Therapeutic PROTOCOLS

2nd Ed.

HPA Axis Optimization

Understanding the **4 Stages** of HPA Axis Dysregulation and Therapeutic Targets

Botanicals · Orthomolecular · TCM Formulas · Lifestyle · Nutrition

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Acknowledgement:

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Vita Aid Professional Therapeutics

HPA Axis Optimization

Addressing the 4 Stages of HPA Axis Dyresgulation

The term "adrenal fatigue" describes the adrenal glands' response to chronic stress following 3 stages: alarm, resistance, and exhaustion. It was based on Dr. Hans Selye's theory of General Adaptation Syndrome (GAS) in the 1950's.

However, "adrenal fatigue" was poorly accepted by the medical community because it over-simplifies the intricate pathways communicating multiple organ systems outside the adrenals, particularly the hypothalamas-pituitary-adrenal (HPA) axis.

The involvement of the HPA axis explains why chronic stress causes myriad problems in the nervous system, such as mood and autonomic disorders, as well as chronic fatigue syndrome.

HPA Axis Regulation

Cortisol is one of the major tools the body uses to counteract adverse effects from stress.

In other words, its level dictates the threshold of stress the body can tolerate. Cortisol has several important functions:

» Increasing the serum glucose level for ATP generation; chronically disrupted cortisol rhythm can increase the risk of developing insulin resistance.
» Exerting anti-inflammatory effects
» Helps to promote alertness and cognitive function.
(*Cortisol too High ➔ Anxiety)

Normally, our cortisol levels rise and fall throughout the day, following a circadian rhythm. The diurnal cortisol levels are relatively high to help maintain alertness and cognitive function while the nocturnal levels are low to promote relaxation and sleep.

The HPA axis is activated upon receiving stress signals. The paraventricular nucleus (PVN) of the hypothalamus would first secrete corticotropin releasing factor (CRF) and arginine vasopressin (AVP), which in turn would stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then binds to the adrenal cortex to promote the release of cortisol to help the body cope with stress.

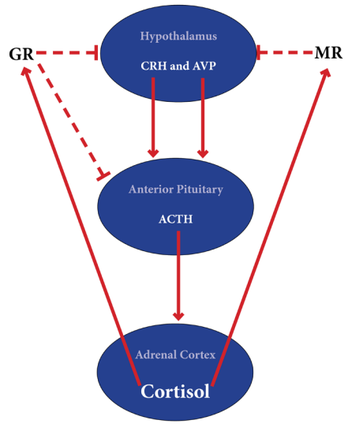

Figure 1. Auto-Modulation of the HPA-Axis

To protect against prolonged activity of the adrenals, the secretions of CRF, AVP, and ACTH are precisely controlled by cortisol via the binding of two types of receptors - mineralocorticoid (MR) and glucocorticoid (GR) receptors. Cortisol has higher binding affinity for the mineralocorticoid receptors (MRs) than the glucocorticoid receptors (GRs). This difference in affinity allows the MRs to closely maintain the circulating cortisol levels relatively low for normal daily activity. Only when the cortisol concentration is high in response to stress does it bind to the GRs to keep the HPA axis from becoming too overactive. (Figure 1)

This delicate negative feedback mechanism maintains the secretion of ACTH and cortisol within a relatively narrow bandwidth. However, when it fails to function properly, the HPA axis progresses through, not 3, but 4 stages of dysregulation.

HPA Axis Dysregulation in 4 Stages

Stage 1 - Over-Stimulation (Restlessness)

- HPA axis responds to stressors robustly.
- Chronic stress results in overactive HPA axis overwriting the negative feedback loop and, consequently, increases the overall cortisol levels - both diurnal and nocturnal.

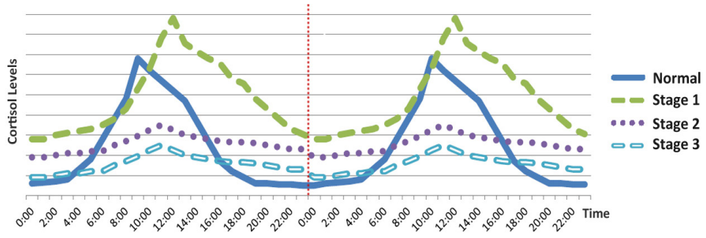

Figure 2. Cortisol circadian rhythms of the 3 stages of Adrenal Fatigue over a course of 2 days.

Signs & Symptoms: restlessness, insomnia, sleep difficulty, high blood sugar, elevated DHEA & catecholamines (epinephrine and norepinephrine).

Stage 2 - Over-Exertion (Wired & Tired)

- HPA axis activation is sustained but exerting to keep up with continuous stress.
- Long-term high outputs of ACTH and cortisol begin to affect the physiology of the HPA axis. The circadian rhythm becomes disrupted (ie. the diurnal cortisol levels not high enough to provide energy while the nocturnal levels not low enough to promote relaxation).
- Chronic elevated cortisol baseline levels also affect the immune function rendering the individual susceptible to frequent infections and autoimmune responses.

Signs & Symptoms: fatigue, anxiety, irritability and depression under moderate stress, IBS, and chronic muscle/joint pain.

Stage 3 - Exhaustion (Extreme Fatigue & Multiple Systems Affected)

- Tolerance to stress becomes extremely low due to the hypoactivity of the HPA axis.
- The CRH, ACTH, cortisol, DHEA, and catecholamine levels are low in response to stress.
- Cumulative stress and chronically elevated cortisol result in wear and tear on multiple systems of the body from excessive exposure to the catabolic properties of glucocorticoids, stress peptides, and proinflammatory cytokines.

Signs & Symptoms: Extreme lethargy, suboptimal or hypo-thyroidism, sleep-deprived, depression, anxiety, chronic myalgia and arthralgia, IBS, low pulse & blood pressure, and dysglycemia.

Stage 4 - Mitochondrial Dysfunction

- While the mitochondria are technically not considered a part of the HPA axis, they play a crucial part in regulating the body's neuroendocrine, metabolic, inflammatory and transcriptional responses to stress via energy transformation and intracellular signalling.
- Chronic oxidative stress from long-term HPA dysregulation depletes the body's antioxidant capacity (ie. glutathione) and wreaks damage on a cellular level, particularly the mitochondria of cells involved in the HPA axis signalling.
- Typically non-responsive to cortisol/ glandular supplementation because tissue regeneration is compromised.

Signs & Symptoms: chronic degenerative disease(s), slow wound-healing, cognitive/ memory decline, and chronic fatigue syndrome.

HPA Dysregulation Affects Other Systems

Chronic HPA axis dysregulation has been associated with a number of chronic diseases, such as hypothyroidism, metabolic syndrome, cardiovascular disease, anxiety and depression, chronic fatigue syndrome, and neurodegenerative diseases (eg. Parkinson's and Alzheimer's diseases). Disrupted cortisol rhythm can directly impact other endocrine systems including, but not limited to, **thyroid and reproductive hormones.**

When our body is under chronic stress to the point of exhaustion, the protective mechanism is turned on to **conserve energy and reduce metabolism by inhibiting thyroid hormone bio-activity and secretion ➔ ↑ TSH.**

High stress can also greatly affect the reproductive system. Progesterone is one of cortisol's precursors, and therefore, **excess cortisol production in response to stress can cause progesterone to deplete ➔ estrogen dominance**. Moreover, excessive cortisol can disrupt the pulsatory secretion of GnRH (gonadotropin releasing hormones) and affect the Hypothalamus-Pituitary-Gonad Axis ➔ fertility issues.

HPA Axis Optimization: Tolle Totum

HPA dysregulation is a multi-factorial problem involving multiple systems, and therefore, its treatment approach should also be multifaceted and individually tailored based on the individual's symptoms and lifestyle.

Combining the adaptogenic herbs and nutrients with lifestyle changes that include stress management, diet, and exercise, we can start to promote tissue repairs, optimize the body's tolerance to stress, and restore the modulatory actions on the HPA axis, improving the overall health and well-being.

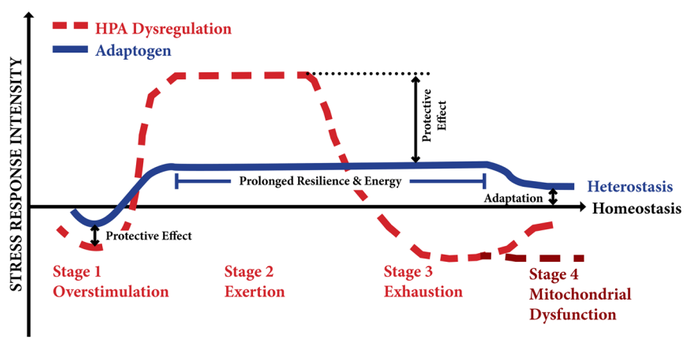

Figure 3. Adaptogens increase the non-specific resistance to stress by decreasing the sensitivity to stress and prolonging the phase of resilience.

Adaptogens: Promote Resilience & Establish Optimal "Heterostasis"

While lifestyle interventions, such as stress management, relaxation techniques, exercise, eating a whole-food, low-glycemic diet, and getting regular sleep, are vital to restoring overall health and well-being, patients often need additional aid to overcome the 'therapeutic hump' from being chronically ill before they can start incorporating these lifestyle changes. This is where the adaptogenic herbs come in.

When the body responds to stressors, many systems are forced out of homeostasis. The HPA axis activation would bring the body to a 'heterostatic' state - a higher level of homeostasis, or an adaptation to stress. The closer the gap between heterostasis and homeostasis, the easier it is for the body to later return to the original state after stress subsides.

Adaptogens are a group of herbs that act to render stress protection and prolong the phase of resilience. In other words, adaptogens can help modulate the magnitudes of stress response and 'narrow the gap' between heterostasis and homeostasis allowing the body to restore normal physiological activities sooner. (Figure 3)

The mechanisms of action of various adaptogens may include hepatoprotective, cardio-protective, neuroprotective, CNS stimulating (ie. enhancing physical and cognitive performances), anti-inflammatory, antidepressive, anxiolytic, immunotropic, and antioxidative effects.

- HPA Axis Optimization - continued on p.5 -

The Progression of HPA-Axis Dysregulation

Therapeutic Targets

Assessing HPA Dysregulation

- **Ragland's Sign** - Take patient's blood pressure when sitting or lying down. Then ask the patient stand up and immediately take another blood pressure. The systolic pressure, should rise at least 8 mm. If it is not or if it drops, HPA axis dysregulation is indicated.
- **Pupil Constriction** - Shine a penlight into one eye. The pupil should constrict. If after 30 seconds with the light shining in your eye, the pupil dilates and/or shivers, this likely indicates adrenal fatigue.
- **4-Point Cortisol Panel** - Using 4-point saliva samples to help evaluate cortisol rhythm.

Clinical Pearl

It usually takes LONGER for Stages 3/4 patients to get better as their recovery will **regress from Stages 3/4 to Stage 2, then to Stage 1**.

Therefore, it is important for the clinician to periodically review the patient's symptoms and adjust the therapy accordingly.

Focus on **finding the appropriate level of stimulation** (correct medicine and dosing schedule) while continuing to **restore HPA-axis' capability to respond**, to help the patients recover both symptomatically and physiologically.

	Clinical Pictures	Signs/Symptoms	Treatment Goals	Adaptogenic Support	Vita Aid/Synerplex Formulas
Stage 1 : Over-stimulation	» Overactive HPA-axis overwriting the negative feedback →overly stimulated » Liver Qi Stagnation/ Exuberance of Heart Fire	» Insomnia » Hypertension » Hyperglycemia » Palpitation, ↑heart rate » Easily Agitated » IBS	» Calm the person (mentally & physically) » Modulate the cortisol levels	» Chamomile, Lemon Balm - Nervine » Passionflower - Nervine/ Sedative » L-Theanine - Nervine » Wild Jujube Seed - Nervine/ Sedative » Magnesium - Relaxant » Melatonin - sleep-aid » Cordyceps Cs-4 - Cortisol Modulating » Rhodiola - Cortisol Modulating » Eleuthero - Cortisol Modulating » Ashawagandha - Cortisol Modulating	» **Resolaxin** » **Adrenergyn** » **Bisglycino-Mg** » Melatonin » 5-HTP » SJW450 » **Harmovex*****
Stage 2 : Over-Exertion	» Disrupted cortisol circadian rhythm becomes the new "norm" » Spleen & Heart Def./ Disharmony of Heart & Kidney	» Insomnia, restless sleep, tiredness » Anxiety » IBS	» Support Adrenals & body's stress-coping mechanism with Adaptogens	» Cordyceps Cs-4 - Cortisol Modulating » Rhodiola - Cortisol Modulating » Eleuthero - Cortisol Modulating » Ashawagandha - Cortisol Modulating » St. John's Wort - Anxiolytic	» **Adrenergyn** » Bisglycino-Mg » 5-HTP » SJW450 » Bio-B5 Forte » **Femalance***** » **Harmovex*****
Stage 3 : Exhaustion	» Tolerance to stress becomes extremely low due to the hypoactivity of the HPA-axis. » Qi & Blood Def./ Spleen & Kidney Qi Def. ***	» Fatigue » Fibromyalgia (due to chronic inflammation) » Weakened immune system » Cognitive decline » ↓Blood Pressure » Hypothyroidism	» Tonify the adrenal functions » Relieve pain/ inflammation » Supports immune system » Support cognitive function	» Licorice - Replenish Cortisol Levels » Panax Ginseng - Adrenal Tonic, Immune Support » *Cortisol Modulating Herbs** (balance cortisol)* » Adrenal Glandular Tissue* » Astragalus - Immune Support, Elevates *SP & LU Qi* » Bacopa - Cognitive Tonic » Ginkgo biloba - Cognitive Tonic » *Anti-inflammatory Support* - Curcumin, Boswellia, Hops, Grape Seed, NAC, Vitamin A/C/E » St. John's Wort & 5-HTP - pain relief, sleep-aid	» **AdrenoForte DP** » **Adrenergyn** » Bio-B5 Forte » Inflamlief » SJW450 » 5-HTP » Thyroaide » **Femalance***** » **Spirityang*****
Stage 4 : Mitochondrial Dysfunction / Chronic Fatigue Syndrome	» Burnout at cellular level in other organs » Mitochondria damaged by excessive oxidative stress and become depleted → Fail to respond to stimulation » Spleen and Kidney Yang Def./ Blood Stagnation ***	» SSx in Stage 3 + » Persistent Exhaustion » Non-responsive to adrenal glandular supplement » Chronic Fatigue Syndrome » Myalgia/Arthralgia » Muscle weakness	» Reduce oxidative damage in mitochondria » Supplies essential cofactors/ coenzymes for energy generation	» CoQ10 - ATP synthesis (ETC); antioxidants » L-carnitine - enhances beta-oxidation and ATP production » Taurine & Lipoic Acid - mitochondrial antioxidants » Magnesium - cofactor in ATP production » Vitamin B2/B3/B5 - glycolysis, Kreb's cycle » *Cortisol Modulating Herbs***	» **Neuromin** » **H.C.Q10-Cardio** » **AdrenoForte DP** » **Adrenergyn** » Bio-B5 Forte » Inflamlief » **Femalance***** » **Spirityang*****

*Glandular Tissue – should only be administered short-term; it is essentially feeding cortisol to our system.
Long-term use might put our adrenal cortex to "sleep" as the body detects no need for endogenous secretion of cortisol.

** Cortisol Modulating Herbs - Cordyceps, Eleuthera, Rhodiola, Ashwagandha; at Stage 3, these herbs may help elevate the baseline cortisol levels without overshooting it.

*** These TCM patterns and formulas are commonly seen in Stage 3 & 4; however, other patterns might be present depending on each patient's tongue & pulse diagnosis.

For more information on our Synerplex TCM formulas:

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Lifestyle Modifications

- **Exercise Regularly** - at least 20 minutes per day, four times a week. **Exercising at the appropriate time** of the day (morning or afternoon) has been shown to **increase the secretion and the uptake of cortisol.** That being said, intense exercises should be **avoided 3 hours before bedtime** as cortisol levels are supposed to be low during that time. Exercise can also elevate the endorphin and serotonin levels and help stabilize the mood.
- **Anti-inflammatory Diet** - Help patients to select fresh foods containing **rich amounts of antioxidants and vitamins/minerals (Magnesium, Selenium, Zinc).** Avoid consuming fried foods, foods containing common allergens (eg. gluten, dairy), and processed foods.
- **Sleep Hygiene:**
  1. Fixed bedtime (before 11 pm) and awakening time.
  2. Avoid napping for longer than 45 minutes.
  3. Use comfortable bedding & temperature setting, and keep the room well ventilated.
  4. Block out all distracting noise and **keep the room as DARK as possible.** Turn off as many electronics and appliances as possible to minimize Electriomagnetic Field exposure.
  5. **Practice relaxation techniques** before bedtime eg. meditation, yoga, deep breathing, progressive muscle relaxation.
- **Positive Thinking** - Positive thinking doesn't mean to ignore life's less pleasant situations, rather, to approach these situations in a more comprehensive and productive way. Contemplate the best outcome as well, not just the worst.
- **Minimize stimulants** eg. caffeine and alcohol.

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Product Index

Adrenergyn

Stages 1-4

Adrenal Modulator

- **Cs-4 strain of *Codyceps sinensis* - the most well-studied strain in human clinical studies to enhance oxygen** utilization, ATP generation, anti-oxidation, as well as body's immune function.
- **Eleuthero** have been shown to modulate the blood pressure & cortisol levels under stress, enhance oxygen usage in cells, and increase endurance of the muscles.
- In TCM, **Cordyceps** tonifies *Kidney Yang* and *Lung*; **Eleuthero** tonifies *Spleen* and *Kidney* and anchors the mind.
- **Ashwagandha** supports hypothalamic-pituitary-adrenal axis, as well as the thyroid function by enhancing T4 to T3 conversion.
- **Rhodiola** is shown to affect multiple systems to promote emotional well-being, mental clarity, and physical endurance. Like Eleuthero, it also modulates the overshooting cortisol levels. In TCM, rhodiola tonifies *Lung Qi* and promote blood flow.

Ingredients (per capsule):

Rhodiola Extract 18:1 (*Rhodiola rosea*) (root).....75 mg
(3% rosavins, 1% salidroside) (equivalent to **1350 mg of dried herb**)
Cordyceps Cs-4 Extract 8:1 (*Cordyceps sinensis*) (mycelium)...200 mg
(7% cordycepic acid) (equivalent to **1600 mg of dried herb**)
Eleuthero Extract 10:1 (*Eleutherococcus senticosus*) (root).....70 mg
(0.8% eleutherosides) (equivalent to **700 mg of dried herb**)
Ashwagandha Extract 6:1 (*Withania somnifera*) (root).....170 mg
(1.5% withanoloids) (equivalent to **1020 mg of dried herb**)
Vitamin B5 (from d-calcium pantothenate).....10 mg

Resolaxin

Stages 1

Herbal GABA Agonist for Stress Relief

- **Wild jujube seed & passionflower** are potential GABA receptor agonists to promote the mind and muscle relaxation.
- **Wild jujube seed**, a TCM herb used for **calming the *Shen* (mind) and nourish Heart *Yin***, improving sleep quality & digestive function, and reducing the high blood pressure & relieving IBS caused by stress.
- **Chamomile & lemon balm** - excellent nervine tonics to help support the nervous system.
- **L-theanine** induces a sense of inner calm and promote restful sleep without affecting alertness.
- Not only useful in calming the mind and promoting relaxation, **but also ideal for IBS (diarrhea or constipation dominant).**

Ingredients (per capsule):

Chamomile Extract 8:1 (*Matricaria chamomilla*).....120 mg
(flower) (1% apigenin) (equivalent to **960 mg dried herb**)
Lemon Balm Extract 5:1 (*Melissa officinalis*).....53.3 mg
(leaf) (5% rosmarinic acid) (equivalent to **267 mg dried herb**)
Wild Jujube Extract 17:1 (*Zizyphus spinosa*) (seed).....110 mg
(2% triterpene saponins) (equivalent to **1980 mg dried herb**)
Passion Flower Extract 4:1 (*Passiflora incarnata*) (flower).....45 mg
(3.5% vitexin) (equivalent to **180 mg dried herb**)
L-Theanine (from *Camellia sinensis*) (leaf).....50 mg
Magnesium (from magnesium citrate).....25 mg
Vitamin B6 (from pyridoxine hydrochloride).....5 mg

AdrenoForte DP

Stages 3-4

Herbal Cortisol Depletion Support

- **Free of animal glandular tissue.**
- **Licorice** helps to increase the cortisol level via its inhibitory effect on cortisol breakdown (ie. inhibition of 11-beta-hydroxysteroid dehydrogenases). In TCM, licorice tonifies *Spleen Qi.*
- **Panax Ginseng** helps to tonify the adrenal functions. In TCM, Panax ginseng tonifies Qi and Yang.
- In TCM, **Eleuthero** tonifies *Spleen* and *Kidney* and anchors the mind.
- **Astragalus - "The King Herb of Qi" in TCM** - to tonify *Spleen* and *Lung* and enhance the immune functions.
- Highly concentrated **Bacopa Extract (30:1; 50% bacopasides)** - a potent Ayurvedic brain tonic to support cognitive function and memory.

Ingredients (equivalent to **6110 mg dried herb** per capsule):

Asian Ginseng Extract 10:1 (*Panax ginseng*) (root).....85mg
(20% ginsenosides) (equivalent to **850 mg of dried herb**)
Astragalus Extract 12:1 (*Astragalus membranaceus*).....100 mg
(root) (equivalent to **1200 mg of dried herb**)
Licorice Extract 8:1 (*Glycyrrhiza glabra*) (12% glycyrrhizin).....170mg
(root) (equivalent to **1360 mg of dried herb**)
Eleuthero Extract 10:1 (*Eleutherococcus senticosus*).....75mg
(root) (equivalent to **750 mg of dried herb**)
Bacopa Extract 30:1 (*Bacopa monnieri*) (whole plant).....65mg
(50% bacopasides) (equivalent to **1950 mg of dried herb**)
Vitamin B5 (from d-calcium pantothenate).....10 mg

Neuromin

Stages 4

Comprehensive Neuro-Protective Formula

- **Pyrroloquinoline quinone (PQQ)** facilitates nerve regeneration by promoting nerve growth factor, and also acts as a neuro-protectant via it's antioxidant effects. Its benefits for memory & attention are enhanced by the addition of CoQ10 according to clinical data.
- PQQ protects mitochondria by significantly reducing levels of inflammatory markers such as CRP and IL-6.
- **Benfotiamine combined with folate and B12** resulted in significant improvement in nerve conduction velocity and is effective in the treatment of diabetic neuropathy.
- **Active R-alpha lipoic acid** provides additional antioxidant effects and protects nerves and mitochondria from damage.
- Phosphatidylserine has been shown to enhance memory and cognitive function in elderly patients.
- Active forms of vitamin B12 and folate to support methylation process in neurons.

Ingredients (per capsule):

Pyrroquinoline quinone (BioPQQ®).....5 mg
Coenzyme Q10 (ubiquinone).....37.5 mg
R-alpha-lipoic acid (sodium salt) (stabilized).....75 mg
Benfotiamine.....35 mg
5-Methyltetrahydrofolate (from Ca 5-MTHF).....100 mcg
Niacinamide.....25 mg
Vitamin B2 (riboflavin-5'-phosphate (sodium salt)).....5 mg
Vitamin B6 (pyridoxal 5'-phosphate).....5 mg
Vitamin B12 (methylcobalamin).....100 mcg
Mixed Phospholipids (from *Glycine max*) (seed).....50 mg
(phosphatidylserine, phosphatidylcholine,
phosphatidylinositol, phosphatidylethanolamine)

Inflamlief

Stages 3-4

Natural COX-2 inhibitor to help relieve inflammation. Bioavailability enhanced by Bioperine®

- Contains daily dosage of 1000 mg of patent iso-alpha acid standardized *Humulus lupulus* extract clinically proven to be a COX-2 (Cyclyoxygenases) inhibitor with comparable effect to 400 mg ibuprofen.
- Reduces PGE2 production of the specific target cells. Provides effective anti-inflammatory support without the cardiovascular, gastrointestinal and renal adverse effects.
- Contains highly concentrated phyto–antioxidants to scavenge free radicals and reduce oxidative stress in inflamed tissues such as arthritis, muscle tearing, and any discomfort caused by inflammation.

Ingredients (per capsule):

Hops Extract 30:1 (*Humulus lupulus*).....167 mg
(cone) (30% alpha and iso-alpha acids)
(equivalent to **5000 mg of dried herb**)
Boswellia Extract 20:1 (*Boswellia serrata*) (gum resin).....60 mg
(65% boswellic acid) (equivalent to **1200 mg of dried herb**)
Curcumin (from *Curcuma longa*).....200 mg
(root, rhizome) (C3-Complex®)
Rosemary Extract 6:1 (*Rosmarinus officinalis*).....15 mg
(leaf) (equivalent to **90 mg of dried herb**)
Piperine (from *Piper nigra*) (Bioperine®).....1.7 mg

C3-Complex® and Bioperine® are registered trademarks of Sabinsa Corp.

H.C.Q10-Cardio

Stages 4

Comprehensive Mitochondrial Support

- **900 mg dried herb equivalent Hawthorn** and **100 mg CoQ10 from KanakaQ10™** carry inotrophic actions to help strengthen the cardiac contraction (without increasing its oxygen demand) and increase coronary blood flow.
- **L-carnitine** help shuttle fatty acids into the mitochondria for beta-oxidation and promotes energy production. Numerous clinical studies have proven the efficacy of the treatment in CHF patients with sufficient dose of CoQ10 and L-carnitine.
- **Taurine** is one of the most important antioxidants in the mitochondria to help modulate the oxidative stress from ATP synthesis in the Electron Transport Chain.
- **Magnesium** is one of the most important cofactors in ATP synthesis.

Ingredients (per capsule):

Coenzyme Q10 (ubiquinone) (KanekaQ10™).....100 mg
(from bacterial/ yeast fermentation process)
L-Carnitine (from L-carnitine tartrate).....150 mg
Hawthorn Extract (*Crataegus laevigata*) 12:1.....75 mg
(fruit) (5% procyanidins) (equivalent to **900 mg dried herb**)
Taurine.....50 mg
Magnesium (from magnesium AAC (glycine)* and citrate).....20 mg