

# Botanical Strategies to Address the Three Phases of Stress Response



Beverly Yates, ND

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# Introduction

Each year, more than 19 million people are affected by stress and anxiety-related conditions in the United States. Less than one third of those 19 million people seek direct help for their stress. Addressing issues of stress when treating a patient can serve as an opportunity to greatly improve that patient's health and happiness.

When stress is not addressed properly it can become expensive to treat. An estimated 75-90% of doctor visits are stress-related. Disorders related to stress cost the U.S. more than \$42 billion annually. The Property and Casualty Insurance Edition estimates that \$150 billion in productivity in the workplace is lost due to issues related to stress. Habits such as absenteeism, poor decision making, mental illness and substance abuse are often side effects of an individual's inability to cope with stress.<sup>1</sup>

## Identifying and treating the cause of stress

### Talk to patients about stress

There are several ways to identify stress when evaluating a patient. First, it is important not to make assumptions. Taking the time to ask a patient what they perceive as stress can be very revealing. Second, it is important to ask a patient how they respond to stress and what coping mechanisms they use.

There are several simple ways to help patients reduce stress without medication. The following are some suggestions to give patients.

- Ask patients to make themselves a priority.
- Help patients learn to forgive and move forward from difficult events.
- Regular exercise helps burn off hormones and chemicals released during stressful times.
- Sound nutrition can reduce the impact of stress.

Stress can cause a variety of issues if untreated. For some people stress can affect sleep, weight, the ability to heal from illnesses, hormonal imbalances, and accelerate the aging process. Stress can also affect a patient's family members and friends. Teaching patients how to reduce stress can be a valuable tool to improving their quality of life.

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<sup>1</sup> Property and Casualty Insurance Edition

# The three phases of stress

## Phase 1: Acute, non-recurring and mild response

Acute, non-recurring stress is the mildest form of stress. In this phase, the patient suffers from stress for a short time, but is not incapacitated by it. The patient will need support, but they are able to function normally.

## Phase 2: Acute, recurring and poor recovery

In the second phase of stress, patients have stress that is acute, recurring and they experience extended recovery time. Their sleep can become affected and they may be feeling anxious. If that is the case, it is advisable to perform lab tests to evaluate cortisol levels.

## Phase 3: Chronic, prominent symptoms and poor recovery

The third stage of stress causes the patient to suffer from chronic, prominent symptoms with poor recovery time. A four point cortisol test would clearly reveal adrenal fatigue in this patient. The patient may also exhibit unusual sleep patterns, sleep apnea and excessive fatigue. Short-term memory will also likely be affected.

## Botanical treatment options for the three phases of stress

Each phase of the stress response can be treated with different botanicals.

### Phase I stress treatment: recommended botanicals

For this acute, non-recurring, mild response phase of the stress response, the following herbs are recommended:

- Ashwagandha
- Rhodiola
- Maca

### Phase II stress treatment: recommended botanicals

For this acute, recurring poor response phase of the stress response, the following herbs are recommended:

- Ashwagandha
- Rhodiola
- Passionflower
- Holy Basil
- Others (Avena, Scutellaria, Hypericum and Magnolia)

### **Phase III stress treatment: recommended botanicals**

For this chronic, permanent and poor recovery phase of the stress response, the following herbs are recommended:

- Licorice
- Ashwagandha
- Rhodiola
- Passionflower
- Holy Basil
- Others (Ginseng, Nervines such as Scutellaria and Avena)

## **Ashwagandha- Withania somnifera**

Ashwagandha is a member of the Solanaceae family. Somnifera means, “sleepmaking.” Ashwagandha improves and conserves energy in the body and helps the body to adapt to various demands that are placed upon it. The root is the active form and is typically prescribed in tonic form. Patients who have an acute anaphylactic reaction to herbs of the Solanaceae family should not be prescribed Ashwagandha.

### **Ashwagandha uses**

Clinical trials and animal research support the use of ashwagandha for the treatment of anxiety, cognitive and neurological disorders, inflammation and Parkinson’s disease. The chemo-protective properties of this herb make it a potentially useful partner for patients undergoing radiation and chemotherapy. Ashwagandha is also used as an adaptogen for patients with “nervous exhaustion” and debility due to stress. For patients experiencing low white blood cell count, ashwagandha also serves as an immune stimulant.<sup>2</sup>

### **Withania clinical trials**

#### **Study 1: Clinical trial of withania**

In a 2008 clinical trial, participants were given a standardized extract of three dosages of withania standardized extract (WSE), 125 mg per day, 125 mg twice per day and 250 mg twice per day. Participants in the trial reported reduced experiential feelings of stress and anxiety. Also observed were reduced serum concentrations of cortisol and CRP and lowered pulse rates and blood pressure. In addition, participants showed increased serum concentrations of DHEAS. Figure 1 demonstrates the stress response patients displayed in the ashwagandha group versus the placebo group. This study showed patients had improved fasting blood sugar levels, liver profile and cardiac risk ratios. This study confirms that daily use of WSE may benefit people suffering from the effects of stress and anxiety. No adverse side effects were reported in this study.<sup>3</sup>

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<sup>2</sup> Altern Med Rev. 2004 Jun;9(2):211-214

<sup>3</sup> Biswajit Auddy, PhD1 et al; A Standardized Withania Somnifera Extract Significantly Reduces Stress-Related Parameters in Chronically Stressed Humans: A Double-Blind, Randomized, Placebo-Controlled Study JANA Vol.11,No.1, 2008

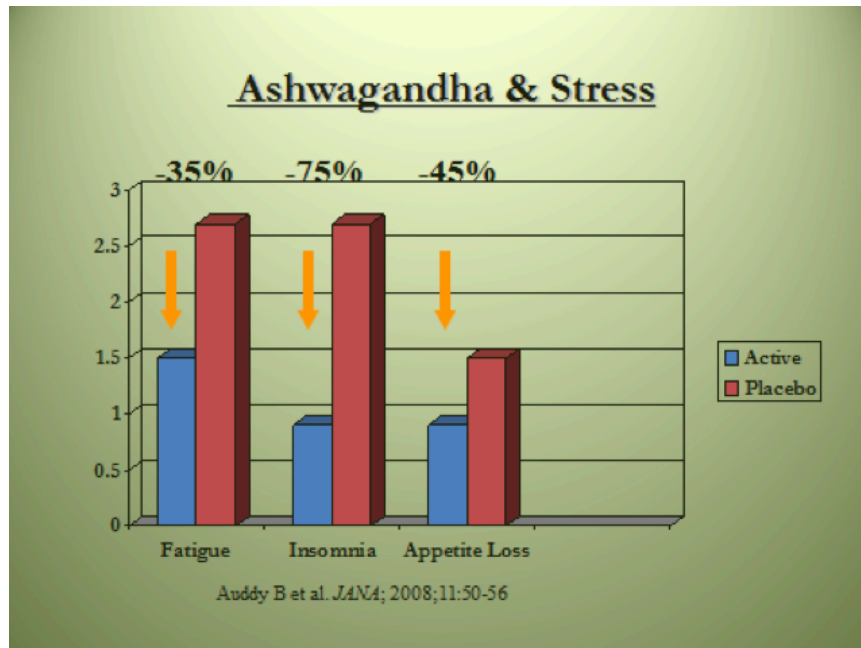


Figure 1

### Study 2: Rat model of chronic stress

In this clinical trial, rats received a mild, unpredictable foot shock daily for 21 days. In response to the foot shock, they displayed hypoglycemia, glucose intolerance, elevated plasma corticosteroids, gastric ulceration, cognitive deficits, immunosuppression and mental depression. The males also displayed sexual dysfunction. The rats were then administered *Withania somnifera* one hour prior to receiving the daily shock. The herb was shown to attenuate their chronic stress-induced responses. The study concluded that *Withania somnifera* has significant anti-stress adaptogenic activity, confirming the clinical use of the plant.<sup>4</sup>

### Dosing

Ashwagandha is recommended in the following dosages:

- 3 to 6 grams of the dried root per day
- 6 to 15 ml of a 1:2 fluid extract per day
- 300 to 500 mg of an extract standardized to contain 1.5% withanolides per day

For patients with small body mass, dosages can be prescribed at lower ranges. For those who are overweight or have larger body mass, dosages can be prescribed at higher ranges. Ashwagandha has been found to be safe; however, large doses have been shown to cause GI upset, diarrhea and vomiting in some patients.

<sup>4</sup> Adaptogenic activity of *Withania somnifera*: re rat model of chronic stress. *Pharmacol Biochem Behav.* 2003 Jun;75(3):547-55.

## Contraindications

Based on animal studies, it is recommended to use Ashwagandha cautiously in:

- Patients with low blood pressure or those using anti-hypertensive drugs
- Patients with bleeding disorders or those taking anticoagulant or anti platelet drugs
- Patients taking sedative, inotropic or chronotropic agents
- Patients with thyroid disorders (to avoid any kind of hyperstimulation)
- Patients taking respiratory depressants or who are at risk for respiratory depression
- Children (due to lack of data to show clear safety in this population)

There are no studies of Ashwagandha that show clear safety in women who are pregnant or lactating, so caution is advised when prescribing this herb to these patients. Large doses may possess abortifacient properties, though there is no definitive research to date that proves this. Ashwagandha should be avoided with alcohol, sedatives and anxiolytics as it is a mild central nervous system depressant.<sup>5</sup>

## Rhodiola rosea

Rhodiola rosea, also known as golden root, is grown in the Siberian Alps. It contains the active constituents rosavin and salidrosides. It is traditionally used to improve physical performance and mental enhancement and to reduce fatigue.

## Clinical indications

Clinical indications for Rhodiola include the following:

- Fatigue
- Anxiety
- Depression
- Moodiness
- Physical and mental performance

Rhodiola is also used to protect against the extreme effects of stress, hypoxia, temperature and intense physical activity. It is also neuroprotective.<sup>6</sup>

## Rhodiola mechanism of action

Rhodiola has been shown to be a mood regulator. Rhodiola's mood regulating effects are potentially related to the herb's ability to optimize serotonin and dopamine levels. These effects are likely due in part to the monoamine oxidase inhibition and its influence on the opioid and peptides, such as beta endorphins (also known as "feel-good" chemicals). As such, Rhodiola can be a helpful herb for those who struggle with substance abuse problems, other addictions or depression.<sup>7</sup>

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<sup>5</sup> Monograph, *Alternative Medicine Review* 2004 Vol. 4, #2

<sup>6</sup> Winston, D.; Maimes, S. *Adaptogens. Herbs for Strength, Stamina and Stress Relief*, Healing Arts Press: Rochester, Vermont, USA, 2007.

<sup>7</sup> Gregory S. Kelly, ND, *Alternative Medicine Review*, 2001, 6(3): 293-302

## Clinical trials

### Clinical trial: Rhodiola's effect on stress-related fatigue

A randomized, double-blind, placebo-controlled clinical study examined Rhodiola's effect on stress-related fatigue. The trial was comprised of 60 participants randomized in two groups. The first group of participants took an extract at 576 ml of Rhodiola per day while the second group was given a placebo. The study concluded that Rhodiola exerted anti-fatigue effects that increased mental performance and concentration. Rhodiola also decreased cortisol response to awakening stress in the "burnout" patients with fatigue syndrome. Rhodiola was found to naturally enhance mental function and be non-habit forming.<sup>8</sup>

### Clinical trials: Rhodiola's effect on depression and anxiety

#### Depression

A phase III, randomized, double-blind, placebo-controlled study looked at the effects of Rhodiola on depression. The trial ran for six weeks and was comprised of three parallel groups (Groups A, B and C). In Group A, 31 patients received 340 mg of Rhodiola per day. In Group B, 29 patients received 680 mg of Rhodiola per day. In Group C, 29 patients received a placebo. Groups A and B reported overall improvements with depression, insomnia, emotional instability and somatization. The only area where Groups A and B did not report improvements was with their self-esteem.<sup>9</sup>

#### Anxiety

This pilot study was comprised of ten people with generalized anxiety disorder. Participants received 340 mg of Rhodiola extract per day for ten weeks. By the end of the trial, participants reported significant improvements in anxiety. Rhodiola can be a beneficial treatment option for patients because unlike pharmaceutical agents, it is non-habit forming. It also does not disrupt or destroy the nervous system.<sup>10</sup>

## Dosing

Rhodiola is recommended in the following dosages:

For mild to moderate depression: 170 mg or 340 mg twice per day for six weeks

For anti-fatigue: 200 mg three times per day

For insomnia: 600 mg per day<sup>11</sup>

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<sup>8</sup> Olsson EM, von Schéele B, Panossian AG. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Standardized Extract SHR-5 of the Roots of *Rhodiola rosea* in the Treatment of Subjects with Stress-Related Fatigue. *Planta Med.* 2009 Feb;75(2):105-12.

<sup>9</sup> Darbinyan V, Aslanyan G, Amroyan E, et al. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry.* 2007;61(5):343-8

<sup>10</sup> Bystritsky A, Kerwin L, Feusner JD. A pilot study of *Rhodiola rosea* (Rhodax) for generalized anxiety disorder (GAD). *J Altern Complement Med.* 2008 Mar;14(2):175-80.

<sup>11</sup> Darbinyan, V. et al; A. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. *Nord. J. Psychiatry* 2007, 61, 2343–2348

\*\* Panossian A and Wikman G, Effects of Adaptogens on the CNS and the Molecular Mechanisms Associated with Their Stress-Protective Activity, *Pharmaceuticals* 2010, 3,188-224; doi:10.3390/ph3010188



# Passionflower (*Passiflora incarnata*)

Passionflower is a sedative and is effective for treating nervousness and insomnia. Passionflower has GABA-like effects and inhibitory neurotransmitter benefits. Passionflower is considered the most bioactive species in the *Passiflora incarnata* plant family. Purple passionflower, *Passiflora edulis*, is often confused with *Passiflora incarnata*, so it is important to read labels carefully when recommending treatment for patients. Purple passionflower, is the source of passion fruit.

## Clinical indications

Clinical indications for passionflower include the following:

- Anxiety or nervousness
- Generalized anxiety disorder (GAD)
- Pre-surgical anxiety
- Insomnia
- Opiate withdrawal symptoms
- Seizure disorder
- Attention deficit hyperactivity disorder (ADHD)
- Palpitations
- Dysrhythmia
- Hypertension
- Low libido, anxiety and nervousness

## Clinical trial

A four-week, double-blind, randomized trial comprised of 36 patients with generalized anxiety disorder (GAD) examined the effectiveness of passionflower. Half of the patients were given passiflora extract at 45 drops per day, and a placebo tablet. The other half were given oxazepam at 30 mg per day, plus placebo drops. The study concluded that the Passiflora extract and oxazepam were equally effective. Some participants reported that the oxazepam was more effective for sedation; however, those taking oxazepam demonstrated more side effects relating to impairment of job performance. Passionflower is a good alternative to oxazepam because patients are able to function normally while reducing stress.<sup>12</sup>

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<sup>12</sup> Akhondzadeh S, Naghavi HR, Vazirian M, et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther.* 2001 Oct;26(5):363-7.

## Dosing

Passionflower is recommended in the following dosages:

- Dried herb: 2 grams, three to four times per day
- Infusion: 2 grams in 150 ml of water, three to four times per day
- Fluid extract, 1:1 or 1:2 (g/ml): 2 ml, three to four times per day
- Liquid Phyto-Cap form: Two capsules, three to four times per day
- Tincture 1:5 (g/ml) extract, three to four times per day

## Contraindications

There are no known contraindications or adverse interactions for passionflower. The FDA has granted passionflower the “Generally Recognized as Safe” status.

## Holy Basil

Holy Basil promotes a healthy response to inflammation. When working with patients with high levels of stress who have inflammatory problems, Holy Basil can be an effective treatment option. Holy Basil promotes a healthy response to stress and is a powerful antioxidant. It is also hepatoprotective. Holy Basil soothes stomach spasms often referred to as “butterflies in the stomach.”

## Clinical trial

A clinical study analyzed several compounds (displayed in Figure 2).

**Holy Basil Study**

- Three new compounds, ocimumosides A (1) and B (2) and ocimarin (3), were isolated from an extract of the leaves of holy basil (*Ocimum sanctum*), together with eight known substances, apigenin, apigenin-7-O-beta-D-glucopyranoside, apigenin-7-O-beta-D-glucuronic acid (4), apigenin-7-O-beta-D-glucuronic acid 6"-methyl ester, luteolin-7-O-beta-D-glucuronic acid 6"-methyl ester, luteolin-7-O-beta-D-glucopyranoside, luteolin-5-O-beta-D-glucopyranoside, and 4-allyl-1-O-beta-D-glucopyranosyl-2-hydroxybenzene (5), and two known cerebrosides.
- Promising anti-stress effects by normalizing hyperglycemia, plasma corticosterone, plasma creatine kinase, and adrenal hypertrophy.

Gupta P, Yadav DK, Siripurapu KB, et al. Constituents of *Ocimum sanctum* with antistress activity. *J Nat Prod.* 2007 Sep;70(9):1410-6.

Figure 2

The study demonstrated promising anti-stress effects by normalizing hyperglycemia, plasma corticosterone, plasma creatine kinase and adrenal hypertrophy.<sup>13</sup>

<sup>13</sup> Gupta P, Yadav DK, Siripurapu KB, et al. Constituents of *Ocimum sanctum* with antistress activity. *J Nat Prod.* 2007 Sep;70(9):1410-6.

## Dosing

Holy basil is recommended in the following dosages:

300 to 600 mg per day in divided doses (does not need to be taken with food)

## Contraindications

Holy Basil is contraindicated in patients with hypoglycemia and those with fertility concerns because it may be anti-spermatogenic. Holy Basil may increase bleeding time and is therefore not recommended for patients on anticoagulant therapy. Caution should be used when prescribing Holy Basil to pregnant or lactating patients as no studies have been conducted for these populations. A few studies suggested that Holy Basil might stimulate uterine contractions, so caution should be taken when considering this herb as a treatment option for this population.

## Licorice

A recent clinic study investigated the wider effects of oral ingestion of licorice on steroidogenesis. The study found that licorice showed inhibitory effects of glycyrrhetic acid on adrenal sulfotransferase activity, and enhanced cortisol synthesis within four (4) hours. In addition, the glycyrrhetic acid constituent of licorice increased circulating and salivary levels of unconjugated deoxycorticosterone and dehydroepiandrosterone (DHEA) by inhibiting their conjugation at source within the adrenal cortex.<sup>14</sup>

## Dosing and contraindications

Licorice is recommended in the following dosages:

- 30 to 40 drops of root extract three times per day (with or without food)

It is important to match lab tests for cortisol lows, particularly in the morning and late afternoon. Patients who report fatigue during these times often can benefit from licorice because it will quickly boost cortisol levels.

Licorice is contraindicated in patients with hypertension.

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<sup>14</sup> *Mol Cell Endocrinol.* 2011 Apr 10;336(1-2):102-9. Epub 2010 Dec 22.

Liquorice and glycyrrhetic acid increase DHEA and deoxycorticosterone levels in vivo and in vitro by inhibiting adrenal SULT2A1 activity.

Al-Dujaili EA, Kenyon CJ, Nicol MR, Mason JJ.

# Three phases of stress: Case studies

The following are case studies of typical stress related scenarios and the suggested botanical treatment protocol.

## Phase I stress

### Scenario:

A 38-year-old woman is feeling stressed at work. She wants to succeed and has an annual job review coming up. She has occasional, mild anxiety and is worried about being evaluated at work. She finds her work environment stimulating, but also challenging. She often has issues meeting deadlines. She is sleeping, but often does not feel rested when she wakes up.

### Treatment:

- **Rhodiola:** 240 mg extract in capsule form, twice a day without food
- **Ashwagandha:** 350 mg extract, one capsule twice per day, with or without food
- Monitor blood pressure

## Phase II stress

### Scenario:

A 52-year-old woman is caring both for her children and her parents. She reports having little time for herself. She reports waking up two or three times during the night and has recurring fatigue.

### Treatment:

- **Ashwagandha:** 350 mg extract, one capsule twice per day, standardized to 2.5 mg withanolides
- **Holy Basil leaf:** 300 mg extract, two capsules twice per day (away from food), standardized to 17 mg eugenols, rosmarinic acid 7.6 mg
- **Passionflower:** 700 mg, two capsules per day
- Monitor blood pressure

## Phase III stress

### Scenario:

A 47-year-old male with chronic obstructive sleep apnea, lifelong obesity, depression and anxiety reports feeling overwhelmed. The patient's four-point cortisol lab tests were below the normal range. He does not have high blood pressure and has a normal cholesterol profile. His triglycerides are also at normal levels.

### Treatment:

- **Licorice:** 30 to 40 drops, three times per day matching lab test lows and monitoring blood pressure
- **Rhodiola:** 240 mg extract, one capsule twice per day
- **Ashwagandha:** 350 mg extract, one capsule twice per day, standardized to 2.5 mg withanolides
- **Holy Basil:** 300 mg leaf extract, two capsules twice per day, standardized to 17 mg eugenols, rosmarinic acid 7.6 mg
- **Passionflower:** 700 mg, two capsules as needed daily for anxiety

## Contributor

Dr. Beverly Yates is a California-licensed doctor of naturopathic medicine and a graduate of the National College of Natural Medicine (NCMN) in Portland, Oregon. She maintains a clinical practice in California, where she focuses on the use of plant-based, nature-derived solutions to chronic health problems. Dr. Yates, an integrative medicine pioneer, has served as the lead supervising doctor for the first fully accredited naturopathic and integrative medical residency in California. She also serves as a governor-appointed member of California's Naturopathic Medicine Committee. Dr. Yates is a national media representative for the American Association of Naturopathic Physicians, and an accomplished author and speaker, featured frequently on television and radio, and in print media. Dr. Yates is a member of the Scientific Advisory Board of *Gaia Herbs Professional Solutions*.