

# Herbs and Nutrients for Stress Resiliency that may be Beneficial for COVID-19 Prevention or Recovery

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# Professional Disclaimer

- Dr. Richard Brown and Dr. Patricia Gerbarg have no conflicts of interest regarding this lecture.
- They do not receive any financial benefits from the promotion or sale of the supplements mentioned in this lecture.
- They are co-authors on some of the references included in this lecture.

Consultation with your doctor is advised before trying supplements for serious illnesses such as COVID-19.

- Some of the treatments covered in this lecture have been tested for efficacy against COVID-19 in vitro or in vivo.
- Some treatments have been tested against infections that have similar properties, e.g. other coronaviruses, influenza, respiratory infections, or inflammatory conditions
- Some of the treatments which we have found to be beneficial in patients treated in clinical practice, have not yet been tested in controlled studies of COVID-19, but are promising candidates for further study. These are low in side effects and could be tried to improve immune defense or recovery from COVID-19.

# Treatment Targets for Coronavirus

- Anti-viral: cell penetration, replication of viral RNA
  - Anti-inflammatory: dysregulated cytokine and immune response “cytokine storm”
  - Anti-stress: anxiety, depression, PTSD
- 
- Sun X., et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020 Apr 25.

# Recovery from COVID-19

- Post-infection symptoms can last for days or months:
  - chronic fatigue, myalgia (muscle aches)
  - Anxiety, depression, PTSD
  - cognitive dysfunction
  - persistent respiratory symptoms
- Rongfeng Qi, et al. Psychological Morbidities and Fatigue in Patients With Confirmed COVID-19 During Disease Outbreak: Prevalence and Associated Biopsychosocial Risk Factors. medRxiv. 2020 May 11;2020.05.08

# Post-COVID Fatigue

- 30 - 50 % hospital discharged COVID patients
- Chronic Fatigue Syndrome needs further study in this population
- Findings of autonomic nervous system exhaustion underlying Chronic Fatigue, PTSD, Fibromyalgia Syndrome are similar.
- In US most common events preceding CFS have been car accident or severe infection (e.g. influenza, Lyme disease)
- After other symptoms resolve, patients report extreme fatigue, frequent long naps, erratic sleep cycles

(Qi R, et al. medRxiv . 2020 May 11. Psychological Morbidities and Fatigue in Patients With Confirmed COVID-19; Wang X, et al. QJM. 2020 May 22;hcaa178. The Clinical Features and Outcomes of Discharged Coronavirus Disease 2019 Patients)

# Herbs and Nutrients

- Adaptogens: *Rhodiola rosea*, *Eleutherococcus senticosus*, *Schizandra chinensis*
- Red Mangrove of Fiji (*Rhizophora mangle*)
- Black elderberry (*Sambucus nigra*)
- Beta Glucan from mushrooms
- Olive Leaf Extract (*Olea europaea*)
- Green chiretta (*Andrographus peniculata*)
- French Oak wood Extract (*Quercus Robur Extract*)
- Zinc
- Traditional Chinese Medicine (TCM)

# Adaptogens

- Arctic root, Golden root (*Rhodiola rosea*)
- Chinese magnolia, Schizandra (*Schizandra chinensis*)
- Siberian Ginseng (*Acanthopanax* or *Eleutherococcus senticosus*)
- Asian Ginseng (*Panax ginseng*)
- Ashwaganda (*Withania somnifera*)



# Defining Adaptogens

- Herbal extracts Protect against multiple stressors
  - increase attention and endurance under stress
  - reduce/mitigate/prevent stress-induced impairments and disorders related neuro-endocrine-immune systems.
  - **Metabolic Regulators**
  - Cellular repair: mitochondria, heat shock proteins, neuropeptide Y, glucocorticoid receptors
  - Roots contain many Antioxidants
  - Epigenetic effects
- (A Panossian & G Wikman, 2009)

# Single Dose Adaptogen Effects

- R. rosea, S. chinesis, E. senticosus
- SAS stimulation
- No addiction, tolerance, abuse, rebound hypersomnolence
- R.rosea most active stimulating effect in 30 min lasts 4-6 hrs
- HPA axis adaptation to repeated stress by multiple doses

(Panossian A & Wagner H, Phytother Res 2005, 19:819-38)

*Rhodiola rosea*



# Molecular Mechanisms of Adaptogen *Rhodiola rosea* (Arctic root)

- **Metabolic Regulators**
- Rich in antioxidants
- Increase ATP (energy transport molecules) and Creatine in brain cells
- Enhance Cellular repair: mitochondria, heat shock proteins, neuropeptide Y, glucocorticoid receptors
- Epigenetic effects
- Saratikov AS, Krasnov EA (1987) *Rhodiola rosea* is a valuable medicinal plant. Tomsk. Russia .91-105. Panossian A, Psych Clin NA, 2013; Panossian A. in *Complementary and Integrative Treatments in Psychiatric Practice*. APAP 2017; Gerbarg, Brown. in *Complementary and Integrative Treatments in Psychiatric Practice*. APAP 2017)

## *Rhodiola rosea* (Artic Root, Roseroot)

- Adaptogen: improve energy, mood, focus, memory
- Enhance physical and mental performance under stress
- Stimulative effects can be additive
  - Caffeine in coffee, sports drinks
  - Mild anti-platelet at higher doses (above 800 mg/day)
- Patients susceptible to stimulative effects
  - Anxiety disorder, Bipolar disorder, Elderly
  - Patients with underlying cardiac arrhythmia

(Panossian AG. Adaptogens in mental and behavioral disorders. *Psych Clin NA*. 2013:49-64; Gerbarg & Brown. Phytomedicines for prevention and treatment of mental health disorders. *Psych Clin NA*. 2013:37-47; Panossian A. Complementary and Integrative Treatments in Psychiatric Practice. APAP 2017)

## *Rhodiola rosea*

- Dose bell curve: 50–800 mg/d; average 300-450 mg/d
- 95% ethanol *R. rosea* root extracts (Norway) showed *in vitro* inhibition of CYP3A4 and P-glycoprotein (P-gp).
- SHR-5 extract fed to rats with two CYP450 substrates, warfarin and theophylline. *R. rosea* SHR-5 *in vivo* had no significant effect on CYP450, theophylline pharmacokinetics, or warfarin pharmacokinetics or anticoagulant activity.
- No published *in vivo* studies of *R. rosea* effects on P-gp or serum levels of digoxin

(Hellum et al., *Planta Med.* 2010. 76(4):331-8; Panossian, et al. *Planta Med.* 2009. 23(3):351-7)

# SHR-5 Rhodiola rosea for Depression

- RDBPC 6-wk trial mild-mod depression
- N = 60
- A - 340mg/d B – 680mg/d C – placebo

Mean drop in Scores

	A	B	C
HAMD	25→16	24→17	24 → 23
		↑self-esteem	

(Darbinyan V. et al. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nordic J of Psychiatry 2007;61(5):343-8)

# Clinical Uses for *Rhodiola rosea*

- Relieve fatigue and cognitive dysfunction caused by medical illness or medications
- Anti-bacterial and anti-viral (Coxsackievirus B3, Hepatitis C)
- Increase energy, motivation
- Improve mental and physical and endurance
- Antidepressant
- Improve age-related decline in memory and cognitive function

(Gerbarg P, Illeg P, and Brown RP. *Rhodiola Rosea* in Psychiatric and Medical Practice. In *Rhodiola rosea*, Ed. A Cuerrier, and K Ampong-Nyarko. Series Traditional Herbal Medicines for Modern Times. Ed. R Hardman. Taylor & Francis Group, NY. 2015; 14:225-252.; Wang H. The in Vitro and in Vivo Antiviral Effects of Salidroside from *R. rosea* against Coxsackie B3), *Phytomedicine*. 2009;16(2-3):146-155)



# Additional Benefits of *Rhodiola rosea*

- Improve stress tolerance and resiliency for physical and emotional stress
- Prevent/Treat Post-traumatic Stress Disorder
- ADHD – helps improve mental focus
- Improve cognitive recovery from neuro-lyme disease
- Prevent/relieve: high altitude sickness, jet lag
- Used for sexual enhancement
- Antibacterial

# ADAPT: *Rhodiola rosea*, *Eleutherococcus senticosus*, *Schizandra chinensis*

- Improved ANS balance, function and resilience
- Corrects abnormal levels of neuropeptide Y (also found in PTSD)
- Suggested Treatment:
  - a. *R. rosea* (Rosavin by Ameriden or Energy Kare by Karenherbs.com)
  - b. *E. senticosus* + *S. chinensis* (Kare-N-Liver by Karenherbs.com)

(Illeg and Gerbarg Gerbarg P, Illeg P, Brown RP. *Rhodiola Rosea* in Psychiatric and Medical Practice. In *Rhodiola rosea*, Ed. Alain Cuerrier and Kwesi Ampong-Nyarko. Series Traditional Herbal Medicines for Modern Times. Series Ed. Roland Hardman. Taylor & Francis Group, New York. 2015, vol 14:225-252. ISBN: 978-1-4398-8841-4.

## Rhodiola Side Effects

- Excess stimulation
- Bipolar –caution, may induce mania
- Vivid dreams (usually not nightmares)
- Rare sedation
- Rare hypersexuality
- Rare agitation with ↑ BP in post MI patients
- Mild GI upset
- Advise not to combine with MAOIs

## Administration of *Rhodiola Rosea*

- 20 minutes before food (breakfast and lunch) or 2 hours after a meal
- Start 1 capsule AM (100-150-170-180 mg)
- Increase by 1 cap/tab every 3-14 days
- Average dose 300-600 mg/day
- High dose: 900 mg/day
- Above 900 mg risk of bruising increases

# Quality Rhodiola Rosea Brands

- **Energy-Kare:** Kare-n-Herbs 180 mg tab (4%rosavins) (higher potency)
- **Rosavin:** Ameriden 100 or 150 mg (3% rosavins)
- **Arctic Root:** Swedish Herbal Institute 180 mg (4% rosavins)

# ADAPT Formula

- Balance of adaptogens to optimize physical and intellectual performance under stress: mental alertness with emotional calmness
- *Rhodiola rosea*
- *Eleutherococcus senticosus*
- *Schizandra chinensis*

(Brown RP, Gerbarg PL. How to use Herbs, Nutrients and Yoga in Mental Health; The Rhodiola Revolution)

Eleutherococcus senticosus  
(Acanthopanax or Siberian ginseng)

***In vitro* & animal studies:** inhibits P450 enzymes 1A2, 2C9, 2D6, and 3A4.

**Human studies:** no impact on **CYP3A4** or **CYP2D6**, no clinically significant change in isozymes. No effect on digoxin.

(Kennedy & Seely, 2010)

# Schisandra chinensis

***In vitro*: inhibits** CYP3A4 enzymes.

***In vivo*: induces** CYP3A4

Animals: decreased warfarin levels

**Humans: no change in warfarin levels**

(Wang, Hu, et al. Curr Pharm Biotechnol. Herb-drug interactions. 2012, 13(9):17-30; Wang, Hu, et al. 2011)



# ADAPT for Cognitive Performance

- ADAPT-232: *Rhodiola rosea* + *Eleutherococcus senticosus* + *Schizandra chinensis*
- DPRPC 40 women (20-68 yo) c/o chronic stress
- 1 dose ADAPT or placebo → 2 hrs later stressful cognitive tests
- ADAPT significantly improved focus, processing speed, and accuracy.

(G. Aslayan et al. *Phytomedicine*. 2010, 17:494-99)

# Red Mangrove Tree of Fiji - *Rhizophora mangle*

- Long use for activating protective cells in respiratory tract
- Numerous antiviral, immune enhancing, anti-inflammatory, antinociceptive constituents:
  - Flavonols (Kaemferol, quercetin)
  - 7-hydroxycoumarin (does not affect coagulation)
  - Polyphenols
  - Glucans
  - Hexose
- Quercetin Suppresses proinflammatory cytokine production in macrophages. Could reduce “cytokine storm”

(Kelly G. 2011. Quercetin Monograph. *Alternative Med Rev.* 16:172-194; Tais et al. 2010. *J Pharmacy Pharmacology.* 62:2015-213; Yi, et al. 2004. Small molecules blocking the entry of severe acute respiratory syndrome coronaviruses into host cells. *J Virology.* 11334-11339)

# Red Mangrove Tree of Fiji - Respigard®

- [www.Naturesnurse.com](http://www.Naturesnurse.com), [Amazon.com](http://Amazon.com).
- Directions on bottle.
- Limited supplies
- Nature's nurse uses sustainable harvesting techniques, but new groves of trees are much needed.

# Black Elderberry Syrup from European elder (*Sambucus nigra*)

- Inhibits viral replication
- Long traditional use for flu, respiratory infections
- Controlled studies are needed.
  
- Nature's Way Sambucus
- No need to get formulas with added ingredients
- Acute infection: 2 tsp 4x/day
- Prevention: 1 – 2 tsp/day

Rhodiola rosea root, Sambucus nigra fruit,  
and Nigella sativa seeds

- Infectious bronchitis virus (IBV) a chicken coronavirus
- Vero cells pretreated with extract, infected with virus, incubated
- Herbal extract inhibited viral replication

(Chen C. BMC Vet Res. 2014.10:24)

## 373 extracts from 128 TCMs tested for Anti-Ebola Virus Effects

- Rhodiola rosea: potent inhibition of cell entry for Ebola and Marburg
- Polyphenols Ellagic Acid and Gallic Acid: most effective constituents
- French Oakwood Extracts also contains ellago-tannins (ellagic acid + tannins)
- Rhodiola enhances cellular immunity and humoral immune function in animal model
- Rhodiola inhibits Dengue Virus multiplication.
- Salidroside boosts host immunity and inhibits viral protein synthesis

(Cui Q, et al. *Viruses*. 2018 Mar;10(4):152. Liu M-W, et al. *Int J Mol Med*. 2015. 36:386-98)

# Beta Glucan

- Extract from cell walls of mushrooms, yeast
- Immunomodulatory and cytoprotective
- Beta Factor from Ameriden.com
- 1 – 2 caps/day taken on empty stomach

# Shiitake mushroom (*Lentinus edodes*)

- $\beta$ -glucan extracts reduce pro-inflammatory cytokines and oxidative stress.
- Immunomodulatory and cytoprotective properties in 'house' (IH-Lentinan, IHL) and commercial (Carbosynth-Lentinan, CL) extract in vitro models of lung injury and macrophage phagocytosis.
- CL higher amounts of  $\alpha$ -glucans; less  $\beta$ -glucans. Both extracts reduced cytokine-induced NF- $\kappa$ B activation in human alveolar epithelial A549 cells. In activated THP-1 derived macrophages, CL more effectively attenuated pro-inflammatory cytokine production (TNF- $\alpha$ , IL-8, IL-2, IL-6, IL-22) and TGF- $\beta$  and IL-10. CL extract attenuated oxidative stress-induced early apoptosis; IHL extract attenuated late apoptosis.
- Murphy EJ.  $\beta$ -Glucan extracts from the same edible shiitake mushroom *Lentinus edodes* produce differential in-vitro immunomodulatory and pulmonary cytoprotective effects — Implications for coronavirus disease (COVID-19) immunotherapies. *Science Total Environ.* 2020 Aug 25; 732: 139330. online 2020 May 11.



# Olive Leaf Extract

- salidroside (tyrosol), adaptogen used to protect against many infections for several hundred years
- polyphenols, notably oleuropein and hydroxytyrosol, that have antiviral, antibacterial, anti-inflammatory and antioxidant properties that may reduce Upper Respiratory Infections
- Evidence of inhibiting viral replications in vitro
- Olive Factor from Ameriden - 2pills 2x/day

(Somerville V, The Effect of Olive Leaf Extract on Upper Respiratory Illness in High School Athletes: RCT. *Nutrients*. 2019; 11(2): 358.)

# Creast or Green Chireta (*Andrographis peniculata*)

- Protects against influenza.
- Native to India and Sri Lanka
- No data for COVID-19 yet.
- Kold Kare from KarenHerbs
- 1 pill 1-2 X/day for prevention
- 1 pill 4x/day when symptoms

# Zinc

- Essential for immune function
- Considerable data on zinc inhibiting viral replication
- 25% of population in developing countries have zinc deficiency
- Zinc deficiency associated with compromised immune defense
- In China: 100 – 200 mg/day are used, but these doses can cause toxicity and block copper absorption
- Safety for various lengths of use is unknown

(Read SA et al. Role of Zinc in anti-viral immunity. 2019 Jul 1;10(4):696-710.)

# French Oak Wood Extract (Robuvit)

- RCTS showed benefits for CFS and PTSD
- Helpful for CFS
- Reduced oxygen free radicals and homocysteine
- Contains 40% polyphenols called ellagotannins. Also found in Red Mangrove tree of Fiji
- 20 cases relieved fatigue after COVID-19 [Dr. Brown's practice]

# French Oak Wood Extract References

- Gianni Belcaro et al. Supplementation With Robuvit® in Post-Traumatic Stress Disorders Associated to High Oxidative Stress. Edmondo Ippolito, et al. Robuvit®: Improvement of Fatigue in Medical Convalescence. J Sports Med Phys Fitness. 2018 May;58(5):678-683.
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- G Belcaro , et al. Improved Management of Primary Chronic Fatigue Syndrome With the Supplement French Oak Wood Extract (Robuvit®): A Pilot, Registry Evaluation, Panminerva Med. 2014 Mar;56(1):63-72.

# Traditional Chinese Medicine (TCM)

- Role of TCM herbs is unclear and requires training in Chinese Medicine, acute observation of the patient, takes time to obtain
- Low quality of research published – controlled studies needed
- Screening hundreds of herbal formulas now to identify most promising compounds for in vitro and in vivo testing
- (2020 Lotus Institute of Integrative Medicine [www.lotus.org](http://www.lotus.org) Compiled by Chen JK, Hsu Lori. Eds: Ford N., et al. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. <https://doi.org/10.1002/jia2.25489>

# Current and Future Directions: Prevention & Recovery

- Determine natural compounds that can have anti-viral effects and which can prevent humans from infection by this coronavirus
  - Molecular docking to find high binding affinity between the herbal compound molecules and the COVID-19 receptor
  - Prevent entry into human cells
  - Prevent replication of virus RNA and/or damage viral cells
- Identify natural compounds with known anti-inflammatory effects for trials in COVID treatments
- Synthesize molecules and evaluate *in vitro*, in animal models and in humans for activity against COVID-19
- Trials of natural compounds known to reduce symptoms similar to those in post-COVID patients: fatigue, myalgia, depression, PTSD, cognitive dysfunction, pulmonary fibrosis

# Integrative Psychiatry Resources

- ***How to use Herbs, Nutrients and Yoga in Mental Health Care***

RP Brown, PL Gerbarg, PR Muskin. WW Norton 2008

- ***Complementary and Integrative Treatments in Psychiatric Practice***

Ed. Gerbarg PL, Brown RP and Muskin PR.

American Psychiatric Association Publishing, 2017

- **[www.Breath-Body-Mind.com](http://www.Breath-Body-Mind.com)**

RP Brown & PL Gerbarg. Updates Integrative Psychiatry, Videos, Workshops

- **American Psychiatric Association CAIM Caucus:**

<https://www.psychiatry.org/psychiatrists/practice/professional-interests/integrative-medicine>



# Online Resources Websites

[www.Breath-Body-Mind.com](http://www.Breath-Body-Mind.com)

RP Brown & PL Gerbarg: Videos of BBM Practices, Free Integrative Psychiatry Newsletter

Breath Pacing Audio Track: <https://naturalsinger.com/5-breaths>

Breath-Pacing 2-Bells track (60 Minutes): Spotify [App], Amazon.com,  
Coherentbreathing.com

[www.RobertPeng.com](http://www.RobertPeng.com) QiGong DVDs, meditation CDs

[www.STWS.org](http://www.STWS.org) – low fee and pro bono BBM programs for disaster survivors, first responders, veterans

[www.globalgrassroots.org](http://www.globalgrassroots.org) (women's empowerment) programs in Africa

[www.nolimitgen.org](http://www.nolimitgen.org) (child refugees) Free Child teaching Videos

HealthFlix.online (youtube) Webinars with Dr. Brown & Dr. Gerbarg

## Key References

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