities.
- They shut down T cell mediated immunity at the end of the immune reaction.
- They maintain homeostasis and tolerance to self-antigens.

T memory cells

- They remember the pathogen long after the pathogen is eliminated.
- In recurrent event, they quickly reproduce and initiate the immune response.
Humoral Immunity

- B cells originate from stem cells and mature in the bone marrow
- B cells do not fight the pathogen directly, but produce antibodies that bind to the antigen.

Antibodies

- Definition: they are immunoglobulins produced by B cells that bind to antigen and cause lysis, neutralization, agglutination and precipitation of the antigen.
- Types of antibodies
  - IgE: causes Type 1 allergic response
  - IgG, IgM, IgA, IgD: causes Type 2, 3, 4 inflammatory response

Complement

- Activated when antibodies bind to antigens, complement is a group of proteins that help to clear pathogens through many mechanisms, including cytolysis, chemotaxis, opsonization, immune clearance, inflammation, and marking of pathogens for phagocytosis.
**Cytokines**

- Cytokines are proteins produced by immune cells (macrophages, B lymphocytes, T lymphocytes and mast cells) to coordinate between humoral and cell-based immunity.
- Cytokines include interferons, interleukins, lymphokines, tumour necrosis factor and chemokines.
- Cytokines balance between rest and response of the immunity to antigen.
  - Stimulant cytokines for activation and growth of cells: IL-2, IL-4.
  - Pro-inflammatory cytokines to induce inflammation, lysis and apoptosis: IL-1, IL-6, IL-8, TNF-alpha.
  - Regulatory cytokines on differentiation and growth of cells: IL-3, IL-7.

**Pathogen Barrier (skin, mucous); Cellular (macrophage, NK cells)**

- **Th1 (helper)**
  - T-killer cells
  - B cells
  - Macrophage
  - IgE binds to mast cells and basophils release histamine
  - IgG binds to and destroys antigen

- **Th2 (helper)**
  - T-memory
  - B-memory
  - Complement binds to and destroys antigen
  - Macrophage

**Immune tolerance**

- Immune system’s ability to distinguish between “self” and “non self.”
- Balance between hypo- and hyper-immunity
- Balance between T-helper and T-suppressor cells
Antigen

- Exogenous antigens
  - Bacteria, virus, fungus, parasite, allergens, chemicals, toxins, etc.
- Endogenous antigens
  - Cells that contain all or part of bacteria, virus, fungus, parasite, allergens, chemicals, toxins, etc.
- Autoantigens
  - A normal "self" protein that is mistaken by the immune system as "none self."

Autoimmune diseases

- Normally the immune system's army of white blood cells helps protect the body from harmful substances, called antigens. Example of antigens include bacteria, viruses [and] toxins…
- But in patients with autoimmune disorder, the immune system can't tell the difference between healthy body tissues and antigens. The result is an immune response that destroys normal body tissues.
  - National Institute of Health (NIH)


"The good physician treats the disease; the great physician treats the person who has the disease."

- Sir William Osler, M.D.
Drugs for Autoimmune Disorders

- **Corticosteroids**
  - Prednisone, prednisolone, dexamethasone, triamcinolone and betamethasone
- **Immune suppressants**
  - Methotrexate (Trexall), cyclophosphamide (Cytoxan), azathioprine (Imuran)
- **Biologics**
  - Adalimumab (Humira), infliximab (Remicade), etanercept (Enbrel), abatacept (Orencia), rituximab (Rituxan)

Corticosteroids, effect

- **Corticosteroid drugs**
  - prednisone,
  - prednisolone,
  - dexamethasone,
  - triamcinolone,
  - betamethasone
- **Strong effect to suppress inflammation**
- **Strong effect to suppress cell-mediated immunity**
- **Moderate effect to suppress humoral immunity**

Corticosteroids, side effects

- Infection
- Urinary tract infection
- Herpes
- Oral candidiasis
- Water and fat retention
- Peptic ulcer disease
- Psychiatric and mood changes
- Osteoporosis
- Diabetes mellitus
- Hypertension Increase weight
- Hyperlipidemia
- Pancreatitis
- Growth suppression
- Adrenal gland atrophy
Immune suppressants, effect

- Immune suppressant drugs:
  - methotrexate (Trexall)
  - cyclophosphamide (Cytoxan)
  - azathioprine (Imuran)
- Suppress immune system and response
- Suppress inflammation
- Treat autoimmune disorders

Immune suppressants, side effects

- Bone marrow suppression
- Liver and kidney damages
- Increased risks of infection
- Increased risks of cancer
- Hair loss

Biologics

- T-cell blocker
  - abatacept (Orencia)
- B-cell destroyer
  - rituximab (Rituxan)
- Anticytokine; Anti-TNF-alpha
  - adalimumab (Humira),
  - infliximab (Remicade),
  - etanercept (Enbrel),
**Biologics, effect**

- Potent and more precise effect to block T-cells, destroy B-cells, and inhibit specific inflammatory pathways
- Treats autoimmune disorders

**Biologics, side effects**

- Immune suppression
- Significant increase in risk of infection and cancer
- They are foreign antibodies that may trigger a separate autoimmune reaction
- Blood disorders (leukopenia, neutropenia)
### Integrated pathology

<table>
<thead>
<tr>
<th>Cause</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria, Virus, Fungus, Parasite, Allergens, Toxins</td>
<td>Wind, Cold, Heat, Summer-heat, Dampness, Dryness</td>
</tr>
<tr>
<td>Barrier (skin, mucous), Cellular (macrophage, NK cells)</td>
<td>Wei (defensive) qi</td>
</tr>
<tr>
<td>T cells</td>
<td>Zheng (upright) qi</td>
</tr>
<tr>
<td>B cells</td>
<td></td>
</tr>
</tbody>
</table>

### Acute Inflammation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>Heat</td>
</tr>
<tr>
<td>Warmth</td>
<td>Fire</td>
</tr>
<tr>
<td>Swelling</td>
<td>Damp and phlegm</td>
</tr>
<tr>
<td>Pain</td>
<td>Qi stagnation, blood stasis</td>
</tr>
</tbody>
</table>

### Chronic Inflammation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell lysis and apoptosis; destruction of tissues and organs</td>
<td>Yin deficiency</td>
</tr>
<tr>
<td>Loss of organs and their functions</td>
<td>Yang deficiency</td>
</tr>
</tbody>
</table>
**TCM Pattern Differentiation**

- **Liu Jing Bian Zheng (Six Stages Differentiation):** taiyang, yangming, shaoyang, taiyin, shaoyin, jueyin
- **Wei Qi Ying Xue Bian Zheng (Defensive, Qi, Nutritive, Blood Differentiation)**
- **San Jiao Bian Zheng (Triple Burner Differentiation):** upper, middle and lower burner

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**Pathogen**

- **Wind, cold, heat, damp, etc.**
  - Wei (defensive) level
  - Qi (energy) level
  - Ying (nutritive) level
  - Xue (blood) level

**Innate Immunity:**
- Barrier (skin, mucus, macrophage, NK cells)
- Cellular (macrophage, NK cells)

**Acquired Immunity:**
- T cells, B cells

**Acute Inflammation:**
- Redness
- Warmth
- Swelling
- Pain

**Chronic Inflammation:**
- Cell lysis/apoptosis
- Tissues/organs destruction
- Loss of organs, functions

---

**Wen Bing (Warm Disease)**

<table>
<thead>
<tr>
<th>Wei (defensive) level</th>
<th>Pathogen attacks body surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, intolerance to cold and wind, sweating, red tongue tip, superficial rapid pulse; headache, thirst, cough, sore throat.</td>
<td>Innate immunity: skin, mucus, macrophages, NK cells</td>
</tr>
</tbody>
</table>

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### Wen Bing (Warm Disease)

<table>
<thead>
<tr>
<th>Qi (energy) level</th>
<th>Pathogen moves to the interior</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fever, heat intolerance, profuse sweating, extreme thirst, red tongue with yellow tongue coating, full and rapid pulse; irritability, dark urine, diarrhea, chest fullness, cough, thick sputum, delirium.</td>
<td>Acquired immune response, activation of T cells and B cells, increased production of various pro-inflammatory cytokines</td>
</tr>
</tbody>
</table>

### Wen Bing (Warm Disease)

<table>
<thead>
<tr>
<th>Ying (nutritive) level</th>
<th>Breakdown of immune tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever with high temperature at night, thirst with no desire to drink, irritability or delirium, faint skin rashes, crimson tongue, thready rapid pulse</td>
<td>The immune system mistakes normal cells and tissues and &quot;autoantigen;&quot; attacks and damages various tissues and organs</td>
</tr>
</tbody>
</table>

### Wen Bing (Warm Disease)

<table>
<thead>
<tr>
<th>Xue (blood) level</th>
<th>Tissue damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark or purple skin rashes, hemorrhages at various parts of the body, crimson tongue, deep and rapid pulse, fever at night, flushed face, dry mouth, red eyes, burning sensations in the chest, palms and soles.</td>
<td>Fibrosis, scar tissue formation, atrophy of tissues and organs, dysfunction of the organism</td>
</tr>
</tbody>
</table>
**Treatment Principles**

1. Avoid exposure to pathogens
2. Eliminate accumulated toxins and pathogens
3. Clear heat to treat acute and chronic inflammation
4. Nourish yin to repair tissue damages and restore normal forms
5. Move blood to treat fibrosis and scar tissues, and eliminate CIC
6. Dry dampness and eliminate phlegm
7. Tonify qi and yang to restore normal functions
1. Avoid exposure to pathogens

- Avoid exposure to environmental toxins
- Install air and water filters at homes
- Avoid contact with infected individuals
- Wear masks, wash hands
- Maintain moist mucous membrane
- Drink plenty of water and use humidifier

2. Eliminate accumulated toxins and pathogens

- Eliminate accumulated allergens and toxins from the blood and tissues
- Enhance liver metabolic function
- Improve kidney excretion function

- **Lu Dou** (Semen Phaseoli Radiati) + **Gan Cao** (Radix et Rhizoma Glycyrrhizae)
- **Lian Qiao** (Fructus Forsythiae) + **Fang Feng** (Radix Saposhnikoviae)
- **Bai Mao Gen** (Rhizoma Imperatae) + **Da Huang** (Radix et Rhizoma Rhei)
- Enhance liver metabolic function
- Improve kidney excretion function
2. Eliminate accumulated toxins and pathogens

- Eliminate accumulated allergens and toxins from the blood and tissues
- Enhance liver metabolic function
  - Xiao Chai Hu Tang (Minor Bupleurum Decoction)
  - Da Chai Hu Tang (Major Bupleurum Decoction)
  - Yin Chen Hao Tang (Artemisia Scoparia Decoction)
  - Ge Hua (Flos Puerariae)
  - Wu Wei Zi (Fructus Schisandrae Chinensis)
- Improve kidney excretion function

3. Clear heat in acute and chronic inflammation

- Clear excess heat associated with acute inflammation due to invasion of pathogens
- Clear deficiency heat associated with lysis and apoptosis of cells/tissues/organs
3. Clear heat in acute and chronic inflammation

- Herbs that clear heat
  - Select herbs based on *wei/qi/ying/xue* diagnosis
  - Select herbs based on pharmacology

### Wei, Qi, Ying, Xue Levels

- **Wei** (defensive) level
  - *Yin Qiao San* (Honeysuckle and Forsythia Powder)
- **Qi** (energy) level
- **Ying** (nutritive) level
- **Xue** (blood) level

---

- **Bai Hu Tang** (White Tiger Decoction), 321
- **Huang Lian Jie Du Tang** (Coptis Decoction to Relieve Toxicity), 341
- **Long Dan Xie Gan Tang** (Gentiana Decoction to Drain the Liver), 371

- **Ying** (nutritive) level
- **Xue** (blood) level
3. Clear heat in acute and chronic inflammation

- **Wei, Qi, Ying, Xue Levels**
  - **Wei** (defensive) level
  - **Qi** (energy) level
  - **Ying** (nutritive) level
    - **Qing Ying Tang** (Clear the Nutritive Level Decoction), 330
    - **Qing Hao Bie Jia Tang** (Artemisia Annua and Soft-Shelled Turtle Shell Decoction), 412
    - **Zhi Bai Di Huang Wan** (Anemarrhena, Phellodendron, and Rehmannia Pill), 636
    - **Qi Ju Di Huang Wan** (Lycium Fruit, Chrysanthemum, and Rehmannia Pill), 640
  - **Xue** (blood) level

- **Xi Jiao Di Huang Tang** (Rhinoceros Horn and Rehmannia Decoction), 333
  - Note: Replace **Xi Jiao** (Cornu Rhinoceri) with **Shui Niu Jiao** (Cornu Bubali).

- **Qing Wen Bai Du Yin** (Clear Epidemics and Overcome Pathogenic Influences Decoction), 337

3. Clear heat in acute and chronic inflammation

- **Wei, Qi, Ying, Xue Levels**
  - **Wei** (defensive) level
  - **Qi** (energy) level
  - **Ying** (nutritive) level
  - **Xue** (blood) level
    - **Xi Jiao Di Huang Tang** (Rhinoceros Horn and Rehmannia Decoction), 333
      - Note: Replace **Xi Jiao** (Cornu Rhinoceri) with **Shui Niu Jiao** (Cornu Bubali).
    - **Qing Wen Bai Du Yin** (Clear Epidemics and Overcome Pathogenic Influences Decoction), 337

3. Clear heat in acute and chronic inflammation

- **Heat-clearing herbs that suppress immune system**
  - **Di Huang** (Radix Rehmanniae)
  - **Xuan Shen** (Radix Scrophulariae)
  - **Zhi Mu** (Rhizoma Anemarrhenae)
  - **Shi Gao** (Gypsum Fibrosum)
  - **Ren Dong Teng** (Caulis Lonicerae Japonicae)
  - **Zhi Zi** (Fructus Gardeniae)
Zhi Zi (Fructus Gardeniae)

- **Immunosuppressive:**
  significant inhibition of human peripheral blood T cells and IL-2 secretion.\[i\]

- **Anti-inflammatory:**
  suppresses vascular inflammation via inhibition of tumor necrosis factor (TNF)-alpha.\[i\]


4. Nourish yin to repair tissue damages

- Increase generation of new cells/tissues
- New cells and tissues do not have antigen, and therefore will not trigger antibody production or autoimmune reactions

4. Nourish yin to repair tissue damages

- Select herbs based on zang/fu diagnosis
- Select herbs based on pharmacology
4. Nourish yin to repair tissue damages

**Zang Fu** diagnosis
- Heart / Small Intestine / Tongue / Blood Vessels
  - *Sheng Mai San* (Generate the Pulse Powder), 554, modified
    - *Mai Dong* (Radix Ophiopogonis)
    - *Di Huang* (Radix Rehmanniae)
    - *Wu Wei Zi* (Fructus Schisandraceae Chinensis)
    - *Remove: Ren Shen* (Radix et Rhizoma Ginseng)

4. Nourish yin to repair tissue damages

**Zang Fu** diagnosis
- Spleen / Stomach / Mouth / Muscles
  - *Mai Men Dong Tang* (Ophiopogonis Decoction), 1043
  - *Sha Shen Mai Dong Tang* (Glehnia and Ophiopogonis Decoction), 1047
  - *Zeng Ye Tang* (Increase the Fluids Decoction), 1054
4. Nourish yin to repair tissue damages

**Zang Fu** diagnosis
- Lung / Large Intestines / Nose / Skin
  - *Bai He Gu Jin Tang* (Lily Bulb Decoction to Preserve the Metal), 1036
  - *Mai Wei Di Huang Wan* (Ophiopogonis, Schisandra, and Rehmannia Pill), 642
  - *Du Qi Wan* (Capital Qi Pill), 644

- Kidney / Urinary Bladder / Ear / Bones
  - *Liu Wei Di Huang Wan* (Six-Ingredient Pill with Rehmannia), 627
  - *Zhi Bai Di Huang Wan* (Anemarrhena, Phellodendron, and Rehmannia Pill), 636
  - *Qi Ju Di Huang Wan* (Lycium Fruit, Chrysanthemum, and Rehmannia Pill), 640
  - *Da Bu Yin Wan* (Great Tonify the Yin Pill), 649
  - *Zuo Gui Wan* (Restore the Left [Kidney] Pill), 645

- Liver / Gall Bladder / Eyes / Tendons
  - *Liu Wei Di Huang Wan* (Six-Ingredient Pill with Rehmannia), 627
  - *Zhi Bai Di Huang Wan* (Anemarrhena, Phellodendron, and Rehmannia Pill), 636
  - *Qi Ju Di Huang Wan* (Lycium Fruit, Chrysanthemum, and Rehmannia Pill), 640
4. Nourish yin to repair tissue damages

- Yin-nourishing herbs with regulatory or inhibitory effect on humoral and cell-mediated immunity
  - *Di Huang* (Radix Rehmanniae)
  - *Xuan Shen* (Radix Scrophulariae)
  - *Mai Dong* (Radix Ophiopogonis)
  - *Tian Dong* (Radix Asparagi)
  - *Nan Sha Shen* (Radix Adenophorae)
  - *Bei Sha Shen* (Radix Glehniae)

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**Shu Di Huang** (Radix Rehmanniae Praeparata)

- Hematopoietic: increases multiplication and differentiation of bone marrow hematopoietic cells (CFU-S and CFU-E).\[i\]
- Osteoprotective: stimulates the proliferation and activities of osteoblasts and prevents osteoporotic bone loss.\[ii\]
- Renoprotective: relieves progressive renal failure.\[iii\]
- Neuroprotective: improves cognitive functioning by stimulating cholinergic enzyme activities and alleviating inflammatory responses.\[iv\]


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**Mai Dong** (Radix Ophiopogonis)

- Cardioprotective: potent cardioprotective effect in cardiac cells.\[i\]
- Anti-inflammatory: exerts anti-inflammatory activity by inhibiting the release of the inflammatory chemokine, suppressant effects on nitric oxide production.\[ii\]


**Tian Dong (Radix Asparagi)**

- Hepatoprotective: protects against alcohol-induced hepatotoxicity via the suppression of tumour necrosis factor-alpha (TNF-alpha) secretion and the TNF-alpha-induced cytotoxicity.\[i\]
- Anti-inflammatory: suppresses the production of pro-inflammatory cytokines (tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta) to treat acute and chronic inflammation.\[ii\]


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5. Move blood and eliminate blood stasis

- Reverses fibrosis
- Eliminates scar tissues
- Eliminates circulating immune complex (CIC)
- Treats vasculitis
- Relieves pain
- Facilitates overall healing

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5. Move blood and eliminate blood stasis

- Select herbs based on sanjiao diagnosis
- Select herbs based on pharmacology
5. Move blood and eliminate blood stasis

- **Sanjiao diagnosis**
  - *Xue Fu Zhu Yu Tang* (Drive Out Stasis in the Mansion of Blood Decoction), 879
  - *Ge Xia Zhu Yu Tang* (Drive Out Blood Stasis Below the Diaphragm Decoction), 885
  - *Shao Fu Zhu Yu Tang* (Drive Out Blood Stasis in the Lower Abdomen Decoction), 889
  - *Shen Tong Zhu Yu Tang* (Drive Out Blood Stasis from a Painful Body Decoction), 893
  - *Tao Hong Si Wu Tang* (Four-Substance Decoction with Safflower and Peach Pit), 571

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**Chuan Xiong (Rhizoma Chuanxiong)**

- Anti-inflammatory: inhibits TNF-alpha production and TNF-alpha bioactivity, and are promising agents in the treatment of inflammation and related diseases.\[i\]


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**Tao Ren (Semen Persicae)**

- Antiallergic and anti-inflammatory: treats mast cell-mediated allergic symptoms and diseases, such as asthma and sinusitis. It reduces histamine release from mast cells and inhibited artificially-induced systemic anaphylaxis and immunoglobulin E (IgE)-mediated local allergic reactions.\[i\]

Mu Dan Pi (Cortex Moutan)

- Anti-inflammatory: Mu Dan Pi significantly suppresses histamine release and prostaglandin D(2) synthesis from mast cells.[i]
- Anticomplement: The monoterpenoid glucosides from Mu Dan Pi, including suffrupaeniolin A and galloyloxypaeoniflorin, have been shown to exhibit anticomplement effects.[ii]


6. Dry dampness and eliminate phlegm

- Pleural effusion, pericardial effusion, edema, ascites, intracranial edema, ocular edema, exudation in the joints
  - Ting Li Zi (Semen Descurainiae seu Lepidii), Jie Zi (Semen Sinapis), and Sang Bai Pi (Cortex Mori) reduce exudation and promote absorption of effusion.

7. Restore yang to increase adrenal gland functions, raise corticosteroids production

- Kidney yang tonic formulas as replacement for corticosteroids
  - Jin Gui Shen Qi Wan (Kidney Qi Pill from the Golden Cabinet), 668
  - Ba Wei Di Huang Wan (Eight-Ingredient Pill with Rehmannia), 672
  - You Gui Wan (Restore the Right [Kidney] Pill), 678
7. Restore yang to increase adrenal gland functions, raise corticosteroids production

- Fu Zi (Radix Aconiti Lateralis Praeparata)
- Rou Gui (Cortex Cinnamomi)
- Lu Jiao (Cornu Cervi)
- Rou Cong Rong (Herba Cistanches)
- Yin Yang Huo (Herba Epimedii)
- Dong Chong Xia Cao (Cordyceps)
- Gui Ban (Plastrum Testudinis)
- Ge Jie (Gecko)

Autoimmune Diseases

Autoimmune diseases include a wide range of conditions characterized by the body's immune system attacking its own tissues. These conditions can affect almost any system in the body, leading to inflammation, tissue damage, and a variety of symptoms. Some common autoimmune diseases are listed below:

- Acute Disseminated Encephalomyelitis (ADEM)
- Acute necrotizing hemorrhagic leukoencephalitis
- Addison’s disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome (APS)
- Autoimmune aplastic anemia
- Autoimmune dysautonomia
- Autoimmune hepatitis
- Autoimmune hyperthyroidism
- Autoimmune immunodeficiency syndromes
- Autoimmune inner-ear disease (AIED)
- Autoimmune myocarditis
- Avicennia rosea
- Avicennia pacifica
- Avicennia nilotica
- Avicennia nilotica
- Aviulus thomocarpus
- Autoimmune thrombocytopenic purpura (ATP)
- Autoimmune thyroid disease
- Autoimmune urticaria
- Axonal & neuronal neuropathies
- Behçet’s disease
- Biliary disease
- Bacterial pneumonia
- Celiac disease
- Celiac disease
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Churg-Strauss syndrome
- Crohn’s disease
- Cogan's syndrome
- Cold agglutinin disease
- Congenital heart block
- Coxsackie myocarditis
- CREST disease
- Essential mixed cryoglobulinema
- Dermatitis herpetiformis
- Dermatomyositis
- Devic’s disease (neuromyelitis optica)
- Discoid lupus
- Dressler’s syndrome
- Endometriosis
- Eosinophilic esophagitis
- Eosinophilic fasciitis
- Erythema nodosum
- Exacerbated allergic encephalomyelitis
- Euchi syndrome
- Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Giant cell myocarditis
- Goodpasture’s syndrome
- Guillain-Barré syndrome
- Henoch-Schönlein purpura
- Herpes gestationis
- Hypogammaglobulinemia
- Idiopathic thrombocytopenic purpura (ITP)
- IgA nephropathy
- IgG4-related sclerosing disease
- Immune-regulatory lipoproteins
- Inclusion body myositis
- Intestinal isletitis
- Juvenile arthritis
- Juvenile diabetes (Type 1 diabetes)
- Juvenile myeloid leukemia
- Kawasaki syndrome
- Lambert-Eaton syndrome
- Leukoclastic vasculitis
- Lichen planus
- Lichen sclerosus
- Lignieres conjunctivitis
- Linear IgA disease (LAD)
- Lupus (SLE)
- Lyme disease, chronic
- Malignant neoplasia
- Malignant mixed connective tissue disease (MMCTD)
- Mooren’s ulcer
- Mucha-Habermann disease
- Multiple sclerosis
- Myasthenia gravis
- Myelitis
- Neuromyelitis optica (Devic’s) syndrome
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palatine neoplasia
- Papillary adenocarcinoma
- Panda syndrome
- PANIC
- Paraneoplastic cerebellar degeneration

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Autoimmune Diseases

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Perry Romberg syndrome
- Parsonage-Turner syndrome
- Pan-panitis (peripheral uveitis)
- Pemphigus
- Periarteritis nodosa
- Type I, II, & III autoimmune polyglandular syndromes
- Polyarteritis nodosa
- Polyradiculoneuropathy
- Polymyalgia rheumatica
- Polyneuropathy
- Polycystic ovaries
- Polycythemia vera
- Psoriasis
- Psoriatic arthritis
- Idiopathic pulmonary fibrosis
- Pyoderma gangrenosum
- Pure red cell aplasia
- Raynaud's phenomenon
- Reactive Arthritis
- Reflex sympathetic dystrophy
- Reiter's syndrome
- Relapsing polychondritis
- Reiter's syndrome
- Retinopathy
- Rheumatic fever
- Rheumatoid arthritis
- Sarkoidosis
- Scleroderma
- Sjogren's syndrome
- Sperm & testicular autoimmunity
- Still's disease
- Subacute bacterial endocarditis (SBE)
- Sudeck's syndrome
- Sympathetic ophthalmia
- Takayasu's arteritis
- Temporal arteritis/Giant cell arteritis
- Thrombotic thrombocytopenic purpura (TTP)
- Trousseau-Hunt syndrome
- Transverse myelitis
- Type 1 diabetes
- Uveitis
- Vasculitis
- Vesiculobullous dermatoses
- Villous
- Wegener's granulomatosis

Autoimmune diseases

1. Raynaud's disease
2. Sjogren's syndrome
3. Hashimoto's thyroiditis

Raynaud's disease

- A disorder characterized by periodic vasospastic attacks of pallor and coldness of the fingers, toes, ears and nose
- More common in women
- Onset in patients under 40 years of age.
Auguste Gabriel Maurice Raynaud, 1809-1877

The French doctor who discovered Raynaud's Disease, a rare vasospastic disorder which contracts blood vessels in extremities, in the late 19th century.

Clinical Manifestations

- Early phase: vasospasm with ischemic manifestations, such as pale skin, cold fingers, stabbing pain, numbness and rigidity of fingers.
- Late phase: skin swelling and cyanosis, turning dark blue or dark brown, with stabbing pain and throbbing sensation

Etiology

- Cause: unknown
- Risk factors:
  - Emotional stress
  - Chronic exposure to cold environment
  - Smoking
  - Physical injuries
  - Drugs (beta blockers, ergotamine, sumatriptan, chemotherapy agents; and drugs that cause blood vessels to narrow
  - Certain chemicals, such as vinyl chloride
Pathology

- Exposure to pathogen
- Triggers the immune system to attack the blood vessels
  - Physiological change: increased vasoconstriction of the arteries and arterioles
  - Physical change: increased platelet activation, increased blood viscosity, impaired fibrinolysis
- Sudden attacks of pallor and coldness to the fingers, toes, ears and nose, lasting from minutes to longer than one hour.

Diagnosis

- Positive antinuclear antibody (ANA)
- Abnormal erythrocyte sedimentation rate (ESR)
- Vasospastic attacks of pallor and cyanosis
- Abnormal nailfold pattern
- Pitting scars, ulcers, or gangrene of the skin, fingers or toes

医宗金鉴 Yi Zong Jin Jian (Golden Mirror of the Medical Tradition), in 1742

"In blood vessel bi zheng (painful obstruction syndrome), blood does not flow harmoniously in the vessels, leading to a change in color."

- 吳謙 Wu Qian
### Differential Diagnosis & Customized Treatment

<table>
<thead>
<tr>
<th>Impaired blood circulation due to vasoconstriction and increased blood viscosity</th>
<th>Blood stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>More pallor with numbness of the affected area</td>
<td>Blood stasis with qi stagnation</td>
</tr>
<tr>
<td>More cyanosis with sharp stabbing pain</td>
<td>Blood stasis with cold</td>
</tr>
<tr>
<td>Warm/burning sensation of the body, cold and pain of the fingers and toes</td>
<td>Blood stasis with yin deficiency</td>
</tr>
</tbody>
</table>

### Blood stasis

- *Xue Fu Zhu Yu Tang* (Drive Out Stasis in the Mansion of Blood Decoction), 879
- *Ge Xia Zhu Yu Tang* (Drive Out Blood Stasis Below the Diaphragm Decoction), 885
- *Shao Fu Zhu Yu Tang* (Drive Out Blood Stasis in the Lower Abdomen Decoction), 889
- *Shen Tong Zhu Yu Tang* (Drive Out Blood Stasis from a Painful Body Decoction), 893
- *Tao Hong Si Wu Tang* (Four-Substance Decoction with Safflower and Peach Pit), 571

### Blood stasis with complications

- Qi stagnation
  - *Si Ni San* (Frigid Extremities Powder), 233
- Cold
  - *Dang Gui Si Ni Tang* (Tangkuei Decoction for Frigid Extremities), 494
- Yin deficiency
  - *Liu Wei Di Huang Wan* (Six-Ingredient Pill with Rehmannia), 627
- Localized toxic heat
  - *Si Miao Yong An Tang* (Four-Valiant Decoction for Well-Being), 1344
Blood movers with anti-inflammatory effect

- *Chi Shao* (Radix Paeoniae Rubra)
- *Mu Dan Pi* (Cortex Moutan)
- *Dan Shen* (Radix et Rhizoma Salviae Miltiorrhizae)
- *San Leng* (Rhizoma Sparganii)
- *E Zhu* (Rhizoma Curcumae)
- *Shui Zhi* (Hirudo)

Diet

- Cool and cold foods should be avoided because they will further impair blood circulation.
- Hot or spicy foods should also be avoided because they will generate internal heat.
- Eat neutral temperature foods, such as green vegetables, black jelly fungus, coarse food grain (such as maize, millet or bean).

Lifestyle

- Regular exercise to improve circulation and keep body warm.
- Avoid exposure to cold. Always keep the body and limbs warm.
- Stop smoking. Control stress.
<table>
<thead>
<tr>
<th>Clinical Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Coldness with pallor and cyanosis appearance of the hands is not a symptom of qi or yang deficiency; but an indication of internal heat with qi or yang stagnation due to blood stasis.</td>
</tr>
<tr>
<td>• Therefore, treatment should focus on using herbs to invigorate blood circulation, move qi and yang, but not to tonify qi and yang.</td>
</tr>
<tr>
<td>• Note: Raynaud’s disease usually occurs prior to, or in conjunction with, other autoimmune disorders, such as scleroderma, Sjogren’s, SLE, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sjogren’s Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A disorder of the immune system identified by its two most common symptoms — dry eyes and a dry mouth.</td>
</tr>
<tr>
<td>• The mucous membranes are affected first, followed by destruction of the lacrimal and salivary glands.</td>
</tr>
<tr>
<td>• More common in women than men, 9:1.</td>
</tr>
<tr>
<td>• Usually diagnosed in people older than 40 yo.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Henrik Sjögren, 7/23/1899 - 9/17/1986</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Swedish ophthalmologist who first identified a group of women and correlated the triad of dry eyes, dry mouth and polyarthritis</td>
</tr>
</tbody>
</table>
Clinical Manifestations

- Dry eyes due to destruction of lacrimal glands
- Dry mouth due to destruction of salivary glands
- Skin rashes or dry skin
- Vaginal dryness
- Persistent dry cough
- Prolonged fatigue
- Joint pain, swelling and stiffness

Etiology

- Cause: unknown
- Risk factors:
  - Genetics
  - Infection: bacteria or virus (i.e., EBV)
  - Environmental toxins
  - Smoking
  - Air travel

Pathology

- Pathogen triggers immune response
- Migration of lymphocytes to target organs
- Increased production of inflammatory cytokines (IL-2 and interferon-gamma)
- Increased inflammation and apoptosis of target organs
Diagnosis

- Sjögren’s syndrome antibody (anti-SSA)
- Antinuclear antibody (ANA)
- Elevated IgA, IgM, IgG, IgE, IgD.
- Decreased tear and saliva production

**Tong Su Shang Han Lun** (Plain Version of Discussion of Cold-Induced Disorder), 1916

- “[Pathogenic dryness] first damages the Lung channel, then Stomach fluids and finally Liver blood and Kidney yin.”
- It can therefore be said that dryness symptoms are related to damage to the zang fu organs, in particular the Lung, Stomach and Kidney.

  – Yu Genchu
### Differential Diagnosis & Customized Treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eyes</td>
<td>Liver yin deficiency</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Stomach yin deficiency</td>
</tr>
<tr>
<td>Dry skin with skin rashes</td>
<td>Lung yin deficiency</td>
</tr>
<tr>
<td>Persistent dry cough</td>
<td>Lung yin deficiency</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>Kidney yin deficiency</td>
</tr>
</tbody>
</table>

### Lung yin deficiency
- *Qing Zao Ji Fu Fei Tang* (Eliminate Dryness and Rescue the Lung Decoction), 1029
- *Bai He Gu Jin Tang* (Lily Bulb Decoction to Preserve the Metal), 1036

### Stomach yin deficiency
- *Yu Nu Jian* (Jade Woman Decoction), 398
- *Mai Men Dong Tang* (Ophiopogon Decoction), 1043
- *Sha Shen Mai Dong Tang* (Glehnia and Ophiopogon Decoction), 1047
- *Zeng Ye Cheng Qi Tang* (Increase the Fluids and Order the Qi Decoction), 190
Liver and Kidney yin deficiency

- Liu Wei Di Huang Wan (Six-Ingredient Pill with Rehmannia), 627
- Qi Ju Di Huang Wan (Lycium Fruit, Chrysanthemum, and Rehmannia Pill), 640
- Zhi Bai Di Huang Wan (Anemarrhena, Phellodendron, and Rehmannia Pill), 636

Blood stasis

- Xue Fu Zhu Yu Tang (Drive Out Stasis in the Mansion of Blood Decoction), 879

Herbs to stimulate salivary and lacrimal glands

- Di Huang (Radix Rehmanniae)
- Xuan Shen (Radix Scrophulariae)
- Shi Hu (Caulis Dendrobii)
- Bei Sha Shen (Radix Glehniae)
- Mai Dong (Radix Ophiopogonis)
- Bai Mao Gen (Rhizoma Imperatae)
- Lu Gen (Rhizoma Phragmitis)
- Gou Qi Zi (Fructus Lycii)
- Shi Gao (Gypsum Fibrosum)
- Zhi Mu (Rhizoma Anemarrhenae)
Diet

- Avoid hot and spicy foods
- Avoid foods that are warm or hot in nature.
- Drink tea made from *Wu Mei* (Fructus Mume) and *Gan Cao* (Radix et Rhizoma Glycyrrhizae) throughout the day.
- Eat sweet, cool, nourishing and moistening foods, preferably in liquid or semi-liquid form.
- Eat in small quantity several times daily.

Lifestyle

- Get adequate rest
- Avoid dry environment
- Use humidifier
- Avoid prolong exposure to TV and computers
- Use artificial tears and saline nose drops
- Drink fluids throughout the day
- Reduce frequency of shower/bath, avoid soaps with fragrance, use body lotion.

Hashimoto’s thyroiditis

- A chronic autoimmune disease of the thyroid gland characterized by destruction of the thyroid gland and reduced production of thyroid hormones.
- Also known as
  - Autoimmune thyroiditis
  - Chronic lymphocytic thyroiditis
Hakaru Hashimoto, 1881-1934

A Japanese physician who first described chronic thyroid disorder with diffuse lymphocytic infiltration, fibrosis and parenchymal atrophy.

Clinical Manifestations

- Goiter, pale face, fatigue, weight gain, sleepiness, loose stools, intolerance to cold, cold limbs, reduced body temperature, coarse dry skin, hair loss.
- Women: Men - 20:1
- Most common in middle ages of 40-50

Etiology

- Cause: unknown
- Possible factors:
  - virus
  - bacteria
  - heredity
  - sex
  - age
### Pathology

- Pathogen activates the immune system
  - Increased T helper cells
  - Increased B cell
  - Increased production of antibodies against thyroglobulin, TSH receptors, TPO enzymes
- Increased inflammation causing destruction of thyroid cells and atrophy and fibrosis of the thyroid glands

### Diagnosis

- Low T4, low T3, high TSH
- Antibodies against
  - Antithyroglobulin antibodies [anti-TG Ab]
  - Thyroid-stimulating antibodies [TSAb]
  - TSH receptors binding immunoglobulins [TBII]
  - Anti-thyroid peroxidase antibodies [anti-TPO Ab]

### TCM View of Hashimoto's thyroiditis

- Inappropriate diet or unhealthy lifestyle causing internal damage
- Spleen qi and yang deficiencies
- Kidney qi and yang deficiencies
### Differential Diagnosis & Customized Treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerance to cold, cold limbs, reduced body temperature</td>
<td>Kidney qi and yang deficiency</td>
</tr>
<tr>
<td>Pale face, fatigue, weight gain, sleepiness, loose stools</td>
<td>Spleen qi and yang deficiency</td>
</tr>
<tr>
<td>Coarse dry skin, hair loss, destruction of thyroid cells, atrophy / fibrosis of thyroid glands</td>
<td>Yin deficiency</td>
</tr>
<tr>
<td>Goiter</td>
<td>Phlegm accum., blood stasis</td>
</tr>
</tbody>
</table>

### Kidney qi and yang deficiency

- *Jin Gui Shen Qi Wan* (Kidney Qi Pill from the Golden Cabinet), 668
- *Ba Wei Di Huang Wan* (Eight-Ingredient Pill with Rehmannia), 672

### Metabolic effect

- *Rou Gui* (Cortex Cinnamomi) and *Fu Zi* (Radix Aconiti Lateralis Praeparata) have stimulating effects on the body and elevate basal metabolism, leading to excitation of the cardiovascular, gastrointestinal, and immune systems.\[iii\]

\[iii\] Wang, YS, *Pharmacology and Applications of Chinese Herbs*, 1985; 443
Spleen qi and yang deficiency

- *Si Jun Zi Tang* (Four-Gentlemen Decoction), 522
- *Liu Jun Zi Tang* (Six-Gentlemen Decoction), 527

Yin deficiency

- *Liu Wei Di Huang Wan* (Six-Ingredient Pill with Rehmannia), 627

Goiter (phlegm accumulation)

- *Xia Ku Cao* (Spica Prunellae)
- *Shan Ci Gu* (Pseudobulbus Cremastrae seu Pleiones)
- *Ban Xia* (Rhizoma Pinelliae)
- *Tian Nan Xing* (Rhizoma Arisaematis)
- *Chuan Bei Mu* (Bulbus Fritillariae Cirrhosae)
- *E Zhu* (Rhizoma Curcumae)
Blood stasis

• *Xue Fu Zhu Yu Tang* (Drive Out Stasis in the Mansion of Blood Decoction), 879

Diet

• Eat a highly nutritious diet with fresh vegetables.
• Avoid fatty, aromatic, pungent and spicy foods.
• Do not eat foods that are cold in nature.
• Stop drinking and smoking.

Lifestyle

• Avoid stress and emotional stimulation.
• Do not squeeze the neck or the thyroid gland.
• Refrain from strenuous exercise.
Clinical note

- Caution:
  - Qi tonics
  - Yang tonics

The Effects of Traditional Antirheumatic Herbal Medicines on Immune Response

Cells  

**OBJECTIVE:** Clinically, some traditional Chinese herbal medicines have been thought to be effective in treating rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. In examining the mechanism by which such herbal medicines might be effective, we investigated the ability of Tripterygium wilfordii Hook F (TTW) and terbinafine (TFA) to affect human immune responsiveness in vitro.

**METHOD:** We measured the ability of these agents to affect cytokine secretion from monocytes or THP-1 macrophages. Poly(I:C) stimulation from monocytes, IgG production from B cells, and the phagocytosis of bacteria by neutrophils.

**RESULTS:** These observations revealed that both TTW and TFA significantly inhibited interleukin-2 (IL-2), tumor necrosis factor (TNF-α), IL-6, and IL-10 secretion from monocytes, IgG secretion from B cells, and phagocytosis of bacteria by neutrophils; however, only TTW inhibited IL-1 and IL-6 production from monocytes, and IL-6 secretion from macrophages. 

**CONCLUSION:** TTW and TFA exert a powerful suppressive effect on human immune responses. This suggests that their therapeutic effectiveness in rheumatic diseases, and might support broader and more rigorous clinical trials.

Current Events

- *Lei Gong Teng* (Radix Tripterygii Wilfordii)
**Lei Gong Teng (Radix Tripterygii Wilfordii)**

- **Immunosuppressive and antirheumatic**: *Lei Gong Teng* is a herb with an immunosuppressive effect that inhibits the expression of proinflammatory cytokines, proinflammatory mediators, adhesion molecules, and matrix metalloproteinases by macrophages, lymphocytes, synovial fibroblasts, and chondrocytes. It is considered an alternative disease modifying anti-rheumatic drug (DMARD) for patients with rheumatoid arthritis refractory to conventional therapy.[i]

  [i] Bao J, Dai SM. A Chinese herb *Tripterygium wilfordii* Hook F in the treatment of rheumatoid arthritis: Mechanism, efficacy, and safety. Department of Rheumatology & Immunology, Changzheng Hospital, Second Military Medical University, Shanghai, China. Rheumatol Int. 3011 Mar 2.

- In a multicentre, open-label, randomised controlled trial, 207 patients with active rheumatoid arthritis were divided into three groups: *Lei Gong Teng* only, methotrexate only, or *Lei Gong Teng* and methotrexate. After 12 weeks of treatment, the researchers evaluated and concluded that treatment with *Lei Gong Teng* or methotrexate with *Lei Gong Teng* showed comparable effectiveness, and both are better than methotrexate as monotherapy.[i]


**Toxicities**

- Adverse reactions: local irritation of the gastrointestinal tract, damage to the central nervous system, internal bleeding and necrosis of the organs.
- Gross overdose may cause bleeding in the stomach, intestines, liver and lungs. Other symptoms include dizziness, dry mouth, palpitations, necrosis of mucous membranes and irregular menstruation.[ii]

  [ii] Zhong Yao Du Li Xue (Toxicology of Chinese Herbs) 1989;154-155.
Antidote

- General toxicity of the herb may be treated with the following herbs in decoction:
  - *Lu Dou* (Semen Phaseoli Radiati) 120 grams and *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 30 grams.
  - *Feng Wei Cao* (Herba Pteris) 90 grams.
  - *Wu Jue* (Folium Stenolomatis) 60 grams.
  - *Xian Di Huang* (Radix Rehmanniae Recens) 90-100 grams.[i][ii]

  [i] Shi Yong Zhong Yao Du Li Xue (Practical Toxicology of Chinese Medicine) 2007; 315-325
  [ii] Hu Nan Yi Yao Za Zhi (Hunan Journal of Medicine and Herbology), 1977; 5:3

Antidote

- Other options?

Current Events

- *Chang Shan* (Radix Dichroae)
Chang Shan (Radix Dichroae)

- **Anti-inflammatory and immunosuppressant**: Halofuginone, a febrifugine derivative from Chang Shan, showed great promise to treat autoimmune disorders by preventing inflammatory pathology without inducing generalized immunosuppression.

- Halofuginone inhibits T helper 17 (T h17) cell differentiation by activating the amino acid starvation response to exert a potent and selective regulation of inflammatory T cell differentiation in vivo. According to the researchers, halofuginone holds great promises in the treatment of certain types of autoimmune and inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, eczema, and psoriasis.\[^i\]\[^ii\]

Toxicities

- Overdose reactions generally occur 30 minutes to 2 hours after the ingestion of the herb. Early reaction is characterized by nausea, vomiting, abdominal pain, diarrhea, blood in the stool, and upper gastrointestinal bleeding. In severe cases, there may be palpitation, irregular heart beat and rhythm, and possibly death.\[^i\]\[^ii\]

Antidote

- Overdose of Chang Shan (Radix Dichroae) may be treated with the following herbal decoction:
  - *Chen Pi* (Pericarpium Citri Reticulatae), *Ban Xia* (Rhizoma Pinelliae), *Fu Ling* (Poria), *Zhi Shi* (Fructus Aurantii Immaturus), *Zhu Ru* (Caulis Bambuseae in Taenia), *Gan Cao* (Radix et Rhizoma Glycyrrhizae) and post-decocted *Da Huang* (Radix et Rhizoma Rhei), 9 grams each.\[^i\]
  - *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 45g and *Lu Dou* (Semen Phaseoli Radiati) 60g.
  - *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 30g, *Sheng Jiang* (Rhizoma Zingiberis Recens) 30g, *Huang Qin* (Radix Scutellariae) 9g, and *Da Zao* (Fructus Jujubae) 10 pieces.
  - *Bai Fan* (Alumen) 3g, *Da Huang* (Radix et Rhizoma Rhei) 15g and *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 15g.\[^i\]\[^ii\]


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Stress

- Chronic stress triggers the release of IL-6, a strong pro-inflammatory cytokine

Yin Yang Balance

Yin Yang

Normal State
Yin Yang Balance

Acute Inflammatory State
Autoimmune Diseases

Yin Yang Balance

Chronic Inflammatory State
Autoimmune Diseases


“阳常有余，阴常不足．”

“Yang is often in excess.
Yin is often insufficient.”
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