

## *Rehmannia glutinosa*

# Dì huáng

### Indications

Allergic, inflammatory, and autoimmune conditions including asthma, urticaria, eczema, hayfever, rheumatoid arthritis, chronic renal disease, thyroid disease, and multiple sclerosis.

### Mechanism of Action

**Oligosaccharides:** *Rehmannia* contains raffinose family oligosaccharides that are found in many plants and are credited with immune-stimulating properties.<sup>1</sup> Raffinose oligosaccharides are difficult to digest and often produce flatulence, another reason why many traditional *Rehmannia* formulations steam processed the roots.<sup>2</sup> Stachyose and verbascoside are raffinose oligosaccharides shown to significantly stimulate fibroblast proliferation.<sup>3</sup> Immune polysaccharides including stachyose, raffinose, and verbascoside may exert immune modulation via effects on gastrointestinal microbiota.<sup>4</sup> Like inulin and other more vigorously studied oligosaccharides, these compounds are referred to as “prebiotics” because of their support of beneficial intestinal bacteria. The oligosaccharides<sup>5</sup> and the ionone glycosides in *Rehmannia* are both credited with hepatoprotective activities.<sup>6</sup>

**Iridoid Glycosides:** *Rehmannia* also contains at least 11 iridoid glycosides, called rehmaglutosides A–K; these glycosides are also known by individual names as many of the related compounds also occur in other plants. Rehmataglutosides A–K include catalpol, geniposide, acteoside, hydroxyaeginetic acid leucosceptoside, martynoside, isomartynoside, purpureaside, geniposidic acid,<sup>7</sup> jionoside, rehmapicroside, and rehmanpicrogenin.

*Rehmannia* also contains the ionone glycosides dihydroxy- $\beta$ -ionone and trihydroxy- $\beta$ -ionone<sup>8</sup>; three phenethylalcohol glycosides; and one furfural derivative,<sup>9</sup> feruloyl ajugol and ajugol isomers; the carotenoid glycosides neo-rehmannioside and oxyrehmonioside,<sup>10</sup> a polyoxygenated triterpene named glutinolic acid; and two new aeginetic acid quinovosides.<sup>11</sup>

The iridoid glycosides, particularly catalpol, are the most studied compounds in *Rehmannia*. Catalpol occurs in other plants (*Buddleja*, *Pikrorrhiza*, *Catalpa*, *Chelone*, *Callicarpa*), and when isolated it is shown to affect T-cell balance, modulating T helper-to-T regulatory cell ratios in animal models of allergic airway disease.<sup>12</sup> Catalpol has been shown to affect DNA polymerase enzymes and thereby affect DNA metabolism including replication, repair, transcription, recombination, and chromosome segregation during mitosis, thought to contribute to anticancer effects.<sup>13</sup>

Molecular research on iridoid alkaloids has provided a good example of how whole plants can exert a tonic or modulating effect on the immune system. Whereas catalpol may support inflammatory proliferation of epidermal cells, its metabolites L-shikonin and paeonol are shown to inhibit T-cell–

induced proliferation.<sup>14</sup> Furthermore, catalpol and acubin, when hydrolyzed, have shown apoptotic effects on leukemia cells, but when not hydrolyzed they have not,<sup>15</sup> supporting the traditional practice of steaming or processing *Rehmannia* roots.

The numerous immune-modulating effects of catalpol and other iridoids glycosides are via inhibitory effects on proinflammatory pathways including NADPH oxidase enzymes,<sup>16</sup> nitric oxide (NO) production, and the expression of inducible NO synthase, cyclooxygenase, prostaglandin E2, proinflammatory interleukins,<sup>17</sup> tumor necrosis factor (TNF)- $\alpha$ , and activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B)<sup>18,19,20</sup> in tandem with promotion of anti-inflammatory pathways and compounds including superoxide dismutase and glutathione.<sup>21,22</sup>

All of these modulating effects on T-cell, cytokine, chemokine, and inflammatory pathways are credited with analgesic effects and an ability to reduce neuropathic pain.<sup>23</sup> However, iridoid glycosides may also provide analgesia by antinociceptive actions. Catalpol and geniposide are shown to bind a nociceptive pain receptor call glucagon-like peptide 1 (GLP-1R). Catalpol and geniposide are reported to be agonists of GLP-1Rs, yet they block the activation and resulting pain by inhibiting formalin- and hydrogen peroxide-induced inflammation.<sup>24</sup>

**Anticancer Effects:** Many of these same T-cell and immune-modulating mechanisms are credited with some of catalpol's anticancer and apoptotic effects in cancer cells. Catalpol may induce apoptosis via promotion of caspase and polymerase enzymes, shown to deter human bladder cancer.<sup>25</sup> Animal and cell culture studies show *Rehmannia* to optimized T-lymphocyte release of cytokines including up-regulating interleukin and interferon production (in bone marrow-derived dendritic cells).<sup>26</sup> *Rehmannia* polysaccharide B is noted to increase the release of interleukin 2 from cytotoxic T lymphocytes, an effect credited with antitumor effects.<sup>27</sup>

**Antiallergy- and Autoimmune-Regulating Effects:** Atopic conditions such as allergic airway diseases and eczema involve increase T-helper 2 cell responses, leading to increased serum immunoglobulin E and increased leukocyte infiltration. *Rehmannia* can help reduce atopic reactivity by reducing the secretion of cytokines, chemokines, and cellular adhesion molecules. Animal models of allergic dermatitis show *Rehmannia* to limit dermal infiltration of inflammatory cells when provoked by TNF- $\alpha$  and interferon- $\gamma$ .<sup>28</sup> *Rehmannia* decreases blood levels of TNF- $\alpha$ , interleukin-6, and other proinflammatory mediators, and it corrects elevated blood levels of superoxide dismutase in diabetic mice.<sup>29</sup>

**Effect on AGEs:** Advanced glycation products (AGEs) are formed from metabolic by-products or carbohydrate metabolism. When AGEs are bound to glycoprotein receptors on blood cells, endothelium, renal, and other tissues, they contribute to inflammation, cell death, and loss of function. Because of inadequate carbohydrate metabolism and processing, AGEs contribute to the inflammatory burden in diabetes; therefore, agents that inhibit AGE and cellular AGE receptors can decrease pathologic degeneration in chronic inflammatory diseases. Catalpol has been shown to suppress AGE-mediated inflammation by inhibiting the production of reactive oxygen species and NF- $\kappa$ B activation, which may help mitigate diabetic complications.<sup>30,31</sup>

## Evidence-Based Research

*Rehmannia* may promote equilibrium within the immune system, helping to limit autoimmune activity and allergic hyperactivity without overly suppressing needed and healthy immune responsiveness.

*Rehmannia*'s immune-related characteristics are related to its capacity to increase leucocyte production and balance T- and B-lymphocyte biosynthesis. Its antioxidant properties can also aid in the prevention of oxidative damage to the liver. *Rehmannia glutinosa* has antioxidation, anti-inflammation, antiapoptosis actions.<sup>32</sup> Compounds in *Rehmannia* are credited with neuroprotective,<sup>22,33</sup> vascular endothelial protective,<sup>34</sup> and hepatoprotective actions<sup>6,35</sup> that are capable of protecting against ischemia and reperfusion injury,<sup>22</sup> reducing inflammation in animal models of acute pancreatitis,<sup>20</sup> and attenuating tissue injury in animal models of diabetes. *Rehmannia* may also benefit allergic and autoimmune hyperreactivity. Although immunosuppressive fractions<sup>36</sup> have been identified in *Rehmannia*, overall the plant is demonstrated to be immune modulating, as have iridoids glycosides in general<sup>37</sup>, one of the main active molecular groups in *Rehmannia*.

Catalpol, an iridoid glucoside and one of the main active components of the dried *Rehmannia* roots, is reported to be altered or degraded when steam processed, but in the presence of the amino acids also found in the roots, the antioxidant properties of the metabolites are significantly increased,<sup>38</sup> accounting for the use of steam dried roots in many traditional formulas. Catalpol in *Rehmannia* roots exerts anti-inflammatory, antitumor, and antiapoptotic effects. Catalpol also exerts neuroprotective effects and is shown to protect against levodopa-induced dyskinesia in animal models of Parkinson's disease by modulating neurotransmitter signaling in the corpus striatum.<sup>39</sup> *Rehmannia* oligosaccharides at a dose of 200 mg/kg have an ameliorating effect on stress-induced impaired glucose metabolism, in part, via neuroendocrine immunomodulation.<sup>40</sup>

*Rehmannia* leaves have also been used as a medicine, although less commonly than the roots, and one study has shown benefit in chronic glomerulonephritis in human subjects as a dose of 400 mg twice a day, improving proteinuria.<sup>41</sup> Human trials have also shown *Rehmannia* root in combination with the angiotensin receptor blocker irbesartan improves proteinuria in chronic glomerulonephritis patients better than irbesartan alone.<sup>42</sup>

## Safety in Pregnancy and Breastfeeding

There is no published or anecdotal evidence regarding the use of *Rehmannia* in pregnancy or lactation.

## General Safety

Animal studies dosing *Rehmannia* have not noted toxicity or side effects.

## Dosage

*Rehmannia* is generally considered safe, even at high doses up to 50 g/day. Traditional formulas have often included 10–50 g of *Rehmannia* or steamed *Rehmannia* root as a daily dose, often decocted with other herbs and taken as a tea on regular basis, but also with regular breaks in the treatment, anywhere from 1 day to 5 days to a month, depending on the dose and overall intended long-term duration of the course of therapy. Modern formulas typically mix *Rehmannia* root with similarly acting herbs such as *Cordyceps* and have between 75–500 mg of *Rehmannia* per dose. It is possible to concentrate the herbal constituents and get more activity with a smaller dose.

## Traditional Uses

*Rehmannia* has been used for a variety of allergic, inflammatory, and autoimmune conditions in traditional Chinese medicine including asthma, urticaria, eczema, rheumatoid arthritis, and chronic renal

disease. It is a traditional medicine listed in the *Pharmacopoeia of the People's Republic of China*; however, it has not yet attracted great use in the western herbal arena. *Rehmannia* has often been combined with *Astragalus* for managing inflammatory and immune disorders and is included in many traditional formulas for allergy, autoimmune disease, liver support, and chronic inflammation including kyon-ok-ko formula.<sup>43</sup> Qi-ju-di-huang-wan (*Lycium* berry, *Chrysanthemum*, and *Rehmannia* pill) is commonly prescribed to Sjögren's patients,<sup>44</sup> and Zhi-Bai-Di-Huang-Wan (*Anemarrhena*, *Phellodendron*, and *Rehmannia* pill) is commonly prescribed to lupus erythematosus patients.<sup>45,46</sup> The dried and steamed roots of *Rehmannia glutinosa* have different pharmacological functions and indications.

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