

OPTYGEN HP RESEARCH PACKET

THE FOUNDATION FOR
EXTREME PERFORMANCE



SUPPLEMENT FACTS

30 servings per container

Use Directions: Take 4 tablets daily with a meal

Serving Size

4 Tablets

Amount Per Serving	% Daily Value*
Chromium (as Chromium nicotinate glycine chelate)** 200 mcg	167%
Ashwagandha Extract (Withania somnifera)(root) 150mg	*
Rhodiola Extract (Rhodiola rosea)(root)(5% rosavins) 150mg	*
Cordyceps (from Cs-4 Paecilomyces hepiali and Cordyceps militaris extracts) (mycelia biomass) 800 mg	*
Beta-Alanine 1500mg	*
ActiGin Proprietary matrix (Panax notoginseng extract, Rosa roxburghii fruit extract) 50mg	*
ATPro Matrix (Calcium Pyruvate, Sodium Phosphate, Potassium Phosphate, Ribose) 500mg	*
* Daily Value Not Established	125%
Levagen®+ (Palmitoylethanolamide with Lipisperse®)† 300mg	*
Immulink MBG® Organic Reishi Extract(Ganoderma lucidum) (Min. 70% 1,3/1,6 Beta D-Glucan) 200 mg	*
Agave Inulin 200 mg	*
Green Tea Extract (Camellia sinensis) (leaf) 50% polyphenols (decaffeinated) 200 mg	*
Ginkgo biloba Extract (Ginkgo biloba) (leaf)	*
(24% Ginkgoflavone glycosides, 6% terpenoids) 120 mg	*
Spectra® Total ORAC5 Blend‡ 100 mg	*
Boron (as FruiteX-B® Calcium Fructoborate) 1 mg	*

*Daily Value Not Established

**Chelavite® is a registered trademark of Albion Laboratories, Inc. Covered by Albion International, Inc., U.S. Patent 5,614,553

***Senactive® is a registered trademark of NuLiv Sciences. U.S. Patent 2019/0374592 A1

NOTE: SOY is from soy lecithin, and is used to ensure consistent blending and accuracy of dosages per capsule. Soy lecithin does not contain soy proteins or lectins.

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III. OPTYGENHP OVERVIEW

CHOOSE STRESS, CHOOSE OPTYGENHP, CHOOSE ANTISTRESS, CHOOSE PERFORMANCE

Being a serious endurance athlete means you have already chosen to seek and endure extreme stress. You train hard, you plan hard, you race hard, you play hard, and you think hard. Serious endurance exercise is both a physical and mental stress, and more extreme means more stress.

Common signs of physical exercise stress are: decreased performance, fatigue, aches and pains, overuse injuries, delayed recovery, elevated oxidative stress biomarkers, elevated inflammatory biomarkers, and competitive incompetence. Common signs of mental stress from exercise are: mental fog, sleep disorders, loss of interest/pleasure in your sport, worse judgement & decision-making, anxiety, depression, eating disorders, and even PTSD.

Your body has built-in antistress repair and recovery processes, but even your normal processes can be overcome by increased physical exercise and mental fatigue. You know what I am talking about, and you love it!

OptygenHP (High Performance) was introduced in 2007 to give your stressed body and mind more resources to do what you chose to do. By combining herbal adaptogens with essential minerals involved in basic metabolism, OptygenHP gives you increased ability to resist physical and mental stress by promoting homeostasis, keeping you healthy, happy, and performing maximally. Homeostasis literally means “stable human,” as in stable health, unimpeded physical function, and mental well-being. Balance. An even keel. Good as new. Upward and onward.

OptygenHP makes a difference that users feel. Backed by hundreds of human studies on the ingredients and by a clinical study on its formula, OptygenHP’s combination of adaptogens, metabolites (especially Beta Alanine), and Chromium make a positive difference in your overall ability to perform physically and mentally. The key to optimizing performance with OptygenHP is long-term, continuous use. A deluge of scientific research on the adaptogens, Beta Alanine, and Chromium in OptygenHP supports continuous use for best results.

Think of it this way: OptygenHP has anti-stress nutrients that exert better effects after 4-8 weeks of usage. These nutrients have many ways to work to make your body adapt successfully to maintain peak performance. Our bodies have built-in processes to adapt to their environment by sensing deviations from normal which signal responses from cells to counteract the stressors. As you train and compete, your body’s needs also change, and these changes are also affected by the multitude of active agents in a wide spectrum of adaptogens (as in OptygenHP), and by the basic need for reducing excess acid production in exhausted muscles (as supported by Beta Alanine).

After you see how OptygenHP works you’ll understand that your body needs the many-faceted activities so you can stay your best, both physically and mentally. Individually, these adaptogens have continued use for

millennia by humans to improve health. Now imagine all the physiology you can support in so many ways that even essential vitamins, minerals, and fatty acids cannot accomplish. OptygenHP is additive to good nutrition.

Citations for Exercise Stress: Almekinders 2019; Cheng 2020; Colangelo 2023; DiFiore 2014; Garbisu-Hualde 202; Gratwicke 2021; Kajaia 2021; Knechtle 2018; Knez 2006; Lehman 1993; Millet 2018; Reardon 2019; Scheer 2021, 2022; Schiphof-Godart 2018; Simpson 201; Thuany 2023; Vitale 2019

OptygenHP Origin Story

After stunning and unprecedented world-record performances of Chinese middle-distance runners in 1994 were attributed to an obscure adaptogen called Cordyceps, the race was on to study and incorporate adaptogens into all types of exercise (Steinkraus 1994). Adaptogens were forever more not only for resisting aging.

Also in 1994, dietary supplements (including adaptogens) had just been given a defined, separate regulatory status as foods by the Dietary Supplement Health and Education Act (DSHEA). Supplements were allowed Structure-Function Claims (unlike foods) in the United States. Although the types of claims are still being modified by the USFDA, the new-found deluge of claims resulted in a boon for educating consumers and for taking supplements. Adaptogens became a major category of “herbal” supplements, and the supply chain went through an expansion phase to meet consumer demands.

In 2002, usage of adaptogens for exercise increased to the point they could no longer be ignored. For millennia, Asian/Chinese/Korean ginseng (*Panax ginseng*) was the predominant adaptogen, and various preparations were shown to improve exercise performance (Bucci 2000, 2004), but research studies gave variable results, and although adaptogens were widely used by athletes, adaptogens were not widely accepted in the academic exercise research world. (More on this issue later in this Research Packet.) Plus, adaptogens had an old-fogey tag from their use since prerecorded history to fight aging and poor health by indigenous cultures. More lore than science?

In 2002, First Endurance was formed by veteran sports supplement company experts – who were also endurance athletes – to provide a trustworthy source of the adaptogens most coveted by endurance athletes: Cordyceps and Rhodiola, along with other essential minerals and metabolites. Optygen (Optimal Oxygen) was born based on the latest adaptogen research, along with real-life use in field testing from its harshest critics – elite endurance athletes. Optygen itself showed improvements in endurance exercise physiology parameters in a controlled human clinical study (Larson 2007). Feedback was and still is overwhelmingly positive. An effective, science-backed, and successfully field-tested formula is a characteristic of First Endurance products, and that testing is continuously ongoing.

OptygenHP was introduced in 2007 to provide even more adaptogenic nutrients and effects. Two additional adaptogens (Ashwagandha and Senactiv®) and Beta-Alanine for intracellular pH control were added to Optygen to boost adaptogenic properties for the most elite endurance efforts. Successful field testing by OptygenHP users was followed by a human clinical study (Creer 2007) that also showed improvements in exercise performance parameters. Both Optygen and OptygenHP have thrived together since.

How OptygenHP can help your exercise performance and recovery can now be explained in simple terms in this OptygenHP Research Packet – and it makes sense.

Citations for Optygen Origin Story: Bucci 2000, 2004; Calabrese 2021; Creer 2007; DSHEA 1994; Jia 2009 2475, 2009 2924; Larson 2007; Kim 2021; Steinkraus 1994; Zhang 2017

1 Not from Charles Darwin, according to Quote Investigator, but sums up his work, and also adaptogens.
2 From [www.vocabulary.com](https://www.vocabulary.com/dictionary/adapt), <https://www.vocabulary.com/dictionary/adapt>
3 From [www.vocabulary.com](https://www.vocabulary.com/dictionary/genesis), <https://www.vocabulary.com/dictionary/genesis>
4 Gale Encyclopedia of Medicine, 2008, <https://medical-dictionary.thefreedictionary.com/adaptogen>

IV. OptygenHP Science

Understanding Adaptogens

It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change.¹

The major actives in OptygenHP are its adaptogen herbal extracts – Ashwagandha, Cordyceps, Rhodiola, and Senactiv®. Beta Alanine, Chromium, and the ATPPro Matrix (minerals, pyruvate, and ribose) are not actually adaptogens, but they add to adaptogen effects. Adaptogens have been misunderstood and even maligned, but the science has soundly supported their benefits, especially for exercise performance and recovery.

Defining Adaptogens

Adaptogens is a catch-all term to lump together various herbs and traditional medicines that have a long history of keeping humans healthy, even more so under periods of stress, both physical (intense exercise) and mental.

“Adapt” is derived from a Proto-Indo-European language, its root meaning grab, grasp, or take.² “Gen” is derived from “genesis,” meaning a beginning.³ Thus, the meaning of the word adaptogen is “grab anew” or “take a new beginning.” The credit for coining the word “adaptogen” goes to N.V. Lazarev, a Soviet researcher, in 1947. He referred to an adaptogen as a substance that increases ‘non-specific’ resistance to adverse influences that threaten homeostasis (normal health and functioning). There are many definitions of “adaptogen” but the simplest is: a substance that improves the body’s ability to adapt to stress⁴. Notice adaptogens help you adapt to stress and are not simply antistress – a subtle but important distinction. Removing all stress also removes impetus to adapt, and that means no progress towards gaining physical and mental functions.

Table 1: Adaptogen Definitions

1. Having non-specific properties (i.e., work on anything and everything);
2. Increasing resistance of the organism to a wide range of adverse factors (i.e., stressful exercise);
3. Normalizing organ systems;
4. Working better as stress increases*;
5. Almost non-toxic.**

*Remember Definition #4 – this will be important for interpreting “modern” human exercise study results – very important. This is the “if it ain’t broke, don’t fix it” attribute of adaptogens that have bumfuzzled researchers (who naturally are trying to find something, not nothing).

** Almost non-toxic? Why not just non-toxic? This phrase was a direct quote from an English translation from Russian and something was lost in translation...what was originally meant is that no toxicity was found/known, and it came out awkward into English.

1 Not from Charles Darwin, according to Quote Investigator, but sums up his work, and also adaptogens.

2 From www.vocabulary.com, <https://www.vocabulary.com/dictionary/adapt>

3 From www.vocabulary.com, <https://www.vocabulary.com/dictionary/genesis>

4 Gale Encyclopedia of Medicine, 2008, <https://medical-dictionary.thefreedictionary.com/adaptogen>

Adaptogen Origins

Adaptogens have been in use around the world since before recorded history. When you have no medical industry, you are reliant on your own initiative to maintain and improve your health, no matter what your condition is. Prehistoric humans figured out that certain plants had healing properties, likely from watching what animals ate when they were sick, and trial and error testing passed from generation to generation for millennia. Every culture devised uses of local herbs and other natural products in an effort to live healthier, longer lives. Other “treatment” modalities (acupuncture, exercise/martial arts, meditation, mind exercises, and more) accompanied adaptogen usage, leading to generations of treatises (cookbooks) on how to maintain and enhance health, especially in Asiatic areas.

Traditional Chinese Medicine (TCM) and Ayurveda are two well-known health systems that are highly sophisticated and prevalent to this very day, and both have extensive adaptogen usage, but every culture used adaptogens. From day one, the major emphasis of these healthcare systems is intended to work with one’s body, mind, and spirit to help normalize, balance, resist, and restore the whole person so your own body could use all its natural strength to become and stay healthier, no matter what you do. In other words, help your body to help itself.

Stress Definition Origins

Adaptogens target stress, which has only recently in history become codified and examined in detail. In 1897, the Fourth Triennial Congress of American Physicians and Surgeons was about Adaptation in Pathological Processes⁵. (Notice the theme of the meeting was Adaptation – Adaptogens!) Their President, William H. Welch, said the following in his opening monologue to the Congress of medical doctors: “The most wonderful and characteristic attribute of living organisms is their active adaptation to external and internal conditions in such a way as tends to the welfare of the individual or of the species.” This is one of the first “modern” medical/scientific mentions about adaptogenic actions to “conditions,” which later were described as biological stress.

The Godfather of Stress is Janos Hugo Bruno “Hans” Selye (1907-1982), an Austrian-Canadian endocrinologist credited with proving and popularizing the existence and impact of biological stress. His 1936 letter “A Syndrome produced by Diverse Nocuous Agents” in the still-prestigious journal Nature laid the foundation for what stress is, how it affects all of us all the time, and – more importantly – how our bodies handle it (Selye 1936, 1998). He also included exercise as a stress:

It seems to us that more or less pronounced forms of this three-stage reaction represent the usual response of the organism to stimuli such as temperature changes, drugs, muscular exercise, etc., to which habitation or inurement can occur. (Selye 1936, p. 32) [Emphasis mine.]

Dr. Selye deduced how to counteract the effects of stress – increase metabolic energy output past the norm, just like a stressed body does. Thus, deficiency of energy production was the root of all ill health, and thus, stress. Notice the emphasis on energy output – exactly what long-duration, intense exercise demands. This is where adaptogens come in for exercise performance.

⁵ <https://www.jstor.org/stable/pdf/1625471.pdf> p.814-5

Citations for Adaptogens & Stress: Brekhman 1969; Gorban 2021; Lazarev 1958; Panossian 2011; Selye 1936, 1998; Szabo 2012; Tan 2018; Wagner 1994; Welch 1897;

Adaptogens Are Multiple Energy Metabolism Custodians!

Adaptogens are not supplying energy itself – that comes from metabolism of oxygen, carbs, fats, and proteins. Instead, adaptogens have many universally active components that act together, allowing your metabolism to function more normally and allowing you to perform maximally with improved overall health. It's the multitudinous number of compounds and their multitudinous activities that make adaptogens so, well, adaptable to fighting stress for them and you. Some of these components are identical to what is in the human body, and simply balance a lack or an increased need – similar to vitamin/mineral supplements. But the differentiator for being an adaptogen is the multitude of slightly different, molecular mimics to human endogenous molecules, giving each adaptogen unique and additive properties. The multitude of adaptogen-specific molecules help further balance metabolic deviations caused by stress, smoothing both deficient and excessive deviations. Like the high school janitor/custodian that has a key to every lock, adaptogens can affect any and every bodily function – and try to keep them going – from behind the scenes, out of sight.

Understanding Adaptogens – If You Want Something Done, Give It to a Busy Person

It's a simple concept – when you are under any stress that adversely affects your life, you want/need to affect many processes simultaneously. How many processes are we talking about? More than 46,000 metabolic signaling pathways with over 217,920 different metabolites (Bongiovanni 2022, Khoramipour 2015, Wishart 2022). And these metabolites are smaller than 1,500 daltons – there are hundreds of thousands more types of proteins and other entities larger than 1,500 daltons. That busy enough for you?

Stress simultaneously causes cell signaling and responses in your body that affect antioxidants, mental calming, energy metabolism, receptor binding, enzyme interactions, and so on. Adaptogen components have different effects simultaneously on the body – antioxidant, mental calming, energy metabolism, cell signaling, receptor binding, enzyme interactions, and so on. (And yes, both of those sentences list the same terms, but the effects of stress and adaptogens are operating in different directions.) In general, the combination of all these actions allows your body to better resist stress effects.

During total body stress – especially intense, long-lasting exercise – our cells are automatically looking for help, constantly responding to their environment and adding, deleting, and changing concentrations of cell membrane receptors to give and take what they need to normalize their (energy) metabolism. Your cells are simultaneously emitting and receiving all kinds of biochemical signals. In alphabetical order, acyl carnitines, ADP/AMP/ATP, amino acids, ammonia, antioxidants, cyclicAMP, cytokines, eicosanoids, endocannabinoids, exosomes, enzymes, fatty acids, free radicals, glucose (and other sugars), hormones, lactate, metabolic intermediates, microbiome byproducts, microRNAs, minerals, nitric oxides, nucleosides/nucleotides, organic acids, oxidized (damaged) molecules, phospholipids, peptides small and large, polyamines, polyphenols, proteins, quinones, sterols, sulfhydryls, urea, vesicles, and vitamins are playing a symphony in your body. The field of metabolomics and other -omics is starting to peer into the complexity of the adaptogenic process.

⁶ From www.vocabulary.com, <https://www.vocabulary.com/dictionary/homeostasis>

Citations for Busy Adaptogens (Metabolomics): Astle 2007; Beger 2017; Bei 2017; Belhaj 2021; Bester 2021; Bongiovanni 2019, 2022; Calabrese 2013, 2021; Castro 2019, 2021; Coehlo 2016; del Castillo 2013; Enea 2010; Erofeeva 2022; Fernandes 2017; Goodacre 2007; Hargreaves 2018, 2020; Hawley 2014; Heaney 2019; Hintikka 2022; Judge 2020; Khoramipour 2022; Kistner 2020, 2023; Lawton 2008; LeVatte 2022; Lewis 2010; Li 2017 333; Liu 2020; Lustgarten 2013; Malsagova 2023; Maunder 2018; Maurer 2021; Morville 2020; Nemkov 2023; Peake 2014; Pontzer 2023; Resende 2011; Sahlin 1990; San-Millan 2018, 2020; Schmidt 2013; Schraner 2020; Shi 2020; Skaperda 2022; Spinelli 2018; van Milgen 2002; Wang 2013; Walsh 2007; Wishart 2008, 2022; Zagatto 2020

Adaptogens are Multigens, Too

Adaptogens are busy, too. Being living organisms, adaptogens are loaded with many capable biochemical effectors – the metabolites just mentioned and also more not normally found in the human body. Adaptogens cajole and coddle your body’s web of metabolomics and interactive processes to maintain your health and homeostasis (in other words, a return to stability). Homeostasis is a scientific term that describes staying in a home state, in other words, the way your body wants to be, or should be, or a return to stability).⁶ More simply put, adaptogens help you perform your best.

Thousands of published animal studies show the propensity for adaptogens to “work” on many stressful conditions. Animal studies on adaptogens are mostly successful because their genetics, diets, lifestyles and adaptogen doses are optimized for health and lack of variability, making it easier to find effects in studies. But humans are not lab animals, and this large literature will not be considered further. Many published in vitro (“test tube”) biochemical/cell/tissue studies have also pinned down exact molecular mechanisms of how adaptogens and their components “work,” whether it be the entire herbs or combinations of its components or single components. Again, we’ll not review this large body of scientific literature, since the same mechanisms are operative in humans. Instead, we’ll review the human study evidence that adaptogens work when used properly for exercise. This is scientific reality, and explains their historic and present popularity. If you statistically cannot deny, then you must accept. Adaptogens are well accepted.

Like all other fields of science, there are divergent and diametrically opposed findings and views from the published research literature and popular literature (i.e., the Internet) about efficacy of adaptogens. This is normal, and actually has more to do with investigator biases, high subject variability, and study design shortcomings than with real-life efficacy.

How to Look at Human Studies on Exercise and Adaptogens Properly

In 2004, my coauthors and I were invited to write a review chapter on ginseng (*Panax ginseng*), the poster child for adaptogens, for an academic book on nutrients as ergogenic aids (Bucci, 2004).⁷ We did not have commercial interest in ginseng – we did not really care if it “worked” or not for exercise or mental performance. But we were curious about the polarity of obvious biases, and kept an open mind.

In preparing the chapter, we included more studies than any prior review – we were thorough. We noticed diametrically opposed results from the same substances, similar subjects, similar exercises, and similar settings

⁶ From www.vocabulary.com, <https://www.vocabulary.com/dictionary/homeostasis>

⁷ Also presented at: Adaptogenic Herbs, Bucci L, presented at the 1st Annual ISSN Conference, Lake Las Vegas, NV, June 18-19 2004.

- only the researchers were obviously different. This did not make sense. How can this be? We smelled a rat and dug deeper. We found many experimental designs that missed the mark of what they were aiming for. Shoddy science (fewer subjects and shorter time periods and insensitive measurements) led predictably to find conclusions of no or few benefits, sometimes ignoring significant results. Other studies were designed with common sense, and found statistically significant benefits. Unfortunately, this allows cherry-picking only the studies that support one's views, which quickly becomes gospel without scientific rigor.

For ginseng and other adaptogens (Cordyceps, Rhodiola), we statistically and clearly showed: 1) studies with larger numbers of subjects (>13 per group) showed significant positive results for physical performance; 2) studies lasting longer than 8 weeks showed significant positive results for mental and physical performance; and 3) doses were less important (as would be expected from knowing how adaptogens work). And yes, studies looking at more intense, longer-term exercise found better results more often, suggesting a higher exercise intensity was a key factor for success of adaptogens.

In other words, there are some obvious rules for designing human studies to fairly estimate effects of adaptogens on human performance – physical exercise and mental functions, too.

Studies with fewer subjects (<13) or shorter durations (<8 weeks) usually did not find effects. Researchers call these kinds of studies “quick and dirty,” meaning they are not definitive because they have a high risk for a Type II error – in plain English, not finding an effect that is really there. Missed the mark. And yet, these are the studies most cited as “proof” adaptogens do not work for exercise performance, without mentioning the positive studies.

There are two important questions that should have been asked and then studies designed to test this concept: 1) adaptogens are NOT stimulants, although they have been studied like caffeine is studied, looking only for immediate enhancements in physical performance; and 2) there needs to be significant stress for adaptogens to have a chance to work. Without knowing physiological stress levels, or without looking at settings that are not stressful enough, then adaptogens, by definition, should not show any changes in performance, physiology, health, or even biomarkers. In other words, many human studies on adaptogens were doomed to fail (find significant differences from a placebo) before they even started. How can you rightfully measure what you do not understand?

Critical, careful, and thorough review of the research on multifactorial ginseng and exercise yields a bigger picture that supports efficacy for other multifactorial adaptogens and human performance. The same findings apply to each adaptogen with sufficient human studies. Human studies on adaptogens and exercise are actually much more likely to be poorly designed, fatally flawed, and also to be misinterpreted along lines of bias. And be careful with reviews – they are usually incomplete, and cherry-pick negative studies, ignoring or heaping criticisms that should have but were not applied to the cherry-picked studies). This is called selection and reporting bias, which from over-reliance on poorly designed studies leads to incomplete and erroneous conclusions.

What is important to understand adaptogens is the TOTALITY OF EVIDENCE. At First Endurance, we put much more emphasis on human studies, but with a wary eye on study design, author intent (many studies were performed specifically to show adaptogens did not “work”), and knowing the strengths and weaknesses of human clinicals. When all things about adaptogens are considered, it's clear that adaptogens have the capability

of efficacy when used correctly – see Rules section below. If you read and comprehend all the articles in the Reference list, the adaptogen picture for exercise performance becomes clear. We'll save you that trouble – continue reading!

Bottom line - adaptogens work for extreme endurance exercise.

A Missing Link in Adaptogen and Exercise Performance Research

One very important item about adaptogens (and exercise studies in general) that is seldom considered in human research is this: if the body is not sufficiently replete for nutritional status and function it may decrease effects of any intervention, including adaptogens to some extent. In other words, any nutritional/nutrient deficiencies – whether from insufficient or variable nutrient intakes, genetics, or poor health practices (lack of sleep, alcohol/substance abuse, pollutant exposure as examples) – will increase variability among subjects, which decreases finding statistical significance in human studies ability. That's not a fault of the adaptogen, but of experimentation. You cannot adapt if you cannot run the adaptive processes. *This is a major uncontrolled experimental variable in human exercise studies of adaptogens and exercise.*

Since elite athletes in general have high incidences of low status/function of iron, magnesium, vitamin D and omega-3s (see MultiV Research Packet), these factors have likely impeded the results of human studies of adaptogens to be able to find efficacy for sports/exercise and more (aging, immune function, mental functions, etc.). Remember, adaptogens work with your body, and if your body is healthy, then adaptogens can restore homeostasis from stress better. Adaptogens can still be beneficial if there are missing nutritional needs, but not to the same extent.

The antidote to deficient functions? Simple! Taking a comprehensive multiple vitamin/mineral (MVM) supplement (such as MultiV or MultiV-PRO) and adequate omega-3 intake (which HALO provides) ensure optimal adaptogen (Optygen, OptygenHP) enhancement effects. How do we know? Field testing of OptygenHP with users of MultiV.

Unalterable truth: adaptogens are scientifically supported for health and exercise performance benefits, as illustrated in this Research Packet.

Adaptogens Have Rules in Order to Work - A Metabolic 'Multipass'

Adaptogens are broad-based multi-taskers with multiple active compounds, multiple bioactivities, multiple mechanisms of action, and multiple targets. The types of compounds in adaptogens are many, and include polyphenols, triterpenoids, alkaloids, amino acids, peptides, nucleotides, polysaccharides (beta-glucans, for example), microRNAs – all of which have their own actions and benefits. Adaptogens have identical and similar compounds to what your cells already have – and thus know how to use. In spite of all this complexity, adaptogens have simple rules that give you benefits if followed.

Stress is a deviation from normal metabolism. Extreme long-duration exercise causes metabolic deviation from normal. Metabolism is what fuels response to stress, physical activity, and recovery. Our bodies have a multitude of interlocking ways to stay in or get back to normal metabolism. Adaptogens work by supplying a plethora of recognizable regulatory signals that your body already has (and can utilize more) or that mimic what your body uses to control getting back to health and overcoming deviations. By having numerous micromechanisms that are supportive rather than demanding, they nudge your body back to normal. After all, our bodies are highly interactive and interdependent on the function of all systems for health. Why not use something that effects all-of-the-above instead of a single target? Even adding a good thing can unintentionally imbalance something else – that’s not homeostasis. This concept of balance is different from reductionist drug mentality (take ‘this one thing’ for ‘that’ and take more if it does not “work” at first). **Moral of the story: Take adaptogens for everything, and whatever ‘that’ is will also get better.**

Table 2: Top 10 Adaptogen Rules for Success:

1. You need to be under considerable physical, mental, or emotional stress, enough to not be your usual self;
2. The further from your usual self (homeostasis) the better adaptogens work;
3. Adaptogens are not stimulants or fuel;
4. Adaptogens need to be taken regularly and consistently to work best – give them time to adapt you;
5. You need to take enough adaptogen for antistress effects, but not too much;
6. More adaptogens taken together work better than a single adaptogen;
7. Adaptogens cannot rescue you from bad lifestyle decisions – they are not antidotes for stupidity;
8. Adaptogens are called “non-specific” – they work on your entire body and find the weakest links to specifically improve;
9. Adaptogens work with your gut microbiome, helping to normalize it, too;
10. Adaptogens can fix many deviations simultaneously in different ways.

The more you look into adaptogens, the more they become MULTIGENS.

Citations for Adaptogen Efficacy, Multigenicity, & Rules: Amir 2023; Arring 2018; Attele 1999; Bahrke 2009; Billia 2020; Bucci 2000, 2004; Choi 2013; Ernst 2010; Gerontakos 2020, 2021; HMPC 2008; Jin 2020; Kennedy 2003; Liao 2018; Oliyink 2013; Panossian 1994, 2011, 2021; Perdrizet 1997; Ratan 2021; Saggiu 2009; Sellami 2018; WHO 1991.

New Insights on Adaptogens & Exercise

Importantly, these learnings can be applied to other antistress adaptogens, either as single agents or as combinations. And more and more studies are finding out intricate details of how adaptogens affect our bodies to keep us healthier and performing better, along with improvements in practical matters of production – farming, shipping, quality control, availability (see Table 3 below).

Table 3: New Insights on Adaptogens

Better Identification of Plant/Fungal Species and Strains	DNA technology is now being used to confirm adaptogen identity and quality, for evidence of safety, choosing strains with more bioactivity, preventing counterfeiting & adulteration, determining mechanisms of actions, finding new active compounds, and finding more ways they work (mechanisms of action)
More Devoted and Sustainable Farming or Culturing	Sustainability, improved supply for demand, better pricing, consistency of materials, increased jobs and job stability
Better Stress Measurement Tools	More sensitive measurements to find effects in human studies, more targets/biomarkers/pathways to observe, better applicability to real-life settings, newly found mechanisms of action
More Human Clinicals	Support for benefits, new uses, determining dosages, documenting mechanisms of action, evidence of safety
Genetics, Epigenetics, Metabolomics, Polymorphisms	Evidence of safety, support benefits, responders vs. non-responders, explaining the spectrum of efficacy
Better Ingredients	Standardization of extraction for key active components, ensuring reproducible potency, ensuring bioactivity, ensuring safety

Adaptogens -They Work as Multifactorial Facilitators

Sooner or later, all of us will confront enough stress for adaptogens to have utility. Consistent use of adaptogens gives your body additional tools to help resolve stress when it does happen, whatever the stress is. From reading hundreds of scientific articles, conversing with experts in the field, and seeing real-life results of adaptogens, it's clear adaptogens can work, and work well. The many satisfied users of Optygen and OptygenHP for over 20 years is another measure of success and efficacy. How they work is a common thread. Adaptogens are multifactorial, just like our bodies.

Adaptogens – usually herbs or fungal sources – have developed thousands of molecules to enable them to resist deadly environmental stresses. Some of these compounds are structural, usually called polysaccharides, like yeast beta-glucans, that trigger human cellular responses. Some of these compounds are DNA- or RNA-based with both biochemical and cell messenger activities, such as cordycepin in Cordyceps. Some are antioxidants,

both familiar and unfamiliar, like rosavins in Rhodiola. Some are weak steroidal hormone mimics, such as ginsenosides, that fine-tune hormonal responses by toning down or ramping up effects of your own hormones. Some are neuroendocrine stress response modifiers, receptor agonists/antagonists or precursors for endogenous synthesis of critical control biomarkers. Some are antioxidants and pH buffers. In short, there are many ways

adaptogens can cover a lot of ways for your body to help adjust its own responses to many types of stress, including intense, long-duration exercise. Better stress response = better physical and mental performance.

LITERATURE QUOTES FOR UNDERSTANDING ADAPTOGENS

"Adaptogenic herbs: a natural way to improve athletic performance."

Amir 2023, Title

"In conclusion, adaptogens are a powerful natural remedy to help the body resist stress, improve focus, and enhance athletic performance."

Amir 2023, p.4

"Most (seven of eight) studies that showed significant improvements in fatigue were trials that lasted 4 weeks or more."

Arring 2018, p.632

[Note: Ginseng human studies were reviewed for fatigue in persons with chronic illnesses]

"Taken together, our data demonstrates for the first time that neuropeptide Y and heat shock protein Hsp70 can be used as molecular biomarkers for adaptogenic activity."

Asea 2013, Abstract

"Many studies examining the pharmacological effects of ginseng and related products on humans engaged in physical performance such as that pursued by athletes frequently have not employed sound scientific design and methodology. For example, small numbers of participants might have been inadequate to provide the statistical power needed to detect significant changes."

Bahrke 2009, p.317

"To date, from 114,100 to 217,920 different metabolites have been observed in the human body, and more than 46,000 metabolite or metabolic signaling pathways have been described. However, the majority of the published exercise/physiology metabolism studies measured fewer than dozens of metabolites and examined only one to two pathways at a time; this scenario limits our knowledge of the complex connections between exercise, physiology, and metabolism."

Bongiovanni 2022, p.2

[NOTE: This review shows how the research to date on adaptogens and exercise is not considering how adaptogens actually work, which makes study design details important for finding or not finding effects from adaptogens.]

"Longer times of administration (over 12 weeks) during periods of substandard performance (for a variety of reasons, including advancing years and stressful conditions) seem to augur for modest but not universal improvements in feelings of well-being, mood, reaction times, neuromuscular control, mental functions, work capacity and endurance performance. Short-term use of Asian ginseng (four weeks or less) appears to have no effects on mental or physical performance beyond a placebo effect. Adding other nutrients or herbs to Asian ginseng appears to produce significant effects more often or in shorter time periods."

Bucci 2004 379, p.400

"The results of this systematic review showed that ginseng appears to be effective for various medical conditions, particularly exercise capacity..."

Choi 2012, p.13

"...Adaptogens regulate the internal environment and tend to maintain the body stable, what is called Homeostasis, and thus, achieve greater athletic performance to physical and mental stress."

Domene 2013, p.1062

"Like all herbal extracts, ginseng preparations are complex mixtures of a range of pharmacologically active ingredients. [...] These compounds have complex biological activities. The mechanisms of action of Panax ginseng are therefore diverse, complex and somewhat uncertain."

Ernst 2010, p. 262

"Adaptogens are generally referred to the substances, mostly found in plants, which non-specifically increase resilience and chances of survival by activation of signaling pathways in affect cells."

Esmaealzadeh 2002, Abstract

"It is concluded that the main modes of action of the selected adaptogenic plants are stress modulatory, antioxidant, anti-fatigue, and physical endurance enhancement."

Esmaealzadeh 2002, Abstract

"Other properties were nootropic, immunomodulatory, cardiovascular, and radioprotective activities."

Esmaealzadeh 2002, Abstract

"Adaptogens are herbs and plants used to help the body adapt to stressors of all kinds."

Food Revolution Network 2020 (<https://foodrevolution.org/blog/what-are-adaptogens/>)

"A nutritional supplement – e.g., ginseng, maitake mushroom – which allegedly helps the body adapt to various stressors – e.g., heat, cold, exertion, trauma, sleep deprivation, toxic exposure, radiation, infection, psychological stress; ginseng is regarded by some as the prototypic adaptogen."

The Free Dictionary by Farlex 2012 (<https://medical-dictionary.thefreedictionary.com/adaptogen>)

"Substance that improves the body's ability to adapt to stress."

Gale Encyclopedia of Medicine, 2008 (<https://medical-dictionary.thefreedictionary.com/adaptogen>)

"In summary, three broad areas of outcome measures have been used to measure the outcome and effect of adaptogens, which include cognitive measures, mood measures, and biological measures. [...] Individually, these studies give some level of information regarding the action and efficacy of certain herbal medicines in stress related conditions [...] Comprehensive cognitive testing holds promise as a measurement tool when used with additional measures relevant to the scope of adaptogenic activity as it is understood today."

Gerontakos 2020, p.337

"The application of molecular techniques to exercise biology has provided greater understanding of the multiplicity and complexity of cellular networks involved in exercise responses, and recent discoveries offer perspectives on the mechanisms by which muscle "communicates" with other organs and mediates the beneficial effects of exercise on health and performance."
Hawley 2014, Abstract

"From Brekhman 1969:

3. An adaptogen is incapable of influencing normal body functions more than required to gain non-specific resistance."
Kelly 2001, p.294 (<https://pubmed.ncbi.nlm.nih.gov/11410073/>)

"The findings of present study demonstrated that PGC exerted anti-fatigue function, mainly through antioxidant stress, regulation of carbohydrate metabolism, delaying the accumulation of metabolites, promotion of mitochondrial function, neuroprotection and antiapoptosis, and regulation of neurotransmitter disorder. And the findings supported, at least to an extent, the use of PGC for fatigue."

Jin 2020, p.28

[NOTE: PGC = Panax ginseng CA Meyer]

"Medicinal substances causing a state of nonspecifically increased resistance of the organism."

Lazarev 1947, p.579

"To date, various studies and practical applications have shown that plant-originated adaptogens are a kind of elite herbal medicine, playing an important role in human health and helping the human body resist various stress factors."

Liao 2018, p.10

"Any agent, e.g., an herb or nutrient, that stimulates immunity or provides resistance to disease."

Medical Dictionary, Farlex and Partners 2009 (<https://medical-dictionary.thefreedictionary.com/adaptogen>)

"a nontoxic substance and especially a plant extract that is held to increase the body's ability to resist the damaging effects of stress and promote or restore normal physiological functioning"

Merriam-Webster 2021 (<https://www.merriam-webster.com/dictionary/adaptogen>)

"Despite these difficulties, large quantities of data received from animal and human studies allow for making some preliminary conclusions about potential actoprotective properties of ginseng preparations: 1) results of some animal experiments and human studies attest that P. ginseng (administered as extract) can significantly increase physical and intellectual work capacity."

Oliyynyk 2013, p.159

"In summary, adaptogens may be regarded as a novel pharmacological category of anti-fatigue drugs that:

(i) induce increased pharmacotherapeutic attention and endurance in situations of decreased performance caused by fatigue and/or sensations of weakness."

Panossian 2009 198, p.216

"Strong scientific evidence is available for Rhodiola rosea SHR-5 extract, which improved attention, cognitive function and mental performance in fatigue and chronic fatigue syndrome."

Panossian 2009 198, Abstract

“Regardless of the formal indication for use in official medicine as tonics, adaptogens are widely used in sports medicine to promote quicker recovery after heavy exercise and overstraining.”

Panossian 2021, p.635

“The idea to combine two or more plants or substances, which will be stronger than any ingredient alone, is very attractive for several reasons: the ingredients may have different targets and mechanisms of action in human organisms, and therefore better effect as a combination; and the combination can be used at lower doses and may be less toxic if any ingredient contains a toxic impurity. The ingredients can also act synergistically, thereby providing new unique effects that are not possible to obtain by any ingredient independently.”

Panossian 2021, pp.667-8

“The reductionist concept, based on the ligand–receptor interaction, is not a suitable model for adaptogens, and herbal preparations affect multiple physiological functions, revealing polyvalent pharmacological activities, and are traditionally used in many conditions. This review, for the first time, provides a rationale for the pleiotropic therapeutic efficacy of adaptogens based on evidence from recent gene expression studies in target cells and where the network pharmacology and systems biology approaches were applied. The specific molecular targets and adaptive stress response signaling mechanisms involved in nonspecific modes of action of adaptogens are identified.”

Panossian 2022, Abstract

“Adaptogens are currently defined as a therapeutic category/pharmacological group of herbal medicines or / and nutritional products, increasing adaptability, survival, and resilience in stress and aging by triggering intracellular and extracellular adaptive signaling pathways of cellular and organismal defense systems (stress system, e.g., neuroendocrine-immune complex). Furthermore, adaptogens trigger the generation of hormones (cortisol, corticotropin-releasing hormone [CRH], gonadotropin-releasing hormones, urocortin, neuropeptide Y), playing key roles in metabolic regulation and homeostasis.”

Panossian 2022, p.2

“Such interventions [adaptogens] for increasing endurance performance are largely concerned with increasing energy supply and influencing biosynthesis of proteins and nucleic acids.”

Saggu 2009, p.41

“...we have found that most herbs (Table 2) used in sports have a low-moderate effect on oxidative stress, fatigue resistance, and endurance capacity.”

Sellami 2018, p.11

“Adaptogens were also used by the sports persons to improve body’s physical endurance and on neutralizing the stress.”

Sharma 2021, Abstract

“Adaptogens are substances that increase organism resistance to a broad range of chemical, biological and physical stressors.”

Snow 2022, p5

“The data from the meta-analysis showed that plant adaptogens could provide a number of benefits in the treatment of chronic fatigue, cognitive impairment, and immune protection.”

Todorova 2021, Abstract

"I shall employ the epithet 'adaptive' to describe morbid processes which bring about some sort of adjustment to changed conditions due to injury or disease. [...] The most wonderful and characteristic attribute of living organisms is their active adaptation to external and internal conditions in such a way as tends to the welfare of the individual or of the species."
Welch 1897, p.814-5 (<https://www.jstor.org/stable/pdf/1625471.pdf>)

"1st formal definition (1968 by Brekham [sic] & Darymovhe [sic]):

1. An adaptogen is nontoxic to the recipient.
2. An adaptogen produces a nonspecific response by the body – an increase in the power of resistance against multiple stressors including physical.
3. An adaptogen has a normalizing influence on physiology, irrespective of the direction of change from physiological norms caused by the stressor."

Whole New Mom 2021 (<https://wholenewmom.com/what-are-adaptogens/>)

LITERATURE QUOTES FOR ADAPTOGEN DENIERS

"ERROR. No matches found."

American Medical Association, 2023

[NOTE: Yes, you see nothing from the AMA. A search of the AMA website does not find the search terms adaptogen or adaptogens – and thus, access to information on adaptogens is invisible to most medical doctors in the USA and thus, ignored.]

[NOTE 2: A survey of 14 Journals published by the American Medical Association found five articles, only one since 2001, with adaptogens as a search term.]

[Obviously, the AMA is not an expert on or even informed about adaptogens and is not a credible source of information or opinions on adaptogens.]

"While some adaptogens like ashwagandha and Asian ginseng have a number of studies on their varied actions, supplements are not regulated by the FDA, and FDA approval does not equate to safety."

Anonymous, Cleveland Clinic 2023.

[NOTE: There are only three explanations for this statement being made in public: 1) ignorance; 2) intentional lying; and/or 3) following the mainstream medical community bias against supplements. Additional proof of how the mainstream US medical community badly misunderstands supplements, and thus, adaptogens. FACT: FDA has ALWAYS regulated supplements as foods since the 1934 FD&C Act. FDA does indeed specifically regulate supplements since 1994 – see DSHEA 1994 in the Reference List and many resulting laws and Guidance Documents refining how FDA has been regulating supplements the last 30 years. In addition, the FTC regulates commercial speech (ads and product claims) and has published an advertising guide for dietary supplements for over 20 years, updated this past year (FTC 2001, 2022).

[NOTE 2: FDA has not, cannot, does not, and will not "approve" supplements – this statement is blatantly false, misleading, and shows a decided ignorance of current food regulations or worse.] (see NOTE above).

[NOTE 3: Notice they never said adaptogens do not work!]

"The term [adaptogens] is currently not accepted in pharmacological, physiological, or mainstream clinical practices in the European Union."

Anonymous, Wikipedia 2022

[NOTE: This statement is incorrect as several herbal adaptogens and advertised as such are registered as pharmaceuticals in most European countries.]

“The research to date provides little support for taking ginseng to enhance exercise or athletic performance.”
Office of Dietary Supplements, National Institutes of Health, 2022

[NOTE: Obviously the editors of this topic did not see my publications on adaptogens, even though one was presented at the National Institutes of Health, peer-reviewed and published (Bucci 2000). This statement is erroneous and shows a lack of objective command of the research.]

Citations for Adaptogens Deniers: AMA 2023; Anonymous 2022, 2023; ODS 2022

V. OPTYGENHP Ingredients and What They Do

Ashwagandha (*Withania somnifera*, Indian Winter Cherry, “Queen of Herbs”) Extract

For over 4,000 years, Ashwagandha has been used in Ayurvedic health practices in India and surrounding regions for many health-promoting purposes, similar to how Asian Ginseng (*Panax spp.*) has been used in China, Korea, and surrounding regions – as an adaptogen. Roots are the usual plant part used, but increasing use of leaves and whole plants are in vogue, because all plant parts contain withanolides, the major active agents. Ashwagandha uses were founded on centuries of trial-and-error observation to determine which conditions derive benefit from Ashwagandha. These benefits have been the focus of a growing body of human scientific research published in the last 30 years, mostly in India. Given the known basic science and overall promising results, including exercise performance and recovery, it is odd that Ashwagandha has seldom been studied by researchers outside India. Having a concentrated Ashwagandha extract in OptygenHP means you are not missing out on its benefits.

Being an adaptogen, Ashwagandha has been used for restoring or improving a breadth of health issues. Ashwagandha is normally used with other herbs in Ayurvedic practice, but the last 40 years of human research has generated numerous human studies on Ashwagandha extracts given alone. The latest human clinical studies and reviews support Ashwagandha’s longstanding, major role for maintaining health, and other studies have determined the major active agents in Ashwagandha and how they work. Like other adaptogens in OptygenHP, Ashwagandha assists overall health by interacting with many bodily processes and pathways with its own set of unique molecules, showing significant improvements and return to normality – called rejuvenation. Thus, Ashwagandha has shown benefits for a wide range of bodily processes and systems both mental and physical. Specifically of interest for intensely exercising individuals are: anxiety, cognition, exercise performance, fatigue, immune system, mood, pain (normal, everyday aches and pains), QOL (Quality of Life), sleep, and stress responses.

Sleep benefits are well-documented, and reinforced by the species name of Ashwagandha – *somnifera*, Latin for sleep-inducing. That sums up one of its major activities. Sleep quality is often improved when “stress” is reduced, and a good night’s sleep often further reduces stress – chicken/egg thing, both helpful and reinforcing, especially for strenuous exercisers who are travelling. Fortunately, Ashwagandha does not make people drowsy during the day – it is not a knockout pill.

The daily doses showing benefits ranged from 120-2,000mg of powder or more concentrated extracts. OptygenHP contains 150 mg of Ashwagandha extract standardized to alkaloids, withaferin-A, and withanolides, the major active ingredients in Ashwagandha. In fact, OptygenHP contains 1,150 mg of total herbal adaptogen extracts, each at daily amounts associated with benefits. The total amount of adaptogens in OptygenHP conforms to the high end of daily dosage for any single adaptogen that has found beneficial outcomes in human

studies. Extracts provide higher amounts of the more active components of each adaptogen, while also supplying the overall milieu of compounds found in lower potency extracts or the original herb itself, thus encompassing the breadth of use and substantiation for adaptogenic effects. In other words, it's the sum total of all the adaptogenic compounds that make OptygenHP work so well to keep you going at your best.

Citations for Ashwagandha & Health: Human Studies (Antioxidant, Antistress, Anxiety, Cognition, Immune, Infertility, Joint Discomfort, Memory, QOL, Pain, Sleep): Agnihotri 2013; Ahmad 2010; Ambiyi 2013; Andrade 2000; Auddy 2008; Baker 2022; Chandrasekhar 2012; Chauhan 2022; Chegappa 2018; Choudhary 2017; Cooley 2009; Deshpande 2020; Dongre 2015; Fuladi 2021; Gannon 2019; Gopal 2021; Gopukumar 2021; Gupta 2013; Jahanbakhsh 2016; Kaushik 2017; Kelgane 2020; Khyati 2013; Kuchewar 2014; Langade 2019, 2021; Lopresti 2019 1557, 2019 e17186; Mahdi 2011; Mamidi 2011; Mikolaj 2009; Murthy 2019; Nalini 2013; Nasimi Doost 2018; Nayak 2015; O'Connor 2022; Pingali 2013; Ramakanth 2016; Remenapp 2022; Salve 2019; Sengupta 2018; Tharakan 2021; Xing 2022

Citations for Ashwagandha & Health (Reviews): Abdelwahed 2019; Afewerky 2021; Ahmad 2017; Akanksha 2022; Akhgarjand 2022; Alanazi 2023; Bano 2015; Bashir 2023; Bharti 2016; Burns 2023; Cheah 2021; Czyzewska 2020; D'Cruz 2022; Dar 2015; Durg 2018; Elgar 2021; Engels 2013; Gomez Afonso 2023; Gaurav 2023; Gupta 2021; Hooda 2022; Hussain 2023; Informa 2020; John 2014; Joshi 2021; Kanjilal 2021; Kashyap 2022; Khanal 2020; Khanna 2006; Khatyi 2011; Krutika 2016; Kulkarni 2008; Kumar 2015; Logie 2020; Lopresti 2021; Mallick 2020; Mandlik 2021; Mikulska 2023; Mishra 2000; Mukherjee 2021; Ng 2020; Paul 2021; Polumackanycz 2020; Potocka 2023; Pratte 2014; Saggi 2009; Saleem 2020; Sharifi-Rad 2021; Singh 2011; Speers 2021; Syed 2021; Tandon 2020; Tetali 2021; Tiwari 2014; Uddin 2012; Ven Murthy 2010; Wai 2013; Wagner 1994; Xu 2023

Latest Research on Ashwagandha Health Benefits

- Improved speed, muscle strength, and neuromuscular coordination;
- Improved oxygen capacity (cardiorespiratory endurance, VO2max);
- Reduced muscle fatigue/exhaustion;
- Speedier post-exercise muscle recovery (DOMS);
- Improved QOL (Quality of Life);
- Reduced mental anxiety & stress;
- Improved mental functions (cognition, psychomotor functions);
- Better sleep;
- Immune health;
- Thyroid function support;
- Reduced perimenopausal symptoms.

Ashwagandha (Withania somnifera) & Exercise

You're looking at the most comprehensive review of Ashwagandha and exercise on the planet. At least 15 human studies have been reported on exercise effects of Ashwagandha up to June 2023. No other review has considered all these exercise studies and the listed non-exerciser studies yet. You'll get the overall, full picture of what Ashwagandha can do for strenuous, intense endurance exercise. At least eight reviews focused on Ashwagandha and exercise performance have been published, and many other general reviews of Ashwagandha have reported on exercise usage, all concluding positive benefits for aspects of physical exercise. Lessons learned from human study findings on physical performance and supplementation with Ashwagandha alone to date:

- Duration of use is more important than dose;
- Although benefits have been seen as soon as five days after starting Ashwagandha, best results were found between 4-8 weeks of use, and grew stronger out to 12 weeks;

- Inactive adults, recreationally active adults, and elite athletes all responded with benefits from Ashwagandha;
- Both anaerobic and aerobic exercises showed benefits;
- Improved oxygen capacity and muscular strength were routinely observed;
- Adaptation to exercise training being sped up is one interpretation that fits the data;
- Athletes already at or near peak performance and training found improvements;
- No concerns about excessive changes in heart rate or blood pressure during exercise;
- Only one reported adverse event from one study – increased appetite & libido, hallucinations with vertigo after three days of 750 mg water extract of Ashwagandha roots – symptoms disappeared three days after cessation.

Ashwagandha extracts from 300-1,000 mg daily and Ashwagandha root powder from 750-12,000 mg daily were given to healthy volunteers or athletes lasting from five days to 12 weeks in 16 different studies that measured different aspects of physical performance. A total of 710 subjects ranging from 15 to 108 per study averaged 44 subjects per study. All but two studies (both in USA) were conducted in India. Five studies used athletes for subjects, and one study used children 8-12 years old – the other studies used healthy young adult volunteers. For types of exercise studied, three utilized resistance (weight) training (Verma 2023; Wankhede 2015; Ziegenfuss 2018), two specifically measured post-exercise recovery or DOMS (Diehl 2021; Tiwari 2021) and the rest measured high-intensity (i.e., sprints), short-term aerobic or endurance capacity and strength parameters. Five studies using trained athletes – state-level medalist elite cyclists (Chaskar 2013, Shenoy 2012 209, 2012 1909), field hockey (cricket) players (Malik 2013; Mehta 2022), or sprinters (Yadav 2014). Nine studies used both female and male subjects.

Overall, Ashwagandha exhibited significant improvements between 4-8 weeks, in keeping with how adaptogens are presumed to work. Studies lasting longer (8-12 weeks) showed numerically larger improvements and more differentiation from control groups. In a few studies comparing different doses of Ashwagandha, no dose-responses were clearly seen, again supporting adaptogenic mechanisms of action. Dose was less important than duration for Ashwagandha benefits. 7/13 Studies included both women and men as subjects, in equivalent ratios. Women and men both showed similar results, but there was a trend for women to derive larger improvements from anaerobic exercise measurements than men, and for men to exhibit larger improvements in aerobic measurements.

Thus, Ashwagandha has been studied for effects on physical performance in humans of both genders ranging from nominal health to untrained and active healthy volunteers to elite endurance athletes and sport teams. At least one – but usually several – parameters attained statistical significance, showing that in general, Ashwagandha has ergogenic benefits from human exercise performance.

Recent meta-analyses and focused reviews of Ashwagandha and exercise have reinforced the positive findings (Achini 2020; Amir 2023; Bonilla 2021; Mazur 2021; Perez-Gomez 2020; Riese 2021) – see Literature Quotes below for details. Simply put, no single nutrient can replicate Ashwagandha exercise findings, except other adaptogens.

Ashwagandha & Exercise Summary

Citations for Ashwagandha & Exercise: Human Studies: Chaskar 2013; Choudhary 2015; Diehl 2021; Malik 2013; Mehta 2022; Raut 2012; Sandhu 2010; Shenoy 2012 209, 1209; Sukumar 2021; Tiwari 2021; Tripathi 2016; Venkataraghavan 1980; Verma 2023; Wankhede 2015; Ziegenfuss 2018
Citations for Ashwagandha & Exercise: Reviews: Achini 2020; Akhgarjand 2022; Amir 2023; Bonilla 2020, 2021; Cheah 2021; Elgar 2021; Gonzalez-Matarin 2023; Lopresti 2021; Mazur 2021; Mikulska 2023; Mishra 2000; Pareek 2020; Potocka 2023; Perez-Gomez 2020; Riese 2022; Sachin 2017; Sanchez 2023; Speers 2021; Wal 2013; Wissink 2018

LITERATURE QUOTES FOR ASHWAGANDHA

"Withania Somnifera found to enhance aerobic and anerobic exercise capacity, muscle strength, recovery process, anti-fatigue activity, endurance and immune-modulatory effect."

Achini 2020, Abstract

"This study has demonstrated significant scientific evidence of Ashwagandha on its usage of sports medicine along with Ayurveda elucidation. It enhances skills by improving strength, endurance, and recovery of the athlete. Hence, WS can be performed as a perfectly safe ergogenic aid."

Achini 2020, p.4226-7

[NOTE: WS = Withania somnifera extract, aka Ashwagandha]

"Adaptogens are natural substances that help the body adapt to physical and mental stress, and they can help athletes improve their endurance, strength, and overall performance, reduce fatigue and help athletes recover faster."

Amir 2023, p.4

"A root extract that warrants special attention is Withania somnifera (mostly known as ashwagandha) given some research have found ergogenic effects in athletic and physically active individuals. Moreover, the adaptogenic, anti-inflammatory, and antioxidant properties of ashwagandha turns this herbal extract into a potential strategy to optimize recovery and promote exercise-induced adaptations."

Bonilla 2020, p.11

"The findings of this comprehensive systematic review and Bayesian meta-analysis revealed that Ashwagandha supplementation was more efficacious than placebo for improving variables related to strength/power, cardiorespiratory fitness and fatigue/recovery in healthy men and women."

Bonilla 2021, Abstract

[NOTE: From 12 controlled human studies]

"In this present study, under the experimental conditions set up, we conclude that there are significant beneficial effects of Ashwagandha (Withania Somnifera) supplementation on gender differences. Thus it can be concluded from our study that responsiveness in male elite cyclists showed an increased effect on their aerobic capacity, while in female elite cyclists on their anaerobic capacity had increased effect upon the supplementation."

Chaskar 2013, p.223

"In this study, oral administration of a high concentration root extract of Ashwagandha led to increased VO2 max, enhanced cardiorespiratory endurance, and improved QOL in healthy athletic adults."

Choudhary 2015, p.67

"Ashwagandha is known primarily for its adaptogenic properties."
Czyzewska 2020, p.435

"Its properties could be helpful in mental and physical fatigue, sleep disorders, depression and anxiety states treatment. Ashwagandha's adaptogenic, neuroprotective, [...] and anti-stress activity were carried out in detail in many studies."
Czyzewska 2020, p.437

"Clinical research in humans has shown ashwagandha to be safe and of benefit in a range of conditions, including stress/anxiety, athletic performance, cognition, [...] insomnia and male infertility."
Elgar 2021, Abstract

"VO2 max, a measure of cardiovascular fitness, has been shown to increase by 6–14% over study periods of 4–12 weeks."
Elgar 2021, p.70

"Ashwagandha appears to support mitochondrial function and as such energy levels, while its adaptogenic effects on the nervous system may also have benefits in terms of athletic performance."
Elgar 2021, p.70

"As conclusions of this review, it is highlighted that the intake of Ashwagandha has beneficial effects for both strength and endurance exercise. ... in the case of endurance exercise, the intake of Ashwagandha improved VO2 max, cardiorespiratory endurance and the quality of life."
Gonzalez-Matarin 2023, p.4

"Multipurpose efficacious medicinal plant *Withania somnifera* (L.) Dunal (Ashwagandha)."
Khanna 2006, Title

"Overall, the strongest evidence for therapeutic efficacy of ashwagandha is the alleviation of stress and anxiety symptoms."
Lopresti 2021, Abstract

"Supplementation of *Withania Somnifera* improves VO2max and hemoglobin concentration in young hockey player [sic]."
Malik 2013, Abstract

"A significant improvement in the sprint fatigue level after 4 weeks ($t = 1.83, p < 0.10$, on tail rest) [sic – NOTE: should be "one tail test"] and 8 weeks ($t = 2.45, p < 0.02$, one tail test) in experimental group was found. Whereas, no significant improvement in the control group for sprint fatigue level after 8 weeks of placebo supplementation was found. Conclusion: Supplementation of *Withania Somnifera* improves sprint fatigue level in young hockey players."
Mehta 2022, Abstract

"An added benefit of this stress reduction is that many people feel an enhanced mood when taking Ashwagandha. [...] Thus, the above findings clearly indicate that the traditional use of Ashwagandha has a logical and scientific basis."
Mehta 2022, p.1454

"In addition to being already known for its medicinal value, Ashwagandha has also been found to improve cardiorespiratory and cardiovascular endurance, muscular strength, neuro-muscular coordination, and physical performance of the elite athletes."

Pareek 2020, p.116

"The results of this meta-analysis showed that supplementation with Ashwagandha may be useful to improve VO₂max in athletes and healthy adults."

Perez-Gomez 2020, p.7

"In general terms, the overall effects were better in those studies with a sample comprised of athletes compared with the studies with healthy adults. This is interesting since, as expected, baseline levels were higher in athletes and, consequently, larger improvements were expected in non-athlete healthy adults. It could be that the effects of supplementation with Ashwagandha might be linked to the physical activity levels of the participants, promoting and increasing the physiological adaptations to physical exercise."

Perez-Gomez 2020, p.7

"...it seems that this Ayurvedic herb "Ashwagandha" (Withania somnifera) can be safely used for improving cardiovascular fitness in healthy adults and also in athletes, offering an additional alternative as a nutritional supplement to enhance VO₂max."

Perez-Gomez 2020, p.7-8

"Contemporary research confirms that it is a strong adaptogen, i.e., it can effectively support increasing resistance to stress."

Polumackanycz 2020, Abstract

"It has also been noted that Ashwagandha root extract has positive effect on cardiovascular system, as well as enhancing muscle strength and recovery in otherwise healthy adults."

Potocka 2023, Abstract

"This study has also demonstrated muscle strengthening, lipid lowering, and improved quality of sleep."

Raut 2012, p.114

"Aumento de VO₂ máximo foi o parâmetro de maior relevância, além de alterações hematológicas e capacidade de gerenciamento de estresse." [Increase in VO₂max was the parameter of major relevance, in addition to hematological alterations and capacity for management of stress.]

Riese 2022, Abstract

"Withania somnifera may therefore be useful for generalized weakness and to improve speed and lower limb muscular strength and neuro-muscular co-ordination."

Sandhu 2010, Conclusion

"Considering the fact that it is difficult to detect minor changes in elite athletes, this study was the first of its kind to document the significant improvements in aerobic performance with regard to cardiorespiratory and cardiovascular endurance of elite athletes."

Shenoy 2012 209, p.213-4

"We conclude Ashwagandha is a substantial herb that could improve power and strength in well-trained athletes."

Shenoy 2012 1909, p.1913

[NOTE: Subjects were at least state-level Indian cyclists randomly selected]

"The finding of this study suggests that Ashwagandha improves cardiovascular dynamics by increasing VO2 max levels, thereby enhancing cardiorespiratory endurance, and also increases hemoglobin in healthy subjects."

Sukumar 2021, p.913

"Withania somnifera has been used for more than 2500 years as a useful medicinal plant to [...] prevent aging, rejuvenate the body in a vulnerable situation, and generate a feeling of mental well-being."

Syed 2021, Abstract

"The present findings suggest that Ashwagandha root extract can successfully enhance cardiorespiratory endurance and improve quality of life in healthy athletic adults."

Tiwari 2021, Abstract

"In the present study, Withania somnifera in doses of 330 mg and 500 mg, significantly increased the distance travelled and average speed compared to placebo. An increasing trend compared to baseline was observed in muscle power and VO2max after one month of drug administration in healthy individuals in presence of physical stress. WS 330 and 500 groups showed significant decrease in mean systolic BP in fixed workload exercise, compared to placebo reflecting its antistress and adaptogenic effects."

Tripathi 2016, p.2515

"Eight weeks of AG root extract supplementation along with resistance training is effective in improving muscle strength, growth, endurance and recovery in both male and female participants. AG root extract could be a safer, effective and low-cost alternative for athletes to improve muscle endurance."

Verma 2023, Abstract

"Withania has immunomodulatory, anti-inflammatory but most significantly adaptogenic effects, which may result from the complex of the many steroidal withanolides found in the root of the herb."

Wal 2013, p. 344

"The adaptations [to eight weeks of resistance training] were found to be statistically significantly greater, at a p-value threshold of 0.05, with ashwagandha supplementation than under placebo for all parameters (muscle strength, muscle size and body fat percentage, testosterone, and muscle recovery) except for thigh muscle size, though some effects were marginal."

Wankhede 2015, p.9

"As important as the modest benefits observed in measures of endurance and recovery, the improvements in ratings of perceived exertion and quality of life may be even more relevant."

Wissink 2018, Conclusion

"With reference to the physical fitness between Ashwagandha consumption (experimental) and control, significant difference is noted in all diameters including standing broad jump, 50 yard dash, Pull-ups, Sit-ups, Shuttle run, 12 min. run/walk."

Yadav 2014, p.47

"A 500 mg dose of an aqueous extract of Ashwagandha improves upper and lower-body strength, supports a favorable distribution of body mass, and was well tolerated clinically in recreationally active men over a 12-week resistance training and supplementation

period.”

Ziegenfuss 2018, Abstract

[Note: Ashwagandha group also showed significant improvement from baseline for 7.5 km time trial performance]



ATPro Matrix

ATPro Matrix adds Phosphate salts for supplying Sodium and Potassium in soluble forms that also delivers phosphate, which has evidence of ergogenic effects at higher doses. Calcium Pyruvate supplies the energy intermediate Pyruvate that is part of the process of glucose conversion to ATP energy, as well as soluble calcium. Ribose is the backbone of RNA and DNA (as deoxyribose) and enters energy producing pathways. ATPro Matrix has been part of Optygen and OptygenHP formulas that have exhibited improvements in exercise performance and post-exercise cortisol levels in human studies

Citations for ATPro Matrix: Addis 2012; Allen 2008; Atanasovska 2014; Barry 2007, 2011; Berchtold 2000; Bredle 1988; Brini 2000, 2011, 2013 81, 119, 5385; Bouassida 2006; Bucci 1993; Cao 2020; Clausen 2003; Creer 2007; Diaz-Garcia 2021; Dodd 2004; Ebashi 1968; Hellsten 2004; Larson 2007; Leppik 2004; Lindinger 2021; Mahoney 2018; McKenna 2008; Nielsen 1998; Seifert 2009, 2017; Szent-Gyorgyi 1975; Weaver 2006; Yang 2022

BETA-ALANINE (3-Aminopropanoic acid)

Beta Alanine Introduction - Cut to The Chase for Endurance Exercise

Beta Alanine (3-Aminopropanoic acid) is closely related to the amino acid L-Alanine, but with the amino group moved over one carbon – thus called a beta-amino acid (where the amino group is in relation to the organic acid [carboxy] end). This molecular shift gives Beta Alanine different properties – instead of being used in proteins, it combines with L-histidine (another amino acid in foods and proteins) to form the dipeptide carnosine (beta-alanyl-L-histidine), rich in muscles and brain. Carnosine helps buffer acid inside muscle cells formed during endurance exercise at lower oxygen conditions, such as the kick to the finish line (going anaerobic) or breaking away (or keeping up) in endurance events. Another overlooked function of Carnosine is to move calcium ions into moving parts of muscles to keep contractions and relaxations going. Beta Alanine gives OptygenHP an extra biochemical edge that other herbal endurance products cannot give.

KEY POINTS:

- Beta Alanine is an amino acid that can boost muscle levels of Carnosine, a major buffer of acidity generated by strenuous exercise;
- Beta Alanine has become well-accepted in academic and worldwide sports organizations for benefiting short-term, high-intensity exercise for intermittent, repeated and continuous exercise lasting 0.5-10 minutes;
- Benefits have been reported for combat sports, high-intensity interval training, middle distance running, military activities, racquet sports, resistance training, rowing, swimming; team sports (rugby, soccer), track cycling, training sessions, water polo and more;
- Beta Alanine delays fatigue and increases exercise capacity & performance when exercise is intense enough to increase muscle and systemic acidity levels;

- Beta Alanine needs to be ingested daily for at least 4 weeks, with better results after 6-12 weeks to achieve benefits – beta alanine is not fast-acting after a single dose, like caffeine is;
- Beta Alanine uptake and conversion to Carnosine is greater for trained muscles and when taken with carbohydrates;
- Daily doses from 1.0-12 grams are associated with benefits;
- Some persons may experience paraesthesia (itching or prickly-feeling skin) soon after a high dose (this is normal, short-lived and not problematic, so go with the tingle);
- We'll show why we put Beta Alanine in OptygenHP in 2007 before the evidence supported its use for long-duration endurance exercise – it gives you a bigger kick at the end of long-duration endurance events, helping you finish faster.

Even a cursory look at the science behind Beta Alanine for exercise finds a consensus of over six dozen reviews of human studies on its benefits for short-duration, high-intensity exercises (HIIT) lasting 0.5-10 minutes. As long as a daily dose was given long enough to increase muscle carnosine levels (and thus, able to increase acid buffering capacity of muscle) and exercise is of sufficient intensity to increase muscle acidity (very strenuous, max effort), almost all studies showed one or more of the following results: 1) increased muscle carnosine; 2) better muscle pH buffering during intense exercise; 3) increased lactate threshold; 4) reduced muscle fatigue; 5) improved exercise capacity; and 6) increased time to exhaustion. These findings are summarized by one recent reviewer:

“For the past 10 years, a large body of evidence has been accumulated supporting the ergogenic benefit of elevating muscle carnosine.” (Hoffman 2018, p. 193).

Note that any dose of Beta Alanine needs to be taken daily for several weeks before muscle carnosine levels are increased enough to provide more acid buffering from all-out muscular activity. Efficacy might start sooner, but is evident by 4-8 weeks after starting, and can be maintained by continued supplementation with Beta Alanine, even at lower doses of 1,000-2,000 mg daily. If Beta Alanine intake is stopped, muscle carnosine levels slowly decrease over the same time period (4-8 weeks) and the performance benefit is slowly lost.

Traditionally conservative sports organizations have agreed on and condoned beneficial effects of Beta Alanine on HIIT exercise and sports, including: Academy of Nutrition and Dietetics, American College of Sports Medicine, Australian Institute of Sports, Dietitians of Canada, International Associations of Athletics Federations, International Olympic Committee, International Society of Sports Nutrition (ISSN), National Strength and Conditioning Association (NSCA), and Sports Dietitians Australia. Importantly, all agree that Beta Alanine supplementation increases muscle carnosine levels, decreases acid (H⁺ and lactate) output in exercising muscles, and improves exercise capacity (work).

Citations for Reviews of Beta Alanine Exercise Benefits: Abe 2000; Artioli 2010, 2013; Australian Institute of Sports 2021 Infographic, 2021 AIS Sports Supplement Framework; Bellinger 2014; Blancquaert 2015; Boldyrev 2013; Braun 2011; Brisola 2019; Burke 2019 73, 2019 156, 2021; Caruso 2022; Close 2016, 2022; Culbertson 2010; Derave 2010; Dominguez 2015; EFSA 2014; Fernandes 2021; Forbes 2020; Gonzalez 2022; Harris 2012 1, 2012 5, 2013; Hobson 2012; Hoffman 2012, 2015 2463, 2018; Kerksick 2018; Kim 2020; Ko 2014; Lancha 2015; Lopez-Torres 2023; Mahmoudinezhad 2022; Mahomoodally 2022; Matthews 2019; Maughan 2018 104, 2018 439; Murphy 2022; Naderi 2016; NSCA 2021; [No authors listed] 2016; ODS 2022; Oliveira 2017; Ostfeld 2023; Peeling 2018; Perim 2019; Quesnele 2014; Ravindra 2020; Rezende 2020; Sale 2010; Saunders 2017, 2020, 2021; Sports Dietitians Australia 2023; Stautemas 2018; Stecker 2019; Stellingwerf 2011, 2019 106; Tambalis 2022; Thomas 2016 501, 2016 543; Trexler 2015; Turnes 2019; Varanoske 2019; victoris.be 2023; Vicente-Salar 2022; Woitas 2022; Zanella 2017

Short-term Endurance Benefits from Beta Alanine

Because of the accepted mechanism of muscle buffering capacity of acid by Beta Alanine, human studies have focused on short-term types of exercise almost to the exclusion of long endurance exercises, following the lead of sodium bicarbonate and other acid-buffering nutrients. Short-time endurance exercises (>70% aerobic ATP production) that rely on combined glycogen, lactate, and fatty acid utilization also benefited, such as 1,500 m runs, 2,000 m rowing, 3,000 m steeplechase, 5,000 m runs, military training, multi-hour resistance training sessions, repeated sprints, rowing, rugby and soccer/football. Benefits were seen for untrained subjects, elite athletes, women, and men of all ages, attesting to the universal importance of muscle pH buffering as an ergogenic aid for any kind of maximal effort. The diversity of exercise types with ergogenic effects from Beta Alanine illustrate a common theme – if you increase muscle carnosine levels, any exercise intense enough to raise muscle acid (H⁺ and lactate) or lower pH will be improved by Beta Alanine supplementation.

Beta Alanine Human Endurance Exercise Study Results - 15 to 60 Minutes

Two human studies highlight the effects of Beta Alanine supplementation. First, a sub-maximal endurance study in 27 well-trained cyclists/triathletes used cycle ergometry at each subject's preferred cadence at 75% maximal work for a one-hour time trial performance before and after Beta Alanine supplementation (Chung 2014). Only water was given during cycling. Muscle carnosine after six weeks of 6.4 grams of Beta Alanine daily was increased by 143-161% in calf muscles – the largest increase ever recorded to date. Oddly, after six weeks, both placebo and Beta Alanine groups had slower (worse) times for the same work amount at the beginning of the study. After six weeks, the placebo group was significantly slower by 2.4 minutes and the beta alanine group showed a trend for being slower by 1.9 minutes for approximately 60 minutes of cycling, but was not statistically different between groups. What went wrong? Does this mean that Beta Alanine does not improve endurance exercise performance? Not at all. Why? This study did not reproduce all conditions necessary for beta alanine supplementation to show effects for endurance exercise.

1. Sufficient dose of Beta Alanine? Check!
2. Increased muscle carnosine levels? Check!
3. Sufficient duration? Shorter than most studies but long enough to boost muscle carnosine levels. Check!
4. Acidosis lowered? Beta Alanine group showed a significantly better lactate/H⁺ ratio compared to the placebo group (209 vs. 162) indicating less acidosis. Check!
5. Sufficient exercise intensity to elicit acidosis? Systemic acidosis stayed between 7.3-7.4, basically normal and nowhere near acidity levels from long-duration, exhausting exercise. Failure!
6. Relevance for real-life races? If you enter a race and keep the same easy pace that you start with, without speeding up at any time, do you win? Not relevant to real races. Failure!

The findings of increased muscle carnosine and decreased acidity support the ability of Beta Alanine supplementation to boost performance at the end of a competitive event during max effort when lactate levels were highest – *which this study did not attempt*. But the basic efficacy for controlling muscle acidity to allow for improved bursts of maximal anaerobic power during an event, and a better kick at the finish, when lactate/acid becomes an ergolytic problem was attained.

Second, a study by Ghiasvand gave 2,000 mg Beta Alanine daily for six weeks to male physical education

students (Ghiasvand 2012). They performed a typical incremental VO₂max time trial before and after six weeks, lasting about 15 minutes, which is not true endurance exercise. The Beta Alanine group had a one-minute improvement to TTE (Time to Exhaustion), but the placebo group did not change. VO₂max was increased by Beta Alanine, but not by placebo. These results hint that rapidly going from lower to higher cycling exercise intensity may show benefits from Beta Alanine when intensity is maximum. Like at the end of a long race with a sprint to the finish? Enticing concept!

Citations for Middle Distance Activities (Partial List): Burke 2019 73; Chung 2014; Ducker 2013; Fernandes 2021; Ghiasvand 2012; Grgic 2021; Hamzekolaei 2023; Oliveira 2017; Rosas 2017; Stellingwerf 2019 106;

What Can Beta Alanine Do for Endurance Events? Help You WIN!

But what about longer endurance and ultra-endurance events that depend more on slow-twitch muscle fibers, which have about half the muscle carnosine of fast-twitch fibers? Where 90-95% aerobic ATP production until supramaximal bursts are needed? Endurance athletes typically have lower muscle carnosine than untrained persons. And carnosine is easy to increase with Beta Alanine. What would adding Beta Alanine to endurance athletes do for events over one hour in duration? Could extra carnosine buffering actually allow better supramaximal bursts hours into aerobic exercise conditions? Could Beta Alanine make your steep climbs, breakaways, chases, and especially the kick to the finish line faster and easier – or possible at all? The evidence is pointing to YES!

Evidence for Beta Alanine Improving Endurance Events

Military operations (MilOps) are another type of exercise and stress over a long time period (greater than six hours and studied up to 24 hours). Although MilOps are not continuously intense aerobic exercise, they are physically demanding, mentally demanding, often under hypocaloric and dehydrated conditions, have several short periods of maximal efforts, cause physical stress such as oxidation and inflammation, and cause deficits/errors in mental functions. Thus, MilOps human studies fulfill the dose, duration, and part of the intensity conditions needed for beta alanine to have ergogenic effects, and thus have relevance to endurance exercise.

Taken together, results from several studies of subjects undergoing simulated SUSOP (Sustained Operations) and loaded with Beta Alanine to achieve high muscle levels of carnosine showed maintenance of physical and mental performances under long-duration stress instead of deterioration exhibited by placebo/control groups (Hoffman 2014, 2015; Varanoske 2018, 2021). Subjects given Beta Alanine had less fatigue, had less soreness, produced fewer errors on reaction time, showed faster motor reaction time, had faster 1 km run times, showed better lower body power, higher peak jump power, added 50m casualty carry, raised target engagement speed, and increased shooting accuracy compared to placebo groups. Not all measured parameters were different

between placebo and Beta Alanine groups – for some studies, muscular endurance, litter carries, power measurements, and inflammatory markers were similar between placebo and Beta Alanine groups. Overall, Beta Alanine supplementation did show significant benefits during close-to-real-life, stressful, maximal intensity physical activity, findings which are relevant for endurance and other extreme exercise events. MilOps studies

also showed that effects of Beta Alanine go beyond the physical, beneficially influencing mental functions, especially mood – something rarely tested in exercise studies.

Beta Alanine Benefits for Endurance: Real-life Case Study of 6-Hour Event

An elite long-distance stand-up paddler (SUP) added Beta Alanine (3 grams daily) and HMB (beta-hydroxymethylbutyrate – 2 grams daily) to her six-month pretraining diet. (Burgess 2019). She participated in the ultra-distance 32-mile open ocean SUP race from Molokai to Oahu (Hawaii), with high winds (up to 20-25 knots head- and tailwinds) and wave heights of 2-10 feet. She also included a carb, sodium, potassium, and caffeinated drink from a backpack during training sessions and the race. Unlike other endurance events, SUP heart rate increases with distance, and the event requires more upper body anaerobic power requirements. That makes SUP a unique power-endurance sport needing a different skill set than running or cycling. She finished the event in 6:37:36 and placed sixth overall female at the M20 Stand-up Paddleboard Championship. Increased protein intake as well as supplementation with Beta Alanine and HMB during the six-month training period were statistically associated with her improved personal performance. This study showed that endurance performance was maintained to a higher degree for at least six hours with long-term Beta Alanine use, along with other supplemental nutrients.

Clincher Study for Beta Alanine Improving Endurance Event Performance - The Forgotten Study

Importantly for endurance athletes, one study did examine if Beta Alanine supplementation would improve end-of-race, exhausting sprint performance (van Thienen 2009). And it worked! 17 Moderately to well-trained male cyclists were given placebo or 2-4 grams Beta Alanine daily for eight weeks (daily dose was started at 2 grams daily then was upped to 3, then 4 grams daily by week 5). At the start and end of eight weeks, they performed a cycling exercise protocol designed to simulate an endurance race. They cycled for 110 minutes with varied percent of predetermined maximum lactate steady state intensity, a situation closer to usual racing. Ten-minute blocks varied from 50 to 90% of intensity, then a maximal 10-minute time trial (as fast as they could go) was performed, followed by 5 minutes of 50% intensity, then a 30-second sprint to finish. Each “race” was performed on each subject’s favorite race bike, and all subjects had a high-carb dinner the night before and a high-carb (80%), 1,200 calorie breakfast. During exercise, each subject consumed 10 mL/kg per hour of a 10% carb-electrolyte drink. This study is a good approximation of real-life endurance racing.

Baseline sprint performance at start of the study showed equivalence for placebo and Beta Alanine subjects. Both groups improved their 10-minute time trial workload similarly, and blood pH and lactate levels were also similar. But after eight weeks, peak and mean Power outputs at the end of simulated racing were significantly improved by Beta Alanine: +11.4% for peak and +5.0% for mean Power. Beta Alanine increased Power production in every subject, but the majority (5/8) of placebo subjects showed decreased Power. Blood lactate and pH was similar between placebo and Beta Alanine groups. Which group would you want to be in?

As the authors stated, victory in long-distance running and cycling depends on the ability to develop high anaerobic power outputs during decisive race stages (steep climbs, breakaways, break chases, and particularly the sprint to the end). In their words:

“We observed here for the first time that such BetaALA administration regimen enhances sprint power output at the end of a simulated endurance race and therefore could be an effective strategy to improve sprint performance in a real-life competition.” p.901.

A recent study attempted to reproduce the findings of van Thienen by a different simulated road race exercise (Perim 2022). 17 Trained cyclists (>60km/wk) were administered placebo or 6.4 g of sustained-release Beta Alanine for 28 days, which led to a 38% increase in thigh muscle carnosine. The simulated road race on a cycle ergometer was 120 min at their self-selected cadence, with 30 second slowdowns followed by 10-second sprints every 20 min. Cyclists consumed 12 g carbohydrates every 20 min (36 g/h). After 120 min cycle ergometry, subjects switched to a road bike with resistance to simulate a 5% incline for a 4 km time trial (as fast as possible, ~13 min). This was a departure in study design from van Thienen and less like a real race, which is a shorter supramaximal sprint to the finish. Although numerical differences and effect sizes from pre to post favored the Beta Alanine group, statistical significance was not reached for power output during 10-second sprints or 4km time trial performance, even though the Beta Alanine group showed an average of 19.2 seconds faster time (a 4.6% faster time than placebo group) which is a practical advantage in real races. The authors stated that their sprint times were too low to evoke acidosis, thus not being able to find statistical significance between groups. Also, blood lactate levels were lower than other Beta Alanine studies of 4 km time trials, indicating their exercise protocol was less intense than other positive Beta Alanine studies. Thus, the results of this study produced higher interindividual variability, making finding significance between groups difficult. The van Thienen study is also more relevant to cycle racing events.

Finally, sports associations have taken notice and recommend that Beta Alanine can improve RESULTS from endurance races. From the Australian Institute of Sport 2021 Infographic:

“WHEN TO CONSIDER ITS USE: When high intensity efforts are undertaken within or at the end of endurance exercise.” [emphasis mine]

Citations for Endurance Activities: Australian Institute of Sports 2021 Infographic; Burgess 2019; Gonzalez 2022; Hoffman 2014; 2015 627, 2463; 2018; Ko 2014; Perim 2022; Tambalis 2022; Trexler 2015; van Thienen 2009; Varanoske 2018, 2021

BETA ALANINE SUMMARY

Beta Alanine for real-life long-duration and endurance exercise has scientific support from relevant human clinical studies for the expectations of better all-out effort at the end of a long race. The study by Creer shows that the amount of Beta Alanine in OptygenHP is sufficient for benefits (as are the adaptogens, too) (Creer 2007). The simulated race event by van Thienen comes closer than any other study to ultraendurance races, and – along with strongly suggestive evidence from many other human studies, especially MilOps, and published expert opinions – shows that consistent intake of Beta Alanine has the ability to improve cycling and running performance *throughout and at the end of* all-out events lasting 2 hours or more.

Another positive factor for including Beta Alanine in extreme endurance supplements is that endurance athletes increase their predominantly slow-twitch muscles' carnosine content about double that of high-intensity, short-duration athletes. This means that a lower daily amount of Beta Alanine will be sufficient uptake to increase muscle carnosine levels to ergogenic levels in trained endurance athletes consuming a high carbohydrate diet.

All the known positive factors for Beta Alanine working are operative in OptygenHP users. Thus, adding a supposed non-adaptogen to an adaptogenic formula supporting long-duration aerobic exercise that quickly becomes anaerobic adds another dimension of ergogenic effect – lactate and acid buffering, which is often a major difference maker during maximal efforts portions of long-duration endurance exercise. Breaking away, keeping up, and outsprinting at the end of a race with significantly improved personal performance can make a large difference in race results and PRs – just what many OptygenHP users report!

LITERATURE QUOTES FOR BETA ALANINE

"In conclusion, β -alanine supplementation has a beneficial effect on repeated sprint performance in soccer players, probably due to effective vasodilatation mechanism."

AbuMoh'd 2020, Abstract

"WHEN TO CONSIDER ITS USE: When high intensity efforts are undertaken within or at the end of endurance exercise."

AIS Infographic, 2021

[Emphasis mine]

"Moreover, this finding highlights the ability to maintain focus during stressful, anxiety-inducing conditions (i.e., close-by gunfire) following the 30 days of beta-alanine supplementation."

Gonzalez 2022, p.277

"Conclusions: Our results suggest that beta-alanine [...] may improve the aerobic power of soccer players."

Hamzekolae 2023, Abstract

"This suggests that while the overarching outcomes of many female beta-alanine studies are null in terms of direct exercise outputs, beta-alanine may serve as an ergogenic aid by delaying the onset of both anaerobic and aerobic fatigue to allow for longer or more intense training sessions which, in turn, provide greater physiological adaptation for subsequent performance."

Murphy 2022, p.313

[NOTE: This review was based on nine studies using women subjects with widely varying exercise types.]

"Intake of 1.2 g/d β -alanine was demonstrated the optimum dose to maintain muscle carnosine at 30-50% above the baseline."

Naderi 2016, p.4

[NOTE: Daily amount of Beta Alanine in one serving of OptygenHP is 1,500mg, enough to keep muscle levels of carnosine effective.]

"Another interesting study aimed to determine if beta-alanine could help to improve sprinting performance at the end of an endurance competition. This is interesting for team sports, as performance detriments tend to increase by the end of a match and the ability to perform a maximal intensity exercise by then may be decisive for the match result. Therefore, subjects performed a

10-min time trial and a 30-s isokinetic sprint (100 rpm) after a 110-min simulated cycling race and it was found that during the final sprint after the time trial, beta-alanine supplementation resulted on an average increased peak power output by 11.4% and a mean power output increased by 5.0% [258].”

Oliveira 2017, p.18 reporting results of van Thienen 2009

“In summary, the body of scientific data indicate that athletes may not only be using beta-alanine supplementation to enhance sports performance but also as a training aid to augment bouts of high-intensity training, to decrease rates of perceived fatigue and to perform higher training volumes in team-sport athletes, which may allow for greater overload and superior adaptations compared with training alone.”

Oliveira 2017, p.18

“Time-to-completion did not change from pre- to post-supplementation for BA (-19.2±45.6 s, P=0.43) or PL (+2.8±31.6 s, P=0.99).”
Perim 2022, Abstract

[NOTE: BA = Beta Alanine, PL = Placebo. See discussion above.]

“The training and duties of military personnel and other regular athletes often consisted of prolonged and strenuous exercise, resulting in reductions in physical and cognitive performance. β-alanine administration may bring benefits to this population, such as possibly reducing fatigue, enhancing neuromuscular performance, and reducing oxidative stress.”

Tambalis 2022, p.12

“In conclusion, the current study provides novel evidence that supplementary βALA intake is an effective strategy to enhance power output during the final sprint at the end of an endurance cycling competition.”

van Thienen 2009, p.903

CHROMIUM - A MANY-COLORED METAL

First Endurance OptygenHP has 200 mcg chromium per serving (from chromium nicotinate glycinate chelate) to satisfy your obligatory need for more chromium. This form of chromium is one of a very few chromium compounds with human clinical evidence of efficacy (chromium picolinate and chromium histidinate are the others) (Swaroop 2019). Along with MultiV (at 100 mcg chromium per serving) and dietary sources (which can vary widely from 20-200 mcg daily), OptygenHP helps you maintain a healthy chromium status to keep you fuel-efficient and extend performance and improve recovery.

Chromium was given its name based on the Greek root word for colors, χρομα (chroma), for making many intensely hued salts of many colors. Just as chromium has many colors, so does chromium’s research on human effects, especially for exercise effects. After being involved in published research on chromium for over three decades (Blum 1997, 1998; Bucci 1989, 1991, 1993 65, 1994, 1998, 2006; Fernyhough 2004, 2010), this author has an uncolored bias towards chromium, so we will focus on the facts about chromium and endurance exercise and what that means for you, instead of the colored extremes for and against chromium. The key to understand chromium importance for endurance exercise is how it really works, which has been forgotten, ignored, and misunderstood. See the evidence and decide for yourself.

First, research on chromium and exercise is a confused, contentious, and concerning mess, but for exercise, attention has been mostly focused on being an ill-conceived, anabolic steroid alternative for increasing strength and muscle mass (resistance training). This Research Packet will not consider resistance training or high-intensity interval training/sports (HIIT) studies because chromium simply does not work the same for those physical efforts. Also, chromium efforts on treating diabetes, obesity and weight loss are not relevant for endurance exercise for the same reason. And we do not care what the ever-changing, clueless regulatory Daily Values are for chromium. All the human studies on exercise need to be re-evaluated because of new and overlooked findings on chromium nutriture. Here's why: We know how chromium really works.

Citations for Chromium Colors: Blum 1997, 1998; Bucci 1989, 1991, 1993 65; 1994, 1998, 2006; Fernyhough 2004, 2010; Preuss 2008; Swaroop 2019

How Does Chromium Work? - Chromodulin - You Won't See This Anywhere Else

"... the participation of chromium in metabolism is limited to an increase on the insulin sensitivity by the binding of four chromium atoms to a specific intracellular protein denoted apochromodulin, that, in turn, binds to the insulin receptor of peripheral tissue cells concomitantly with insulin ..."
Gomes 2005, Abstract

This quote sums up what chromium does as simply as possible. This is how chromium really works, and is the only thing that chromium does – making insulin work better to deliver more glucose inside cells immediately, when needs are increased – exactly what working muscles need during intense, long-duration exercise.

Chromium turbocharges glucose and amino acid delivery into cells when metabolism is cranked up to max and needing more fuel to maintain energy (ATP) output.

Chromium potentiates insulin actions by being the activator of a unique, chromium-containing peptide called chromodulin. When a muscle cell needs to make more energy, chromodulin attaches to the intracellular part of the insulin receptor complex, instigating a chain of events that bring more glucose into cells.

Easiest way to understand chromium is to realize that chromodulin is like a volume control knob on a guitar amplifier. Volume is insulin activity/function (more glucose into cells). You want more and max volume during intense, long-duration endurance exercise. No chromium, no chromodulin activity, and volume is barely audible – you're unplugged acoustic playing to a noisy crowd of hard rockers. Less chromium means less chromodulin activity, and the audience will be clamoring for more volume (this scenario is common in human populations). Plenty of chromium and you, the musician (athlete), can turn up the volume (insulin function) when needed, even to full blast, which is vital for maximal endurance exercise performance. And when the show is over, you can unplug just as quickly.

Chromodulin acts as gatekeeper for rapid, massive glucose entry into muscles, by making insulin more effective, increasing energy production quickly on demand. Chromium is always hanging around in cells and shares transport and metabolism with iron. Why is chromium hanging around inside cells? To activate chromodulin to potentiate insulin if and when needed. It's likely part of the antistress fight or flight response of

your body, with long-term, glucose-draining endurance exercise being the stress. Chromodulin finds and attaches four chromium atoms to itself when cells need more glucose. Chromodulin (plus four chromium atoms) then attaches to a specific tyrosine kinase enzyme (part of the complex insulin receptor inside of the cell) that specifically amplifies ways to get glucose into the cell.

Chromodulin enhances a major part of how insulin brings glucose into cells by moving GLUT4 receptors to the cell surface. GLUT4 receptors are always hanging around inside of muscle and gut lining cells like firemen waiting in fire stations for a fire alarm – chromodulin is the alarm. Insulin, via chromodulin boost, makes more GLUT4 receptors available to take in more glucose immediately, and it also activates mitochondria to generate more ATP (energy) from that glucose – among other cellular metabolic changes. Because insulin is the primary vehicle for increasing entry of glucose and amino acids into working muscles and liver – which indirectly also helps trigger fat mobilization for fuel during exercise, it mobilizing all of your major energy sources – chromodulin has many indirect, downstream ways to make your body cooperate to make more cellular energy during intense exercise.

When less insulin action is needed, excess chromium-loaded chromodulin is sent out of cells into the bloodstream, and kidneys specifically look for it and dump it into urine to remove it safely from the body. If your cells need to potentiate insulin more (like a low blood sugar level), they make more chromodulin and pull in more chromium from transferrin always circulating in your bloodstream (transferrin also transports iron). In this way, your body has a very finely tuned ability to ramp up increased insulin actions to keep you exercising and ramp down insulin actions back to normal when a boost is not needed (most of the time, or all the time if one is not exercising strenuously). This is why athletes show higher blood and urine levels of chromium – their chromodulin system is up-regulated compared to sedentary persons – part of training adaptation. This also means that consistent endurance exercise can deplete body chromium stores if dietary intake is low.

Citations for Chromium Chromodulin: Clodfelder 2001; Edwards 2020; Frauchiger 2004; Gomes 2005; Maret 2019; Racek 2003; Vincent 2000, 2010, 2013, 2015;

Chromium and Endurance Exercise

Compared to earlier human studies of chromium supplementation to weightlifters, studies on long-duration exercise are few, but adhere to the now-known chromodulin mechanism of action for chromium. Looking at the big picture of chromium and human metabolism, chromium has been designed to improve fueling during long-duration endurance exercise. Most studies used whatever subjects they could find, did not clearly define what kind of endurance exercise was being studied, and measured chromium status in different ways. Studies on ultra-endurance athletes are few, and are sometimes lumped together with other endurance athletes, but a consistent picture of chromium and endurance exercise has appeared.

Whole blood samples from 13 marathon runners (2 women, 11 men) were collected before, immediately after, and one week after running a marathon (Berger 2002). Chromium levels were increased immediately after the marathon, but significantly decreased one week after the marathon. This pattern suggests increased mobilization of chromium from body stores into circulation (and from what is known about chromium in blood, that also means more urinary loss of chromium). Trained athletes showed less loss (excretion) of chromium when not

exercising than untrained persons, indicating a retention of chromium and/or increased uptake from the diet and larger tissue stores (Anderson 1991). A study of endurance exercisers (biathletes, cyclists, middle-long distance runners, rowers, and skiers) showed increased body content of chromium by hair mineral analysis compared to HIIT sports (basketball, boxers, handball, soccer, volleyball, wrestlers), showing a concentration of chromium into tissues from endurance exercise (Milasius 2016).

Chromium intakes and serum levels from different types of male athletes were compared to sedentary men (Maynar 2018). The serum levels of combined sportsmen were 10x higher than sedentary controls, but the dietary chromium intakes were not significantly different. Looking at different types of exercise, the long-distance runner group showed higher basal levels of chromium than judo/speed athletes and professional football/soccer athletes. This study showed that long-duration aerobic exercise increases serum levels more than shorter duration exercises. The same researchers compared erythrocyte (red blood cell, RBC) levels of chromium in sedentary, moderately trained, and professional (highly trained) male cyclists (Maynar 2020). Based on hemoglobin content, which was very close in each group, the cyclists showed 1/3 the level of RBC chromium (0.12 ± 0.11) compared to sedentary controls (0.32 ± 0.16) and 1/2 the level of moderate exercisers (0.25 ± 0.14). Cyclists were significantly lower than sedentary controls, but the two exercise groups were not significantly different, and the variability meant statistical significance among the three groups was not reached. However, it is likely that normal variation means that statistical significance may have little relation to clinical significance. Taking the findings of these two studies together suggests that RBCs may not be a good model for determining long-term chromium status (~three months) because they are not insulin-dependent and do not have the same energy metabolism as muscle and liver. It is likely that RBCs do not have chromodulin, and thus, would only contain background chromium levels from when they were made, reflecting a three-month average of chromium body status.

Elite and amateur swimmers (800 meters) and sedentary controls (400 meters), swam uninterrupted and serum levels of chromium were measured pre-, immediately post-, and one hour post-swims (Doker 2014). Elite swimmers showed lower plasma chromium levels immediately and one hour after swimming, compared to amateur swimmers and sedentary persons, although each group did not show significant differences between before and after swimming. This finding indicates that shorter-term exercise is not like longer-term endurance exercise for chromium metabolism, supporting the need for long-term, adequate chromium intakes in long-duration endurance exercisers.

Another study of long-term status of chromium measured toenail levels from men and women over 50 years of age, both "inactive" and "most active" (Sureda 2017). Men showed 43% lower toenail chromium levels than women, but the difference was not statistically significant ($P=0.238$). Comparing active (522 mcg/kg) to inactive men (578 mcg/kg) showed no difference, but active women showed a significant 2.5 times more toenail chromium than inactive women (1,230 vs. 482 mcg/kg, $P=0.015$). Results need to be considered in light of environmental exposure to nondietary chromium also being in toenails, and lower iron levels in exercising women in general (which would allow for more chromium in the body), since men and inactive women levels of toenail chromium were similar to other studies. Also, active women consume healthier diets richer in chromium than men and inactive women.

In short-term endurance exercise, after a six-mile maximal run, serum chromium was increased immediately after the run and for the next two hours, and urinary chromium was elevated doubled the day after the run (Anderson 1982, 1984). Direct comparison of sedentary to trained men exercising to exhaustion at 90% VO₂max again showed increased urinary chromium levels after exercise in trained men but not sedentary men (Anderson 1988). Whether a regular diet or a diet fixed in chromium content was fed, trained subjects showed significantly lower urinary chromium levels. Thus, exercise training shows that chromium is mobilized from stores during exercise and sent out of the body immediately after strenuous exercise, but sedentary subjects showed no change in chromium status, meaning their ability to increase glucose usage was less than trained subjects. Kidneys do not resorb chromium, meaning that increased blood levels also increase excretion (loss) of chromium. This study exhibits why trained athletes may need a higher intake of chromium compared to sedentary persons to maintain adequate stores for long-duration endurance exercise. This study also supports the unexpected inactivity of chromium supplementation found in many human clinical studies of sedentary subjects.

Another study subjected wrestlers to a 2,000 m cycle ergometry exercise at 75% VO₂max and found increases in serum chromium immediately after exercise (Otag 2014). Another study of 10 men over 50 years old found higher urinary chromium levels acutely at the start and after 16 weeks of resistance training with a fixed daily intake of ~30 mcg chromium daily (Rubin 1998). Other tests showed improved insulin responses to exercise after 16 weeks.

Two studies from Taiwan studied women's and men's basketball teams given 500 mcg daily of chromium as picolinate (Lee 2005; Wu 2005). Women were given chromium for two days (a very short time!) and showed reduced insulin sensitivity (Lee 2005). Men were given chromium as picolinate for the season and showed a significant improvement in insulin sensitivity (Wu 2005). These studies suggest that for chromium to reach equilibrium and efficacy with exercise, it needs to be taken chronically, not acutely – an argument for daily ingestion of a chromium supplement.

Another factor in chromium status is intake of refined sugars – higher intakes lead to increased loss of chromium at the same time foods low in chromium make up a larger proportion of the diet (Anding 1997; Clarkson 1995). More exercise also means more need for micronutrients involved in energy metabolism,

including chromium (Deakin 2011). While this factor may account for the differences between trained and untrained persons, the bottom line is that endurance athletes have more chromium stored and use and lose more chromium during endurance exercise.

Chromium and Endurance Exercise Summary

The prevailing findings of chromium levels during endurance exercise in healthy individuals is congruent with increased absorption and/or concentration of dietary chromium in tissues, probably muscle (Lukaski 2004). Coupled with recent advances in understanding of chromodulin functions to increase cellular uptake of glucose from insulin during exercise, and increased chromodulin chromium in urine after exercise, it is logical to conclude that a long-term, steady supply of dietary chromium assists and improves the training adaptation to intense endurance exercise, increasing fuel (glucose) utilization. Acute supplementation with chromium does not help exercise performance – it takes time to upregulate chromodulin and its activity. The best way to ensure

maximal, safe intakes of dietary chromium is by supplementation with at least 100 mcg daily with chromium chelates, as in OptygenHP and MultiV/MultiV-PRO.

Chromium & Endurance Exercise Citations: Anderson 1982, 1984, 1988, 1991; Anding 1997; Berger 2002; Clarkson 1995; Deakin 2011; Doker 2014; Lee 2005; Lukaski 2004; Maynar 2018, 2020; Milasius 2016; Otag 2014; Rubin 1998; Sureda 2017; Wu 2005

LITERATURE QUOTES FOR CHROMIUM

"Chromium improves insulin binding, insulin receptor number, insulin internalization, beta cell sensitivity and insulin receptor enzymes with overall increases in insulin sensitivity."

Anderson 1997, Abstract

"The chromium-binding oligopeptide chromodulin (also known as low-molecular-weight chromium-binding substance) has been shown to activate the tyrosine kinase activity of the insulin receptor in response to insulin and has been proposed to be part of a novel autoamplification mechanism for insulin signaling."

Clodfelder 2001, Abstract

"Cells appear to maintain constant levels of apochromodulin such that they are in a ready state to process Cr(III). The results of this study are, thus, in accord with a recent proposal that chromodulin may have a role in the autoamplification of insulin signaling."

Clodfelder 2001, p.617

"Physical activity increases the metabolic requirements for vitamins and minerals associated with energy metabolism (particularly B vitamins, magnesium, chromium and iron)."

Deakin 2011, p.87

"... the participation of chromium in metabolism is limited to an increase on the insulin sensitivity by the binding of four chromium atoms to a specific intracellular protein denoted apochromodulin, that, in turn, binds to the insulin receptor of peripheral tissue cells concomitantly with insulin."

Gomes 2005, Abstract

"Due to excessive chromium loss and marginal chromium intake, athletes may have an increased requirement for chromium. Therefore, in some circumstances the dietary supplementation of a chromium compound may be efficacious. The restoration and maintenance of chromium stores via supplementation would promote optimal insulin efficiency, necessary for high-level athletic performance."

Lefavi 1992, Abstract

"Two hours after the test, however, serum chromium concentration almost doubled in the trained men, whereas the untrained men showed no apparent change; these changes were not statistically significant. The trained men excreted significantly more chromium in urine than did the untrained men who had no significant change in urinary chromium loss."

Lukaski 2004, p.640

"At the center of the discussion is our failure to have established a molecular structure and a specific site of action of a biological chromium complex."

Maret 2019, Abstract

"Because improved Cr metabolism and exercise both lead to improved glucose and insulin metabolism and body composition, it is likely that some of the improvements due to exercise are related to increased Cr absorption."

Rubin 1998, p.77

"Cr³⁺ is transported into cells by the iron-transport protein transferrin. Eventually the chromic ion is bound to the oligopeptide chromodulin, excreted from cells, and lost in the urine. Chromodulin has been proposed to serve a role in insulin signaling, amplifying the tyrosine kinase activity of insulin receptor."

Vincent 2004, Abstract

"... the failure to identify the responsible biomolecules(s) that bind chromium(III) and their mode of action, particularly a postulated species named glucose tolerance factor or GTF, resulted in the status of chromium being questioned in recent years."

Vincent 2013, Abstract

[NOTE: Old news! Ten years later, chromodulin has been well worked out and characterized to be the mysterious GTF, and its effect of potentiation of insulin (increased insulin sensitivity) is unquestionable.]

"... the movement of Cr(III) in the body, particularly in response to changes in insulin concentration, suggests that Cr(III) could act as a second messenger, amplifying insulin signaling."

Vincent 2015, Abstract

CORDYCEPS **(Cordyceps sinensis aka Paecilomyces hepiali, Cordyceps militaris extracts)**

From Sherpa Magic to Accepted Adaptogen

Cordyceps has been a standard ingredient for exercise performance since it first gained attention when researchers discovered Sherpas were making a special tea concoction with it. Despite their diminutive stature (most Sherpas average 5'5" and weigh around 140 lb), these ultra-efficient climbers are capable of carrying up to 150 lb in gear while climbing high-elevation peaks like Mount Everest, which summits at 29,032 ft. As mentioned earlier, after the stunning and unprecedented world-record performances of Chinese middle-endurance runners in 1993 were attributed to an obscure adaptogen called Cordyceps, the race was on to use Cordyceps in dietary supplements for all types of exercise (Steinkraus 1994). At the same time, adaptations to hypoxia (lack of oxygen), along with a long history of use in Traditional Chinese Medicine for stamina led researchers to start testing effects of Cordyceps on elite endurance athletes. Studies demonstrated that Cordyceps plays a critical role in allowing the body to adapt to high levels of physical and mental stress – the kind of performance-under-duress that has earned Sherpas and endurance athletes a reputation for amazing physical capabilities.

Cordyceps - From Caterpillars to Standardized Cultures

First, what is Cordyceps? It's a weird, mushroom-like fungus. Cordyceps is an adaptogenic herb that's been naturally harvested in Tibetan mountainous areas for centuries, and a big business for the local inhabitants. Cordyceps is a specialized fungus that lives in soil high in the Himalayan and Tibetan valleys and infects and slowly consumes specific underground caterpillars of white ghost moths from the inside out, replacing the caterpillar, then culminating into a mushroom fruiting body that pops up out of the ground from the caterpillar's head. Think of harvested Cordyceps as a "trufflepillar" – an underground mushroom wrapped in caterpillar skin.

Table 4: The Many Descriptions of Traditional Cordyceps from the Scientific Literature

Source	Definition
Bucci 2021	"trufflepillar"
Cao 2015	"Himalayan Viagra"
Cheng 2016; Lee 2012; Lo 2013	"Dong Chong Xia Cao" ("winter worm summer grass")
Dong 2014	"...integrated micro-ecosystem..." and "...multiple intrinsic fungi..."
Dong 2015	"fungus-caterpillar complex"
Hu 2013	"...mummified ghost moth larvae..."
Liu 2015	"a worm and fungus combined mixture..."
Lo 2013	"...caterpillar fungus <i>Ophiocordyceps sinensis</i> (syn.- <i>Cordyceps sinensis</i>)...'yartsa gunbu' or 'DongChongXiaCao (冬蟲夏草 Dōng Chóng Xià Cǎo)' ('winter worm-summer grass')..."
Numerous	"...caterpillar fungus..."
Numerous	"Cordyceps (<i>Cordyceps sinensis</i> [Berk.] Sacc)"
Zhang 2018	"Chongcao (the sexual stage of <i>Ophiocordyceps sinensis</i>)..."

Citations for Cordyceps Identity Cao 2105; Cheng 2016; Dong 2014, 2015; Hu 213; Lee 2012; Liu 2015 106; Lo 2013, Zhang 2018

Currently, Cordyceps Is Cultivated by Clean Mycelial Culture Methods

But don't gross out yet – zombified caterpillars are not in OptygenHP. Original caterpillar Cordyceps is extremely hard to harvest and yields are low, and with a high demand in China, the prices are very high – near \$10,000/pound (~\$18,000/kilogram). In fact, the only way to know Cordyceps is the original version is to preserve the caterpillar and then consume it or make tea.

Today's naturally harvested supply of caterpillar fungus is endangered after global Cordyceps demand exploded, because Cordyceps cannot be farmed like other plant herbs (*Rhodiola*, for example). Cordyceps is naturally harvested (dug out by hand) only in small, harsh, hard-to-reach, high-altitude areas each short summer. Cordyceps is also an important part of Traditional Chinese Medicine, or TCM (ACTM 2021), that uses almost all of the harvested stock. Fortunately, the Cordyceps usage boom forced an eco-friendly, safe, and reliable solution: commercial cultivation (also called fermentation).

Using the original TCM caterpillar fungus (mushrooms) as seed stock, commercial Cordyceps production grew quickly without the need for harvesting caterpillars. The once-rare fungus is now produced just like the mushrooms you put on a salad – by cultivation. This little-known Cordyceps fact has allowed a stable supply for both modern TCM use and global export since the 1990s. Cultivation of Cordyceps from original stocks yields what is called a mycelial culture – growing the same fruiting body as in the original caterpillars, but no caterpillars; instead, the process uses a starch-based, fungal growth medium. Standardized Cordyceps extracts remove most if not all of the leftover growth medium, meaning potential allergic concerns over growth media sources are moot.

Additionally, commercial cultivation is a controlled, clean process, removing the potential for allergenic bug parts, heavy metal contamination, counterfeiting, and seasonal variability of active agents. Plus, there is no seasonality – Cordyceps can be cultivated anytime, anywhere. Quality control of cultivation by Good Manufacturing Practices (GMPs) also means that Cordyceps supply today is stable, verified and standardized, which is reflected in Supplement Facts panels of products. Guaranteed supply and guaranteed quality at a much lower cost.

But does the grown-in-a-jar Cordyceps grown without caterpillars match the caterpillar fungus Cordyceps? Yes, and has benefits over the traditional caterpillar source. In fact, cultivated Cordyceps has higher bioactive contents and stronger bioactivities compared to original sources. Most Cordyceps materials are standardized, usually to one of the major active components, assuring reproducible quality, and thus, biological results. In China, the use of standardized extracts of cultivated Cordyceps has mostly replaced original caterpillar sources for medical purposes, with similar or better results. Cordyceps – both harvested and cultured – smells like chocolate, cacao or cocoa, with an umami flavor profile.



Cordyceps sinensis fruiting bodies cultivated in sterile culture reproducibly allows for consistent content of active compounds without unwanted contaminants.



Cordyceps Identity

Cultivation is extremely important for maintaining Quality Control of commercial Cordyceps. Turns out there are numerous Cordyceps and closely-related caterpillar species and many types of Cordyceps life-stages, which was unknown until the boom in DNA technologies precisely nailed down the nuances of what Cordyceps actually is. Turns out that what was previously thought to be one Cordyceps species is actually several different, closely-related species intertwined together – a melting pot of fungal bliss. As a result, an explosion of renaming Cordyceps-style fungi is continuing as more taxonomic information becomes available, with dozens of new species names, where before there was only one name.

So far, this has led to Cordyceps sinensis being renamed to Ophiocordyceps sinensis, a name which hardly anyone but scientists use, and also Paecilomyces hepiali, which is another new name for Cordyceps sinensis Cs-4 (as in OptygenHP). These new names are for more precise naming of Cordyceps strains, just like different kinds of apples have different names – Red Delicious, Golden Delicious, Gala, Fuji, etc. Looking at the scientific literature on Cordyceps, it is like comparing apples to apples, or Cordyceps to Cordyceps. Even though Cordyceps has new scientific names, it's still the same Cordyceps used by Traditional Chinese Medicine, human clinical studies, and supplements worldwide. We will not get into the ever-evolving fungal nomenclature and taxonomic classification, or the fact that different life stages looked like completely different fungi because they change their DNA, confusing classification based on DNA sequencing. Fortunately, all these new-named species are very closely related, with little differences amongst them. Until now, they were thought to be one species. Now that the supply industry knows what Cordyceps is, commercial cultivation can reproducibly acquire and label it accurately. Although the name has changed, the stuff in the pills is the same as always. We'll use the generic term Cordyceps throughout this blog.

Citations for Cordyceps Cultivation & Identity: Cao 2015; Chen 2022; Dong 2015 121; Gu 2022; Huang 2015; Jung 2019; Ko 2017; Kontogiannatos 2021; Lin 2020; Liu 2018; Lo 2013; Sah 2022; Zhang 2018

What's In Cordyceps That Makes It So Special?

Like other adaptogens, Cordyceps extracts have multiple bioactive ingredients that work many ways with your body systems to improve overall functioning. It's a major part of OptygenHP, and largely responsible for its success. The complex effects it produces mean it's not easy to study, and how it works has often been misunderstood by researchers and reviewers. Table 5 below lists the major identified components of Cordyceps. The most important components are the polysaccharides (similar to yeast Beta Glucan but even more complex), cordycepic acid (a sugar), cordycepin (a nucleotide like your RNA and DNA has), and the sterols, which resemble the active compounds in ginseng and other adaptogenic herbs.

Table 5: Bioactive Components of Cordyceps and Their Actions

Component	Actions
Carotenoids	Antioxidant
Cerebrosides (aminoethanol-sugar-fatty acid complexes)	Membrane functions, Neuroprotective

Cordycepic acid (a form of D-mannitol)	Antioxidant, Cytokines expression
Cordycepin (3'-deoxyadenosine)	Circulation, oxygen delivery, Cell receptors interactions (Control)
Cyclic peptides	Antioxidant
GABA	Neurotransmitter
Nucleotides (Adenosine, Guanine)	Antifatigue, ATP, DNA & RNA precursors, Circulation, Organ protective functions
Polyamines	Cell growth & development, Signals for gene expression & regulation, Cell-cell interaction control, Immune responses
Polysaccharides (Glucans, cordyglucans, galactomannans & conjugates)	Antifatigue, Antioxidant, Apoptosis, Cytokines expression, Glucose-related enzymes activation, Esterase inhibitor, Hormonal interactions, Immunomodulation
Sterols (ergosterol) & epoxysterols	Hormonal interactions, Organ protective functions
Epoxy sterols	Hormonal interactions

From Chiu 2016; Das 2021; Dong 2015 121, 2015 e109083; Lee 2012; Lo 2013; Miao 2022; Sagar 2021; Yan 2014

Confirmed Health Effects from Cordyceps

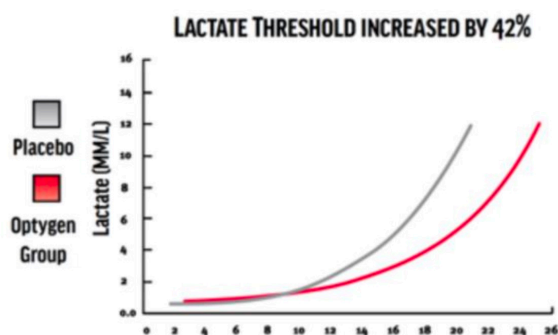
Cordyceps research has a long history in China and is expanding all over the world as cultivated Cordyceps becomes common. Cordyceps has been used for many purposes of health and medicine, including anti-aging, anti-fatigue, and restoring vigor/stamina – in addition to an increasing number of medical uses. Cordyceps is regarded as more powerful than ginseng.

Cordyceps is a well-researched topic, with that research comprising over 2,265 articles in PubMed (with 31 on Cordyceps + Exercise), over 4,325 in cnki.net (China's PubMed analog), over 5,825 in Europe PMC (PubMed Central – with 232 on Cordyceps + Exercise), and over 58,000 on Google Scholar as of September 2023. Needless to say, Cordyceps active components have been identified and thoroughly tested to show their effects from in vitro, animal, and human studies (see Table above).

But what are those effects? Simply put, elements of Cordyceps interact beneficially with normal control elements that run your body's systems and functions, promoting full-body health. Because Cordyceps' beneficial molecules are closely related to ones your body uses routinely to maintain healthy functions, they can fill in many gaps or shortcomings. For example, cordycepin is a slightly altered adenosine molecule (the A in ATP). It interacts with adenosine receptors on blood vessels that control local circulation, improving blood flow and tissue oxygenation when needed.

If you're not into scientific literature, you may not realize that cordycepin and nucleotide analogues have garnered the most attention as bioactive agents in Cordyceps research. You may also not realize that those aren't the predominant parts of Cordyceps extracts. That distinction belongs to polysaccharides – long, complicated carbohydrate chains with beneficial structural and biological activities. Their chemistry has been

difficult to decipher, but science marches on, and recent research reveals new secrets.



This brings us to the other half of Cordyceps in OptygenHP: Cordyceps militaris extract, itself another one of the strains normally found in traditional caterpillar-based Cordyceps.

Recent research on *C. militaris* has shown that the polysaccharides in Cordyceps extracts are powerful bioactive agents with signaling properties to support immune and GI tract health (Das 2021; Jung 2019; Kang 2015; Miao 2022; Sah 2022; Yuan 2022; Zheng 2022). In addition, *C. militaris* polysaccharides have adaptogenic effects on biomarkers of health which are relevant to supporting mental functions and extreme exercise performance – especially recovery. Those polysaccharides are not just useless fiber, they provide the following activities in the list below, to name only a few. Like Beta Glucan from yeast (itself a fungus), complex polysaccharides from adaptogens, especially Cordyceps, are a hidden benefit.

Short List of Confirmed Health Effects from Cordyceps

1. Antioxidant effects;
2. Production of immune system signalling cytokines;
3. Support of immune system foot soldiers: Dectin-1, macrophage activation, NK cell activation, MAPK & tyrosine kinase binding/triggering;
4. Gut microbiome prebiotic changes that upregulate multiple genes and proteins related to lipid absorption & metabolism;
5. Suppression of inflammatory signalling: eotaxins COX2, IL-4, IL-5, IL-13, IL-18, IFN-gamma, Smad2/3 protein phosphorylation, TGF-beta1 & IgE levels;
6. Mediation of inflammatory pathways by activating toll-like receptors (TLRs);
7. Upregulation of pro-recovery effectors heme oxygenase, liver vascular regeneration, Nrf2, signal regulatory protein alpha1, stromal cell-derived factor-1alpha & VEGF.

Because structure = function, there is no way that Cordyceps extracts cannot do these activities. The overall net effect of the above list is health-promoting. If one mechanism doesn't work, then others will, and they don't all necessarily need to "click" at the same time. For example, the microbiome mechanisms alone take time to remodel gut bacteria, which accounts for some of the several weeks of adaptation period before the full effects of OptygenHP can be felt or measured.

Citations for Cordyceps Health Effects Reviews: Buenz 2005; Chiu 2016; Das 2010, 2021; Esteban 2007; Holliday 2008; Jedreko 2021, 2022; Joshi 2016, 2020; Jung 2019; Kala 2024; Kang 2015; Krishna 2023; Lee 2012; Lin 2011; Liu 2015 575063; Lo 2013; Miao 2022; Olatunji 2018; Panicker 2017; Paterson 2008; Sah 2022; Shashidhar 2013; Shweta 2023; Tastekin 2023; Xu 2023; Yan 2014; Yuan 2022; Yue 2013; Zhang 2022; Zheng 2022; Zhou 2009; Zhu 1998 289, 1998 426

Cordyceps and Endurance Exercise - Research Updates

More recent research demonstrates that Cordyceps has a wide scope of antistress actions that benefit key measures of exercise performance: aerobic capacity, cardiovascular functions, tissue oxygenation, time to exhaustion, VO₂max, anaerobic threshold, energy generation efficiency, and overall endurance performance. Those studies also demonstrate that the key to reaching these benefits is to exercise at or beyond your threshold – really pushing your limits – and to take Cordyceps continuously for best effects. The effects accumulate with

consistent supplementation; Cordyceps works with your body to adapt to and counteract exercise stress, culminating after 3-4 weeks and then maintaining with continued dosage.

Unfortunately, some human studies did not take into account the multifaceted effects of Cordyceps and had serious design flaws that prevented finding statistical significance for exercise parameters, even when results favored Cordyceps. Flaws from these studies have been glossed over and are not the final word on Cordyceps. This author published two reviews on adaptogens and exercise performance in 2000 and 2004 (Bucci 2000, 2004) that clearly illustrated how studies with larger subject numbers and longer durations found benefits from adaptogens that were missed by flawed, smaller and less comprehensive studies. You'll see Cordyceps-specific statistics that clearly support how to use Cordyceps correctly, below.

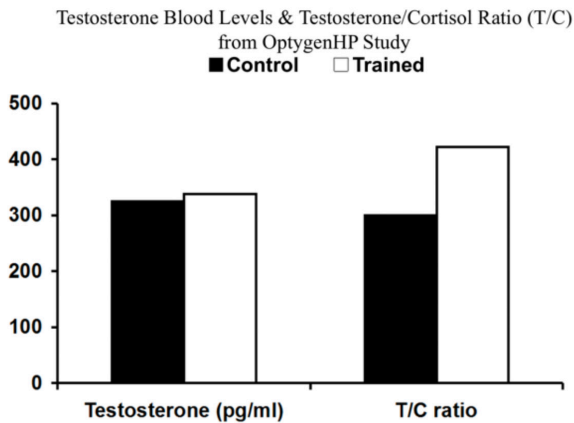
Fortunately, recent research has conducted studies with better designs, and has shown more and more statistically significant improvements and performance benefits from Cordyceps administration when subject numbers and/or duration and/or exercise stress were sufficient. Cordyceps has grown in popularity and remains a common ingredient for many antistress, immune, and exercise endurance products, including Optygen and OptygenHP.

Here's the rundown on the Cordyceps endurance exercise research, starting with the most relevant studies for strenuous, long-term exercise. Like OptygenHP, some studies administered combinations of Cordyceps with other adaptogens. Since the total adaptogen intake is similar to OptygenHP, combo studies are considered equivalently to Cordyceps-only studies. You be the judge.

Cordyceps and Combinations Exercise Benefits: Trained Endurance Athletes

- Highly trained collegiate male runners were given placebo or OptygenHP (4 capsules daily) for eight weeks during an intense training period of ~50 miles/week (Creer 2007). OptygenHP provides 1,150 mg of total adaptogens/4 capsules: Ashwagandha, Cordyceps, Rhodiola and Senactiv™ (with two adaptogens). VO₂max and Stress Scores were unchanged between groups, but training volume increased 21% (by 27 km/wk more) by OptygenHP vs. Placebo. The OptygenHP group had decreased salivary cortisol levels

(26% less vs. Placebo) and a higher Testosterone/Cortisol Ratio (36% increase vs. Placebo). For the same amount of perceived effort, OptygenHP reduced biomarkers of stress and improved training volume significantly.



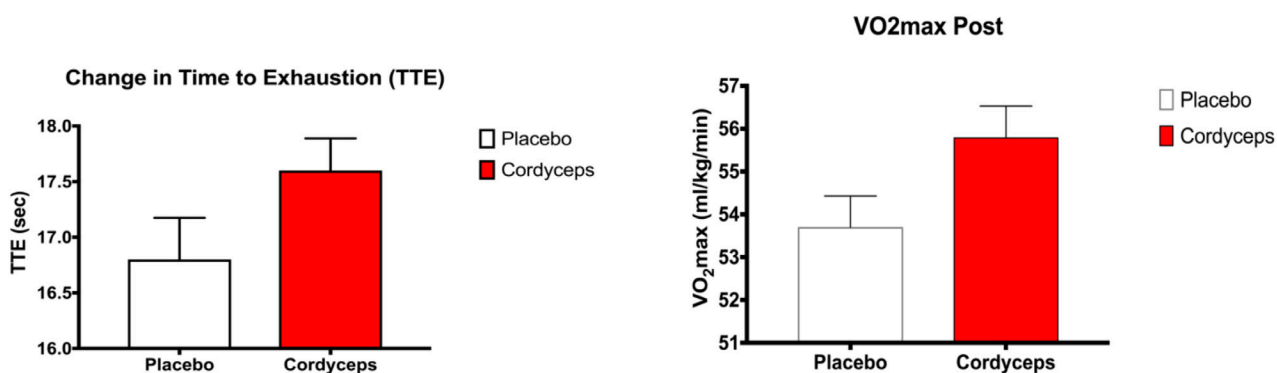
Adapted from Creer 2007

- Nine collegiate cross-country runners took placebo or Optygen for seven weeks during the pre-competition, increased volume phase of training – with sufficient duration and intensity of stress in spite of low total subject number (Larson 2007). VO₂max, hemoglobin, serum ferritin, and salivary cortisol were unchanged after seven weeks, but time to onset of lactate threshold was 42% longer with Optygen than placebo, suggesting increased performance benefits.

Adapted from Larson 2007

- Thirty amateur marathoners in Brazil took placebo or 2,000 mg of Cordyceps sinensis for 12 weeks, which ties for the longest duration of study reported for Cordyceps and endurance exercise (Savioli 2022). This marathon study was randomized, double-blind, placebo-controlled, and used more subjects than other Cordyceps and exercise studies (meaning more power to find significant results). By eight weeks, Cordyceps showed lowered heart rate for the same amount of effort, and by 12 weeks, aerobic performance was significantly better than placebo – results similar to other C. sinensis studies (Chen 2010; Thongsawang 2021; Zhu 2004).

- Twelve male long-distance runners (~37y) were given Cordyceps sinensis (four grams powder – not an extract) for two weeks and placebo in a randomized, repeated measures, counterbalanced, single-blind, crossover design VO₂max protocol for two-week periods. Time to exhaustion, VO₂max, and anaerobic threshold in lab testing were significantly improved during the cordyceps period vs. placebo period. (Thongsawang 2021).



Improved Time to Exhaustion (TTE) ($P < 0.05$).
(Adapted from Thongsawang, 2021).

Improved aerobic capacity (VO₂max) ($P < 0.05$).

- A relevant crossover study of seven male road cyclists given placebo or Cordyceps (as *Ophiocordyceps sinensis* + *Ganoderma lucidum* [Reishi] extracts) for three months found improved salivary testosterone/cortisol ratio and antioxidant activity immediately after long Gran Fondo races (85-110 km with mountains) compared to the placebo period, suggesting increased protection against overreaching and overtraining syndrome (Rossi 2014).
- Thirty highly fit athletes were given either placebo or cordyceps (CordyMax) for six weeks and tested for changes in exercise physiology (Nicodemus 2001, Zhu 2002). The cordyceps group showed increased peak O₂ pulse at max intensity and decreased blood glucose, RER, and lactate during one hour of submaximal exercise at 70% VO₂max, but placebo did not, indicating more efficient exercise capacity. Glucose usage was spared by an increase in fat burning, and the lactate threshold was pushed back significantly, all indicating that long-duration endurance exercise would be favorably increased.
- Twenty-one trained runners (5 women and 16 men) were given either placebo, arginine+citrulline, or Cordyceps *militaris* with arginine+citrulline, and tested on days 0, 7 & 14 under hot conditions (Ler 2022). Exercise was running for 45 min at 65% VO₂max, followed by an incremental exercise test. The Cordyceps group showed a significant improvement in the incremental exercise test from 10.7 to 11.4 min from days 7 to 14, with a significantly lower oxygen uptake than baseline. These results showed that Cordyceps improved running economy and performance under hot conditions, and also that Cordyceps *militaris* is similar to Cordyceps *sinensis* for efficacy.
- Eighteen male long-distance track athletes (~20 y) trained at altitude for two weeks and received either placebo or a Cordyceps/Rhodiola blend (Chen 2014). The Cordyceps blend significantly improved prolonged exhaustive run time after altitude training compared to baseline and placebo (+5.7% vs. 2.2%). The Cordyceps blend also better prevented parasympathetic nervous system activity decline by altitude, which would help explain the adaptive benefits. Even though this study had low subject numbers and a short duration, the exercise stress was more relevant to endurance training.

- As reported by other authors (without experimental details made available), long distance runners improved cardiovascular responses and increased performance after Cordyceps sinensis supplementation (Hiroshi 1998; Nagata 2002, 2004).

Cordyceps and Combinations Exercise Benefits: Untrained Persons

Studies on non-athletes or lightly active/newly training subjects showed similar findings for performance over a wide age range, and also found health benefits important for continued performance by endurance athletes:

- Twenty-eight recreationally active women and men (18-35y) consumed either placebo or a Cordyceps mushroom blend for one week (Hirsch 2017). After one week, the Cordyceps group showed significant improvements in high-intensity cycle ergometry time to exhaustion (+28.1 sec), but VO₂max and anaerobic threshold were not significantly changed. Ten subjects continued out to three weeks and results improved even more for the Cordyceps group – +68.9 seconds in time to exhaustion and improvements in VO₂max and anaerobic threshold. This study showed that Cordyceps needed to be taken for at least three weeks to demonstrate improved results.

- Twenty-two college-aged men started a 14-week exercise training period of two days of periodized whole-body resistance training (RT) and two days of high-intensity interval running (HIIT) per week (Kriepke 2020). They consumed either a placebo or 2,130 mg of MIPS – a blend of Cordyceps with other adaptogens (Ashwagandha, Rhodiola, Astragalus and Green Tea), chromium, and vitamin B12 daily. After 14 weeks, sprint performance amount of time was increased, and improved weekly volume for bench press

+ squat performance, along with an improved training workload. The authors speculated that these ergogenic findings would help with a competitive edge in performance.

- Another study used two different groups of 40-42 recreationally active women and men (19-34y) each for a placebo-controlled comparison of a Cordyceps mushroom blend on typical cycle ergometry testing and a Wingate anaerobic power test for peak power (Dudgeon 2018). One group received a low dose (1-2 g/d) across a longer time (28d); the other received a high-dose (12 g/d) for a shorter time (7d). Time to exhaustion was significantly improved from baseline for the low-dose/long-term Cordyceps group, and showed a trend ($p=0.07$) vs. placebo for the high-dose group. VO₂max was significantly improved from baseline, but the placebo group showed no change. Lactate levels showed a corresponding decline in the Cordyceps group. The high-dose/short-term trial showed few differences between Cordyceps and placebo groups. This study showed benefits from longer duration of supplementation, a classic adaptogen response. Dose is less important, another characteristic of adaptogens – 1,000-2,000 mg total adaptogens per day (similar to OptygenHP) improved performance, but not a high dose (12,000 mg total adaptogens per day).

- Thirty-six healthy, sedentary males were given either placebo or Cordyceps for two weeks and embarked on aerobic exercise training (Nagata 2006). Exercise capacity was increased by Cordyceps vs. placebo, as were beneficial responses to systemic stress.

- Another crossover study of 14 healthy males (~20y) given Cordyceps and Rhodiola for seven days while starting a running training program showed higher muscle glycogen resynthesis immediately after exercise on day seven mediated by insulin and fat oxidation, indicating improved exercise recovery (Tsai 2019).
- Healthy subjects (131 between 40-70y) were given either placebo or Cordyceps for 12 weeks (Zhu 2001, 2004). Endurance performance (+4.1%), aerobic capacity, and exercise metabolism were significantly improved from baseline, whereas placebo group changes were not significant or worsened.
- Similarly, 37 healthy elderly Chinese were given either Cordyceps or placebo for six weeks (Xiao 1999, 2004). VO2max, aerobic capacity, anaerobic threshold, and resistance to fatigue were improved from baseline by Cordyceps but not by placebo.
- Twenty untrained subjects aged 50-75y were divided into placebo and Cordyceps groups (Chen 2010). Exercise testing for aerobic capacity was done before and after 12 weeks, without changing their lifestyle habits. Although VO2max was unchanged in both groups, the Cordyceps group increased their anaerobic metabolic threshold and ventilatory thresholds significantly. The placebo group did not.
- Seventy-nine healthy men were given either placebo or Cordyceps militaris for four weeks (Kang 2015). NK-cell activity, lymphocyte proliferation index, and Th1 cytokine secretions were improved vs. baseline and placebo.
- Eighty healthy subjects were given either Cordyceps or placebo for eight weeks. NK-cell activity was increased significantly more by Cordyceps (Jung 2019).

Cordyceps & Exercise: Null Effects

Some human studies administering Cordyceps – with or without other adaptogens – did not show any significant changes from placebo or baseline for exercise parameters (Buchanan 2011; Colson 2005; Earnest 2004; Herda 2008; Hsu 2011; Liao 2019; Parcell 2004; Tsuk 2018). Design issues (fatal flaws) in these null studies exhibited one or more of the following factors for not finding benefits as compared to the larger number of studies with beneficial results:

- 1) Exercise intensity was insufficient to be enough stress for Cordyceps to have effects;
- 2) Exercise type was not strenuous, exhaustive, long-duration endurance;
- 3) Durations of administration were often too short (4 wks or less);
- 4) Fewer than 24 total subjects;
- 5) Subjects who were sedentary, active but not trained or just starting a training program.

Even so, some showed statistical trends in favor of Cordyceps for certain physiological and performance changes (Liao 2019; Tsuk 2018). Statistical trends usually become significant when more subjects or longer durations are studied.

Cordyceps & Endurance Exercise Summary

Adding the centuries of traditional Cordyceps use to modern clinical studies of sufficient statistical power and encouraging conclusions from reviews (that are becoming more comprehensive) affirms the benefits from continuous use of Cordyceps (sometimes with other adaptogens like Ashwagandha or Rhodiola) for stressful exercise performance and metabolism. Emphasis on STRESSFUL. Human studies on Optygen and OptygenHP themselves also showed significant improvements in reduction of stressors from strenuous exercise, exercise performance and physiological measurements when used for more than two weeks.

Immune functions in normal healthy adults were also improved by Cordyceps supplementation at reasonable doses, with implications for improving recovery from exercise and preventing downtime during training and competition seasons. When used with MultiV or MultiV-PRO, OptygenHP adds adaptogenic benefits with provision of sufficient essential vitamins and minerals intakes, along with other beneficial nutrients (Levagen[®]+, beta glucan, green tea polyphenols, Ginkgo biloba extract, Spectra[®] broad-based antioxidant support).

Furthermore, many animal and in vitro studies have found specific mechanisms of actions for Cordyceps that explain why it has benefits for ameliorating exercise stress, but we'll spare the details for now – the data is not in humans, but is massive and firmly backs up the benefits found in human studies.

Cordyceps has multiple ways of working to change your body to resist stress, depending on the severity of the stress levels – more stress means more activation of degradative processes and inhibition of helpful recovery processes like cell/tissue repair and metabolism. By interacting with the normal signaling processes of recovery and metabolism, Cordyceps effects for exercise stress and general health are being documented in an ever-increasing number of modern research papers.

What can you expect from taking Cordyceps if you are an endurance athlete? Remember that the key to using herbal adaptogens is longer, not stronger (more). As continued research has shown us, Cordyceps is not like caffeine – it does not normally have physical effects immediately after taking it. Instead, somewhere in a period of 1-3 weeks of high stress, heavy training, and/or competition, you might notice you feel better, perform better, and recover better than you should or did before. You should see a steady improvement to a new plateau of performance and recovery after 4-8 weeks of intake, with maintenance or even some additional improvements thereafter.

These timelines appear to be typical for combinations of adaptogens (Rhodiola plus Cordyceps, for example), as all adaptogens work similarly with subtle differences in their molecular action mechanisms. You might notice other fringe benefits from combinations of adaptogens for your health – mental, gastrointestinal, hormonal, immune, mood, and sleep effects are also evidenced but not fully considered here.

Finally, dose is less important than continuous ingestion during times of continuous exercise stress. That said, a total daily dose of around 3,000 mg of adaptogen powders matches almost all of the scientific literature for beneficial results for strenuous exercise, and lower daily doses of standardized extracts (1,000-2,000 mg/d) have

also shown benefits. Adaptogens, including Cordyceps, encourage your body to adapt and thrive. OptygenHP has 1,150 mg total adaptogens as enriched extracts, not simply dried powders, which more than meets the daily dosage requirements for active effects of adaptogens. Taking OptygenHP consistently provides maximal benefits and grows stronger with time as you grow stronger.

Citations for Cordyceps Endurance Exercise Human Studies: Buchanan 2001; Chen 2010; Colson 2003; Creer 2007; Dudgeon 2018; Earnest 2004; Herda 2008; Hirsch 2017; Kang 2015; Jung 2019; Kang 2015; Larson 2007; Ler 2022; Nagata 2002, 2004, 2006; Nicodemus 2001; Parcell 2004; Rossi 2014; Savioli 2022; Smith 2001; Thongsawang 2021; Tsai 2019; Tsuk 2018; Xiao 1999, 2004; Zhu 2002, 2004
Citations for Cordyceps Endurance Exercise Reviews: Brigham 2013; Bucci 2000, 2004; Das 2021; Milasius 2016; Sellami 2021;

LITERATURE QUOTES FOR CORDYCEPS

“This pilot study suggests that supplementation with Cs-4 (Cordyceps sinensis) improves exercise performance and might contribute to wellness in healthy older subjects.”

Chen 2010, Abstract

“Over the course of the project, runners assigned to S trained on average 27 km/wk more than P; however, salivary cortisol levels seen in S decreased by 26%, contributing to a 36% increase in the T/C ratio by the end of the study.”

Creer 2007, Abstract

[NOTE: S = OptygenHP, P = Placebo]

“Taken together, these findings suggest that Cordyceps militaris, administered in the blend provided by PEAKO2, can have significant impacts of endurance exercise performance.”

Dudgeon 2018, p.5

“Despite these limitations, we conclude that an herbal-based commercial formula containing Cordyceps sinensis and Rhodiola rosea as its primary ingredients and other matrix material postulated to improve ATP production has no effect on cycling performance when ingested for 14 d.”

Earnest 2004, p.509

[NOTE: This study is a classic example of how not to study adaptogens – small total subject number, short duration, insufficient exercise stress, as shown in the Chi-Square Analysis above, and no control group]

[Note 2: A similar study (Creer 2007) on the same formula found significant improvements in exercise performance, stress reduction scores, reduced cortisol levels, and improved testosterone/cortisol ration, and it was of longer (8 weeks) duration]

“Results of the current study demonstrate that one week of supplementation with a Cordyceps militaris-containing mushroom blend at 4 g/d did not significantly improve performance compared to a placebo. However, an exploratory three-week supplementation period resulted in significant improvements in maximal oxygen consumption, with potential improvements in ventilatory threshold and time to exhaustion, suggesting the potential for greater benefits with chronic supplementation.”

Hirsch 2017, p.7

[NOTE: This study showed that beneficial performance effects were not observed at one week, but appeared by three weeks, showing how adaptogens work with continued use]

“The primary findings of the present study demonstrated that supplementation with MIPS resulted in statistically significant

improvements in weekly exercise training performance. [...] MIPS may serve as an ergogenic aid to performance lending a competitive edge.”

Kriepke 2020, p.11

[NOTE: MIPS = Multi-Ingredient Performance Supplement based on 2,320 mg daily Cordyceps with Ashwagandha, Rhodiola, Astragalus, and Green Tea used for a 14-week HIIT & RT training program]

“Results do suggest supplementation being effective in reducing lactic acid production and delaying onset of lactate threshold and therefore improving endurance in distance runners.”

Larson 2007

[NOTE: This study was on Optygen lasted seven weeks when training volume increased for collegiate cross-country runners, a time of increased physical stress.]

“In conclusion, 14 days of AC + CM supplementation can improve endurance runners’ running economy and running performance under hot conditions.”

Ler 2002, Abstract

[NOTE: AC = Arginine + Citrulline, CM= Cordyceps militaris, compared to AC only and placebo]

“There have been appeared an augmentation of the energy generation and the anti-fatigue ability in taking with this supplement during the exercise test. During this prolonged exercise, ingesting with this Cs might elicit the superior efficiency and the economical function on the energy metabolism.”

Nagata 2006, Abstract

[NOTE: the odd grammar of this verbatim quote is from whoever translated the Japanese language draft into English – oftentimes this is by a journal editor who is not an expert in scientific writing. If you can’t figure out the message, perhaps you need to start taking OptygenHP to improve your efficiency and function!]

“Our findings suggest that Cs-4 supplementation may have positive circulatory and metabolic effects during submaximal exercise in endurance-conditioned athletes. Cs-4 may enhance fat mobilization and beta-oxidation, thereby sparing glycogen usage during prolonged exercise ”

Nicodemus 2001, Abstract

“The results show that, after 3 months of supplementation, the testosterone/cortisol ratio changed in a statistically significant manner, thereby protecting the athletes from NFO and OTS.

Rossi 2014, Abstract

[NFO = nonfunctional overreaching, OTS = overtraining syndrome. Also, When OptygenHP and MultiV-PRO are used together, you get both Cordyceps and Ganoderma extracts in addition to the other nutrient and adaptogens]

“...supplementation with Cordyceps sinensis improves the aerobic performance of amateur marathoners.”

Savioli 2022, Abstract

“... similar chemical composition and biological characteristics to *C. sinensis*, a species difficult to cultivate with significant therapeutic potential, suggests that *C. militaris* maybe a suitable substitution for *C. sinensis*.”

Tastekin 2023, p.360

“The results demonstrated a statistically significant difference in time to exhaustion (TTE), ventilatory threshold (VT2), and VO2

max between CS and ST ($P < 0.05$) ... "

Thongsawang 2021,

[NOTE: CS = Cordyceps sinensis, ST = Placebo]

"... this study has demonstrated the power of Cs-4 to improve aerobic capacity supporting the belief held in China that Cs-4 has the potential for improving capacity for exercise and resistance to fatigue."

Xiao 2004, p.192

"Cs lowered basal blood glucose (-7%, $p < 0.01$), and reduced RER (-3%, $p = 0.059$) and blood lactate (-11%, $p = 0.03$) during CWR exercise. [...] These findings indicated CordyMax improved cardiovascular and metabolic functions of the highly-fit athletes during exercise, favoring more robust physical conditions."

Zhu 2002, Abstract

[NOTE: RER = Respiratory Exchange Ratio – lower means more fat burning for exercise energy; CWR = submaximal exercise for 60 min @ 70% VO_{2max}]

"Consistent with previous findings in healthy, elderly and athlete individuals, these data indicate that oral CM supplementation improves aerobic capability, exercise metabolism, and endurance performance in healthy, mid-age to elderly sedentary humans."

Zhu 2004, A193

RHODIOLA (Golden root, roseroot, Arctic root) (Rhodiola rosea root extract standardized to 5 % rosavins)

Rhodiola Background

Like Cordyceps, Rhodiola originated in the Himalayas and mountains of southwest China and grows in high and dry altitudes, mostly in arctic areas, especially in Russia and Scandinavian countries (Iceland, too). Rhodiola is a hardy plant with yellow flowers and a thick rhizome (root) that smells like roses when cut.

Rhodiola root has been a traditional medicine in Mongolia, middle Asia and China, and Scandinavian and Russian areas as a tonic to treat fatigue and high-altitude sickness, improve mood, and provide the usual immune, gastrointestinal, nervous system, and reproductive benefits.

Most of the usage and modern research on Rhodiola has been published in Scandinavian and Russian language journals and has only slowly been seeping into consciousness of worldwide science. In the early 1960s, Russian scientists were looking into local traditional herbal medicines to fight fatigue and increase worker productivity and the performance of military forces. By 1975, Rhodiola was approved, registered, and put into wide-scale production as Rhodiola Extract Liquid by the Soviet Ministry of Health (in 40% alcohol) for fatigue and mental productivity. In 1985 Sweden and Denmark listed Rhodiola rosea as an Herbal Medicinal Product and Botanical Drug for general tonic, psychostimulant, mental stress uses. Other countries in Europe and middle Asia also have Rhodiola rosea root extracts in their pharmacopeias.



Rhodiola rosea plant

Adapted from lookfordiagnosis.com



Rhodiola rosea dried roots

Adapted from istockphoto.com

With stable supply of Rhodiola extracts, research into Rhodiola extracts focused on its traditional uses of antifatigue and antistress actions, and initially identified salidroside as the active agents in Rhodiola rosea, which was used first to standardize root extracts. More research found that unique phenolics in Rhodiola rosea, called rosavins, were actually more important for activity than salidroside, and today rosavins are the primary active agent used to standardize Rhodiola root extract materials for pharmaceuticals and dietary supplements. Both salidroside and rosavins are glycosylated phenolics also found in olive oil and wine. Other compounds also confer biological activities.

Biological effects of Rhodiola rosea extracts have been well-documented:

- Adaptogenic activities;
- Altitude adaptation;
- Antiaging;
- Antianxiety;
- Antifatigue, anti-asthenia (sensations of weakness);
- Anti-inflammatory;
- Antioxidant;
- Antistress, anti-burnout;
- Central nervous system activity (stimulation);
- Cytokine regulation (COX1, COX2, PLA2, TGF- β);
- Eicosanoid signaling;
- Exercise & sports performance benefits;
- Glucose & insulin metabolism;
- Heat stress;
- High altitude; anti-hypoxia
- Hormone receptor regulation;
- Immune support;
- Mental performance (e.g., attention, cognition, concentration, intellectual capacity, memory);
- Molecular chaperone regulation (e.g., AMPK, Foxo, Hsp70, mTOR, neuropeptide Y);
- Mood balancing;

- Neuroendocrine influences (monoamines, opioid peptides [e.g., beta-endorphins]);
- Safety (no serious adverse events reported);
- Work productivity increase;

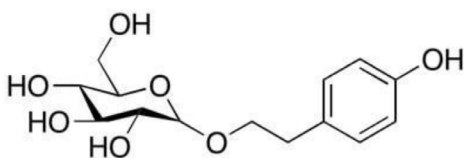
Citations for Rhodiola Background Reviews: Amir 2023; Amsterdam 2016; Anghelescu 2018; Asea 2013; Bai 2019; Brown 2002; Bucci 2000, 2004; Burns 2023; Calabrese 2023; Domene 2013; EMA 2012; Galambosi 2003; Gupta 2019; Iovieno 2011; Kelly 2001; Kosanovic 2013; Li 2017 384; 2017 1692, 2021; Liao 2018; Limanaqi 2020; Markovic 2019; Panossian 2003; 2004, 2005, 2009, 2010 188, 2010 481; 2018, 2020, 2021; Polumackanycz 2022; Pu 2020; PubChem 2022; Recio 2016; Rodriguez-Morato 2016; Ross 2014, 2023; Saggiu 2009; Sandberg 2002; Sarris 2011, 2013; Sellami 2018; Shikov 2014; Stojcheva 2022; Sun 2020; Tao 2019; Wilson 2007; Yu 2014; Zheng 2019; Zhong 2018, 2020; Zhuang 2019

Salidroside

Salidroside is p-Tyrosol with a glucose sugar attached to the hydroxy group (phenylethanoid). When ingested, up to 90% of salidroside is converted to p-tyrosol that circulates in the bloodstream, unlocking the healthy benefits of olive oil phenolics. Tyrosol, a major phenolic in olive oil, is a well-researched contributor to the healthy effects of extra virgin olive oil and the classic Mediterranean Diet. This is important for exercise performance because tyrosol is also produced in your body from the neurotransmitters dopamine and tyramine. It interacts with brain neurotransmitters beneficially, accounting for mental effects of salidroside and Rhodiola.

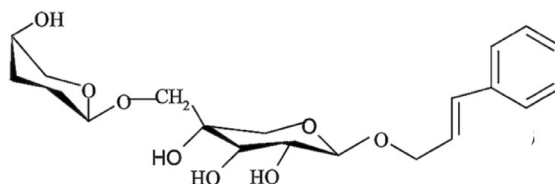
By itself, salidroside and its biological metabolites after ingestion have a wide range of biological effects, including antiaging, antifatigue, antidepressant, anti-hyperlipidemic, anti-hypoxia, anti-inflammatory, antioxidant activities, with immune and metabolic support by modulating gene expression of important cytokines and other signaling pathways.

Salidroside Structure



Adapted from scbt.com

Rosavin Structure



Rosavins

Rosavins are the other major active agent in *Rhodiola rosea* extracts, but they are not found in other commercially available *Rhodiola* species. Rosavin, the predominant active agent in *Rhodiola*, is a cinnamic acid glucoside (phenylpropanoid), meaning a common plant polyphenol attached to glucose and arabinose sugars. Cinnamates are found in many plant foods, spices, and herbs. *Rhodiola* also has rosin and rosarin, which differ from rosavin by having different sugars. Thus, rosavin, rosin, and rosarin have similar characteristics and are commonly lumped together for determining standardized extracts of *Rhodiola*. For example, OptygenHP contains 150 mg of *Rhodiola rosea* extract standardized to 5% rosavins (7.5 mg/serving). Thus, benefits from *Rhodiola rosea* studies are at least partly dependent on rosavins.

Citations for Rosavins and Salidroside Background: Bai 2019; Han 2022; Jin 2022; Magani 2020; Zhang 2021; Zhao 2021; Zhong 2018

Rhodiola and Non-exercise Effects

Exercise performance is highly dependent on mental state, mood, and feelings. Mental prowess in the form of strategic planning for both starting and fulfilling a successful training and competition strategy is another well-known factor for success. Also, resistance to fatigue, pain, stress, and negative thoughts are critical for physical performance. Rhodiola has been studied for mental effects outside of exercise and the predominance of mental improvement findings argue that brain effects of Rhodiola may be more important than physical effects. The mental categories are broken down into brain mental functions, including mood and antianxiety, antifatigue, and antistress categories.

Rhodiola and Non-exercise Mental Effects - Research Updates

- Mental effects are also extremely important for long-duration, grueling endurance events and training. Overall, Rhodiola supplementation has repeatedly shown significant benefits for mental functions in controlled human trials in healthy, unhealthy, and exercising people.
- Alertness / arousal improvements (Boyle 2021; Dimpfel 2020; Li 2017 384; Olsson 2009; Panossian 2010 188; Stojcheva 2022);
- Brain plasticity (Concerto 2018; Limanaqi 2020);
- Brainwaves EEG (relaxed but alert) (Boyle 2021; Dimpfel 2020);
- Cognitive improvements (Al-Kuriashy 2015; Darbinyan 2000; Dimpfel 2020; Fintelman 2007; Gupta 2019; Kasper 2017; Li 2017 384; Limanaqi 2020; Ma 2001; Panossian 2010 188; Stojcheva 2022; Walker 2006);
- Memory improvements (Al-Kuriashy 2015; Gupta 2018; Panossian 2005);
- Mental fatigue (Kasper 2017; Li 2017 384; Panossian 2003; Ross 2023; Shevtsov 2003; Spasov 2000);
- Mood improvements (Amsterdam 2016; Bangratz 2018; Boyle 2021; Bystritsky 2008; Cropley 2015; Darbinyan 2007; Gao 2020; Goyvaerts 2012; Iovieno 2010; Kasper 2017; Konstantinos 2020; Lekomtseva 2017; Limanaqi 2020; Mao 2015; Noah 2022; Olsson 2009; Panossian 2010 188; Sarris 2011; Shevtsov 2003; Shikov 2014);
- Neurotrophic factors (Limanaqi 2020; Panossian 2010 188);
- Psychomotor functions (Al-Kuriashy 2015; Ma 2001; Panossian 2005; Shevtsov 2003; Spasov 2000);
- Sleep quality (Darbinyan 2007; Goyvaerts 2012; Kasper 2017; Lekomtseva 2017; Noah 2022; Sarris 2011);
- Wellbeing (Bystritsky 2008; Edwards 2012; Gao 2020; Kasper 2017; Lekomtseva 2017; Mao 2015; Olsson 2009; Spasov 2000; Stojcheva 2022).

Overall, Rhodiola exhibited improvements in mental functions in almost all human studies. Few studies did not find any significant results on mental parameters from Rhodiola (Ryan 2020). An example of a typical study with significant positive outcomes for mental parameters is provided by Al-Kuriashy. Improvements in cognitive function (psychomotor vigilance and short-term working memory) were found vs. placebo in 112 normal, healthy volunteers by Ginkgo biloba, Rhodiola rosea, or their combination (Al-Kuriashy 2015). (Note that the combination produced significantly better effects than either single adaptogen.)

Citations for Rhodiola Mental Effects: Al-Kuraishy 2015; Amsterdam 2016; Bangratz 2018; Boyle 2021; Bystritsky 2008; Concerto 2018; Cropley 2015; Darbinyan 2000; Dimpfel 2020; Edwards 2012; Fintelman 2007; Gao 2020; Goyvaerts 2012; Gupta 2019; Kasper 2017; Lekomtseva 2017; Li 2017 384; Limanaqi 2020; Ma 2001; Mao 2015; Noah 2022; Olsson 2009; Panossian 2003, 2005, 2010 188; Ross 2023; Ryan 2020; Sarris 2011; Shevtsov 2003; Shikov 2014; Spasov 2000; Stojcheva 2022; Walker 2006

Rhodiola and Non-exercise Antifatigue / Antistress / Antianxiety - Research Updates

Stress and fatigue often happen together. Centuries of traditional use of Rhodiola to counteract stress and fatigue for strenuous non-exercise conditions is still popular in Russia and Scandinavian countries. In countries that have government-approved Rhodiola products, human studies were conducted to provide evidence of safety and efficacy. Also, these products are usually consumed over long time periods as a tonic, which is when adaptogens show benefits.

A number of controlled human trials have reported the following significant benefits for reducing fatigue and/or stress from Rhodiola supplementation:

- Anxiety (Boyle 2021; Bystritsky 2008; Cropley 2015; Dimpfel 2020; Li 2017 384; Noah 2022; Ross 2023; Sarris 2013; Shikov 2014; Stojcheva 2022);
- Burnout (Kasper 2017; Goyvaerts 2012; Olsson 2009; Ross 2018, 2023; Stojcheva 2022);
- Fatigue (chronic, generalized) (Kasper 2017; Lekomtseva 2017; Li 2017 384; Lekomtseva 2017; Limanaqi 2020; Panossian 2003, 2010 188; Stojcheva 2022);
- Fatigue (work-related) (Darbinyan 2000; Goyvaerts 2012; Lekomtseva 2017; Olsson 2009; Panossian 2005; Ross 2018, 2023; Schutgens 2009; Shevtsov 2003);
- Pain sensitivity (Noah 2022);
- Stress (Angelescu 2018; Boyle 2021; Cropley 2015; Dimpfel 2020; Edwards 2012, 2016; Goyvaerts 2012; Gupta 2019; Kasper 2017; Li 2017 384; Noah 2022; Olsson 2009; Panossian 2003, 2005, 2010 188; Ross 2018, 2023; Schutgens 2009; Shevtsov 2003; Shikov 2014; Stojcheva 2022).

An objective measurement of stress – Ultraweak Biophoton Emission (UBP) – was used on normal healthy subjects before and after ingesting Rhodiola SHR-5 for one week (Schutgens 2009). Compared to a placebo group, the UBP group showed significantly reduced UBP levels and fatigue. This finding supports the subjective questionnaire data from other studies showing Rhodiola benefits for stress. Studies using Rhodiola crenulata showed fewer benefits than studies using Rhodiola rosea extracts. R. crenulata has less rosavins than R. rosea, indicating the importance of using extracts standardized to rosavins.

Citations for Rhodiola Antifatigue/Antistress/Antianxiety Effects: Angelescu 2018; Boyle 2021; Bystritsky 2008; Chen 2014; Cropley 2015; Darbinyan 2000; Dimpfel 2020; Edwards 2012, 2016; Goyvaerts 2012; Gupta 2019; Kasper 2017; Lee 2023; Lekomtseva 2017; Li 2017 384; 2008; Limanaqi 2020; Lo 2018; Ma 2001; Noah 2022; Olsson 2009; Panossian 2003, 2005, 2010 188; Ross 2018, 2023; Sarris 2013; Schutgens 2009; Sellami 2018; Shikov 2014; Stojcheva 2022; Wang 2003; Wing 2003; Zhang 1998, 2003

Rhodiola and Altitude / Hypoxia Effects - Research Updates

Several human studies have reported on the effect of Rhodiola extracts or combination of adaptogens with Rhodiola extracts on symptoms from rapidly ascending to high altitude (usually over 10,000 feet). These are acute studies that follow a change in altitude for up to one week, and some studies measured high-altitude mountain sickness symptoms or prevalence. Some studies compared Rhodiola to acetazolamide, the pharmaceutical drug of choice for preventing acute mountain sickness. Rhodiola crenulata was used in several studies based on its traditional use for altitude adaptation. The following significant benefits from Rhodiola supplementation included:

- Acute mountain sickness scores / incidence (Lee 2023; Li 2008; Shi 2011; Zhang 1989, 2003);
- Adaptation time (Shi 2011);
- Antioxidant activity (serum lipid peroxides) (Wing 2003);
- Attention (Lee 2023);
- Cognition (Lee 2023);
- Executive functioning (Lee 2023);
- Exercise performance (Chen 2014; Li 2008; Wang 2003);
- Hypoxia (Oxygen saturation) (Lee 2023; Li 2008; Wang 2003);
- Memory (short-term, working) (Lee 2023; Ma 2001);
- Parasympathetic nervous system functions (Chen 2014; Li 2008);
- Psychological tests (Ma 2001);
- Sleep architecture (Ha 2002).

The following studies did not show any significant outcomes from Rhodiola supplementation (Chiu 2013, Lo 2018; Wing 2003). Note that both Chiu and Lo used non-standardized *R. crenulata*, which has lower rosavins content than *R. rosea*. Wing et al showed benefits for antioxidant effects but not for oxygen saturation in a lab environment simulating 4,600 meters for one hour, a much shorter hypoxic time than travel to high altitudes, thus an insufficient time to elicit acute mountain sickness symptoms and oxygen saturation changes. Overall, in a majority of human studies, supplementation with Rhodiola, alone or combined with other adaptogens, helped to decrease the ill effects of high-altitude exposure and support mental and physical performance. Using Rhodiola prior to altitude exposure worked best, although starting Rhodiola during exposure also showed benefits. The findings fit adaptogenic properties from Rhodiola.

Citations for Rhodiola Altitude & Hypoxia Effects: Amir 2023; Chen 2014; Chiu 2013; Ha 2002; Kelly 2001; Lee 2023; Li 2008; Lo 2018; Ma 2001; Panossian 2005; Saggu 2009; Sellami 2018; Shi 2011; Wang 2003; Wing 2003; Zhang 1989, 2003

Rhodiola and Endurance Exercise - Research Updates

Like other adaptogens in OptygenHP (Ashwagandha, Cordyceps, Notoginseng), Rhodiola has a long history of maintaining physical performance under stressful conditions. Rhodiola and its combinations with other adaptogens has been a relatively popular topic for human exercise studies, especially since 2002 when Optygen was first released. OptygenHP is a combination of five adaptogens and has also been clinically studied.

For the purposes of this Research Packet, we already have plenty of evidence that adaptogen combinations are the sum of their parts and give roughly equivalent results as higher daily doses of single adaptogens. Another reason to combine Rhodiola only with combinations is that adaptogens do the same thing in the body, even if some specific mechanisms are emphasized differently between adaptogens. Thus, we will consider any reports studying Rhodiola given by itself or as part of an adaptogen combination for effects on exercise physiology and performance from human studies. Also, dosages are not listed because of potency differences among adaptogen materials – they range from low potency powders to highly concentrated, almost pure single compounds. As stated earlier from the empirical evidence of adaptogens, dose is less important than continuous ingestion.

Endurance, ultra-endurance, HIIT, and resistance (strength) training athlete types will be considered together since hardcore strength athletes spend about as much time per day training as endurance athletes (but not in competitions). Studies will be stratified into what really matters for getting results from adaptogens: exercise intensity linked to volume. Similar to the Cordyceps section, we will include trained endurance athletes, untrained persons (whether active or sedentary – both nowhere near the exercise intensity/volume of trained athletes), and studies with no significant changes (all effects null).

Study results will be listed by study if statistically significant or a statistical trend (which are usually clinically significant). No study showed decreased exercise performance from adaptogens. Afterwards, an exercise summary will help explain what OptygenHP can do for you based on the published scientific evidence.

Rhodiola and Combinations Exercise Benefits: Trained Endurance Athletes

Significant improvements in the following exercise parameters were found in the controlled clinical trials presented below:

- Aerobic exercise performance (Evdokimov 2009; Li 2008; Shao 1998; Zhang 2009);
- Antioxidant Effects (Skarpanska-Stejnborg 2009);
- Delayed Onset Muscle Soreness / Exercise-Induced Muscle Damage (Parisi 2009, 2010);
- Fatty acid oxidation (Parisi 2009, 2010);
- Lactate accumulation/production/threshold (Larson 2007; Parisi 2009, 2010; Williams 2021);
- Mental affects (arousal, pleasure, vigor) (Duncan 2014);
- Muscle endurance (Liu 2023; Williams 2021);
- Muscle strength (Liu 2023);
- Ratings of perceived exertion (RPE) (Duncan 2014; Evdomikov 2009);
- Work capacity / Total workload (Evdokimov 2009; Shao 1998).

A few studies are highlighted for more detail: A Russian study by Evdomikov in 2009 utilized Rhodiola cryopowder during a seven-hour cycle ergometry test (Evdokimov 2009). Energy-supplying mechanisms were increased by Rhodiola and fatigue was prevented. Efficiency of cardiopulmonary systems also improved.

Four weeks of supplementation with placebo or Rhodiola rosea (175 mg daily) found a significantly longer time to exhaustion (by 5%) in a maximal cycle ergometry test in the Rhodiola group (Parisi 2009).

Another study on male recreational exercisers given placebo or 200 mg Rhodiola extract one hour before cycling trials showed that Rhodiola significantly reduced Ratings of Perceived Exertion after 30 minutes compared to a placebo period (Duncan 2014).

Rhodiola and Combinations Exercise Benefits: Untrained Persons

Significant improvements in the following exercise parameters were found in the controlled clinical trials presented below:

- Aerobic exercise performance (Chen 2014; Noreen 2009, 2013; You 2017; Zhang 2009);
- Anaerobic exercise performance (Ballmann 2019);
- Anaerobic threshold (VT) (De Bock 2004; Qian 1993; Wang 2003);
- Body composition (Liao 2019);
- Cortisol Levels (Jurcau 2012; Zhang 2009);
- Delayed Onset Muscle Soreness / Exercise-Induced Muscle Damage (Abidov 2004; Lin 2019; Wang 2000);
- Fatigue feelings (Lamadrid 2019);
- Heart rate (Ayala 2016; Lamadrid 2019; Noreen 2009, 2013);
- Immune parameters (Panossian 2020; Recio 2016);
- Lactate accumulation/production/threshold (Jowko 2018);
- Memory during exercise stress (Ma 2001);
- Mood improvement (Ryan 2020);
- Muscle endurance (Kreipke 2020; Liu 2023);
- Muscle strength (Kreipke 2020; Liu 2023);
- Power / Watts (Ballmann 2019);
- Ratings of perceived exertion (RPE) (Ayala 2016; Lamadrid 2019);
- Reaction times (Jowko 2018);
- Testosterone/cortisol ratio (Zhang 2009);
- Time To Exhaustion (TTE) (Chen 2014; De Bock 2004; Qian 1993; Noreen 2009, 2013);
- Sprint performance (Kreipke 2020);
- VO₂max / VO₂peak (De Bock 2004; Zhang 2009);
- Work capacity / Total workload (Ballmann 2019; Qian 1993; Wang 2000, 2003).

A few studies are highlighted for more detail: A 70:30 combination of 175 mg of Rhaponticum carthamoides and Rhodiola rosea extracts was given to 30 young, healthy men in a crossover design, followed by five sets of 30 maximal, concentric leg extensions 90 minutes later (Ryan 2020). Compared to the placebo period, ratings of perceived exertion (RPE) were improved by the combination, but torque and total work were unchanged. This shows that the combination affected the mental state during an intense strength exercise period after a small, single dose of adaptogens including Rhodiola, making strenuous exercise feel less demanding.

In another study, healthy male college students were given 600 mg/day Rhodiola rosea extract (3% rosavins) for four weeks, with psychomotor tests and cycle ergometry to exhaustion exercise trials before and after

(Jowko 2018). Rhodiola led to faster psychomotor reaction times, lower peak lactate levels, and a non-significant but clinically significant improvement in TTE vs. placebo (30 seconds).

In the final study to highlight, Rhodiola-Ginkgo combination or placebo was given to 70 total healthy male volunteers for seven weeks undergoing endurance performance exercise (Zhang 2009). This study had sufficient subject number (33 per group), study duration (7 wks), total adaptogen dose per day (1,080 mg), and relevant measurements to assess endurance performance – unlike the majority of underpowered studies on Rhodiola. Endurance performance was improved by Rhodiola-Ginkgo, along with increased VO₂max and normalized testosterone/cortisol ratios. The study design and results were similar to Optygen and OptygenHP studies (Creer 2007; Larson 2007).

Rhodiola and Combinations Exercise Null Effects

No studies showed results that decreased exercise performance or adversely affected physiological measurements. Some human studies administering Rhodiola or Rhodiola combinations with other adaptogens/herbs/nutrients did not show any significant changes from placebo or baseline for exercise parameters (Ayala 2016; Colson 2005; De Bock 2004; Dulacki 2009; Duncan 2016; Earnest 2004; Liao 2019; Muniz-Pumares 2011; Ryan 2020; Shanely 2013; Timpmann 2018; Walker 2007). Design issues (fatal flaws) in these null studies exhibited one or more of the following factors compared to the larger number of studies with beneficial results:

- 1) exercise intensity was insufficient to be enough stress for Rhodiola to have effects;
- 2) exercise type was not strenuous, exhaustive long-duration endurance (i.e., resistance training (RT) or high-intensity interval training (HIIT));
- 3) durations of administration were often too short (4 wks or less) or acute (single dose);
- 4) fewer than 24 total subjects;
- 5) subjects who were sedentary, active but not trained, or just starting a training program;
- 6) very low dose (dose lower than any other study [Shanely 2014]).

The study by De Bock showed enhancement of exercise performance after acute administration (Phase I), but all null results after four weeks of supplementation to healthy women and men (Phase II) (De Bock 2004). This was in spite of other authors advocating eight weeks of study. Even so, some studies showed statistical trends in favor of Rhodiola for certain physiological and performance benefits (Liao 2019). Statistical trends usually become significant when more subjects or longer durations are studied.

Rhodiola & Endurance Exercise Summary - Take-Home Lessons

Optygen and OptygenHP contain a standardized Rhodiola rosea extract (5% rosavins) and have been discussed in the Cordyceps section above. Combinations of Cordyceps with Rhodiola have also been discussed in the Cordyceps section. Like other adaptogen studies on exercise, experimental design predicts efficacy – longer duration (continuous supplementation), more subject numbers, and – most importantly – truly stressful endurance exercise is where OptygenHP shows its benefits. Keep in mind that even “exhaustive” exercise in a



lab setting is still mostly submaximal HIIT exercise and not close to overall intensity in long-duration, maximal effort events. That's when OptygenHP shines.

Simply put, most of the published studies on Rhodiola and exercise have one or more design issues: underpowered (subject numbers too low), too short duration (less than eight weeks or acute) with insufficient exercise intensity. The improvements reported in many of these studies in spite of these issues is a testament to the efficacy of Rhodiola. Interestingly and most relevant, the five endurance exercise studies that used long-duration, endurance-trained subjects in demanding exercise settings all found significant benefits from Rhodiola combinations – two of those studies used Optygen and OptygenHP.

Bottom line: for strenuous, all-out, long-duration exercise performance maintenance and improvement, a focused view on the most relevant and better-designed human studies finds that Rhodiola significantly contributes to ergogenic effects.

Citations for Rhodiola Exercise Human Studies: Abidov 2004; Ayala 2016; Ballmann 2019; Chen 2014; Colson 2003; Creer 2007; De Bock 2004; Earnest 2004; Evdomikov 2009; Jowko 2018; Jurcau 2012; Kreipke 2020; Lamadrid 2019; Larson 2007; Liao 2019; Lin 2019; Liu 2023; Ma 2001; Muniz-Pumares 2011; Noreen 2009, 2013; Parisi 2009, 2010; Qian 1993; Ryan 2020; Shao 1998; Timpmann 2018; Walker 20007; Wang 2000; Williams 2021; Zhang 2009

Citations for Rhodiola Exercise Reviews: Amico 2013; Baker 2014; Blomkvist 2009; Bucci 2000, 2004; Calabrese 2023; Chiang 2015; Domene 2013; Duncan 2017; Gong 2001; Harty 2019; Hung 2011; Jurcau 2018; Khanum 2005; Li 2002; Lu 2022; Morgan 2005; Panossian 2003, 2005, 2009, 2010 188, 2010 481, 2011, 2021; Partar 2022; Ranchordas 2015; Sandberg 2020; Sanz-Barrio 2023; Sellami 2018; Shikov 2014; Stojcheva 2022; Ulbricht 2011; Wal 2013; Walker 2006; Yu 2010

LITERATURE QUOTES FOR RHODIOLA

"According to the results of our review, the prevalent effect is adaptogenic rather than ergogenic, with a better tolerance of the exercise induced stress, related to enhancement of the whole immune system and decrease of the oxidative damage."
Amico 2013, Abstract

"R. rosea has been used for generations to improve physical endurance, work productivity, lifespan, and resistance to high-altitude illness and cure weariness, depression, anemia, impotence, gastrointestinal diseases, infections, and nervous system abnormalities."
Amir 2023, p.3

"R. rosea demonstrates multi-target effects on various levels of the regulation of cell response to stress, affecting various components of the neuroendocrine, neurotransmitter receptor and molecular networks associated with possible beneficial effects on mood."
Amsterdam 2016, Abstract

"Administration of 1.5 g/d for 75 d of Rhodiola crenulata root extract led to increased work capacity (run time to exhaustion), VO₂max, and ventilation in a comparison with placebo."
Bucci 2000, p.622S
[NOTE: study was Qian 1993]

"Taken together, the results indicate that some parameters of physical and mental performance were improved by Rhodiola extract administration: increased work, increased run time to exhaustion, heart rate recovery post-exercise, and lessening of fatigue."

Bucci 2004, p.395

"The provision of an RC supplement during altitude training provides greater training benefits in improving aerobic performance."
Chen 2014, Abstract

[NOTE: RC = Rhodiola crenulata + Cordyceps sinensis]

"Over the course of the project, runners assigned to S trained on average 27 km/wk more than P; however, salivary cortisol levels seen in S decreased by 26%, contributing to a 36% increase in the T/C ratio by the end of the study."

Creer 2007, Abstract

[NOTE: S = OptygenHP, P = Placebo]

"The primary finding is that acute Rhodiola rosea intake (200 mg) increased endurance capacity during an incremental exercise test to volitional exhaustion on a bicycle ergometer. Time to exhaustion on average increased by ~3% (range, -3.2% to +9.7%), and this was accompanied by a similar increase of oxygen uptake and CO₂ output rate at peak exercise (~exhaustion)."

De Bock 2004, p.305

"Ingestion of R. rosea favourably influenced RPE and exercise affect without changes in energy expenditure or substrate utilization during 30 minutes of submaximal cycling performance at moderate intensity in regularly active adults. These changes support the efficacy of acute R. rosea ingestion in positively enhancing psychophysiological responses to submaximal exercise performance."

Duncan 2014, p. 6

"Comparing with the control, the preparation facilitated activation of the energy-supplying mechanisms in human organism during physical work. In addition, it increased efficiency of the cardiovascular and respiration systems and prevented fatigue growth. The medical herb powder demonstrated explicitly the protective action and can be recommended for use in extreme conditions."

Evdokimov 2009, Abstract

"R. rosea may have beneficial effects on physical performance, mental performance, and certain mental health conditions."

Hung 2011, Abstract

"In conclusion, we found that chronic R. rosea ingestion can improve some parameters of psychomotor performance in young, healthy, and physically active men."

Jowko 2018, p.479

"The PP used may be an effective, safe and accessible modulation path for stress caused by intense short duration physical exercise in sedentary persons."

Jurcau 2012, Abstract

[NOTE: PP = Phytotherapeutic Product as Rhodiola rosea]

"RR in sport: relieves fatigue; increases time to exhaustion, pulmonary ventilation and endurance exercise performance; decreases heart rate and perception of effort. RR also have antioxidant effects during and after heavy physical activity..."

Jurcau 2018, Abstract

"The trial reported here was the first to investigate clinical outcomes in patients suffering from burnout symptoms when treated with *R. rosea*. During administration of the study drug over the course of 12 weeks, a wide range of outcome measures associated with the syndrome clearly improved."

Kasper 2017, Abstract

"*Rhodiola rosea* is a popular plant in traditional medicine systems in Eastern Europe and Asia with a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high altitude sickness. [...] Research also indicates great utility in asthenic conditions (decline in work performance, sleep difficulties, poor appetite, irritability, hypertension, headaches, and fatigue) developing subsequent to intense physical exercise or intellectual strain."

Kelly 2001, Abstract

"The findings of the current study describe the potential of botanical sources as a means to augment exercise performance, specifically *Rhodiola Rosea* and *Cordyceps Sinensis*. In conclusion, MIPS resulted in some statistically significant weekly exercise training performance improvements for weekly lifting volume and work completed, and amount of time spent sprinting during "fast" days of high-intensity interval running compared to PLA."

Kreipke 2020, p.4

"... it was observed that moderately intense aerobic exercise was perceived as easier for participants at follow-up who were taking the supplement. The observed differences were both significant and also included rather robust effect size differences that ranged from almost two thirds up to a full standard deviation, suggesting both a statistical and practical significance. More specifically, ratings of perceived exertion were reduced after supplementation on average by a full unit on the 0-10 scale and overall represented a reduction from baseline that was no less than 10% and up to 20%. These changes may be meaningful for active, healthy individuals suggesting that they were able to perform the same amount of work at a reduced effort cost. This could allow for work to be increased compared to pre-supplementation without an increase in perceived exertion."

Lamadrid, p.715

"Results do suggest supplementation being effective in reducing lactic acid production and delaying onset of lactate threshold and therefore improving endurance in distance runners."

Larson 2007

[NOTE: This study was on Optygen, lasting 7 weeks when training volume increased for collegiate cross-country runners, a time of increased physical stress.]

"RC supplementation did not change the oxidative stress/antioxidant capacity status, but did elicit certain degrees of improvements in body composition in these young sedentary individuals."

Liao 2019, p.10

[RC = *Rhodiola crenulata* + *Cordyceps sinensis*]

"In detail, they rescue alterations in neurotransmitter and neuro-endocrine systems, stimulate neurogenesis and the synthesis of neurotrophic factors, and they counteract oxidative stress, mitochondrial dysfunction and inflammation."

Limanaqi 2020, Abstract

8 Senactiv® was formerly named ActiGin®. But with many Acti-something supplement ingredients running around, there was confusion about which Acti-X was in what products. Senactiv® keeps the ACTIVE part of the name but makes it more specific to ginseng: ginSENG + ACTIVE = SENACTIV, or "active ginseng."

"In summary, the present study demonstrates that a 30-day supplementation of RHO combined with a single dose of CAF seems to improve the performance of resistance exercises in resistance exercise-untrained volunteers. [...] For resistance exercise-trained volunteers, RHO+CAF may also have a positive effect, contributing to pushing their limits further."
Liu 2023, p.17

"RR appears to act as a safe and effective supplementation for sport and exercise."
Lu 2002, Abstract

"Conclusion: Rhodiola and Acetazolamide can improve the achievement in psychological tests under stress in high altitude areas."
Ma 2001, Abstract
[NOTE: Soldiers stationed at 3,700 meters were tested for mental and physical functions after 24-hour sleep deprivation and physical exercise]

"Rhodiola rosea ingestion significantly decreased heart rate during the standardized warm-up (R. rosea = 136 ± 17 b·min⁻¹; placebo = 140 ± 17 b·min⁻¹; mean \pm SD; $p = 0.001$). Subjects completed the TT significantly faster after R. rosea ingestion (R. rosea = 25.4 ± 2.7 minutes; placebo = 25.8 ± 3.0 minutes; $p = 0.037$). The mean RPE was lower in the R. rosea trial (R. rosea = 6.0 ± 0.9 ; placebo = 6.6 ± 1.0 ; $p = 0.04$). This difference was even more pronounced when a ratio of the RPE relative to the workload was calculated (R. rosea = 0.048 ± 0.01 ; placebo = 0.057 ± 0.02 ; $p = 0.007$)."
Noreen 2013, Abstract

"A substantial number and range of uncontrolled as well as placebo controlled, randomized, double-blind clinical studies have consistently reported standardized extracts of *E. senticosus*, *R. rosea*, and *S. chinensis* as efficient agents for increasing mental and physical work capacity in situations of fatigue and stress."
Panossian 2003, p.327

"*R. rosea* is the most active of the three plant adaptogens producing, within 30 min of administration, a stimulating effect that continues for at least 4-6 h."
Panossian 2005, Abstract

"Strong scientific evidence is available for *Rhodiola rosea* SHR-5 extract, which improved attention, cognitive function and mental performance in fatigue and in chronic fatigue syndrome."
Panossian 2009, Abstract

"... *Rhodiola rosea* intake reduced, in a statistically significant manner, plasma free fatty acid levels. [...] Blood lactate and plasma creatine kinase levels were found significantly lower ($P < 0.05$) in *Rhodiola rosea* treated subjects when compared to the placebo treated group."
Parisi 2010, Abstract

"The results, for the most part, demonstrated potential benefits of RR supplementation, with better exercise performance, shorter time to exhaustion, less perceptions of exertion and increased concentric velocity. It can be concluded that *Rhodiola rosea* has a promising effect in improving physical performance."

⁹ Siberian ginseng has been permanently renamed to *Eleutherococcus senticosus* or *Eleuthero* – only *Panax* species can be called ginseng.

Partar 2022, Abstract

"...participants felt better, had an improved mood, and felt more aroused following testing ($p < 0.047$)."

Ryan 2020, Abstract

[NOTE: Combination of *Rhaponticum carthamoides* with *Rhodiola rosea* extract]

"During the past few decades, an increasing number of research studies have been published in connection with improving physical and mental capacity, strengthening memory and achieving better stress tolerance."

Sandberg 2002, p.20

"RR has been used to treat stress and anxiety syndrome, prevent high altitude sickness, and stimulate the nervous system. These benefits are due to natural components of the root that would activate the production of four molecules: norepinephrine, serotonin, dopamine and acetylcholine. These molecules act directly on the cerebral cortex and increase attention, memory, concentration and intellectual capacity, increase fatigue resistance, and physical performance."

Sellami 2018, p.6

[NOTE: RR = *Rhodiola rosea*]

"Compared with placebo, [...] *Rhodiola Rosea* Capsule significantly reduced the symptoms of fatigue, drowsiness, chest tightness, palpitations, vertigo, lack of attention and memory loss ($P < 0.05$)."

Shi 2011, Abstract

"In conclusion, supplementation with *R. rosea* increased antioxidant levels in the plasma of professional rowers."

Skarpanska-Stejnborn 2009, p.199

"*R. rosea* L. has a long history of use for improving physical work capacity and physical stress endurance."

Stojcheva 2022, p.5

"While those investigations have produced mixed results, several have indicated that *Rhodiola rosea* ingestion may produce such positive effects as improved cognitive function, reduced mental fatigue, anti-adrenergic resistance to stress-induced arrhythmias, free radical mitigation, and enhanced endurance performance."

Walker 2006, p.306

"These results suggest that CRP has the function of improving exercise capacity to some degree and accelerating recovery from exercise-induced fatigue."

Wang 2000, Abstract

"These results showed that *rhodiola* was effective in anti-plateau fatigue and had certain application value."

You 2017, Abstract

"The combined herbal supplement of *Rhodiola* and *Gingko* could improve the endurance performance by increasing oxygen consumption and protecting against fatigue."

Zhang 2009, Abstract

“Salidroside has been identified as one of the most potent compounds isolated from various Rhodiola plants, which have been used for a long time as adaptogens in traditional Chinese medicine.”

Zhang 2021, Abstract

Senactiv® - Small Dose, Big Effects for Endurance Exercise

What is Senactiv®?

Senactiv® is a patented combination of two adaptogenic extracts – Notoginseng root (Panax notoginseng, aka san-chi ginseng) and a specific rose hips (*Rosa roxburghii*). Senactiv® amount is 50 mg per serving, but that amount has the clinically tested daily dose of the major active agent in Notoginseng. Senactiv® has been carefully designed and clinically studied in exercising humans to improve exercise performance and recovery. Senactiv® improves exercise capacity by increasing muscle energy (ATP) production and speeds up normal muscle repair processes after strenuous exercise. But Senactiv® also introduces a relatively little known but absolutely essential mechanism of action common to ginseng adaptogens to speed up exercise recovery and training adaptation (performance) – autophagy (literally meaning eating yourself). Let’s do a little digging into what Senactiv® actually is, how it produces these effects, and why you want to literally digest yourself.

Notoginseng is the forgotten ginseng behind Chinese/Korean ginsengs (Panax ginseng), Japanese ginseng (Panax japonicus), and American ginseng (Panax quinquefolium) (see Senactiv® Figure 1). Eleuthero (ex-Siberian⁹ “ginseng” – *Eleutherococcus senticosus*) is unrelated to Asian ginsengs. Notoginseng has the usual spectrum of ginseng’s primary active agents – polysaccharides and hormone-like saponins, specifically ginsenosides – but with different amounts and ratios than the other ginsengs.

Senactiv® Figure 1: Comparison of Ginseng Roots



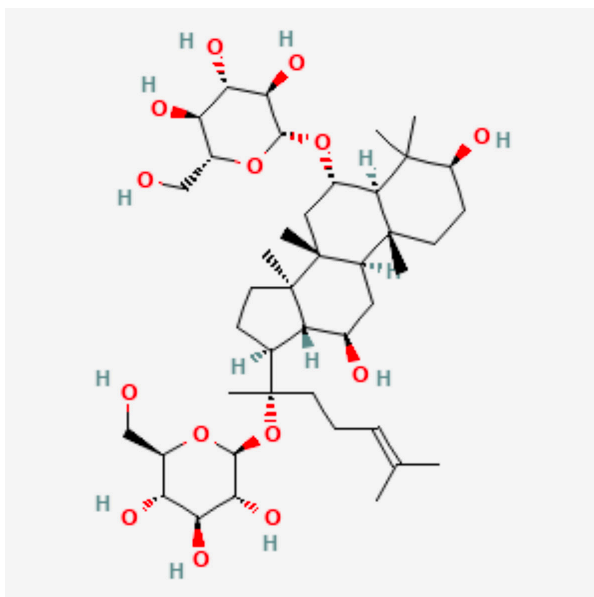
Ginsenosides interact with enzymes, receptors, and sensing machinery to trigger your body to make specific signals for adapting you to stay healthy (hence “adaptogenic”). But ginsenosides can be tricky. Typically, Asians respond beneficially to ginseng supplements, but Westerners are hit or miss. Different microbiomes are

the culprit, heavily dependent on overall diet. Assuming that you have the right (Asian) microbiome, some of the active ginsenosides are made by your gut bacteria and reabsorbed; however, modern sugar-fed microbiomes tend to not have the right gut bugs to convert ginsenosides into their more active forms. Thus, Westerners have trouble responding well to ginseng adaptogens. This explains a lot of the regional variability for results in human studies. Senactiv® fixes this issue.

Senactiv® concentrates the more active, microbiome-produced ginsenosides that are rich in Notoginseng to take variables – where you live, who you are, and what your microbiome is – out of the efficacy equation, ensuring beneficial responses at low doses. The specific rose hips extract acts synergistically with Notoginseng to stabilize the unique ginsenosides, further ensuring beneficial responses.

Notoginseng's main claim to fame is that, with the right patented processing, it yields a concentrated extract of ginsenoside Rg1 (see Senactiv® Figure 2), similar to what a healthy gut microbiome produces. This highly effective concentration is what enables the lower dose mentioned earlier (less than 50 mg) than other ginseng materials, and it delivers a very active and absorbable ginsenoside before it gets to your gut bugs. In short, Notoginseng in Senactiv® is a supercharged concentrate of the best ginseng root actives for exercise.

Senactiv® Figure 2: 2D Chemical Structure of Ginsenoside Rg1
(PubChem <https://pubchem.ncbi.nlm.nih.gov/compound/Ginsenoside-RG1>)



The second component of Senactiv® is something more familiar: rose hips. This is the bulbous thing that forms after the rose bloom falls off – it's the seed pod (fruit) for rose bushes. But this is not your garden variety rose hip; Senactiv® uses a specific variety of antique Chestnut Rose (*Rosa roxburghii*) fruit from the Guizhuo province in China, widely cultivated and used as a functional food for centuries. *Rosa roxburghii* hips look gnarlier than other rose hips, and its phytochemicals match that difference (see Senactiv® Figure 3).

Senactiv® Figure 3: Rosa roxburghii hips (fruit)



R. roxburghii extract in Senactiv® has high levels of unique and rare molecules that are different from the usual vitamin C and antioxidant flavonoids in garden variety rose hips. These rare molecules are flavonoids, triterpenes, phenylpropanoids, and pyranosides. Some of these closely resemble and act similarly to ginsenosides, which should clue you in to what this extract can do. Processing is the key to concentrating these rare molecules (most have unfathomable names, but our bodies know how to use them – good thing our bodies can’t spell). When added to Notoginseng, R. roxburghii extract brings additional and/or synergistic biological effects, reducing the effective dose compared to using Notoginseng itself.

Citations for What Is Senactiv®? Duan 2017; Kim 2012; Kuo 2020; Li 2016; Liu 2016, 2020 105263; Marmol 2017; NCBI 2023; Piao 2020; Ginsenoside RG1 2023; Qi 2011; Shen 2023; van Rensburg 2005; Wang 2021; Wu 2019 1; Zhang 2016

Senactiv® for Endurance Exercise

Senactiv® has been specifically designed and clinically studied to improve exercise recovery and thus, performance. It improves exercise capacity by increasing muscle energy (ATP) production like other adaptogens, but also has a neat trick up its sleeve. Senactiv® also specifically speeds up normal muscle repair processes after strenuous exercise. It involves killing off cells in stressed tissues, like muscle – part of the inflammatory processes. But this is why No Pain, No Gain is a true axiom – to recover faster and push training adaptation forward, you need extreme measures to rebuild your body temple’s structure. It’s called autophagy – literally, eating oneself.

Autophagy, Exercise-Induced Inflammation & Muscle Damage: Overlooked Importance of Taking Out the Garbage During Home Renovation

Intense, demanding exercise increases rate of fuel oxidation, which increases spinoff of free radicals in mitochondria, which causes subcellular structural damage, triggering an inflammatory response, aka Exercise-Induced Muscle Damage or EIMD.¹⁰ This is why you feel Delayed-Onset Muscle Soreness (DOMS) from intense, demanding exercise for a few days.

Muscle, immune, and blood/lymphatic vessel cells can repair damage, survive, and thrive – they need to or else you would not survive, grow, or age – instead, you would die. The first step in repair (and adaptive training, too) is to clear out the defective cells that have enough subcellular damage, especially the mitochondrial furnaces that generate energy from fuel. That's autophagy, and it's part of the circle of homeostasis, or maintaining health. It's what all living creatures do all the time, and yes, this process is brutally induced by endurance exercise.

All cells have a well-developed system to turn over broken subcellular components, from whole organelles to individual proteins or lipids and, of course, DNA and RNA. Ultimately, damaged molecules are sent to intracellular scrap heaps (phagosomes) and recycling centers (lysosomes). The resulting pieces are used to make more cell proteins, lipids, DNA, RNA, all sorts of molecules, membranes, organelles, and even new cells. All this intracellular traffic needs orchestration, which is accomplished by a massive signaling and receiving network running inside and outside of cells through which cells communicate to the rest of the body for their information and for their help.

Autophagy Process (It's A Good Thing)

The first step in autophagy is what we call inflammation – perfectly normal and essential for life. More exercise (extreme) causes more inflammation and results in more molecular damage inside cells. Cells and cell organelles that have been disrupted cause localized pain, and because pain is part of the massive signaling process and our brains have been conditioned to not like pain (to prevent too much pain from incapacitating you), we look at inflammation as a bad thing and try to suppress it. This is why high doses of antioxidants can short-circuit training adaptation – damaged muscles are not fully repaired, meaning you plateau or even regress your performance. Overtraining is oxidants gone wild with damage not repaired to a greater degree.

Likewise, pain and even inflammation can be suppressed effectively with administration of exogenous, synthetic, unnatural molecular mimics of endogenous signals (NSAIDs, opioids, corticosteroids, and more), but the underlying homeostasis has already begun thanks to autophagy. Damage still ensues, but without as much. ¹⁰ DOMS = Delayed Onset Muscle Soreness; EIMD = Exercise-Induced Muscle Damage repair. As you are now suspecting, EIMD speeds up the background rate of autophagy and homeostasis so muscles can repair and improve (adaptive training).

The amount of damage determines the amount of autophagy. At first, individual cells use their own machinery (enzymes and phagosomes) to break down damaged macromolecules, recycling the components (simpler

carbohydrates, phosphoglycerols, fatty acids, other fats, amino acids, DNA/RNA nucleotides) for use in repairing and rebuilding inner cell structures.

If the amount of damage spills out to tissue structural damage, the immune system is activated and helps coordinate the autophagy process to remove larger areas of damage while sowing the seeds to repair and rebuild the tissues, usually stronger than before. This is why you can see immune cells in intensely exercised muscles after exercise stops. They are part of the wrecking crew and the renovation team.

This process means that one can find conflicting signals in the same place at the same time, and depending what you are measuring, can come up with the small picture, leading to erroneous conclusions about the big picture, which is ... recovery! That is why conclusions based on scouring the research literature can be misconstrued easily. But the answer to understand the process is to put yourself in your muscle's shoes – Be Your Muscle, Feel Its Pain, Fix Its Pain. Microscale physiology becomes macroscale DOMS. And to reach homeostasis takes time, which we all want to finish sooner.

Senactiv® Takes out the Garbage and Recycles, Too

We have all seen the news reports of the garbage workers strikes in Manhattan. After a few days, the city is paralyzed by the piles and piles of garbage. Your body without autophagy would be like that, but with no end, and would eventually choke and die on its own waste. Autophagy is always happening, but much more so when strenuous exercise occurs.

The upside to autophagy is recycling nutrients, which helps fuel recovery and training adaptation. Autophagy after exercise is not simply throwing away the trash, it's also returning the pieces back to the cells/tissues to use again – simple carbohydrates, phosphoglycerols, fatty acids, other fats, amino acids, DNA/RNA nucleotides. A predigested supplement in concept, in the right place and time to restore energy metabolism and physical structures in cells and tissues.

This is where Senactiv® comes in. It's a cocktail of molecular mimics, especially ginsenoside Rg1, that reinforce your cell and tissue signals, speeding up the process in the way your body wants, like adding additional workers to the wrecking crew and the renovation team with close, proper supervision. In other words, Senactiv® helps your body adapt to hasten homeostasis (so your new tissue construction passes code and you have an upgrade).

Citations for autophagy, homeostasis, inflammation & EIMD during exercise: D'Amico 2023; Erlich 2019; Jamart 2012 1529, 3173; Ji 2007; Jordan 2021; Kuo 2019, 2020; Liu 2019, 2020 605; Margaritelis 2017; Martin-Rincon 2018; Oomaladewi 2011; Ren 2023; Sanchez 2014; Schirmacher 2021; Sousa 2014; Tipton 2018; Tota 2019; Wu 2019 1, 2020

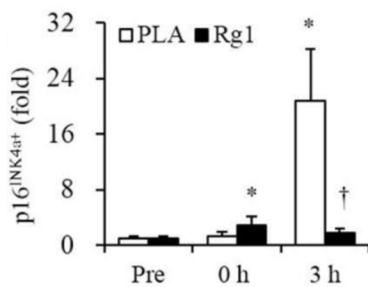
Senactiv® and Exercise Benefits

Senactiv® interacts with, bolsters, and speeds up the normal subcellular repair processes in muscles and other organs after intense exercise. Those odd compounds from the combination of Notoginseng and rose hip

concentrates, unique to Senactiv®, mimic normal signals our bodies use for constant, ongoing repair, adding to your body's response – IF you have exercised enough to produce EIMD and autophagy.

Post-endurance exercise muscle biopsies in humans illustrate this effect (Wu 2020). Measurement of a protein called p16INK4a is a marker for senescent blood vessel lining cells (cells marked for disposal). Blood vessel cells need to help start the autophagy/recycling process – they are an early marker of the process. Three hours after exercise, when senescent cells usually peak, 5 mg of ginsenoside Rg1 from Notoginseng returned the senescent cell levels back to normal – notice the small uptick at time zero after exercise for Notoginseng, but not placebo. This finding is interpreted as speeding up senescent cell removal – taking out the garbage and recycling waste. The difference is both clear and significant. Rg1 speeds up the muscle recovery process, which over time, can improve training effects and thus, performance (see Senactiv® Figure 4).

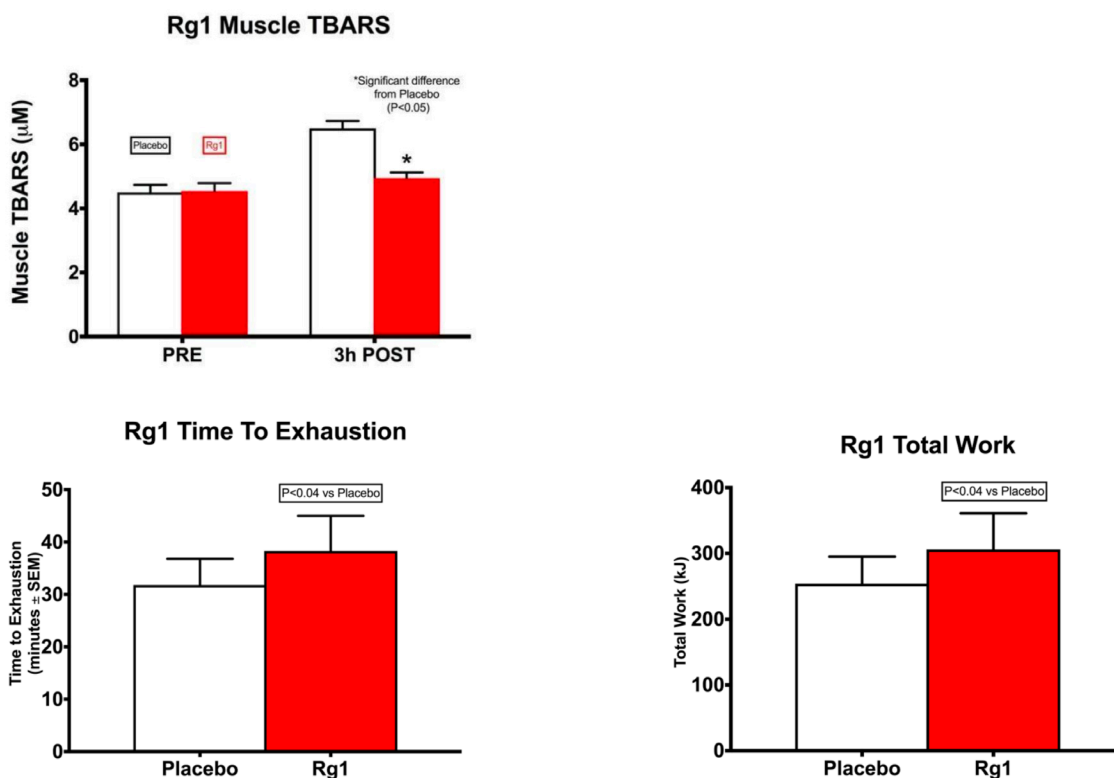
Senactiv® Figure 4: Senescent blood vessel progenitor cells in muscle biopsies 3 hours after 3 hours of cycling exercise were returned to normal faster by ginsenoside Rg1 (adapted from Wu 2020).



Other findings from the same exercise stress of shorter duration (one hour of cycling) found that giving 5 mg ginsenoside Rg1 one night and one hour before exercise led to fewer free radical damage indicators (TBARS), enhanced muscle glycogen replenishment, decreased inflammatory markers (TNF-alpha, restored IL-10 mRNA), and increased time-to-exhaustion and total work by 20% (38 vs. 32 minutes cycle ergometry at 80% VO2max and 306 vs. 254 kJ) (Hou 2015) (see Senactiv® Figure 5). In another, similar study, the majority of subjects (75%) bettered their time to exhaustion (Wu 2019 580). Reproduction of exercise performance benefits in different human studies is a large win for any substance, and it shows there is really something to Senactiv® for exercise.



Figure 5: Significant Free Radical (TBARS) Reduction in Leg Muscle, and Significant Improvement in Exercise Performance (Time to Cycling Exhaustion) and Total Work by Ginsenoside Rg1 After Exercise by Rg1 (adapted from Hou 2015).



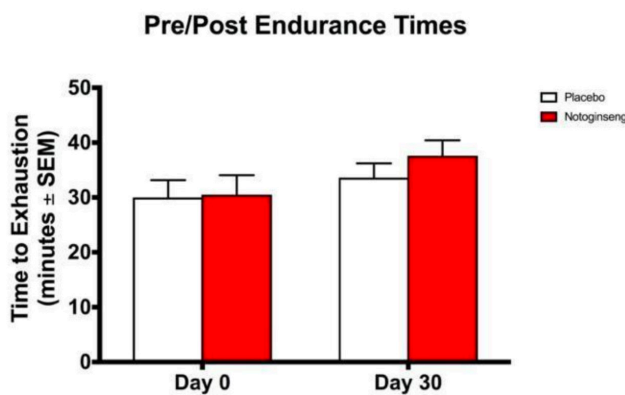
Other findings from additional human studies after exercise using ginsenoside Rg1 found similar improvements in muscle repair after strenuous exercise, including:

- reduced muscle satellite (stem) cell aging (Lee 2021);
- reduced senescent cells (Wu 2019 580, 2020);
- increased activation, proliferation, differentiation, and fusion of muscle satellite cells (Wu 2019 27);
- decreased leukocyte infiltration (Wu 2019 580);
- increased macrophage presence and activities (Wu 2019 580, 2020);
- reduced apoptotic DNA fragmentation after exercise (Wu 2019 580);
- increased inducible nitric oxide synthase (iNOS) and IL-6 mRNA synthesis (Wu 2019 580);
- reduced IL-10 mRNA synthesis (Wu 2020), decreased collagenase activity (Wu 2019 580); and
- more myogenesis (new muscle formation) (Wu 2019 27), making muscles stronger and better trained.

Likewise, in a resistance training (squats) study, ginsenoside Rg1 decreased perceived exertion, muscle cell senescence, and myeloperoxidase while endothelial progenitor cells increased – all good signs for improved recovery and adaptation to strenuous exercise (Lee 2021).

Interestingly, Notoginseng studies that combine Rg1 with other ginsenosides, which have differing activities that might blunt the desired effects of Rg1, still showed positive results. The first was a study with 29 subjects that found improvements in cycle ergometry exercise from 1,350 mg daily Notoginseng supplementation for one month, compared to placebo (Liang 2005). The daily dose of ginsenoside Rg1 was 50 mg out of 200 mg of total ginsenosides. Ginsenoside Rb1 was present at the same amount, and is known to be a relaxant and central depressant (in other words, anti-ergogenic). Thus, this study illustrates the importance of a concentrated Rg1 Notoginseng extract (Senactiv®) in order to maximize results for exercise performance and recovery.

Figure 7: Increased Cycling Time to Exhaustion by Unstandardized Notoginseng (adapted from Liang 2005).



Another human study gave 4,000 mg of unstandardized Notoginseng powder or placebo to 20 exercising men to produce delayed-onset muscle soreness by downhill running (Pumpa 2014). At two hours post-exercise, some markers of performance and recovery were significantly improved by Notoginseng, but other markers were not significantly different, even though numerically favoring Notoginseng. Also, the timing of 2 hours post-exercise is a very short window to test for DOMS, which usually worsens after 2 hours. Some of the rules for using adaptogens successfully were not obeyed.

Accordingly, this study showed a large variation in each measurement, decreasing statistical power to find meaningful differences. This study further differs from the Senactiv® ginsenoside Rg1 series of studies by not determining if or how much ginsenosides were actually given, and thus, shows that ensuring ginsenoside Rg1 without the other ginsenosides is highly relevant to the beneficial findings from Senactiv®, but not intact Notoginseng.

These human study results suggested that making a Notoginseng extract rich in Rg1 without conflicting ginsenosides would be effective, and Senactiv® was born, using the clinically tested 5 mg dose of Ginsenoside Rg1 per 50 mg serving. Ginsenoside Rg1 by itself is considered a central stimulant with anti-fatigue activity – very relevant to Senactiv® as a key for success!

Chestnut Rose Fruit Contribution

What about the contribution of *Rosa roxburghii*? Although Chestnut Rose fruit does not have human clinicals on exercise performance itself, its traditional use for centuries has been to promote healthy aging, just like

ginseng. *Rosa roxburghii* fruit has flavonoids, polysaccharides, triterpenes, and lipid components that have been shown to have antioxidant, anti-apoptosis, and antistress signaling effects that are a perfect match to ginsenoside Rg1's effects without interfering (Li 2016; Liu 2016; Marmol 2017; Shen 2023; van Rensburg 2005; Wang 2021).

Senactiv®: The Custodian of Muscles

Every well-operating facility needs a good custodial crew. Sooner or later, if you train/exercise hard enough, you will confront enough stress for adaptogens to have utility by speeding up recovery processes and repurposing the trash. Endurance exercise is a sure bet to reach enough cellular stress. Just as interesting, speeding up recovery by taking out the garbage is the same process of slowing aging, which is where adaptogens got their start.

Long-term, consistent use of adaptogens helps your body resolve stress and preserve homeostasis, and Senactiv® is only one of the homeostatic adaptogens in OptygenHP. Each of the other adaptogens in OptygenHP work slightly differently, meaning an additive mechanism of action.

Citations for Senactiv® & Exercise Performance/Recovery: Duan 2017; Hou 2015; Lee 2021; Liang 2005; Liu 2020 105263; Kuo 2019, 2020; Marmol 2017; Pumpa 2013; Wu 2019 27, 2019 580, 2020

LITERATURE QUOTES FOR SENACTIV®

"Another ginseng mixture (e.g., *Panax notoginseng*) provides markedly different proportions of chemical constituents." Calabrese 2020, p.34

"...ginseng reinforces vital energy and notoginseng promotes blood circulation." Liu 2020, 105263, Abstract

VI. OPTYGENHP Summary & Conclusions

Optygen (1,300 mg of Cordyceps and Rhodiola with Chromium and ATPPro Matrix) was launched in 2002 to help withstand the rigors of long-duration endurance exercise. Almost immediately, Optygen was tested by one research group in two similar human studies and did not find significant effects on exercise physiology or performance (Conrad 2005, Earnest 2004). However, what is not generally known is that these studies, and thus conclusions, were limited by several fatal flaws. Short study durations using a non-standard, short-term, attenuated, mostly submaximal laboratory VO₂max exercise did not approach the level of intensity or mental/physical stress of competitive, long-duration exercise and study design was not in keeping with adaptogenic principles well-known at the time, rendering these results inapplicable to long-duration, serious competitive events with much longer training periods. Another more relevant and appropriately controlled study design (Larson 2007) did find significant benefits from Optygen for lactate threshold using longer study duration and appropriately intense, long-duration exercise training.

In 2007, OptygenHP (with 1,500 mg of Beta Alanine and 1,150 mg of five adaptogens plus chromium and ATPPro Matrix) quietly introduced Beta Alanine for endurance athletes based on empirical field-testing feedback and results from a placebo-controlled pilot study of highly trained collegiate runners (~50 miles/week) (Creer 2007). Field trials leading up to determining the formula for OptygenHP reported performing better than normal and not being as fatigued at the end of long events. In a pilot study, after eight weeks, OptygenHP significantly increased training volume 27%. OptygenHP also significantly reduced the Stress Score Performance by 28%, including a significant 26% decrease in salivary cortisol and a 36% increased testosterone/cortisol ratio.

These findings indicate that taking OptygenHP led to less physiologic stress compared to a placebo group after eight weeks of use. Supplementation with OptygenHP allowed training at higher volumes without experiencing a stress-induced increase in cortisol levels and a reduction in the T/C ratio, which are considered symptoms of overreaching/overtraining. Therefore, OptygenHP was beneficial to trained athletes undergoing high training volumes by an anti-stress effect reducing adverse overtraining/overreaching effects.

OptygenHP follows the pattern for successful results from adaptogen research on exercise performance:

1. Multiple adaptogens as standardized (high-potency) extracts;
2. Sufficient total dose (1,150 mg) of adaptogens per day;
3. Sufficient Beta Alanine dose for long-term increase of muscle carnosine levels and ability to reduce acid production at maximal exercise output;
4. Support from the majority of published scientific research on adaptogens showing maintenance and/or improvement in exercise and physical performance;
5. Support from the majority of published scientific research on adaptogens showing maintenance and/or improvement in immune and mental performance.

Inclusion of Beta Alanine gives OptygenHP a "secret" weapon to improve supramaximal, short-term bursts of exercise very important and critical for maximizing training effects as well as real-life performance in actual races and events. Beta Alanine provides acid-damping actions that allow going beyond your pacing several

times during and at the finish of competitive events, when others are less able to keep up. This means you have a better chance to exceed your expectations and truly perform at your best.

Citation for OptygenHP Summary: Conrad 2005; Creer 2007; Earnest 2004; Larson 2007

VII. OPTYGENHP Research Packet

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VIII. Corporate Philosophy

Our Mission

Integrate our passion for racing, knowledge of sports nutrition, integrity, and values to provide endurance athletes with the ultimate, scientifically validated, high-performance racing formulations.

Research Philosophy

Research is the most important value at First Endurance. We are driven by a desire to ensure our products are proven to enhance endurance performance and have scientific validation. All products that First Endurance develops are based on human scientific research. At First Endurance, we refuse to reduce costs by using “pixie dust” amounts of ingredients just to dress up the label. Our formulations utilize the same levels (sometimes more) of active ingredients that were used in actual human scientific research. We assure effective products by using the same ingredients used in the human clinical studies, especially better-studied branded ingredients. We are meticulous about research and go out of our way to make sure we have addressed each of our stringent requirements. We maintain a large library of scientific articles from peer-reviewed publications and stay up-to-date on new findings and ingredients. We have written scientific books on exercise and nutrition, along with scholarly review articles and book chapters, and have participated in conducting clinical research and publishing results in peer-reviewed journal articles on human performance. But uniquely, we listen to you. This gives us a deeper insight into what the science and the human body tells us, so we can provide you with what your body wants and needs for top performance. From our experience and hands-on knowledge of what athletes need, we have a Top Ten List of Nutrition Needs we follow:

Table 1: Top 10 Nutritional Needs

1. Nutritional supplementation to support and maximize intense training and long-duration endurance exercise performance at elite levels – realizing that small improvements = big differences in outcomes;
2. Support and maintain overall health;
3. Simplicity: Products are designed to interlink with little redundancy – a systematic approach to sports nutrition;
4. Pre-exercise, during exercise and post-exercise recovery with overall basic nutritional supplementation;
5. Adaptable product use strategies for training level, body weight, duration, intensity, frequency, recovery and stress of exercise/events to individualize nutrition;
6. Protect musculoskeletal integrity (DOMS, EIMD,¹¹ overtraining, overuse injuries);
7. Mental performance, gastrointestinal tolerance, cardiopulmonary functions;
8. Meet hydration and energy (calories, protein) demands to support maintenance of lean muscle mass and body fat levels;
9. Convenience, portability, utility, taste, mixability, pleasant experiences;
10. Education via website pages, Research Packets, Blogs, Q&As, Features.

Commitment to Quality

Everybody says they use the finest quality ingredients, but First Endurance is over the top. We have a long history of being from the supply side and making dietary supplements in-house. We know all the right players when it comes to sourcing and using the

¹¹ DOMS = Delayed Onset Muscle Soreness; EIMD = Exercise-Induced Muscle Damage

best ingredients. Because dietary supplement labeling is terse and not detailed, we may look similar to other products' ingredients, but rest assured we go beyond the norms. Ingredients are chosen for their merits, purity, identity, and reliability – pricing is not the main consideration. Having a long experience in the dietary supplement industry, we know lowest pricing is usually the primary selection criteria for ingredients for others, not us.

Even the best ingredients can be short-changed by merely adequate, compliant manufacturing practices. First Endurance knows who to use to make each product, using ISO-certified, cGMP compliant, FDA-inspected facilities. We have been using these facilities for years, and they know our requirements and appreciate the opportunity to make superior products. Competency, reliability, safety and innovation are hallmarks of the manufacturers we partner with to make First Endurance products.

For example, OPTYGEN utilizes opaque, colored capsules packaged in an amber glass bottle to reduce UV light, moisture, oxygen, ensuring the highest quality, potency and purity.

Safe and Legal

First Endurance is committed to developing the most advanced endurance supplements on the market. First Endurance has taken additional measures to assure that our products are safe legal and stimulant free. First Endurance supplements are legal to use in any sporting event governed by the World Anti-Doping Association (WADA), the US Anti-Doping Association (USADA) and by the UCI (Union Cycliste International). One or more of the aforementioned governing bodies govern all US Cycling, International Cycling, US Triathlon and International Triathlon and USA Track & Field events.

Some commonalties among these governing bodies include banned substances which fall into one or more of the following categories as listed in Section I A-E of the UCI Prohibited Classes of substance and Prohibited Methods document. A) Stimulants B) Narcotics C) Anabolic agents D) Diuretics and E) Peptide hormones, mimetics and analogues. This document goes on to list banned substances within each of these classes. Regulations also ban 'Compounds chemically or pharmacologically related to the products mentioned'.

First Endurance products contain NO ingredients which are explicitly listed under the banned substance list, and none of the ingredients are related chemically or pharmacologically. First Endurance has also contacted the USADA and received verbal confirmation that our ingredients are not banned based on their regulations. Note: USADA, WADA and UCI do not offer any certification or written confirmations.

First Endurance manufactures its formulations to the highest GMP (Good Manufacturing Practice) standards available. In addition, a proprietary manufacturing method is used for added safety and assurance.

All ingredients used in First Endurance formulations come from audited suppliers who do not carry, broker or supply any banned substances.

Part XIV Article 7 of the Anti-doping Examination Regulations contains the following warning:

Riders must refrain from using any substance, foodstuff or drink of which they do not know the composition. It must be emphasized that the composition indicated on a product is not always complete. The product may contain prohibited substances not listed in the composition.

For a complete list of regulations and banned substances please use one of the following links:

UCI Banned Substance List [<https://www.uci.org/inside-uci/clean-sport/anti-doping/wada-the-prohibited-list>]

WADA [https://www.wada-ama.org/sites/default/files/resources/files/code_2021_october2019.pdf]

USADA [<https://www.usada.org>]

