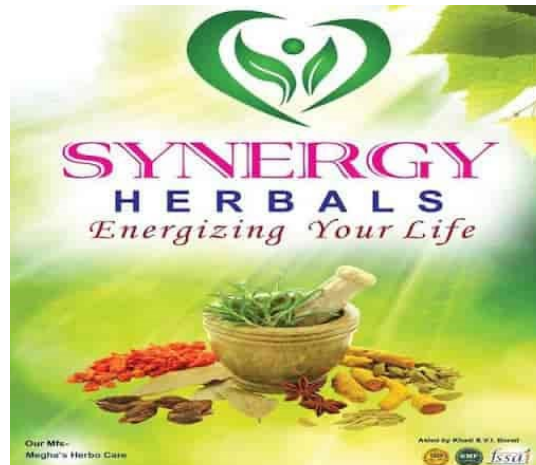


Synergy

Bona fide or balderdash?





SYNERGY HERBALS
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The interaction or cooperation of two or more organisations, substances, or other agents to produce a combined effect greater than the sum of their separate effects.

OR

$$1 + 1 = 3$$

Multidrug therapy

To overcome

- Resistance
- Ineffectiveness
- Side effects
- The basis of using multidrug therapy for various disorders is the recognition that for each, more than one mechanism and gene is identified
- It is difficult to suppress cancer and other diseases by targeting a single gene or a single pathway that may vary amongst patients and that can be subject to mutations

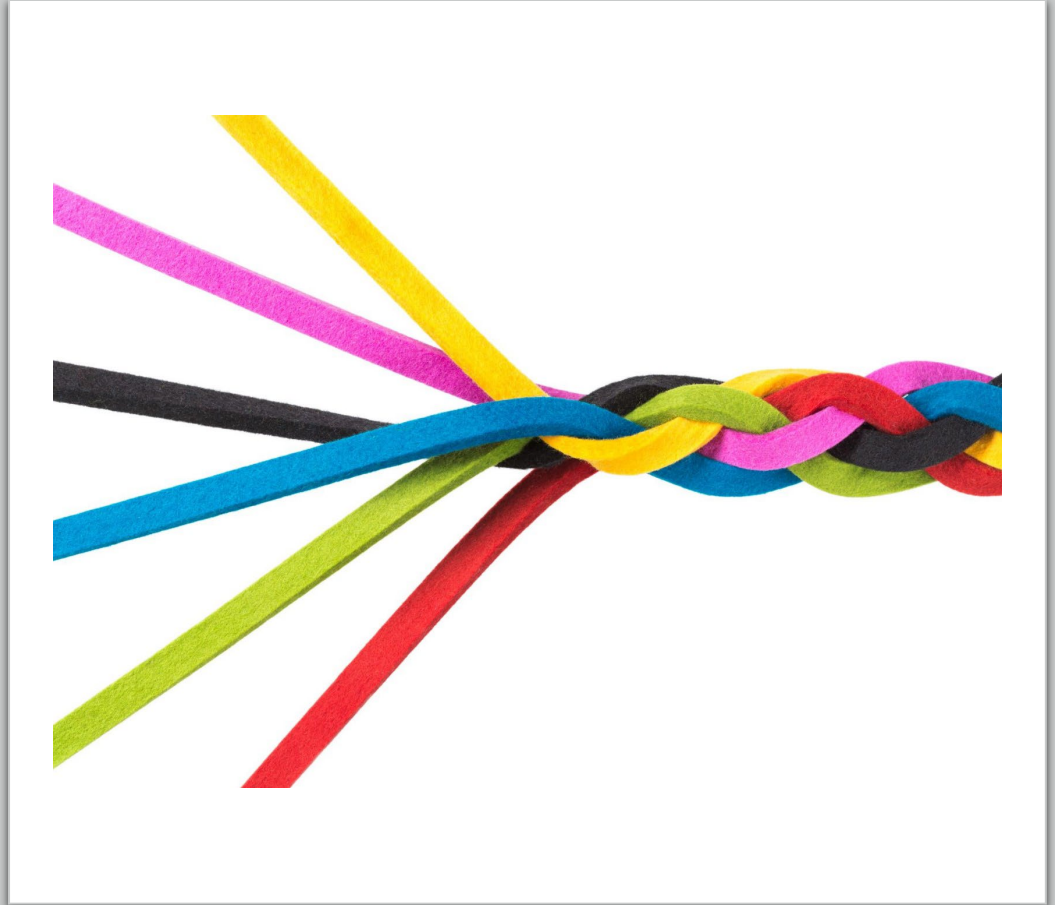
Herbal synergy

- Although synergistic therapeutic actions of herbal ingredients have been frequently reported, few reports have offered clear underlying mechanisms
- The multi-component nature of medicinal herbs makes them particularly suitable for treating complex diseases and offers great potential for exhibiting synergistic actions

Kinds of synergy

Synergy occurs within single herbs and within herbal complexes

- Enhancing absorption / bioavailability
- Modulating multiple receptors / enzyme systems to achieve a therapeutic effect or 'potentiation'
- Overcoming resistance mechanisms
- Reducing toxicity
- Working on multiple aspects of the same condition





Synergistic formulating

- Decoction of Ephedra (Mahuang Tang) contains ephedra, cinnamon twig, bitter apricot seed and licorice root
- Used for multiple symptoms: diaphoretic, anti-tussive, bronchodilatory, reduces headache and general aching during common cold
- Chinese medicine theory states all these symptoms are caused by excessive 'coldness' and 'wind' in the body
- Co-administration of multiple ingredients result in complementary interactions to combat symptoms of common cold or influence the illness



Formulation hierarchy in traditional Chinese herbal medicine

Follows principles of compatibility with interrelationships of ingredients including:

- ✓ Synergism (Xiang Xu)
- ✓ Assisting (Xiang Shi)
- ✓ Detoxication (Xiang Sha and Xiang Wei)
- ✓ Antagonism (Xiang Wu)
- ✓ Rejection (Xiang Fan)



CHIEF / EMPEROR HERB



DEPUTY HERB/S



ASSISTANT HERB/S



ENVOY / COURIER HERB

Six Ingredient Rehmannia Pill



CHIEF / EMPEROR HERB

Rehmannia glutinosa



DEPUTY HERBS

Cornus officinalis, Dioscorea oppositifolia



ASSISTANT HERB

Paeonia suffruticosa



ENVOY / COURIER HERBS

Alisma orientale, Poria cocos

Six Ingredient Rehmannia Pill

- First recorded in a medical text for paediatric diseases in 1119 CE
- Rehmannia (prepared), Cornelian cherry, Chinese yam, poria mushroom, moutan cortex (*Paeonia suffruticosa*) and alisma at a weight ratio of 8:4:4:3:3:3.
- Originally used for treating children with growth retardation
- Now widely used for treating adults with symptoms related to ageing, such as weakness, poor memory and dizziness
- Liver and kidney yin deficiencies
- Studies in animal models indicate a range of effects: anti-inflammatory, neurogenesis, improved learning and memory, anti-diabetic, antioxidant, lifespan extension



Six Ingredient Rehmannia Pill longevity study

Nematodes (*Caenorhabditis elegans*)

- Extended lifespan by 42.6%
- Downregulated expression of genes involved in redox processes, lipid metabolism, innate immune response and proteolysis
- Elevated expression of antioxidant-related genes which encode a catalase and superoxide dismutase and are associated with reducing oxidative damage and in lifespan extension

Aged mice

- Extended lifespan ~20%
- Reduced adipose tissue and body weight
- Increased SOD and decreased MDA (marker of lipid peroxidation)
- Glossier hair!

- ✓ Rehmannia and Cornelian cherry individually extended lifespan, but were less effective than the complete formula
- ✓ Omitting each individual herb weakened the overall effect significantly

Danshen-Tienchi

Chief herb:
Danshen



Deputy herb:
Tienchi ginseng



Envoy:
**Borneol from
camphor tree**



Danshen-Tienchi



- **Anti-inflammation**

Nine combination ratios screened for anti-inflammatory effects on murine macrophage cells. Danshen-Tienchi 8:2 was the optimal ratio and exerted a synergistic effect in inhibiting nitric oxide (NO), tumour necrosis factors (TNF) and monocyte chemoattractant protein-1 (MCP-1) ¹

- **Angiogenesis**

Nine combination ratios screened for angiogenic effects on human vascular endothelial cells. Danshen-Tienchi ratios 2:8 and 3:7 potentiated angiogenic synergistic effects cells via cell proliferation, cell migration and tube formation activities against damage by DL-homocysteine (Hcy) and adenosine ²

- **Cell survival**

Nine combination ratios screened for cell protective effects on human cardiovascular endothelial cells. Danshen-Tienchi ratio 6:4 synergistically protected from Hcy – adenosine – TNF and oxidative stress (H₂O₂) -mediated cell injury ³

Human trials

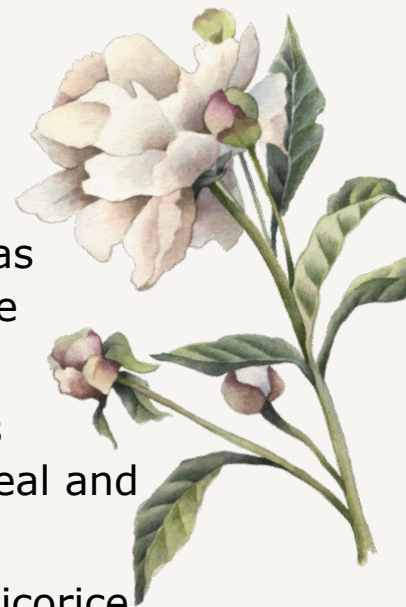
- **Hypertension:** Meta-analysis (2021) found Compound Danshen Dripping Pills (CDDP) combined with conventional antihypertensives superior to conventional antihypertensive drugs alone ¹
- **CHD:**
 - Meta-analysis (2021) found CDDP combined with aspirin had a superior effect on hemorheology and blood lipids in middle-aged and elderly patients with CHD ²
 - Overview of SRs (2015) suggested benefits for patients with CHD, such as improving symptoms and electrocardiogram (ECG) results, with few adverse reactions, while benefits in endpoints were unproved ³
 - SR (2012) found CDDP more effective than isosorbide dinitrate (ISDN) in treating coronary heart disease angina pectoris ⁴



1. Chen *et al.* Chin J Chin materia medica. 2021;46(10):2578-87
2. Liu *et al.* Front Pub Health 2012;9:664841
3. Luo *et al.* AM J Chin Med 2015;43(1):25-43
4. Jia *et al.* Int J Cardiol 2012;158(3):330-40

Paeonia and licorice

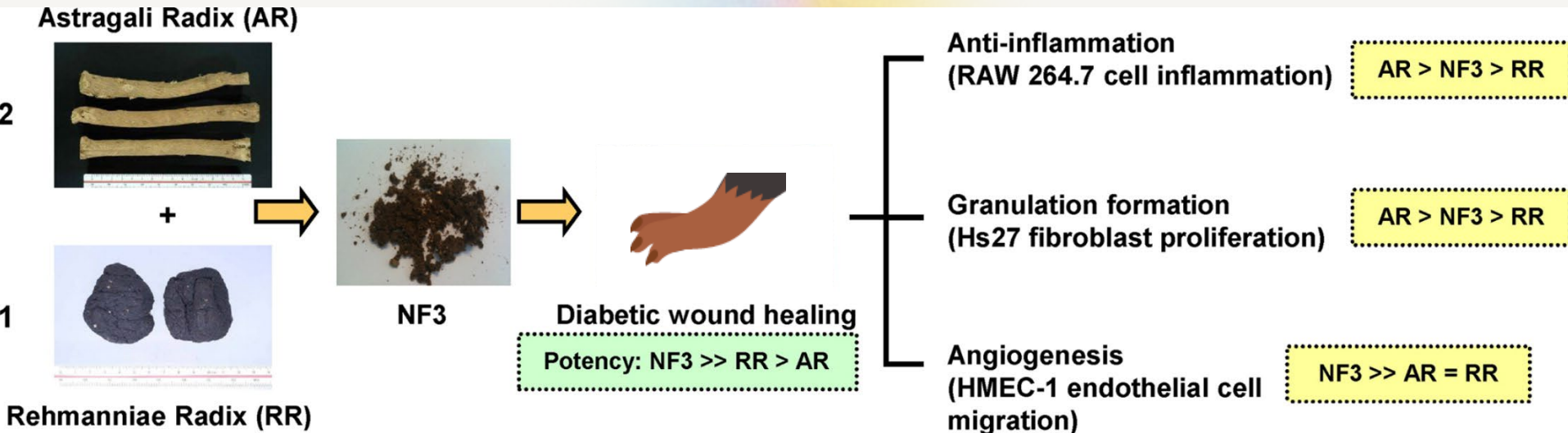
- 'Potentiation' of therapeutic efficacy is described in a formula known as Shaoyao Gancao Decoction (*P. lactiflora* root with *G. uralensis*) for the treatment of pain ¹
- The formula nourishes the liver, relaxes spasm, and relieves pain. It's used for many causes of pain, particularly adenomyosis, dysmenorrhea and abdominal pain, muscle spasm and pain, irritable bowel ¹
- Key active constituents include paeony glycosides (paeoniflorin) and licorice flavonoids (liquiritin) ²
- A study in a rat neuropathic pain model compared individual herb extracts against the combination. Individual extracts produced analgesic effects, but the combination demonstrated a synergistic effect with paeony glycosides and licorice flavonoids at a ratio of 3:1 ³



1. Che *et al.* Molecules 2013;18:5125-41
2. Zehua *et al.* J Sep Sci 2017;40(12):2558-64
3. Zhang *et al.* Pharm Biol 2013;51(4):455-62

Astragalus and rehmannia

- Widely used in China for treating Type 2 diabetes and its complications
- In the foot ulcer animal model, neither herb at clinically relevant dose (0.98 g/kg) promoted diabetic wound healing. However, when used in combination in the ratio of 2:1, they significantly reduced wound area when compared to water group



Honeysuckle (*Lonicera japonica*) flower and *Forsythia suspensa* fruit

- Said to reinforce each other's actions and are often prescribed together to eliminate heat, wind and toxic components from the body, for the treatment of common cold or flu ¹
- In combination they indirectly suppress virus proliferation via regulating the immune system in hosts and directly by inhibiting virus proliferation through targeting viral proteins essential for the viral life cycle ²
- 2021 systematic review finds inhibition of SARS-COV-2 viral replication plus anti-inflammatory effects. Capsules approved in China for treatment ³



1. Che *et al.* *Molecules* 2013;18:5125-41
2. Wang *et al.* *Integr Biol (Camb)*. 2013;5(2):351-71
3. Liang *et al.* *Phytomed Plus* 1 (2021) 100027

Artemisia annua

- Sesquiterpene lactone artemisinin considered to be the anti-malarial active constituent and widely used as an antiplasmodial drug
- A clinical trial in DRC found decoction of *A. annua* containing far lower levels of artemisinin than isolated drug provided 74% cure rate indicating there is more the artemisia than artemisinin
- Flavonoids in *A. annua* decrease resistance of *Plasmodium* spp. to artemisinin
- Chrysosplenol D, chrysosplenitin, circilineol, casticin, and artemetin significantly lower (by 20%–50%) the half minimal inhibitory concentration (IC₅₀) of artemisinin against *Plasmodium* spp. *in vitro*



Artemisia annua

- Artemisinin is readily and stably extracted by aqueous decoction, flavonoids are best extracted by alcohol
- *In vitro* evidence indicates that only ethanolic and not aqueous extracts are antiplasmodial, but human research on aqueous infusions finds they are effective
- Traditional preparation in Chinese medicine involves soaking combined with wringing or pounding then juicing, leading to extracts with 20 times higher levels of artemisinin than infusion
- Other active constituents: other sesquiterpene lactones, Qinghao acid – a sesquiterpene precursor, rosmarinic and chlorogenic acids



Licorice and aconite



- Licorice reduces cardiotoxic effects of aconite
 - *G. uralensis* prevented increase in pulse frequency of cardiomyocyte cells induced by aconite *in vitro*
 - Adding ginger further increased protective effect
- Licorice eliminated aconite-induced CYP3A4 induction
 - *G. uralensis* increases rate of metabolism of potentially toxic alkaloids in aconite in a rat model

‘There are clear chemical differences between isolated extracts of *Aconitum* and a combination of *G.uralensis* and *Aconitum*, suggesting that the protective effect of *G. uralensis* begins during preparation and is not only due to pharmacologic effects.’

Licorice and.....

A photograph of a glass bowl filled with sliced licorice root, showing the characteristic yellowish interior and reddish-brown exterior. The slices are piled up, and some are scattered on the surface in front of the bowl.

Glycyrrhizin is thought to be an agent that solubilises substances in other herbs to increase their absorption

- Increased solubility of saikosaponins from bupleurum
- May inhibit P-glycoprotein thus allowing increased absorption of other substances

‘*G. uralensis* is the king of guide herbs. It appears in 50% of the 283 formulas in one of the most important materia medica of Chinese medicine known as *The Divine Husbandman’s Classic of the Materia Medica*, compiled between 300 BCE and 200 CE.’

Some mechanisms

During decoction chemical composition may be altered or new compounds formed due to a solvent's polarity, heating effects or changed pH. For example:

- Amount of main volatile chemical components in ligusticum and paeonia, which are commonly used to promote blood circulation and remove stasis, were markedly altered when given together due to the formation of non-volatile, water-soluble salts ¹
- Four new compounds identified in a polygala root and *Acorus tatarinowii* rhizome combination not detected in individual extracts (biological effects not evaluated but may explain changes in pharmacological properties of herb combination) ¹
- Different constituents have affinity to different molecular structures
 - Polyphenols: strong binding ability to proteins or glycoproteins
 - Terpenoids: affinity to cell membranes and therefore, a high potential to permeate through cell walls of the body or bacteria ²

1. Zhou *et al.* Front Pharmacol 2016;7:201

2. Yang *et al.* Fitoterapia 2014;92:133-47

It goes
both ways

The Eighteen Antagonistic Medicaments

<i>Glycyrrhiza</i> root (licorice) is antagonistic to:	<i>Euphorbia pekinensis</i> root <i>Euphorbia kansui</i> root <i>Daphne genkwa</i> flower <i>Sargassum</i> spp. (seaweed)
<i>Aconitum carmichaelii</i> root (aconite) is antagonistic to:	<i>Fritillaria</i> spp. bulb <i>Trichosanthes kirilowii</i> fruit <i>Pinellia ternate</i> rhizome <i>Ampelopsis japonica</i> root <i>Bletilla striata</i> rhizome
<i>Veratrum nigrum</i> root is antagonistic to:	<i>Panax ginseng</i> (ginseng) root <i>Salvia miltiorrhiza</i> root <i>Adenophora stricta</i> root <i>Scrophularia ningpoensis</i> root * <i>Sophora flavescens</i> root <i>Asarum sieboldii</i> herb <i>Paeonia lactiflora</i> root

The Nineteen Contraindicating Medicaments

Sulphur is contraindicated to:	Sodium sulphate
Mercury is contraindicated to:	Arsenic trioxide
<i>Euphorbia ebracteolata</i> root is contraindicated to:	Litharge
<i>Croton tiglium</i> seed is contraindicated to:	<i>Pharbitis purpurea</i> seed
<i>Eugenia caryophyllata</i> flower bud is contraindicated to:	<i>Curcuma</i> spp. root
Sodium sulphate is contraindicated to:	<i>Sparganium stoloniferum</i> rhizome
<i>Aconitum carmichaelii</i> and <i>A. kusnezoffii</i> roots are contraindicated to:	Rhinoceros horn
<i>Panax ginseng</i> root is contraindicated to:	<i>Trogopterus</i> faeces
<i>Cinnamomum cassia</i> bark is contraindicated to:	Red halloysite

Enhancing drug effects

- Epigallocatechin gallate (EGCG), the most abundant catechin in tea, enhances therapeutic efficacy of temozolomide in patients with glioblastoma. EGCG can cross the blood–brain barrier enough to cause chemosensitisation in a mouse glioma model
- A constituent of holy basil (vicenin-2) combined with docetaxel provides greater anti-tumour effects in prostate cancer than either agent alone (decreased proliferation marker, Ki67 and angiogenic marker-CD3; increased tumour suppressor E-cadherin expression)
- Actein in black cohosh enhances the growth inhibitory effect of digoxin on human breast cancer cells
- Berberine enhances the effect of fluconazole against fluconazole-resistant *Candida albicans*



In summary

- Herbal synergy is a well-established concept with a growing body of scientific evidence to support that it's real
- The development of synergistic formulations has occurred over thousands of years of systematic use and observation
- Traditional medicine still has stacks to teach us!

“Aged ginger is more powerful and spicy”

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