The Stress Response, Women's Health & the Role of Adaptogens

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July 27, 2016

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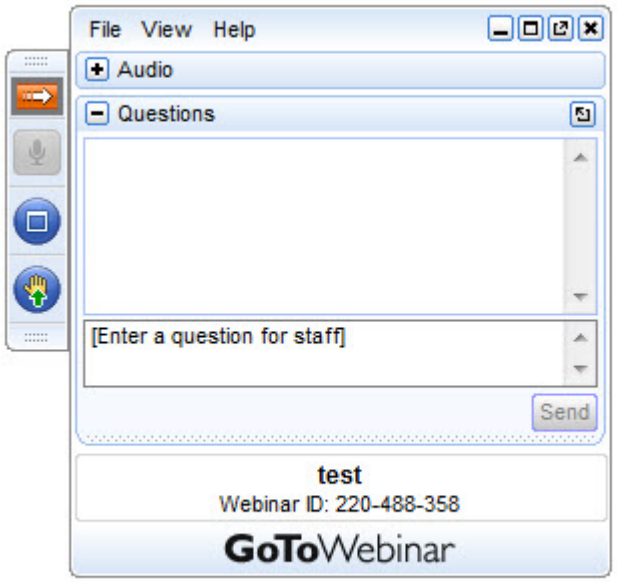
- We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



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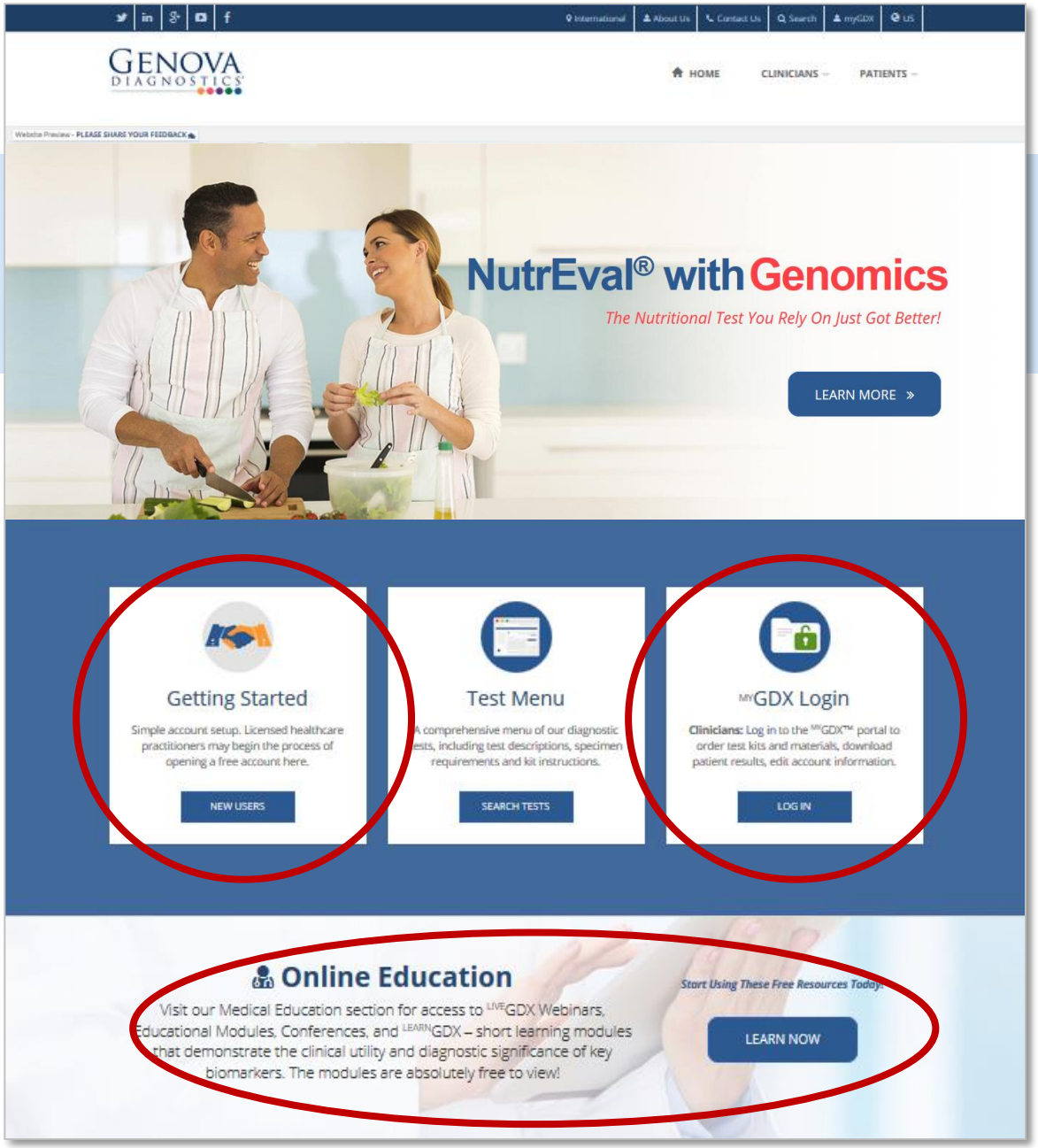

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Disclaimer

- The suggested dosages are for educational purposes only.
- They are suggestions for patients with normal renal and hepatic function.
- They are not intended as a substitute for a personalized approach to each patient but are designed instead to be a guideline.
- Genova Diagnostics and Aviva Romm, MD, are not responsible for any adverse effects or consequences resulting from the use of any of these suggestions or preparations in this seminar.

Women & Stress

- 75% - 90% of doctor visits are for stress-related ailments/concerns
- APA 75% of all Americans have moderate to severe stress
- 30% more likely to report experiencing a great deal of stress
- Greater physical and emotional symptoms of stress than men:
  - Headache (41% vs. 30%),
  - Weepiness (44% vs. 15%),
  - Stomach upset or indigestion (32% vs. 21)
- Lean in, do it, have it all, be it all

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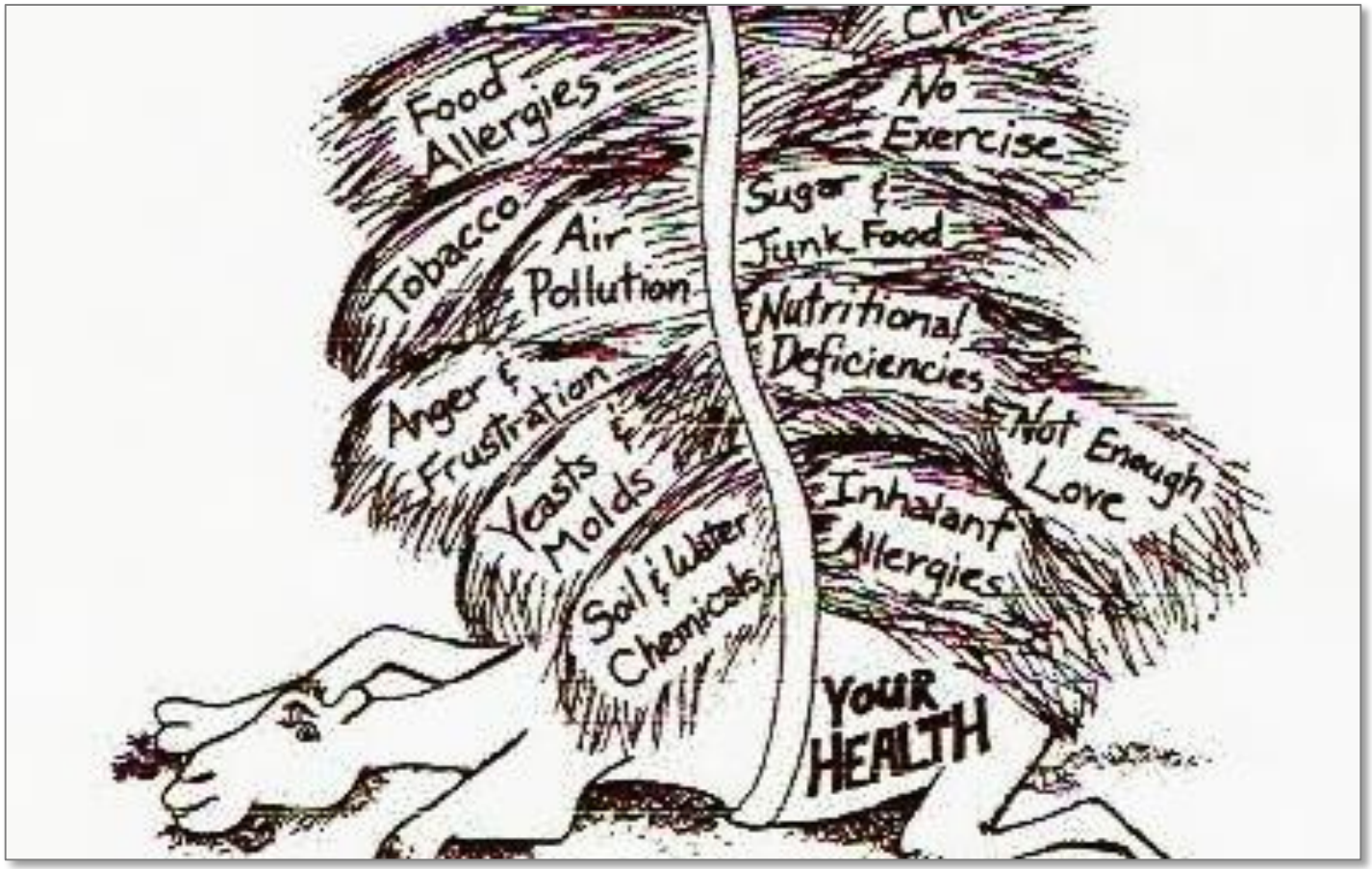
Allostatic Load



"The price the body pays over long periods of time for adapting to challenges."

Measuring for Allostatic Load:

MacArthur Study of Successful Aging

Primary Mediators

- Cortisol (overnight)
- Catecholamines
- DHEA-S

Secondary Mediators

- Waist-to-Hip
- S:D BP Ratio
- Albumin
- Total Cholesterol and HDL
- Hemoglobin
- Fibrinogen
- CRP

Beyond Salt, Sugar, Fat:
Cravings, Obesity, and Insulin Resistance

- Allostatic load is a major driver of fat, sugar, and salt consumption
- Fuel for HPA axis responses
- Major determinant of insulin resistance
- Chronically high levels of Glucocorticoids (GC's) →
  - Increase CRF mRNA in amygdala – a critical node in the emotional brain
  - GC's increase the salience of pleasurable or compulsive activities (fat, sugar consumption) –> ingestion of "comfort foods"
  - Self soothing: sugar, high fat foods QUIET the stress response via GC's
  - Increased abdominal fat depots → decreased CRF release and GC's into the brainstem.
  - Peripheral hormones that raise BP (angiotensin, aldosterone, and cortisol) modulate brain regions that stimulate hunger for sodium and energy-rich substrates
  - Chronically elevated appetite in the context of "industrial agriculture" is a recipe for "metabolic syndrome"
  - Relationship to eating disorders/ disordered eating (including orthorexia)

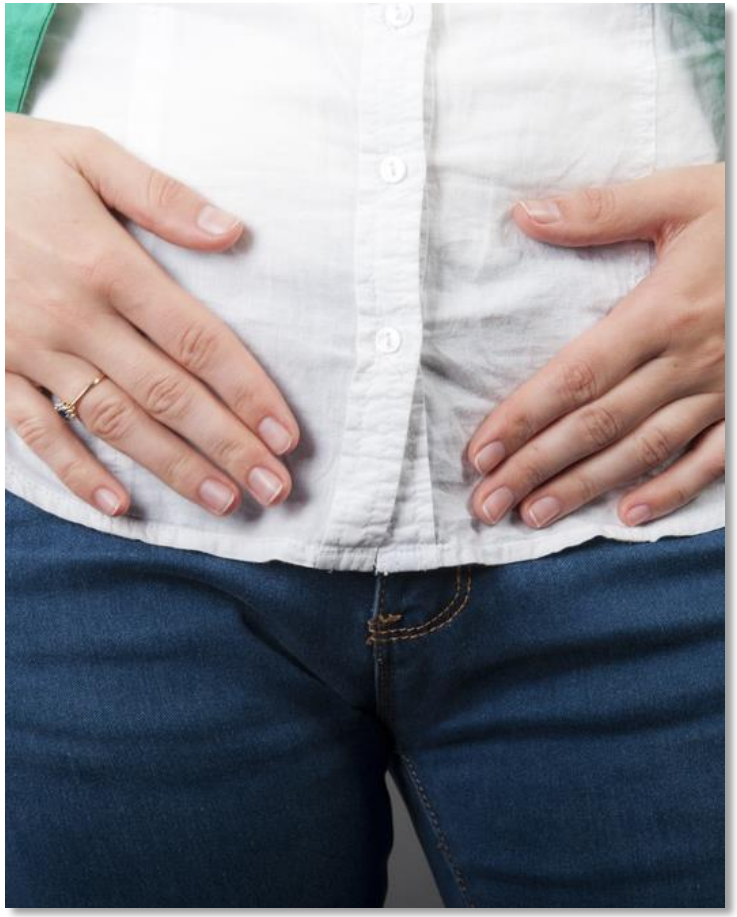
Women, Food, and Allostatic Load

- Women eat as a way to manage stress (31% women/21% men)
- Women report having eaten too much or eaten unhealthy foods because of stress in the past month far more often (49% women/30% men)
- 34% cite lack of willpower as a barrier to best health choices
- 56% say that for their willpower to improve, they'd have to feel less fatigue/more energy

Stress affects functioning of neurons in frontal cortex →
Difficulty and poor decision making

Impact on Gut Health

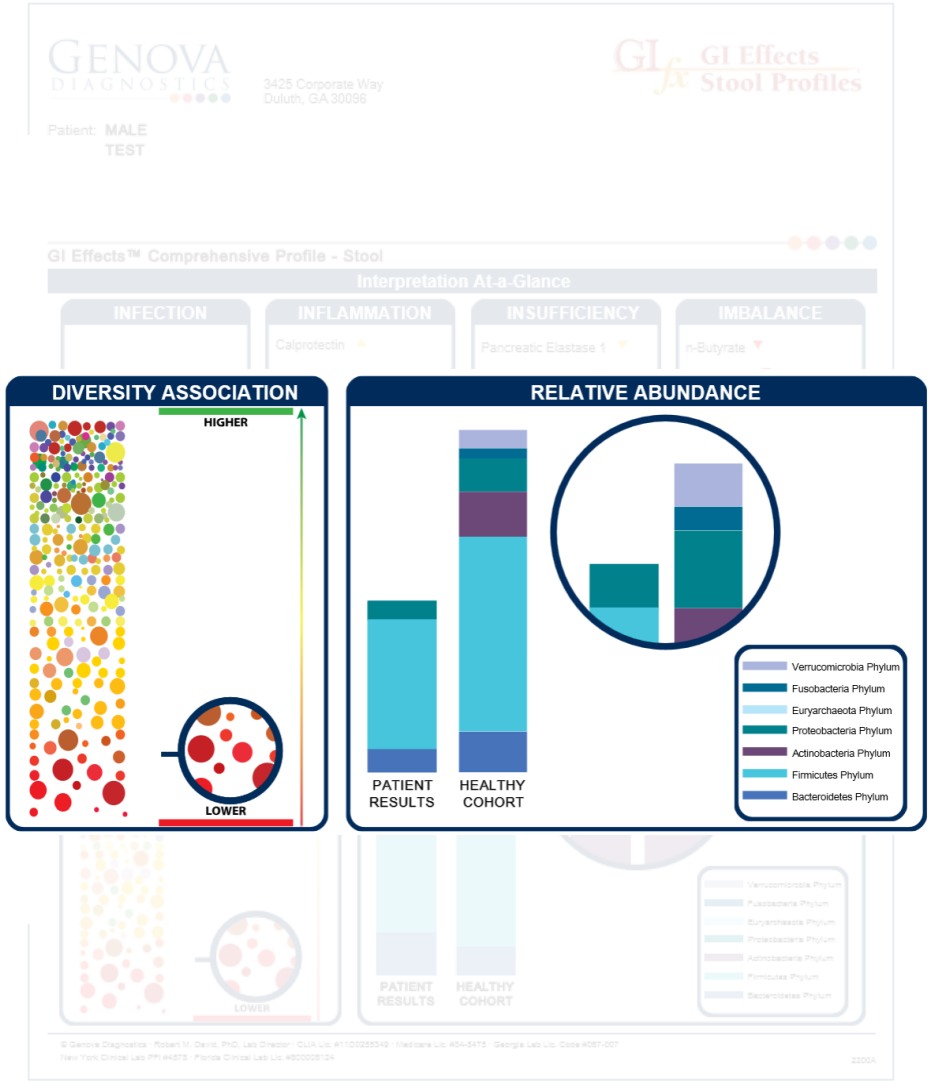
- Emotion-gut connection
- Decreased intestinal blood flow
- Changes in intestinal milieu/balance of microflora → dysbiosis (Decreased *Lactobacillus* and *Bifidobacter*; increased *E coli* and *Enterobacter*)
- Statistically significant shifts in the proportions of some species noted in individuals under conditions of anger or fear stress
- Decreased secretory IgA
- Decreased willpower and cravings → poor food choices → dysbiosis



Gut Health

Therapeutic interventions around gut microflora abundance and imbalance have proven helpful for clinical conditions

Targeted therapy with dietary manipulation, prebiotics, and probiotics, to heal the gut may modulate commensal bacteria levels



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Cardiovascular Disease

Multiple pathways → to increased risk of CVD

- Increased reactivity of the fibrinogen system, CRP, IL-6 , TNF, and platelets
- Activation of HPA-axis → hypercortisolemia → central obesity and insulin resistance
- Repeated sympathetic stimulation increases HR and BP → decreased HR variability, baroreflex dysfunction, and decreased myocardial electrical stability
- Decreased HR variability and higher morning cortisol
- Mental stress-induced ischemia with a decrease in LVEF associated with increased CV events over 5 years

INTERHEART: Loneliness & CVD

Loneliness, depression and hopelessness increased risk of CVD > DM2, HTN, smoking, or obesity

- 11,119 cases and 13,638 controls
- Odds ratio (adjusted)
- Moderate or severe stress 1.65 for acute MI
- Permanent general stress 2.17 for acute MI

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Reproductive Function

Hypothalamic–pituitary–adrenal axis	Effect on the female reproductive system
CRH	Inhibition of GnRH secretion
β-Endorphin	Inhibition of GnRH secretion
Cortisol	Inhibition of GnRH and LH secretion, inhibition of ovarian estrogen and progesterone biosynthesis, inhibition of estrogen actions

Reproductive CRH	Potential physiologic roles	Potential pathogenic effects
Ovarian CRH	Follicular maturation Ovulation Luteolysis Suppression of female sex steroid production	Premature ovarian failure (↑ secretion) Anovulation (↓ secretion) Corpus luteum dysfunction (↓ secretion) Ovarian dysfunction (↓ secretion)
Uterine CRH	Decidualization Blastocyst implantation Early maternal tolerance	Infertility (↓ secretion) Recurrent spontaneous abortion (↓ secretion)
Placental CRH	Labor Maternal hypercortisolism Fetoplacental circulation Fetal adrenal steroidogenesis	Premature labor (↑ secretion) Delayed labor (↓ secretion) Preeclampsia and eclampsia (↑ secretion)

Mood

"Chronic stress creates a hyper-reactive, hysterical amygdala, and this tells us tons about what stress has to do with anxiety disorders." *~ R. Sapolsky*

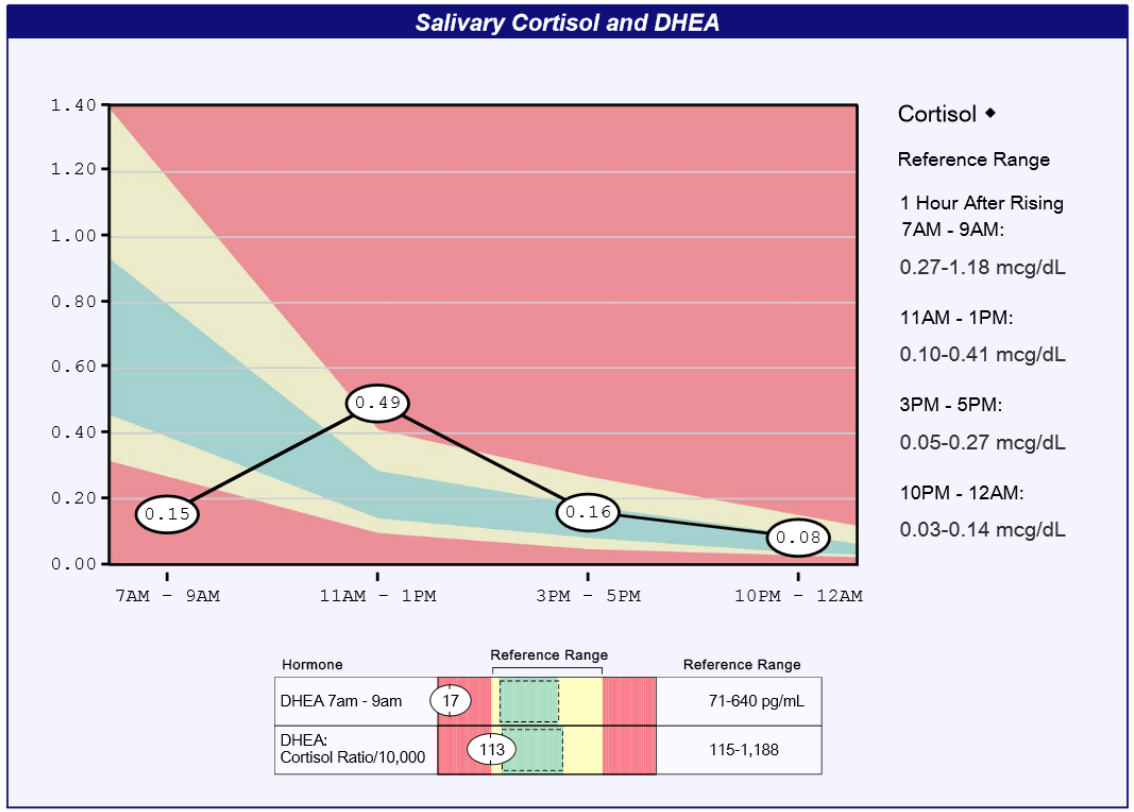
- Major depression affects women twice as often as men (15% vs 8%)
- 1 in 6 women on an antidepressant
- GAD twice as high in women as in men
- Exacerbations are worse during stressful times
- Women 2.5x more likely than men to use ADs; many on anxiety meds (Benzo anybody?)
- Chronic stress depletes dopamine; stress precipitates major depression
- Melancholic depression (MDD) associated with hyperarousal & HPA activation
- Atypical depression (MDD) associated with lethargy, fatigue, down-regulated HPA activation

Sleep Disturbance

- 49% of all women say they have lain awake at night in the past month because of stress
- Major presenting co-morbidity and QOL issue for women
- High PM, low AM cortisol, low DHEA common findings on adrenal stress testing via salivary tests
- Sleep affects everything – weight, food choices, self-regulation, mood, hormones, immunity (including cancer cell monitoring), cognitive function

Adrenocortex Stress Profile (Saliva)

- A salivary hormone test measuring 4 separate salivary samples over 24 hour period
- Provides insight into cortisol levels throughout the day as well as one early morning DHEA measurement



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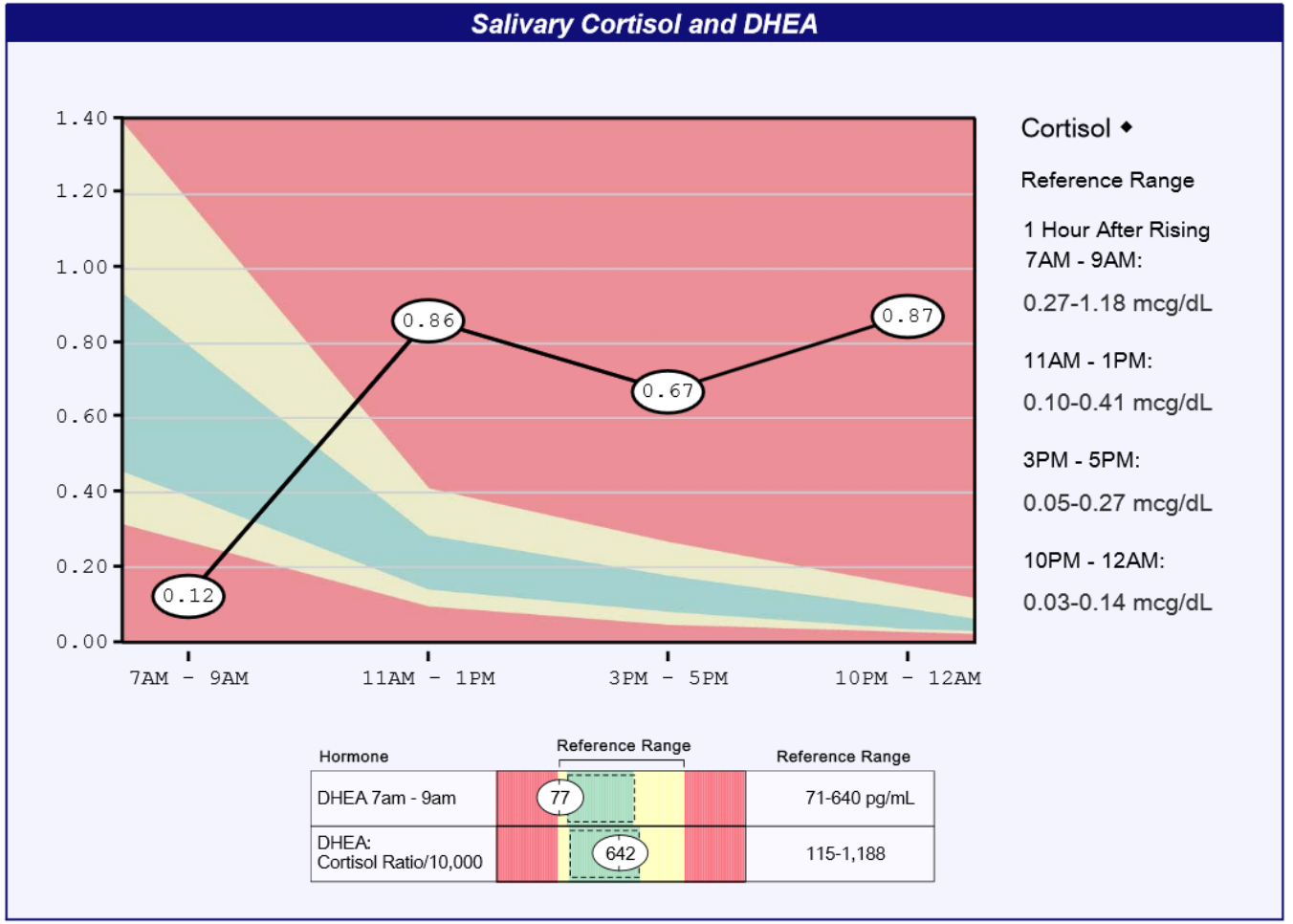
Adrenocortex Stress Profile (Saliva)



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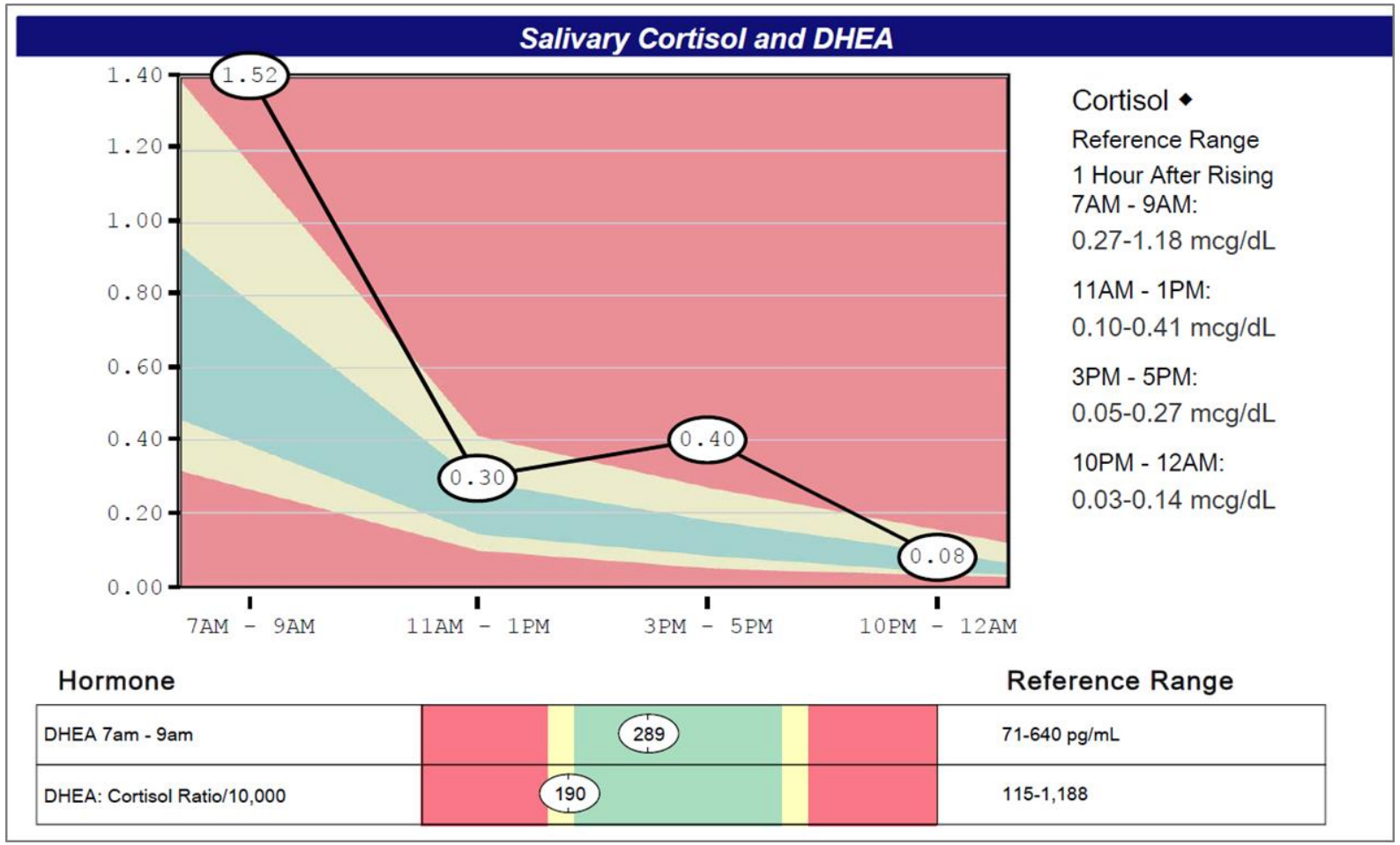
One Day Hormone Check (Saliva)



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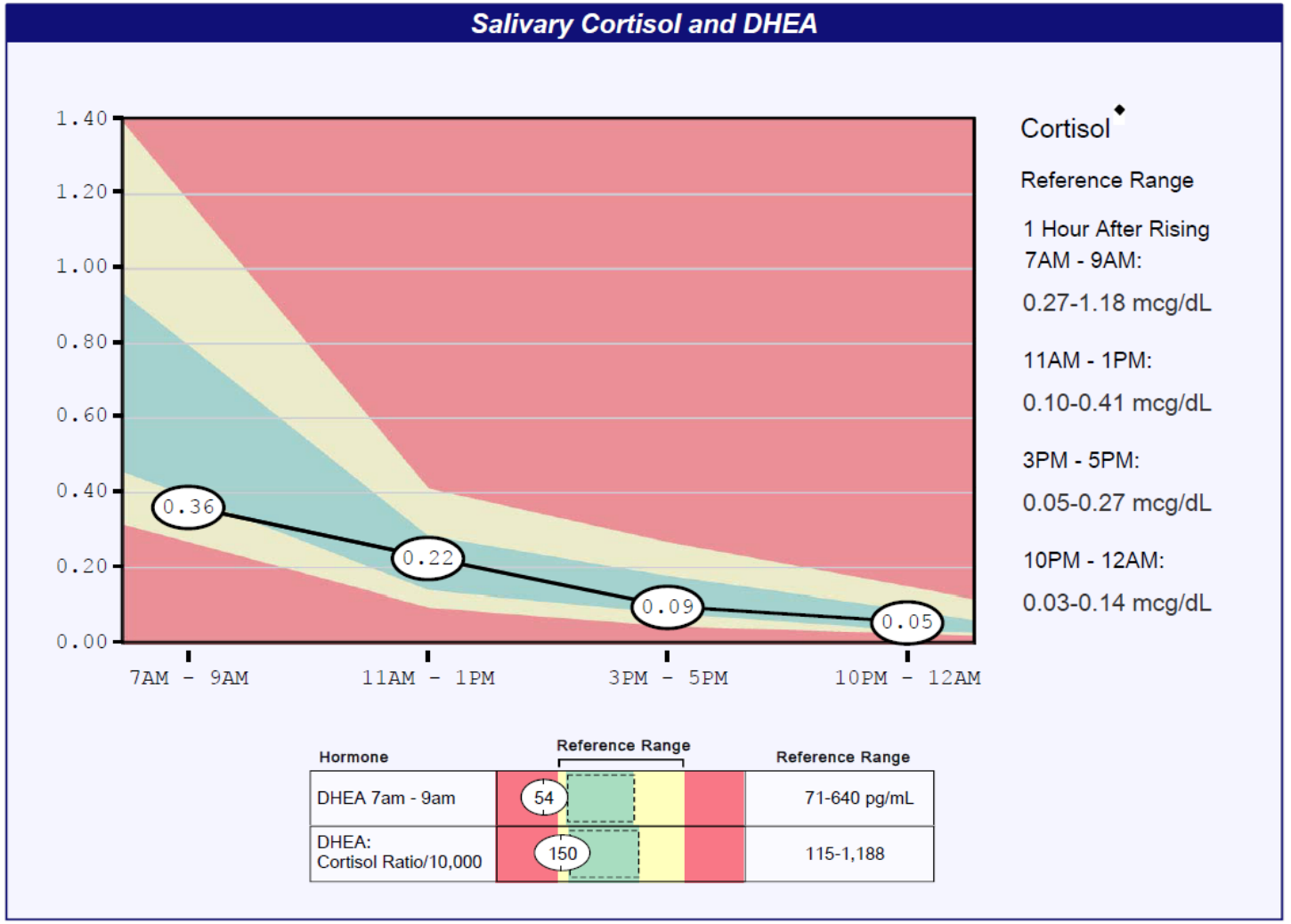
Adrenocortex Stress Profile (Saliva)



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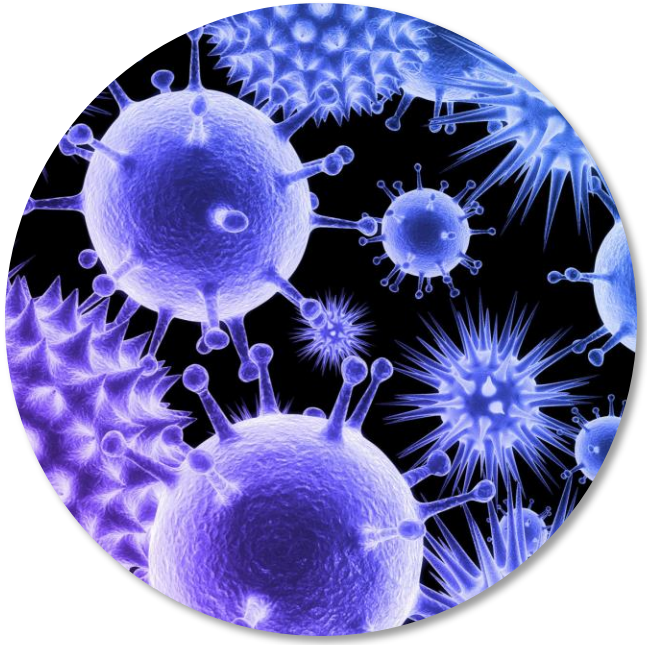
Memory & Cognitive Function

- Acute stress → increases cortisol secretion → suppressed mechanisms in the hippocampus & temporal lobe that serve short-term memory
- Repeated stress → GCs and excitatory AA's that → atrophy of dendrites of pyramidal neurons in the hippocampus
- Participates in emotional, verbal and "contextual" memory
- The hippocampus also regulates the stress response and acts to inhibit the response of the HPA axis to stress
- Sweden, population-based sample of 800 women, aged 38 to 54 years
- Chronically "stressed out," jealous, moody, anxious or worried
- 38-year follow-up: 153 women developed dementia; AD was diagnosed in 104 cases

Immunity

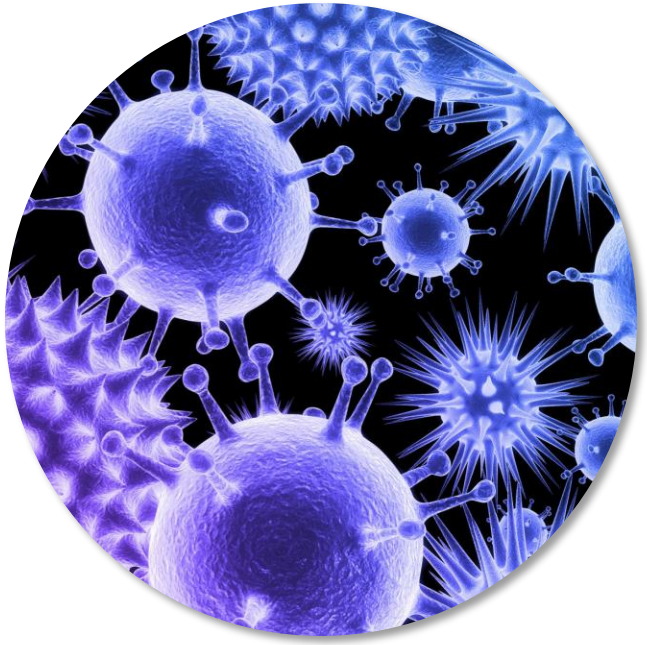
- Repeated/chronic exposure to high allostatic load → different immunologic response than acute exposure
- Goes from beneficial to potentially pathological
- Repeated high allostatic load → recurrent endotoxemia, decreases reactivity of the HPA axis and decreases cytokine production
- Chronic allostatic load → suppressed cellular immunity



Immunity

Clinically:

- Increased susceptibility to and severity of common cold, increased cold-virus antibody titers
- Decreased healing time
- Chronic inflammation
- Autoimmunity > in women at critical times in lifespan due to decreased estrogens
- Higher levels of chronic stress have been associated with a higher rate of breast cancer, correlated with lower nfKB



“Inflamm-Aging"

Stress = Antigen; Antigen → conserved immunologic stress response

Upregulation of evolutionary-conserved inflammatory mediators Free radicals, NO, proinflammatory cytokines (IL-1, IL-6, TNFα), propiomelanocortin-derived peptides (ACTH, β-endorphin, α-MSH), (cortisol, biogenic amines (noradrenaline, adrenaline, dopamine), & neuropeptides (CRH)

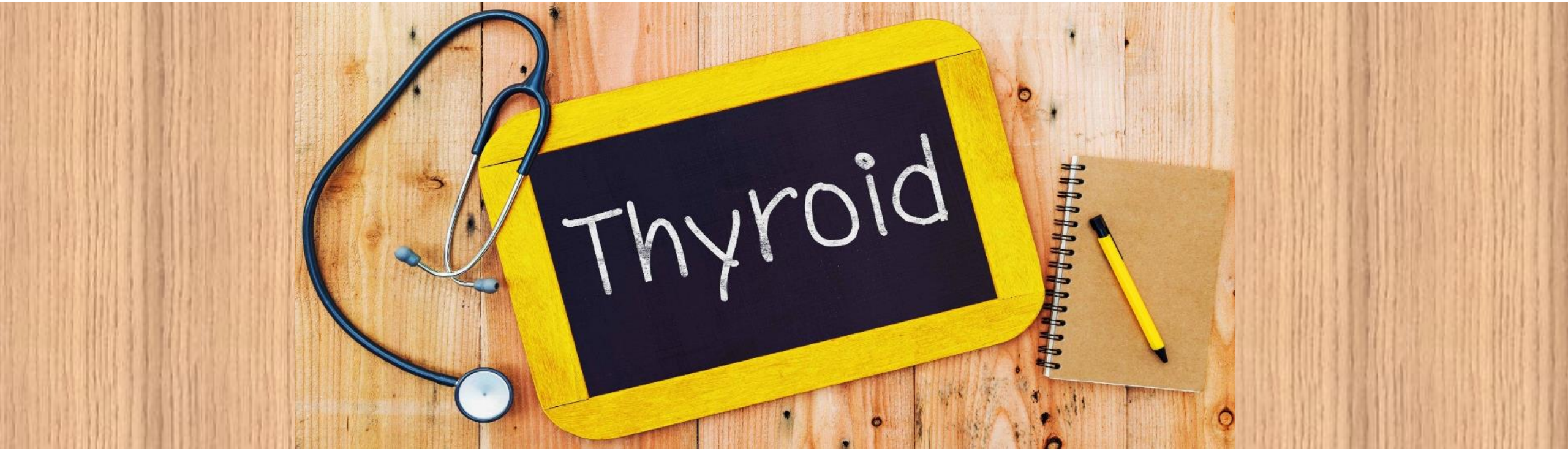
Global reduction in coping strategies with increased antigen exposures (allostatic load!) → proinflammatory status

First hit + absence of robust genes →↑ vulnerability to specific diseases i.e., Alzheimer’s, DM2, CA

Positive role for lifestyle, diet, positive epigenetic stimulus and removal of harmful stimuli in promoting longevity and genetic robustness

Thyroid Impact

- Down regulation of T3 production
- Increased rT3

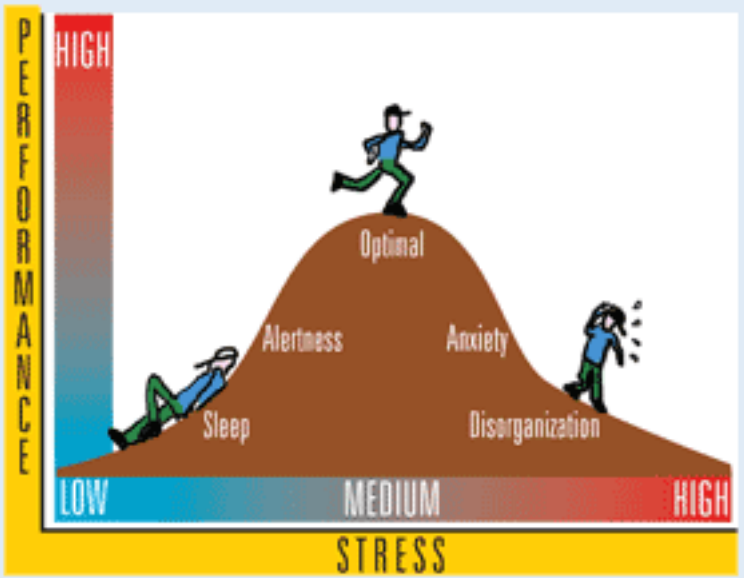


How Do We Break the Stress Cycle?

Reframe & Reset

- Reframe Hormesis & Perceptions of Stress
- Introduce patients to concepts of resilience & self-efficacy
- Tend and Befriend
- Discuss & emphasize supportive lifestyle changes/stress reduction tools
  - Blood sugar balance
  - Sleep support/Sleep hygiene
  - Life coaching
- Nutritional supplements
- **Adaptogens**

Stress Performance Connection



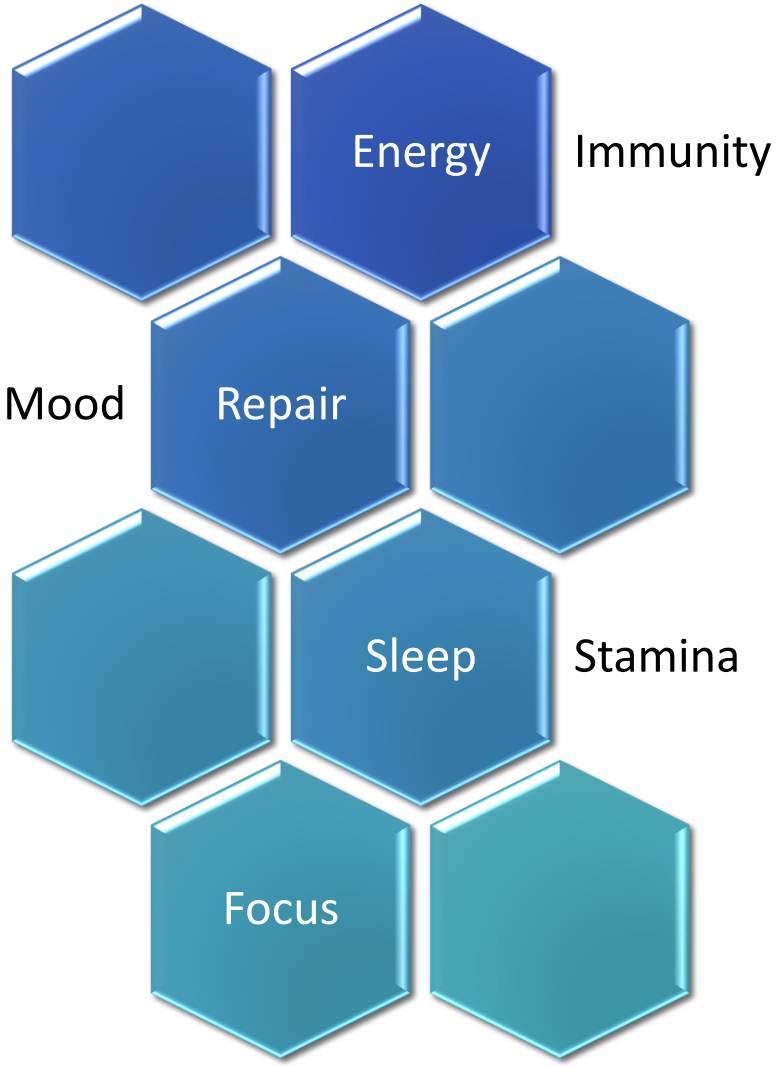
Adaptogens: What Are They?

Primary class of herbs used to support and restore HPA axis function

To be considered an adaptogen, the substance must demonstrate/be:

- Non-specific effects in that the adaptogen increases resistance to a broad spectrum of stressors of physical, chemical, and biological natures
- Normalizing effect, that is, it counteracts or prevents disturbances brought about by stressors
- Innocuous to the normal functioning of the organism
- “Herbal preparations that increase attention and endurance in fatigue, and reduce stress-induced impairments and disorders related to the neuroendocrine and immune systems.”

Psychoneuroimmuno Benefits



Modes of Action: “Amphoteric” Regulation

- Phenolic compounds structural resemblance to catecholamines
- Tetracylic triterpenes similar to the corticosteroids
- Modulate ACTH & corticosteroid formation; normalize stress hormones, allowing the organism to resist stress at higher levels of challenge
- Regulation of CRH, ACTH, NO, PGE2, LTB4, and corticosteroid secretion
- Limit overproduction of catecholamines via COMT inhibitory action
- Regulation of CNS and immune “on-off” switches → reduction in host susceptibility to damage
- Faster recovery of m-RNA after exhausting exercise;
  increased protein synthesis
- Increased recovery of leukocyte counts after exposure to chemical stressors
- Energetic regulation during stress via glucose-6-phosphate leading to an insulin-like effect
- Reduction in oxidative stress/lipid peroxidation

Adaptogen Safety

- Generally well tolerated, historically considered very safe
- Precautions, theoretical or based on limited animal and human clinical research include, some possibly ”advantageous”
  - Increased BP
  - Decreased BP due to vaso*relaxant* effects
  - Increased digoxin levels in combination
  - Inhibition of platelet aggregation
  - Blood glucose lowering effects
  - Blood glucose increases post-prandially
  - Caution in patients with autoimmune disorders & post-transplant patients
  - Potential for activation in patients with agitation/sedation
  - Caution w/combined steroid use as ES binds steroid receptors

Adaptogen Safety

- Safety not determined in pregnancy;
  I personally consider questionable due to
  - Effects on blood sugar
  - Immune regulation
  - Placentation
  - Impact on normal metabolic
    & immunologic changes in pregnancy
- Undetermined during lactation;
  likely safe

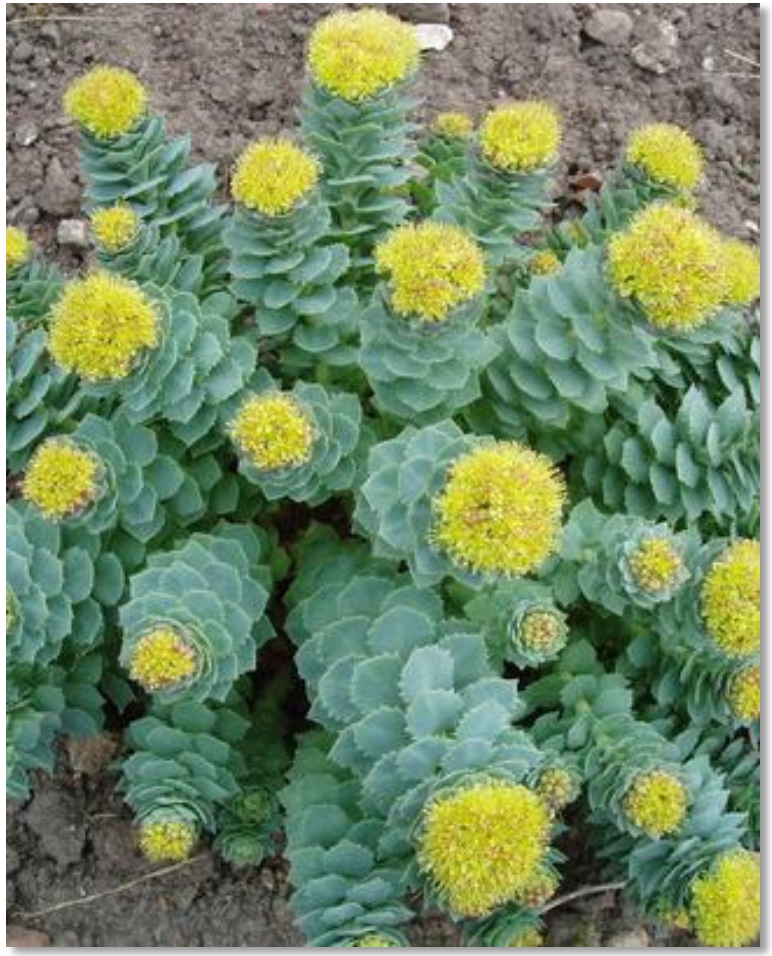
Intended Duration of Use

- Most studies up to 12 weeks
- Traditionally not limited and may be used for extended durations
- Recent data suggests beneficial effects of single doses and statistically significant benefits off shorter treatment periods vs. long term use

Rhodiola

Traditional Use

- “Asthenic” conditions
- Decline in work performance
- Sleep disturbance
- Poor appetite
- Irritability
- Sexual dysfunction
- Fatigue subsequent to intense physical or intellectual strain or illness
- Headache



Rhodiola Systematic Review

Hung et al. conducted a systematic review to evaluate the randomized controlled trials evaluating *Rhodiola rosea*.

- Twelve randomized controlled trials were included, all of which were placebo controlled trials
- Six trials evaluated rhodiola **for exercise performance**, four for **mental performance**, and two for **mental health conditions**
- Significant benefit was noted in eight studies
- Adverse effects were mild and infrequent
- Five of the studies had a Jadad score of 3 or higher, indicating good quality

Rhodiola & Anxiety

Open-label study on effects in the treatment of generalized anxiety disorder (GAD) in 10 patients, men and women, ages 18-64, with a DSM-IV diagnosis of GAD.

- Hamilton Depression Rating Scale (HDRS) scores > 17 and Hamilton Anxiety Rating Scale (HARS) 16 or >
- Patients allowed to take SSRIs, SNRIs and benzodiazepines daily prn
- Rhodax® (Phoenix Laboratories by Bodyonics Ltd.) 340 mg daily for 10 weeks
- Assessments included the HARS, HDRS
- *Rhodiola group found to have significant decreases in mean HARS scores at endpoint (p=0.01), as well as a significant difference in HDRS scores (p=0.001)*

Randomized cross-over trial looking at Rhodiola & Mental Performance/Mental Fatigue

- 56 young, healthy physicians
- Standardized extract of Rhodiola (SHR-5) study of fatigue during night duty
- Treated with SHR-5 (170mg daily) or placebo, followed by a 2 week washout and 2weeks with the opposite treatment
- During the first two weeks of testing, SHR-5 treatment resulted in *significant improvement in the mental performance tests.*

Cognitive Stress in Students

RCT with placebo arm Rhodaxon on physical and intellectual working capacity and psychoemotional state of foreign students in their first year of studies

- 60 male Indian students studying in Russia
- 660 mg daily for 20 days
- Treatment group showed a 60.7% ($p<0.05$) increase in strength of work executed
- Slight improvement in concentration (volume of information reviewed and number of mistakes)
- Only rhodaxon group showed improvement in self-evaluation
- Physical state, activity level, and mood improved by 9.1, 10.8, and 10.5%, respectively
- The rhodaxon group reported a 30% decrease in psychological fatigue, while the control and placebo groups both experienced an increase.
- Readiness to work improved by 74%
- Greater “adaptability” demonstrated

Rhodiola & Exercise Performance

RCT/PC to examine the effect of acute and chronic Rhodiola intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention

- 24 healthy young subjects over two sessions
- 200 mg rhodiola
- Speed of limb movement, aural and visual reaction time, and the ability to sustain attention were assessed 1 hr after administration, crossed over to placebo and endurance tests repeated the next day
- Following a 5-day washout period, the experiment was repeated with the opposite treatment group
- In the second, longer-term study, 12 subjects were included
- Rhodiola vs placebo, 4 weeks, and then crossed over to placebo
- ***Short-term use of Rhodiola significantly increased time to exhaustion peak compared with placebo***
- Longer-term use of Rhodiola lacked effect on any variables

Rhodiola on Exercise Induced Inflammation and Muscle Damage

Randomized, double-blind, placebo trial to evaluate the effects of Rhodiola on CRP and CK

- 36 healthy volunteers, 21-24 yo.
- 340mg of Rhodiola bid 30 days before and 6 days after exhausting physical exercise (intense mechanical bicycling)
- CRP and CK measured 30 minutes before exercise, 5 hours after, and five days after. The increase in CRP following exercise was less pronounced in the rhodiola group five hours after exercise ($p<0.05$).
- *After five days, CRP levels did not change ($p<0.05$) in the rhodiola group but increased in groups 2 and 3.*
- *In group 1, CK content decreased and sevenfold surpassed the initial level ($p<0.05$), while in groups 2 and 3 it increased and 15-fold surpassed the initial level.*
- *Rhodiola was found to have anti-inflammatory effects and protected muscle tissue during exercise.*

RCT/ DB/PCO to evaluate the effects of SHR-5 in the treatment of mild-to-moderate depression

- 89 subjects ages of 18 to 70 participated in the 6 week study.
- Participants with initial scores of ≥13 on the Beck Depression Inventory and ≥21 on the HAMD eligible
- Randomized to one of three groups. Group 1 340mg daily, Group 2 two 680mg daily, and Group 3 two placebo tablets daily.
- Statistically significant differences not reported in the average depression scale scores before the herb extract or placebos were given.
- Post treatment, both groups given SHR-5 experienced statistically significant declines in total levels of symptoms compared to placebo ($p<0.0001$).
- *HAMD scores declined from 24.52 to 15.97 and from 23.79 to 16.7 while the placebo group did not show statistically significant decreases.*
- *Improvements were also noted in Beck Depression Inventory scores ($p<0.0001$) as well as symptoms of insomnia, emotional instability, and level of somatization.*

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Randomized, double-blind, placebo controlled, parallel-group study to evaluate SHR-5 in the treatment of chronic fatigue syndrome

- 60 participants aged 20 to 55 years, diagnosed with CFIDS.
- Participants received 576mg of extract daily (N=30) or 4 placebo tablets daily (N=30).
- QOL (SF-36 questionnaire), symptoms of fatigue (Pines' burnout scale), depression (Montgomery-Asberg depression rating scale-MADRS), attention (Conners' computerized continuous performance test II; CCPT II), and saliva cortisol response to awakening were assessed on days 1 and 28 after treatment.
- *Compared to placebo, significant effects of rhodiola were observed in Pines' burnout scale and the CCPT II indices omissions , Hit RT SE, and variability.*
- *Pre- vs. post-treatment cortisol responses to awakening stress were significantly different in the rhodiola group compared to placebo.*
- Adverse effects were not noted.

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Rhodiola & Fertility

- Forty women suffering from amenorrhea
- 100 mg of Rhodiola twice daily for 2 weeks or an injection for 10 days
- In some women, the regimen was repeated 2-4 times
- Normal menses were restored in 25 women, 11 of whom became pregnant

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Rhodiola Safety & Dosing

Safety

- Very low level of toxicity in animal studies.
- The toxic dose for humans is calculated to be about 235,000 mg; the typical daily dose for chronic problems is 360-600 mg per day when standardized for 1% rosavin, 180-300 mg when standardized for 2% rosavin, or 100-170 mg when standardized for 2.6% rosavin.
- May be activating in some individuals, not recommended for patients with BPAD

Dose

- Clinical trials use products containing 2-3% rosavin and 0.8-1% salidroside
- Dose 100 mg-400 mg/day

Eleutherococcus (ES)

Traditional Use

- Increased endurance
- Memory improvement
- Immunological enhancement
- Overall well-being

Farnsworth et al review of of Russian clinical trials on > 2,100 healthy human subjects, ranging in age from 19-72 yo indicates increased ability to accommodate to adverse physical conditions, improvement in mental performance, and enhancement of the quality of work under stress.

ES & HSV-2

A specific ES extract, standardized to contain eleutheroside 0.3% (Elagen), orally seems to reduce the frequency, severity, and duration of herpes simplex type II infections.

- In a double-blind study to examine the effect of ES extract on symptoms of genital herpes in 93 men and women. a pure standardized extract of ES was used.
- *After 3 months patients using the ES extract reported a reduction in severity, duration, and frequency of outbreaks compared with placebo*.

ES & Common Cold

- A specific combination product containing ES plus andrographis (Kan Jang, Swedish Herbal Institute) orally significantly improves symptoms of the common cold when started within 72 hours of symptom onset.
- Some symptoms can improve after 2 days of treatment. It typically takes 4-5 days of treatment before there is maximal symptom relief .
- *The combination of ES and andrographis relieves cold symptoms better than Echinacea or placebo in children.*

ES & Upper Respiratory Infection

Melchior et al. conducted 2 randomized, double-blind, placebo controlled, parallel-group trials to investigate the effect of Kan Jang® in the treatment of uncomplicated URI.

- Forty-six patients in the pilot study and 179 patients in the phase III study completed the study.
- Medication was taken tid for a minimum of 3 days and a maximum of 8 days for the pilot study, and for 3 days in the phase III study.
- Primary outcome measures were related to pain in the muscle, cough, throat symptoms, headache, nasal symptoms, eye symptoms, and temperature.
- The physician's fixed-score diagnosis was based on ear, nose, oral cavity, lymph gland, tonsil, and eye symptoms.
- *The total symptom score showed a tendency toward improvement in the pilot study (p=0.08), while both the total symptom score and total diagnosis score showed highly significant improvement (p≤0.0006 and 0.003, respectively) compared with the placebo group.*
- In both studies, *throat symptoms showed the most significant improvement.*

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ESES & Influenza

Kulichenko et al. conducted a randomized controlled study comparing Kan Jang® (a combination product containing ES) vs. amantadine in the treatment of influenza.

- 540 patients enrolled in the first phase of the study; the second phase enrolled 66 patients.
- Outcomes were the duration of sick leave and frequency of post-influenza complications.
- *AKan Jang® contributed to quicker recovery and reduced the risk of post-influenza complications.*
- Kan Jang® was well tolerated by patients.

ES & General Immunity

Bohn et al. conducted a placebo controlled study to examine the effect of a ES extract (Eleu-kokk®) on immune system function in 36 healthy volunteers.

- Volunteers received 10mL of an ethanolic extract of ES or placebo (wine) three times daily for four weeks.
- The main endpoint was cellular immune status, as determined by quantitative flow cytometry.
- *ES use resulted in an increase in the absolute number of immunocompetent cells, mainly T helper cells. There were also effects on cytotoxic and natural killer cells.*
- There were no side effects observed over a six-month period.

Osteoarthritis/Inflammation

Double-blind, randomized, placebo controlled study to determine the effect of anti-inflammatory factor (AIF) on knee osteoarthritis in Korean patients.

- AIF is a water-soluble extract *of Panax notoginseng, Rehmannia glutinosa*, and *ES*.
- Fifty-seven patients with knee OA, from 43 to 73 years of age, who fulfilled the American College of Rheumatology classification of idiopathic osteoarthritis of knee with radiographic criteria
- Randomized to receive two capsules of 400mg of AIF or similar identical placebo twice daily for six weeks.
- Outcome measures included pain intensity using a visual analog scale, as well as changes in the Korean version of the Western Ontario and McMaster Universities (K-WOMAC) index score.
- *Pain was significantly reduced (at visit 2: 54.64 ± 14.72, at visit 4: 37.32 ± 16.58, p<0.001) after AIF administration.*
- *There was an improvement in the physical function of K-WOMAC scale that was significantly higher in the AIF group (p=0.013).* Decreases of total K-WOMAC score were also significantly higher in the AIF group (p=0.030).
- No serious adverse effects observed.

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ES & Exercise Performance

- Traditionally used as an exercise performance enhancement agent, due to its supposed beneficial effects on cardiorespiratory fitness, fat metabolism, and performance endurance
- More effective than placebo in two clinical trials. In four human trials, not more effective than placebo
- More effective than Chinese ginseng

RCT equivalence study to compare the effects of ES with that of echinacea on physical fitness.

- 50 healthy volunteers, male and female, 21-73 years of age
- Subjects randomly divided into two groups: ES root extract or echinacea for 30 days.
- Of these study subjects, 20 healthy males underwent an ergospirometric study.
- *Following use of ES, there was a higher oxygen plateau, indicating increased oxygen consumption during maximal physical exercise.*
- *There was an increase in aerobic metabolism of tissues. In the ES group, there was an increase in cellular immunity as determined by an increase in the rate of blastic transformation of lymphocytes in the presence of mitogen and the phagocytic activity of neutrocytes.*
- *Total cholesterol, LDL cholesterol, and free fatty acids were all reduced in the ES group. There was a significant reduction in triglyceride levels and glucose found in the ES group.*

McNaughton et al. compared the effects of ES and Chinese ginseng with placebo on exercise tolerance in a randomized crossover study.

- Thirty trained runners were included and assigned to ES (1g daily), Chinese ginseng, or placebo, for six weeks each.
- Major endpoints included VO2max, heart rate recovery, and strength. ES had no effect on VO2max, heart rate recovery, or grip strength, compared with the placebo.
- *There was a significant increase in pectoral and quadriceps strength, by 15 and 13%, respectively.*

Asano et al. conducted a single-blind crossover study to examine the effect of ES on physical working capacity in six healthy male athletes.

- Subjects belonged to the same baseball team and ate the same food.
- No other inclusion or exclusion criteria were provided. Subjects were given 2mL of ES extract (150mg of dried material) or placebo twice daily for eight consecutive days.
- The main endpoints were maximal work on a bicycle ergometer and aerobic capacity.
- *Total work increased significantly with ES compared with the placebo group (23.3% vs. 7.5%), as did exhaustion time (16.3% vs. 5.4%).*
- Maximal oxygen uptake was only increased compared with control (pre-supplementation).
- Limitations to this trial include the single-blind nature of the study and no mention of randomization.

Comparison of the effect of ES to a combination ES, Cordyceps, and ginseng on cardiorespiratory fitness during submaximal cycling exercise

- 16 healthy male volunteers
- Group A (N=8) received 10 mL of oral ES preparation (Endurox®) equivalent to 800 mg of ES daily, 30 minutes before breakfast. Group B (N=8) also received the same dose of Endurox®, in addition to 400 mg of Cordyceps and 200mg of ginseng liquid extract, in the form of an oral liquid preparation.
- 2 week duration of study
- Both groups received placebo medication for three days prior to treatment initiation.
- Subjects completed aerobic and anaerobic exercise tests, once after three days of placebo, and again after two weeks of active treatment.
- Outcome measures included heart rate, lactate accumulation, and respiratory quotient.
- The submaximal cycling test started at an initial load of 60W for three minutes and then increased every three minutes by 30W, up to 210W.
- *Following ES supplementation, both heart rate and lactate accumulation decreased (34%, in group A), load increased (12% in group A), VO2 at anaerobic threshold) increased (7%, in group A), and fat metabolism increased (43%).*
- *ES supplementation alone was more effective than the combination with Cordyceps and ginseng.*

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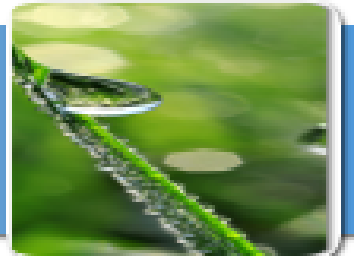

Evidence from a Phase II DB,PC, RCT that ADAPT-232 (containing *Rhodiola rosea*, *Schisandra chinensis*, and ES) improved cognitive function in females

Forty healthy females (20-68 years of age) that reported living under chronically psychologically stressful conditions participated. The participants were randomized into to receive a single tablet of 270 mg of ADAPT-232 (N=20) or a single tablet of placebo (N=20)

- A Stroop color-word test was used to exhaust the volunteers before the assessment of cognitive function of patients. The effects of ADAPT-232 extract were measured prior to treatment and two hours after treatment using the d2 test of attention (d2)
- *The subjects in the ADAPT-232 group quickly gained improved attention and increased speed and accuracy during stressful cognitive tasks, in comparison to placebo ($p<0.05$)*
- *There was a tendency of ADAPT-232 to reduce percentage of errors*
- A few minor adverse events, such as sleepiness and cold extremities, were observed in both groups. The effects of ES alone cannot be determined from this study

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RCT to Examine the Effect of ES for Chronic Fatigue Syndrome

- Subjects were required to have substantial fatigue for 6 months or more, with no identifiable cause
- Patients with HTN and certain medications, diseases, and abnormal laboratory results were excluded
- 96 subjects (~ 80% female) were included, and 76 patients completed the study. The remaining patients were lost to follow-up or to side effects, such as nervousness, headache, and breast tenderness
- Patients were given placebo or four 500mg capsules of ES (Frontier Herbs, Norway, IA) for 2 months
- Main endpoint: mean change in a fatigue measure, compared with placebo, at one and two months
- *Fatigue was reduced in study subjects overall, with no differences between groups.*
- *In patients with less severe fatigue, fatigue severity and duration were reduced in those taking ES*

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Other Interesting ES Data

Neurocirculatory Hypotension

(i.e., Potts Syndrome, Autonomic Dysfunction)

- Preliminary data suggest that use of ES extract increases systolic and diastolic blood pressure in individuals with neurocirculatory hypotension
- Kaloeva examined the efficacy of ES extract on neurocirculatory hypotension in children aged 7-10 years. Systolic and diastolic blood pressures were increased with treatment

ES Safety & Dosing

Safety

- According to a review, side effects of ES are considered to be minimal
- Root extract has been used safely in clinical trials lasting up to 2 months
- A specific combination product containing ES plus andrographis (Kan Jang, Swedish Herbal Institute) has also been safely used in multiple short-term clinical trials lasting 4-7 days
- One clinical trial used this combination (with andrographis) product in low doses for up to 3 months

Dosing

- Powder: 400 mg bid-tid
- Tincture (1:4) 60-100 drops 3-4 times daily or a fluid extract (1:1) 20-40 drops three times daily has been use
- Variably standardized to eleutherosides B and E

Ashwagandha

Traditional Use

- *Rasayana* herb in Ayurveda
  - Increased vitality
  - Longevity
  - Prevent disease
  - Relieve fatigue, nervous exhaustion, anxiety
  - Insomnia
  - Memory-enhancing
  - Retard “brain aging”
  - Regenerate neural tissue
  - Arthritis
  - GI disorders

Ashwagandha Clinical Studies

Anxiety

RCT studying ashwagandha in a combination naturopathic care model for anxiety treatment **(N=81)** in subjects with moderate-to-severe anxiety lasting six weeks or longer

- Treatment was composed of dietary counseling, deep breathing exercises, a multivitamin, and ashwagandha root 300mg twice daily (standardized to 1.5% anolides) for 12 weeks vs. control therapy without ashwagandha
- *Beck Anxiety Inventory scores decreased 56.5% from baseline ($p<0.0001$) in the treatment group and 30.5% ($p<0.0001$) in the control group*

Hypercholesterolemia

A case series including 6 subjects with hypercholesterolemia showed that *ashwagandha 3 grams daily for 30 days decreased serum cholesterol, triglycerides, low density lipoproteins (LDL), and very low density lipoproteins (VLDL)*

Osteoarthritis

- A specific combination containing ashwagandha 450 mg, zinc complex 50 mg, guggul 100 mg, and turmeric 50 mg (Articulin-F), 2 capsules tid for 3 months improved symptoms in patients with joint deformity, pain, stiffness, and swelling. No radiological improvements were seen after treatment
- *32 week RCT of 90 patients with OA of knee found extract containing ASH, boswellia, ginger, and tumeric was superior to placebo for relieving pain & improving function*

Diabetes

A case series including 6 subjects with type 2 diabetes showed that ashwagandha 3 grams daily for 30 days *decreased blood glucose to a degree similar to oral hypoglycemic drugs;* however, it wasn't specifically compared to oral hypoglycemic drugs

Enhanced Immunity

- Combination Ayurvedic herbal tea *increased NK cell activity* (N=32). *Elettaria cardamomum, Glycyrrhiza glabra, Ocimum sanctum, Withania somnifera,* and *Zingiber officinale* were compared to regular tea in healthy volunteers aged ≥55 years with low baseline NK cell activity and recurring coughs and colds.
- 6mL of ashwagandha root extract with whole milk twice daily for 96 *increased CD4, CD8, CD19, CD56, and CD69 receptor cell surface expression and increased CD4 expression on CD3+ T cells* after 96 hours. CD56+ NK cells were also activated. (N=5)

Ashwagandha Safety & Dosing

Safety

- Used safely in clinical trials lasting up to 12 weeks.
- Orally, well tolerated at typical doses.
- Large doses may cause GI upset and vomiting secondary to irritation of the mucous membranes.
- While pregnancy abortifacient activity found in some literature it is based on erroneous reporting of a single case history, safety during pregnancy is not conclusive though there is evidence of traditional use.
- Theoretical condition or drug interactions: CNS additive effects, antihypertensive effects, thyroid stimulating effects, aggravation of PUD, reduction in blood glucose levels.

Dose

- 1 to 6 grams daily of the whole herb in capsule or tea form in 2-3 divided doses
- Standardized extracts can be taken at 500 mg, 2-3 x/day.
- The tea is prepared by boiling ashwagandha roots in water for 15 minutes and cooled. The usual dose is 3 cups daily.
- Tincture or fluid extracts are dosed 2 to 4 mL 3 times per day.

Additional Support

Botanical “Nervines”

- SJW
- Lavender
- Passion flower
- Valerian
- Lemon balm
- California poppy
- Kava kava

Nutritional Supplements

- B-complex
- Magnesium
- 5-HTP
- P-S
- Methylfolate
- GABA
- L-tyrosine, L-theanine
- Inositol

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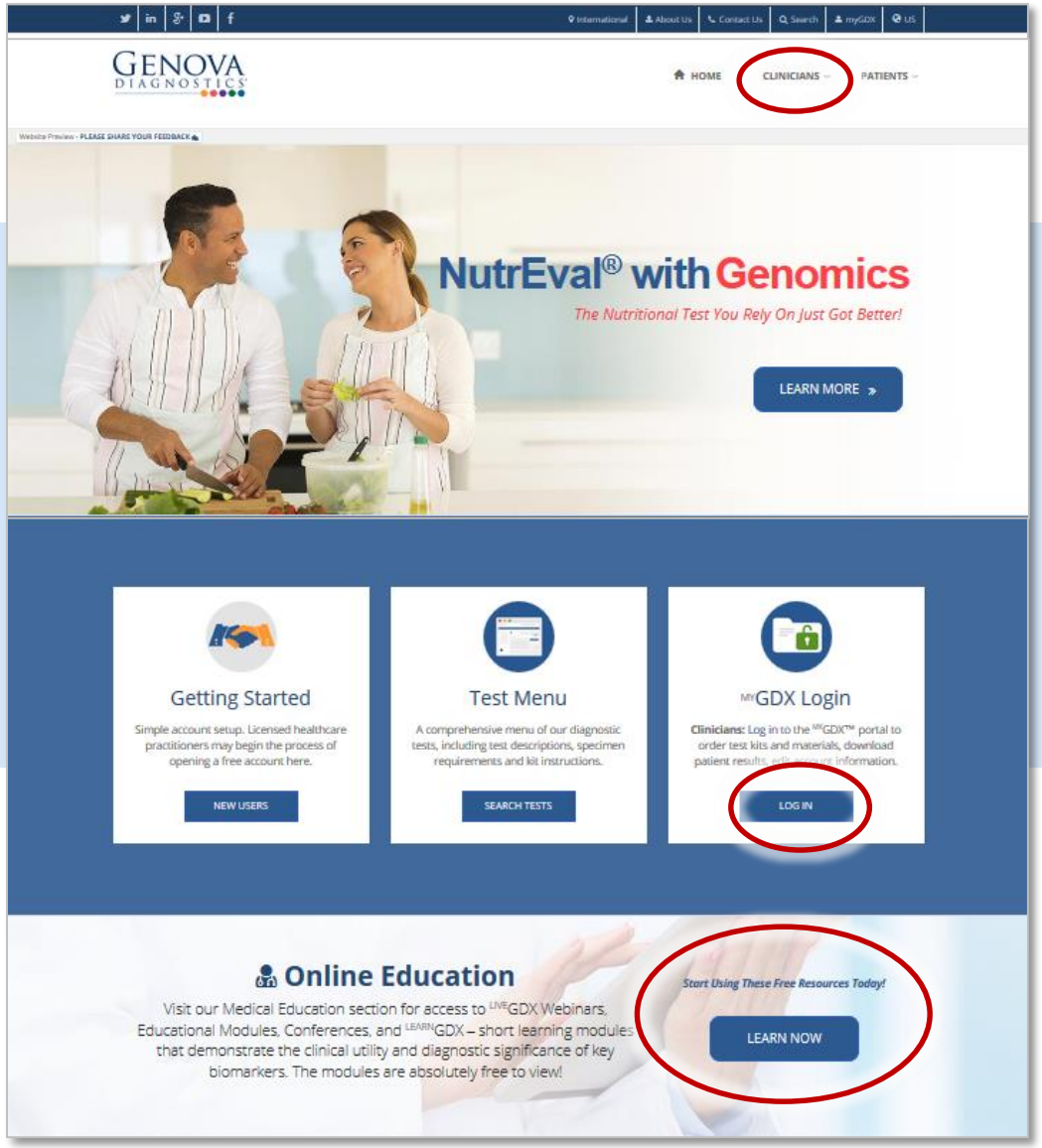

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The Stress Response, Women's Health & the Role of Adaptogens

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References

Slide 2

American Psychological Association. *Stress in America: Missing the Healthcare Connection*. (2013, February 7). Retrieved October 13, 2014, from https://www.apa.org/news/press/releases/stress/2012/full-report.pdf

Darling, C et. al. Women in Midlife: Stress, Health and Life Satisfaction. *Stress and Health* 28:1, 31–40, Feb. 2012

McEwen,B. Protective and Damaging Effects of Stress Mediators. *N Engl J Med*, 338:171-179.

Perkins, A. Saving money by reducing stress. *Harvard Business Review*, 72(6), 12.

Centers for Disease Control. *STRESS...At Work*. (2014, June 6). Retrieved October 13, 2014, from http://www.cdc.gov/niosh/docs/99-101

Slide 3

Hung SK, et. al.(2001). The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. *Phytomedicine*, 8(4):235-244.

Schulkin, J. (2004). *Allostasis, homeostasis and the costs of physiological adaptation*. New York: Cambridge University Press.

Slide 4

Flier, J., Underhill, L., & McEwen, B. (n.d.). Protective and Damaging Effects of Stress Mediators. *NEJM*. 338, 171-179.

Slide 5

Dallman, M. (2003). Chronic Stress And Obesity: A New View Of “Comfort Food" Proceedings of the National Academy of Sciences, 100(20), 11696-11701.

Slide 6

American Psychological Association. *Stress in America: Missing the Healthcare Connection*. (2013, February 7). Retrieved October 13, 2014, from https://www.apa.org/news/press/releases/stress/2012/full-report.pdf

Slide 7

Jemmott, J., & Magloire, K. (1988). Academic Stress, Social Support, And Secretory Immunoglobulin A. *Journal of Personality and Social Psychology*, 55(5), 803-810.

Kiecolt-Glaser JK, Glase R. (1991). Stress and immune function inhumans. In: Ader R, Felton D, Cohen E., eds. *Psychoneuroimmunology*, 2nd ed. Orlando: Academic Press.

Valdimarsdottir, H., & Stone, A. (1997). Psychosocial Factors and Secretory Immunoglobulin A. *Critical Reviews in Oral Biology & Medicine*, 8(4), 461-474.

Slide 8

Carney, R. (2005). Depression, The Autonomic Nervous System, And Coronary Heart Disease. *Psychosomatic Medicine*, 67, S29-S33.

Figueredo, V. (n.d.). The Time Has Come For Physicians To Take Notice: The Impact Of Psychosocial Stressors On The Heart. The American Journal of Medicine, 122(8), 704-712.

Jiang, W. (1996). Mental stress-induced myocardial ischemia and cardiac events. JAMA: The Journal of the American Medical Association, 275, 1651-1656.

Slide 9

Rosengren A, Hawken S, Ounpuu S, et al, for the INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:953-962.

Yusuf S, Hawken S, Ounpuu S, on behalf of the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-952.

Slide 10

Kalantaridou, S., Makrigiannakis, A., Zoumakis, E., & Chrousos, G. (2004). Stress and the female reproductive system. Journal of Reproductive Immunology, 62(1-2), 61-68.

Slide 11

CDC Fast Fact Antidepressant Use in Persons Aged 12 and Over: United States 2005- 2008. (2011, October 19). Retrieved October 13, 2014, from http://www.cdc.gov/nchs/data/databriefs/db76.htm

Gold, P., & Chrousos, G. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. Molecular Psychiatry, 7(3), 254-275.

Sapolsky, R. (2013, March 27). *How to Relieve Stress*. Retrieved October 13, 2014, from http://www.beinghuman.org/article/how-relieve-stress

Slide 12

American Psychological Association. *Stress in America: Missing the Healthcare Connection*. (2013, February 7). Retrieved October 13, 2014, from https://www.apa.org/news/press/releases/stress/2012/full-report.pdf

Slide 13

Sapolsky, R. (2013, March 27). *How to Relieve Stress*. Retrieved October 13, 2014, from http://www.beinghuman.org/article/how-relieve-stress

Johansson, L. et. al. *Midlife personality and risk of Alzheimer disease and distress A 38-year follow-up*. Published online before print October 1, 2014, Neurology.

Slide 14

Segerstrom, S., & Miller, G. (2004). Psychological Stress and the Human Immune System: A MetaAnalytic Study of 30 Years of Inquiry. *Psychol. Bull*., 130(4), 601-30.

Slide 15

Franceschi, C., et.al. (2000). Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Annals of the New York Academy of Sciences,* 908, 244-254.

Slide 18

Cohen, S., Wills, TA. (1985). Stress, social support, and the buffering hypothesis. *Psychological Bulletin* 98 (2): 310–57.

Franceschi, C., et.al. (2000). Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Annals of the New York Academy of Sciences*, 908, 244-254.

Taylor, S., et. al. (2000). Biobehavioral Responses To Stress In Females: Tend-and-befriend, Not Fight-or-flight. *Psychological Review*, 107(3), 411-429.

Slide 19

Brekhman, I. "What can oppose stress?" Adaptation and Adaptogens. *Proceedings of the 2nd Symposium: Processes of Adaptation and Biological Active Substances* (May 1975). Vladivostok: Far East Scientific Center of the Academy of Science of the USSR, 1977: 81.

Panossian, A.; Wikman, G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Current Clin.Pharmaco*l. 2009, 4, 198– 219

Slide 20

Brekhman, I., & Dardymov, I. (1969). New Substances of Plant Origin which Increase Nonspecific Resistance. *Annual Review of Pharmacology*, 9, 419-430.

Panossian et. al., A. (1999). Plant adaptogens. New concepts on their mode of action. *Phytomedicine*, 6(4), 1-14.

Slide 21

Panossian et. al., A. (1999). Plant adaptogens. New concepts on their mode of action. *Phytomedicine,* 6(4), 1-14

Slide 23

Panossian, A.; Wikman, G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Current Clin.Pharmacol*. 2009, 4, 198– 219

Slide 24

Hung SK, et. al.(2001). The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. *Phytomedicine*, 8(4):235-244.

Slide 25

Hung SK, et. al.(2011). The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. *Phytomedicine*, 8(4):235-244.

Slide 26

Bystritsky, et al., A. (2008). A pilot study of Rhodiola rosea (Rhodax) for generalized anxiety. *J Altern Complement Med.*, 14(2), 175-80.

Slide 27

Darbinyan G, Aslanyan G, Amroyan E. (2007). Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry*, 61:343-8.

Slide 28

Spasov A, Wikman G, Mandrikov V, et al. (2000). A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-% extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomedicine,* 7(2):85-89.

Slide 29

De Bock, K., Eijnde, B. O., Ramaekers, M., and Hespel, P. Acute Rhodiola rosea intake can improve endurance exercise performance. *Int J Sport Nutr.Exerc.Metab* 2004;14(3):298-307.

Slide 30

Abidov, M., Grachev, S., Seifulla, R. D., and Ziegenfuss, T. N. Extract of Rhodiola rosea radix reduces the level of C-reactive protein and creatinine kinase in the blood. B*ull Exp.Biol.Med* 2004;138(1):63-64.

Slide 31

Darbinyan G, Aslanyan G, Amroyan E. (2007). Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry*, 61:343-8.

Slide 32

Olsson, E. M., von, Scheele B., and Panossian, A. G. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue. *Planta Med* 2009;75(2):105-112..

Slide 33

Gerasimova H. Effect of Rhodiola rosea extract on ovarian functional activity. *Proceedings of Scientific Conference on Endocrinology and Gynecology*. Sverdlovsk, Russia. 1970 Sept 15-16. Siberian Branch of the Russian Academy of Sciences. P. 46-48.

Slide 34

Darbinyan V et al. (2000). Rhodiola rosea in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine*, 7(5):365-71.

Spasov A, Wikman G, Mandrikov V, et al. (2000). A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-% extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomedicine*, 7(2):85-89.

Slide 35

Farnsworth NR et al. (1985). ES (Eleutherococcus senticosus):current status as an adaptogen. *Econ Med Plant Res*, 1:156-215.

Slide 36

Gabrielian ES, Shukarian AK, Goukasova GI, et al. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. *Phytomedicine* 2002;9:589-97

Spasov AA, Ostrovskij OV, Chernikov MV, Wikman G. Comparative controlled study of Andrographis paniculata fixed combination, Kan Jang and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children. *Phytother Res* 2004;18:47-53.

Slide 37

Melchior, J. et al. Double-blind, placebo-controlled pilot and phase III study of activity of standardized Andrographis paniculata Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection. *Phytomedicine*. 2000;7(5):341-350.

Slide 38

Bohn et al. Flow-cytometric studies with eleutherococcus senticosus extract as an immunomodulatory agent. Arzneimittelforschung. 1987;37(10):1193-1196.

Kulichenko et al. A randomized, controlled study of Kan Jang versus amantadine in the treatment of influenza in Volgograd. *J.Herb.Pharmacother*. 2003;3(1):77-93

Williams M. Immuno-protection against herpes simplex type II infection by eleutherococcus root extract. *Int J Altern Complem Med* 1995;13:9-12.

Slide 39

Park, S. H., Kim, S. K., Shin, I. H., Kim, H. G., and Choe, J. Y. Effects of AIF on Knee Osteoarthritis Patients: Double-blind, Randomized Placebo-controlled Study. *Korean J Physiol Pharmacol*. 2009;13(1):33-37.

Slide 40

Szolomicki J, et al. The influence of active components of Eleutherococcus senticosus on cellular defense and physical fitness in man. *Phytother.Res* 2000;14(1):30-35.

Slide 41

Asano, K., et al. Effect of Eleutherococcus senticosus extract on human physical working capacity. *Planta Med* 1986;(3):175-177.

McNaughton, L. G. Egan and G. Caelli. A comparison of Chinese and Russian ginseng as ergogenic aids to improve various facets of physical fitness. *Int.Clin.Nutr.Rev*. 1989;9:32-35.

Slide 42

Wu, Y. N. X. Q. Wang Y. F. Zhao J. Z. Wang H. J. Chen and H. Z. Effect of Ciwujia (Radix acanthopanacis senticosus) preparation on human stamina. *J.Hyg.Res*. 1996;25:57-61.

Slide 43

Aslanyan G1,et al. Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions. *Phytomedicine*. 2010 Jun;17(7):494-9.

Slide 44

Hartz, A. J., Bentler, S., Noyes, R., Hoehns, J., Logemann, C., Sinift, S., Butani, Y., Wang, W., Brake, K., Ernst, M., and Kautzman, H. Randomized controlled trial of Siberian ginseng for chronic fatigue. *Psychol.Med* 2004;34(1):51-61

Slide 45

Kaloeva, Z. D. [Effect of the glycosides of Eleutherococcus senticosus on the hemodynamic indices of children with hypotensive states]. *Farmakol.Toksikol*. 1986;49(5):73.

Slide 46

Caceres DD, Hancke JL, Burgos RA, Wikman GK. Prevention of common colds with Andrographis paniculata dried extract: a pilot, double-blind trial. *Phytomedicine* 1997;4:101-4.

Caceres DD, Hancke JL, Burgos RA, et al. Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized Andrographis paniculata extract SHA-10 in reducing the symptoms of common cold. A randomized, double-blind, placebo study. *Phytomedicine* 1999;6:217-23.

Cicero AF, Derosa G, Brillante R, et al. Effects of ES (Eleutherococcus senticosus maxim.) on elderly quality of life: a randomized clinical trial. *Arch Gerontol Geriatr Suppl* 2004;9:69-73

Slide 48

Cooley K, Szczurko O, Perri D, et al. (2009) *Naturopathic care for anxiety: a randomized controlled trial* ISRC TN78958974. PLoS One;4:e6628.

Rege, N. et al. (1999). Adaptogenic Properties of Six Rasayana Herbs Used in Ayurvedic Medicine. *Phytother. Res*. 13, 275–291.

Upton, R, et al. (2000). *American Herbal Pharmacopoeia and Therapeutic Compendium: Ashwagnadha*, Soquel, CA: American Herbal Pharmacopoeia

Slide 49

Kulkarni RR, Patki PS, Jog VP, et al. (1991). Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled,

cross-over study. *J Ethnopharmacol*, 33:91-5.

Upton, R, et al. (2000). *American Herbal Pharmacopoeia and Therapeutic Compendium: Ashwagnadha*, Soquel, CA: American Herbal Pharmacopoeia

Slide 54

Bhat, J., Damle, A., Vaishnav, P. P., Albers, R., Joshi, M., and Banerjee, G. In vivo enhancement of natural killer cell activity through tea fortified with Ayurvedic herbs. *Phytother.Res* 2010;24(1):129-135.

Mikolai, J., Erlandsen, A., Murison, A., Brown, K. A., Gregory, W. L., Raman-Caplan, P., and Zwickey, H. L. In vivo effects of Ashwagandha (*Withania somnifera*) extract on the activation of lymphocytes. *J.Altern.Complement Med*. 2009;15(4):423-430.

Rhodiola Mechanisms

- Krasik E, Petrova K, Rogulina G, et al. New data on the therapy of asthenic conditions(clinical prospects for the use of Rhodiola extract). *Proceedings of All-Russia Conference: Urgent Problems in Psychopharmacology* 1970 May 26-29. Sverdlovsk, Russia: Sverdlovsk Press; 1970.p. 215-7.

- Krasik E, Morozova E, Petrova K, et al. Therapy of asthenic conditions: clinical perspectives of application of *Rhodiola rosea* extract. In. *Proceedings Modern problems in psycho-pharmacology.* Kemerovo-city, Russia: Siberian Branch of Russian Academy of Sciences: 1970.p. 298-330.

- Stancheva SL, Mosharrof A. (1987) Effect of the extract of *Rhodiola rosea* L. on the content of the brain biogenic monamines. *Med Physiol*, 40:85-87.

ES Mechanisms

- Facchinetti F et al. (2002). *Eleutherococcus senticosus* reduces cardiovascular response in healthy subjects: a randomized, placebo-controlled trial. *Stress Health*, 18:11-17

- Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* 2000;72:345-93.

- Hacker B, Medon PJ. Cytotoxic effects of *Eleutherococcus senticosus* aqueous extracts in combination with N6-(delta 2-isopentenyl)-adenosine and 1-beta-D-arabinofuranosylcytosine against L1210 leukemia cells. *J Pharm Sci* 1984;73:270-2.

- Hikino H, Takahashi M, Otake K, Konno C. Isolation and hypoglycemic activity of eleutherans A, B, C, D, E, F, and G: glycans of *Eleutherococcus senticosus* roots. *J Nat Prod* 1986;49:293-7.

- Dasgupta A, Wu S, Actor J, et al. Effect of Asian and ES on serum digoxin measurement by five digoxin immunoassays. Significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003;119:298-303.

- Glatthaar-Saalmuller B, Sacher F, Esperester A. Antiviral activity of an extract derived from roots of *Eleutherococcus senticosus*. *Antiviral Res* 2001;50:223-8.

- Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V. Decreasing, null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: the role of ginsenosides. *J Am Coll Nutr* 2004;23:248-58.