

Herbal pharmacology and Drug interaction of the Herbs that Remove Blood Stasis

—— For 2010 Acupuncture Continue Education

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Introduction of Herbal pharmacology and Drug Interaction of the Herbs that Remove Blood Stasis

1. Actions of the herbs ^(1,2,3)

(1) Improve the microcirculation

Blood stasis is the most common pathogenesis of disorders of microcirculation, such as coronary heart disease, cerebral diseases. This group herbs can improve the fluid, state, permeability of microcirculation.

(2) Improve hematology and against coagulation

Blood stasis is related to thrombus formation due to “thickness, stickiness, coagulation and accumulation” of blood in circulation. Most of the herbs that remove blood stasis have excellent function of improving the tendency of “thickness, stickiness, coagulation and accumulation” of blood in circulation. They have inhibitory influence on thrombus formation, and are used in treatment of angina, embolism and stroke. The herbs include Dan Shen(Radix Salviae Mitiorrhizae), Chuan Xiong(Rhizoma Ligustici Chuanxiong), Hong Hua(Flos Carthami).

(3) Dilate blood vessel and increase blood perfusion to small vessels.

The herbs that dilate coronary arteries include Shui Zhi(Hirudo), E Zhu(Rhizoma Curcumae), Tao Ren(Semen Persicae), Chuan Xiong(Rhizoma Ligustici Chuanxiong)

(4) Antineoplastic: Some of the herbs can inhibit the growth of cancer cells in vitro.

The examples are San Leng(Rhizoma Sparganii), E Zhu(Rhizoma Curcumae), Sanqi (*Panax notoginseng*).

(5) Lower cholesterol

The herbs are Sanqi (*Panax notoginseng*), Dan Shen (Radix *Salviae Miltiorrhizae*), Pu Huang (Pollen *Typhae*).

2. Potential Herb-drug Interactions ⁽³⁾

(1) Antiplatelets and anticoagulants: The group herbs may enhance the actions of antiplatelets and anticoagulants medications, and prolong bleeding, such as warfarin, heparin, lepirudin, salicylate .

(2)Antihypertensives: Some of the group of herbs may dilate the blood vessels, which may potentiate the effect of antihypertensiv medications.

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Dan Shen (Radix Salviae Miltiorrhizae)



BEIJING, Aug. 7 (Xinhua) -- A China-made pill to treat cardiovascular conditions has been tested safe and effective by the U.S. Food and Drug Administration (FDA), and, hopefully, will be marketed in the U.S. as early as 2013, a pharmaceutical company said here Saturday. (http://news.xinhuanet.com/english2010/china/2010-08/07/c_13434173.htm)

FDA reports: Dan Shen and Ge Gen are in clinical trial-
Phase II:

Cardiovascular-Protective Effects of Herbal Medicine

Danshen-Gegen(<http://clinicaltrials.gov/ct2/show/NCT01033630?term=Danshen&rank=1>)

Dan Shen is the root and rhizome of *Salvia miltiorrhiza* Bge., family Labiatae.

Properties: Bitter and slightly cold

Channels entered: Heart, pericardium, and liver

1. Actions and indications ⁽¹⁾

Actions and indications in TCM

(1) Invigorates the blood and breaks up blood stasis:

It is used for blood stasis disorders in lower abdomen such as dysmenorrhea, amenorrhea, masses. It is also used for Chest pain.

(2) Clears heat and smoothes irritability

It is used for restlessness, irritability, palpitation.

(3) Cools blood and expels pus

It is used for heat in the blood level, skin sores due to toxic heat.

2. Chemical Ingredients in Danshen^(2,3,4)

Dan Shen has more than 50 compounds:

Tanshinone I , Tanshinone II A, Tanshinone II B,
Cryptotanshinone, Cryptotanshinone,
Danshensu(Salvianic acid A), Isotanshinone I ,
Isotanshinone II , Isocryptotanshinone, Tanshinol I ,
Tanshinol II . Methyl tanshinonate,
hydroxytanshinone II B , Vitamine E.

3. Pharmacokinetics⁽⁵⁾

- Major components absorbed rapidly after oral administration
- Metabolized extensively by liver
- Excreted from stool and urine,
- Some components have low short half life, low bioavailability, because of extensive metabolism

4. Actions and indications in Herbal pharmacology

Danshensu^(6,7,8,9)

Dilates coronary arteries, inhibits platelet aggregation, improves microcirculation, and protects the myocardium from reperfusion injury of the ischemic heart.

Mechanisms:

- prevent intracellular calcium increase
- remove oxygen free radicals
- Inhibit myocardial cell apoptosis
- protect the endothelial cells against homocysteinemia (risk factor for cardiovascular diseases and atherosclerosis)

Salvianolic Acid B_(10, 11)

Protect the brain from ischemia-reperfusion injury

Mechanisms:

- Inhibit platelet aggregation and oxidative modification of lowdensity lipoprotein(LDL), leading to the prevention of the uptake of LDL_(12,13).
- Inhibit erythrocyte hemolysis and lipid peroxide production₍₁₄₎
- Inhibit DNA synthesis of noncardiomyocytes and inhibit stress-activated protein kinase activity, leading to protection of ischemia-reperfusion injury₍₁₅₎

Tanshinone IIA

Dan shen

Reduce myocardial infarct size⁽¹⁶⁾.

-Inhibit LDL oxidation and angiotensin II activity, resulting in attenuation of cardiac cell hypertrophy.

The other actions:

■ Prevent cancer metastasis⁽¹⁷⁾

Tanshinone II-A significantly inhibited in vivo metastasis of colon carcinoma SW480 cells. It inhibited in vitro and in vivo invasion and metastasis of colon carcinoma cells by reducing levels of urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMP)-2 and MMP-9, and by increasing levels of tissue inhibitor of matrix metalloproteinase protein (TIMP)-1 and TIMP-2. Tanshinone II-A was also shown to suppress the nuclear factor-kappaB (NF-kappaB) signal.

Protect the liver injury⁽¹⁸⁾

Clinic researches:

1. Angina Pectoris

- Danshen products were found to be better than isosorbide dinitrate (ISDN) for long term use
- None of the Danshen products was found to be superior in efficiency to nitroglycerin, fewer side effects such as headache were found in Danshen group compared to that in the nitroglycerin group⁽¹⁹⁾.
- Danshen dripping pill was found to achieve a higher rate of effectiveness in treating patients with angina pectoris in comparison to the Danshen Tablet.
- Fufang Danshen Spray and injection were similar or better efficacy when compared to ISDN⁽²⁰⁾

- The improvement of exercise ECG from the Fufang Danshen Dripping Pill was found to be significantly better than ISDN.
- The sublingual Fufang Danshen Dripping Pill is at least as effective as sublingual ISDN and comparable to sublingual nitroglycerin⁽²¹⁾

2. Hyperlipidemia⁽²²⁾

- Danshen products can reduce the level of cholesterol, triglyceride, and LDL, and raised the level of HDL.

3. Acute Ischemic Stroke^(23,24)

- Improve the short-term effect of acute stroke patients
- conducive to the recovery of patients with traumatic intracranial hematoma (TICH)
- improves the microcirculation of femoral head, which is beneficial to repair and reconstruction of femoral head.

Side effects⁽²⁵⁾

- No major side effects

Patients who are taking Fufang Danshen Dripping Pill may felt thirsty(3/100), dizziness, drowsiness, abdominal discomfort(2/34), decrease appetite and itching.

- LD50 of water soluble extract was almost 4000 times higher in mice than the clinical human oral dosage.

HERB-DRUG INTERACTION

Dan shen

1. The anticoagulant response to warfarin could be exaggerated when coadministered with Danshen (26,27).
2. Salicylate in therapeutic concentration was reported to be significantly decrease free Danshen concentration as measured by free-digoxin-like activity(28)

DOSAGES:

1. Loose Danshen: 6-15g
2. Fufang Danshen Dripping Pill: 10 pills orally or sublingually each time, 3 times daily
3. Fufang Danshen Tablets 3 tablets orally each time, 3 times a day.



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Dan shen

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Sanqi (*Panax notoginseng*)



- The root of Panax Notoginseng
- It is the largest ingredient in 云南白药 (Yunnan Bai Yao), a famous hemostatic herbal remedy
- Sweet and slightly bitter in taste, and nontoxic.
- The dose in decoction for clinical use is 5-10 g. It can be ground to powder for swallowing directly or taking mixed with water: the dose in that case is usually is 1-3 grams.

1. Action and Indications in TCM

(1) Stops bleeding and transforms blood stasis:

Used for internal and external bleeding

(2) Reduces swelling and alleviates pain:

2. Chemical constituents.

- Saponins derivatives (PNS), which is a mixture of more than 20 types of saponins, four or five of them are considered as the principle active ones
 - Notoginenoside R1, ginsenoside Rg1, Rd, Re and Rb1 (75-80% total PNS)
- Flavonoids et al.

3. Pharmacokinetics

- Oral administration, most Saponins derivatives (powder) tested in rats, reached peak concentration in plasma rapidly within about 0.75 h - *hint their absorption were quick.*
- Maximum concentration in rat plasma were low
 - *indicated that it may be poorly absorbed and / or extensive metabolized (intestinal microflora, liver)*

- Half time was changed from 1 to 20 hrs in rat plasma after oral administration of the constituents
- *Iv* in rats, most constituents were cleared quickly except a couple of PNS
 - the pharmacokinetic profile diversities of these constituents are probably one of the mechanisms of the multiple pharmacology activities

4. Actions and indications in Herbal pharmacology

(1) Hemostatic effect

San-qi and a saponin (PNS) extract provide hemostatic effects. External application reduces bleeding time⁽¹⁾.

(2)Thrombogenicity effects

- PNS reduces platelet activation, adhesion and aggregation⁽²⁾.
- Prevent thrombosis and improve microcirculation in patients with blood hyperviscosity syndrome⁽³⁾.

(3)Thrombogenicity effects

- PNS iv or oral 200 mg/kg need 20 days to appear
 - *hint a slow effect compare to hemostatic*

(4) Fibrinolytic effects

- Sanqi (*the extract as notoginsenoside R1*) increased the fibrinolytic potential in *in vivo* lab test, which may be beneficial to cardiovascular disease⁽⁴⁾

(5) Cardiovascular effects

- Dilate the coronary artery, increase coronary blood flow, providing more blood to the heart muscle
- Improves micro-circulation in and around damaged heart tissue
- Reduces cardiac load, lowers arterial pressure⁽⁵⁾

- Decrease the size of myocardial infarction
- Anti-arrhythmia
- PNS increases PGI₂ and reduces thromboxane A₂ in platelets – correct the unbalance between the two prostaglandins

(6) Anti-atherosclerotic effect

- It helps lower cholesterol and triglycerides, to prevent the progression of atherosclerotic lesion. PNS possess anti-hyperglycemic and anti-obese activities by improving insulin- and leptin sensitivity, and Rb1 is responsible for the anti-hyperglycemic effect among the five saponins in KK-Ay mice.^(6, 7)

(7) Effects on brain

- Protect ischaemic brain damage⁽⁸⁾.

Ginsenoside Rb(3) could markedly protected OGD-Rep induced ischemic injury and the mechanisms maybe related to its suppression of the intracellular Ca^{2+} elevation and inhibition of apoptosis and caspase activity. Ginsenoside Rb(3) could be a promising candidate in the development of a novel class of anti-ischemic agent.

- Decrease brain edema, infarct size and neuron damage
- Inhibit uptake calcium by neuron cells isolated from rats
- Protect cultured rat cortical neuron from glutamate neurotoxicity⁽⁹⁾

(8) Tumor Radio-sensitivity

Taiwanese scientists studied the sensitization effect of Panax notoginseng extract and purified Saponin (Rb1) on the radiation response of an experimental tumor (KHT sarcoma) in comparison with its effects on a normal tissue (bone marrow) in mice.

- Panax notoginseng extract at a concentration of **0.1-100 mg/kg** produced an increase in tumor radiosensitivity.
- Rb1 at a concentration **0.001 to 1 mg/kg** produced an increase in tumor radiosensitivity, with maximum effect at 1 mg/kg.
- The effect was maximal at 10 mg/kg and at 30 minutes after injection.
- Further purified or synthetic versions are useful in cancer therapy.

(9) Anti-inflammatory effects and stop pain

- San Qi can stop pain caused by inflammation and trauma through anti-inflammation and disturbing the central nervous system.

5. Toxicity

- Low
- Esophagitis from consuming tablets (*drink enough water*) may occur
- Allergic reactions including dermatitis, shock, purpura, blisters, or other idiosyncratic reactions.

6. Clinical research

(1) Coronary artery disease

(2) Hypercholesterolemia

(3) Bleedings:

- Upper gastrointestinal bleeding
- Stomach bleeding
- Hemoptysis
- Pain

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Chuan Xiong (*Rhizoma Ligustici Chuanxiong*)



Chuanxiong is the root and rhizome of *Ligusticum*
Chuangxiong Hort

Properties: Acrid, warm.

Channels entered: Liver, pericardium, and gallbladder.

1. Actions and indications in TCM ⁽¹⁾

(1) Regulate Qi and invigorates the blood

It is widely used for irregular menstruation, menorrhagia, dysmenorrhagia, and headache due to qi stagnation and blood stasis.

(2) Expel wind and relieve pain

It is used for headache, aching body and Bi syndrome due to wind cold.

2. Major Chemical Ingredients⁽²⁾

Alkaloids: Chuanxiongine, tetramethylpazine,

Organic acid: Ferulic acid, sedanonic acid,

Essential oil: ethyl pentadecanoate,

3. Pharmacological effects^(2,3)

(1) Cardiovascular⁽⁴⁾

- Chuan Xiong dilates blood vessels, increases myocardial blood flow and oxygen-supply, keeps myocardial oxygen balance. The mechanism is related to ChuanXiong decreases invascular endothelial growth factor (VEGF) expression.

(2). Improves the circulation

- Dilates arteries: dilates the arteries of the heart, brain, lungs: for example, increases blood perfusion to and reduce swelling of the brain. Used for migraine, cerebral ischemia, Alzheimer's disease.
- Antiplatelet and anticoagulant:

(3) Stop pain

- Sedative: effects on the central nervous system
- Relaxes the spasm of muscles

(4) Others

- Decreases the side effects of kanamycin and cyclosporin A
- Anti-radiotherapy:

4. Herb-drug Interaction^(2,3)

- Antiplatelet and anticoagulant: Though this potential interaction has not been documented, it should be used with caution. Examples of antiplatelet are aspirin, dipyridamole (persantine), and clopidogrel (plavix). Examples of anticoagulant are heparin, warfarin (coumadin), and enoxaparin (lovenox).

5. Toxicology^(2,3)

- When continuous oral administered in mice with 5mg-10mg/kg for 4 weeks, no abnormalities of liver, kidney, blood exam. and pathological exam were observed.
- The LD50 for it preparation in mice was 66.42g/kg with intravenous injection.

6. Clinical Indication of Research

- Headache
- Diseases of the heart and brain

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**Thank
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