

REHMANNIA GLUTINOSA – A PHYTO-PHARMACOLOGICAL REVIEW

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Summary

Rehmannia glutinosa, a widely used traditional Chinese herb, belongs to the family of Scrophulariaceae, and is taken to nourish Yin and invigorate the kidney in traditional Chinese medicine (TCM) and has a very high medicinal value. In recent decades, a great number of chemical and pharmacological studies have been done on *Rehmannia glutinosa*. More than 70 compounds including iridoids, saccharides, amino acid, inorganic ions, as well as other trace elements have been found in the herb. Studies show that *Rehmannia glutinosa* and its active principles possess wide pharmacological actions on the blood system, immune system, endocrine system, cardiovascular system and the nervous system. Currently, the effective monomeric compounds or active parts have been screened for the pharmacological activity of *Rehmannia glutinosa* and the highest quality scientific data is delivered to support the further application and exploitation for new drug development.

Keywords: *Rehmannia glutinosa*; Chemical component; Pharmacological action.

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Introduction

Rehmannia glutinosa Libosch. (Dihuang), a comprehensive traditional Chinese medicinal herb, is in the family of Scrophulariaceae. It was recorded in Chinese medical classics “Shennong’s Herba” and is thought as a “top grade” herb in China¹. In terms of the processing method, there are three types of *Rehmannia glutinosa* used as medicinal materials: fresh rehmannia root (Xian Dihuang), with the effect of clearing away heat and promoting salivation, removing heat from the blood to stop bleeding; Rehmannia dried rhizome (Sheng Dihuang), with the effect of removing pathogenic heat from blood, nourishing Yin (Yin means negative, dark, and feminine and Yang, positive, bright, and masculine in traditional Chinese medicine, TCM) and promoting the production of body fluids; and prepared rehmannia root (Shu Dihuang) with the effect of nourishing Yin and supplementing the blood and benefiting the marrow, etc.². *Rehmannia glutinosa* is basically thought as a drug for nourishing Yin and tonifying the kidney (which has the functions of storing essence, dominating growth, development and reproduction and regulating water metabolism and has a close relationship with the neuroendocrine system in the body by TCM theory), suggesting that *Rehmannia glutinosa* has varied pharmacological actions and chemical compositions. In recent decades there have been many reports of the pharmacological functions and activities of *Rehmannia glutinosa* and its active principles on the blood system, immune system, endocrine system, cardiovascular system and nervous system and of anti-tumor, anti-senescence, etc.).

Rehmannia refers to the root of *Rehmannia glutinosa*, a herb of the Scrophulariaceae family. The species named glutinosa comes from glutinous, referring to the sticky nature of the root. *Rehmannia glutinosa* is distributed in the provinces of Henan, Shandong, Shan’xi, Shanxi, Hebei, Liaoning, Inner Mongolia, Jiangsu, Zhejiang, Hunan, Hubei, Sichuan in China; mainly cultivated but also wild in places like mountain slopes and trails, near sea level to 1100 m. *Rehmannia glutinosa* produced in Wen County, Meng County, Bo’ai County, Qinyang County in Henan province is called *Rehmannia glutinosa* f. *hueichingensis* or Huai Dihuang, the genuine medicinal herb. The root of the wild *Rehmannia glutinosa* is slight and often used as fresh rehmannia root. Professor Zhao Bing-Huang and Shi Zhi-Long named *Rehmannia glutinosa* f. *hueichingensis* as *Rehmannia glutinosa* Libosch. Var. *hueichingensis* Chao et Schih according to the characteristics of its massive roots and sparse raceme of flowers. Thereafter, Professor Xiao Pei-Geng claimed that there were less morphological differences between *Rehmannia glutinosa* f. *hueichingensis* and *Rehmannia glutinosa* and then reset it as a new forma with a scientific name of *Rehmannia glutinosa* f. *hueichingensis* (Chao et Schih) Hsiao. Considering its major species, both Flora of China and Pharmacopoeia of People’s Republic of China merged the above three scientific names as *Rehmannia glutinosa* (gaertn.) Libosch. That is, both wild *Rehmannia glutinosa* and cultural *Rehmannia glutinosa* f. *hueichingensis* in Henan province use the same scientific name in China³.

Herbs of *Rehmannia glutinosa* are 10–30 cm tall, densely villous with glandular and eglandular hairs. Rhizomes to 5.5 cm, fleshy, stems purple–red, basal leaves usually rosulate. Stem leaves are gradually or abruptly decreasing in size or reduced to bracts upward; leaf blade ovate to narrowly elliptic, 2–13 x 1–6 cm, base tapering, margin irregularly crenate or obtusely serrate to toothed.

Flowers are axillary or in terminal racemes. Pedicel 0.5–3 cm, slender and ascending. Bracteoles absent. Calyx 1–1.5 cm, 10-veined; lobes 5, oblong-lanceolate, ovate-lanceolate, or subtriangular, 5–6×2–3 mm, rarely 2 lower lobes further lobed. Corolla 3–4.5 cm, white villous; tube narrow; lobes outside purple–red, inside yellow–purple, 5–7×4–10 mm, apex obtuse to emarginate. Stamens 4; anther locules oblong, ca. 2.5 mm, base divaricate. Ovary 2-loculed when young, 1-loculed with age. Capsule ovoid to narrowly ovoid, 1–1.5 cm. Fl. and fr. April–July⁴.

PHYTOCHEMICAL STUDIES

Chemical studies of *Rehmannia glutinosa* established a foundation of pharmacological research. About 70 monomeric compounds have been separated from *Rehmannia glutinosa*, among them saccharides including polysaccharides, oligosaccharides, especially stachyose and monosaccharide, are with a largest content⁵. The majority in quantity is iridoid compounds such as catalpol, dihydrocatalpol, others included are phenol glycoside ionone, flavonoid, amino acid, inorganic ions and microelement, etc. The content of some components may be changed after the drug processing and results in their differences of pharmacological actions though fresh rehmannia root, rehmannia dried rhizome and prepared rehmannia root have similar chemical components. More recently DNA sequence analysis technique was used in phytochemical studies of *Rehmannia glutinosa* and will be useful for chemotaxonomy of the species of the genus⁶.

Iridoids, monoterpenes and glycosides

Since the Japanese scientist Kitagawa et al. reported the first iridoid glycoside monomer, catalpol⁷ from *Rehmannia glutinosa* f. *hueichingensis*, more than 33 iridoid monomers, which are the most important components in the herb, as well as monoterpenes and glycosides have been separated and identified: dihydrocatalpol, danmelittoside⁸, acetylcatalpol, leonuride, aucubin, melittoside, rehmaglutin A, B, C, D^{9,8,10}, cerebroside glutinoside, rehmannioside A, B, C, D¹¹, rehmaionoside A, B, C, rehmapicroside¹², purpureaside C, echinacoside, cistanoside A, F, jionoside A1, B1¹³, jioglutoside A, B, geniposide, ajugoside, 8-epiloganic acid, ajugol, 6-O-vanilloylajugol, 6-O-p-coumaroylajugol, 6-O-E-feruloylajugol, 6-O-Z-ferulylajugol, 6-O-(4-O-L-rhamnopyranosyl), vanilloyl-ajugol¹⁴, methoxyrehmagluti, 6,8-dihydroxyboschnialactone D, E, rehmaglutin¹⁵, jioglutin A, B, C, jioglutoside, jiofuran¹⁶, jionoside A2, B2, C, D, E, 2'-acetylacteoside, martynoside¹³.

Catalpol is the main active principle of radix of *Rehmannia glutinosa* Libosch. and belongs to iridoid monosaccharide glycoside, which has the hypoglycemic, diuretic and laxative effects, its water soluble component has antiphlogistic, liverprotecting effects; the fat-soluble component has an anti-anoxia effect, its water- and alcohol-extract posses immune regulative effect¹⁷. It is found that the content of catalpol in the genuine *Rehmannia glutinosa* f. *hueichingensis* from Wen County in Henan province is higher than that of *Rehmannia glutinosa* Libosch. produced in other areas in China by Laminae scanning method and HPLC, with the highest catalpol content of 5.95 mg/g, but it is lower in that from Xiangfeng County in Shanxi province with the contents of 0.143, 0.85

and 0.285 mg/g, respectively, suggesting that the genuine drug is very necessary in the preparations of *Rehmannia glutinosa*^{17,18}. Further study showed that the difference of the content of catalpol demonstrates that the different action of three types of *Rehmannia glutinosa* supplies a scientific basis for its clinical application¹⁹. Reports also showed that by comparing the catalpol contents in the different conditions of sand covered, refrigerated and cold storage, the content of catalpol in sand covered *Rehmannia glutinosa* did not decrease, thus sand covered method is thought of as good for the storage of *Rehmannia glutinosa* radix²⁰.

There is some relationship between catalpol content and shape of root tuber of radix of *rehmannia glutinosa* Libosch., the larger the root, the higher the content of catalpol, and vice versa. There is a good positive correlation between catalpol content and the diameter of root tuber, so it is important that in the cultivate process the root tuber should be kept podgy. Usually the robust root tuber of *Rehmannia glutinosa* is often used in the processing, but the thinnish and venter root with about 16–27% catalpol of the total content was given up, so the remaining root should be used to the greatest extent^{21,22}.

Glycoside A is also an important iridoid glycoside compound from *Rehmannia glutinosa* and belongs to iridoid disaccharide glycoside and is more stable than catalpol. The content of glycoside A in rehmannia dried rhizome is not less than 1.0 mg/g by laminae scanning method and supplies a method for controlling quality of *Rehmannia glutinosa*²³.

Other glycosides

Daucosterol, 1-ethyl- β -D-galactoside, acteoside¹¹, isoacteoside¹³ were isolated from *Rehmannia glutinosa*. Subsequently, forsythiaside, 3,4-dihydroxy-O- β -d-glucopyranosyl-(1 \rightarrow 3)-4-O-caffeoyl- β -D-glucopyranoside, 3,4-dihydroxy- β -phenethyl-O- β -d-glucopyranosyl-(1 \rightarrow 3)-O- α -L-rhamnopyranosyl-(1 \rightarrow 6)-4-O-caffeoyl- β -D-glucopyranoside (24), 3,4-dihydroxy- β -phenethyl-O- α -L-rhamnopyranosyl-(1 \rightarrow 3)-O- β -D-glucopyranosyl-(1 \rightarrow 6)-4-O-caffeoyl- β -D-glucopyranoside were also isolated²⁵.

Saccharides

Three types of monosaccharides were extracted from *Rehmannia glutinosa*: glucose, galactose and fructose; five types of oligosaccharides were also found: mannitol and sucrose, raffinose, mannotriose, stachyose and verbascose^{7,26,5,27,10,28,11}. In addition, *Rehmannia glutinosa* polysaccharide a, b were separated and identified. Stachyose is an oligosaccharide and possesses the effects of cancer prevention, anti-cancer and keeping good health. Fresh rehmannia root contains the highest content of 64.9% stachyose of the total sugar⁹, but only 30% is in rehmannia dried rhizome. *Rehmannia glutinosa* polysaccharide b is an immunological and tumor-inhibiting active principle.

Amino acids and microelements

Fresh rehmannia root contains more than 20 amino acids. The content of arginine is the highest. Rehmannia dried rhizome possesses 15 amino acids and alanine is the highest^{27,10}. More than 20 microelements including iron, zinc, manganese, chromium, etc., can be contained in *Rehmannia glutinosa*²⁹.

Organic acids

By GC–MS method, benzoic acid, caprylic acid, phenylacetic acid, nonanoic acid, decanoic acid, cinnamic acid, 3-methoxy-4-hydroxybenzoic acid, lauric acid, tetradecanoic acid, pentadecanoic acid, oleic acid, palmitic acid, heptadecanoic acid, linoleic acid, stearic acid, nonadecanoic acid, eicosanic acid, heneicosanoic acid and docosanoic acid were identified¹⁷, palmitinic acid and succinic acid were separated³⁰.

PHARMACOLOGICAL STUDIES

Hemostasis

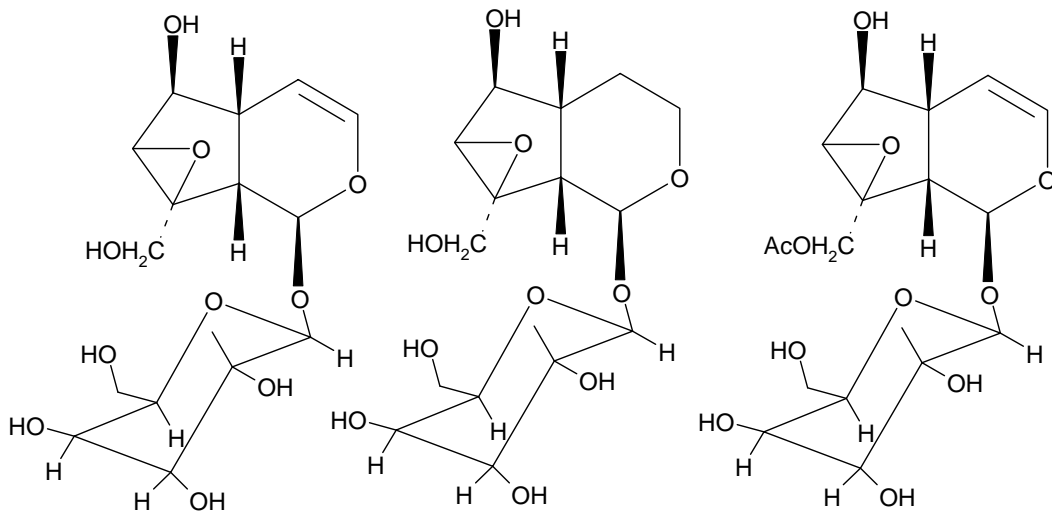
According to TCM theory, *Rehmannia glutinosa* has the effect of hemostasis, removing heat from the blood and enriching the blood, in other words, it affects hemorheology of hematopoietic system.

Water extract of radix rehmanniae, prepared rhizome of rehmannia showed an improvement of proliferation and differentiation on hematopoietic stem cells and bone marrow erythropoiesis progenitor cells³¹. Both fresh rehmannia root and rehmannia dried rhizome showed an antagonism of coagulation time prolonged by aspirin, whereas the effect of fresh rehmannia root was stronger than that of rehmannia dried rhizome³².

Effects on hemorheology

Report showed that effects of 50% ethanolic extract (JR-ext, 200 mg/kg, p.o.) from Chinese Rehmanniae Radix can prevent an inducement of impediment in the peripheral microcirculation of various chronic diseases through the improvement of hemorheology³³. They further investigated the relation between constituents and the effects on hemorheology with processing of root of *Rehmannia glutinosa*. The processing of dried or steamed root from crude root decreased the contents of stachyose, iridoid glycoside and catalpol and increased that of mannanotriose, the changes of the contents of carbohydrates and catalpol made it possible to estimate the quality of rehmanniae radix by processing. Also, the change of pharmacological activities with the processing was investigated and the results suggested that the crude or dried root and prepared rehmannia root showed different pharmacological activities, and the quality of rehmanniae radix by processing may be estimated by investigation of the correlation between the changes of constituents and improvable effects of hemorheology³⁴.

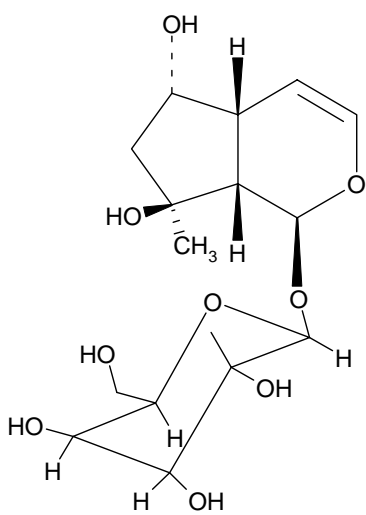
The anti-thrombic properties of the Korean herbal medicine, Dae-Jo-Hwan (DJW), which is consisted of 11 herbs (of 24% Rehmanniae radix), its extracts have the protection on the ischemic infarction induced artificially, which might be related to their inhibitory effects on DIC, platelet coagulation and thrombic action³⁵.



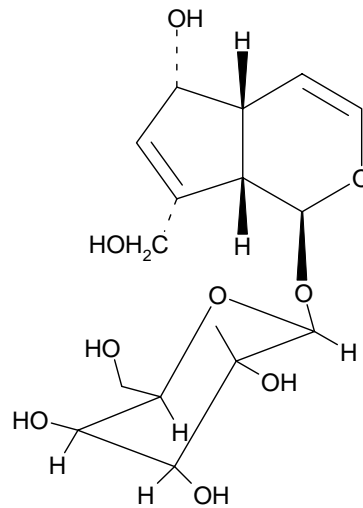
Catalpol

Dihydrocatalpol

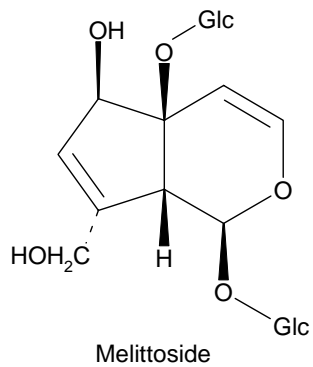
Acetylcatalpol



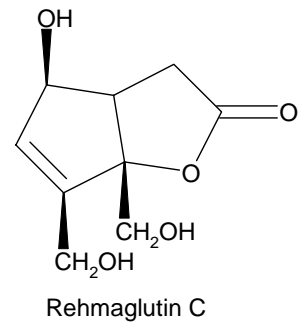
Leonuride



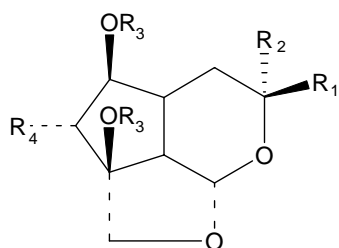
Aucubin



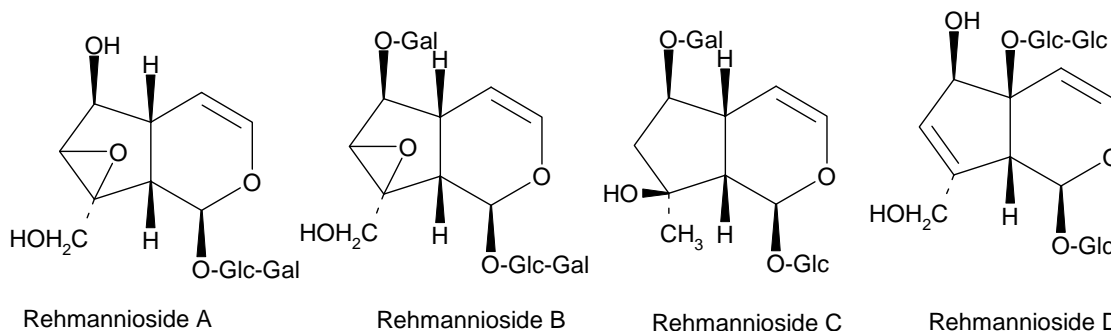
Melittoside



Rehmaglutin C



Rehmaglutin A: $R_1 = R_2 = R_3 = H$, $R_4 = OH$
 Rehmaglutin B: $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = Cl$
 Rehmaglutin D: $R_1 = R_2 = R_3 = H$, $R_4 = Cl$



Effects on hemopoiesis of bone marrow

Liu et al. reported the effects of *Rehmannia glutinosa* polysaccharide (RGP) on the bone marrow hematopoietic system; the results suggest that *Rehmannia glutinosa* polysaccharide can stimulate hemopoiesis function by administration of some doses in mice^{36,37}. In addition, they also found that *Rehmannia glutinosa* oligosaccharide can activate body tissue through a great variety of approaches, especially some cells in hematopoietic microenvironment, promote the secretion of a great variety of hemopoiesis growth factors (CFU-GM, CFU-E and BFU-E) to enhance proliferation of hemopoiesis progenitor cell in SAMP8 mice³⁸⁻⁴⁰.

The other investigators demonstrated that *Rehmannia glutinosa* glycoside d can significantly increase the numbers of leucocyte, thrombocyte, reticulocyte and the content of bone marrow DNA and body weight in blood deficiency in mice induced by thyroid and reserpine (p.o.) and in cyclophosphamide, i.p. to mice⁴¹.

Anti-tumor effects

Chao et al. found that crude hot water-extracts of *Rehmannia glutinosa* (RGE, 2–10 g/L) showed a dose-dependent inhibition on the proliferation of H-4-II-E cells and HA22T/VGH cells and RGE (5–10 g/L) inhibited the proliferation and stimulated p53-mediated apoptosis in HCC cells⁴². *Rehmannia glutinosa* polysaccharide b possesses some antineoplastic activity and participates in the maintenance of body homeostasis, further study demonstrated that *Rehmannia glutinosa* polysaccharide significantly enhanced T lymphocyte proliferation *in vivo* in tumor bearing mice and exerted an inhibition on tumor growth⁴³, the mechanism may be related to the improvement of lyt-2+CTL production and its cytotoxicity⁴⁴.

Kohji et al.⁴⁵ found that the growth of Hela cell was suppressed by *Rehmannia glutinosa* extracts with concentration-dependent way and proposed that the combination of anti-cancer drugs with *Rehmannia glutinosa* extracts contributes to the enhancement of clinical treatment⁴⁵. Quantitative polymerase chain reaction and auto radiography methods were used to detect the effect of low-molecular weight *Rehmannia glutinosa* polysaccharide (LRPS) on P53 gene expression level in Lewis pulmonary carcinoma tissue, the results showed that LRPS markedly increased P53 and C-fos gene expression increased intracellular gene expression in Lewis pulmonary cancer tissue⁴⁶⁻⁴⁸.

Effects on immune system

It is believed from the reported studies that different prepared products or solvent extracts from *Rehmannia glutinosa* possess different effects on the immune system. Water decoction of prepared rhizome of rehmannia increased the number of mice periphery leucocytes⁴⁹; water decoction of radix rehmanniae significantly accelerated Con A-activated lymphocyte biosynthesis of DNA and protein in the spleen and significantly enhanced interleukin-2 production⁵⁰. Juice decoction of fresh rehmannia root and rehmannia dried rhizome given by oral administration has an enhancement of body non-specific immunity and the functions of T and B lymphocytes of spleen in *Yin* deficiency-like mice. Aqueous extract of radix rehmanniae reversed an accentuation of immune function in *Yin*-deficiency mice model⁵¹. Aqueous extract of prepared rehmannia root (RGAE) may inhibit TNF-alpha secretion by inhibiting IL-1 secretion and that RGAE has an anti-inflammatory activity in the central nervous system curing some pathological disease states⁵². Further investigation showed that RGAE may be beneficial in the regulation of immediate type allergic reaction⁵³.

It is concluded from the above that there are both immune-enhanced and immune-suppressed substances in *Rehmannia glutinosa*. Sasaki et al. separated a series of phenethyl alcohol glucoside-like compounds with the effect of immunosuppression from radix rehmanniae and prepared rhizome of rehmannia, and among them acetoside has a strong effect⁵⁴. Chen et al. reported RPS-b also had an immunoenhancing effect^{43,44}. Tomoda et al. separated two acids heterosaccharide, rehmannan SA, SB from water decoction of radix rehmanniae with molecular masses of 6.4×10^4 and 7.9×10^4 , showed a remarkable reticuloendothelial system-potentiating activity in a carbon clearance test⁵. *Rehmannia glutinosa* polysaccharide (10, 20 ml/kg/d \times 6d, i.p.) significantly enhanced the proliferation of T, B lymphocytes of spleen in aged mice, phagocytosis of peritoneal macrophage and the cytotoxic effect against S180, TNF sensitive cells WEHI164.13⁵⁵. Other authors reported *Rehmannia glutinosa* polysaccharide possessed an immunity excitement and anti-senescence effect⁵⁶; *Rehmannia glutinosa* oligosaccharide (RGOS, 20, 40 mg/kg, i.p.) can promote antibody production of B lymphocytes in immunosuppressed mice and enhance the splenocyte proliferation and cellular immunity in tumor bearing mice which was closely related to the immunological function state of the animals⁵⁷.

Effects on cardiovascular system

Rehmannia glutinosa possesses a strong biological activity on cardiovascular system and its different extracts exert different effects.

Rehmannia glutinosa inhibited the heart function and self discipline motorial of atria in a Guinea pig, the foundation of this effect linked to adenosine with a content of 0.15 mg/g in radix rehmanniae⁵⁸. As for the effects of *Rehmannia glutinosa* on blood pressure, Chang et al. reported that water extract of *Rehmannia glutinosa* possessed a bilateral effect on blood pressure⁵⁹, decoction of rehmannia dried rhizome suppresses the increased activity of the brain Ca^{2+} , Mg^{2+} -ATP enzyme in isoprenaline-induced ischemia rats^{60,61}. The study of Saeng-Ji-Hwang (SJH, Radix Rehmanniae) on cardiac muscle cells showed that SJH-associated Mn-SOD and Intracellular glutathione (GSH) is an important factor in the mechanism of the SJH-induced protective mechanism in H9C2 cardiac muscle cells⁶².

Effects on central nervous system

Rehmannia glutinosa possess a significantly inhibitory action on central nervous system. Catalpol, an iridoid glucoside separated from the roots of *Rehmannia glutinosa*, has been reported to attenuate apoptosis induced by H_2O_2 in PC12 cells *in vitro*⁶³, protect hippocampal CA1 region neurons from death through anti-oxidative ability and reduce cognitive impairment significantly, which might be of therapeutic value for the treatment of global cerebral ischemia^{64,65}. Catalpol also effectively attenuate LPS-induced microglial activation and subsequent dopaminergic neurotoxicity⁶⁶. *Rehmannia glutinosa* was found to up-regulate the gene expression of glial cell line-derived neurotrophic factor (GDNF) through cPKC and ERK 1/2 pathways in C6 glioblastoma cells and has a potentiality to be used in the therapy of dementia⁶⁷.

Aqueous extract of rehmannia dried rhizome was given (1.5, 3 g/kg, i.p.) to mice showed an antagonistic effect of excitement induced by caffeine sodium benzoate, but not the convulsion induced by strychnine nitrate and metrazol, suggested that rehmannia dried rhizome possessed a significant sedation effect. Furthermore, the site of action may be located in reticulation ascending activating system of brain stem and pallia⁶⁸. Water extract, especially acid part (0.15 g/kg, i.p.) from rehmannia dried rhizome possessed a sedation, hypotensive and anti-inflammatory effects in mice⁶⁹. In addition catalpol was found to be neuroprotective in gerbils subjected to transient global cerebral ischemia⁶⁶. Liuwei Dihuang decoction (LW) is a famous TCM prescription and consists of six herbs including *Rehmannia glutinosa* Libosch., etc. LW-containing serum (LWCS) possessed the effect of modulating or improving neuronal and synaptic function by whole-cell patch clamp recording technique⁷⁰.

Effects on bone metabolism

The study of *Rehmannia glutinosa* Libosch. extracts (RGX) on osteoblasts in bone metabolism showed that RGX treatment had a significant increase in both the proliferation and alkaline phosphatase (ALP) activity of osteoblasts and RGX increased the expression of the bone-related genes and osteoprotegerin secretion. RGX stimulates the proliferation and activities of osteoblasts, while inhibiting the generation and resorptive activities of osteoclasts.

It also had preventive effects on osteoporotic bone loss induced by ovariectomy. Although the active substances have not yet been identified, it is believed that the RGX seems to contain active components that have a potential to enhance the bone metabolism in osteoporosis⁷¹.

Korean herbal medicine Yukmi-jihang-tang (YJ) consisting of seven herbs such as *Rehmannia glutinosa* Libosch., etc., was found to reduce bone resorption *in vitro* and *in vivo* by inhibition of phosphorylation of peptide substrates. The mechanism may be related to the synergy between IL- β , TNF- α , IL-6 on PGE2 production which results in an enhancement of COX-2 gene expression. As a possible Src family kinase inhibitor, YJ may be useful for the treatment of diseases associated with elevated bone loss⁷². Other studies showed that the application of the extract obtained from *Rehmanniae radix* can support bone metabolism in aging individuals. OVX-citrated tuna bone powder (CTBs) with supplemental herb extract can maintain the calcium retention and bone mineral density (BMD) of femur⁷³.

Effects on endocrine system and glucose metabolism

Rehmannia glutinosa can not only improve the symptoms of *Yin*-deficiency, but also regulate abnormal thyroid hormone level. Furthermore, the effect of *Yin*-nourishing mainly represent in nourishing insufficiency of the kidney-*Yin*, accorded with TCM theory⁷⁴. Radix rehmanniae (3 g/kg) to rabbits by oral administration can oppose the decrease of corticosterone level induced by dexamethasone with a pathological support, suggesting radix rehmanniae has an alleviation to the influence of glucocorticoids on the function and formation of pituitary-endocrine system⁷⁵.

Rehmannia glutinosa is regarded as an effective drug for treatment of diabetes in traditional Chinese medicine. Besides R-BP-F (mainly catalpol) and iridoid glycoside, monomer rehmannioside D in *Rehmannia glutinosa* has the hypoglycemic effect^{7,8}; ethanol deposit section RG-WP from water extract of *Rehmannia glutinosa* given by i.v. showed a hypoglycemic effect in normal mice and, its mechanism is to enhance activity of liver glucokinase (GK) and G-6-PD in mice, to stimulate secretion of insulin and to decrease hepatic glycogen content in normal rats⁷⁶. *Rehmannia glutinosa* oligosaccharide (ROS) was found to exert a significant hypoglycemic effect in alloxan-induced diabetic rats, suggesting that ROS is a new antidiabetic principle^{77,78}. ROS can also significantly improve insulin resistance of 3T3-L1 adipocytes induced by dexamethasone⁵⁰. *Rehmannia glutinosa* glycoside D given to alloxan-induced diabetic mice showed a trend to reduce blood glucose in diabetes model mice⁴¹. Radix Rehmanniae could stimulate glucose uptake in both 3T3-L1 adipocytes and Hs68 skin fibroblasts at various concentrations⁷⁹. The effects of rehmannia dried rhizome extract were investigated using a diabetic nephropathy model induced by streptozocin after nephrectomy in rats, suggesting that rehmannia dried rhizome extract may be useful as a therapeutic agent for inhibiting the progression of diabetic nephropathy⁸⁰.

Anti-senescence effects

Rehmannia dried rhizome exerts an anti-senescence function in aged animals⁸¹. The study showed that prepared rehmannia root has the effect of reducing the brain mitochondrion monoamine oxidase activity, enhancing *in vivo* GSH-Px⁸²; chloroform, ethanol and aqueous-extracts of prepared rehmannia root remarkably enhanced brain SOD

activity and the chloroform extract can significantly reduce brain MDA content⁸³, prepared rhizome of rehmanna also enhanced brain NOS and SOD activity in d-galactose amine induced senescence model mice, suggests *Rehmannia glutinosa* possessed the capability of antisenescence and prolonging longevity⁸⁴.

Inhibition of gastric acid secretion and anti-ulcer effect

Yiguanjian, a decoction of tonifying and nourishing *Yin* with a component herb of *Rehmannia glutinosa* had a good curative effect for treatment of some chronic diseases, such as chronic atrophic gastritis⁸⁵. *Rehmannia glutinosa* also possesses an inhibition ability of gastric acid secretion and an anti-ulcer effect⁸⁶. The alcohol section of rehmanna dried rhizome cannot only prevent formation of ulcer, but also accelerate ulcer healing, and the aqueous extract inhibited the epithelia mitosis of vaginal cell proliferation induced by stilbestrol in mice⁸⁷.

Reducing of albuminuria and improve kidney function

Aqueous extract (10%) of *Rehmannia glutinosa* was given by i.g. at the dose of 1 ml/200 g/b.wt for 14 days in nephropathy model induced by puromycin aminonucleoside (i.v.) to SD male rats and the excretion of protein was reduced, glomeruli epithelia food processing fusion was improved, therefore, the kidney function was ameliorated⁸⁸.

Protection of liver

Gao et al. and Liu et al. reported that *Rehmannia glutinosa* can enhance glutathione peroxidase activity, inhibit lipid peroxidation, enhance cellular immune function and restore IL-2 gene expression, therefore, posses hepatoprotective action^{81,89}.

Treatment of inner ear diseases

Several reports have shown that some iridoid glycosides can be effective in scavenging the free radicals. The ethanol extract of prepared rehmanna root (SRG) protects cisplatin-induced HEI0C1 cell from damage through inhibition of lipid peroxidation and scavenging the activities of free radicals⁹⁰ and the mechanism may be explained, in part, by activation of intracellular antioxidant enzyme systems⁹¹.

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