

# The Role of Selected Adaptogens and Nervines in Clinical Practice



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*Fortify Your Life, Healthy At Home, Life Is Your Best Medicine*  
*Guide to Medicinal Herbs*

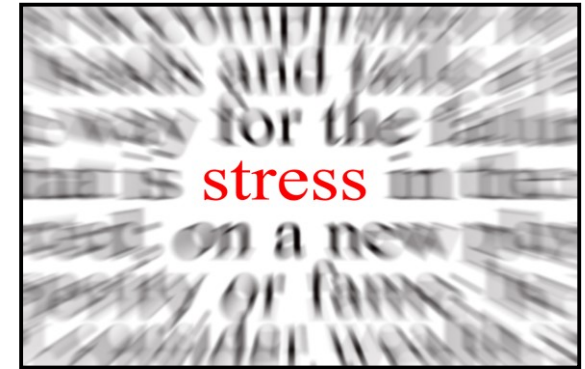


*Tieraona Low Dog, M.D.*

# Disclosure

- Tieraona Low Dog, MD has the following to disclose:
  - Health Advisory Board: Pharmaca
  - Director of Scientific & Regulatory Affairs: Healthy Lifestyle Brands
  - Consultant/Spokesperson: FoodState
- This talk will not discuss off-label and/or investigational use of pharmaceuticals or devices not yet approved by the FDA.

# Stress in the 21<sup>st</sup> Century



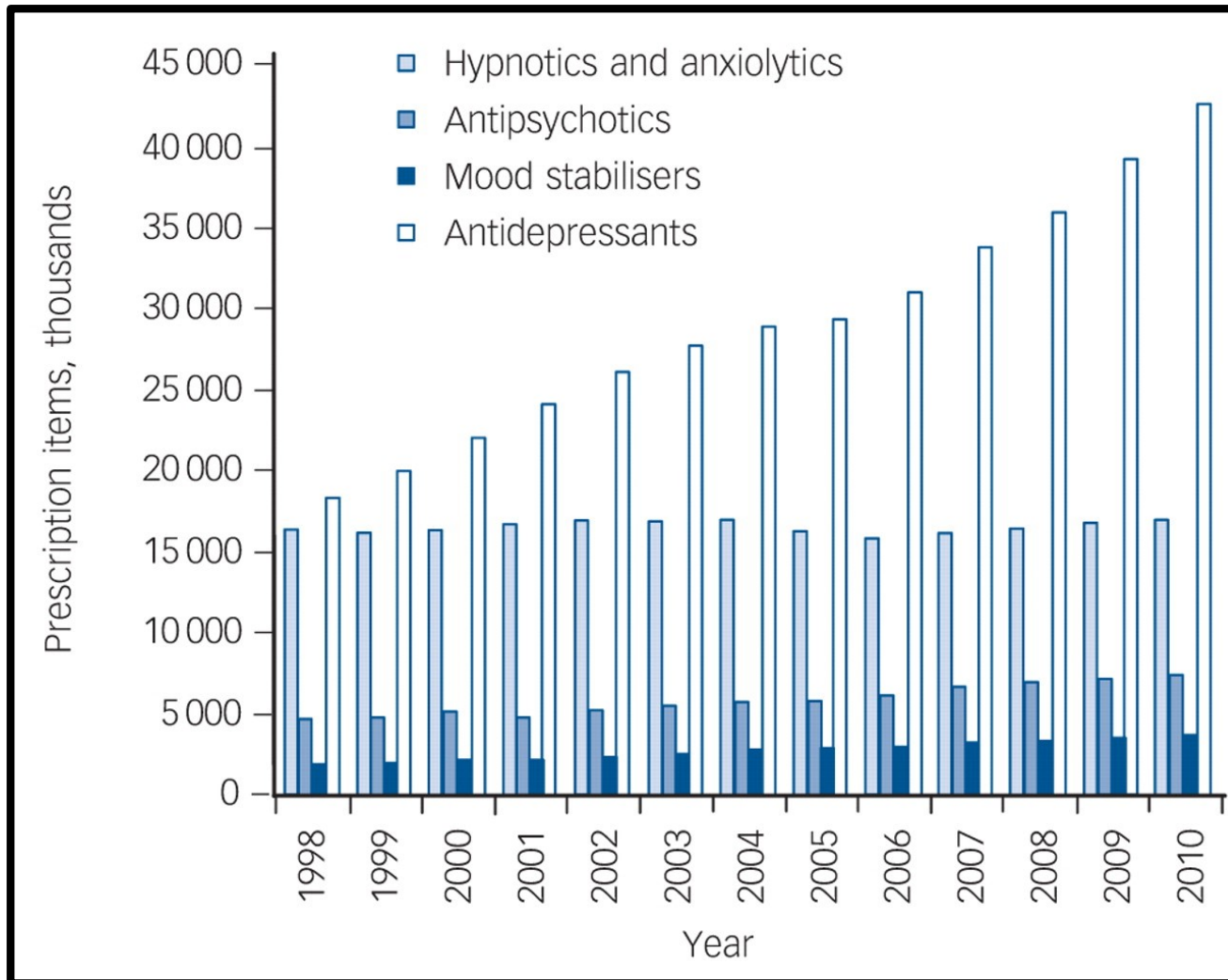
- 75-90% of all physician's office visits are for stress-related conditions/complaints.
- Lifetime prevalence of emotional disorder > 50%.
- 43% of all adults suffer adverse health effects from stress.
- Stress contributes to obesity, diabetes, heart disease, high blood pressure, depression, anxiety, asthma, irritable bowel disease, infertility, headaches, muscle tension and premature aging.

National Institute of Mental Health: "Fact Sheet on Stress."

American Heart Association: "How Does Stress Affect You."

Mayo Clinic: "Stress: Constant stress puts your health at risk."

## Trends in prescriptions of major classes of psychiatric drugs 1998–2010.



Stephen Ilyas, and Joanna Moncrieff BJP 2012;200:393-398

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# Many Factors at Play..... All Must be Addressed...



- Processed, nutrient depleted diet
- Poor gut health
- Persistent low-grade inflammation
- Poor sleep and inadequate rest
- Lack of physical activity
- Social isolation
- Increased exposure to environmental toxins
- Strong focus on image, money, high achievement and having “stuff”
- Weaker personal and community networks

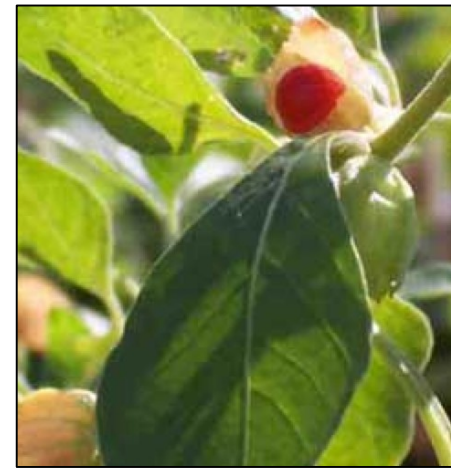
# Adaptogens

*That which adapts, thrives*



- An adaptogen has a normalizing influence on physiological norms caused by stressors; whether environmental or physiological.
- Foundational component of any herbal approach. A few of the most commonly used:
  - Ashwagandha (*Withania somnifera*)
  - Ginseng (*Panax ginseng*, *P. quinquefolius*)
  - Rhodiola (*Rhodiola rosea*)
  - Bacopa (*Bacopa monnieri*)
  - Andrographis (*Andrographis paniculata*)

# Ashwagandha (*Withania somnifera*)



- In Ayurveda indications include:
  - Anemia, muscle weakness, sleep disorders, high stress, overwork, fatigue
  - Balances vata/kapha and pitta in excess
- Calming for anxious, wired, tired, and stressed out individual.
- Preclinical data shows anti-microbial, anti-inflammatory, anti-tumor, anti-stress, anti-depressant, neuroprotective, cardioprotective, immunomodulatory, anti-diabetic activities.

Dar NJ, et al. *Cell Mol Life Sci* 2015; 72(23):4445-60

# Ashwagandha and Chronic Stress

- 64 subjects with history of chronic stress randomized to ashwagandha extract (300 mg) or placebo BID for 60 days.
- Ashwagandha group had significant reduction ( $P < 0.0001$ ) in scores on all stress-assessment scales on day 60 and serum cortisol levels were substantially reduced ( $P = 0.0006$ ), relative to the placebo group.
- Adverse effects were mild in nature and comparable in both groups. No serious adverse events were reported.



Chandrasekhar K, et al. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med.* 2012 Jul;34(3):255-62.



# Ashwagandha and Weight Management?

- RDBPCT 52 subjects under chronic stress received ashwagandha (300 mg) or placebo twice daily for 8 weeks.
- Primary efficacy measures: Perceived Stress Scale and Food Cravings Questionnaire.
- Secondary efficacy measures: Oxford Happiness Questionnaire, Three-Factor Eating Questionnaire, serum cortisol, body weight, and BMI.
- Subjects assessed 0, 4 and 8 weeks.
- Ashwagandha group had significant improvements in primary and secondary measures, with no adverse effects.
- “Ashwagandha root extract might help body weight management in adults under chronic stress.”



Choudhary D, et al. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial. *J Evid Based Complementary Altern Med.* 2017 Jan;22(1):96-106.

# Summary of Other Studies

- RDBPCT found beneficial effect in patients with OCD over placebo.
- Pilot study found increased arousal, orgasm, sexual satisfaction in women at weeks 4 and 8, compared to placebo.
- Review of 5 studies showed greater score improvements on anxiety and/or stress scales than placebo.
- No significant interactions with CYP3A4 or CYP2D6

Jahanbakhsh SP, et al. *Complement Ther Med* 2016; 27:25-9

Dongre S, et al. *Biomed Res Int* 2015; 2015:284154.

Pingali U, et al. *Pharmacognosy Res* 2014; 6(1): 12–18

# Ashwagandha and Thyroid?

- One case report of thyrotoxicosis and two animal studies found high doses of ashwagandha increase T4.
- Small study found some effect on TSH and T4 in patients with bipolar taking 500mg/d standardized ASW (Sensoril®) extract in addition to existing medication regimen (3/30 patients), while placebo showed variable effects (7/30).
- *Possible* that ashwagandha has small impact on thyroid function.



Gannon JM, et al. *J Ayurveda Integr Med* 2014; 5(4): 241–243

# Rhodiola

## (*Rhodiola rosea*)



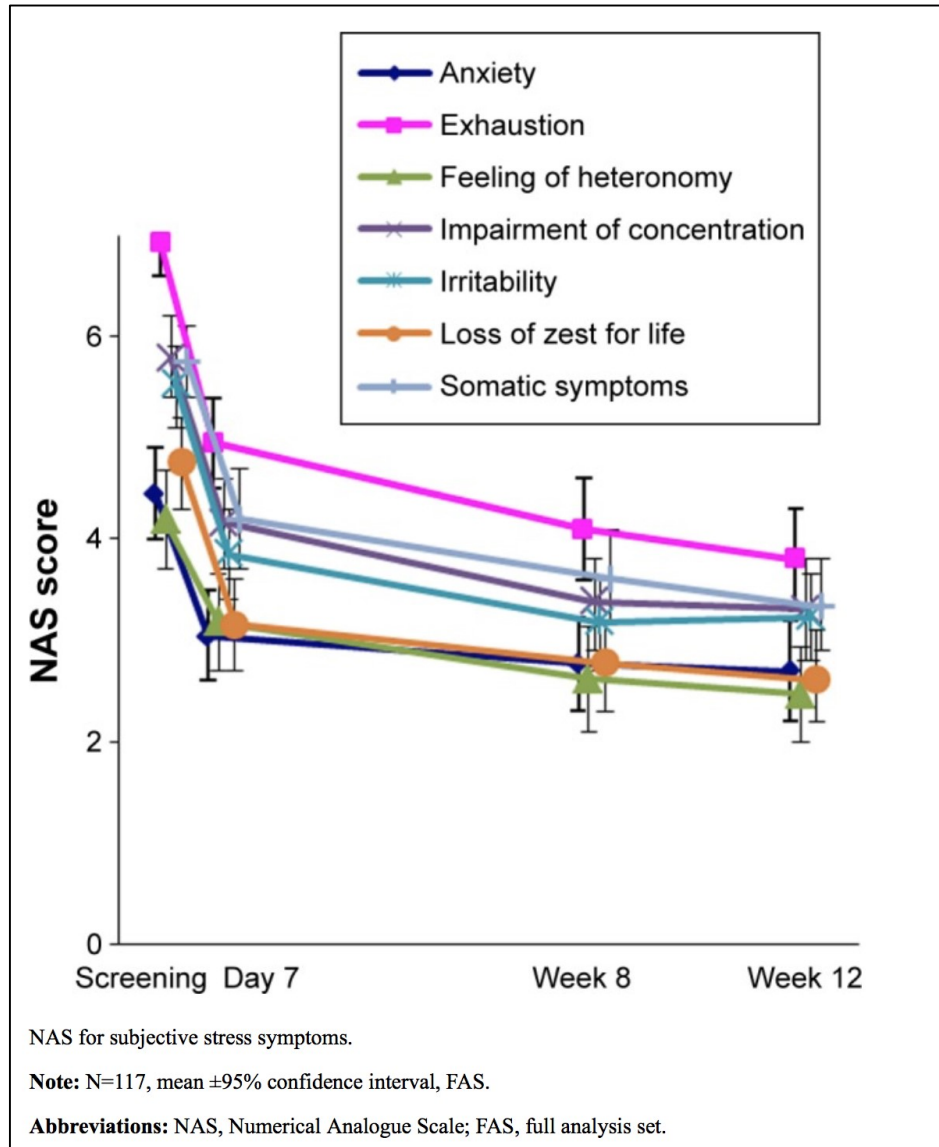
- Used in traditional medicine systems of Eastern Europe and Asia > 3000 years to increase energy, decrease depression, eliminate fatigue, and prevent high altitude sickness.
- Natives of Alaska/northern Canada prepared tea from flowers and ate young succulent leaves and shoots raw or cooked.
- “Anti-fatigue agent” in Sweden, most commonly used psychostimulant in the group of officially registered herbal medicinal products.
- Rhodiola possesses antioxidant, adaptogenic, antistress, antimicrobial, immunomodulatory, angiomodulatory, and antitumoral effects.
- The presence of *salidroside*, *rosavins*, and *p-tyrosol* are responsible for its beneficial effects on depression, fatigue, and cognitive dysfunction.

Nabavi SF, et al. *Phytother Res* 2016; 30(4): 532-9.

Recio MC, et al. *Planta Med* 2016; 82(11-12):952-60.

# Burnout

- Open label multicenter trial of 118 outpatients with burnout syndrome (using multiple validated scales) found 400 mg/d *R. rosea* extract (WS<sup>®</sup> 1375, Rosalin) given over 12 weeks had a significant beneficial effect on symptoms.
- ~10% of participants had adverse events “possibly related” to rhodiola: head pressure, light-headedness, nausea, feeling irritated, and eye swelling.



Kaspar S, et al. *Neuropsychiatr Dis Treat* 2017; 13: 889–898

# Rhodiola: Mood and More

- 11 placebo controlled human clinical trials. Studies suggest benefit for those with depression, physical and mental fatigue, and stress induced chronic fatigue.
- Two RDBPCT (n=146) for major depressive disorder and seven open-label studies totaling 714 individuals with stress-induced mild depression.
- I most often use for those with fibromyalgia, chronic fatigue, chronic pain and atypical depression.

Thu OK, et al. *Eur J Clin Pharmacol* 2016; 72(3):295-300.

Hung SK, et al. *Phytomedicine* 2011; 18(4):235-44.

Amsterdam JD, et al. *Phytomedicine* 2016;23(7):770-83.

# *Rhodiola rosea*



- Recent review suggested rhodiola “can improve many of the neuropsychological symptoms experienced by menopausal women, including fatigue, anxiety, depression, cognitive dysfunction, memory decline, reduced executive functions, and stress intolerance.”
- While few side effects are reported in clinical studies, rhodiola is a stimulating botanical. Possible triggering of mania in bipolar. Dose slow and increase.
- Inhibits CYP2C9 in humans: warfarin, sulfonylureas, phenytoin... (no significant impact CYP1A2, CYP2C19, CYP2D6, CYP3A4).
- Dose 400-600 mg/d extract in divided doses. Products often standardized to ~3% rosavin ~1% salidroside).

Hung SK, et al. *Phytomedicine* 2011; 18(4):235-44.

Gerbarg, PL, et al. *Phytomedicine* 2015; Dec 12. pii: S0944-7113(15)00368-2



*Panax ginseng*

*Panax quinquefolius*

- Human studies in healthy people and clinical studies in patients with fatigue confirm the antifatigue property of *P. ginseng*.
- Most studies (both species) show positive influences on intellectual work capacity in normal subjects and those with decreased cognitive functions.
- Considerable variation in quality of product and dose recommendations. Often standardized to ginsenoside levels.

Oliynyk S, et al *J Ginseng Res* 2013; 37(2): 144-166



# Some of the Ginseng Research

- *P. ginseng* inhibits viral attachment, membrane penetration, and replication, though the foremost antiviral activities of ginseng are attributed to the enhancement of host immunity.
- *P. quinquefolius* may reduce risk of moderate-severe respiratory infections in patients with CLL
- Systematic review found *P. ginseng* improved fasting glucose, postprandial insulin, triglycerides, total cholesterol, LDL-C levels; no difference in postprandial glucose or fasting insulin noted.
- Korean red ginseng shown to improve cold hands/feet, cold hypersensitivity.
- Improved cognitive function in healthy adults post treatment.



Qui QF, et al. *Medicine* 2016; 95(6):e2584  
Park KS, et al. *J Ethnopharmacol* 2014; 158 (PtA): 25-32  
Im K, et al. *J Ginseng Res* 2016; 40(4):309-14

# Cancer Related Fatigue

- *P. quinquefolius* may reduce the risk of moderate-severe respiratory infections in patients with CLL
- Four RCT show that both species improve cancer related fatigue. Largest study 364 participants from 40 institutions.
- Randomized to receive placebo or 2000 mg/d of American ginseng for 8 weeks to determine effect on fatigue.
- Ginseng reduced fatigue by *almost double* that of placebo in those undergoing active cancer treatment. No discernible toxicities.
- Some experts recommend taking breaks every 12 weeks.. Unclear if any clinical benefit or enhanced safety.



High KP, et al. J Support Oncol 2012; 10(5):195-201.

Barton DL, et al. J Natl Cancer Inst 2013; 105(16): 1230–1238

# Herb-Drug Interactions

- No clinically significant drug interactions observed using approved CYP probe drugs and P-gp probe substrates when *P. ginseng* administered for 2 weeks in healthy volunteers.
- *P. quinquefolius* did not interact with indinavir (CYP3A4) in human volunteers.
- *P. ginseng* 1 gram/d for 6 weeks, no significant change in INR in patients on warfarin.



Kim DS, et al. *J Ginseng Res* 2016; 40(4):375-81  
Andrade AS, et al. *BMC Complement Altern Med* 2008; 8:50  
Lee YH, et al. *Int J Cardiol* 2010; 145(2):275-6.

# Ginseng Root and Blood Pressure

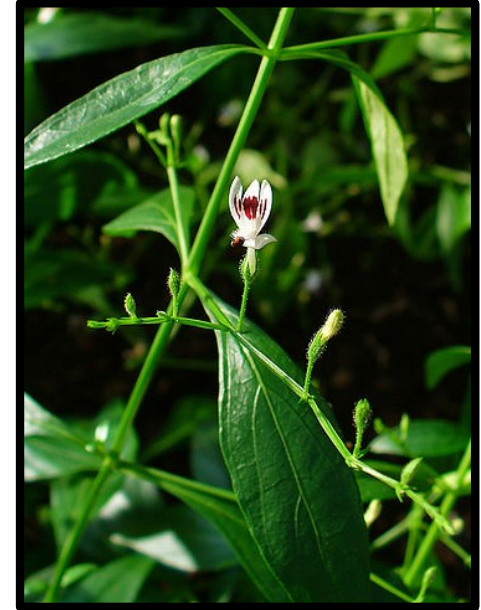
- Ginseng is commonly contraindicated in those with hypertension, particularly “red” or steamed ginseng.
- Systematic review and meta-analysis assessed whether ginseng has an effect on BP.
- 17 studies satisfied eligibility criteria (n=1381).
- No significant effect of ginseng on SBP, DBP and MAP was found.
- *“Ginseng appears to have neutral vascular affects; therefore, should not be discouraged for concern of increased blood pressure.”*



Komishon AM, Shishtar E, Ha V, Sievenpiper JL, et al. The effect of ginseng (genus *Panax*) on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. *J Hum Hypertens*. 2016 Oct;30(10):619-26.

# Andrographis Aerial Parts (*Andrographis paniculata*)

- Andrographis has anti-inflammatory, neuroprotective antifibrotic, and anti-fatigue effects in autoimmune diseases such as rheumatoid arthritis.
- RDBPCT assessed 170 mg of andrographis dried extract tablet (total andrographolides: 85 mg per tablet; 10:1 extract, 75% ethanol) or placebo BID on relapse rate and fatigue using the Fatigue Severity Scores (FSS) over 12 months in 25 MS patients receiving interferon.
- Patients treated with andrographis showed significant reduction in their FSS score compared to placebo (44 % reduction at 12 months).
- No statistically significant differences were observed for relapse rate or inflammatory parameters. One patient in active group presented with a mild and transient skin rash, which was alleviated with anti-histamine treatment for three weeks.



Bertoglio JC, Baumgartner M, Palma R, et al. Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study. *BMC Neurol.* 2016 May 23;16:77.

# Bacopa Herb

(*Bacopa monnieri*)

- Systematic review of 5 studies found bacopa significantly improved memory span as well as verbal and visual memory in children and adolescents.
- Two studies reported improvements in hyperactivity and attention in children diagnosed with ADHD.
- Overall outcome data demonstrated small to medium effect sizes.
- Bacopa was well tolerated with only 2.3% of all participants reporting mild side-effects
- There remains a significant need for replicated study designs and stringent statistical analysis to validate these outcomes.



Kean JD, Downey LA, Stough C. A systematic review of the Ayurvedic medicinal herb *Bacopa monnieri* in child and adolescent populations. *Complement Ther Med.* 2016 Dec;29:56-62.

# Nervines

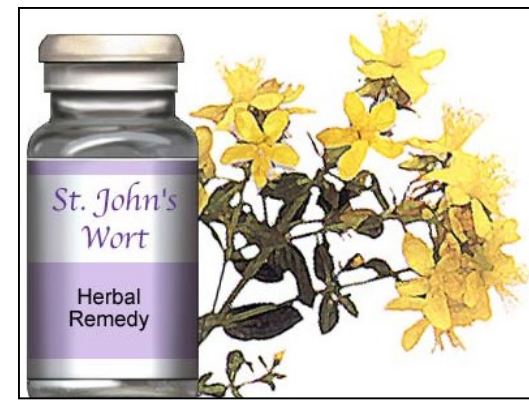
- Adaptogens principally impact autonomic nervous system.
- Nervines work principally on the central and/or peripheral nervous system – *but there is overlap*
  - Stimulant: stimulating effect on nervous system: all caffeine containing plants but also rosemary, peppermint, etc.
  - Relaxant: soothing, calming effect that can range from mild to sedative
  - Tonic: nourishing, strengthening effect

# Common Nervines

Nervine Relaxant Mild	Nervine Relaxant Moderate	Nervine Relaxant Strong	Nervine Tonic
Cramp bark	Black cohosh	Hops	Saint John's wort
Lavender	Vervain	Passionflower	Saffron



# St. John's Wort (*Hypericum perforatum*)



- SJW more effective than placebo, as effective as tricyclics and SSRIs for depression. Improves mood, decreases somatic symptoms, and insomnia related to depression.
- Topically reduces severity of plaque psoriasis and shortens wound healing, while reducing scarring.
- Dose is 300-600 mg TID of extract standardized to 0.3% hypericin and/or 1-3% hyperforin.
- Primary risk is herb-drug interaction (CYP3A4, p-glycoprotein), including oral contraceptives

*Natural Medicines Comprehensive Database: St. John's Wort*

Ng QX, et al. *J Affect Disorder* 2017; 210:211-221

Mansouri P, et al *J Postgrad Med* 2017; Mar 3. doi: 10.4103/0022-3859.201423

# Saffron

(*Crocus sativus*)



- Throughout history, saffron was used for depression.
- Systematic review of 12 studies found saffron may improve the symptoms and the effects of depression, premenstrual syndrome, sexual dysfunction and infertility, and excessive snacking behaviors.
- Recent study of 60 patients with anxiety/depression found 50 mg BID had significant benefit on BDI and BAI.
- Saffron (std. to 0.34% safranal) – 80-160 mg per day

Hausenblas HA, et al. *J Integr Med* 2015; 13(4):231-40  
Mazidi M, et al. *J Complement Integr Med* 2016; 2016;13(2):195-9.

# Chamomile Flowers

## *(Matricaria chamomilla)*

- Patients with moderate-to-severe GAD enrolled for two-phase study at University Penn. Hospital.
- Phase 1: 179 enrolled for 12 weeks open-label with chamomile extract 500mg TID (capsule = 2 grams herb).
- Phase 2: 93 treatment responders randomized to 26 weeks of chamomile therapy or placebo in a double-blinded, placebo-substitution design.
- Chamomile participants maintained significantly lower GAD symptoms than placebo ( $P = 0.0032$ ), with significant reductions in body weight ( $P = 0.046$ ) and MAP ( $P = 0.0063$ ). Both treatments had similar low adverse event rates.
- Long-term chamomile was safe and significantly reduced moderate-to-severe GAD symptoms, but did not significantly reduce rate of relapse.



Mao JJ, et al. Long-term chamomile (*Matricaria chamomilla* L.) treatment for generalized anxiety disorder: A randomized clinical trial. *Phytomedicine*. 2016 Dec 15;23(14):1735-1742.

# Lavender

(*Lavandula angustifolia*)

- RDBPCT of 318 adult out-patients with mixed anxiety-depression (ICD-10);  $\geq 18$  points on HAM-A, moderately severe anxious and depressed mood found 80 mg/d Silexan (oil extracted from flowers via steam distillation) superior to placebo for improving both anxiety and depression scores.
- Eructation was only adverse effect and was significant.
- Meta-analysis 5 studies showed positive association between Silexan and GAD but methodology for most were problematic.



Kasper S, et al. Efficacy of Silexan in mixed anxiety-depression – A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol* 2016; 26(2):331-40.

Generoso MB, et al. Lavender Oil Preparation (Silexan) for Treating Anxiety: An Updated Meta-Analysis, *J Clin Psychopharmacol* 2017; 37(1):115-117

# Kava

(*Piper methysticum*)



- Native to the South Pacific islands where the root has been used medicinally/ceremonially for centuries.
- Inhibits reuptake of norepinephrine and dopamine, GABAergic.
- Clinical trials support kava in treatment of anxiety: 2 meta-analyses.
- Study in patients with GAD found statistically significant increase in women's sexual drive compared to placebo.
- Safety issues suggest that poor quality of kava material was responsible for reports of liver toxicity. Risk appears rare. However, common sense would suggest avoidance in those with liver disorders and periodic liver testing may be indicated if long-term use is warranted.

Teschke R, et al. Food Chem Toxicol 2011; 49(10):2503-16

Sarris J, et al. Aust N Z J Psychiatry 2011; 45(1):27-35.

Sarris J, et al. Phytother Res 2013; 27(11):1723-8

# Reversal of German Decision

- “It came as a surprise when the safety of kava was suddenly questioned based on the observation of a series of case reports of liver toxicity in 1999 and 2000. These case reports ultimately led to a ban of kava products in Europe - a ban that has been contested because of the poor evidence of risks related to kava. Only recently, two German administrative courts decided that the decision of the regulatory authority to ban kava as a measure to ensure consumer safety was inappropriate and even associated with an increased risk due to the higher risk inherent to the therapeutic alternatives.”

Kuchla K, et al. *Planta Med* 2015; 81(18):1647-53

# Harvard South Shore Algorithm: GAD

- Selective serotonin reuptake inhibitors (SSRIs) still basic first-line medication.
- Early alternatives include duloxetine, buspirone, hydroxyzine, pregabalin, or bupropion, in that order.
- If response is inadequate, then second recommendation is to try a different SSRI.
- Additional alternatives now include benzodiazepines, venlafaxine, **kava**, and agomelatine.
- If response to second SSRI is unsatisfactory, then the recommendation is to try an SNRI.

Abejuela HR, et al. *Harv Rev Psychiatry* 2016; Jul-Aug;24(4):243-56.

# Skullcap

(*Scutellaria lateriflora*)



- Nervine tonic, anticonvulsant, anxiolytic. For those who are hypersensitive to touch, highly sensitive, worry excessively.
- Review supports chronic use for easing anxiety.
- RDBPC crossover study (n=43) had skullcap (350 mg) or placebo TID, each for two weeks.
  - Skullcap significantly enhanced global mood without a reduction in energy or cognition, compared to placebo.
- Acute: tincture taken 10 drops every 15 minutes up to 8 doses.  
Chronic: 1-3 grams/d crude herb or equivalent.

Brock C, et al. *Phytother Res* 2014; 28(5):692-8.

Sarris J, et al. *CNS Drugs* 2013; 27(4):301-19.



# A Powerful Combination



- Studies consistently show valerian and hops superior to placebo for insomnia.
- The combination of valerian, hops, passionflower was found equivalent to 10 mg zolpidem when taken nightly for two weeks in 91 patients with primary insomnia.

Maroo N, et al. Indian J Pharmacol 2013; 45(1):34-9



*Plants are all chemists,  
tirelessly assembling the molecules of the world.*

Gary Snyder