

# Treating Adrenal Insufficiency and Hypotension with *Glycyrrhiza*

Jill Stansbury, ND<sup>a</sup>  
 Paul Saunders, PhD<sup>b</sup>  
 David Winston, RH(AHG)<sup>c</sup>  
 Eugene R. Zampieron, ND<sup>d</sup>

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## ABSTRACT

*Glycyrrhiza* may be appropriate as an adjunctive therapy for a variety of disorders involving mild adrenal insufficiency, low aldosterone output, or hyperkalemia due to effects on 11-β-HSD enzymes, direct effects at mineralocorticoid receptors, and downstream effects on aldosterone as well as fluid and electrolyte balance. *Glycyrrhiza* has also been shown to help correct hyperkalemia that may result from spiro lactone therapy in PCOS. Patients with orthostatic hypotension may respond to *Glycyrrhiza* therapy due to its ability to improve blood volume and potassium levels and reduce activation of baroreceptors.

**Keywords:** *Glycyrrhiza*, Adrenal insufficiency, Hyperkalemia, Aldosterone regulation

## CLINICAL IMPLICATIONS

Licorice (*Glycyrrhiza glabra*) can be used to treat certain low blood pressure conditions. Because it can correct low potassium levels via effects on adrenal enzyme systems and support healthy adrenal function and aldosterone metabolism, *Glycyrrhiza* is primarily used to treat orthostatic hypotension.

## KEY HERBS DISCUSSED

Licorice (*Glycyrrhiza glabra*)

## PRIMARY INDICATIONS

Hypotension, orthostatic hypotension, hypokalemia

## ADJUNCTIVE OR STAND-ALONE TREATMENT

Adjunctive or Stand-Alone

## DOSE OF BIOACTIVE CONSTITUENTS

Licorice up to 4 grams a day containing a minimum of 300 mg glycyrrhizic acid a day

## SYNERGISTIC HERBAL FORMULA

Licorice (*Glycyrrhiza*), Eleuthero (*Eleutherococcus*), Sarsaparilla (*Smilax*), Holy Basil (*Tulsi*), Rhodiola (*Rhodiola*), Hawthorne (*Crataegus*), Alfalfa (*Alfalfa*)

## SIDE EFFECTS (AND CAUTIONS)

When used inappropriately at high doses, Licorice may rarely promote the following complications: hypertension, mineralocorticoid excess, pseudohyperaldosteronism, sodium and water retention, increased urinary potassium loss, hypokalemia, and alkalosis. In patients receiving concomitant cardiac glycosides or diuretics, licorice may potentiate cardiac glycosides (digoxin), and may counteract the effects of diuretics. In patients with hypotension, it is advised to monitor blood pressure and maintain the patient at the lowest dose necessary.

## UNSUBSTANTIATED THEORETICAL SIDE EFFECTS

There is some theoretical evidence as to whether licorice should be administered to patients with liver, kidney, and/or cardiovascular disease. No clinical or scientific study has confirmed this. Most scientific studies published about licorice is that it is a hepatoprotectant.

## EDITORS NOTE

Licorice is clinically considered an effective treatment against liver disease and hepatitis. Intravenous Glycyrrhizic Acid is an anti viral that can be used to treat viral hepatitis.

<sup>a</sup> Corresponding author: Battle Ground Healing Arts, 408 E Main Street, Battle Ground, WA 98604, USA

<sup>b</sup> Dundas Naturopathic Centre, Dundas L9H 1V6, Canada

<sup>c</sup> David Winston's Center for Herbal Studies, Broadway, NJ 08808, USA

<sup>d</sup> 413 Grassy Hill, Woodbury, CT 06798, USA

## DISCUSSION

*Glycyrrhiza glabra* and *Glycyrrhiza uralensis* (both known as licorice) are among the most versatile, popular, and widely used of all medicinal plants. *Glycyrrhiza glabra*, in the *Fabaceae* family, was named ‘sweet root’ by Dioscorides (a Greek physician), and it was widely used in Europe during the Middle Ages and Renaissance. The pleasant, sweet taste is due to the saponic glycoside, glycyrrhizin. *Glycyrrhiza* is known to impact hormonal balance and the HPA axis. Considered a possible anti-inflammatory, demulcent, and muco-protective agent, *Glycyrrhiza* has recently been studied for its effect on ACTH feedback loops, corticoids, and androgen steroid metabolism.

Although licorice contains sucrose and glucose, glycyrrhizin is sixty times sweeter than these sugars and gives licorice its characteristic sweet flavor. Glycyrrhizin has become synonymous with glycyrrhizic acid, and researchers often use these terms interchangeably. Glycyrrhizin is composed of the sugar glucuronic acid, and a non-sugar saponin, glycyrrhetic acid. The concentration of glycyrrhizin is variable, from 1-24% of the dried root. Glycyrrhizin is considered responsible for many of the actions of licorice, including its anti-inflammatory and hormonal effects.

### BACKGROUND OF RELATED PHYSIOLOGIC EFFECTS AND PROCESSES

#### *Renin, Angiotensin, and Aldosterone’s Effect on Blood Pressure.*

Renin is released from renal juxtaglomerular cells in response to low blood volume. In turn, this will ultimately result in the retention of water and increased blood volume, and result in increased blood pressure. A cascade of events occurs when renin is released, causing fluid retention. The first event occurring in this cascade is stimulation of angiotensin production and release. Angiotensin causes blood vessels to constrict by its direct effects on peripheral vascular smooth muscle, which in emergency situations would enhance perfusion, even in cases of very low blood volume. Angiotensin causes

aldosterone to be released from *zona glomerulosa* cells in the adrenal cortex. Aldosterone acts on the distal tubules and collecting ducts in the kidneys to promoting resorption of sodium and water back into the blood stream. Potassium must be excreted to enable water retention. Aldosterone also has central nervous system effects, stimulating the release of ADH (anti-diuretic hormone) from the posterior pituitary. ADH acts on the renal system to help conserve water.

#### *Specific Aldosterone Regulation Mechanisms.*

Aldosterone is a mineralocorticoid adrenal steroid that regulates fluid and electrolyte balance by manipulation of electrolytes to help control fluid dynamics in the body. Aldosterone creates osmotic gradients necessary for the kidneys to excrete wastes and yet retain water. Aldosterone does so by enabling the kidneys to spend or excrete important minerals (*i.e.*, potassium) and create the pressure gradients that allow water to be retained.



*Glycyrrhiza* species of the Leguminosea family  
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Aldosterone also supports salivary glands, sweat glands, and intestinal mucosal cells, to concentrate fluids despite challenges of osmotic concentration gradients between intracellular and extracellular fluids. Drugs (*e.g.*, spironolactone) that interfere with aldosterone release, treat hypertension due to its effects on electrolyte and blood fluid volume, and thereby causing fluid loss. In addition to renin, adrenocorticotrophic hormone (ACTH) promotes aldosterone secretion. Therefore, patients with ACTH abnormalities may experience excess or insufficient activation of aldosterone and also related abnormalities and electrolyte imbalances (particularly hypo- or hyperkalemia). Hence, potassium is also a specific modulator of aldosterone release. When

potassium is low, renin release (and the subsequent cascade release of aldosterone) is inhibited in an effort to conserve potassium, even if sodium is high

## THE MEDICINAL USES OF GLYCYRRHIZA

### *Glycyrrhiza* for Orthostatic Hypotension

A sudden change of blood pressure detected by baroreceptors (due to such factors as standing up very quickly) may cause a sequence of physiological actions in order to increase blood flow to the brain, resulting in dizziness and even fainting. High doses of glycyrrhizic acid can increase blood pressure to normal when hypotension is due to mild

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adrenal insufficiency, and patients with orthostatic hypotension may benefit from *Glycyrrhiza* supplementation as part of their treatment regimen. Additionally, licorice increases water retention and blood volume, which improves cerebral blood flow during rapid fluctuations in systemic blood pressure.

### ***Glycyrrhiza* for Adrenal Insufficiency**

Researchers have demonstrated the ability of licorice to treat adrenal insufficiency as well as stress intolerance via enhancement of the adrenal cortisol response. *Glycyrrhiza* inhibits 11 $\beta$ -hydroxysteroid dehydrogenase, the enzyme responsible for inactivating cortisol, and as a result, may elevate abnormally low cortisol levels.<sup>1,2</sup> Glycyrrhizin and glycyrrhizic and glycyrrhetic acids have each been shown to inhibit the 11- $\beta$ -HSD enzymes, thereby allowing cortisol to bind mineralocorticoid receptors.<sup>3</sup> These compounds can also have direct ligand effects on mineralocorticoid and glucocorticoid receptors.<sup>4</sup>

Through its effects on 11- $\beta$ -HSD-1, *Glycyrrhiza* increases activity at mineralocorticoid receptors, and promote potassium excretion and sodium and water retention. This may be therapeutic in cases of hyperkalemia and hypoaldosteronism.<sup>5</sup> *Glycyrrhiza* may also benefit women with PCOS and diminish the side effects of spironolactone use.<sup>6</sup>

It has been noted that *Glycyrrhiza* can promote excessive fluid and sodium retention, leading to hypokalemic hypertension in some cases. In a genetic deficiency of the 11- $\beta$ -HSD enzymes, individuals with preexisting over-stimulation of the mineralocorticoid receptors may be aggravated by *Glycyrrhiza*.<sup>2</sup> Many cases of individuals who have extreme reactivity to licorice have proven to be those persons with 11- $\beta$ -HSD deficiency.<sup>7</sup> Likewise, genetic 11- $\beta$ -HSD abnormalities are increasingly recognized as contributing to some cases of hypertension.<sup>8</sup>

Animal studies have also shown *Glycyrrhiza* to decrease elevated serum cortisol, ACTH, and potassium, while increasing renin, aldosterone, and sodium concentrations.<sup>9</sup> These effects suggest direct activity on the adrenal-renal-pituitary axis. This aldosterone-like action may cause fluid retention

and elevation of blood pressure in some sensitive individuals,<sup>10</sup> but improve symptoms of mineralocorticoid insufficiency. Due to its aldosterone-like effects, *Glycyrrhiza* is also appropriate for those patients with adrenal insufficiency and related hypotension.

Red Ginseng (*Panax ginseng*) is an excellent constituent of the synergistic herbal formula for conditions of adrenal hypofunction.

### ***Glycyrrhiza* for Hyperkalemia.**

Dialysis patients are particularly at risk of electrolyte imbalances (*i.e.*, hyperkalemia), and hyperkalemia can cause life-threatening arrhythmias. *Glycyrrhiza* may be appropriate for dialysis recipients experiencing hyperkalemia by assisting the body to excrete potassium.<sup>11</sup>

Women with PCOS, prescribed spironolactone to help combat hirsutism, may likewise develop hyperkalemia as an unwanted side effect. The concomitant use of *Glycyrrhiza* with spironolactone can help to prevent this side effect of hyperkalemia. In a clinical trial, the addition of *Glycyrrhiza* significantly reduced the activation of the renin-aldosterone system in patients using spironolactone. Furthermore, the group receiving the additional *Glycyrrhiza* experienced less metrorrhagia.

## **SUMMARY**

*Glycyrrhiza* may be appropriate for a variety of disorders involving adrenal insufficiency, low aldosterone output, or hyperkalemia due to effects on 11- $\beta$ -HSD enzymes, direct effects at mineralocorticoid receptors, and downstream effects on aldosterone as well as fluid and electrolyte balance. *Glycyrrhiza* has also been shown to help correct hyperkalemia that may result from spironolactone therapy in PCOS. Patients with orthostatic hypotension may respond to *Glycyrrhiza* therapy due to its ability to improve blood volume and potassium levels and reduce activation of baroreceptors.

## **DISCLOSURE OF INTERESTS**

Dr. Saunders reports personal fees related to employment or seeing patients from CCNM, the

Dundas Naturopathic Centre, and from Beaumont Health Systems, Troy Hospital, MI, outside the submitted work. Dr. Winston reports personal fees from Herbalist & Alchemist, Inc, outside the submitted work. Dr. Stansbury and Dr. Zampieron have nothing to disclose.

## REVIEW ESSAY

Many nutrients and herbs that have not been the subject of randomized controlled studies are used

regularly by clinicians. They have also been used traditionally for hundreds, sometimes thousands of years. Review Essays contain the opinions of professionals and experts in the fields of nutritional and botanical medicine on how to most effectively use herbs and nutrients in clinical practice. The dosages recommended are based on clinical experience. Side effects that are described in “Unsubstantiated Theoretical Concerns” have not been seen in clinical practice or clinical studies but are speculative based on, for example, possible mechanisms of action.

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