Rehmannia

Rehmannia glutinosa (Gaertn.) Libosch

Family: Orobanchaceae.

Also know as the broomrape family, a family of fl owering plants of the order Lamiales which has about 90 genera and more than 2000 species. The phylogeny (the history of the evolution of a species or group, especially in reference to lines of descent and relationships among broad groups of organisms) and circumscription (the defi nition of the limits of a taxonomic group of organisms, a taxon) of families in Lamiales remains one of the most problematic topics in angiosperm systematics. Many of its genera were formerly included in the family Scrophulariaceae sensu lato (s.l.; 'in a broad sense'). Rehmannia also has longstanding controversies surrounding its systematic placement at both the generic and familial levels. Rehmannia Libosch. ex Fisch. et Mey. is a small genus of six species. Five of the six species are endemic to China with Rehmannia glutinosa extending further to Korea and Japan. Rehmannia was originally included within the genus Digitalis in 1770 and was established by Liboschitz in 1835 because of its corolla shape and fruit dehiscence (the spontaneous opening at maturity of a plant structure to release its contents). Since then, rehmannia has usually been placed in the tribe Digitaleae in Scrophulariaceae. Others have suggested rehmannia be part of subfamily Cyrtandroideae in Gesneriaceae based on reports of its unilocular (single compartment) ovary. On the basis of DNA, morphological and anatomical evidence the current placement of the genus is in neither Scrophulariaceae sensu stricto (s.s.; which means 'in the narrow sense'. Added after a taxon to mean the taxon is being used in the sense of the original author, or without taxa which may otherwise be associated with it) nor Plantaginaceae s.l., to which many other former Scrophulariaceae have been transferred. Earlier molecular studies suggested that its closest relatives were the genera Lancea and Mazus, which have been included in the family Phrymaceae. Subsequently, following recent studies, rehmannia and the genus Triaenophora were found to represent the second nonparasitic branch sister to the remainder of the family Orobanchaceae (including the genus Lindenbergia).[1,2]

Parts Used: Root

Description: Rehmannia is a hairy perennial herb, with reddish-violet tubular fl owers, native to China. This genus is commonly referred to as Chinese Foxglove because of its superfi cial resemblance to the genus Digitalis. It is widely distributed in central China and cultivated in Japan and Korea. It grows on well-drained stony ground along roadsides, in woods, mountain slopes and trailsides from near sea level to 1100 metres.3 The species named glutinosa comes from glutinous, referring to the sticky nature of the root. The plant is 10 to 30 cm tall and the fl eshy orange rhizomes can be up to 5.5 cm in diameter.[4]

Traditional and Empirical Use: Rehmannia has been widely used in traditional oriental medicine for more than 2000 years. Rehmannia was known as dihuang (meaning earth yellow or underground yellow) and disui (earth marrow) at the time the Shennong Bencao Jing (Divine Farmer's Materia Medica - a Chinese book on agriculture and medicinal plants) was written (circa 100 A.D.). It was included in this text among the superior class herbs with this description: "Rehmannia is sweet and cold. It mainly treats broken bones, severed sinews from falls and damaged centre. It expels blood impediments, replenishes bone marrow and promotes growth of muscles and flesh." This description indicates that rehmannia was deemed a herb of restoration. Despite this depiction of its properties rehmannia soon became better known for treating fevers and bleeding. In modern times rehmannia is especially used for treating hormonal disorders such as menopause,

thyroid imbalance and adrenal insuffi ciency.[5]

There are several forms of rehmannia mentioned in Chinese medical literature, two of which are readily available to practitioners today. When the fresh root (xian or xiansheng) is collected it may be put into a decoction with herbs, or it may be juiced to yield ehmannia juice (xian zhi), which was used in ancient times and is rarely mentioned today. The fresh herb and its juice clear away heat, promote salivation and remove heat from the blood to stop bleeding. The fresh root may be subjected to minimum drying, sometimes by burying in warm sand. This material is still used in China but because it is not possible to maintain this moist material in good condition on the herb market it is not available for general use. It is especially used to relieve thirst and frequent urination in cases of feverish disease.

The two forms that are generally available to practitioners everywhere are dried rehmannia root (gan dihuang or gansheng dihuang, commonly referred to as sheng dihuang and, in English, usually called raw rehmannia, unprocessed rehmannia or rehmannia dried rhizome) and cooked or cured rehmannia root (shu dihuang).

Processing method: Methods for producing dried or raw rehmannia from fresh rehmannia vary but basically consist of baking the fresh tubers in an oven at carefully controlled temperatures until the inside turns black, followed by kneading to round masses that are further dried to completion or first sliced and then sun dried to completion. Cured or cooked rehmannia is generally produced by two methods: wine curing and steaming. To produce wine-cured rehmannia, dried rehmannia is first partially rehydrated, followed by mixing with wine (30–50% w/w) in a sealed container and steaming with the container sealed until all wine is absorbed. The tubers are then removed, partially dried, cut into thick slices, and further dried to completion. To produce steam-cured rehmannia, dried rehmannia is first partially rehydrated followed by steaming for hours until the tuber turns black and moist, which is then dried or first sliced into thick pieces and then dried. It is believed the steaming process that yields cooked rehmannia breaks down the ordinary starches in the root to simple sugars. The earliest description of cooked rehmannia is in Lei's Treatise on the Preparation of Medicinal Substances (written during the Southern and Northern Dynasties 420~589 AD). The darkness of the processed rehmannia root may be partly due to oxidation of the iridoid glycosides.[6]

According to traditional practitioners, while rehmannia juice and fresh rehmannia are best at purging fi re, the (dried or uncured) raw rehmannia root has somewhat less of this property but is able to nourish yin (yin means negative, dark and feminine and yang means positive, bright and masculine in Traditional Chinese Medicine [TCM]), blood and essence (i.e., benefi t the marrow). TCM has used dried rehmannia as yin nourishing because of its heat-dispersing and blood-cooling properties in treating conditions related to febrile diseases. The cooked or cured rehmannia root is no longer of cold property but is slightly warm and is commonly used for its blood-tonifying properties and benefi cial effects on yang. The dried root can be further processed by frying the root (scorching) which is said to make it more suited to blood defi ciency fever (rather than yin defi ciency fever), or by charring it which is suited to treating bleeding (applied for the syndrome of yin defi ciency bleeding whereas the fresh rehmannia juice is applied for the syndrome of excess-fi re-induced bleeding). Similarly, cooked rehmannia root can be subjected to scorching or carbonising, the former used to nourish blood and the latter to treat blood-defi ciency bleeding. It has been reported that the cooked root has more simple sugar than the other forms (which may have little infl uence on its effects) and that the dried root has more simple sugars and less polysaccharide than the freshly picked root.

In a review of research on selected herbs first reported in 1975, it was mentioned that raw and cooked rehmannia were compared by the method of thin layer chromatography, which revealed that there were apparent differences in the quantities of ingredients extractable by various solvents between these two rehmannia products, but there was no obvious change in the substances present.[7]

Uncured rehmannia is antipyretic, haemostatic (stops bleeding) and removes latent heat from the blood, used for skin rash, diabetes, low-grade fevers and thirst. The roots are also used as a cardiotonic and diuretic agent. Cured rehmannia has been traditionally prescribed to ease the clinical manifestation of inner ear dysfunction and various clinical situations, including inflammatory diseases, high fever, night sweat, headache and dizziness in Oriental Medicine. It has been used to promote blood production, regulate menstruation, as a blood tonic for anemia, weakness, tinnitus, amenorrhea and metrorrhagia, premature greying of the hair, diabetes and vertigo. Recently, it has been reported that the herb possesses antibacterial and anti-inflammatory properties.[8,9,10]

Constituents: More than 70 compounds including iridoids, saccharides, amino acids and inorganic ions, as well as other trace elements, have been found in rehmannia. Rehmannia is composed of irodoids and iridoid glycosides, including aucubin, catalpol (0.3%-0.5%), ajugol, rehmanniosides A-D, ionone glucosides, jioglutosides and rehmaglutins A-D. Rehmannia is also composed of other glycosides, including the phenethyl alcohol glycosides (jionosides): dihydrocatalpol, leonuride, aucubin, monomelittoside, acteoside, isoacteoside, purpureaside C, echinacoside, cistanosides A and F, RPS-b consisting of galactose, glucose, xylose, mannose and arabinose in a 12:6:2:2:1 ratio; fatty acid esters composed mainly of methyl linoleate, methyl palmitate and methyl n-octadecanoate; B-sitosterol, daucosterol, palmitic acid, succinic acid and cyclic compounds; a rich source of α-galacto-oligosaccharides, especially stachyose; other sugars including sucrose and monosaccharides, trace minerals, 1-ethyl-B-Dgalactoside, mannitol, campesterol, alpha-aminobutyric acid, stigmasterol, vitamin A, norcarotenoids; more than 20 microelements including iron, zinc, manganese and chromium are found in rehmannia. While fresh rehamnnia root, dried rehmannia and cured rehmannia have similar chemical components, a portion of some components of the herb may be changed after processing and result in different pharmacological actions. The iridoid monosaccharide glycoside catalpol is one of the main active principles in the fresh plant material but HPLC determination has shown that the content of catapol in rehmannia decreases markedly after being dried and processed. This change of content is related to acidic and alkaline conditions. No marked changes were observed in boiling water or saccharide solution. Glycoside A is an iridoid disaccharide glycoside that is more stable than catalpol. In the course of chemical investigation on the dried roots of rehmannia, a new eremophilane-type metabolite, named remophilanetriol was encountered, together with aeginetic acid.[11,12,13,14]

Pharmacological Activity: The pharmacological actions of rehmannia have not been significantly investigated so traditional use is used. Often rehmannia is used in combination with other herbs, making it difficult to assess which effects are truly due to rehmannia or other ingredients. Rehmannia only studies are recorded here. This monograph will focus on uncured rehmannia studies. In view of the pharmacology, due to the complex constituents of rehmannia, it is usually believed that broad pharmacological actions are mediated at different levels through multi-links and multi-targets.[15]

Uncured vs. cured: The processing of biological raw materials is considered to have an important role in the therapeutic application of TCM. The root of rehmannia has to be processed by nine cycles of rice wine immersing, steaming and drying before being used

in clinical applications. In order to understand the chemical changes resulting from the processing, a comprehensive analysis of rehmannia root was made using (1)H-NMR (proton nuclear magnetic resonance) and Fourier transform (FT)-mass spectrometry in combination with multivariate data analysis. After (1)H-NMR and principle component analysis, hydrolysis was found to be the major chemical process during the treatments. Catalpol, raffi nose and stachyose levels gradually decreased during processing, whereas monosaccharides including galactose and glucose were found to be higher in processed roots. The metabolic profile changed gradually through the processing cycles although the differences became smaller after the fifth processing cycle. During the processing, the number and signal intensity of the smaller glycosides were increased. Therefore, the results indicate that the fresh rehmannia root is rich in polysaccharides, which are hydrolysed during the processing. This partially explains why different types of rehmannia possess a wide variety of pharmacological uses, and different clinical uses, in TCM.[16]

A Japanese study showed that effects of 50% ethanolic extract from steamed rehmannia can prevent obstruction in the peripheral microcirculation of various chronic diseases through the improvement of haemorheology (the study of flow properties of blood and its elements).[17] The scientists then went on to further investigate the relation between constituents and the effects of haemorheology with the processing of rehmannia root. The processing of dried or steamed root from crude root decreased the contents of stachyose and iridoid glycoside catalpol and increased that of manninotriose. The changes of the contents of carbohydrates and catalpol made it possible to estimate the quality of rehmannia root by processing. On the other hand, the change of pharmacological activities with the processing was investigated and the results suggested that the crude or dried root and steamed root of rehmannia showed different pharmacological activities, and the quality of rehmannia root by processing may be estimated by investigation of correlation between the changes of constituents and improvable effects of haemorheology.[18]

Anti-infl ammatory activity: Rehmannia is showing promise as a medication for the treatment of psoriasis after it featured in a 2013 review providing assessments of the effi cacy and safety of oral forms of phytotherapy in psoriasis management and discussing the pharmacological actions of the plants that have been frequently used in clinical trials. Experimental studies on extracts and compounds derived from rehmannia have reported anti-infl ammatory, antiproliferative and other actions of relevance to psoriasis management.[19]

A 2013 study was conducted to investigate prevention of bone loss by a standardised dried root of rehmannia in an ovariectomised (OVX) rat model of osteoporosis. This study showed that rehmannia is able to prevent OVXinduced bone loss without infl uencing hormones such as oestrogen.[20]

It has been demonstrated that rehmannia inhibits the secretion of both interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha) from mouse astrocytes. These cytokines are well known regulators of bone metabolism. IL-1 is known as a highly potent bone resorptive cytokine. TNF-alpha appears to synergise with IL-1 in its ability to increase bone resorption.21,22 In vitro and in vivo studies of the aqueous extract of rehmannia demonstrated the antiosteoporotic effect of the plant. In vitro fi ndings showed a signifi cant increase in both the proliferation and ALP activity of osteoblasts as well as in the expression of the bone-related genes. In an animal model, cured rehmannia by oral route prevented osteoporotic bone loss induced by ovariectomy. Rehmannia alleviated the decrease in the trabecular bone mineral density and increased cortical bone thickness and trabeculation of the bone marrow spaces.[23,24]

Immune activity: A 2013 study has provided valuable information that rehmannia glutinosa polysaccharide (RGP) possesses strong immune enhancement activity, which provides the theoretical basis for further experiment. The aim of the study was to investigate the immunomodulatory effect of RGP on murine splenic lymphocyte and bone marrow derived dendritic cells (DCs). The results showed RGP significantly stimulated lymphocyte proliferation and the growth rate of T cells was more signifi cant.[25]

Water decoction of radix rehmanniae signifi cantly accelerated Con A-activated mice lymphocyte biosynthesis of DNA and protein in the spleen and signifi cantly enhanced interleukin-2 production.[26]

Juice decoction of fresh rehmannia root and rehmannia dried rhizome given by oral administration has an enhancement of body non-specifi c immunity and the functions of T and B lymphocytes of the spleen in Yin defi ciency –like mice. Aqueous extract of radix rehmanniae reversed accentuation of immune function in Yin-defi ciency mice model.[27]

Oral administration (10-500 mg/kg) of several fractions from the ethanol extract of rehmannia had an immune modulating effect in an experimental model. A Japanese study separated a series of phenethyl alcohol glucosidelike compounds from radix and prepared rhizome of rehmannia, which had the effect of immunosuppression, and among them acetoside had a strong effect. The others were jionosides A (1) (4) and B (1) (5), isoacteoside, purpureaside C, echinacoside, and cistanosides A and F.[28]

Adrenal cortex function: Uncured rehmannia (3g/kg) given by oral administration for two weeks to rabbits chronically treated with the glucocorticoid dexamethasone signifi cantly raised serum corticosterone levels (this is a model of adrenal depletion). Continuation of treatment resulted in further increases. Rehmannia treatment also prevented, or reversed, morphological changes in the pituitary and adrenal cortex, appearing to antagonise the suppressive effect of glucocorticoids on the hypothalamicpituitary-adrenal axis. Rehmannia may work by inhibiting the negative feedback from the glucocorticoid to the pituitary gland.[29]

In a study that was conducted to evaluate the effects of rehmannia in the treatment of sheehan's Syndrome patients showed marked improvement in clinical symptoms. The authors conclude that rehmannia has stimulative effects on the hypothalamic-pituitary system. Sheehan's syndrome, also known as postpartum hypopituitarism or postpartum pituitary necrosis, is hypopituitarism (decreased functioning of the pituitary gland), caused by ischemic necrosis (decrease of blood supply) due to blood loss and hypovolemic (decreased blood volume) shock during and after childbirth. The study reports the clinical observations of therapeutic effects of rehmannia on 10 patients with Sheehan's syndrome. Eight patients were given 90g of cleaned and finely chopped rehmannia root and 900mL of water were boiled down to 200mL. This was the daily amount given to eight of 10 patients in three day courses with an intermission of 3, 6 and 14 days. After a one-month cessation, the second round of treatment commenced. In the other two patients the dose of rehmannia was 45 to 50g daily, given in 5-day courses with an intermission of five days each time. Patients were treated with rehmannia for 2 to 5 months and it was observed that their signs and symptoms improved and their physical strength and state of health also improved (quantitative data is unavailable). Two patients were bedridden before therapy; after treatment, they were out of bed, moved about, and were able to perform their daily work. In three cases the uterus returned to normal size and one of them was able to menstruate

again. Increased excretion of 17 ketosteroids and 17 hydroxycorticoids was found in all ten cases. Limitations include lack of a control group.[30]

Antidiabetic activity: Rehmannia is regarded as an effective drug for the treatment of diabetes in TCM. The effects of dried rehmanniae radix extract were investigated using a diabetic nephropathy model induced by streptozotocin after nephrectomy (kidney removal) in rats, suggesting that rehmannia may be useful as a therapeutic agent for inhibiting the progression of diabetic neuropathy. The results showed that this crude drug reduced the magnitudes of the increases in glucose, urea nitrogen, 5-hydroxymethylfurfural and thiobarbituric acid-reactive substance levels, with the effects being most marked in the high blood glucose group.[31]

A recent study investigated the effects of an ethanolic extract of rehmannia individually as well as in combination with the oral hypoglycemic agent, metformin in streptozotocin (STZ)-induced diabetic Wistar rats. A reduction in plasma glucose levels caused by the herb was not as signifi cant as metformin compared to the diabetic control ($p < 0.05$). However the rehmannia treated group showed reductions in plasma C-reactive protein (CRP) levels compared to the diabetic controls ($p < 0.05$) as well as metformintreated group ($p < 0.05$). An enhanced reduction in CRP concentration was observed in the group receiving both herb and metformin compared to metformin-treated group ($p < 0.05$). Reduction in CRP levels suggests an anti-inflammatory activity of the herb.[32]

The hypoglycemic effects of water extract and stachyose extract (Part III) from rehmannia were investigated by oral administration to normal, glucose and adrenaline-induced hyperglycemic and alloxan-induced diabetic rats. The results suggested that Part III, which is mainly composed of stachyose, had a signifi cant hypoglycemic effect.[33]

According to a study rehmannia radix is frequently used for the improvement of chronic complications induced by diabetes, e.g., nephropathy, neuropathy, retinopathy, and cataract. It was postulated that rehmannia contains 18 phenyl alcohol glycosides that inhibit aldose reductase and thus may be useful for the treatment of diabetic complications.[34]

Haemostatic activity: Dried and cured rehmannia can promote the recovery of blood deficient animals and proved markedly helpful in the generation of blood following a study in treating haemorrhagic anaemic mice and in fostering bone marrow haematopoietic cells.[35]

Blood clotting in mice induced by aspirin was inhibited by oral administration of juice decoction of fresh rehmannia or decoction of dry rehmannia. The action of fresh rehmannia juice was stronger than that of dry rehmannia decoction.[36]

Anti-tumour activity: A study on cell proliferation and apoptosis in rat and/or human hepatocellular carcinoma (HCC) cells found that crude hot water-extracted rehmannia dose-dependently inhibited proliferation of rat cell lines and stimulates p53-mediated apoptosis in HCC cells.[37]

Rehmannia polysaccaride b plays a part in the maintenance of body homeostasis and possesses some antineoplastic activity. It has been shown to signifi cantly enhance T lymphocyte proliferation in vivo in tumour bearing mice and exerted an inhibition on tumour growth, the mechanism may be related to improving the production of the antigen lyt-2+ cytotoxic T-lymphocytes and its cytotoxity.[38]

Low-molecular-weight rehmannia polysaccharides markedly increased p53 gene expression

in Lewis lung cancer tissue in an in vivo study and this is one of the mechanisms of antitumor activity.[39]

Cardiovascular activity: Uncured rehmannia had a protective effect on experimentally included cytotoxicity in cardiac cells in vitro. A study examining the effect of a water extract of Saeng-Ji-Hwang (SJH: Radix Rehmanniae) on cardiac muscle cells found that SJH-associated Mn-SOD and intracellular glutathione are important factors in the mechanism of the SJH-induced protective mechanism in H9C2 cardiac muscle cells.[40]

Actions: Antipyretic (reduce fever), adrenal trophorestorative (tonic), antihaemorrhagic, anti-infl ammatory, mild laxative.

Indications: Although thorough clinical trials are lacking, rehmannia has been used to treat: menopausal symptoms; rheumatoid arthritis; asthma; urticaria, skin rashes; chronic nephritis (infl ammation of the kidney); fevers; adrenal function support; constipation; diabetes; insomnia; to prevent the suppressive effects of corticosteroid drugs on endogenous (within the body) levels.

Toxicity: Uncured rehmannia showed no mutagenic potential when tested in vivo and with the Ames test (a method that uses bacteria to test whether a given chemical can cause cancer).[41]

Use in Pregnancy: Not recommended due to lack of suffi cient data. In TCM its use is endorsed.[42]

Contraindications: Avoid in patients taking therapeutic immunosuppressives (for treatment of autoimmune disease). Rehmannia is contraindicated in transplant recipients. Avoid in patients with diarrhoea and lack of appetite due to possible irritation of gastrointestinal tract by rehmannia. Avoid where there is a known allergy/hypersensitivity to rehmannia, any of its constituents or any members of the Orobanchaceae family.[43]

Drug Interactions: Concomitant use of rehmannia could result in induction of the drug-metabolising enzyme cytochrome P450 3A4 (CYP3A4), leading to a reduced effi cacy of drugs that are CYP3A4 substrates and have a narrow therapeutic window. Herb-drug interactions between rehmannia and various CYP3A4 substrates can occur. Further research to investigate the clinical relevance of the interactions caused by rehmannia is required.[44]

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