first endurance

MULTIV-PRO RESEARCH PACKET

THE FOUNDATION FOR EXTREME PERFORMANCE

Rev. 1.0, December 2023

SUPPLEMENT FACTS

30 servings per container

Use Directions: Take 4 tablets daily with a meal

Serving Size	**4 Tablets**
Amount Per Serving	% Daily Value*
Vitamin A (100% as Beta Carotene) 900 mcg RAE	100%
Vitamin C (as Ascorbic Acid) 120 mg	133%
Vitamin D (as Cholecalciferol) 100 mcg	500%
Vitamin E (as Alpha Tocopherol from Mixed Tocopherols) 30 mg	200%
Vitamin K (as Phylloquinone and Menaquinone MK-7[1]) 120 mcg	100%
Vitamin B1 (as Thiamin Mononitrate) 4 mg	330%
Vitamin B2 (as Riboflavin) 5 mg	385%
Niacin (as Niacinamide) 20 mg NE	125%
Vitamin B6 (as Pyridoxine Hydrochloride) 4 mg	235%
Folate (as L-5-Methyltetrahydrofolate, Glucosamine Salt) (Quatrefolic®)[2] 400 mcg DFE	100%
Vitamin B12 (as Methylcobalamin) 30 mcg	1250%
Biotin 300 mcg	1000%
Pantothenic Acid (as d-Calcium Pantothenate) 20 mg	400%
Choline (as Choline-L-Bitartrate)(VitaCholine®)[3] 110 mg	20%
Calcium (as Dicalcium Phosphate) 90 mg	7%
Iron (as Ferrous Bisglycinate)(Ferrochel®)[4] 27 mg	150%
Iodine (as Potassium Iodide) 150 mcg	100%
Magnesium (as Dimagnesium Malate) 100 mg	20%
Zinc (as Bisglycinate) 15 mg	135%
Selenium (as L-Selenomethionine) 55 mcg	100%
Copper (as Bisglycinate) 2 mg	222%
Manganese (as Gluconate) 1.15 mg	50%
Chromium (as Chromium Picolinate)(Chromax®)[5] 400 mcg	1143%
Molybdenum (as Sodium Molybdate) 45 mcg	100%
Levagen®+ (Palmitoylethanolamide with Lipisperse®)[6] 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[7] 100 mg	*
Boron (as FruiteX-B® Calcium Fructoborate) 1 mg	*

*Daily Value Not Established

Other Ingredients: Microcrystalline Cellulose, Croscarmellose Sodium, Stearic Acid, Magnesium Stearate, HPMC (Hydroxypropyl Methylcellulose), Silica..

[1] K2Vital® Delta is a registered trademark of Kappa Bioscience AS.
[2] Quatrefolic® is a registered trademark of Gnosis S.p.A.
[3] VitaCholine® is a registered trademark of Balchem Corporation.
[4] Ferrochel® is a registered trademark of Albion Laboratories, Inc., Balchem Corporation.
[5] Chromax® is a registered trademark of Nutrition 21, LLC. Chromax® is patent protected.
[6] Levagen®+ is a registered trademark of Gencor registered in the USA and other countries.
[7] Spectra® is a trademark of VDF Futureceuticals, Inc.

MULTIV-PRO UPDATED

TO BE BETTER THAN ANY OTHER MULTIVITAMIN-MINERAL

MultiV Performance & Health Benefits

- Professional Strength
- Unique formula that goes beyond essential micronutrients
- Maintain healthy exercise performance, body composition & recovery
- Everyday Optimal Health
- Digestive Health
- Immune support
- Helps reduce body fat & preserves lean muscle
- Promotes normal, healthy, exercise-induced inflammatory response
- Increases macro and micronutrient absorption
- Improves aerobic & endurance capacity
- Specific prebiotic gut health ingredients
- Contains specific, carefully-chosen forms of micronutrients
- Levels of essential micronutrients balanced for endurance athletes
- Bioavailable forms with minimal competition for absorption, uptake and bioavailability
- Additional nutrients to maximize exercise benefits

For more information, visit: **www.firstendurance.com/multiv-pro**

MULTIV-PRO UPDATE

GOING WHERE NO MULTI HAS GONE BEFORE

MultiV-PRO has been updated to provide unsurpassed support for professional endurance athletes and extreme exercise, adding nutrients to fill in the gaps that vitamins and minerals alone cannot. In addition to a streamlined supply of essential vitamins and minerals designed for superior absorption and activity, MultiV-PRO has renewed emphasis on your muscles, GI tract, immune system and endocannabinoid signaling system.

New to MultiV-PRO, Levagen®+ with Lipisperse® provides a clinically-studied amount of your primary endogenous autocoid endocannabinoid – PalmitoylEthanolAmide (PEA) – unlocking new levels of reparative actions important for athletic performance and recovery. PEA is what your body's endocannabinoid system is looking for to fight stressors and bolster health of metabolic, musculoskeletal, immune and nervous systems. Adding Levagen®+ alone is earth-shaking, and there are other changes that make MultiV-PRO more than just a comprehensive, high-potency, multiple vitamin-mineral (MVM)[1] . But MultiV-PRO isn't simply a MVM; it's an entire nutritional system for maintaining and extending high-level physical performance.

Like First Endurance's MultiV, MultiV-PRO provides a comprehensive, balanced MVM formula to maintain optimal health during physically and mentally stressful conditions; high-calorie, high carbohydrate diets; strenuous training & competition workloads; oxidative stresses; metabolic overdrives; musculoskeletal integrity burdens; immune system support; multitasking mental functions; frequent everyday aches & pains; as well as accounting for your specific genetic constituency, both genome and epigenome.

NOTABLE CHANGES TO UPDATED MULTIV-PRO

MultiV-PRO is easily at least six different, full-strength dietary supplements all rolled into the same four tablets per day. That's one more than MultiV, but that 4th tablet allows for some major additions and upgrades. MultiV-PRO has everything that MultiV has, but there are improvements in essential vitamins and minerals (both in new forms and different dosages), and upgrades to the non-essential nutrients, both increased amounts and new nutrients.

New Additions

First and foremost, MultiV-PRO has Levagen®+ with Lipisperse®, your body's primary endocannabinoid. Also new is Agave Inulin fructooligosaccharides (FOS), a prebiotic for additional gastrointestinal health. These two new ingredients alone make up most of a single tablet, necessitating changes to other nutrients in order to deliver even more benefits than MultiV. These two new ingredients are not in MultiV. Both these nutrients are discussed in detail later in this Research Packet.

Changes – Amounts

For Vitamins, Vitamin C has been decreased to 133% Daily Value – enough to maintain normal Vitamin C status and antioxidant activity. Vitamin D has been increased 5x to reach levels used in successful human studies for ensuring optimal Vitamin D status – something widely missing in athletes, even with sunlight exposure (tanning decreases skin Vitamin D output). Choline was doubled to reach an Excellent Source of dietary intake – pushing most people to at least sufficiency – something MVMs seldom reach. See the section on Choline below for more information.

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[1] We'll use MVM as an abbreviation for multiple vitamin & mineral products, including those with other active ingredients, which is what First Endurance MultiV-PRO is. Minerals in MVMs usually exclude sodium, potassium, chloride, and phosphorus (mostly as phosphates), which are called electrolytes.

Citations for MultiV-PRO Vitamin Amount Changes – Vitamin C Reviews: *Bender 1975; Bloomer 2006; Braakhuis 2012; Bucci 1993 23; Clifford 2020; Cobley2015; de Lima 2022; Evans 2000; Gerster 1989; Gross 2015; Hemila 1996; Higgins 2020; Kanter 1998; Keith 2006; Li 2022; Martinez-Ferran 2020; Moreira 2007; Neubauer 2015; Nikolaidis 2012; ODS 2021 C; Peake 2003; Peters 1997; Peters-Futre 1997; Righi 2020; Santos de Lima K 2022; Torre 2021; Wagner 2015; Yavari 2015; Zimmermann 2003*

For Mineral changes, Iron was increased to 27 mg per day, like the original MultiV-PRO, an amount used successfully in human studies for maintaining healthy red blood cell production in endurance athletes, especially women. Magnesium and Zinc amounts were reduced compared to MultiV, but 100% of these minerals is now in optimal chelated form (see below). You actually get more bioavailability (actual mineral into circulation) from 100% chelated mineral forms. Chelated Chromium (as Chromax®, Nutrition21's chromium picolinate) was increased from 100 mcg in MultiV to 400 mcg in MultiV-PRO, an amount used in controlled human studies that showed improved body composition.

For additional nutrients, Beta Glucan was switched to a cultured Reishi mushroom (Ganoderma lucidum) source – Immulink MBG® Organic Reishi extract, provided at the clinically-studied amount of 200 mg per serving. Immulink MBG® extract has additional Beta Glucan forms and other molecules to support your immune system. See the Beta Glucan section later for more details. Spectra® Total ORAC5 Blend amount was doubled, reaching the same dose used in successful human studies showing antioxidant protection.

Changes – Forms – Vitamins

Several vitamin forms were changed in new MultiV-PRO: 1) Vitamin E, 2) Folate, 3) Vitamin B12, and 4) Choline.

Vitamin E Story – MultiV-PRO Barks Up the Right Tree

Vitamin E in MultiV-PRO now contains all four tocopherols found in a healthy diet rich in plant foods – alpha, beta, gamma and delta tocopherols, called Mixed Tocopherols – as *Nature intended.* Simply put, Vitamin E research has been barking up the wrong tree since its discovery.

The large number of human supplementation studies with only alpha-tocopherol forms has not been as successful as dietary Vitamin E intake study results for health, even at doses tens or hundreds of times higher.

Almost nobody tries to explain the ***real*** story on Vitamin E. It would be embarrassing for nutrition science, pharmaceutical science, medicine and especially regulatory agencies. It's a long story full of heartbreak. But rest assured that MultiV-PRO is doing Vitamin E right, with stronger benefits for immediate and long-term health – your body knows what to do.

Vitamin E – All Mixed Up Is Alright

Here are the forgotten facts: Vitamin E health benefits are mostly from higher dietary food intakes containing all four natural Mixed Tocopherols – alpha, beta, gamma and delta forms – ***not*** alpha-Tocopherol only, which is the only form of Vitamin E in almost all MVMs and Vitamin E stand-alone supplements. Worse, until recently, much of the research and most MVM supplements used synthetic dl-alpha-tocopherol, which is less active than natural d-alpha-tocopherol. Even worse, pharmaceutical companies colluded with regulatory agencies to make dl-alpha tocopherol the Reference Vitamin E, perhaps because it was cheaper to make and more profitable, completely ignoring beta, gamma and delta tocopherols, and with inferior activity to natural d-alpha tocopherol. This is why Vitamin E was labeled as I.U. (International Units), based on an irrelevant rat fertility feeding assay. This was before anyone knew what antioxidants really were.

Vitamin E research languished until the Advent of Antioxidants in the 1970s, and Vitamin E finally had relevance to humans, spurring all kinds of wrong-minded studies before the real story on Vitamin E was known. 95+% of Vitamin E supplements research (over 25,000 PubMed hits and counting) has been focused on alpha-tocopherol only, by itself, about half from synthetic dl-alpha-tocopherols. You can't fool Mother Nature – Vitamin E in plants and animals is all four tocopherols in natural d-forms for a good reason – balanced antioxidant actions and safety. And we'll not even consider the tocotrienols that usually accompany Vitamin E tocopherols – they are in smaller amounts, and they are in Mixed Tocopherols. Turns out that dl-alpha-tocopherol is not the Alpha Vitamin E.

Vitamin E was misunderstood from its beginning, before antioxidants were understood. Worse, early Vitamin E work developed cheaper synthetic dl-alpha tocopherol, which is only half d-alpha tocopherol and which only became the Reference Vitamin E for defining IU (International Units) based on those irrelevant rat fertility studies. This led to conversion factors for natural Vitamin Es, and the rate fertility studies caused another problem: the other beta, gamma & delta tocopherols did not have activity in rat fertility, so they were hardly ever considered for study. Big mistake!

As a result, dl-Alpha tocopherol has been found to cause more problems than solutions, tainting Vitamin E research for decades. The l-form of tocopherol cannot be recharged or safely disposed of in the body, making it a pro-oxidant in high doses – the exact opposite of what an antioxidant does. Giving more and more alpha-tocopherol (whether natural or synthetic) has frequently not shown expected health benefits and sometimes has shown adverse health consequences. Law of Nature: too much of a good thing is bad, especially antioxidant activity. Balance between antioxidation and oxidation is vital. Ignore at your peril.

Thankfully, in 2016, the US FDA followed the National Academy of Sciences, Institute of Medicine, Food and Nutrition Board recommendations to ditch the IUs and switch to mg (milligrams) of natural d-alpha-tocopherol as labeling units for Vitamin E – much belated but most welcome! Nobody cared. Synthetic Vitamin E is out of the picture, quietly. Much better, but still not the whole story. The emphasis on Alpha Tocopherol and ignoring Gamma Tocopherol is still barking up another wrong research tree.

Real Benefits from Mixed Tocopherols

Mixed Tocopherols are associated with long-term health benefits of Vitamin E, as evidenced by studies of Vitamin E from foods and diets (which in actuality is studying Mixed Tocopherols, not alpha-tocopherol). This is mostly due to the presence of Gamma Tocopherol, which is the major tocopherol in the US diet (twice as much as Alpha Tocopherol), and is largely responsible for those important long-term benefits of Vitamin E.

Gamma Tocopherol protects your DNA from damage better than Alpha Tocopherol and other antioxidants by virtue of neutralizing nitrogen-oxygen free radical species that most other antioxidants cannot quench. Also, Gamma Tocopherol breakdown products are strong signals to initiate cellular (and tissue) repair, meaning better recovery after exhaustive exercise.

This is important for exercise because mitochondria have DNA and are at the epicenter of free radical production, and nitrogen-oxygen free radicals are increased during exhaustive exercise. Any diminution of mitochondrial functions means less energy for your muscles and a drop in exercise performance.

Citations for Mixed Tocopherols & Exercise: Henriquez-Olguin 2020; Knez 2007; Lewis 2015; Machefer 2004; Neubauer 2010, 2015; Pinho 2010; Sachdev 2008; Viña 2000; Wiser 2008

Gamma Tocopherol has been hiding from Vitamin E scientists – it is rapidly converted into metabolites that exert healthy activities that are still being elucidated. The chemistry is complex and has deterred previous research, but now the power of Gamma Tocopherol balanced by Alpha Tocopherol is clear. It's a team effort. New findings argue strongly to cease supplementing supra-dietary levels of Alpha Tocopherol by itself, and to supplement with healthy dietary intake amounts and ratios of Mixed Tocopherols - like MultiV-PRO has.

Another wrinkle – higher doses of Alpha Tocopherol block uptake of Gamma Tocopherol – which explains why high doses of Alpha Tocopherol alone are not the antioxidant panacea once extolled. Worse, by an outdated regulatory quirk, we are only allowed to list Alpha-Tocopherol as Vitamin E, so the label amount of 30 mg (100% DV) is the amount of Alpha Tocopherol only. You are actually getting more than 40 mg of the other Tocopherols, just like healthy food sources associated with Vitamin E benefits.

MultiV-PRO has the right forms, ratios and amounts of Mixed Tocopherols to seamlessly mesh with other major antioxidants (Vitamin C, Glutathione, Carotenoids, antioxidant enzymes) to protect fats in cell membranes and blood lipids, and your DNA.

Citations for MultiV-PRO Vitamin Amount Changes – Vitamin E Story: *Bloomer 2006; Bucci 1993 23, 1995 61; Cansino 2023; Clifford 2020; Cobley 2015; de Lima 2022; Devaraj 2008; DGAC 2019; EFSA 2010 1816; Elmadfa 1999; Evans 2000; Gerstner 1991; Gross 2015; Hensley 2004; Higgins 2020; Higuchi 2023; Huang 2003; Jiang 2001, 2022 347, 2022 375; Kanter 1998; Li 2022; Maras 2004; Martinez-Ferran 2020; Mastaloudis 2006; Neubauer 2015; Nikolaidis 2012; ODS 2021 E; Pinho 2010; Rahim 2018; Sachdev 2008; Santos de Lima 2022; Takanami 2000; Thompson 2020; Torre 2021; Traber 2014; Usoro 2010; Viña 2000; Wagner 2004, 2015; What We Eat in America 2019; Wiser 2008; Wolf 1997, 2007; Zimmermann 2003*

B Vitamin Changes in MultiV-PRO

Folate was changed to Quatrefolic®, the most stable form of the active Folate form (Methyltetrahydrofolate or MTHF) in foods and our bodies (https://quatrefolic.com). Combining MTHF with Glucosamine led to greater stability than other forms of MTHF, both in tablets and in your body.

Similarly, Vitamin B12 was changed from Cyanocobalamin to bioidentical Methylcobalamin (the coenzymatic form for a large part of B12 functions). Choline is still Choline-L-bitartrate, but the source has been switched to VitaCholine®, the form of Choline used in numerous human clinical studies (https://balchem.com/human-nutrition-health/products/vitacholine/). The tartrates are natural L-tartrate, which is extracted from grape musk (leftover wine grape pressings) instead of being synthesized, which makes DL-tartrate. See the section on Choline below for more information.

Citations for MultiV-PRO Vitamin Amount Changes: *Bender 1975; Bloomer 2006; Braakhuis 2012; Bucci 1993 23; Clifford 2020; Cobley2015; Evans 2000; Gerster 1989; Gross 2015; Hemila 1996; Higgins 2020; Kanter 1998; Keith 2006; Li 2022; Martinez-Ferran 2020; Moreira 2007; Neubauer 2015; Nikolaidis 2012; ODS 2021 C; Peake 2003; Peters 1997; Peters-Futre 1997; Righi 2020; Santos de Lima K 2022; Torre 2021; Wagner 2015; Yavari 2015; Zimmermann 2003*

Changes - Forms - Minerals

As mentioned above, we switched forms of Boron, Magnesium and Zinc in MultiV-PRO to clinically studied, 100% chelated minerals with better absorption, uptake, bioavailability and less interference with other minerals and foodstuffs. Chelated forms also extend hang time in the body for minerals, getting more actions out of the same or lesser amounts ingested.
Boron is now FruiteX-B® (Calcium Fructoborate), and is explained in detail later in this report. More information can be obtained from the Futureceuticals website (https://www.fruitex-b.com).

For Magnesium, MultiV-PRO uses the DiMagnesium Malate (DMM) form, which has at least two human clinical studies, showing its acute absorption/uptake in plasma is as good as Magnesium Bisglycinate, regarded as one of the best-absorbed forms of Magnesium. DMM is 20% Magnesium, more than other chelates, which means less volume for a smaller MultiV-PRO pill size.

Citations for MultiV-PRO Magnesium Change: Bohl 2002; DGAC 2019; Dmitrasinovic 2016; EFSA 2015, 2018; Laries 2014; Motyka 2008; ODS 2018; Stendig-Lindberg 1999; Volpe 1993, 2015; Weiss 2018; Zhang 2023

Zinc in the Bisglycinate form is a lower dose than Zinc in MultiV, but with superior bioavailability, meaning less interference with dietary fiber and other minerals. This Zinc change also improves Copper bioavailability. Calcium Fructoborate (FruiteX-B®) is bioidentical to one of the major forms of Boron in plant foods, and has many human studies detailing its absorption, utilization and actions, especially for working with Vitamin D.

Unchanged

MultiV-PRO has the same amounts of Vitamins A, E & K, and all eight B vitamins (but with notable changes to Vitamin E, Folate and B12 forms). For Minerals, Calcium, Copper, Iodine, Manganese, Molybdenum and Selenium are unchanged from MultiV. Boron amount is the same but with a different, clinically-studied form. Green Tea and Ginkgo biloba extracts are also the same as in MultiV and previous MultiV-PRO.

WHY YOU NEED A PROFESSIONAL-STRENGTH ENDURANCE MULTIVITAMIN/MINERAL (MVM) LIKE MULTIV-PRO

REASONS WHY YOU NEED AN ENDURANCE MVM (PROBLEMS & SOLUTIONS)

MVM Problems:

- Micronutrient Intake Gaps (Insufficiencies & Deficiencies);
  - Athletes do not get enough intake of all the MVMs from their diet (low intakes);
  - Athletes show variability of MVM intakes, upsetting balance among MVMs;
  - Athletes typically eat strict, low-micronutrient density, wildly varying daily intakes;
  - Athletes show prevalence of low levels and/or higher turnover of critical MVMs for exercise performance – especially iron, magnesium and Vitamin D;
  - "Vitamin-rich" & "mineral-poor" MVMs do not give you everything you need;

- Imbalanced Micronutrient Intakes & Ratios;
  - Strenuous exercise places additional nutritional demands on some MVMs;
  - Daily Values may not be adequate for exercising athletes to maintain high workloads;
  - A functional deficiency of even one MVM will detract overall performance and imbalance other MVMs;
  - Don't need 100% of everything;
  - Dietary intakes need to be considered too;

- Comprehensive (Avoiding Weakest Link In The Chain)
  - Sufficient Amounts/Doses;
  - Forms of Each Nutrient;
    - ◊ Nutrient-nutrient interactions;
    - ◊ Absorption, uptake, bioavailability, functionality;

- Compliance (Consistent, Daily Use);
- Genetics & Epigenetics – our own idiosyncrasies can worsen nutritional status;
- MVMs seldom contain other micronutrients with known beneficial actions that support muscular functions and maintain optimal exercise performance.

MultiV-Pro Solutions:

- MultiV-PRO goes beyond other MVMs, using the best forms of each essential vitamin and mineral, then adding an endogenous endocannabinoid (Levagen®+) and other clinical studied nutrients for improving exercise and recovery performance;
- Fill micronutrient intake gaps from your diet (comprehensive);
  - Improve dietary micronutrient density;
  - Prevent insufficiencies and deficiencies;
- Balance micronutrient intakes for optimal functionality;
  - Improved bioavailability;
  - Reduced interactions between minerals and other nutrients;
  - When there is a difference, vitamins are in their most useful and active forms;
- Comprehensive (26 vitamins & minerals);
  - Sufficient doses of each micronutrient to cover losses greater than non-exercising persons (for example: heavy exercise workloads, sweat losses);
  - Best forms of each micronutrient that account for common genetic variations and gender differences;
  - Provide individual micronutrients with superior absorption/bioavailability;
  - Provide individual micronutrients with less interactions among other nutrients;
  - Compliance for consistent daily intakes
  - Keep pill number per serving and size of pills as low as possible with easiest shape for swallowing;
- Genetics & Epigenetics
  - Forms and doses of micronutrients balanced to account for genetic variations;
- MultiV-PRO adds additional nutrients with benefits for exercisers, with human clinical study support.

WHY DO I NEED A MULTIVITAMIN (MVM)?

Because you want to give yourself the best chance to train, perform, recover, rest and repeat again, at your peak.

MultiV-PRO Is Designed Unlike Other MVMs
Rather than to meet cost constraints or pill number/size goals, MultiV-PR was designed to be the best for intense endurance exercise. That means MultiV-PRO provides solutions for your essential micronutrient needs – not compromises.

Essential micronutrients (vitamins and minerals) are molecules and compounds that your body cannot make itself, and thus, need to come from your diet – whatever you eat and swallow. There are at least 24 essential micronutrients to consider (and many more helpful but not so-called essential micronutrients). Keep in mind that electrolytes sodium, chloride, potassium, phosphate and calcium are a different story – they are not micronutrients, but are macronutrients, meaning a gram or more per day is a necessary intake. Magnesium is a borderline macro/micronutrient, and should be in an endurance MVM since dietary intakes are highly variable day-to-day and usually insufficient or deficient. To keep your body replete with all those micronutrients, there are certain requirements for a MVM to ensure you are not letting essential micronutrients be a problem.

Taking Exercise Into Account - You're Not Normal (But That's OK)
The Daily Values (DVs) of Calories, Protein, Fats, Carbohydrates, Vitamins and Minerals are generated for the nutritional sufficiency needs of the overall US population, not for intense, long-duration exercise demands. Your exercise load, training frequency, daily scheduling and mental toughness are not "normal." Your typical nutrient intakes are also not normal, with a lower micronutrient density (micronutrients per Calorie ratio), and are heavily weighted to carbohydrate sources often low or absent of micronutrients.

Day-to-day variability of meeting nutrient needs is high – not conducive to maintaining status of nutrients that are not stored and/or are excreted easily. Training causes a myriad of physiological changes in your metabolism (cellular energy production), cardiovascular dynamics, muscular repair processes, nervous system functions, connective tissue turnover and bodyfat content. You spend long time periods of gut hypoxia, altering your absorption, uptake, bioavailability, excretion of micronutrients throughout the day, and perhaps altering your gut microbiome adversely. Exercising in the heat leads to increased loss of minerals not found in non-exercising persons.

You need a MVM that is suited to your needs and lifestyle. Let's look at some of the problems and the solutions that MVMs can fix.

Problem: Endurance Athletes and Micronutrient Intake Gaps
Most studies of endurance athletes find low intakes of key nutrients such as Vitamin D, calcium, magnesium, iron, iodine and seriously low intakes and status of omega-3 fatty acids. These are also the nutrients with big issues for the US population (excepting, perhaps, iron). But endurance athletes are often below their needs for protein and especially carbohydrates, and coupled with long-duration, intense exercise, that means an energy deficit – quite the opposite of average Americans.

Compared to the rest of the population, serious endurance athletes are semi-starved and somewhat malnourished. But micronutrient deficiencies are like pulling spark plugs out of your engine. It becomes obvious that all nutrients, including calories, need to be adequate and balanced for optimal performance.

Another hidden source of micronutrient gaps is nutrient density (ratio of micronutrients to calories). You eat a high-carb diet most of the time, and likely fuel adequately during training, events and recovery with water, calories and electrolytes, but those calories are not micronutrient-dense. Simply put, you are not getting enough micronutrients to help process increased fuel loads efficiently.

You don't need 100% Daily Value (DV) of every essential vitamin and mineral in MVMs. You will not see sodium, chloride, phosphorus (phosphates) or potassium at a meaningful dose in MVMs, if present at all – they are needed in multigram amounts. MVMs are intended to prevent micronutrient deficiencies – this means non-caloric nutrients with intakes of milligrams or micrograms daily. A MVM with 100% of all essential vitamins and minerals is unfeasible – a pill the size of a softball.

You also eat foods that contain vitamins and minerals, and often reach 100% DV intakes from foods alone for some, but never for all vitamins and minerals. You also do not get near 100% DV for calcium and magnesium in MVMs because of the large amounts needed. MVMs can help magnesium intakes significantly if designed properly. With the First Endurance System, regular use of EFS, EFS-PRO and/or Ultragen provide gap-filling amounts of calcium and magnesium in highly absorbable forms.

Solution:
Provide enough of each micronutrient to make low intakes, low nutrient density dietary intakes reach functional sufficiency for each and every essential micronutrient. No weak links in the chain of micronutrient sufficiency and function!

Citations for Endurance Athletes & Micronutrient Intakes: ARS 2018; Baranauskas 2015; Beck 2021; Beerman 2020; Block 2007; Blumberg 2017 849, 2017 1325; Bohl 2002; Brilla 2012; Bucci 1993, 1995; Burke 2019 73, 2019 117; Clarkson 1995 831, 1995 S11; Costa 2019 130, 2019 166; da Silva 2020; Deldicque 2015; Deuster 2006; DGAC 2019; Dias 2021; DiSilvestro 2017; Driskell 2006; Gatrich 2020; Grozenski 2020; Haymes 1998; Heaney 2010; Heffernan 2019; Kisters 2019; Laires 2001, 2008, 2014; Lee 2017; Lukaski 1983, 2000, 2004, 2006; Martin 2007; Maughan 2018 104, 2018 439; McDonald 1988; Mehlenbeck 2004; Moshfegh 2009; Nebl 2019; Newhouse 2000; Nica 2015; Nichols 2023; Nielsen 2006, 2019; Nikolaidis 2018; Oullette 2012; Parnell 2016; Peeling 2018, 2019; Rakhra 2017; Ranchordas 2012; Razzaque 2018; Rogerson 2017; Singh 1990, 1993; Stendig-Lindberg 1987, 1989, 1991, 1992, 1995, 1999; Steward 2019; Tardy 2020; Tiller 2019; Vitale 2019; Volpe 1993, 2015; What We Eat in America 2019; Wierniuk 2013; Williams 2005; Williamson 2016; Zhang 2023

Problem: Micronutrient Balance
So you think that taking a grocery-store MVM takes care of your micronutrient needs? Consider this sobering fact from 2021: over 50% of Americans take a MVM regularly, but more than 95% of us are not getting enough of all the essential vitamins and minerals. This startling fact also shows how imbalanced most MVMs really are ("vitamin-rich, mineral poor").

Balance means using the right amounts and the right forms of each micronutrient – and considering how they work together. This does not mean supplying 100% DV of everything.

No micronutrient is an island, which is how DVs were determined – individually. Vitamins and minerals work in concert to operate your cellular machinery to keep you healthy, active for peak performance and recovery. Your body has a multitude of interactive ways to meet its demands for physical and mental performance. But like any fine-tuned system, even a single missing, excessive or dysfunctional part can limit overall peak performance.

Then consider that there are 24 micronutrients in MultiV-PRO that are deemed essential to go along with essential fat, protein, and macrominerals Sodium, Chloride and Potassium not found in MultiV-PRO (Phosphate is found but is below the 5% DV limit

for requiring to be listed). And we're not even worrying about Fiber and other nutrients hovering on the brink of being considered essential.

Each essential vitamin has its own range of intakes for deficiency (with adverse symptoms), insufficiency, a wide range of sufficiency, excessive amounts that interfere with health, and finally, toxicity. Minerals have wider ranges of deficiency and insufficiency, smaller ranges of sufficiency, lower thresholds for interference from excessive amounts and less margin of safety than vitamins. Defining a deficiency or insufficiency or sufficiency is a moving target that is still debated. Water-soluble vitamins have different ranges for sufficiency/toxicity than fat-soluble vitamins.

Because your body adapts to regular exercise training, more exercise does not necessarily mean needing more of everything. Your body tends to hang on to essential micronutrients by lessening excretion (loss) and releasing stores if necessary. Also, essential micronutrients activate the function of the protein they inhabit, and it takes longer than your exercise event timeframe to make more protein and attach or append the right micronutrients to gain additional function immediately after nutrient intake. Our cells need a stash of essential micronutrients ready for use at any time. MVMs are proactive, not reactive.

Exercise performance (energy metabolism) and recovery after strenuous exercise are both several chains of events (cycles) that are intimately linked. And each micronutrient has to go through its own chain of events to fit into the proteins for each cycle in which they participate. In fact, it is seldom realized or acknowledged that vitamins and mineral forms in MVMs are usually inactive. And even bioidentical vitamin forms for B vitamins, and especially mineral forms, are stripped down to what you get in MVMs. Fortunately, each micronutrient goes through complicated transformations and metabolic steps to fit into its ultimate molecular usages. This forgotten control factor is something seldom considered for designing MVMs, but is a key design feature of MultiV-PRO.

For example, if you took the ultimate, most active Vitamin D form (Calcitriol instead of Cholecalciferol) at the Vitamin D 10% DV, it would be seriously toxic and even deadly. Also, activated vitamins are less stable than forms in MVMs, meaning a short shelf-life in tablets before they degrade into oxidized anti-vitamins or indigestible mineral forms like rust for iron.

Another part of balance is not getting excessive – too much of a good thing. MultiV-PRO does not have megadoses. [Note: the % DVs are not always a good indicator of megadoses.] Taking a large dose of a single micronutrient may lead to unexpected problems, as megadose practices have discovered, usually by imbalancing the function of other micronutrients. Taking high doses of micronutrients also makes your body decrease the percentage absorbed, and worse, get better at disposing of excess, so if your intake suddenly drops to normal levels, you may get a rebound effect of functional insufficiency before your body adjusts to the new intake. Balance also means timing of nutrient functionalities.

Solution:
Balancing MVMs, especially for a specific use like exercise performance, is more of an art based on many fields of science. Deeper knowledge and more experience mean better and more efficient balance. Give enough of each and every micronutrient and then give it time to work with your body's homeostatic mechanisms to utilize the bounty of micronutrients. With MultiV-PRO, based on the extremely large database of micronutrient intakes, especially in endurance athletes, we can safely predict you will have improved intakes and adequate status of essential micronutrient vitamins and minerals. MultiV-PRO also opts on the side of caution for maintaining sufficiency with long-term safety.

Problem: Comprehensive Formula – Everything All The Time

The goal of a MVM for persons engaged in strenuous, exhausting physical and mental exercise is to supply all essential micronutrients, even if some are more necessary than others – preventing weak links in the chain of nutritional sufficiency. Having each and every essential micronutrient is not often seen in MVMs. Again – no micronutrient is an island, which is how DVs are determined. Everything works in concert, but only if everything is present in effective quantities.

The so-called nonessential vitamins and minerals are and always have been essential for our bodies, but a regulatory framework for disease prevention by nutrients rather than health promotion keeps scientists and bureaucrats as opponents. For example, choline was not considered "essential" until 1998 on the basis of a deficiency of intake and levels causing fatty liver was verified beyond a doubt. And even then, it was not allowed to be listed as essential on supplement labels until after 2020.

Boron has incontrovertible evidence it can do what no other nutrient can do because of its unique atomic structure that supports health, but again, scientists and regulators are still debating the details of how essential it is. For both choline and boron, insufficiency of each leads to deficient functions of other micronutrients – folate and B12 for choline and calcium; magnesium and vitamin D for boron. A similar story for Vitamin K2 MK7 will be discussed later. We are not even getting into silicon or lutein/zeaxanthin and lycopene carotenoids yet.

Comprehensive also means sufficiency of doses that take into account all factors, not just nutrient in, nutrient out data. Studies of nutrient intakes and status in athletes is one guide to to meeting comprehensive needs of exercisers, but exercise is only one variable to consider for micronutrients, and other unavoidable factors are at work.

One study showed being comprehensive is better (Block 2007). Compared to a no supplement group and a one-a-day, single-pill, multivitamin supplement (100% DV or less) group, another group took higher doses of vitamins and minerals with omega-3s and additional nutrients – a MVM with benefits. The one-a-day MVM was seldom better than not taking a MVM supplement. The group taking the MVM with benefits showed significantly better results for reaching healthy biomarker levels, felt better and had better physical functions. ***The point is that you need enough of each and every MVM all the time for a long time period to get results.***

Compliance Matters

Consistent intakes are part of being comprehensive – a MVM can't help at all if you don't take it or can't help enough if you don't take it often enough or at full strength. Ideally, you want to supplement your diet so that your consistent average daily intake from diet and supplements remains in the upper part of the sufficiency zone of intake for each nutrient. This prevents any variability into the lower intakes of insufficiency without getting into safety issues for spikes of increased intakes from variations in dietary food intakes.

Nutrient Forms Matter

The specific form of each micronutrient can be crucial. For many vitamins, the typical forms used have been well-tested and used in human clinical studies, and their metabolic activation and deactivation pathways worked out, so that an effective dose is known and supported. Especially for minerals, there are big differences in absorption, uptake, bioavailability and interactions with other nutrients among the various forms available. Sometimes the forms are the same everybody uses (like most B Vitamins); sometimes we choose the best forms (like trace mineral chelates).

The usual forms that have less bulk, size and weight also have less usefulness to your body than expected. They also interfere more with other micronutrients and your food intake for uptake into your body. MultiV-PRO takes this issue seriously, using vitamin and mineral forms with superior capabilities, but more bulk and size – that is why there are four pills per serving. For example, if we used only inorganic mineral forms, we could squeeze everything into fewer tablets daily. But at what cost? Your health and performance.

Attention to Folate Forms

An example of healthy attention to detail for forms of vitamins is Folate, normally supplied as Folic Acid. Folic acid is an inactive synthetic form of the Folate molecular backbone that is not normally found in foods or your body. In Nature, folic acid is briefly formed and converted as an intermediate in the production of MTHF by microbes and plants. Why MTHF form? MTHF is by far the major form of Folate in plant and animal cells. Folic acid requires activation by several metabolic steps in your body to become the active, coenzymatic MTHF form. If folic acid intakes are high, and/or you happen to be one of the ~30% of us who have one or more of the several common genetic polymorphisms in enzymes involved in folate metabolism, the ability of folic acid to be converted into MTHF is slowed, as is the overall function of MTHF. Worse, unmetabolized folic acid (UMFA) piles up in blood and cells, where it blocks MTHF, meaning a decrease in folate function. Since folate function depends on MTHF and is required for your body – it's critical for blood cell formation, making numerous important compounds, and detoxifying homocysteine as well as controlling gene expression – UMFA can be a detriment to health, including birth defects. MultiV-PRO does not take that chance with your health. MTHF is the most active form of folate, and MultiV-PRO uses a stabilized form of MTHF (Quatrefolic® MTHF-Glucosamine).

Citations for MTHF Folate: Cornet 2019; EFSA 2009, 2010 1760, 2013; Fenech 2005; Fohr 2002; Hoch 2009, 2010; Kalmbach 2008; Knowles 2016; Pietrzik 2010; Prinz-Langenohl 2009; Scaglione 2014; Selhub 1996, 2016; Ulrich 2006; Woolf 2006

Solution:

MultiV-PRO has 26 different micronutrient vitamins and minerals – excluding sodium, chloride, potassium and phosphorus, and including Boron and Vitamin K2 MK7. MultiV-PRO is designed to be as easy to take as possible while delivering useful amounts and forms of multiple essential micronutrients. Forms of each micronutrient were carefully chosen to provide your body with the best absorption, uptake, bioavailability, lack of unwanted interactions, integration into metabolic pathways, function and increased safety.

Problem: Your Genetic Achilles Heels

Three more good reasons to regularly take a MVM are you, yourself and your genetics. Modern genetics research has advanced to understand that each one of us has hard-wired genetic differences that are not ideal. Some nutrient functions are commonly affected adversely – Folate, Vitamin D, Iron, Omega Fatty Acids, B12, Magnesium, Calcium, Biotin for starters. For every nutrient, there are many key proteins that help that nutrient fulfill its metabolic perfection. Genetic protein malfunctions exhibit a functional deficiency of a vitamin or mineral even if levels and intakes are normally enough according to the Daily Values. Again, the Chain of Nutritional Functions is Only as Strong as the Weakest Link.

Less is known about the magnitude of even more numerous epigenetic effects of silent changes in DNA sequences, but the cure is the same as for genetic changes. Simply taking more of the effected nutrient improves its overall function. And let's not forget that some genetic changes are improvements, but who knows which ones you may or may not have? And which adverse changes would be actuated by increased intake or status of a particular nutrient? Unless you perform expensive and extensive genetic testing, you may never know that you could have better health and performance by ameliorating genetic changes.

Solution:
Genetic variations themselves are unalterable (this might change in the future), but you can correct most functional deficiencies by simply increasing your affected nutrient intake and/or its form. By taking enough of the right form of micronutrient with common genetic changes, you can usually optimize your nutrient functions, which is the bottom line. A MVM should supply the best forms of nutrients to further increase chances for success (Folic Acid is the poster child for using the wrong form). MultiV-PRO supplies specific nutrient forms with better functionality to bypass common genetic variation effects.

CRITICAL MICRONUTRIENT UPDATES FOR ENDURANCE EXERCISE

Focusing on just a few vitamins illustrates why you need to take a comprehensive MVM. An explosion of human research on exercising individuals has catalogued real-life benefits for exercise performance by ensuring adequate intake of normal, everyday vitamins and minerals. It's not only cycling, running or swimming faster – it's the Big Picture that keeps you training hard and recovering better so you can make performance gains during competition. Researchers are digging deeper to find new insights into the humble MVM.

Choline update - Too new for other MVMs
Although choline was classified as an essential nutrient in the US since 1998, there was no agreed-upon Daily Value (DV) until recently. Choline is another "vitamin" that has multiple forms in foods and our bodies, but choline is not easy to put into supplements.

Choline salts – the simplest, least expensive choline options – are extremely hygroscopic (attracts water from even low humidity air) and are a disaster for shelf life of MVMs. Lecithin forms of choline have low potency and are another gooey mess to put into tablets at the large amounts required. That leaves Choline bitartrate as the most potent, stable, dry, and acceptable form of Choline for tablets.

Tartrate is tartaric acid, the major acid in grapes, and a common food flavor/acidifier. Most tartrate in foods and supplements is DL-form because it is chemically synthesized. Although human bodies can still utilize D-tartrate, L-tartrate simply works more easily with our cells. MultiV-PRO uses a soluble and stable choline salt form – Choline-L-tartrate, aka Choline bitartrate. As mentioned above, the L-tartrate is from leftover pressed wine grapes – the natural form.

In addition to the natural sourcing, the amount of Choline per serving in MultiV-PRO is a whopping 20% - rarely seen in MVMs. That's enough to qualify for a government-approved food claim of being an Excellent Source of a nutrient. It's that important. [Note: see the HALO Research Packet for information on Choline and Exercise Performance.]

Citations for Choline in MultiV-PRO: Atzler 1935; Bjorndal 2018; Buchman 1998, 1999, 2000; Conlay 1986, 1992; de la Huerga 1951, 1952; Deuster 2002, 2006; Ernst 1960; Ganz 2017; HALO Research Packet 2022; Hirsch 1978; Hoeg 2020; Jager 2007; Martinez 2016; Mies 1958; Modinger 2019; Naber 2015; Newsom 2016; Penry 2008; Sandage 1992; Spector 1995; Staton 1951; Storsve 2020; von Allworden 1993, 1995; Wallace 2018; Warber 2000; Wurtman 1977

Chromium update - Chromium demystified

Chromium, a close atomic cousin to iron, has been the victim of overzealous research – both pro and con. Before it was known how chromium really worked with insulin, numerous studies repeatedly administered ever-increasing amounts of chromium in poorly designed studies that did not take into account how chromium was absorbed or actually worked. You can guess the outcome – completely opposing results that usually exposed investigator bias.

How does chromium really work? Chromium potentiates insulin actions when the demand for glucose in working cells is high. Like putting nitro in a dragster, chromium helps insulin signals inside of cells to allow more glucose and amino acids into cells – especially muscle and liver during exercise, when the body is screaming for more glucose. Chromium makes insulin more effective during exercise – stronger longer. That means many things, but most importantly, more GLUT4 receptors flood the cell surface to grab more glucose to make more cell energy. What better situation than long-duration, intense endurance exercise for chromium's mechanism of action to shine?

Chromium does this by binding to a little peptide called chromodulin, which lives inside of insulin-responsive cells/tissues. Chromodulin attaches to the intracellular parts of the insulin receptor, and makes insulin signaling to the cell louder. As an extra layer of cell control, chromodulin can hold up to four chromium atoms each (called chromium saturation) and can fine tune chromodulin levels in cells up or down quickly. Net result is that exercise training increases glucose delivery from insulin effects, mediated by chromodulin that takes more dietary chromium intake to maximize in long-duration endurance exercisers who burn more total glucose per event than other types of exercise.

Oddly, few studies have looked into endurance exercise, even though that would be the major interest for chromium effects on exercise because of reliance on carbohydrate intakes and insulin actions. Unfortunately, misguided research has overemphasized diabetes, weight loss and muscle building, thinking chromium influenced insulin when the reality is the opposite.

The prevailing findings of chromium levels during long-duration endurance exercise in healthy individuals have shown increased absorption and/or concentration of dietary chromium in tissues with improvement of glucose and insulin metabolisms – specifically, increased GLUT4 receptor translocation to muscle cell surfaces to quickly increase glucose uptake for exercising muscle. This mechanism does not work for short-term or anaerobic exercises, which has confused studies' overviews of chromium and exercise.

Endurance athletes turn over more chromium than sedentary persons, and when exercise stops, chromium (as chromodulin) is dumped into circulation, where the only fate is into urine and out of the body. Coupled with long-duration athletes needing a store of chromium in insulin-responsive tissues, and high-carb, low chromium diets, it is easy to see that a steady supply of dietary chromium assists and improves the training adaptation to intense, long-duration endurance exercise, increasing fuel (glucose) utilization. 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/or 400 mcg daily with MultiV-PRO.

Chromium Chromodulin & Endurance Exercise Citations: *Anderson 1982, 1984, 1988, 1991; Anding 1997; Berger 2002; Clarkson 1995 S11; Clodfelder 2001; Deakin 2011; Doker 2014; Edwards 2020; Frauchiger 2004; Gomes 2005; Lee 2005; Lukaski 2004; Maret 2019; Maynar 2018, 2020; Milasius 2016; Otag 2014; Racek 2003; Rubin 1998; Sureda 2017; Vincent 2000, 2010, 2013, 2015; Wu 2005*

Iron Update - Hepcidin link to exercise

Iron is widely regarded as the #1 problem with micronutrients and exercise, and rightly so. In spite of widespread attention to getting adequate iron, 15-50% of women and 5-30% of men who exercise regularly show iron deficiency. Most are consuming at least the DV of iron (18 mg daily), but signs of deficiency exist. By combining dietary iron intakes with 27 mg of iron from Ferrochel® (ferrous bisglycinate), MultiV-PRO provides the best form of iron in amounts used in successful human studies. But the Iron Enigma is not only about getting enough iron – recent research has found that low energy availability during exercise and relative energy deficiency in sport causes low iron stores and iron deficiencies, regardless of iron intakes.

Why is energy intake affecting iron status? Because iron is a double-edged biological sword. Strenuous exercise, especially with low energy stores, causes inflammation that releases iron from its proteins (myoglobin, hemoglobin and many other iron-containing enzymes, storage and transport proteins).

Iron unbound catalyzes an extremely nasty free radical called hydroxyl radical that accounts for a lot of the muscular damage from overexertion and intense exercise. This inflammatory milieu triggers an iron regulatory protein called hepcidin, unknown until recently. Hepcidin is the master regulator of iron metabolism, a police molecule making sure iron does not cause problems. When problems occur from exercise, hepcidin comes out and sequesters iron, reducing the problem. But in so doing, hepcidin purposefully reduces availability of all iron – causing a deficiency syndrome even with plenty of iron around.

Same thing happens if you take too much iron in foods and/or supplements – hepcidin steps in and prevents iron absorption and increases iron excretion. Hepcidin actually depresses iron delivery to your body's iron performance centers: bone marrow and muscles. Less inflammation and damage from iron, but also less performance from less hemoglobin and iron proteins involved in muscle energy production. So simply taking more and more iron (like many human studies on iron and exercise have done) is not the best answer and can backfire, not improving decreased exercise performance.

This new-found knowledge of why iron is so tricky to maximize performance does have a solution! First, ensure sufficient water/electrolyte/carbohydrate supply during exercise to delay/reduce iron-caused inflammation and hepcidin triggering. Muscles need adequate energy to prevent mitochondria from spewing hydroxyl radicals trying to make more ATP. Human studies have shown that high carb diets and high carb intakes during exercise lower hepcidin levels. Low carb diets (keto diets) increase hepcidin levels.

Second, a consistent, steady, non-exorbitant intake of iron from a true organic chelate is vital. Ferrochel® ferrous bisglycinate is the best-studied iron chelate in humans, and has advantages over less expensive, higher potency iron compounds such as reduced iron, ferrous sulfate, ferrous fumarate and other iron sources. Ferrochel® has been shown to provide less iron absorption if you have a sufficiency or excess, and more iron absorption if you are deficient, reducing the risk of triggering hepcidin release. Furthermore, Ferrochel® has less interference with other minerals for absorption, improving overall mineral uptake and status.

Another benefit from MultiV-PRO is the rich polyphenol content from Ginkgo, Green Tea and Spectra® that reduce hepcidin levels by reducing the free radicals and binding loose iron produced by extreme exercise.

MultiV-PRO helps solve the Iron Enigma to provide the best possible form of iron in a generous amount, sufficient to normalize stores and status without triggering a hepcidin response or iron overload. This keeps you training and performing at your best. Again, it's all about balance.

Citations for Iron in MultiV-PRO: Alfaro-Magallanes 2022; Badenhorst 2015 2215, 2015 2521, 2022; Beard 2011; Bonilla 2022; Brzeszczynska 2008; Bucci 1993 63; Dominguez 2018; DiSilvestro 2017; Drakesmith 2012; Fischer 2023; Ganz 2012; Grijota 2022; Hertrampf 2004; Hinton 2014; Houston 2018; Layrisse 2000; Lippi 2012; McKay 2019 548, 2019 635, 2020; Nemeth 2006; Olivares 2001; Peeling 2008, 2009, 2014, 2017; Pineda 2003; Pizarro 2002; Robach 2014; Shoemaker 2022; Sim 2014, 2019; Sumi 2022; Tom 2008; Williams 2004 1

Vitamin Update – Defense Against Outside

Endurance athletes have shown the full spectrum of high, normal and low levels of Vitamin A intakes from food and in blood (Vitamin A status). Ultra-endurance events are associated with decreased levels of circulating Vitamin A (as retinyl esters) after the event.

To satisfy giving enough Vitamin A to prevent deficiencies and also to prevent excesses, MultiV-PRO uses provitamin A as Beta Carotene to avoid any possibility of active Vitamin A (retinol) overload while ensuring a sufficient status for normal Vitamin A activity. The form of Beta Carotene in MultiV-PRO is natural, since large doses of the synthetic version have been associated with adverse pro-oxidant issues. MultiV-PRO avoids the tarnish wrongly given all Beta Carotene from misguided human studies and parroted reviews. No risk of antioxidant overload is possible from the daily amount of Beta Carotene in MultiV-PRO, even when combined with high fruits/vegetable intakes, which are natural dietary sources of Beta Carotene.

All Vitamin A forms can be derived from Beta Carotene. Beta Carotene in MultiV-PRO provides a normal amount of Vitamin A activity for people who do not eat their fruits and vegetables. Your body converts Beta Carotene into retinal/retinol forms of Vitamin A as needed. Vitamin A as retinal is used by eyes for vision, important for sports requiring visual acuity.

Vitamin A as retinol (which becomes retinoic acid) is a major signal for promoting normal cell growth and differentiation, especially for epithelial tissues that replenish their cells regularly because they are exposed to the outside environment of air, wind and sun. Immune system cells, GI tract, skin, eyes, lungs (respiratory tract), kidneys – all receive and protect us from environmental exposures, orchestrating constant tissue renewal. Normal Vitamin A status is also required for normal production of red and white blood cells, working in conjunction with iron.

Bone health and maintenance is another important and overlooked role for Vitamin A (retinol) and Beta Carotene. Vitamin A is also instrumental in normal recovery of minor, everyday injuries to skin and musculoskeletal tissues.

A bonus is what Beta Carotene can do that preformed Vitamin A (retinol) cannot: be an antioxidant. Specifically, Beta Carotene quenches singlet oxygen and peroxide radicals in fat-soluble areas. Beta Carotene also protects against sun exposure in skin and eyes.

Citations for Vitamin A (Beta Carotene) Need in Athletes : Al Tanoury 2017; Bucci 1993 23, 1995 61; Charkos 2022; Fenech 2005; Heinonen 2012; Houtkooper 2005; LeBlanc 1998; Leung 2009; Michelazzo 2013; Neubauer 2010; Stacewicz-Sapuntzakis 2006; Wald 1942; Weber 2012

Vitamin D Update - Performance Enhancement?

You want to fulfill your potential? Here is D way. Vitamin D is ergogenic. What the D? Yes, you read right – Vitamin D can help you exercise better. Numerous unanimous reviews have found this, so it's not a figment of imagination. Recent research has found that higher levels of Vitamin D show improved exercise performance compared to lower levels. Performance gains (ergogenic effects) have been found with Vitamin D supplementation, especially in those with low and borderline or "insufficient" Vitamin D blood levels.

Dozens of human studies have shown high prevalence of low or "insufficient" blood levels in serious exercisers in apparent good health. Low or "insufficient" Vitamin D levels have been shown to be less than ideal for bone, musculoskeletal and immune health and worst of all, physical performance.

Here's D massive but unseen elephant in D room about the huge importance of Vitamin D for healthy exercising athletes: it's fulfillment of potential. With advances in understanding of Vitamin D3 (cholecalciferol) as a pluripotent, hormone-like trigger for overall health in virtually every cell in your body, a surge in human studies on exercise and Vitamin D has found some eye-popping results.

Vitamin D has a ton of human research, but until recently, virtually none was on healthy, exercising persons. Everyone assumed they were outside getting plenty of sunlight to make their own Vitamin D (the major way we humans get Vitamin D) or eating enough foods to reach the DV. Wrong! Unfortunately, in most temperate and higher latitudes, there is not enough sunlight to activate Vitamin D for half a year or more. And dietary Vitamin D is a very poor way to get Vitamin D – unfortified foods have virtually no D3 and plant foods have none. Fortified foods (dairy product and breakfast cereal, mostly) more often add Vitamin D2 (ergosterol), but only contribute low amounts to your dietary intake. So forget about getting enough Vitamin D in your D-iet.

What to do about D? First, you need to use the right form of Vitamin D. There are two forms of Vitamin D in supplements with bioactivity after oral ingestion – D2 (ergosterol) and D3 (cholecalciferol). MultiV-PRO uses the more bioactive, more bioavailable D3 form – what your body makes from the sun.

Much research has shown D3 is superior to D2, so this was an easy decision. In fact, D2 failed in human studies to improve muscle strength in humans, whereas D3 did. But D3 has fallen out of favor in supplements because of the vegan trend, fostering increasing use of less-potent, less-functional D2, derived from plant sources, or more often, from easy chemical synthesis, just to be labeled as vegetarian or vegan. Only recently has plant-based D3 become available.

D3 is found in animals and a few lichens/algae and D2 is found in few plants (mostly mushrooms). Almost all commercially available D3 is from sheep's wool lanolin (superseding fish liver oil sources). Lanolin can be obtained without the demise of animals, by giving them a haircut. This is why MultiV-PRO is not able to be Certified Vegan; everything else in MultiV-PRO is vegan-compliant.

It's easy to see that normalizing a healthy level of Vitamin D year-round is a vital way to ensure you are meeting your performance potential. And getting 500% of the newly increased DV of D3 from your MVM (like MultiV-PRO supplies) is enough to push most people into sufficiency and performance fulfillment.

Citations for Vitamin D Need in Athletes: Abrams 2018; Araujo 2021; Beaudart 2014; Bollen 2023; Brancaccio 2022; Bucci 1993 23, 1995 61; Butscheidt 2017; Byers 2020; Cannell 2009, 2018; Chiang 2017; Dahlquist 2015; de la Puente Yague 2020; DiGuilio 2022; Farrokhyar 2015, 2017; Feng 2023; Grant 2020; Han 2019; Harju 2022; Iolascon 2021; Ip 2022; Knechtle 2020, 2021; Ksiazek 2019; Liu 2023; Neal 2015; Nho 2018; Ogan 2013; Rockwell 2022; Rojano-Ortega 2023; Shoemaker 2022; Sikora-Klak 2018; Stojanovic 2022; Todd 2015; Tomlinson 2015; von Hurst 2014; Willis 2008; Wojtys 2021; Yoon 2021

Vitamin D Update – Why vitamin K2 for endurance exercise?

Vitamin K comes in two basic forms (K1 & K2) with primary functions of activating proteins that bind and transport calcium for specific uses, ensuring proper blood clotting, pliable blood vessel structure and bone & joint health. All these properties are based on the ability of Vitamin K to convert specific amino acids on specific proteins so that they can bind calcium ions that are easily released when the protein is triggered to release them by other proteins in a chain of events – clotting, bone building, or to grab calcium deposits for removal from unwanted places like blood vessel linings and the first step in bone turnover/repair. K1 takes care of clotting proteins, and K2 is a backup. K2 is targeted primarily towards activating calcium-binding proteins for everything else, which turns out to be critical for bone and cardiovascular health, a relatively new understanding.

All Vitamin Ks are fat-soluble, but do not accumulate too much in humans regardless of dose. While K1 (phylloquinone or phytonadione) comes in only one form, K2 (menaquinone or MK) has multiple forms depending on the length of the hydrocarbon side chain "tail." Longer tails have a higher number signifying how many hydrocarbon units are attached, and go from 2-16 or more, with 4 and 7 being predominant and most useful. Thus, K2 MK4 and K2 MK7 have become commercially available, and a growing number of human studies are revealing important health effects for K2 MK7 that K1 and K2 MK4 cannot provide. Also, the effective MK7 daily dose is lower than for MK4 or K1.

K1 is stored in the liver and not used for much else than to ensure clotting can happen. Intakes of Vitamin K1 are seldom deficient, and easily obtained from a diet rich in green leafy vegetables. But risk of travel, road injuries and variable diets associated with an endurance exercise lifestyle means that getting 100% Daily Value of Vitamin K from a MVM is helpful to preserve blood clotting ability. Also, supply of 100% Daily Value for Vitamin K is within normal dietary variability and has minimal to no effect on persons taking coumadin-class anticoagulants (like Warfarin).

That leaves bone and cardiovascular health up to Vitamin K2, which comes in several varieties. K2 is different from K1 and other K2 varieties only by different lengths of the hydrocarbon chain attached. Vitamin K2 (aka Menaquinone-7 or MK7) is the most potent K2 because it stays in the body longer than other Vitamin Ks, and it activates calcium-binding proteins better. This TMI is important for your health and exercise performance! MK4 is utilized by humans much less than MK7, the clear winner in the Vitamin K2 lottery.

Vitamin K2 of any kind is much harder to get from your diet, especially MK7. Unless you eat natto (fermented soybeans) daily, forget about getting enough MK7 to make a difference from your diet. In fact, Vitamin K2 was put on the nutrition map by elderly Japanese who ate daily natto – they showed better longevity, better mental functions, better cardiovascular health and better bone mass than comparable seniors. The difference was tracked down to K2 MK7 in natto. Your gut microbiome also makes K2 varieties, but how much is actually getting into your cells is not encouraging, and some (unhealthy) microbiomes make very little K2. Supplementation of K2 MK7 is by far the best option for reaping its benefits.

Because of the lag of years between scientific discovery, acceptance and regulatory guidelines for food and nutrition, Vitamin K2 has not been considered as essential for clotting (even though it works fine), and so was listed separately from K1 and not given a % Daily Value (as seen on the MultiV label). We recently found we can bundle both K1 and K2 together in the Vitamin K line, meaning both added up provide 100% Daily Value for Vitamin K in MultiV-PRO.

The dose of K2 MK7 in MultiV-PRO is 45 mcg, exceeding the lowest daily amount shown to protect long-term bone and cardiovascular health (Geleijnse 2004; Maresz 2015 21; 2015 34). To ensure that Vitamin K2 MK7 is stable in tablets containing calcium and magnesium salts (like MultiV-PRO), we use K2VITAL® DELTA from Kappa BioSciences, which has been tested to prevent the loss of K2 due to calcium and magnesium salts. We want you to reap the benefits of K2 MK7!

Citations - Vitamins K1 & K2: Geleijnse 2004; Halder 2019; Hariri 2021; Jadhav 2022; Marez 2015 21, 2015 34; Vermeer 2012

Vitamin K2 MK7 & Exercise

Research on Vitamin K2 MK7 has exploded recently, and studies devoted to exercise are increasing. For exercise benefits, human supplementation studies with Vitamin K2 MK7 using doses higher than in MultiV-PRO showed increased maximal heart output during cycle ergometry with lowered lactate. The studies also showed K2 MK7 supported muscle mass and played a backup role in metabolic energy production. Arterial stiffness was decreased by long-term K2 MK7 supplementation in healthy postmenopausal women. Reductions in idiopathic and hemodialysis muscle cramps associated with electrolyte imbalances have been found, but not yet tested for exercise muscle cramps.

MK7 & Bone Mass

Endurance athletes who overtrain are at risk for decreased bone mass. K2 MK7 has shown important benefits for long-term bone health, mostly in postmenopausal women, whereas K1 has not. It remains to be seen if long-term K2 MK7 intakes can maintain bone mass in endurance athletes, particularly in oligomenorrheic and amenorrheic women. Stronger bones are always a healthy option with increased K2 MK7 intake!

Other potential uses are under active investigation, especially for improving circulation during exercise, improving arterial flexibility and even assisting mitochondria in energy production. Also, adequate Vitamin D status is crucial for K2 MK7 to exhibit its biological benefits, and vice versa. Both D and MK7 help your body handle calcium efficiently.

Right now, the science is clear for benefits of K2 MK7 for bone and cardiovascular health. First Endurance is proud to give MultiV-PRO an effective dose of Vitamin K2 MK7 to maintain long-term cardiovascular and bone health.

CITATIONS - Vitamin K2 MK7 & Exercise: Braam 2004; Brancaccio 2022; Crintea 2021; Dahlquist 2015; Jadhav 2022; Knapen 2015; Marez 2015 21, 2015 34; McFarlin 2017; Mehta 2010; Vermeer 2012; Vidula 2022; Volpe 2016; Xu 2022

DO YOU NEED A MULTIVITAMIN-MINERAL (MVM) ... YES!

Yes, you need a comprehensive, well-designed, well-balanced multiple vitamin-mineral with additional benefits – unless you like being mired in metabolic mediocrity. A well-designed MVM can prevent functional insufficiencies from variable dietary intakes and genetic variations, providing sufficient micronutrients for handling surges of need (intense exercise). The trick is to boost what needs boosting without upsetting the balance of nutrient ratios. This takes a deep understanding of nutrition that only comes from experience and familiarity with biological and chemical sciences. This is what MultiV-PRO is and does.

Literature Quotes for why you need an Endurance Multivitam

MVM QUOTES

"The diet of highly trained endurance athletes does not fully meet their requirements and in this situation cannot ensure maximum adaptation to very intense and/or long-duration physical loads. ... Particular attention should be focused on female athletes"
Baranasukas 2015, Abstract

"In conclusion, vitamin-mineral supplementation was found to attenuate cardiac and muscle damage markers, enhance antioxidant levels, and reduce membrane LPO levels in response to 1 month of swim training."
Cavas 2004, p.144
[Note: 30 swimmers (11-13 years old) were given a placebo or One-A-Day Junior MVM, with less number and amounts of nutrients as in MultiV.]

"The absence of an increase in blood levels of cobalamin, folate, zinc and ascorbate during periods of supplementation to the level of the RDA, and the lack of improvement in MVO2 and time to exhaustion during these periods, suggest that the RDA's for these nutrients are insufficient for optimal performance in endurance athletes."
Colgan 1991, p.26
[NOTE: This double-blind, crossover study of 27 endurance runners (men and women) used a One-A-Day type of MVM as the placebo, which in theory should make all subjects replete for essential vitamins and minerals all the time. The intervention was adding extra C, B6, B12, folate, iron, zinc to the RDA intake. This study confirmed that a 100% RDA-level MVM did not affect exercise performance, as echoed by other human studies, and that relatively high doses of hematopoietic MVMs were needed to maximize performance. When switched from high to RDA-level MVM, subjects' performance suffered. This unique study has never been repeated, but answers questions seldom asked by other MVM exercise studies.]

"The results suggest that the initial adaptation to EIMD, associated with RBE [Repeated Bout Effort], modulates the concentration of chemical elements associated with resistance to fatigue (K, Ca, Cl) and to the inflammatory response and glucose metabolism (Zn)."
Dias 2022, p.10

"Also, in a small unpublished study (DiSilvestro, RA), the 3 mineral glycinates used in this study increase plasma readings for the iron used protein ferritin better than a combination of 3 other forms of the same minerals."
DiSilvestro 2017, p. 5
[Note: The 3 mineral chelates were all Albion® minerals: Ferrochel®, Zinc glycinate, and Copper glycinate – Iron & Zinc glycinates are used in MultiV]

"Summarizing previous studies, many researchers have reported that consuming combined minerals and/or vitamins may be more effective way to enhance athletic performance and maintain health especially in athletic population rather than taking minerals or vitamins each."
Lee 2017, p.803

"Substantial and often persuasive scientific evidence does exist to confirm a relationship between the intake of a specific bioactive constituent and enhanced health conditions..."
Lupton 2016, Abstract

"We can conclude that physical training produces a decrease in erythrocyte concentrations of Cu, Mn, Se and Zn, which can cause a decrement in athletes' performance given the importance of these elements."
Maynar 2020, Abstract

"For the past 40 years, data consistently show that Americans have not been and are still not consuming recommended amounts of whole grains, vegetables, fruits, and dairy foods, and to a lesser extent, protein food groups [17]. This translates to significant proportions of the US population who are consuming less than the EAR or AI for essential nutrients even though ~50% of US adults take at least one dietary supplement [32-35]."
McBurney 2021, p.4

IRON QUOTES

"Serum iron concentration increases during endurance running."
Buchman 1998, p.126
[NOTE: Serum iron increases trigger Hepcidin release that sequesters and removes iron to prevent free radical damage, showing how too much exercise can lead to low iron status/function and anemia.]

"Also, in a small unpublished study (DiSilvestro, RA), the 3 mineral glycinates used in this study increase plasma readings for the iron protein ferritin better than a combination of 3 other forms of the same minerals."
DiSilvestro 2017, p. 5
[Note: The 3 mineral chelates were all Albion® minerals: Ferrochel®, Zinc glycinate and Copper glycinate – Iron & Zinc glycinates are used in MultiV-PRO]

"This research supports using iron supplementation in female athletes regardless of their iron status. The literature encourages athletic trainers and physicians to present athletes with the option for the female athletes to begin supplementation during their competitive season regardless of their iron status."
Lamke 2021

"Daily iron supplementation significantly improves maximal and submaximal exercise performance in WRA, providing a rationale to prevent and treat iron deficiency in this group."
Pasricha 2014, Abstract
NOTE: [WRA = Women of Reproductive Age]

"There was a positive effect of iron on aerobic and anaerobic performance."
Shoemaker 2022, Abstract

"Ferrous bis-glycinate"
"Relatively high bioavailability."
"May be less likely to cause GI intolerance than ferrous sulfate, ferrous gluconate, or ferrous fumerate [sic]."
Tom 2008, p.2

"A mineral deficiency may impair performance. In particular, correcting an iron-deficiency anemia will improve aerobic endurance performance."
Williams 2005, p.47

IRON QUOTES

"We conclude that serum and urinary magnesium concentrations decrease significantly, consistent with the possibility of at least transient magnesium deficiency."
Buchman 1998, p.126
[NOTE: serum iron increases trigger Hepcidin release that sequesters and removes iron to prevent free radical damage]

"Magnesium glycine chelates and dimagnesium malate are good choices for improved uptake of magnesium."
Motyka 2008, p.4

"Mg deficiency (MD) is a sequel not only of strenuous effort as reported earlier, but also of attenuated strenuous effort and of prolonged sustained moderate physical training. The significant fall of the mononuclear cell count in the probands indicates impairment of immune response due to MD. Untreated MD implies, in the long-term, a potentially serious health hazard."
Stendig-Lindberg 1999, Abstract
[NOTE: This study looked at chronic training and also a single 80km, 18 hour forced march and found young men had lower magnesium in blood and cells. Importantly and unusually, magnesium content in mononuclear cells from blood (lymphocytes and macrophages mostly), was further decreased by the long-duration exercise event – nobody else has research highly relevant ultra-endurance settings and magnesium status. This and other long-term studies by this author clearly show that magnesium is lost during long-term training and ultra-endurance events, showing that everyday, long-term magnesium supplementation has a solid basis of support – it's a good ideal]

”Supplementation with MagSRT™, a timed-release dimagnesium malate supplement containing vitamins B6, B12, and folate, for at least 30 days significantly improved magnesium status symptoms and increased RBC magnesium with minimal gastrointestinal symptoms.”
Weiss 2018, Abstract
[NOTE: DMM dose was 100 mg Magnesium, same as in MultiV-PRO.]

“Despite higher total dietary magnesium intake, athletes generally have lower serum magnesium concentration and higher 24-h urinary magnesium excretion, demonstrating that the magnesium requirement of athletes is higher than the untrained population.”
Zhang 2023, Abstract

VITAMINS C & E QUOTES

“Prior supplementation of the combination of vitamins C and E attenuates OS (lipid peroxidation), the inflammatory response (interleukin-6), cortisol levels, and muscle damage (creatine kinase) following a session of exercise.”
de Lima 2022, Abstract

“In summary, this study showed that 1) a high intensity resistance exercise bout resulted in significant increases in lipid peroxidation, 2) two weeks of vitamin E supplementation (885mg/day a tocopherol acetate) offers no protection against resistance exercise induced lipid peroxidation”
VIITALA 2004, PP.7-8
[NOTE: Although the exercise was weight training, it was intense, and produced excess free radicals, like exhaustive endurance exercise does. Notice that a very high dose (4425%DV) of only alpha-tocopherol acetate did not show antioxidant activity – a clear case of too much Vitamin E that imbalanced the antioxidant system, an example of too much of a good thing (a single antioxidant) being not good for exercise. Obvious solution is to provide Mixed Tocopherols at same intakes as healthy diets.]

VITAMINS D QUOTES

“According to recent studies, vitamin D deficiency reduces muscle function and strength, and can increase the risk of fractures due to stress and diseases that may have a detrimental effect on training and performance.”
BRANCACCIO 2022, P.6

“Researchers suspect that levels above 50 ng/ml are required for athletes to achieve maximal physical performance.” … “This concentration is associated with a protective effect and enhancement of physical performance.”
BUTSCHEIDT 2017, ABSTRACT
[NOTE: VITAMIN D BLOOD SERUM LEVELS, EASILY DETERMINED BY A BLOOD TEST REQUESTED BY YOUR DOCTOR]

“Furthermore, it is possible that dosages exceeding the recommendations for vitamin D … in combination with 50 to 1000 mcg/day of vitamin K1 and K2 could aid athletic performance.”
DAHLQUIST 2015, ABSTRACT

“The data indicated that adequate vitamin D intake contributes to the health and athletic performance of athletes.”
FENG 2023, P.9

"Prevalence of vitamin D insufficiency (<= 50 nmol/L) in elite athletes is high, ..."
HARJU 2022, ABSTRACT

"Vitamin D has documented effects on muscle regeneration through mechanisms and biological pathways that mainly depend on the interaction with the pool of satellite cells within muscle and that are particularly active during recovery from a traumatic event to enhance the structural and functional restoration of the muscle."
IOLASCON 2021, P.6

"Vitamin D deficiency is highly prevalent in athletes."
IP 2022, P.27

"For those who train intensely on a regular basis and might occasionally overdo it, pro inflammatory cytokines (tumor necrosis factor-alpha and interleukin-6) are increased when vitamin D levels are insufficient. The anti-inflammatory effects of vitamin D include decreased prostaglandin synthesis and decreased musculoskeletal pain."

"Female athletes appear to be especially sensitive to vitamin D deficiency. ...41% were actually categorized as deficient."

"...vitamin D supplementation appears to be essential for optimal athletic health and muscle performance."
WOJTYS 2021, P.110.

"...exposure to sunlight and dietary intake may not be sufficient for vitamin D synthesis; in such cases, vitamin D supplements may be helpful."
YOON 2021, P.23

VITAMINS C & E QUOTES

"...vitamin K is a leading player in the blood clotting process and ensures the functionality of proteins involved in bone remodeling. Low levels of this vitamin have been associated with increased bone turnover and fracture risk."
BRANCACCIO 2022, P3

"Through its involvement in cardiovascular and nervous system function, and bone metabolism, vitamin K supplementation could improve exercise capacity."
CRINTEA 2021, ABSTRACT

"Furthermore, it is possible that dosages exceeding the recommendations for vitamin D ... in combination with 50 to 1000 mcg/day of vitamin K1 and K2 could aid athletic performance."
DAHLQUIST 2015, ABSTRACT

"Various clinical trials for determination of the appropriate dose of vitamin K2 have been performed; also its bioavailability and efficacy have been investigated ... Further, in many trials, vitamin K2-7 is combined with vitamin D as an intervention to augment the beneficial effects."
JADHAV 2022, P.21

"...vitamin K2 is associated with the inhibition of arterial calcification and arterial stiffening. An adequate intake of vitamin K2 has been shown to lower the risk of vascular damage ..."
MARESZ 2015 21, ABSTRACT

"The fact that under-carboxylation of key Gla-proteins is common in the general population suggests that increased vitamin K intake may be an important factor in improving public health."
VERMEER 2012, P.4

"...it seems that a low vitamin K intake may relate to a high bone turnover in athletes."
VOLPE 2016, P.33

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MULTIV-PRO ADDITIONAL NUTRIENTS & EXERCISE

1. LEVAGEN®+ with LIPISPERSE®

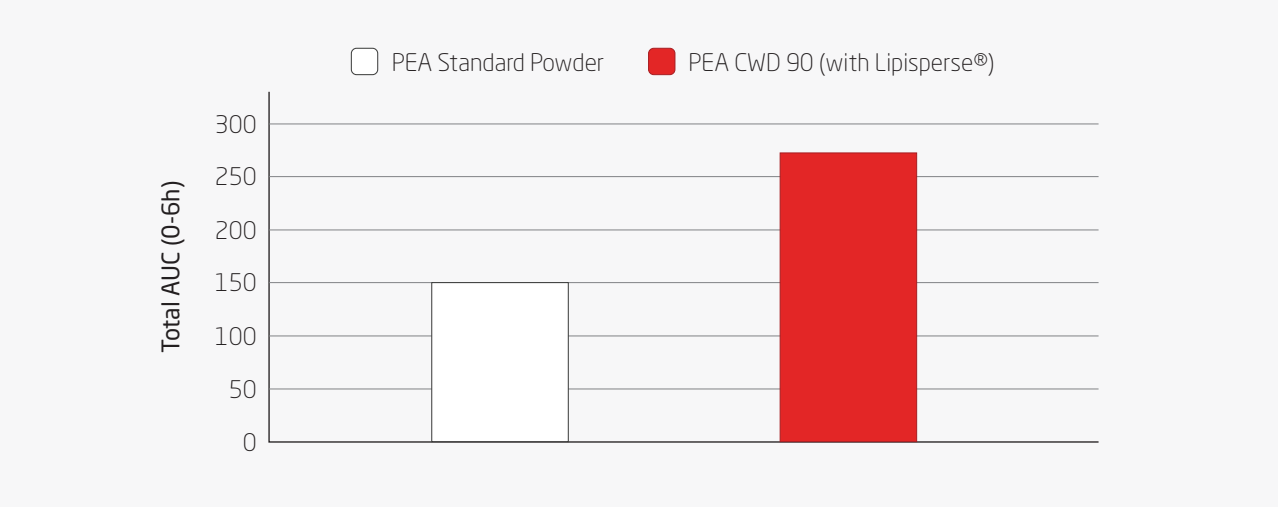
ENHANCED-ABSORPTION PEA "ENDOCANNABINOID" FOR EXERCISE PERFORMANCE, RECOVERY AND ANTI-STRESS PROPERTIES

Levagen®+ is one of the Beyond MVMs ingredients in MultiV-PRO. Levagen®+ is something completely different than anything else nutritional for handling physical stress, and something your body is very familiar with and knows how to reap the benefits of. Simply put, Levagen®+ is the best oral form of PEA, aka PalmitoylEthanolAmide. PEA is the instigator and facilitator of an entire powerful signaling system in our bodies that few have heard about, but which we cannot live without. Levagen®+ from Gencor® is a stabilized, pure form of PEA to ensure reproducible quality, quantity and results. MultiV-PRO provides a clinically tested dose of Levagen®+ with Lipisperse® that matches human studies.

Levagen®+ (90% Palmitoylethanolamide (PEA) with 10% Lipisperse®)6 300mg

[6] Levagen®+ is a registered trademark of Gencor registered in the USA and other countries.

Lipisperse® is a patent-pending delivery technology from Pharmako Biotechnologies Pty Ltd, that increases bioavailability of Levagen®+ PEA to ensure it is utilized properly and also to reduce the size needed per dose. PEA is an unusual lipid (fat) compound and thus has slow absorption, either stifling its beneficial properties or requiring repeated large doses (600 mg or more) daily. Lipisperse® with Levagen®+ has human clinical results to show rapid absorption of PEA (~45 minutes for peak blood levels with a long half-life in the blood of eight hours) and delivers 1.75 times more PEA than umPEA (ultra-micronized PEA) (Briskey 2020).



Lipisperse® is a proprietary combination of polyglycerol polyricinoleate, fractionated coconut oil, citrus oil, olive oil, sunflower lecithin and Vitamin E acetate (Levagen®+ also has colloidal silicate to keep it a free-flowing powder). All ingredients are from plant sources and acceptable for EU food use.

Citations for What Is Levagen®+ with Lipisperse®: Briskey 2020

LEVAGEN®+ EXERCISE PERFORMANCE BENEFITS

PEA = RUNNER'S HIGH: GETTING HIGH ON EXERCISE WITH PEA 'NEUROBIOLOGICAL REWARDS'

Let's get right into why Levagen®+ is in MultiV-PRO – to help you maintain and extend peak performance. Human research has not caught up yet on studying whether or not PEA supplementation can help you be faster, longer, stronger. Those studies are ongoing at this moment. But we have something even better: PEA is the newly anointed cause of the famed "runner's high" – not endorphins. That's right – it's not endorphins anymore and never was – the stake in the feel-good endorphin heart was a study that gave naltrexone to completely block opioid (endorphin) effects – and exercisers still reached the "runner's high" (Siebers 2021). Instead of endorphins, PEA and its N-acylethanolamine (NEA) family are why exercising literally makes you feel better, encouraging more exercise. So next time you come back from an invigorating run feeling great, you can say you released your PEA! And get weird looks if you pronounce PEA like the vegetable, not like Pee Eee Ay.

The stress of aerobic exercise is known to induce a "second wind" or a "runner's high" of euphoria, pain reduction, and improved mood. Initially attributed to endorphins, that has pivoted to being caused by PEA and its NEA family (Dietrich 2004; Matei 2023; Tantimonaco 2014). Numerous human studies of the proper intensity (70-80% maximal heart rates) and duration have found increased blood levels of PEA and other NEAs during and after prolonged aerobic exercise (Brellenthin 2017; Cedernaes 2016; Dietrich 2004; Feuerecker 2012; Heyman 2012; Jurado-Fasoli 2022; Matei 2023; Mourtakos 2021; Raichlen 2012, 2013; Sparling 2003; Stensson 2019; Tantimonaco 2014; Watkins 2018).

For example, intense, stressful cycling exercise for 90 minutes increased PEA and other NEA levels in the bloodstream, mirroring the increase of RPE (Ratings of Perceived Exertion) (Heyman 2012). Daily, long-term, severe exercise (Greek Navy SEAL training for 13 days) showed increases in PEA, along with an increase in Heart Rate Variability (HRV), a positive adaptive response to stress (Mourtakos 2021). The biggest increases in runner's highs were from prolonged aerobic exercise, and adding hypoxic (altitude) conditions caused further increases. PEA as Levagen®+ with Lipisperse® justifies its inclusion in MultiV-PRO by activating internal antidotes to endurance exercise stress and keeping your head in the game.

PEA Stimulates Training Adaptations to Exercise

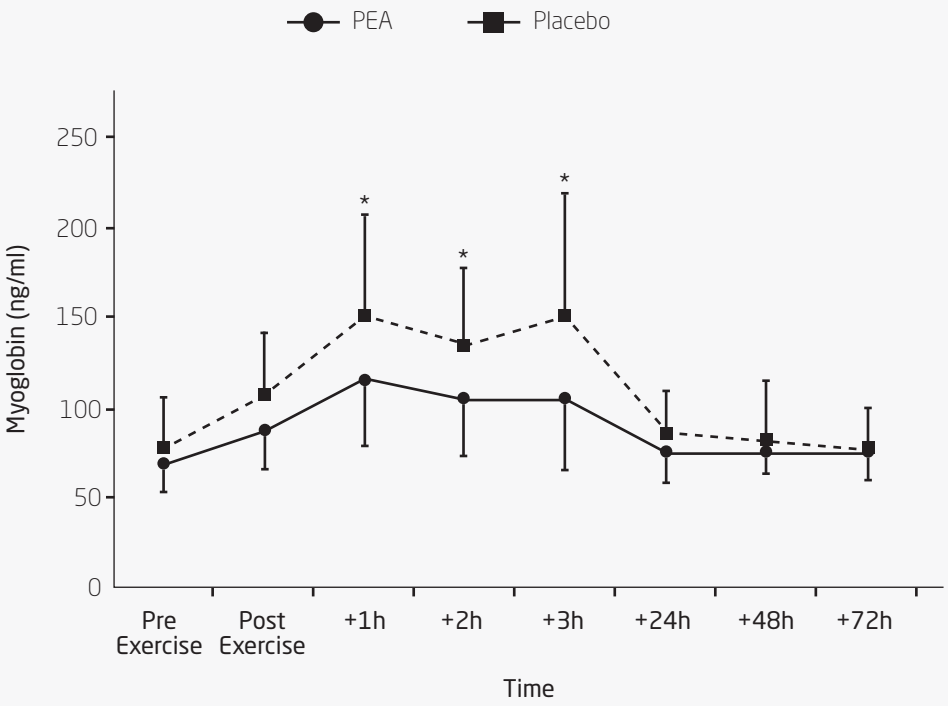
Additional effects of increased endogenous levels of PEA/NEAs during exercise were increased glucose uptake, increased fat oxidation and mitochondrial biogenesis (more mitochondria = more energy) – positive effects for increasing immediate exercise performance. Long-term effects to increase energy intake (hunger), promote energy storage (glycogen and fat) and decrease cost of energy expenditure (Kunos 2008) instigated by PEA is training adaptation. Thus, PEA helps immediate exercise needs and sets up ways to adapt to exercise stress over time, commonly called training effects. That equals performance improvements to your maximal potential.

The goal of Levagen®+ is to add to the normal increase of PEA/NEAs during and right after exercise for increased/prolonged performance, better recovery and continued training adaptation – that's how exercise performance is maintained and improved.

Levagen®+ & Exercise Recovery

Recovery after exercise is part of the adaptation to training, and if PEA has the effects already noted during exercise, then recovery should be improved by adding more PEA. An acute exercise recovery study used leg press exercise to induce muscle soreness and increase muscular damage biomarkers (Mallard 2020). Levagen®+ with Lipisperse® at a dose of 167.5 mg daily or placebo was given before, immediately after, 24 hours after and 48 hours after exercise.

Mean power decreased during the sets similarly for each group, and muscle soreness and thigh circumference were also not different between groups for 48 hours. Myoglobin levels circulating in the bloodstream were lower in the Levagen®+ group the first three hours immediately after exercise. A significant and rapid decrease of myoglobin after strenuous eccentric exercise indicated that acute dosing of Levagen®+ pre- and post-exercise exhibited anti-stress effects by reducing a biomarker of muscle tissue damage.



Blood lactate was slightly lower during the same time period for the Levagen®+ group. Other biomarkers of muscle damage (hsCRP, Creatine Kinase, LDH, IL-6, IL-10 and TNF-alpha were unchanged from pre-exercise levels and between groups. The dose of Levagen®+ was lower than other successful studies and most measures were not changed by the exercise, meaning there was not enough exercise stress to trigger a more significant PEA response – either intensity or duration – and no need for more PEA. This study also shows the wisdom of giving Levagen®+ over time to produce results, as longer-term studies have shown, instead of acutely before and after exercise. Your body needs to build up the downstream resources to take advantage of additional PEA.

Another important road to recovery is a good night's sleep. Levagen®+ has shown improved sleep in normal subjects by getting to sleep faster and waking up more refreshed and with improved cognition (Rao 2021). Sleep patterns are worsened by pain, unfamiliar settings (road travel), snoring companions and overall stress – all applicable to traveling for competition – and Levagen®+ helps sleep in many ways, always a component of exercise performance and recovery.

Another important feature of PEA is that PEA is normally occurring in humans and is not a banned substance for athletic training. Ingredients in Lipisperse® are not banned substances and are common components of foods and the human body. Conversely, natural Cannabis and Cannabinoids (especially THC), excluding CBD, are specifically prohibited (CBD alone has recently been exempted) (WADA 2021). But CBD products are rarely pure CBD – they still have a serious risk of contamination with THC and other banned cannabinoids and cannot be depended on to pass drug testing.

Citations for Levagen®+ Exercise Performance Benefits: Brellenthin 2017; Cedernaes 2016; Chiurchiu 2016; Dietrich 2004; Feuerecker 2012; Heyman 2012; Huschtscha 2023; Jurado-Fasoli 2022; Kunos 2008; Maccarrone 2015; Mallard 2020; Matei 2023; Mourtakos 2021; Raichlen 2012, 2103; Rao 20231; Siebers 2021; Sparling 2003; Stensson 2019; Tantimonaco 2014; WADA 2021; Watkins 2018

Levagen®+ & Musculoskeletal System Comfort

Minor musculoskeletal aches and pains are common in ultraendurance athletes. Levagen®+ effects on joint comfort have been studied twice. In the first study, 111 middle-aged adults with achy knees were given placebo, 300 or 600 mg Levagen®+ for eight weeks (Steels 2019). At 300 mg Levagen®+ daily, there were significant improvements vs. placebo for joint comfort and stiffness after eight weeks, with gradual reductions weekly. Also, other analgesic medications (acetaminophen) were greatly decreased (from 2 to 0.5 times weekly) but the placebo group kept up their usage (3.0 to 2.8 times weekly). Also, after eight weeks, 300 mg Levagen®+ daily reduced anxiety scores compared to placebo. The 600 mg Levagen®+ group had slightly larger improvements compared to the 300 mg group that were not significantly different.

In the second study, 80 healthy adults with joint discomfort were given either placebo or 350 mg Levagen®+ with Lipisperse® for two weeks (Briskey 2021). By 14 days, joint comfort was improved significantly more by Levagen®+ (twice as much) than placebo, both morning and evenings. Also, mood was improved by Levagen®+, but not by placebo.

The studies on Levagen®+ showed similar results to other human studies of musculoskeletal discomfort that used higher daily doses (600-1200 mg) of regular or micronized PEA. One lesson from these studies was the improvement over time (weeks), thus meaning that long-term use of MultiV-PRO with Levagen®+ helps ensure meeting this requirement for feeling better. Although effects of Levagen®+/PEA on endurance athletes with achy bodies have not been specifically studied, part of what PEA normally does is to tone down pain from stressed nerves by a multifactorial downregulation of nociceptive pathways (how pain is felt). In other words, PEA works universally to improve any and all conditions the human body encounters. More on this later – read on!

Citations for Levagen®+ & Musculoskeletal Health: Alshelh 2019; Artukoglu 2017; Briskey 2021; Chirchiglia 2018; Clayton 2021, 2023; D'Amico 2020; Esposito 2013; Evangelista 2018; Gabrielsson 2016; Gatti 2012; Germini 2017; Keppel Hesselink 2013 1, 2013 625; 2014; Lang-Illievich 2022, 2023; Maccarrone 2015; Marini 2012; Paladini 2016; Santonocito 2023; Scuteri 2022; Steels 2019; Tantimonaco 2014; Tsuboi 2018

Immune Support from PEA

PEA is everywhere and has known mechanisms of action affecting important cell receptors to mediate antistress effects. The immune system is everywhere, is involved in responses to stress and has the receptors that respond to PEA. Given that, it stands to reason that PEA supports the immune system. Human studies of PEA supplementation since the 1940s back that up, showing immune support. (Coburn 1943, 1960; Kahlich 1979; Masek 1974; Plesnik 1977; Wiehdermannova 1977; 1978).

Citations for Levagen®+ & Immune Support: Berdyshev 2000; Cabral 2005; Chiurchiu 2015, 2016, 2018; Clayton 2021, 2023; Coburn 1943, 1960; Joshi 2019; Kahlich 1979; Keppel Hesselink 2013 625, 2013 151028; LoVerme 2005; Maccarrone 2015; Masek 1974; Matias 2002; Plesnik 1977; Suarez-Pinilla 2014; Tsuboi 2018; Wiedermannova 1978, 1979

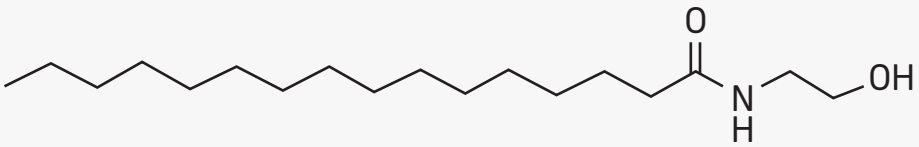
Levagen®+ Summary

Levagen®+ is PEA in a stable form that's well-absorbed because of Lipisperse® and well-suited for dietary supplements, with human clinical support that repeats and adds to decades of human study findings for a wide variety of uses and effects, especially deviations from normality – aka stress. Levagen®+ works to restore homeostasis, which indirectly affects everything. For exercisers, this can be felt as the runner's high and better recovery, but there are also other benefits: supporting immune function, reducing unwanted inflammation, providing energy where needed, improving mood and reducing everyday, stress-induced musculoskeletal pain to manageable levels. These changes manifest as better performance during endurance exercise, better recovery from strenuous exercise, and a faster, stronger training adaptation.

Get Familiar with PEA - The Active Part of Levagen®+

Chemically speaking, Palmitoylethanolamine (PEA) is a fatty acid amide (N-acylethanolamides or NAE), a comparatively simple biomolecule with very big effects. PEA is a member of a small group of endogenous lipid mediators with widespread, powerful and basic signaling properties. PEA has always been naturally occurring in your body and some foods in small amounts. PEA is the ruler of a family of related molecules that are extremely important and overlooked instigators and facilitators of most bodily functions. Its chemical structure looks like a key, and that is exactly how PEA works – unlocking normal healing and reparative processes and locking pathways that are causing inflammation, when and where needed by activating a network of receptors common to all cells.

Palmitopylethanolamine (PEA) Structure



Palmitic acid (Palmitoyl-) Ethanolamine

Chemical structure of PEA – the slash line shows the two parts. Other fatty acids replace palmitic acid to make other PEA family members.

PEA is also found in most foods in tiny amounts, but is at decent amounts in fatty parts of eggs (yolks), soybeans and peanuts. Notice that foods with PEA are associated with healthy properties.

Food Sources of Palmitoylethanolamine (PEA)

Major Sources

Egg yolks (whole eggs)
Soybeans (soy lecithin)
Peanuts

Minor Sources (in Alphabetical Order)

Alfalfa	Apples
Beans (Black-eyed Peas, Kidney, Lentils)	Coffee (Roasted)
Corn	Pea (Garden)
Potato	Tomato

PEA's molecular family includes OEA (oleolyethanolamine), Anandamide (AEA, ANA or arachidonoylethanolamine aka the Bliss Molecule), stearoylethanolamine (SEA), 2-arachidonyl-glycerol (2AG) and others as a family of co-dependent, interactive, and extremely important signaling molecules.

Citations for Get Familiar With PEA: Alhouayek 2014; Carbal 2005; Clayton 2021, 2023; Darmani 2005; de Melo Reis 2021; Joshi 2019; Keppel Hesselink 2013 1, 2013 625; 2014; Kuehl 1957; Kunos 2008; Lambert 2002; Ligresti 2016; Lu 2016; Maccarrone 2015; Petrosino 2016, 2017, 2018, 2020; Piomelli 2020; PubChem 2023; Rahman 2021; Rankin 2020; Rezende 2023; Tsuboi 2018

PEA & Levagen®+ - First Responder to Stress

PEA and the NEA family of lipid mediators is your body's first line of defense against stress – especially physical stress. Anything that perturbs your normal, happy bodily functioning is considered a stress to be dealt with, and the Endocannabinoid System (ECS), including PEA, is like your body's EMTs. They are made on demand, wherever stress changes something, and in proportion to the stressor. This is why Levagen®+ works better when exercise stress is more severe. The ECS is a measured response – just the right amount of signaling other responses to fix what is found.

PEA and its family activate a lot of other systems and processes in cells, tissues, organs and even the whole body as necessary. This means PEA instigates and facilitates an expanding web of body processes favorably to maintain health, including physical function and mood. Studying this very complex process has had scientists chasing their tails and only now is the magnitude and importance of the ECS becoming clearer. Let's understand this process better!

PEA - Antistress How & What

PEA is the tip of the iceberg for the Endocannabinoid System (ECS), and coordinates the multitudinous effects of a family of similar NAEs (N-acylethanolamides), allowing for exquisite, fine-tuned control over many basic bodily responses, including growth, energy metabolism, control of normal inflammation, nervous system regulation, and coordination interaction with other signaling systems (e.g., hormones, eicosanoids, growth factors, etc.).

PEA and its family of related compounds are present in tiny amounts in our bodies, and they are quickly made and destroyed as needed by a series of ever-present enzymes, meaning they hid from researchers for decades before being discovered as a vital and interconnected signaling system. Because of the sticky lipid chemical structure of PEA and its family members, they can quickly move around your body, get to cells, get inside cells, and activate very specific receptors deep inside cells, especially the nucleus.

PEA commands and controls biological homeostasis of everything everywhere. This allows a unique, responsive and robust signaling system to influence important biological actions with assurance of the messages being followed and results controlled to maintain overall health. The simple complexity of this signaling system allows almost limitless ability to control the location, volume, extent and duration of signals in order to enact a seamless amelioration of stressors of all kinds, on demand, anywhere, anytime.

Important: PEA is made by your body on demand. Any sign of molecular damage triggers production (synthesis) of PEA locally at that site. It is made in situ (on-site) from the injured cell's membrane and quickly spreads to its neighboring cells. If the damage is all over your body, blood levels increase too, as we saw increases of PEA/NEAs accompanying stressful exercise (above). Signals of cell damage, such as cell structure pieces, oxidative damage pieces and free radical levels, initiate the PEA production process. Cells take one of the numerous membrane phospholipids that have a palmitic acid, and like a chop shop, a sequence of enzymes separate the other fatty acid and phospho- group, and adds an ethanolamide to make PEA (same process is used to generate other N-acylethanolamides).

PEA is a pro-homeostatic protective response (Clayton 2021). PEA is a facilitator and instigator. PEA immediately activates resources to remedy a problem (deviation from normal) by connecting with many departments and groups our bodies use to maintain healthy function (homeostasis). The size of the insult determines the size of the response. Continued or repeated insults can keep PEA going. And PEA listens to feedback and slows down or stops when homeostasis improves.

PEA Works Precisely with Important Receptors on and in Cells

Unbeknownst to PEA researchers until the mid-1990s, PEA exerts its influences by activating a variety of Receptors (proteins on membranes that specifically fit a certain molecule, causing a cascade of effects). PEA binds to key receptors that are control nodes for metabolic processes – once activated, an entire chain of events happens to enact important functions in cells that affect tissue, organ and eventually, whole body health. This is how our bodies control energy metabolism, oxidative stress, and anti-inflammatory processes everywhere on a big scale.

PEA signals multi-faceted effects by targeting multiple receptors directly that each act as nodes to start a cascade effect, putting out an "all hands on deck" signal locally (nearby cells and tissues). Because PEA is fat-soluble and water-soluble, PEA has Diplomatic Immunity and is given a free pass to travel inside of cells, and outside of cells via the bloodstream, lymphatic vessels, activating cells in nearby or faraway tissues if the insult is big enough. PEA travels through the internal membrane structures inside each and every cell, so it can get to specific receptors anywhere, anytime. PEA is a facilitator and instigator.

PEA's Superpower is being a super-multitasker, affecting all the reasons for stopping problems and all the ways to fix problems – everyone in the body listens. The only drawback to this elegant, interactive system is if the other parts of the body are dysfunctional, whether by genetics or nutritional deficiencies. All the more reason to add PEA to a MVM.

A primary PEA receptor target is nuclear PPAR-alpha (Peroxisome Proliferator-Activated Receptor Alpha). PPAR-alpha tells that cell to make more peroxisomes (tiny intracellular factories with their own membranes and tools such as enzymes that create/destroy in order to ascertain/fix cell damage). Peroxisomes come and go as needed, with PE as the instigator to make more or less Peroxisomes.

PEA also activates other receptors for a well-rounded homeostatic effect. PEA does activate CB2 stronger than CB1, and since CB2 receptors are located more on immune cells, PEA has anti-inflammatory effects. By increasing Anandamide levels, PEA also has analgesic effects. PEA is a facilitator and instigator. The G protein-coupled receptor 119 (GPR119), the newly found cannabinoid receptor G protein-coupled receptor 55 (GPR55) and vanilloid receptors (TRPVs) are other direct targets of PEA to trigger cascades of reparative processes and metabolic energy production/utilization to fuel those processes.

PEA works much like the CEO of a large company, who gives simple orders to several Department Heads (Fix this! Stop that!), who give orders to dozens of Department Section Heads, who give orders to many Supervisors, who then give orders to a lot of Team Leaders, who tell the numerous worker-bees what to do. No PEA and no orders from the CEO means the body's worker-bees sit around on permanent breaks or go home, loitering until (or if) they get a work order. The CEO can also tell anybody else in the company what to do, or do something themself. If there is not enough help, the CEO can hire more worker-bees. The PEA CEO also listens to employee feedback and suggestions and enacts their learnings and hands-on wisdom for the whole company (you).

And here comes one of many links to family interaction for PEA – PEA specifically inhibits the breakdown of anandamide (AEA), which is another endocannabinoid that activates cannabinoid receptors 1 and 2 (CB1 & CB2) and other NEAs. Those healthy effects that would not happen without PEA. Again, PEA is a facilitator and instigator.

Usually, other NEA family members are generated simultaneously with PEA, an efficient way to spread, amplify or slow down the signals and actions – 'autocoidalmatically.' [2] The ability of PEA to interact and boost the levels and/or functionality of other NEAs (like Anandamide) is another positive feature of PEA – if it can't help, it can get other NEAs to help. These intricacies are critical for how PEA works, but that interactive network complexity stymied research in the field until the late 1990s.

Citations for PEA - Antistress How and What: Alhouayek 2014; Cabral 2005; Chiurchiu 2018; Clayton 2021; D'Amico 2020; Darmani 2005; De Fillippis 2008; de Melo Reis 2021; Esposito 2013; Gabrielsson 2016; Joshi 2019; Keppel Hesseink 2013 1, 2014; Lambert 2002; Lang-Illievich 2023; Ligesti 2016; Lu 2016; Maccarrone 2015; Paladini 2016; Peritore 2019; Petrosino 2017, 2020; Rankin 2020; Rezende 2023; Scuteri 2022; Skaper 2015; Tsuboi 2018

Levagen®+ and PEA Summary

Now you know that Levagen®+ is absorbable, clinically tested PEA. And you have an inkling that PEA is the tip of the iceberg of an elegant, all-encompassing, extremely important antistress system that silently but strongly operates all over your body to keep you in good shape and healthy, ready for your nest stressful events. PEA works by orchestrating your body and cells to fix what is not working right. That means working with your normal maintenance and repair pathways and processes, and that can take time to build up all the components so results are faster and stronger. A few weeks is needed for PEA and Levagen®+ to keep your systems maximal. Then all sorts of benefits can manifest and become noticeable.

This antistress response is operative during stressful exercise – a jog around the block will not elicit enough damage for Levagen®+ to make everything better. But work hard enough, and you will feel the difference, because Levagen®+/PEA is the innate, natural source of "runner's high" – telling your brain you are doing something good and healthy and getting the right amount of exercise. Generally, feeling good during long-duration exercising is also good for moving faster, moving easier and finishing stronger. With continued use, Levagen®+ can improve training adaptation and recovery from exercise, which means increased performance via your normal physiological mechanisms. This also includes notoriously slow-responding musculoskeletal tissues. You feel better because you are in a better mood, but more importantly, because your tissues are optimized. At the same time, Levagen®+/PEA is working with your gut and immune system to ensure you stay healthy and can avoid deficits from exercise and other stressors.

Nothing is a panacea, but Levagen®+ comes close enough, and is a perfect complement to a comprehensive, exercise-targeted MVM like MultiV-PRO. A large and growing scientific database is continuing to explore and understand the beautiful complexity of Levagen®+/PEA as the key cog in this elegant system named the ***Endocannabinoid System*** (ECS).

WAIT! Did I say Endo***cannabinoid*** System? As in marijuana, pot, hashish,THC, CBD, etc.)? Yes I did. Huh?

Levagen®+ works via the Endocannabinoid System

The way Levagen®+, PEA and the NEA family of N-acylethanolamides works is named after the active agents in Marijuana (Cannabis sativa). What is going on? How did that happen? Does not make sense! PEA/NEAs are not Cannabinoids, right? Right!

The explanation is Timing Is Everything. ***In a strange quirk of Nature, the hallmark, unique, active Cannabinoid compounds in hemp/marijuana (THCs and CBDs) activate many of the same receptors meant for and used by PEA and its NEA family.***

[2] We made up this portmanteau wordbash that also fits exactly what PEA and its NEA family of signaling molecules do – innate, interactive control and fine-tuning of bodily processes (preprogrammed do-it-yourself-control) – aka Automatic Autocoids.

Heavy stuff, man, but what is the timing all about? By a quirk of human scientific exploration, research on Cannabinoids made all the big discoveries about the Endocannabinoid System before PEA/NEAs were a blip on the scientific map. Science had a case of Reefer Madness, trying to figure out why Marijuana was so popular and so feel-good in spite of legal and regulatory persecution. Unlocking that Secret of Nature would lead to countless fortunes from pharmaceutical use of synthetic, legal cannabinoids. Long story short – it was quickly determined that THC and CBD were the players for Marijuana effects – euphoria (feeling good), hyperphagia (the Munchies), Somnolence (sleepiness), etc. THC is the psychoactive Cannabinoid, but CBD is the silent Cannabinoid (although it does have some psychoactive effects that might be mediated by the ECS itself). Both THC and CBD activate the ECS.

Unfortunately, and against all the rules of logic and scientific rationalism, PEA/NEAs were also named Endocannabinoids, even though PEA/NEAs are most definitely **not** Cannabinoids, and Phytocannabinoids (the proper term for THC & CBD) are most definitely **not** PEA/NEAs.

To say the aberrant, illegitimate, illogical, incorrect and wrongheaded naming of such important bodily processes and their activators is confusing and misleading is painfully obvious, but again, the coolness factor for Marijuana trumps even science. Or the too-late-to-stop-the-runaway-train-of-promise-of-pharmaceutical-profits trumps even Cannabis sativa.

Regardless, much of the inner workings of the ECS were worked out by Cannabinoids THC and CBD. When the real Endocannabinoids (PEA/NEAs or eCBs) were finally characterized, it was too late to change all the naming and years of scientific publications. Plus, the Cannabinoid System just sounded cooler and hipster, compared to pro-homeostatic protective response lipid mediators (PHPRLIMs, or PEA/NEAs). [NOTE: scientists, in spite of mostly being nerds, are always trying to be cool and hip.] In other words, we have to follow the herd and use the lexicon for Cannabis in order to keep explanations and interpretation of the science easier.

PEA versus Cannabis CBD - A Tale of Two Compounds

CBD can mimic (hijack!) the ECS receptors like CB1, CB2 and others named above, and have similar analgesic, anti-inflammatory and pro-healing properties and benefits. In fact, CBD has recently been approved as a drug to treat rare forms of infantile epilepsy, although it has not delivered success in childhood and adult epilepsy. And THC (as Marinol or dronabinol) has been an approved pharmaceutical drug for easing pain and increasing appetite in cancer patients treated with cytotoxic treatments since 1985. However, despite many attempts, THC has not progressed further as drug, Rx or OTC, because of its own side effects and toxicity.

Interlopers or Interdopers?

Cannabinoids (CBs) is the catch-all name for the family of dozens of closely related terpene derivatives found almost exclusively in Cannabis sativa (hemp & marijuana) plants. After their discovery and characterization, any compound that activated the same receptors that Cannabinoids activated were named Cannabinoids too, including PEA/NEAs.

Notice how closely related CBD is to THC by chemical structure in the stick figures below. CBD does not have the psychoactive properties of THC, and has different activities. The difference between CBD and THC hinges (literally) on a chemical bond oddity, here called a "flip-flop" bond (tautomer), indicated by the arrow in the Figure below.

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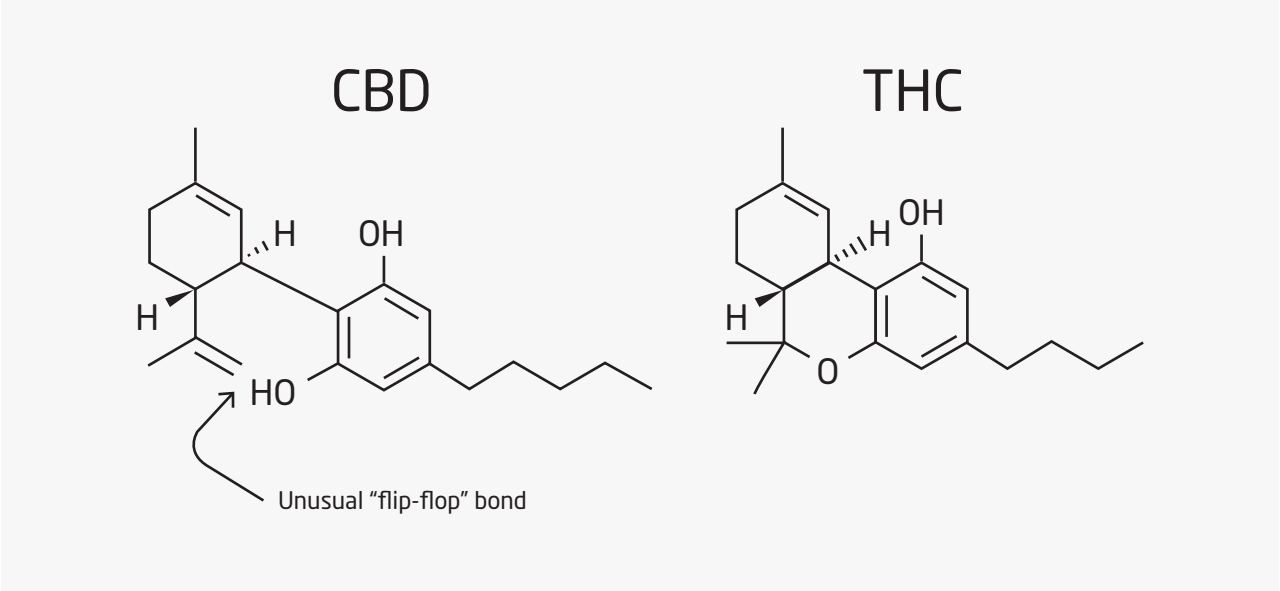
[3] THC = Δ9-Tetrahydrocannabinol, CBD = Cannabidiol



This odd bond means CBD has a bipolar personality, chemically. That bond can form a closed ring, like THC, but normally exists as the open –OH group form, thus being called open Cannabidiol (CBD).

Why should we care about CBD structure if it "works" like PEA/NEAs? Because CBD has a Dark Side that PEA/NEAs will never have.

Citations for PEA Versus Cannabis: Berdyshev 2000; Howlett 1995; Huestis 2011, 2019; Joshi 2019; Ligresti 2016; Lim 2023; Lu 2016; Nelson 2020; Petrosino 2016, 2017, 2018, 2020; Rezende 2023; Schurman 2020; Smith 2023; Stout 2014; Williamson 2020; Zendulka 2016; Zou 2018

CBD / PEA Differences - CBD is not an *Endo*cannabinoid - CBD is a Phytocannabinoid, Period.

Bottom line: CBD controls you, PEA/NEAs are controlled by you. CBD alters your normalcy. PEA/NEAs keep you functioning normally. In other words, CBD has some serious limits and out-of-bounds effects well-mannered PEA/NEAs do not have. CBD is like forcing you to eat cake at every meal. PEA/NEAs gives you a balanced and healthy diet. Both will make you feel good, but which is better for you in the long run? Ultimately, CBD means toxicity. CBD chemically cannot do everything PEA/NEAs do for you, and it can do harm that PEA/NEAs cannot do. Here's how.

CBD is a single molecule that happens to indiscriminately activate a wide range of receptors producing activities shared by your body's real ECS that utilizes the interplay of a dozen or more NEAs. The chemical structures of CBD and NEAs are radically different. Both types have similar effects, but they are not the same in more ways. Simply look at the differences of the chemical structures – they are not handled equivalently by the human body.

CBD is very fat-soluble, with no water solubility like PEA. That hampers its uptake and distribution into the human body, necessitating a higher dose than PEA for similar effects that overlap. That also means CBD has to be taken more often – continuously and repetitively every few hours, which has dose, compliance and exorbitant cost issues. On the other hand, once-daily dosing is workable for PEA and has superior compliance than multiple doses daily.

Because of CBD's chemical structure, it does not have the same systemic (bodywide) effects as PEA. Being more fat-soluble, CBD accentuates ECS neurogenic (nervous system) effects, meaning it emphasizes the brain effects also seen for PEA (pain reduction) but does not have the same effects as PEA throughout the body. This becomes important for immune system support, musculoskeletal healing and muscular (exercise) performance. For example, muscles do not take up CBD, but muscles are loaded with PEA/NEAs. Effects on your gut, gut microbiome and liver metabolism are different between CBD and PEA/NEAs.

CBD activates most of the receptors that PEA/NEAs activate, although with differing potencies and durations. CBD activates the CB1 and CB2 receptors, which PEA does weakly, but PEA controls Anandamide levels that do directly and more efficiently activate CB1 and CB2 receptors exactly when and where needed. Since CB1 receptors are mostly in the nervous system, their activation reduces perception of pain (analgesic actions) and helps reduce neuroinflammation. This explains how CBD and PEA can be used for the same conditions such as analgesia (pain reduction).

PEA works not only by itself on other specific receptors in all tissues of the body (especially PPARalpha receptors), but PEA also activates and controls the other PEA family compounds. The differential receptor binding potencies of PEA and CBD means that PEA has more actions, and thus has more immune support and tissue reparative effects than CBD. Whereas CBD might make you feel better, it more than likely will not help you repair, recover and get better faster.

Clinical studies on CBD have been carefully manipulated (like stacking a deck of cards) and performed in order to prevent lapses in blood levels, something which is difficult to translate into benefits for long-term, everyday usage. This means that what is studied about CBD is not easily attainable in real-life, unlike PEA. For example, if you take PEA before bedtime, it has remained in your bloodstream and only fallen by half when you wake up. CBD at bedtime? It's gone when you wake up.

CBD does have notable effects from a burgeoning number of human clinical studies. CBD has become an approved pharmaceutical drug for treatment of rare infant epilepsies at carefully controlled dosages, something that is beyond what supplements can or should do. But adult epilepsy studies have not been as successful.

CBDs do have some antioxidant activities that could account for some or most of the actions attributed to them. That explains why CBDs are (so far) on a par with individual plant polyphenols (quercetin and curcumin, for example) for treatment of human conditions – some benefits but not always helpful.

Overall, CBDs have not fared as well as expected when compared to a placebo with non-painful conditions. This is partly because CBD cannot do all of what PEA can do, and also because CBDs eventually upset the endogenous PEA (endocannabinoid) system. In fact, there is a distinct possibility of reducing tissue repair from long-term CBD use because of its differences from PEA/NEAs when CBD studies are longer than days or a few weeks. Remember, PEA/NEAs are in your body from the moment of conception and thereafter, your entire life. Coming up, you'll see why CBD is unable to be in your body for life.

Cannabis, CBD and Exercise

CBD use by athletes is mainly based on hearsay and internet searches, with about 25% admitting to using or having used CBD – actual usage is still not well known. About 2/3 of users reported improvements in pain, recovery and/or sleep.

Reviews of anything related to Cannabis and exercise concluded that no improvements in aerobic performance were found in dozens of human studies, although exercise-induced asthma was inhibited (which fits THC/CBD activation of the Endocannabinoid System). Some persons definitely respond poorly to exercise when THC is involved (an ergolytic, or performance-decreasing effect),

and CBD was shown to have some psychoactive effects, ala THC. CBD products often have THC, a problem for drug-tested athletic activities and unwanted effects.

Reviews reported decreased performance, lowered physical capacity, worsened balance, and increased heart and breathing rates when Cannabis was consumed acutely prior to exercise. Adverse side effects were common – some subjects could not complete exercise protocols, strength was reduced and angina was precipitated at lower workloads in exercise stress tests. Other problems noticed with marijuana use were lower resting heart rate, higher CRP levels, lower BDNF levels, and increased depressive symptoms. One study showed that cannabis abstinence improved psychomotor functions when users maintained aerobic exercise amounts, compared to no exercise. These other problems are possibly ergolytic (performance-decreasing), but are definitely unhealthy.

CBD by itself has only recently been tested in exercise settings, but the story is the same – zero or disappointing effects in exercise performance. Indirect effects of pain reduction and psychological effects from CBD may appear to improve exercise performance or recovery to the user, but their objective physical performance and recovery are at best unaffected, and reviews are not advocating CBD use just yet.

Overall, CBD has not shown improvements in exercise performance or recovery in human studies, mostly for endurance exercise. Side effects from marijuana use in dozens of human studies are unhealthy and may decrease exercise performance.

Citations for Cannabis, THC & CBD for Exercise: Bartels 2006; Burr 2021; Charron 2011; Docter 2020; Eichner 1993; Gamelin 2020; Gibson 2023; Huestis 2011; Kasper 2020; Kennedy 2017, 2022; Kramer 2020; Kurlyandchik 2022; Lachenmeier 2019; Langer 2022; McCartney 2020; Nelson 2020; Pesta 2013; Schouten 2022; Trinh 2018; Ware 2018; YorkWilliams 2019

CBD with PEA?

Can you take CBDs with PEA? No data on their direct interactions in humans is available, perhaps because it would be possibly dangerous, thus curtailing human study of combinations. Dangerous? Why? How? Really? Although combination of PEA with CBD is rare in scientific study with humans, animal studies clearly show that a combination of PEA and CBD reduce the overall effects of each – an antagonistic interaction (Rahimi 2015). There is as yet no dose-response curve data of PEA/CBD combinations to determine if there is a practical ratio that reduces interactions and increases efficacy. In vitro and animal studies, and human surveys of CBD use show antagonism of PEA by CBDs, which has a good chance to be problematic if continued chronically. Products that combine CBD and PEA can be obtained today. Fortunately for safety, the dose of CBD is low at 30-50 mg per serving, and less than the PEA dose (100 or more mg) in most products. But that CBD dose is also below doses used in successful human studies, and 10X or more below that tested in epileptics. It is likely that PEA/CBD combinations are not synergistic and only as good as what a smaller amount of PEA alone can do. Long-term imbalance and decreased actions of the ECS are likely.

Citations for CBD / PEA Differences: Joshi 2019; Khalsa 2022; Kurlyandchik 2022; Leen 2022; Maccarrone 2015; Rahimi 2015; Rezende 2023

Dark side pf Phytocannabinoids - CBD Side Effect - with a Hidden and Ignored Bummer

PEA does not have safety issues and has excellent tolerability from many human clinical studies and reviews. Given its pharmacokinetics and disposal mechanisms, PEA has been shown to be exceptionally safe from over 50 years of human and animal use.

Unlike PEA, there is an overlooked/ignored link between marijuana use and many safety issues, including problems with CBD itself. CBD may have a coolness factor, but is it cool to have anhedonia (inability to feel pleasure), cognitive decline, reproductive hormone fluctuations, pregnancy terminations (embryo-fetal mortality), fetal brain changes ("doper" babies aka developmental toxicities),

lower sperm counts, low blood pressure, decreased brain blood flow and accelerated DNA aging? Daily doses that cause these conditions seen in animal studies are dose-dependent – but without proper dose-response studies in humans that will never be done because of real risk, where is the line between safety and toxicity?

CBD side effects are dose-dependent – more CBD, more side effects. CBD side effects in humans seem to become problematic at 100 mg or more per day – about the same dose or more is needed to exhibit non-placebo benefits for pain. Lower doses are more likely to generate placebo responses rather than biochemical benefits.

The reason for Marijuana, CBD and THC side effects is clear – CBD and THC both interfere and block endogenous PEA/NEAs endocannabinoid signaling. Hijacking the receptors depresses the fine control that the PEA/NEA endocannabinoid system provides. Since the endocannabinoid system affects virtually everything, problems ensue when that system is perturbed by interloping Phytocannabinoid mimics.

CBD has two problems PEA does not have: 1) decreasing PEA family effects; and 2) being less potent than PEA. Since it's less potent, a higher daily CBD dose is needed, meaning several other issues that adversely affect potential benefits: 1) higher cost; 2) less compliance; 3) early discontinuation; 4) insufficient dosing for efficacy; 5) progressively higher intakes in order to "feel" a difference easily reaching daily amounts associated with side effects; and 6) doping & drug testing issues.

Ergoltic Properties of CBD

A major difference between CBD and PEA is unwanted side effects. Fatigue and somnolence (sleepiness aka brain fog) is commonly found by CBD users – not something athletes want when in competition, although it might help with sleep. PEA does not have a brain fog effect and it does help with sleep. CBD also decreases appetite (unlike THC) – again, not what endurance athletes need. CBD has immunosuppressant effects, whereas PEA enhances immune responses if needed. Human CBD studies have found GI disturbances (vomiting, diarrhea, liver abnormalities/damage).

Other CBD Problems

Prescription and OTC drug interactions can be problematic, because CBDs are removed by the same liver CYP system that also removes drugs – completely different from PEA/NEAs. This effect can make drugs less effective or more toxic and cause signs of liver damage, depending on which ones – which is still being deduced. A possible link to more depression in women using Marijuana has been noticed for many years. CBD decreases brain blood flow and activation, which changes your behavior. Marijuana has also long been known to adversely affect fertility and reproduction in women and men, an effect that extends to when CBD and THC are given alone. The ECS plays key roles in sperm production, sperm fertilization capability, transport of embryos in the female reproductive tract, implantation of embryos, and the placenta. No reproductive issues have been found for PEA.

New CBD Problems you haven't heard about

One disturbing study found that 0.22 µM CBD caused nuclear aberrations and DNA damage (single & double-strand breaks and missing purine bases) in two human cell lines in vitro (Russo 2019). One of the cell lines was TR146, a cell line from normal buccal epithelial tissue (mouth lining cells) that is relevant to your body. This is disturbing because 0.22 µM CBD is a blood level reached in other human studies, not just test tubes.

Similarly, a recent review of worldwide data confirmed that Cannabis Phytocannabinoids themselves, including CBD and THC, cause transgenerational genetic (DNA) damage, birth defects and cancer in humans – worse than previously suspected (Reece 2023). This is where the chemical structure differences between PEA and CBD are important: the CBD hinge bond is chemically active, but

it does not exist in PEA/NEAs. Phytocannabinoid problems are epigenotoxic, a sneaky way to cause DNA damage only recently able to be measured accurately. If you consume CBD, and feel it's OK to inflict genetic damage on yourself, is it also OK to inflict genetic damage on your children? And their children?

The new epigenotoxic data is reproducible and solid, and it also predicts long-term problems from CBD use similar to chronic Marijuana use.

Citations - CBD Side Effects: Alhouayek 2014; Blum 2021; Burr 2021; Clayton 2021, 2023; Fernandez-Ruiz 2015; Gabrielsson 2016; Gunasekera 2021; Huestis 2011, 2019; Joshi 2019; Kennedy 2017, 2022; Khalsa 2022; Leen 2022; Lim 2023; Maccarrone 2015; Nelson 2020; Rahimi 2015; Reece 2023; Russo 2019; Scheyer 2019; Schurman 2020; Singh 2023; Smith 2023; Stout 2014; Suarez-Pinilla 2014; Wang 2008; Williamson 2020; Zendulka 2016

CBD Summary

CBD does have PEA-mimetic effects on pain perception similar to PEA/NEAs. But other aspects of PEA/NEAs have not been repeated by CBD, on the basis of its very different molecular structure and the inescapable biological effects of that different structure. On the other hand, since PEA is an interactive instigator and facilitator everywhere, and has built-in checks and balances, long-term use gives better and better results.

CBD also has unalterable problems with oxidation because of its very different chemical structure – it's not as safe as PEA/NEAs and never will be. Completely unlike PEA/NEAs, which are easily broken down wherever they are (anywhere) into normally-occurring, safe components that can be reused, CBD is broken down by enzymes in the liver mostly (the Cytochrome P450 [CYP] system), a general process which increases oxidative loads, has interference from normal dietary practices (like eating grapefruits), is subject to nutritional deficiency activity deficits, and the overuse of which is associated with DNA damage. This difference alone can account for the adverse effects being found for CBD.

CBD can also accumulate to levels that overload the sensitive and complicated feedback loops inherent in the PEA signaling system (aka Endocannabinoid System cascades). This overload problem can decrease endogenous PEA family activities, which can decrease a lot of what PEA does to fix problems outside of being an analgesic. Balance between synthesis and breakdown determines how well PEA can work without being noticed. CBD has no synthesis controls; it simply shows up when you ingest it. This feedback balance is one reason why PEA can do more than CBD, and do it at a lower daily intake, without side effects.

CBD is less controllable by human bodies, and activates everything everywhere all the time, whereas PEA/NEAs are much more focused for being turned on and off. The real ligands for the ECS (PEA and NEAs) activate different receptors and have different turnover rates in different tissues than CBD. Because CBD does not fully replace PEA/NEAs, long-term imbalance of the ECS is showing up with longer-term CBD use.

Also, CBD cannot do everything PEA does, and thus, cannot be as comprehensive in healthy effects as PEA. Although it appears that reducing pain is what CBDs are eventually doing in the body, pain means damage, and damage needs to heal, and if you exercise strenuously, you need and want to heal and repair ASAP, not just mask the pain.

Quality of CBD products is not as reliable as dietary supplements and definitely not to pharmaceutical standards. Traces of THC have actually accounted for some of the observed effects of CBD products, and combined with a large placebo effect concerning marijuana, initial benefits do not hold over time.

Completely unlike PEA, CBD has side effects, some of which decrease exercise performance, and some of which are permanently unhealthy. User beware.

All things considered, CBD is an impostor for the ECS. It operates using the same system, just in a contrary way to how PEA does, with the same power being applied for good with PEA – or not, with CBD.

Literature Quotes for Levagen®+ and PEA

"N-Acylethanolamines (NAEs) constitute a family of endogenous bioactive lipids implicated in the regulation of several processes, from the modulation of food intake to pain and inflammation"
Alhouayek 2014, p1

"This meta-analysis provides preliminary evidence that PEA may be effective in the management of chronic pain across a variety of conditions."
Artukoglu 2017, p. 359

"...exercise activates the eCB system, and this activation may contribute to positive mood outcomes with exercise."
Brellenthin 2017, Abstract

"Based on the articles included in this review, the authors conclude that cannabis consumption has an ergolytic effect on exercise performance and therefore does not act as a sport performance enhancing agent as raised by popular beliefs. Thus, cannabis consumption prior to exercise should be avoided in order to maximize performance in sports."
Charron 2011, Abstract

"... it can be generally stated that eCBs, particularly AEA and PEA, could be considered as master regulators of the innate-adaptive immune axis and as valuable immunoresolvents."
Chiurchiu 2016, p.65

"Its [PEA] pleiotropic effects include anti-inflammatory, analgesic, anticonvulsant, antimicrobial, antipyretic, antiepileptic, immunomodulatory and neuroprotective activities."
Clayton 2021, p.2

"...not only is the currently available scientific data concerning CBD's efficacy insufficient, there is also ambiguity surrounding its regulatory status and safety in humans that brings inherent risks to manufacturers."
Clayton 2023, Abstract

"The long association of humans with cannabis made sense now that it was shown that our brain produced its own cannabinoid, although anandamide is entirely different from cannabis by its chemical class."
Crocq 2020p.227

"To live a better life implies in a vigilant ECS, ... ECS is involved in pain, inflammation, metabolic and cardiovascular dysfunctions, general immune responses ... both/either in the brain and/or in the periphery."
de Melo Reis 2021, Abstract
[NOTE: ECS is the Endocannabinoid System]

"... irrefutable evidence demonstrated that the ECS is also a major player in systemic energy metabolism, inflammation, appetite control, and pleasure (acute anxiolysis, analgesia, antidepressant effects, sedation, and euphoria) of the so-called runner's high."
de Melo Reis 2021, p.6
[NOTE: ECS is the Endocannabinoid System]

"As noted by other authors, PEA appears to be well tolerated indeed."
Gabrielsson 2016, p.934

"Our analysis of the pharmacokinetic properties of PEA suggests that the compound has a high volume of distribution. Perhaps the most intriguing finding was the concentration of label in the hypothalamus after oral dosing of PEA ..."
Gabrielsson 2016, p.940

"Preclinical studies suggest that CBD could be useful to athletes due to its anti-inflammatory, analgesic, anxiolytic, neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, almost no clinical data are available on CBD in the context of exercise, which makes its use in this context still premature."
Gamelin 2020, Abstract

"The present findings merit particular interest in view of the complete absence of side effects ascribed to PEA, as confirmed in numerous clinical studies that evaluated PEA ..."
Gatti 2012, p.1127

"Although participants reported more positive effect, dissociation, enjoyment, and runner's high symptoms during their cannabis [THC or CBD] (vs. non-cannabis) exercise appointment, they also reported more exertion and breathlessness."
Gibson 2023, Abstract

"This study demonstrates, in humans, that acute exercise, all the more if intense, induces a large increase in circulating levels of AEA, which persists during recovery, possibly through mechanisms involving cortisol. "
Heyman 2012, p.849
[NOTE: PEA and OEA were also significantly increased during exercise and recovery, with OEA levels doubling.]

"CBD is not risk-free ... Human CBD studies ... reported CBD-induced drug-drug interactions, hepatic abnormalities, diarrhea, fatigue, vomiting and somnolence."
Huestis 2019, Abstract

"The endocannabinoid system, a previously unknown but with ubiquitous signaling pathways is expressed throughout the human body and distributed in almost all tissues."
Joshi 2019, p.10

"This narrative confirms that CBD and tetrahydrocannabinol (THC) do not enhance performance."
Kennedy 2022, Abstract

"However, the molecule remained largely unnoticed in the rest of the world until in the early 1990s Nobel Prize laureate Rita Levi-Montalcini proposed that PEA is an endogenously produced regulator of inflammation."
Keppel Hesselink 2014, p.19

"PEA is synthesized and metabolized in animal cells via a number of enzymes and has a multitude of physiologic functions related to metabolic homeostasis."
Keppel Hesselink 2013 625, Abstract

"Cannabinoids are associated with short-term adverse events including dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, hallucinations, sedation, and possibly death."
Khalsa 2022, p.637

"Current research shows that CBD and other cannabinoids currently are not ready for formal indications as medicines to treat a wide range of clinical conditions as promoted except for several exceptions including limited use of CBD for treating two rare forms of epilepsy in young children and CBD in combination with THC for treating multiple-sclerosis-associated spasticity."
Khalsa 2022, Abstract

As regulators of metabolism, ECBs are anabolic: they increase the intake, promote the storage, and decrease the expenditure of energy."
Kunos 2008, abstract
[NOTE: ECBs are EndoCannaBinoids, which are the PEA family of NAEs, and which are not Phytocannabinoid structures like CBD or THC]

"Several studies reported additional benefits of PEA for quality of life and functional status, and no major side effects were attributed to PEA in any study. The results of this systematic review and meta-analysis suggest that PEA is an effective and well-tolerated treatment for chronic pain."
Lang-Illievich 2023, Abstract

"Apart from having been used and misused for at least four millennia for, among others, recreational and medicinal purposes, the cannabis plant and its most peculiar chemical components, the plant cannabinoids (phytocannabinoids), have the merit to have led humanity to discover one of the most intriguing and pleiotropic endogenous signaling systems, the endocannabinoid system (ECS)."
Ligresti 2016, Abstract

"In line with previous research cannabis use was associated with lower endocannabinoid levels."
Leen 2022, Abstract

"... if one looks at conventional strategies that the pharmaceutical industry has used to develop drugs in recent years, one immediately understands that these cannot be easily applied to the ECS."
Ligresti 2016, p.1633

"Δ^9-tetrahydrocannabinol (THC) and other phytocannabinoids from Cannabis sativa affect a variety of physiological processes by altering, or under certain conditions hijacking, the ECB system. Therefore, phytocannabinoids, in particular THC, may modify the homeostasis of the HPG axis by altering CB receptor signaling and cause deficits in reproductive function."
Lim 2023, Abstract

"...the interactions of THC, CB1, and the endocannabinoids are more complex than THC simply "hijacking" CB1 receptors as another agonist and need to be carefully considered."
Lu 2016, p.8

"eCBs control basic biological processes including cell choice between survival and death and progenitor/stem cell proliferation and differentiation. Unsurprisingly, in the past two decades eCBs have been recognized as key mediators of several aspects of human pathophysiology and thus have emerged to be among the most widespread and versatile signaling molecules ever discovered."
Maccarrone 2015, Abstract
[NOTE: eCBs are Endocannabinoids including PEA]

"eCBs play an important role in maintaining the overall 'fine tuning' of the immune homeostatic balance within the host."
Maccarrone 2015, p.10
[NOTE: eCBs are Endocannabinoids including PEA]

"Taken together, it can be concluded that: i) eCBs are deeply involved in both the control of energy metabolism by the skeletal muscle and the formation of new muscular fibers; ii) both these fundamental actions are mediated preferentially via CB1 and involve AEA and 2-AG to varying degrees; and iii) the ECS ultimately controls the utilization of energy in the skeletal muscle, by either reducing glucose oxidation by myofibers or the extent of muscle formation."
Maccarrone 2015, p.12
[NOTE: eCBs = Endocannabinoids including PEA, CB1 = CannaBinoid receptor1, AEA = anandamide, 2-AG = 2-Arachidonoyl Glycerol, ECS = EndoCannabinoid System]

"Taken together, these results may indicate that PEA supplementation is able to aid in muscle recovery from repeat bouts of exercise performed within 3 h."
Mallard 2020, p.12
[NOTE: PEA was Levagen+ at about half of the dose in a daily serving of MultiV-PRO]

"This wide range of neurobiological rewards induced by physical training, such as the sense of wellbeing, decrease in pain, and reduction in anxiety, was referred to as "runners high". ... Currently, researchers have turned their attention to endogenous endocannabinoids as the true source of analgesia, sedation, anxiolysis, and reduced depression in endurance exercisers."
Matei 2023, p.2
[NOTE: Endogenous cannabinoids include PEA, that also increases the other NEAs.]

"While the verdict on CBD remains to be decided, our perspective is that it is certainly not the universal panacea that it is touted to be. Nor is it an innocuous natural substance that should be unregulated in the marketplace and/or used to fortify products for credulous human consumption."
Nelson 2020, p.12139

"Palmitoylethanolamide (PEA) has emerged as a potential nutraceutical, because this compound is naturally produced in many plant and animal food sources, as well as in cells and tissues of mammals, and endowed with important neuroprotective, anti-inflammatory and analgesic actions."
Petrosino 2017, p.1349

"Palmitoylethanolamide (PEA) is an endogenous fatty acid amide signaling molecule synthesized "on demand" in response to tissue injury/stress, as part of a mechanism to restore/maintain homeostasis with anti-inflammatory, pain-relieving and neuroprotective actions."
Petrosino 2018, p.1

"We show that humans and dogs share significantly increased exercise-induced eCB signaling following high-intensity endurance running."
Raichlin 2012, Abstract

"Accordingly, the endocannabinoid system plays a modulatory role in many physiological processes, thereby generating many promising therapeutic targets."
Schurman 2020, Abstract

"Competitive inhibition of CYP enzymes raises concerns of drug toxicity from clinical medications."
Schurman 2020, p.15
[NOTE: from THC and CBD, not PEA]

"... this study indicates that the development of a runner's high does not depend on opioid signaling in humans, but makes eCBs strong candidates in humans ..."
Siebers 2021, Abstract

"PEA has been shown to exert its anti-hyperalgesic effects by down-modulating several inflammatory mediators such as inflammatory cytokines, neutrophil infiltration, pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS), pro-inflammatory kinases such as mitogen-activated protein kinase (MAPK), neurotrophic factors such as nerve growth factor (NGF) and mast cell degranulation via the 'Autocoid Local Injury Antagonism' (ALIA) mechanism, inhibiting the release of histamine, PGD2 and TNF-α."
Steels 2019, p.483

"We identified 122 articles from 446 references. Overall, endocannabinoids enhanced immune response, whereas exogenous cannabinoids had immunosuppressant effects."
Suarez-Pinilla 2014, Abstract

"The latter data might suggest a possible eCB positive effect on muscles, through alternative pathways that could also be targeted by an eCB-like compound, like OeA and PeA."
Tantimonaco 2014, p.2690
[NOTE: The "positive effect" was increased glucose uptake, increased fat oxidation and mitochondrial biogenesis by exercising muscles – training adaptation attributes that could result in increased exercise performance.]

"Recently, investigators have reported increases in circulating levels of eCB after exercise, with some eCB exerting analgesic effects from exercise."
Watkins 2018, Abstract

2. BETA GLUCAN - IMMULINK® MBG

What is Beta Glucan and why is it important?

Beta Glucan is a generic term for Nature's major structural component (building block) for lower life forms such as algae, bacteria, protozoans, fungi (molds, mushrooms and yeasts) and some plants (oat seeds, for instance). Beta Glucan is a family of polysaccharides –long strings of sugars, in this case mostly glucose, the most common sugar in Nature. Each individual sugar molecule has several different twists and turns (conformations), that determine how sugars attach to each to form long, linear strings (polysaccharides). Beta Glucans form tough fibers that are used to make cell walls and large structures, like a mushroom. To make things exquisitely complicated, a sugar molecule can add more than one sugar to itself, and that branch point can be extended too – as either another long string or a many-branched structure. In this way, Nature can sculpt almost any form and shape in any size it wants.

Technically, the Beta Glucans we want to learn about are called Beta-1/3,1/6-Glucans.

Why is Beta Glucan important for my health?

Because Beta Glucans are signature molecules for lower life forms, and we humans do not use Beta Glucans for our structures, presence of Beta Glucans inside our body (past the lining of skin, respiratory and gastrointestinal tracts) means we have been invaded by something that could kill us. Lower life forms look at us like a giant, living cafeteria for them to digest and devour, whether alive or dead. We survivors have an elegant ancient early warning cell signaling system that is lodged throughout the portals of entry into our bodies to identify the presence of Beta Glucans, where specialized parts of our immune system (mucosal immunity) act as sentinels.

A majority of your immune system is tied up in these places. Your gut is loaded with clusters of immune cells called Peyer's Patches that receive tiny amounts of what you eat for monitoring friend or foe. Gut immune cells sense fungal Beta Glucan, activate Dectin-1 receptors, Complement Receptor 3 and Toll-Like Receptors (TLRs). Dectin-1 specifically identifies presence of fungi (which includes yeasts and mushrooms) that use Beta Glucans as their cell walls. What better signal to specifically alert presence of fungi than their exterior? When signs of invaders are detected, signals are sent all over the body in order to snuff out potential invaders. If invaders are found (an infection), a bonafide immune storm ensues until there is a victor. You feel malaise, fatigue, fever, fuzzy-headed.

If invaders are found, then your immune system has been activated, and looks for anything else that is out of kilter. For you, that means your heightened immune system can tackle other kinds of stress – like exhaustive exercise stress. Activating these receptors by giving Beta Glucans orally, without the risk of invading organisms, starts a cascade that grows into a bodywide immune-modulating response, spilling over to all your tissues, especially the ones screaming for help or screaming about any sort of damage, including the damage normally caused by exercise and overexertion.

In other words, oral Beta Glucans simultaneously activate a lot of recovery pathways and overall health benefits when you are in a non-infected state. Immune cells do their thing by managing cellular and tissue stress, releasing all sorts of messenger molecules (complement, cytokines, eicosanoids and more) locally and systemically. Stress uses many of the same signaling molecules to tell your body to respond, so nothing potentially bad for you is missed. Net outcome is amelioration of normal exercise-induced inflammation and improved recovery along with immune support, if needed, for exercising individuals. This is why Beta Glucans can benefit strenuous exercise recovery – and eventually, performance.

Citations - Why Is Beta Glucan Important?: *Akramiene 2007; Batbayar 2012; Batra 2013; Bishop 2015; Campbell 2019; De Marco Castro 2021; Dennehy 2007; Goodridge 2009; Herre 2004; Kanjan 2017; Lee 2014; Maity 2021; Majtan 2018; Nieman 2008; Renke 2022; Samuelson 2014; Sun 2007, Tsoni 2008; Vetvicka 2014, 2019; Vlassopoulou 2021; Wachtel-Galor 2004, 2011; Ying 2023; Zeng 2018, 2019*

Beta Glucans & Exercise

Beta Glucan, as yeast and mushroom extracts, has been applied to endurance and ultra-endurance exercise in human studies. While the major goals of most of these studies was to prevent formerly-known-as-URTI (Upper Respiratory Tract Infections), there are data on performance as well. Most of the human research used 200 mg Beta Glucan doses, and most used consistent use during training and specific events, just like using MultiV-PRO in real life. The data is relevant and successful for keeping you feeling better after strenuous exercise, recovering better and maintaining peak performance.

Beta Glucan preparations have generally shown reduction of URTS (Upper Respiratory Tract Symptoms) immediately and for days following long-duration, strenuous exercise (such as marathons or longer) when used consistently during race season. Fewer symptomatic days after a race, less severe symptoms and improved levels of stress biomarkers such as increased salivary IgA (a biomarker for immune function and airway mucosal tissue health) have been reported. Overall health and mood were also improved post-exercise by Beta Glucan. Consistent use from taking a MVM daily is a major reason Immulink MBG® was added to MultiV-PRO. Daily use provides consistent, long-term intake of active, highly-concentrated, Beta Glucan. A powerful, broad-spectrum signal for repair, recovery and overall health.

Reishi mushroom and yeast beta glucans are not to be confused with oat beta glucan (1,3/1,4-beta glucan). They have different molecular structures and different biological properties. Oat beta glucans have little effect on immune functions. A study on cyclists ingesting 5600 mg of oat beta glucan daily for 14 days while keeping their normal 1-2 h/d cycling workload found that, for three days, the subjects increased their cycling load by 70% - 3 h/d, and then continued oat beta glucan for one day, followed by 13 more days of observation for URTS (Nieman 2008). Oat beta glucan group showed a nonsignificant increase in number of days of not feeling well compared to the placebo group. Likewise, measurements of immune functions and cytokine levels were not different between the groups. Thus, oat beta glucan did not affect exercise recovery or immune health symptoms in endurance athletes.

Citations - Beta Glucan & Exercise: *Bergendiova 2011; Blocher 2013; Bobovcak 2010; Carpenter 2013; Harger-Domitrovich 2001; Mah 2020 200, 2020 416; Majtan 2012, 2018; McFarlin 2013; Talbott 2009; Zabriskie 2020*

URTI Out - URTS in: Are you really sick or just feel that way?

Every ultra-endurance athlete knows that after a long event, there is a risk for getting ill, called Upper Respiratory Tract Infections (URTI) when an infectious agent is causing those typical symptoms. For many reasons, the URTI dogma is not true. What you are probably experiencing is Upper Respiratory Tract Symptoms (URTS), which mimic and feel just like a true URTI from respiratory viruses.

Much research has looked into the prevalence, severity, outcomes and ameliorations for ultra-endurance athletes and immunity issues. Current findings, along with non-findings, have caused a tectonic shift in URTI that has not caught up with athletes' knowledge. Normally if something quacks like a duck and walks like a duck, everyone thinks it's a duck – until enough people look carefully and scientifically at the quacker and find out it's not a duck, but it's a pigeon in a duck suit.

Gradual awareness has led to a consensus that long-duration, strenuous, exhaustive training and exercise takes a toll on your immune system functionality and can lead to common immune-related symptoms both immediately after exercise and, eventually, chronically when overtrained. This was previously termed URTIs (Upper Respiratory Tract Infections), but recent research has

abandoned that term because of lack of finding proof for presence of infectious agents. There was a gradual realization that all the immune biomarkers are going crazy, but when correctly performed research to identify microbial agents turned up a low, normal incidence of microbes, then the URTIs became URTSs. Yes, a minority of persons exhibit actual, confirmed URTIs, but at the same incidence of travelers and people in crowded conditions of close contact that do not exercise. These two conditions are endemic in endurance exercise events. Strenuous exercise does not increase your chances of getting an upper respiratory viral condition. Repeat – even long-duration, strenuous, grueling, exhausting exercise itself will not make you more susceptible to an actual viral or bacterial infection (LRTI or URTI).

Here's the real story. URTI symptoms are same as the symptoms of the normal recuperative response to heavy-duty endurance exercise stress, and show similar immune system changes, also a normal part of the recovery process. Your body responds the same way to serious stressors, whether that be extreme exercise or an infectious assault. Previous findings have tricked researchers into believing that infections were common after ultra-endurance exercise based on inconclusive research designs – now we know better that it's you being entirely normal and not sick. [For a further explanation, see the Blog on Ultragen and post-exercise recovery.]

URTS (Upper Respiratory Tract Symptoms) is the new name for normal, exercise-associated changes that you and your immune system exhibit after strenuous-enough exercise. Symptoms after excessive exercise are part of the normal recovery response to the tissue damage caused by long-duration, intense exercise that ultimately strengthens immune function over time. Human bodies respond to stress with the same symptoms, and with the same countermeasures, spurred by your immune system. If you are in an airport, and somebody close by looks tired and is sneezing, coughing and bleary-eyed – STAY AWAY and/or mask up! If you are near somebody who just finished a grueling exercise event, and they are fatigued, sneezing, coughing and bleary-eyed, give 'em a hug and some immediate post-exercise nutritional recovery. You'll both feel better.

Some reviews proposed that nutritional problems were a major factor for resolving URTS, including vitamins, minerals and other nutrients, including Beta Glucans. This is why Immulink® MBG Beta Glucan gives MultiV-PRO an extra advantage over other MVMs – it helps your body speed up and intensify the normal recovery processes post-exercise at the same time it prevents essential nutrient deficiencies from slowing down the process. Just add hydration, electrolytes and calories. Win-win strategy. A consistent, daily intake of Beta Glucan along with all the necessary vitamins and minerals is needed to elevate your normal response to extreme physical stress.

The bottom line for including a successful Beta Glucan ingredient in a MVM is to help you feel better and recover faster so you can maintain and improve your training and exercise performance. Continuous use also supports your immune system when not exercising.

Citations - Beta Glucan Ultra-endurance Exercise Immune Reviews: *Bermon 2017; Blocher 2013; Campbell 2018, 2019; Ciecierska 2019; Cerletti 2021; Cox 2014; Cerqueira 2020; Davison 2011; Dhabhar 2014; Gani 2003; Gleeson 2004, 2007, 2013, 2014, 2017; Nieman 2019 201, 2019 341; Rajasekkhar 2022; Renke 2022; Schwellnus 2010; Simpson 2020; Vlassopoulou 2021; Walsh 2019; Wirnitzer 2022*

Reishi Mushroom-based Beta Glucan for immune support - and more

MultiV-PRO opted for additional immune support from Beta Glucan from a different source than MultiV – Immulink MBG® from Reishi mushroom mycelia. Immulink MBG® uses proprietary technology to extract a Beta Glucan-rich ingredient from fermented Ganoderma lucidum mycelia that has been used successfully for aquaculture and dietary supplements for many years. The clincher for deciding to use Immulink MBG® in MultiV-PRO were the convincing results of two recent, well-controlled human clinical studies

that show Immulink MBG® increases immune cells in the bloodstream (meaning a whole-body reach) along with increased NK immune cell function. Both are markers of supporting a healthy immune system response to stress of all kinds.

Like the Baker's yeast Beta Glucan used in MultiV, Reishi mushrooms (Ganoderma lucidum) also contain Beta Glucans that have exhibited similar immune support properties. In fact, many preparations of algae, bacteria, fungi, seaweeds, molds, mushrooms, yeasts and protists that contain 1/3-1/6-beta glucans have all been shown to work the same way – by activating the same mechanisms for bodywide immune support via interaction with gut immune cells. Importantly, all have similar human clinical findings over many years of study all over the globe – evidence for a common mechanism of action, which has been described in detail. As long as clinically studied doses of the same, reproducible materials are used, the same benefits can be expected.

Citations - Beta Glucan from Different Yeasts and Mushrooms Show Similar Effects: *Akramiene 2007; Barsanti 2011, 2023; Batra 2013; Bishop 2015; Blocher 2013; Brown 2003; Ciecierska 2019; Cerletti 2021; Cox 2014; De Marco Castro 2021; EFSA 2011; Goodridge 2009; Immulink 2016; Jesenak 2014 149, 2014 471, 2017; Lin 2005; Kostygov 2021; Lee 2014; Maity 2021; Matjan 2012, 2018; Markovina 2020; Murphy 2020; Nakashima 2018; Patel 2012; Ren 2021; Renke 2022; Rop 2009; Samuelsen 2014; Seweryn 2021; Stier 2014; Swallah 2023; Vetvicka 2019; Villares 2012; Vlassopoulou 2021; Volman 2008; Wachtel-Galor 2004, 2011; Ying 2023; Zeng 2018, 2019; Zhong 2021*

Immulink ® Reishi Mushroom Beta Glucan - Mycelia, not fruiting bodies

MultiV-PRO opted for Immulink® MBG Reishi mushroom extract from Super Beta Glucan Inc. to provide other healthy components along with (1,3/1,6)-Beta Glucan. Reishi mushrooms and their extracts have been used to preserve human health for millennia. Many years of experience and testing have enabled Immulink® MBG to reproducibly maintain the same quality year after year by several proprietary fermentation (growth) and production methods. Instead of grinding up the large mushroom fruiting body into powder, Immulink® MBG is made from the mycelia - the fine, hair-like masses that look like cotton candy. Mycelia are very rich in Beta Glucan and are without the other components of Reishi mushrooms that are useless or less active. This process allows the same strain of mushroom to be cultivated under the same conditions, every batch, without endangering wild sources and ensuring no unwanted spores, contaminants or species are involved. A special ultrasound extraction and purification process without heat or solvents protects Beta Glucan structure and conformation, making it more effective.

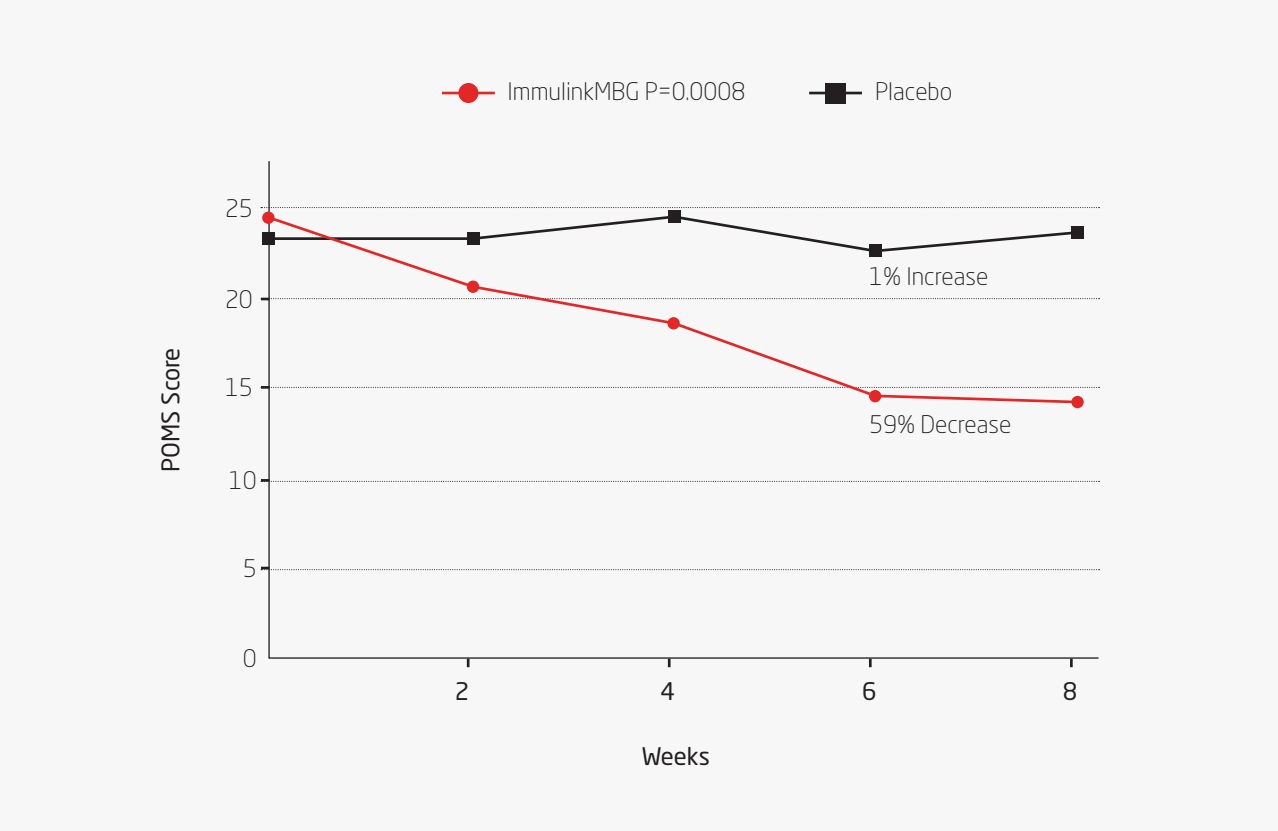
Immulink MBG® is readily soluble in water, and stable under extreme temperatures. Immulink MBG® is GRAS (Generally Recognized As Safe) by the US FDA (FDA GRN 000413 2011), as are other yeast beta glucans (EFSA 2011). Since mushroom allergies are typically caused by airborne or skin contact from spores, Immulink® MBG has not shown any allergic symptoms because its fermentation technology is devoid of spores.

Importantly, Immulink® MBG has been tested in various settings, including with humans, for its antistress and immunosupportive properties. Evidence of success in different species from shrimp aquaculture to stressed humans illustrates the universal benefits of consistent Beta Glucan intakes.

Immulink® MBG, from Super Beta Glucan, has been tested on cells, in animal studies and in human clinical studies. In humans, Immulink® MBG has increased vigor, quality of life (QOL) and biomarkers of immune system functions in healthy persons with chronically high physical and psychological stress in open-label and placebo-controlled studies (Chang 2012; Chen 2013). A study with 132 men and women under chronic work stress (more than 14 hours of pressure-packed work daily) were given either placebo or 200 mg Immulink® MBG for eight weeks (Chang 2012). After two weeks, the Immulink® MBG group showed a significant 45% decrease in Upper Respiratory Tract Symptoms (URTS) and an 80% decrease after eight weeks. From the Profiles Of Mood Survey (POMS) results, improvements in Fatigue-activity, Vigor-activity, tension/anxiety, depression and mood disturbance were significant. Less confusion/bewilderment and anger/hostility showed trends for improvement, correlating with significant mood

changes. These results show real-world, feelable results from Immulink® MBG, and have been found in other Beta Glucan human studies in athletes. Similarly, an open-label study of 300 or 600 mg Immulink® MBG in high-stress office workers found results similar to the 200 mg/day dose, over a 90-day period (Chen 2013).

Immulink MBG POMS Fatigue Score



Adapted from Chang 2012

A recently published study administered placebo or 200 mg Immulink® MBG to 135 healthy adult volunteers for 12 weeks. (Chen 2023). Blood samples were collected before and after supplementation, and various immune tests and safety chemistries measured. Compared to placebo, Immulink® MBG significantly increased Lymphocyte, lymphocyte type (CD3+, CD4+, CD8+), C4/C8 cell ratio, serum IgA and NK cells, with more cytotoxicity (by 83%). Safety measures were unchanged in both groups. Significant improvements in the innate immune system were exhibited by Immulink® MBG .

*P<0.050 = statistically significant
Adapted from Chen 2023, p.7

Immulink® MBG Immune Effects - Percent Differences Between Placebo After 12 Weeks

Immune Parameter	% Difference	P Value
Total Lymphocytes (cells/microliter)	+17.8	0.012*
CD3+ T Lymphocytes (cells/microliter)	+18.7	0.001*
CD4+ T Lymphocytes (cells/microliter)	+31.7	0.003*
CD8+ T Lymphocytes (cells/microliter)	+18.8	0.025
CD4/CD8 cell ratio	+15.4	0.036*
Serum Immunoglobulin A (IgA) (mg/dl)	+14.4	0.048*
NK (Natural Killer) Cells (cells/microliter)	+19.9	0.045*
NK Cells Cytotoxicity (%)	+88.3	0.001*

*P<0.050 = statistically significant
Adapted from Chen 2023, p.7

While these studies were not on exercising individuals, the effect of Beta Glucan is the same regardless of the stress. And considering the considerable research on non-human agricultural uses with Immulink® MBG, where effectiveness is determined by life or death (the ultimate stress), and the dozens of human studies on exercise conditions that were also successful, Beta Glucan is Beta Glucan.

Citations - Beta Glucan Effects from Immulink MBG®: Chang 2012; Chen 2013, 2023; EFSA 2011; FDA 2012; Henao 2018; ImmulinkMBG 2014, 2016

Literature Quotes fro Beta Glucan & URTS

"These substances increase host immune defense by activating complement system, enhancing macrophages and natural killer cell function."
Akramiene 2007, Abstract

"Probing Lingzhi or Reishi medicinal mushroom Ganoderma lucidum (higher Basidiomycetes): a bitter mushroom with amazing health benefits."
Batra 2013, Abstract

"In spite of the voluminous literature available, G. lucidum is used mostly as an immune enhancer and a health supplement..."
Batra 2013, Abstract

"Today it [Ganoderma lucidum] is a multi-billion-dollar industry wherein Lingzhi [Chinese name for Ganoderma lucidum] is cultivated or collected from the wild and consumed as tea, in alcoholic beverages, and as a nutraceutical to confer numerous health benefits."
Bishop 2015, Abstract

"There is limited existing evidence to support the common assumption that strenuous endurance exercise bouts impair immune competency."
Campbell 2019, p.195

"...the dramatic reductions to lymphocyte numbers and function 1-2 h after exercise reflects a transient and time-dependent redistribution of immune cells to peripheral tissue, resulting in a heightened state of immune surveillance and immune regulation, as opposed to immune suppression."
Capmbell 2018, Abstract

"The key findings from this study included that Reishi beta-glucan induce statistically significant modifications of the CD3+, CD4+, CD8+ T-lymphocytes and NK cells, as well as elicited a statistically significant increase in serum IgA concentration in the intervention group vs placebo."
Chen 2023, p.8

"This study demonstrates that β-glucans from G. lucidum increase the frequency of immune system cells in the peripheral blood..."
Henao 2018, Abstract

"Preventive applications of beta-glucans may decrease the frequency of various forms of respiratory tract infection, support protective immune mechanisms, and possibly yield other beneficial effects (increased well-being, decreased missed days from school or work, decreased use of other symptomatic or antibiotic therapy)."
Jesenak 2017, p.10

"Overall, consumption of dairy-based beverages containing dispersible yeast beta-glucan decreased URTI symptomatic days, severity of specific URTI symptoms, and missed postmarathon workout days due to URTI, without affecting duration and number or URTU episodes."
Mah 2020
[Note: 357 subjects ran in the 2017 Austin Texas Marathon. They took Beta-Glucan or placebo for 45 days before and after the run. The wording of results of this and other studies shows the prevailing trend that URTS were previously named "URTI symptoms," not URTI – notice the careful wording of reducing symptoms without saying illness or infection.]

"One of the most promising nutritional supplements is beta-glucan, a well-known immunomodulator with positive effects on functioning of immunocompetent cells. "
Majtan 2012, Abstract

"In summary, the present study provides confirmation of the observations from other investigators that this commercially available sources of baker's yeast BG decreases URTI symptom prevalence postmarathon. Here we add the novel insight that salivary IgA concentration following a strenuous exercise session is improved in subjects supplementing with BG."
McFarlin 2013, p.182

"Taken together, the best evidence supports that high exercise training workloads, competition event, and the associated physiological, metabolic, and psychological stress are linked to immune dysfunction, inflammation, oxidative stress, and muscle damage."
Nieman 2019, p.203

"Excessive or uncontrolled inflammatory and oxidative stress could induce considerable negative effects even on the performances of the elite athletes during their competition. Triggers of uncontrolled and excessive inflammatory and oxidative stress during the training may impair the recovery process and may lead to the plateau in performance."
Rajasekhar 2022, p.3

"Polysaccharides obtained from Ganoderma lucidum show a wide range of pharmacological antioxidant, immunomodulatory, antineurodegenerative, ... anti-inflammatory ... properties."
Seweryn 2021, p.1

"This review presents an updated and comprehensive summary of the studies on the immunomodulatory therapies and nutritional significance of G. lucidum, with the focus on recent advances in defining its immunobiological mechanisms..."
Swallah 2023, Abstract

"Key Points

- *Beta-Glucan supplementation maintains immune function in endurance athletes.*
- *Beta-Glucan supplementation reduces post-exercise URTIs in marathon runners.*
- *Maintenance of post-exercise immune function is associated with improved mood state, including reduced fatigue and increased vigor in athletes."*

Talbott 2009, p.514

[Note: 75 subjects ran in the 2007 Carlsbad Marathon, and started to take Beta Glucan right after the run for the next 45 days.]

"Here, we focused on natural polysaccharides with biomedical application potential, reviewed the recent advancement in their immunomodulation function and highlighted the importance of their signaling transduction feature..."

Ying 2023, Abstract

"The results showed that the receptors which could interact with Ganoderma lucidum polysaccharide GLPs included Dectin-1, DC-SIGN, langreen, Kupffer cell receptor, macrophage mannose receptor, TLR2 and TLR4 (90)."

Ying 2023, p.6

"Mood state analysis (POMS) indicated a significant improvement in vigor and reduction in anger in the YBG group in conjunction with a greater reduction in total mood disturbance in comparison to PLA. [placebo]

Zabriskie 2020, p.19

"We aimed at providing a molecular picture as well as a clinical basis to comprehend GLPS as one of few polysaccharide-based modern medicines with complicated chemical and pharmacological properties that prevent it from entering the world's market."

Zeng 2018, Abstract

[NOTE: GLPS = Ganoderma Lucidum PolySaccharide, aka Beta Glucan. Authors illustrated how a multi-factorial, complicated yet clinically effective molecule does not fit current drug regulatory standards that favor simple, single-molecule compounds, even though the efficacy and method of manufacture is consistent and well-documented. This issue also applies to herbal adaptogens. In other words, Nature is too smart for current drug regulations.]

3. AGAVE INSULIN PREBIOTIC FOR GI HEALTH

WHY GI HEALTH IS IMPORTANT FOR LONG-DURATION EXERCISE AND HOW YOU CAN HELP YOUR GUT

Ultra-Endurance Exercise is stressful to your gut

Almost everyone performing ultra-endurance activities for maximal results has experienced gastrointestinal (GI) issues. 30-50% of participants in exhausting endurance events have one or more GI symptoms.

- GI Symptoms:
  - Stomach ache (nausea);
  - Gastric reflux (burping);
  - Heartburn;
  - Abdominal ache (nausea);
  - Borborygmus (gut gurgling);
  - Intestinal (abdominal) cramps;
  - Flatulence;
  - Urge to defecate;
  - Diarrhea;
  - Bloody stools (hematochezia)

- Offending Factors:
  - Running - 50% more than stable body position exercise (cycling, skating, skiing, swimming);
  - Elite athletes – 1.5-3x more often than recreational exercisers;
  - Dehydration;
  - High/exhaustive exercise intensity (over 60% VO2max);
  - Decreased blood flow to gut (gut ischemia) – up to 80% decrease;
  - Trying something new for a competition;
  - Physical & emotional stress;
  - Untrained persons, training resumption after a period of time, inadequate training;
  - Younger athletes / less exercise experience;
  - Women report more GI issues, especially during menses;
  - Changes in nervous system activity;
  - Circulating secretory hormone/peptides & metabolic end products changes;
  - Foods rich in dietary fiber, fat and protein;
  - Timing of eating and drinking (too large a meal before exercise);
  - Hypertonic drinks/foods during exercise (glucose syrup, honey/maple syrup, salt tablets, excessive caffeine, high protein intakes)
  - Excessive fluid intake;
  - Not consuming carbohydrates before exercising;
  - Malabsorption, Maldigestion, Indigestion, decreased gut permeability;
  - Gut barrier dysfunction;
  - Decreased gut motility;
  - Small intestine transit time (too slow or too fast);

- Increased colonic transit, reduced whole gut transit time;
- Illnesses (especially inflammatory bowel disease, stomach ulcers);
- Hypothermia;
- Heat & humidity (sweat evaporation limitations);
- Microbiome makeup/changes;
- Certain medications;
- Coffee instead of caffeine;
- Ignorance of how your body and GI tract work;

- Adverse Outcomes:
  - Mucosal damage (small intestines);
  - Blood loss;
  - Endotoxemia (microbiota invasion or ingress of microbial poisons);
  - Anaphylaxis / allergic reactions (food-born or airborne allergen ingestions);
  - Decreased exercise performance and recovery;
  - Hemorrhagic gastritis;

- Plus Side
  - Usually symptoms are mild;
  - Usually no health risks;
  - Nutritional (gut) training reduces risk of GI discomfort;
  - Training/practice sessions to trial new nutritional practices;
  - Appropriate hydration & nutrition choices;
  - Choose rapid gastric emptying foods/drinks;
  - Carbohydrate mouth rinses (for exercise less than an hour);
  - Multiple transportable carbohydrates (MTCs – glucose- & fructose-containing carbohydrates during exercise);
  - Certain amino acids (BCAAs, L-Glutamine) specifically support GI health, including the GALT (Gut-Associated Lymphoid Tissue);
  - Increased nitric oxide production;
  - Additional prebiotic and/or probiotic supplementation (microbiome manipulation) can be added when using MultiV-PRO;

Citations for Ultra-endurance Exercise GI Issues: Brouns 1987, 1993; Burke 2019 73; Chantler 2021, 2022; Clark 2016, 2017; Clauss 2021; Costa 2017, 2019 58; de Oliveira 2009, 2011, 2014 4191, 2014 S79, 2017; Fine 2013; Gu 2021; Hughes 2021; Jeukendrup 2011; King 2021; Lim 2016; Murray 2006; Ogden 2020; Pearce 2011; Peters 1999 767, 1999 1570; Pfeiffer 2012; Rehrer 1992; Simons 2004; Stuempfle 2015; Tai 2021; ter Steege 2012 516, 2012 931; Urwin 2021; van Wijck 2011, 2012; Wegierska 2022; Wilson 2022; Wright 2011; Zeppa 2020; Zhang 2022, 2023 1158, 1787

GI Health is dependent on your guy microbiome

Your GI tract is loaded with more microorganisms than you can count (trillions), outnumbering your own cells thousands of times. Not only bacteria, but fungi, viruses and sometimes multicellular creatures are also part of gut microbiomes. This is collectively called the gut microbiome, and great strides in understanding its importance have been made recently, but some basic knowledge is apparent. The shortest way to convey the importance of your gut microbiome is to think of all those germs as another entire, multi-pound organ, like a liver or brain or heart, fully connected with your body and dependent on your dietary intake. Or an entire other symbiotic organism that adapts, changes, communicates and depends on what happens to you, what you do and what you do to it.

Gut microbiomes rely on what you eat to survive in harmony with your GI tract and fellow microbes (microbiome), and they provide numerous biochemical compounds, such as B & K vitamins, butyrate, and more that are part of your overall health and well-being. Many of these your cells cannot make. Your microbiome keeps you healthy by protecting against opportunistic invaders. In short, your microbiome needs attention, too, just like your muscles, brain, eyes, etc. It's a part of you, like it or not.

Why your gut microbiome is important for your ability to exercise

The following Table outlines some of the many ways your gut microbiome, and thus, your GI tract, is indispensable for health and physical performance.

- Microbiome Facts
  - Your digestive tract, from mouth to esophagus to stomach to small intestine to colon to rectum to perineum has vastly different types and amounts of microbes;
  - Gut microbes are in intimate contact with your gut lining cells;
  - Dietary changes cause reproducible changes in types and numbers of microbes that help metabolize any macronutrients you ingest;
  - Microbiome is part of your intestinal barrier, inhabiting the mucus layer touching gut lining cells;
  - Microbiome participates in immune functions bodywide;
  - Mucus from your gut lining cells plays a huge role in microbiome health (and thus your overall health);
  - Microbiome acts like an endocrine organ that secretes hormones and neurotransmitters that controls the hypothalamus-pituitary axis (HPA);

- Microbiome Exercise
  - Type of exercise, more than type of diet composition, affects what kind of microbiome athletes have;
  - Training load / exercise stress are more important than diet composition for microbiome changes;
  - Elite endurance athletes have a different microbiome from sedentary or casual exercisers;
  - Among elite endurance athletes, there are microbial patterns that can identify and distinguish what kind of exercise an athlete does – for example, microbiomes are different between runners and cyclists, and both are different from cross-country skiing;
  - An elite endurance athlete's microbiome contributes to energy metabolism by producing metabolites your body can use, both to keep your gut active when its blood supply dwindles, and to send signals to your muscles to tweak your energy production.
  - Elite athlete diets (and dietary recommendations) show reduced microbiome diversity and function because of reduced plant polysaccharide (i.e., fiber) intake;
  - Microbiome is suspected to participate in catabolic effects that decrease exercise performance and recovery – there are some patterns you do not want;
  - Microbiome is suspected to play a role in causing psychological conditions (behavior, depression, mental fatigue, lack of clarity) that affect exercise performance;
  - Inflammatory cytokines from microbial molecules exacerbate GI permeability and health, decreasing exercise performance and recovery;
  - Microbial molecules increase with increasing psychosocial and physical stress – typical of elite endurance athletes;

The complexity of the microbiome cannot be emphasized enough. The advent of several meta-technologies was needed to delve into the intricacies, which are still being sorted out. In the future, it might even be possible to do a fecal transplant and become an instant winner (with apologies to all the Tom Brady poop jokes – but there is science behind the humor). More likely is instillation of high-dose mixtures of probiotics to give you a competitive edge in endurance exercise.

But these practices are still not ready to make a difference (and be banned by sports regulatory agencies – you'll have to pee in a cup and poop in a bag for prohibited substances testing). And just upping your intake of the usual probiotic suspects (*Lactobacilli* and *Bifidobacteria*) is not enough to improve performance across the board, although health improvements are possible.

What can you do to coerce your gut microbiome to help your performance and health other than exercise and train hard? One way is prebiotics – foods that we humans do not metabolize but our favored gut bugs do. Feed those microbes with unpronounceable-names something they like. In short, keeping your gut microbiome happy and well-fed with prebiotics favors your gut microbiome to be more resilient to the ravages of extreme exercise, and a partner in performance.

Citations for Importance of Microbiome for Exercise: Aya 2021; Boisseau 2022; Bragina 2021; Campaniello 2022; Cataldi 2022; Cella 2021; Clark 2016, 2017; Clauss 2021; David 2014; Dorelli 2021; Dziewiecka 2022; Galle 2019; Han 2020; Hintikka 2022; Hughes 2021; Kulecka 2020; Langlands 2004; Lee 2022; Mankowska 2022; Marttinen 2020; Mohr 2010, 2020; Nysten 2023; O'Brien 2022; O'Donovan 2020; Ortiz-Alvarez 2020; Petersen 2017; Sandroni 2022; Wegierska 2022; Wright 2011; Zeppa 2020, Zhang 2023 1158, 1787

Agave inulin is a prebiotic for gut health

One lesson so far from gut microbiome studies is that a proactively exercise-friendly gut microbiome type and amount is partly dependent on plant fiber intake, especially fermentable (meaning food for gut microbes) carbohydrates. The premier fermentable carbohydrate that your gut cannot digest but your microbiome can is the Fructans, aka Fructose OligoSaccharides, aka FOS. Like MTCs for your microbiome.

Other fibers are less active than FOS, and foods rich in FOS are few and far between in typical modern human diets. For example, when was the last time you ate an entire Jerusalem artichoke instead of a baked potato? What is your Jerusalem Artichoke/Potato intake ratio? Thought so – close to zero.

This is where FOS supplements come into play: supplying Fructans that you cannot digest or extract caloric energy from, but that your exercise-friendly gut microbes thrive on. Inulin is the predominant Fructan in our diets, mostly from chicory roots and Jerusalem Artichokes – but those are not important sources in reality. Inulin supplements from those roots have been the major source for extraction of inulin, but a new source – Agave cactus roots as a byproduct of tequila production, has emerged as a readily available, higher-yield, ecologically friendly, renewable source of inulin. MultiV-PRO uses Agave inulin, which happens to have better properties for feeding gut microbiomes than other dietary Fructan sources.

Inulin is FOS – a chain of fructose molecules strung together like glucose is strung together in starch. But because fructose has that keto group that makes it considerably chemically different from glucose, fructose chains cannot be broken down (digested) by human amylase starch-digesting enzymes or by acid. When you consume inulin, it goes straight to the mob of colonic microbes, specifically to exercise-friendly microbes like Bifidobacteria and many more species. No or very little of the fructose released by inulin digestion in the colon gets into your bloodstream, so inulin is not a fuel source for your muscles – but it is for your friendliest gut microbes, and they can help fuel you.

A recent human study administered 100 mg of inulin – a lower amount than in MultiV-PRO – to healthy persons 60-80 years of age

(De Giani 2022). Fecal beta-defensin2 levels were increased after 28 days. These results lend additional support for the 200 mg Agave Inulin daily amount in MultiV-PRO providing gut health and immune health support.

Why is a lower dose of inulin so important? It might seem oxymoronic that lower doses of prebiotics are more helpful than big doses, but in fact, higher doses start to feed the less-friendly gut microbes that beat up on the favored microbes. The dose-response curve for prebiotics goes up, then down, with increasing dosages – we aim for the high point of the hump.

Citations for Agave Inulin as Prebiotic: Clark 2016; De Giani 2022; Dou 2022; Du 2023; Heimer 2022; Jager 2019; Miles 2020; Mohr 2022; Pandey 2015; Pugh 2019; Roberfroid 2010; Schreiber 2021; Shing 2014; Tavares-Silva 2021; Tiller 2019; Wiacek 2023; Yadav 2022; Zhang 2022

Inulin & Exercise

Prebiotic supplementation for eight weeks increased iron status in female athletes with low iron status (Sandroni 2022). Six weeks of inulin with other prebiotics administered to male soccer student-athletes led to a 33% decrease in URTS, and decreased levels of CRP, IL-6 and IL-8 (Zhang 2022, 2023). After prolonged aerobic exercise, IL-4, IL-10 and TGF-beta1 levels were reduced. This product also contained Vitamin D, selenium and zinc, making it closer to a MVM with inulin and probiotics. Twelve weeks of inulin with low doses of Vitamin D and calcium administered to Japanese female athletes significantly decreased TRACP-5b, a biomarker of bone resorption, and increased Bifidobacteria occupancy counts, showing that inulin can increase "friendly" gut bacteria in athletes and favor bone maintenance (Ishizu 2020).

The most relevant human study to MultiV-PRO and the gut health/endurance performance link is a study that observed 50 participants (6 women, 44 men) running the 330 km Tor des Geantes ultra-trail competition, lasting between 75-150 hours (Sponsiello 2015). For 30 days before the race, during their training, athletes ingested one serving daily of Nutrimonium, a comprehensive MVM with 1500 mg inulin, 1500 mg L-Glutamine and a Bifidobacterium probiotic, as a powder reconstituted in water. MultiV-PRO has more vitamins, minerals and green tea extract than Nutrimonium, but less Inulin (200 mg), and no L-Glutamine or probiotic. Almost all subjects (91%) reported GI disturbances over the last two years, and two-thirds (65.9%) DNF at least once from GI problems. Questionnaires used for all runners in the event provided data. 36/47 took Nutrimonium during the race. Nutrimonium was well-tolerated during the race (90% of users), and only one subject quit because of GI problems. Only about half of the subjects finished the race before 150 hours, and most of the non-finishers attributed joint problems as the reason to quit, even though half of the subjects also took NSAIDs during the race. A majority of Nutrimonium users (58%) reported benefits compared to previous races, including better GI health, fewer GI symptoms and more power and resistance. Compared to the rest of the racers, the dropout rate attributed to GI problems was less than half for the Nutrimonium group (4.2%, 1/24 vs. 11.3% 6/52). Overall, the provision of inulin, a probiotic and a MVM before and during an ultra-endurance event showed promise for real-life benefits for gut health and performance in one of the most grueling exercise efforts known.

Combining prebiotics with probiotics is called a synbiotic. Reviews have found that synbiotics have shown positive results in exercising populations (Mohr 2022). Also, by taking a prebiotic such as inulin, individuals supplementing with probiotics can select the probiotic of their choice and expect additive effects.

Supplementing inulin (400 mg daily) along with probiotics for 12 weeks to triathletes found significant improvements in gut health six days after the triathlon, compared to a placebo (Roberts 2016). Usually, 1-3 weeks are required for a return to normal for gut health biomarkers. Another synbiotic (Gasteel Plus®) containing 200 mg FOS (Inulin) per serving was given to professional soccer players for a month, and showed improved physical activity, antistress, anxiety and sleep (Quero 2021), but cytokines were unchanged (Quero-Calero 2022).

A high dose of inulin (12 grams daily for six weeks) or maltodextrin placebo was given to healthy sedentary adults, who then performed HIIT training three times weekly (Williams 2022). While VO2max was unchanged in either group, the inulin group showed significant improvements in ventilation thresholds (lactate accumulation and lactate threshold) compared to the placebo group. The inulin group also had an increase in fecal Bacteriodes A and Bifidobacteria. More Bifidobacteria meant better responses to exercise training. Heat maps showed that the inulin group had a more metabolically active microbiome that increased acetate.

In a human study related to exercise, two groups of overweight subjects were given a very large dose of inulin (16 grams) or maltodextrin daily, along with charting physical activity. The inulin group showed significant improvements in BMI and metabolic measurements, and the subjects who exercised more had larger increases of "friendly" gut bacteria (Rodriguez 2022). This study shows the interaction of prebiotics with exercise to improve gut microbial types and metabolic effects of improved metabolism (fuel oxidation).

Prebiotics improve numbers and types of "friendly" gut inhabitants that are also the strains used in commonly used probiotic supplements. Thus, another line of evidence from probiotic human studies and exercise also offers support for daily, long-term use of prebiotics, since the gut outcome (more "friendly" gut bacteria, especially Bifidobacteria and Lactobacilli) is similar. In general, findings from long-term, multi-strain probiotics supplementation for ultraendurance events found less GI symptoms and faster paces, especially in later stages of races (Heimer 2022; Jager 2019; Miles 2020; Mohr 2022; Pugh 2020; Schreiber 2021; Shing 2014; Tavares-Silva 2021; Wiacek 2023).

Prebiotics feed and increase more types of "friendly" gut bacteria than simple addition of single or a few probiotic strains, working in harmony with each person's unique microbiome. Thus, moderate daily doses (~200 mg daily) of inulin FOS Fructans help to maintain gut integrity and function for ultra-endurance athletes.

Citations for Inulin & Exercise: *Clark 2016; Heimer 2022; Ishizu 2020; Jager 2019; Miles 2020; Mohr 2022; Pandey 2015; Pugh 2020; Quero 2021; Quero-Calero 2022; Roberts 2016; Rodriguez 2022; Schreiber 2021; Shing 2014; Sponsiello 2015; Tavares-Silva 2021; Wiacek 2023; Williams 2022; Yadav 2022; Zhang 2022, 2023 1158, 1787*

Literature Quotes for Inulin, Exercise & Gut Health

"In conclusion, FOS supplementation could increase the number of colonic Bifidobacterium spp. while higher dose (7.5–15 g/d) and longer duration (>4 weeks) showed more distinct effects and was well tolerated."
Zeng 2018, Abstract

"Numerous recent animal and human experimental studies have shown that functional inulin possesses multiple bioactivities, including immunomodulatory, antioxidant, ... hepatoprotective, hypoglycemic, and gastrointestinal protective activities."
Du 2023, Abstract

"These results suggest that the prebiotic food [with 2.5 grams inulin daily for 12 weeks] used in this study might have beneficial effects on bone health and gut microbial environment among female athletes."
Ishizu 2021, Abstract

"[Probiotics] Research has produced promising results in GI health, exercise performance and recovery, physical fatigue, immunity, and body composition."
Mohr 2022, p. 14

"Studies have demonstrated enhancement of Ca absorption with prebiotic intake, mainly fructans."
Pandey 2015, 7583

"In the light of current knowledge, it seems that intestinal microbiota intervention may have beneficial effects on the human body, resulting in better athletic performance."
Przewlocka 2020, p.12

"Chronic multistrain pro/prebiotic supplementation during periods of endurance training may provide individual support to minimise GI symptoms through maintenance of intestinal permeability."
Roberts 2016, p. 14
[NOTE: This study followed first-time triathletes during training and after a triathlon, and showed that consistent, long-term use of prebiotics and probiotics improved gut health over a placebo. There were also indications that race times were faster with prebiotics and probiotics. MultiV-PRO is designed for long-term, daily use.]

"This systematic review and meta-analysis showed that probiotic supplementation exerts a positive effect on performance with aerobic metabolism predominance in trained population."
Santibanez-Gutierrez 2022, p.20

"The inclusion of dietary prebiotic nutrients (e.g., fructooligosaccharides, inulin, pectin) may also play an important role in short-chain fatty acid production, which may support epithelial integrity..."
Tiller 2019, p.15

"...prebiotics and non-digestible food substances selectively promote the growth of probiotics and human health through nutrient enrichment, and modulation of gut microbiota and immune system."
Yadav 2022, Abstract

"The concentrations of IL-4, IL-10 and transforming growth factor-β1 (TGF-β1) were significantly reduced in the PG and SG group immediately after the constant load exercise."
Zhang 2023, Abstract

4. GREEN TEA POLYPHENOLS

GREEN TEA (*CAMELIA SINENSIS*)(LEAVES)(DECAFFEINATED)(50% POLYPHENOLS)

Why green tea for Endurance Exercise?

Green tea is a well-known and common source for a class of powerful polyphenols, mostly of the catechin variety. Like other dietary polyphenols (those in Ginkgo, for example), catechins have antioxidant actions, but more importantly, they provide overlooked additional antistress benefits of their own – hormesis. These cellular pathway signaling cascade actions positively affect many inner body workings to fortify exercise metabolism, performance, and overall health.

MultiV contains a concentrated extract of Green tea (Camellia sinensis) leaves, standardized to 50% total polyphenols, without caffeine. MultiV has 100 mg of Green tea polyphenols per serving, mostly as EGCG (epigallocatechin gallate).

Green tea polyphenols are much more than mere antioxidants – they are also antistress, with multiple mechanisms of action. Green tea polyphenols activate hormesis – the body's adaptive response to physical stress. Lower doses activate normal antistress mechanisms, and high doses suppress those mechanisms. (Calabrese 2020, 2021; Mattson 2008; Schirrmacher 2021; Son 2008). Thus, modest doses of Green tea polyphenols (100 mg) cajole your body to help itself when under stress by activating several pathways that affect many important bodily processes including energy metabolism, fat burning, cardiopulmonary functions, normal exercise-induced inflammatory responses, immune functions, brain support, and more.

Another newly discovered and important way Green tea polyphenols helps your overall health is by interacting with your gut microbiome to convert polyphenols to other metabolites with healthy activities (Dingeo 2020; Perez-Burillo 2021; Reygaert 2014; Zhang 2021), another part of how hormesis works.

However, hormesis means that research examining effects of Green tea polyphenols needs to look at exercise that is really stressful, and conduct a dose-response to find the zone of efficacy – both conditions are seldom done, unfortunately. Of course, First Endurance has sifted through a mountain of research to provide the "less is more" amount of Green tea polyphenols, without caffeine or L-theanine (those are in other First Endurance products).

Thus, Green tea extracts, mostly because of those characteristic catechin polyphenols, support your body's cells and tissues in numerous ways, with more help to cells and tissues under stress, adding up to better health, and thus, better overall exercise performance and recovery.

Citations for Why Green Tea for Exercise?: Afzal 2015; Cabrera 2006; Calabrese 2020, 2021; Chacko 2010; Chopade 2008; Cisneros 2017; Cooper 2005; d'Unienville 2021; Dingeo 2020; Higdon 2013; Hodgson 2013 129; Hursel 2009, 2011; Kim 2016; Kruk 2022; Malongane 2017; Jowko 2015 123; Kochman 2020; Mattson 2008; McKinley 2009; Myburgh 2014; Namita 2012; Nobari 2022; Perez 2015; Perez-Burillo 2021; Phung 2010; Reygaert 2014; Ruiz-Iglesias 2021; Santangelo 2007; Schirrmacher 2021; Sinija 2008; Son 2008; Tipoe 2017; Williams 2004; Willems 2018 18; Zhang 2021

EFFECTS OF GREEN TEA POLYPHENOLS (CATECHINS) ON EXERCISE PERFORMANCE & RECOVERY

Effects (What)	Mechanisms (How)
ANTIOXIDANT	• Advanced Glycation End Products (AGEs) formation inhibition • COX, NADPH-Oxidase suppression • DNA damage inhibition • Endogenous antioxidant enzyme (Catalase, GPx, SOD) increase • Excess iron binding, preventing additional ROS formation • Free radical scavenging (deactivation & removal) • FoxO receptors activation (increased synthesis of endogenous antioxidant enzymes – catalase, MnSOD, selenoprotein P, ceruloplasmin) • Lipid peroxidation (fat rancidity) reduction • LDL oxidation (damage) decrease • NF-kappaB stress signaling inhibition • Oxidative stress reduction • Peroxynitrate formation reduction • Protein/enzyme damages prevented by AGEs reduction • ROS (Reactive Oxygen Species) reduction • TNF-alpha stress signaling inhibition
ANTISTRESS	• FoxO receptors (antistress) activation • Hormesis (Antistress) • Reduces NF-kappaB, AP-1 • Regulates the 'cellular thiostat' of cell signaling cascades towards antistress effects • Reduces excess pro-inflammatory cytokines/mediators
BODY COMPOSITION	• Akt/protein kinase B (Akt/PKB) regulation • AMPK receptor signaling • Appetite modification • Fat oxidation (burning) • Gene expression • Glucose control • Increased energy expenditure • Leptin regulation • Mitogen-Activated Protein Kinase (MAPK) regulation • Protein kinase C (PKC) regulation • Sympathetic nervous system activation • Tyrosine kinase signaling • Reduction in body weight in overweight persons is hit or miss – other factors help (caffeine) or hinder (cultural practices, genetic variations and long-term compliance) effects

Effects (What)	Mechanisms (How)
ENERGY METABOLISM	• Akt/protein kinase B (Akt/PKB) regulation • AMPK receptor signaling • Appetite modification • Beta receptor activation increased • Norepinephrine increased via COMT inhibition • Protein kinase C (PKC) regulation • Sympathetic nervous system activation • Increased ketones formation • Increased BCAAs into energy-producing pathways • Increased lipolysis & fat oxidation • Increased insulin sensitivity • Lipolysis stimulation • Increased muscle GLUT4 receptors (glucose influx) • PPAR receptor activation • Increased whole body energy expenditure • Synergy with caffeine • Activates FoxO receptors (fuel metabolism regulation)
EXERCISE PERFORMANCE	• Increased VO2max • Faster endurance performance times • Increased arterial-venous oxygen ratio • Increased catalase in serum • Increased energy expenditure • Increased fat utilization for energy during exercise • Increased SIRT-1 • Synergy with caffeine
EXERCISE RECOVERY (DOMS, EIMD, MUSCLE DAMAGE)	• Glucose uptake & utilization increased in muscle • Malondialdehyde (MDA), marker for oxidative stress, reduced • Markers of tissue damage reduced (CK, Myoglobin) • Mesenchymal stem cells activated to remove degraded collagen • Neutrophil/Lymphocyte ratio decreased
FAT BURNING	• Adipose cell GLUT4 receptors decrease (less glucose uptake for fat synthesis) • Beta-hydroxybutyrate serum levels increased (more fat burning during exercise) • Norepinephrine increased via COMT inhibition • Beta receptor activation increased • Glycerol serum levels increased (more fat burning) during exercise • PPAR-gamma coactivation • Sympathetic nervous system activation • Synergy with caffeine • Thermogenesis

Effects (What)	Mechanisms (How)
HEALTH (HORMESIS)	• Adaptive responses to stress improved • Epigenetic effects
IMMUNE	• Protects immune cells • Regulates T cell functions by influencing miRNAs that regulate expression of calcium channel signaling
GUT MICROBIOME	• Improves ratio of healthy microbes • Reduces unhealthy microbes • Healthy microbes produce beneficial metabolites

Green Tea Exercise Effects - How to do it right

The Table above lists some of the many ways that Green tea polyphenols can positively affect exercise performance. Green tea polyphenol/catechin extracts have multiple roles promoting endurance exercise and recovery that affect many metabolic pathways. This is why it is important to include multifactorial, broad-spectrum, active ingredients like Green tea extract or Ginkgo in a daily MVM – to ensure long-term, consistent intake of essential micronutrients (vitamins and minerals) necessary for maximal responses to non-essential nutrients like Green tea and Ginkgo polyphenols.

Green tea's catechins and metabolites are well-studied antioxidants, adding to overall antioxidant status and cell signaling as part of hormesis. Like exercise training, it's important to take Green tea extracts continuously for long time periods. Weeks are better than days and months/years are better than weeks. Why? This is what an overview of Green tea extract scientific literature tells us. More often, not more. How come? Because they exert their effects by cell signaling and changing cell behavior over longer time periods built up with chronic, daily use. After a single dose, the absorption, uptake and bioavailability of Green tea catechins is spread over six or more hours, and longer for any gut microbiome effects. Green tea polyphenols are not stimulants with immediate effects like caffeine – they need time to reach and change metabolic pathways to show their potential. The same mechanisms that affect exercise performance also affect overall health, and there is plenty of evidence for better human health with long-term ingestion of green tea.

To illustrate that this process takes time to show exercise benefits because it works with your body's adaptive responses, a human study of a single dose of Green tea catechins taken immediately before a resistance training bout did not show improvements in performance or recovery (Jowko 2011, 2012). The same research group used four weeks of Green tea polyphenol supplementation with sprinters and found increased antioxidant activity without hindrance of training adaptation (Jowko 2015 783). Other studies showed that green tea polyphenols taken over 10 weeks of aerobic cycle ergometry training at 60% VO2max for 60 min/day, three days per week significantly lowered RER (Respiratory Exchange Ratio), indicating greater whole-body fat utilization during moderate exercise (Ichinose 2011). The strength of this study (and many others with long durations of intake) was the relatively long-term supplementation period, compared to other less positive studies of acute, single-dose supplementation, or duration for only a few days, not allowing Green tea polyphenols to build up adjustments to metabolism. Duration matters. For results in humans, days are better than once, Weeks are better than days, months to years are better than weeks. Again, another reason for Green tea polyphenols to be taken daily in MultiV-PRO.

Green Tea Extracts for Endurance Performance

Reviews of the human exercise findings acknowledge that Green tea polyphenols have evidence for enhancing aerobic exercise performance with more fat burning for energy (Bowden 2016; Hodgson 2013 129; Jowko 2015 123; Kim 2016; Nobari 2022; Turkozu 2017).

At least 68 separate human study reports have examined many facets of exercise performance in many types of subjects from elite athletes to sedentary obese postmenopausal couch potatoes, and results range from enhanced endurance exercise performance to no difference from baseline or placebo groups. 29 Studies used endurance exercise, 24 used HIIT or resistance training exercise, and 21 studies used overweight, obese or diabetic subjects and exercise. Thus, the large number of Green tea extract studies is scattered over a wide range of exercise types and subject types, without getting into actual measurements of performance and physiology.

In other words, by cherry-picking the published research, one can come up with any conclusion one wants about Green tea extracts and exercise performance. Research being what it is, no one study is perfect, and there are multiple endpoints to measure and report from each study, so that means pulling together the entire gaggle of studies and looking for relevant, common patterns is more important for figuring out what this means for you. We prefer to pick sweet ripe cherries from the most prolific trees. Picking anything else is sour, dour cherries. As expected, the more studies that are examined, the stronger the conclusion has become that nobody can say that Green tea extracts have no benefits for exercising individuals (unless one is an ostrich with their head buried in sand). The corollary is that Green tea extracts do have significant benefits for exercising individuals.

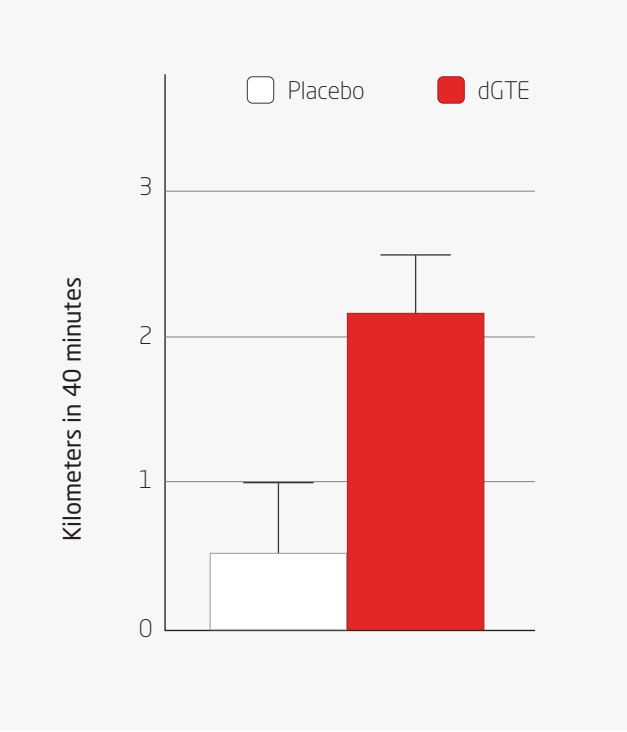
At First Endurance, we believe in being thorough when looking at published research, and acknowledge the strengths and weaknesses of each study, and synthesize the bottom line. For Green tea extracts, that bottom line is that endurance exercise performance is improved when used in moderate doses chronically (daily), which is why Green tea extract is in MultiV-PRO – so you will ingest it daily. Let's take a look at studies showing benefits for endurance exercise performance

Green Tea extracts & Endurance Performance - Human Study Results

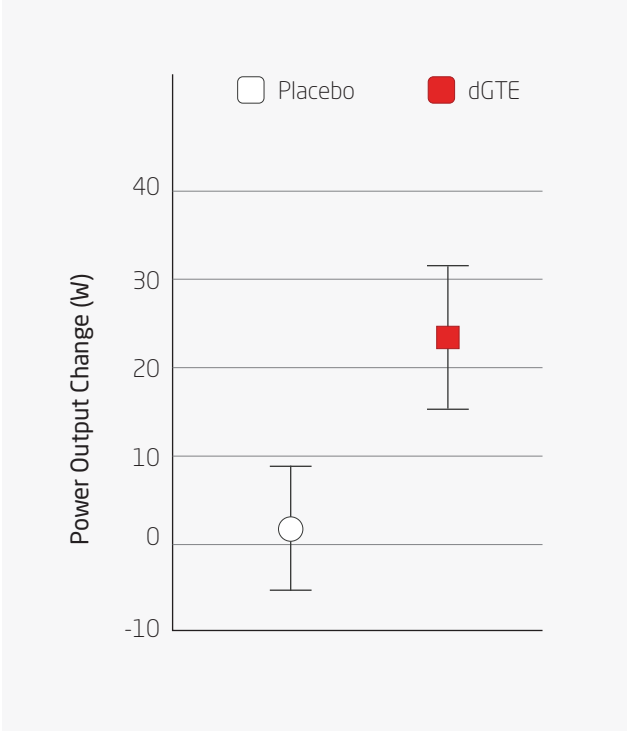
The first green tea and exercise study highlighted is by Roberts from Anglia Ruskin University and University of Hertfordshire, UK (Roberts 2015). This study was originated to explore the modest results from previous findings of short-term Green tea extract studies lasting 28 days or less (Dean 2009; Eichenberger 2009, 2010; Randell 2014). A dose of 571 mg decaffeinated green tea extract supplying 400 mg EGCG given daily for four weeks was chosen. Fourteen subjects were divided evenly into two groups of seven men each – placebo and Green tea extract. Cycle ergometer exercise was conducted at 0, 2 and 4 weeks, consisting of one hour at 50% VO2max followed by a 40-minute self-paced performance trial. Diets were standardized the day before exercise testing.

Fat oxidation during exercise was significantly increased 24% by Green tea extract compared to placebo. Body fat percentage was decreased significantly more in the Green tea extract group (-1.63 vs. -0.66 %) without raising resting heart rate or blood pressure. Total and percent carbs oxidized were reduced in the Green tea group but did not change in the placebo group. Likewise, respiratory exchange ratio (RER) was reduced in the Green tea extract group, supporting the finding of more fat burning. After four weeks, distance covered in the 40-minute performance trial was significantly increased 11% by Green tea extract but not significantly in the placebo group. Similarly, average Power output (Watts) was not increased in the placebo group but significantly increased 23% in the Green tea extract group. These two measurements are illustrated in the figures below.

Distance Change 0-4 Weeks



Power Output Change 0-4 Weeks



Adapted from Roberts 2015, page 7.

Similarly, a significant improvement for run time to exhaustion was found over inactive controls, inactive controls plus Green tea extract, and a trend for improvement over exercise-only group (15 vs. 8 %) by Green tea extract with exercise after four weeks of supplementation with 250 mg Green tea extract (82% catechins for 200 mg catechins per day) (Kuo 2015).

Another endurance human study in active, non-elite athlete adults found improved (4.4%) VO2max, but not other measures of exercise metabolism, after short-term (two day) supplementation with a high-dose EGCG green tea extract (Jowko 2015 123, Richards 2010). Cycling times were 10-12 minutes, which is less relevant to long-duration endurance exercise, but does illustrate that a high dose of green tea catechin has benefits for exercise performance. [EGCG is epigallocatechin-3-gallate, the predominant catechin in green tea leaves.] Other studies also found increased VO2max after Green tea extract administration.

Most studies that looked found increased fat oxidation and increased antioxidant activity/protection during exercise from Green tea extracts. Longer times of administration (at least four weeks) of Green tea extracts was more often associated with finding improved exercise parameters.

Green Tea & Excercise Studies - Tea cup shell game or looking under the wrong cup?

Other studies examined effects of Green tea polyphenols on endurance exercise performance and found few improvements in physiological measurements and performance, likely because supplementation was acute (not chronic) and exercise durations were too short and/or not stressful enough to illustrate antistress effects (Eichenberger 2009, 2010; Martin 2014). Other confounders were crossover periods too short to remove all effects of chronic Green tea polyphenol effects, and not allowing caloric intake during exercise, which would allow Green tea polyphenols to have more opportunity to improve carbohydrate and fat oxidation. And as is true for almost all exercise performance studies, variation in nutritional adequacy of essential micronutrients is never measured, accounting for greater variability between subjects, especially in studies with low subject numbers. This is why it is important to include broad-spectrum ingredients like Green tea extract or Ginkgo in a daily MVM – to ensure long-term, consistent intake of essential nutrients necessary for maximal responses of pathways dependent on non-essential nutrients, like fat burning. Some improvements in biomarkers of stress (CRP, serum creatine kinase levels, heart rate, serum glycerol) were found, indicating that Green tea polyphenol doses were active for their main effects, including lipolysis. Also, studies on ultra-endurance athletes with usual during-exercise nutrient intakes has yet to be performed. However, the increased stress from intense, long-duration exercise also gives Green tea extracts a chance to produce a more measurable difference in exercise measurements.

One overlooked crossover study simultaneously measured hundreds of compounds in blood or urine to track system-level metabolic changes from a green tea drink after strenuous exercise by NMR-based metabolomics (Miccheli 2009). Three blood samples and two urine samples were collected at rest, immediately after exercise and two hours after exercise around a morning rowing ergometer protocol of warm-up, 1000 meters max speed and 50 minutes of submaximal exercise to produce dehydration. Then an isotonic sports drink with green tea (~400 mg polyphenols) and fructose or mineral water placebo was administered. Multivariate analysis found an effect of green tea hydration drink on energy metabolism and glucose homeostasis, with blood glucose, insulin and ketone body production with depressed lactate and lipogenesis being significantly greater than mineral water placebo. This type of study also confirmed that variation between individuals is greater than the effect of the nutritional intervention. This means Green tea extract can make you perform better, but that might still not be enough for you to overcome your nemesis. Or it might if you are close!

Summing up, there are sufficient well-designed, well-conducted, statistically powered studies to show endurance performance benefits from a wide range of Green tea extracts doses. Conditions for success are: 1) doses of 100 mg catechins or more daily, but less than 1000 mg; 2) chronic intakes (weeks, months years) – not once and done or 1-3 days of intake; 3) exercise intensity enough to elicit stress (long enough and/or hard enough) and 4) subjects healthy enough to not have essential micronutrient deficiencies that hold back metabolic performance.

Citations: Green Tea & Exercise Performance: Human Studies: *Afzalpour 2014; Alikhani 2021; Azizbeigi 2019; Bagheri 2020; Bajerska 2010; Banitalebi 2016; Beak 2017; Blicher 2021; Bowden 2016; Chen 2020; Dean 2009; Eichenberger 2009, 2010; Fathei 2016; Fox 2020; Gahreman 2015, 2016; Ghasemi 2012, 2020; Goewanan 2013; Haghighi 2015; Hoseini 2016; Hodgson 2013 325; Hoseini 2016; Ichinose 2011; Jacobs 2014; Jo 2006; Jowko 2007, 2011, 2012, 2015 783; Jurcau 2013; Khosravi 2019; Kondori 2021; Kuo 2015; Lin 2014; Lloyd 2014; Martin 2014, 2016 1057, 2016 1282; Miccheli 2009; Moradi 2014; Nejati 2019; Ota 2005, 2016; Pourmohamadi 2020; Qu 2007; Rad 2020; Rahimi 2017 9; 2017 e55438; Randell 2013, 2014; Richards 2010; Roberts 2015; Rostamian 2017; Sadowska-Krepa 2019; Shahidi 2019; Sobhani 2020; Sugita 2016; Suzuki 2015; Tsai 2017; Vakili 2015; Venables 2008; Willems 2018 536, 2021; Zolfaghari 2018*

Citations: Green Tea & Exercise Performance Reviews: *Cabrera 2006; d'Unienville 2021; Goncalves 2022; Higdon 2003; Hodgson 2013 129; Hursel 2011, 2013; Jowko 2015 123; Kim 2016; Kochman 2021; Myburgh 2014; Nobari 2022; Perez 2015; Rains 2011; Rasaei 2021; Rojano-Ortega 2021; Ruiz-Iglesias 2021; Sinija 2008; Stohs 2016; Turkozu 2017; Willems 2018 18*

Green Tea DOMS, EIMD, Recovery

At least 21 reports of human studies administered green tea extracts to exercising humans and reported on Delayed Onset Muscle Soreness (DOMS), Exercise-Induced Muscle Damage (EIMD) or recovery post-exercise. Only three studies used endurance athletes (Hadi 2017; Machado 2018; Michnik 2017), and four other studies used sedentary subjects starting endurance exercises (Jordan 2007; Kuo 2015; Moradpourian 2014 192, 2014 520; Ota 2016). All seven studies had male subjects.

54 Team soccer players were studied at Day 0 and six weeks later for three muscle damage markers (serum enzymes AST, CK, LDH), Malondialdehyde (MDA, a marker of oxidative damage) and Total Antioxidant Capacity (TAC) of serum (Hadi 2017). Green tea extract dose was 450 mg (50% polyphenols) for six weeks. MDA levels were significantly lowered by Green tea extract, but no other markers were changed – the Placebo group showed no change in any marker, indicating the exercise was insufficient to elicit muscle damage. Green tea extract did reduce markers of oxidative damage – an antioxidant effect without changing or decreasing exercise effort.

16 trained competitive cyclists and/or runners were tested for Peak Power Output and then given Placebo or Green tea extract (500 mg, 37% polyphenols) for 13 days, followed two days of exhausting knee extensions and the next day, one hour cycling at 60% peak power output (Machado 2018). Measurements were made before and after a non-fatiguing, one-hour cycling at 60% peak power output before taking Green tea extract, and before and after the final cycle test at day 15. Compared to the Placebo group, Green tea group less impaired neuromuscular activity, less muscle damage and less oxidative stress. The authors stated: "Green tea extract supplementation before an event of cumulative fatigue minimizes muscle damage and oxidative stress in trained athletes. It also shows positive effects on neuromuscular parameters related to muscle activation and muscle fatigue. Therefore, GTE supplementation can be considered a valid strategy in the context of competitive endurance sport aiming at exercise recovery and performance of athletes."

Michnik and coinvestigators studied 20 CrossFit exercisers divided evenly between Placebo and Green tea extract groups (Michnik 2017). They received Placebo or 250 mg 98% polyphenol Green tea extract (245 mg polyphenols) daily for six weeks. Before and after six weeks, all subjects performed a VO2max cycling test to exhaustion. Post-exercise blood lactate levels increased from 0-6 weeks in both groups, but creatine kinase (CK) serum levels, a marker of muscle damage, decreased in the Green tea group but increased in the Placebo group from 0-6 weeks. Serum LDH were not different between groups, but differential scanning calorimetry temperature measurements showed some changes by Green tea extract that were related to VO2max. Thus, Green tea extract reduced post-exercise muscle damage from endurance exercise after six weeks of CrossFit exercise.

Four other human studies reported on effects of Green tea extracts after sedentary persons started endurance exercise and found protective effects after downhill running stresses or aerobic training (Jordan 2007; Kuo 2015; Moradpourian 2014 192, 2014 520; Ota 2016). Eight human studies used High Intensity Interval Training (HIIT) or resistance training (RT) exercise protocols (two studies had women subjects) (da Silva 2018; Ghaedi 2021; Herrlinger 2015; Kerksick 2010; Kondori 2021; Jowko 2011, 2012; Panza 2008). All but two studies found some improvements in exercise recovery measurements. Three out of four studies found improvements post-exercise from Green tea extracts in overweight or obese subjects starting exercise programs (Alikhani 2021; Azizbeigi 2019; Martin 2016 1057, 2016 1282).

Reviews of Green tea extracts for recovery (DOMS) found that 250 mg or more for at least four weeks reduced cell damage and biomarkers of oxidative stress and exercise-induced, normal inflammation post-exercise (Volpe-Fix 2023). In addition, combining polyphenols from different sources (like Ginkgo extracts) led to better recovery.

Overall, although most research efforts for exercise recovery were more focused on antioxidant or fat-burning effects of Green tea extracts, relevant studies for endurance athletes found beneficial recovery effects from chronic supplementation with Green tea polyphenol extracts at about twice the dosage as found in a serving of MultiV-PRO. Keep in mind that all these subjects were forbidden to use other supplements, which introduces variability of effects because of deficiencies of essential micronutrients that Green tea polyphenols require for optimal effects, and which MultiV-PRO is designed to make sufficient. Interestingly, high daily doses of Green tea polyphenols (over 1000 mg daily), and acute/short-term supplementation did not show clear benefits, which fits the known mechanism of action for Green tea polyphenols as signaling molecules for muscle repair processes. Thus, Green tea extract at moderate doses has shown benefits for improving muscle recovery, even after daily exercise.

Citations for DOMS, EIMD & Recovery: Alikhani 2021; Azizbeigi 2019; da Silva 2018; Eichenberger 2009; Ghaedi 2021; Goncalves 2022; Hadi 2017; Haramizu 2013; Herrlinger 2015; Jordan 2007; Jowko 2011, 2012, 2016; Kerksick 2010; Khosravi 2019; Kondori 2021; Kuo 2015; Machado 2018; Martin 2016 1057, 2016 1282; Miccheli 2009; Michnik 2017; Moradpourian 2014 192, 2014 520; Ota 2016; Panza 2008; Rickards 2021; Rojano-Ortega 2021; Zapata 2021

Green Tea Antioxidant Effects - No problems with training adaptation

Green tea polyphenols (catechins) have a long and extensive history of providing healthy, beneficial antioxidant actions for humans, both as green tea itself and as Green tea polyphenol extracts like that in MultiV-PRO. Antioxidant effects are noticeable after one cup of green tea, and MultiV-PRO provides more catechins (100 mg), without caffeine, than a cup of green tea. Catechin antioxidant activity has been shown to be the main activity of green tea associated with long-term health, although the many other activities of green tea catechins have also shown benefits.

Most human studies of Green tea extracts and endurance exercise have found beneficial changes in antioxidant status, functions and results. These effects may be a major reason why Green tea extracts show ergogenic effects as already presented. What about the prevailing opinions that antioxidants wreck training adaptations to exercise? Or worse, decrease exercise performance? Not with Green tea extracts, even at high doses. Sedentary people given Green tea extract for a week starting a treadmill exercise program showed decreased fatigue and improved antioxidant functions, with better results after a stress exercise test than the training itself (Jurcua 2013; Kuo 2015). Another study on obese sedentary subjects starting a resistance training program also found improved antioxidant activity (Rahimi 2017). Numerous studies on post-exercise effects of Green tea extracts has not shown worsened recovery, and usually, shows improved recovery – a necessary part of training adaptation. Some of these studies are less relevant to intense, long-duration endurance exercise and are rather short for determining exercise training and adaptation effects, but show that exercise training adaptation is unaffected by large doses of Green tea catechins that provide significant antioxidant activity. Green tea antioxidants are not like nutrient vitamins antioxidants. Likewise, other studies and reviews have not found a negative effect of Green tea polyphenols on exercise training or adaptation. Again, Green tea extract is not like essential nutrient antioxidants.t

Citations for Green Tea Antioxidants & Adaptation: Afzal 2015; Azizbeigi 2019; Ghasemi 2012, 2020; Goewanan 2013; Goncalves 2022; Higdon 2013; Jowko 2007, 2011, 2012, 2015 123, 2015 783; Jurcau 2013; Kim 2014; Klotz 2014; Kondori 2021; Kuo 2015; Lopez-Alarcon 2009; Myburgh 2014; Nobari 2022; Rahimi 2017; Rasaei 2021; Rietveld 2003; Rojano-Ortega 2021; Sinija 2008; Talhi 2014; Tipoe 2017; Yiannakopoulou 2013; Zapata 2021

Green Tea Energy Expenditure / Fat Metabolism

Human studies have found increased fat oxidation and energy expenditure by Green tea extracts, even more so if caffeine is included, in obese, overweight, sedentary, and physically active subjects at rest and during both aerobic and anaerobic exercise. These effects are due to multiple mechanisms of action, including AMPK receptor signaling, PPAR receptor activation and antioxidant activity as well as direct effects on norepinephrine and the sympathetic nervous system (see Table above).

In addition, effects on insulin allow for more carbohydrate used as fuel by making more GLUT4 receptors appear in muscles and fewer in fat cells, decreasing fat synthesis in fat cells and increasing fat and carb burning in muscle. These effects have not been well-studied in endurance athletes, and the dose of Green tea catechins was generally higher than that in MultiV-PRO. These results also suggest that Green tea extracts should be administered chronically, but not necessarily just before exercise. Again, chronic intake of Green tea polyphenols lends itself to daily MVM use rather than pre-exercise supplementation.

As an example, a study of 14 men taking tea catechins for two months while doing treadmill walking at 5 km/hour for 30 minutes three times weekly showed 32% (1.4x) better fat oxidation during exercise and at rest compared to the exercise-only group (Ota 2005). RER (Respiratory Exchange Ratio) showed a trend for a lower value, indicating more fat burning for exercise.

Citations for Green Tea Energy Expenditure / Fat Metabolism: Berube-Parent 2005; Bowden 2016; Chopade 2008; Cisneros 2017; Dean 2009; Esmaeelpanah 2021; Gahreman 2015, 2016; Hodgson 2013 129, 2013 325; Hursel 2009, 2011; Ichinose 2011; Janssens 2015, 2016; Kelemen 2009; Kim 2016; Lloyd 2014; Lonac 2011; Namita 2012; Ota 2005; Rains 2011; Roberts 2015, 2021; Sinija 2008; Stohs 2016; Turkozu 2017; Venables 2008; Westerterp-Plantenga 2010; Willems 2018 536, 2021; Yoneshiro 2017; Yun 2009

Green Tea gastrointestinal health benefits impact performance

Green tea and green tea extracts rich in catechins also have been shown to benefit gut health in human studies. As covered in the Agave Inulin section of this Research Packet, both probiotic and prebiotic supplements improve the ratio of beneficial gut microbes such as Bifidobacteria and Lactobacilli. Green tea extracts with selenium have also shown benefits for gut bacteria ratios (Molan 2013). This additional health benefit of green tea extracts has been underrated, given the significant problems with gastrointestinal issues that serious athletes continuously face.

Green tea polyphenols are only partially absorbed into circulation, and most get into your colon where the majority of your microbiome lies in wait. Those billions of tiny biochemical factories (friendly gut bacteria) convert green tea polyphenols into other compounds that get reabsorbed into circulation, accounting for a major portion of green tea effects, including exercise performance enhancement.

Citations for Green Tea & Gastrointestinal Health: Duda-Chodak 2015; Espin 2017; Fraga 2019; Ikbal 2020; Jin 2012; Marin 2015; Molan 2013; Shin 2007

Green Tea Body Composition / Weight

Many studies have examined the effects of green tea and green tea polyphenols (especially EGCG) on body weight and body composition (decreased body fat percentage with muscle mass maintenance), mostly in overweight, obese, diabetic, elderly and sedentary subjects. Green tea polyphenols have thermogenic actions that participate in maintenance of weight loss that counteract the decrease in metabolic rate during weight loss. Co-administration of caffeine increases these effects. Green tea polyphenol effect on body fat composition is small compared to that of caffeine in sedentary, overweight and obese subjects, although one study found similar results for body weight from aerobic exercise or green tea extract supplementation (Gholamreza 2013).

Effects of green tea or Green tea extracts on body composition/weight in athletes is not as well-studied in lean exercising persons. One study of 30 male wrestlers given Green tea or Oolong tea extracts (with 37 or 186 mg caffeine daily, respectively) for six weeks showed significant losses of body fat (Bajerska 2010). Endurance athletes have low body fat percentages and are possibly less responsive to the benefits of Green tea polyphenols seen for body composition in sedentary, overweight persons, but the activation of thermogenesis in cold conditions was found in lean subjects.

Citations for Body Composition / Body Weight: *Alikhani 2021; Bajerska 2010; Cabrera 2006; Chacko 2010; Cisneros 2017; El-Elimat 2022; Esmaeelpanah 2021; Gholamreza 2013; Haghighi 2015; Hursel 2009, 2010, 2011, 2013; Janssens 2015; 2016; Jo 2006; Jowko 2015; Namita 2012; Phung 2010; Rains 2011; Roberts 2021; Sinija 2008; Stohs 2016; Takeshita 2013; Thieleke 2009; Westerterp-Plantenga 2010; Yoneshiro 2017; Yun 2009*

Green Tea Immune

Green tea polyphenols have shown multiple activities with immune system cells to assist them to respond appropriately and without unnecessary excesses – an important, normal part of exercise recovery as well as overall health.

Citations for Green Tea Immune: *Cabrera 2006; Chacko 2010; Chopade 2008; Cooper 2005; Kochman 2020; Kundu 2021; Lin 2014; Malongane 2017; Reygaert 2014, 2018; Ruiz-Iglesias 2021; Singh 2021; Sinija 2008; Sun 2022; Wang 2021*

Green Tea & Exercise Summary

Green tea extracts containing catechin polyphenols have more than simply antioxidant effects. They also bolster cell signaling for burning fats (lipolysis), increasing glucose uptake into muscles and signal hormesis – the adaptive response to stress, perhaps by additional effects on the gut microbiome. In some human endurance exercise studies, increases in oxygen capacity and better utilization of fats and carbs for energy has been found. For best results, Green tea extracts need to be taken daily at moderate doses, as low and high doses do not work as well. In MultiV-PRO, a moderate dose of Green tea catechins adds to the overall dietary antioxidant supply, but also adds cell signaling properties that work towards better utilization of carbs and fats for energy and antistress effects important for exercise performance, recovery and adaption to training.

Literature Quotes for Green Tea

"The combination of GTE [Green Tea Extract] and exercise also produced greater changes in anti-inflammatory (increases in adiponectin) and metabolic (decreases in hs-CRP) markers than exercise alone.".
Bagheri 2019, Abstract

"Tea is the most consumed drink in the world after water. Green tea is a 'non-fermented' tea, and contains more catechins, than black tea or oolong tea. Catechins are in vitro and in vivo strong antioxidants. "
Cabrera 2006, Abstract

"The review also provides a focus on the adaptive features of hormesis, i.e., its capacity to upregulate acquired resilience and how this can be mediated by numerous plant-derived extracts, such as curcumin, ginseng, Ginkgo biloba, resveratrol, and green tea, that induce a broad spectrum of chemopreventive effects via hormesis."
Calabrese 2021, Abstract

"Polyphenols can impact the composition of the gut microbiota (which are independently associated with health benefits), and gut bacteria metabolize polyphenols into bioactive compounds that produce clinical benefits."
Fraga 2019, Abstract

"A number of studies have observed positive effects of GTE on fat metabolism at rest and during exercise, following both shorter and longer term intake."
Hodgson 2013 129, Abstract

"...CCRTs [catechin- and caffeine-rich teas] may be useful agents that could help in preventing a positive energy balance and obesity."
Hursel 2013, p.1682S

"These results suggest that habitual GTE ingestion, in combination with moderate-intense exercise, was beneficial to increase the proportion of whole-body fat utilization during exercise."
Ichinose 2011, Abstract

"In conclusion, green tea consumption might act as a prebiotic and improve the colon environment by increasing the proportion of the Bifidobacterium species."
Jin 2012, Abstract

"Therefore, EGCG is a typical example of a hormetic substance that does have an effect at low concentrations which is actually inverted at higher concentrations."
Klotz 2014, p.138
[NOTE: This means that less Green tea polyphenols has beneficial effects, a guidance for the dose of 100 mg Green tea polyphenols per serving in MultiV. Too much of a good thing (antioxidants) is not always good in biology – the U-shaped curve effect.]

"In any case, when discussing cellular responses to a given signal, the idea of a signaling cascade embedded in an entire network of sensors, checkpoints, controls, response elements, and feedback mechanisms and loops needs to be taken seriously."
Klotz 2014, p.128

"Moreover, endurance training combined with GTE [Green Tea Extract] not only increases antioxidant capacity without attenuating endurance training adaptations, but also further attenuates exercise-induced CK (Creatine Kinase) release."
Kuo 2015, Abstract

"Green tea extract supplementation before an event of cumulative fatigue minimizes muscle damage and oxidative stress in trained athletes. It also shows positive effects on neuromuscular parameters related to muscle activation and muscle fatigue. Therefore, GTE supplementation can be considered a valid strategy in the context of competitive endurance sport aiming at exercise recovery and performance of athletes."
Machado 2018, p.7

"In the fields of biology and medicine hormesis is defined as an adaptive response of cells and organisms to a moderate (usually intermittent) stress. Examples include ischemic preconditioning, exercise, dietary energy restriction and exposures to low doses of certain phytochemicals. ... As a result, cells increase their production of cytoprotective and restorative proteins including growth factors, phase 2 and antioxidant enzymes, and protein chaperones."
Mattson 2008, Abstract

"Due to its many properties, green tea improves physical and physiological function of the body during exercise by diminishing oxidative stress..."
Nobari 2022, p.11

"In conclusion, it was found that body fat utilization for energy expenditure was more effectively increased in both sedentary and exercising conditions by the combination of tea catechins intake and regular exercise than by the exercise alone.
Ota 2005, p.236

"The administration of GTCs with caffeine is associated with statistically significant reductions in BMI, body weight, and WC; however, the clinical significance of these reductions is modest at best. Current data do not suggest that GTCs alone positively alter anthropometric measurements."
Phung 2010, Abstract
[NOTE: Reported lack of effect from Green tea catechins alone was based on only two human studies. The larger study showed significant decreases in BMI, body weight, and waist circumference. The smaller study had a large variability that made the statistical analysis not significant when both studies were lumped together. Also, later studies found improvements in body composition from Green tea polyphenols.]

"Consuming polyphenol-rich foods, juices and concentrates accelerated recovery of muscle function while reducing muscle soreness in humans."
Rickards 2021, Abstract

"A dose-response relationship to stressors, according to the hormesis theory, is characterized by low-dose stimulation and high-dose inhibition. It is non-linear with a low-dose optimum. Stress responses by cells lead to adapted vitality and fitness. Physical stress can be exerted through heat, radiation, or physical exercise."
Schirrmacher 2021, Abstract

"There is hardly any other food or drink reported to have as many health benefits as green tea."
Sinija 2008, pp.232-3

"Because green tea diet has an inhibiting effect on insulin, green tea diet therefore helps keep sugar from being stored as fats and, instead, sends them directly into the muscles for immediate use."
Sinija 2008, pp.232-3

"...the majority of human epidemiological and intervention studies demonstrate beneficial effects of green tea or green tea extracts, rich in EGCG on weight management, glucose control and cardiovascular risk factors."
Thieleke 2009, Abstract

"Overall, pre-clinical and clinical studies have shown that body weight and fat mass of human subjects and animals given green tea catechins decreased significantly."
Yun 2009, p.142

"It is interesting to note that EGCG significantly stimulated the glucose uptake for the antiobesity action, which was accompanied by a decrease in translocation of glucose transporter 4 (GLUT4) in adipose tissue, while it significantly stimulated the glucose uptake with GLUT4 translocation in skeletal muscle."
Yun 2009, p.143

"TPs [Tea Polyphenols] can act indirectly on the central nervous system by affecting the "microflora–gut–brain axis", in which the microbiota and its composition represent a factor that determines brain health. Bidirectional communication between the intestinal microflora and the brain (microbe–gut–brain axis) occurs through a variety of pathways, including the vagus nerve, immune system, neuroendocrine pathways, and bacteria-derived metabolites. This axis has been shown to influence neurotransmission and behavior..."
Zhang 2021, Abstract

5. GINKGO BILOBA

ALTITUDE, ANTISTRESS, CIRCULATION, ENERGY METABOLISM, EXERCISE PERFORMANCE & RECOVERY, FAT METABOLISM, GUT MICROBIOME, OXYGEN, NITRIC OXIDE, RECOVERY

Why is Ginkgo for Endurance Exercise?

When First Endurance added a Ginkgo biloba extract to MultiV, eyebrows were raised. Why add something to a MVM that had not been studied yet in endurance performance, taking up valuable room for other essential nutrients? Did we have secret knowledge or information? The answer required an educated leap of faith about what Ginkgo does based on use in older humans with poor cardiovascular, mental and physical health. The leap of faith has turned out to be inspired genius. Although Ginkgo was a promising idea years ago when MultiV was first launched, scientific research has been catching up to its promise of cardiovascular and energy metabolic support, with more than 1000 human clinical trials published, mainly focused on mental health in the elderly. New research methods are providing more evidence on how the unique polyphenols in Ginkgo have far-reaching, additive beneficial effects that also help maintain endurance performance and improve recovery – effects that are not found by any other single ingredient. In other words, synergy with adequate status of all essential micronutrients, which MultiV & MultiV-PRO supply.

Ginkgo's Secret

Ginkgo trees are oddly unique. They have distinctive, fan-shaped leaves and tiny apricot-looking seeds. Now a commonplace ornamental tree originally from East Asia, Ginkgo trees are living fossils – the oldest tree on Earth and the only member of its taxonomic Order, a rare occurrence in Nature. Ginkgo trees appeared 290 million years ago, preceding anything except ferns and cycads on land. Its name is a mistake by Europeans mispronouncing the original Japanese name (gin kyo) while categorizing Asian plants in the 1600s. Because Ginkgo is unique, it is no surprise its longevity (some trees are over 1500 years old) is due to something unusual. Ginkgo trees hundreds of years old within 1-2 km of the atomic bomb ground zero at Hiroshima survived and are still growing. Testimony to powerful, secret compounds?

Ginkgo biflavone chemistry secrets

Ginkgo leaves contain a series of common and unique polyphenols (flavonoids), including quercetin glycosides, found in many fruits, vegetables and herbs. 653 flavonoid metabolites and 8146 metabolites have been identified in Ginkgo leaves. But its previously secret, unique ingredients are classified as biflavones (two polyphenols stuck together) and double flavonoid glycosides. Cocoa, tea and wine are other sources of similar biflavonoids, and all have well-known biological benefits. This general class of biflavonoid plant compounds have better absorption and stronger effects than common monoflavonoids like quercetin. Ginkgo also contains unique ginkgolide and bilobalide terpene trilactones with complicated 3-D structures that mimic endogenous nutrients and signaling compounds in our bodies, activating receptors for cell signaling in beneficial ways, especially in blood vessels.

Because Ginkgo chemistry was unusual and had already known, common flavonoids with known antioxidant effects, the secret actives were missed for years. Human studies of Ginkgo extracts have been hit or miss for biological effects because of the different extraction fates and thus, potencies of biflavones and flavonoids. Empirical evidence settled on a particular extraction method that is now the most common source of Ginkgo biloba extracts used as dietary supplements (and herbal medicines in other non-US countries), and these contain biflavones and the other more common flavonoids. This extraction method also removes ginkgolic acids, potentially troublesome compounds.

Ginkgo biloba Extract Research Myopia – Looking in the Wrong Places?

Based on traditional herbal medicine usage from Asia, standardized Ginkgo extracts were developed into herbal medicines in Europe, and used for improving circulation in older persons in need of improved blood circulation for mental and physical functioning. Overall, summaries of many human studies have been less than enthusiastic about Ginkgo extracts used as medical treatments, but many human studies and reviews have found significant improvements in blood circulation and real-life mental and physical functions. With over 1000 human clinical trials published, one can find scientific support for any viewpoint they wish (cherry-picking). We prefer to let repeated and reproducible data and other experts speak (See Literature Quotes for Ginkgo biloba Extracts below after the References). We did not rely on studies of normal elderly or elderly diseased or diseased populations, and focused on young, healthy adults. Like most natural products that show efficacy, one can find polarization of opinion – both glowing advocacy and ruthless trashing in the research literature. A lot of differences in results can be explained by methodological issues – it is much easier to not find significance than to hit conditions that enable finding efficacy. Still, there's something good about Ginkgo that only a negatively biased cherry-picker would ignore or not believe.

Thus, the bulk of published human studies on Ginkgo are less relevant to aerobic exercise performance in regularly-exercising, normal, healthy persons. What all the mouthwash means is that using Ginkgo supplements looks better suited to healthy persons that can accommodate the now known effects of those unique and common compounds at realistic doses, like those in MultiV-PRO.

Recent and exciting (for us researchers, at least) metabolomic/metabonomic studies in humans and in animals have found new ways that Ginkgo extracts can affect exercise performance. Looking at the core mechanisms of action of the unique and common flavonoids/terpenes in Ginkgo show improved cardiovascular performance and blood circulation by multiple ways, similar to their close chemical polyphenolic cousins in green tea (also in MultiV-PRO), cacao/cocoa/chocolate (PreRace, anyone?) and grape seeds/wine that also have a large number of positive results in thousands of human clinical studies. For Ginkgo extracts, a combination of antioxidant activity, gut microbiome health, increased cellular omega-3 fatty acids, increased lipid (fat) metabolism, insulin signaling, membrane fluidity, nitric oxide effects, and best of all, improving energy metabolism has been shown. Also, metabolomic studies have found how Ginkgo does all those different benefits by helping to restore healthy levels of fatty acids, sphingolipids, phosphoglycerides and glycerides (fats) that are part of the normal cellular repair processes after damage caused by ischemia, ischemia-reperfusion, and oxidative stress. This is also a large part of the metabolic profile of exhaustive aerobic exercise. All these mechanisms favor improved aerobic exercise performance, or at least longer maintenance of normal performance, as well as more robust recovery. This is why Ginkgo extract is in MultiV-PRO!

Ginkgo extracts exhibit many mechatnisms of action that are beneficial for exercise performance and recovery: antioxidant activity, cellular repair, energy and fat metabolism, microvascular blood vessel function, neuroprotective actions – all are important for healthy, exercising persons.

Citations for Ginkgo Mechanisms of Action: Blume 1996; Cao 2019; Diamond 2013; Dubey 2004; Field 2011; Fransen 2010; Guo 2022; Horsch 2004; Kaschel 2009; Li 2018; Lorca 2022; Nash 2015; Nicolai 2013; Noor-E-Tabassum 2022; Roe 2021; Scholey 2013; Singh 2017; Tian 2017; Tao 2022; Wang 2016; WHO 1999; Xiong 2014; Yan 2022; Yang 2016; Zhang 2009 1674

GINKGO BILOBA & EXERCISE PERFORMANCE IN HEALTHY PERSONS

Exercise Performance

The effects of 6 weeks supplementation with 80 mg daily Ginkgo extract in healthy, physically active young men found increased endurance performance, improved VO2max, and increased BDNF levels (neuroprotection) (Sadowska-Krepa 2017). Antioxidant effects were also found – TBARS were reduced and superoxide dismutase activity, glutathione and ability of blood to reduce ferric ions were all increased, showing a multifactorial improvement in antioxidant defenses within normal limits.

If you use Optygen or OptygenHP with MultiV-PRO, then the study by Zhang et al applies to you (Zhang 2009 177). Rhodiola and Ginkgo combination was given for seven weeks to male volunteers and endurance performance parameters measured at baseline and end of study. VO2max was increased from baseline and placebo group, and cortisol did not change in the Rhodiola-Ginkgo group, but was increased in the placebo group. The testosterone:cortisol ratio was unchanged in the Rhodiola-Ginkgo group, but decreased in the placebo group, indicating increased fatigue and overtraining. Thus, Rhodiola and Ginkgo led to adaptogenic improvements in oxygen consumption, less fatigue and better adaptation to endurance exercise.

Human studies found that Ginkgo supplementation improved tissue microcirculation, decreased blood viscosity and increased serum levels of BDNF, cortisol and endorphins in women after eight weeks of endurance swimming training,

Citations for Ginkgo & Exercise Performance: Cui 2003; Hajirezaei 2015; Goncalves 2022; Kennedy 2019; Sadowska-Krepa 2017; Zhang 2009 177

Exercise Recovery

A recent human study of young, healthy, untrained women undergoing High Intensity Interval Training (HIIT) found that after three weeks of supplementation, compared to the placebo group, the Ginkgo group showed significantly reduced levels of exercise damage biomarkers CRP, CK and LDH at one and 24 hours post-exercise. This study exemplifies the newly found, detailed mechanisms of action from Ginkgo extracts, showing utility for endurance exercise recovery benefits.

Citations for Ginkgo & Exercise Recovery: Atashak 2021

Ginkgo biloba Extract (GBE) – Improvement in Blood Flow & Improved Oxygen Use

Looking into Ginkgo effects on blood flow in normal, healthy humans finds consistent improvements in blood flow, accompanied by vein relaxation/widening usually without changes in blood pressure or heart rate. As an example, one study measured fingernail capillary bed microcirculation for four hours after administration of Ginkgo (Jung 1990). Blood flow increased 57% one hour after Ginkgo was given, a highly significant improvement. A crossover study in 16 healthy persons 21-47 years old found a 99% increase in forearm blood flow vs. 19% in placebo period after three and six weeks (Mehlsen 2002). Measuring forefoot skin blood flow found that Ginkgo increased the change in blood flow relative to the placebo response, whether that would be an increase, decrease or no change. Metabolic fingerprinting of blood levels of Ginkgo actives correlated with the magnitude of effect, showing that Ginkgo enhanced vasoregulatory changes (Boelsma 2004). Another crossover study in 15 males aged 19-35 years found an increased blood flow in the optic nerve head (visible through the eye), indicating Ginkgo's blood flow effect was throughout the body and into the brain, which provides rationale for improved mental functions. Supporting this finding was contrast MRI brain imaging in nine normal, healthy men 50-70 years old after taking 120 mg Ginkgo extract daily for four weeks (Mashayekh 2011). Cerebral blood flow significantly increased 15% in white matter and 13% in gray matter. Previously, a SPECT scan of cerebral blood flow in 48 males aged 60-70 years found improved cerebral perfusion (blood supply) in specific areas and decreased blood viscosity (Santos 2003). These changes were associated with improved global cognitive functions, as would be expected with better brain

blood flow. Placebo groups showed opposite effects. Finally, blood viscosity in normal volunteers 18-60 years old, women and men, was reduced by Ginkgo extract (Galduroz 2007). Ginkgo was more effective than garlic extracts. Blood viscosity increases with age and overexercise, impairing circulation.

These effects are attributed to the polyphenols in Ginkgo, and mirror effects of other polyphenols from cacao, green tea and grape seeds in human studies. Animal studies also support vasorelaxation effects from Ginkgo. The effects happen within three hours, and with consistent daily use, lead to long-term improvements in blood flow. Effective doses range from 80-240 mg daily. Needless to say, blood flow is important for endurance exercise performance. Blood flow in healthy exercising athletes from Ginkgo has not been measured yet, but athletes are humans too, and with exercise stress, might be more sensitive to Ginkgo's benefits.

Citations for Ginkgo and Blood Flow & Oxygen: Anonymous 2003; Boelsma 2004; Galduroz 2007; Jung 1990; Kiesewetter 1992; Mashayekh 2011; Mehlsen 2002; Field 2011; Santos 2003; Wimpissinger 2007; Zhang 2009 177

Antistress, Mental & Mood Performance

Ginkgo, both by itself and combined with other nutrients (ginseng, phosphatidyl choline or phosphatidyl serine), has reproducibly shown improvements in various aspects of mental performance – antianxiety, antifatigue, antistress, attention, calming, cognition, memory, mental speed and vigilance at daily doses of 80-320 mg acutely and daily (up to 90 days). Validated mental tests were used to determine mental functions. These actions can be explained by general anti-stress effects on physiology (lowering blood pressure when stressed) and normalizing mental responses.

Attention-Deficit Hyperactivity Disorder (ADHD) in children, adolescents and adults has been repeatedly examined with Ginkgo extracts and Ginkgo-Ginseng combinations. Most studies found significant improvements compared to placebo, but usually less than improvements by methylphenidate; however, side effects in the Ginkgo groups were not different from placebo but were increased by methylphenidate. One study did find that Ginkgo was more effective than methylphenidate for excitability, frustration tolerance and mood (Lyon 2001). The evidence for Ginkgo for supporting normal mood is promising but preliminary.

Citations for Ginkgo & Mental Performance: Alge 2017; Anheyer 2017; DeFeudis 2004; Helmut 2010; Jezova 2002; Kennedy 2007 199, 2007 559, 2019; Liu 2020; Lyon 2001; Reay 2019; Salehi 2010; Sarris 2011; Schaffler 1985; Scholey 2002; Sharma 2021; Subhan 1984; Warot 1991; Wesnes 1997, 2000; Woelk 2007

Ginkgo biloba protects oxygen saturation at high altitudes

One outcome that illustrates how the multitude of Ginkgo effects can benefit aerobic endurance exercise performance is a series of human studies examining blood flow, oxygen saturation, nitric oxide metabolism and peripheral and cerebral blood flow at high altitudes. Ginkgo's ability to improve oxygen use and peripheral circulation at high altitudes is of particular importance to winter-sport endurance athletes.

A battery of human studies administered Ginkgo to healthy humans that went from low to 10000-15000+ feet in altitude rapidly with or without taking Ginkgo. Some studies only looked for AMS (Acute Mountain Sickness) symptoms of headaches, fatigue, shortness of breath, insomnia and anorexia, but some actually measured exercise-related physiological functions such as oxygen saturation, nitric oxide metabolism and circulation. Studies showed mixed results for Ginkgo reducing AMD symptoms giving Ginkgo in a narrow window of time before, during and after ascents. Reasons for the mixed results were blamed on different preparations of Ginkgo – some worked, some did not, and scientists conducting their studies did not understand this variable and research stopped because of the difficulty of determining if they chose the right source of Ginkgo or not. Later, different years of harvest showed differences in active agents, suggesting that the most active agents of Ginkgo are not the two standardized ones (Ginkgoflavones and terpenes) – suggesting biflavones are important.

Although this speaks to Quality Control of Ginkgo and extraction differences among Ginkgo sources, those that mirrored or used EGb 761 produced improvements in physiological adaptations. Since these studies were published, the consistency of quality for Ginkgo products has improved. Also, the dosing regimens for Ginkgo were generally too short to take advantage of Ginkgo's mechanisms of action. Add on gut dysfunction during rapid ascent, which would decrease uptake of active agents from oral Ginkgo, and more was learned about how not to use Ginkgo properly, since we know now the metabolomics of Ginkgo becomes more effective with more time. Most subjects were not endurance athletes, and thus, more susceptible to problems with altitude. Each study fastidiously made sure their subjects were not adapted to altitude. Also, some studies found low incidence of AMS symptoms, or started too low in altitude, making it difficult to find a difference between groups (in other words, placebo groups did not show sufficient intensity of symptoms to find a difference between treatments).

The latest review of Ginkgo studies at altitude found a significant risk reduction of AMS compared to placebo by pooled risk difference (-25%, p=0.011) (Tsai 2018). Combining seven studies, Tsai et al conducted a meta-analysis on AMS prophylaxis (preventing AMS) and found a trend for prevention (p=0.08). This is where statistical difference and real-life difference means something – which group would you want to be in knowing those odds? Placebo or Ginkgo?

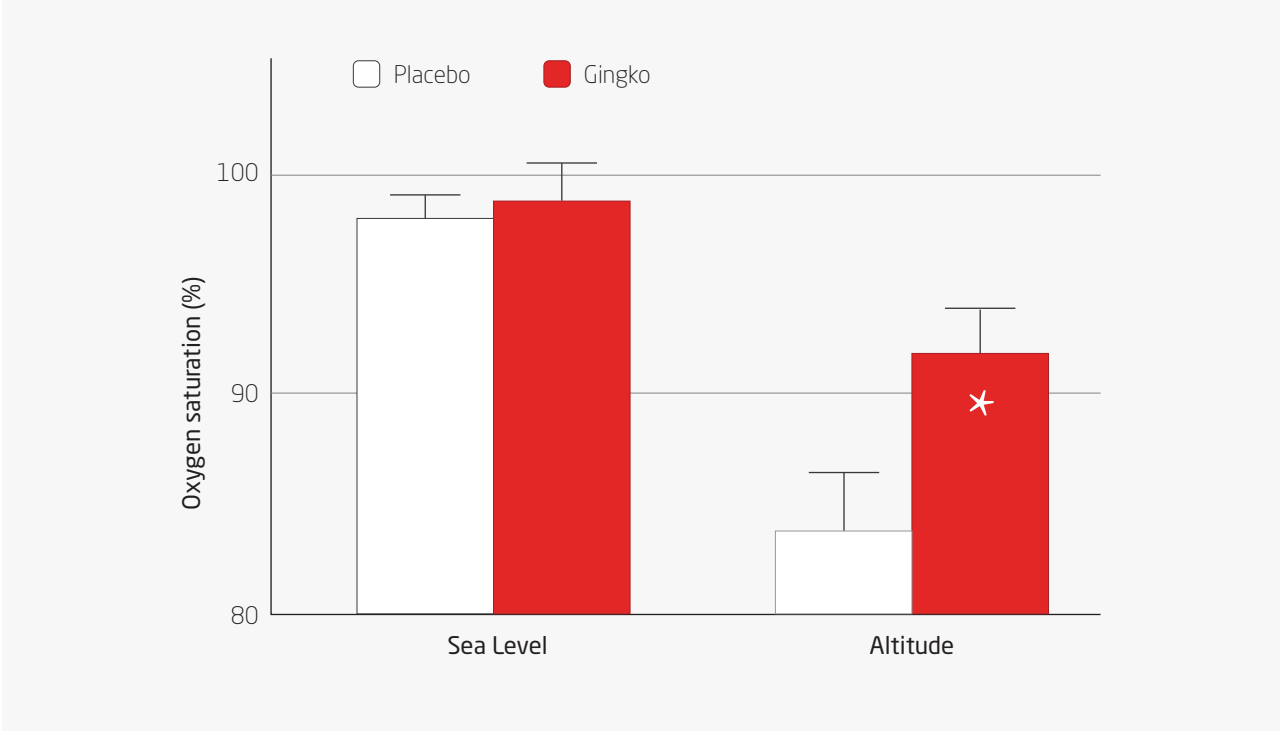
The review by Tsai also mentioned a Chinese report from Northwest Chine Defending Forces in 2003 that reported Ginkgo was the most effective of six Chinese Traditional Medicines for preventing AMS, but no details were presented (Tsai 2018). Four of seven Ginkgo/altitude human studies found that Ginkgo significantly reduced AMS incidence and symptoms, maintained better oxygen saturation (see Figures), reduced use of analgesics, oxygen or corticosteroids, reduced number of prompt transport to lower altitudes (serious AMS incidence), decreased vasomotor disorders of extremities (cold hands/feet) and improved erythrocyte deformability in altitude-adapted men and women (Gertsch 2002; Leadbetter 2009; Moraga 2007; Roncin 1996). Another marker for success was gradual ascent rather than sudden ascent, more in keeping with putative mechanisms of action and absorption for Ginkgo.

Citations for Ginkgo & Altitude: Adams 2004; Bartsch 2004; Chow 2005; Cui 2003; Dubey 2004; Elphick 2004; Franco 2019; Gertsch 2002, 2004; Ke 2013; Leadbetter 2009; Moraga 2007; Roncin 1996; Tissot van Patot 2009; Tsai 2018

Ginkgo and altitude - Summary

Thus, Ginkgo extracts have shown improvements in adaptation to altitude if certain conditions are followed: 1) chronic use of Ginkgo before ascent; 2) ascent of more than 2500 meters (~7500 feet) and 3) more gradual ascents. The issue of which compounds in Ginkgo are the most important is still at large. Also, physiological measurements which Ginkgo has shown benefits for, such as antioxidant actions, cerebral blood flow and nitric oxide metabolism, were not measured. The combination of positive results in multiple studies and the well-known effects of Ginkgo on circulation and antioxidant protection argue strongly that Ginkgo is a worthy supplement to take before ascending to high altitudes, and more attention to methodology needs to be paid in future studies.

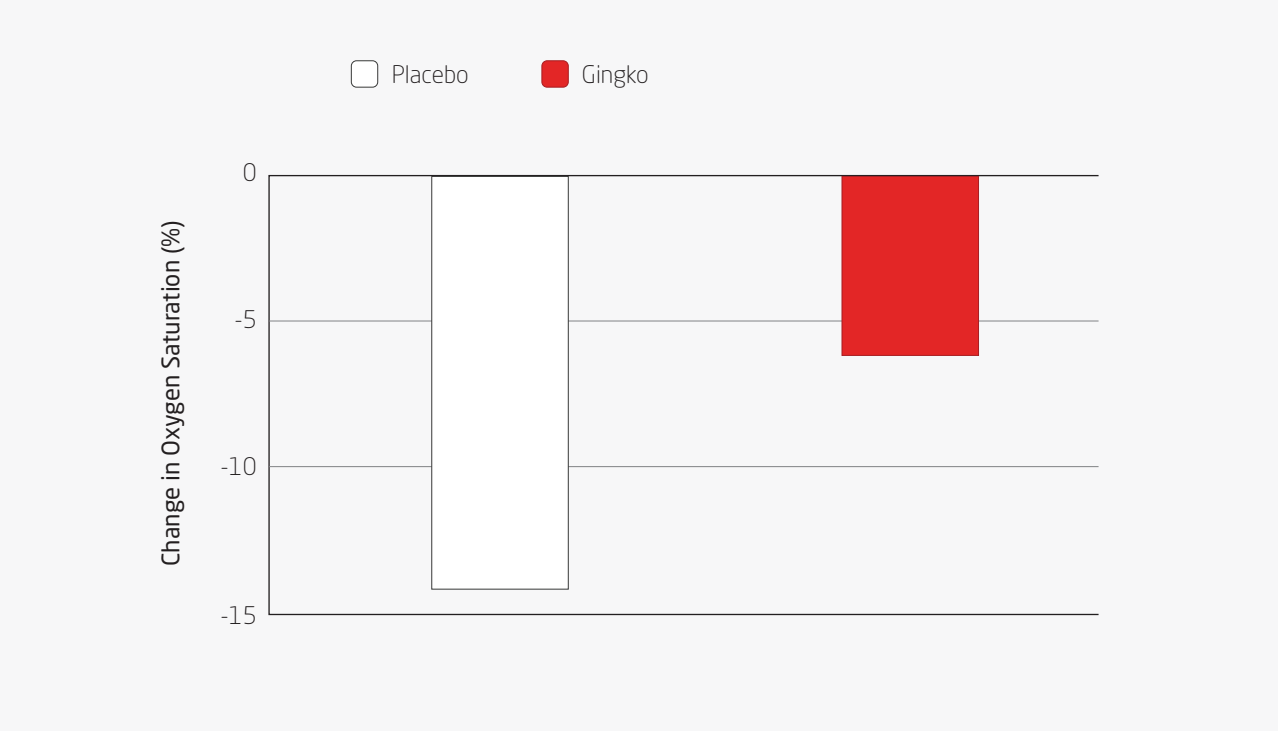
Ginkgo biloba Extract & Oxygen Saturations



Oxygen Saturation at 12125 feet altitude after 3 days.
Placebo or Ginkgo (160mg/day) was given one day before and three days at altitude.
12 male subjects (~22 years old) per group. Oxygen Saturation % ± SD.

*Significant difference from placebo group, P<0.05)

Decrease in Oxyden Saturation at Altitude



Another way to look at what standardized Ginkgo biloba leaf extracts can do for maintaining Oxygen Saturation at altitude (3696 meters) – reduce the loss of Oxygen Saturation in blood.

Reference: *Moraga FA, Flores A, Serra J, Esnaola C, Barriento C. Ginkgo biloba decreases mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. Wilderness Environ Med. 2007 Winter;18(4):251-7.*

Ginkgo & Exercise Summary - Ginkgo Belongs

Evidence has accumulated in normal, healthy persons showing that Ginkgo delivers beneficial effects on altitude adaptation, antioxidant actions, blood flow, blood viscosity, fatigue, mental functions, mental stress, microcirculation, nitric oxide metabolism, and oxygen saturation that are favorable for endurance exercise performance. Ginkgo shows effects both acutely (after a single dose) and consistently over time (weeks to months). The few studies on healthy exercising individuals are promising, showing increases in oxygen capacity, hormone regulation, post-exercise recovery biomarkers, and improved aerobic endurance performance.

Importantly, best effects have been shown by relatively modest daily doses of Ginkgo extracts (80-120 mg daily – the dose in MultiV) and sometimes up to 240 mg daily. Higher doses of Ginkgo (300 mg and more) have not fared as well in a wide range of human clinical studies, especially when studied as a pharmaceutical at increasing dosages. This finding of an inverted-U shape dose-response curve or a bimodal curve (two peaks/troughs) mirrors effects of many other nutrients and natural products, especially multicomponent regulatory mixtures like Ginkgo (and adaptogens). Brain wave studies of Ginkgo in normal humans is a classic example of this phenomenon (Le Bars 2000). If a mixture has many activities, giving more and more might cause interferences, imbalances or even excess efficacy that detracts from other desirable outcomes. There is a Zone of Efficacy for Ginkgo and exercise effects, and 120 mg appears to be in that zone for blood flow, mental benefits, and exercise performance. Less is more once again.

Human studies on ultraendurance activities are lacking, and a true dose-response for maximizing exercise benefits of interest remains to be done, but so far Ginkgo is showing it can help with training, racing, and recovery. Assuming that status of essential nutrients is maintained by other nutrients in MultiV, the benefits of Ginkgo may exceed those in clinical studies where subjects' nutritional status was not ideal.

Literature Quotes for Ginkgo biloba extract

"Moreover, it [Ginkgo biloba extracts] can improve cerebral blood flow supply, executive function, attention/ concentration, non-verbal memory, and mood, and decrease stress, fasting serum glucose, glycated hemoglobin, insulin levels, body mass index, waist circumference, biomarkers of oxidative stress, the stability and progression of atherosclerotic plaques, and inflammation."
Barbalho 2022, Abstract

"The action of platelet activating factor is antagonized and platelet aggregation is reduced. Blood flow is increased. Release of prostacyclines and nitric oxide was shown to be stimulated."
Dubey, 2004, Abstract

"...the daily intake of Ginkgo biloba leaves (80 mg/day) by healthy and physically active young men increased their endurance performance, VO2max and blood antioxidant capacity [330]."
Goncalves 2022, p.27
[Note: Refers to Sadowska-Krepa 2017 Quote below]

"Evidence collected in normal healthy samples suggests that secondary metabolite phytochemicals from each of the main structural groups – phenolics (polyphenols), terpenes and alkaloids – may result in improvements to cognitive function and psychological state that could be relevant to sports performance."
Kennedy 2019, p.S39
[Note: Caffeine is considered an alkaloid by this author, and Ginkgo supplies unique and common polyphenols and terpenes.]

"There is consistent evidence that chronic administration improves selective attention, some executive processes and long-term memory for verbal and non-verbal material."
Kaschel 2009, Abstract
[Note: these findings included "...healthy young and elderly subjects."]

"Overall, Ginkgo biloba and its extract EGb761 show promise as a clinically significant compound for improving cognitive function in cognitively normal adults..."
Lewis 2021, p.598

"Ginkgo biloba was the most relevant nootropic regarding perceptual and motor functions."
Lorca 2022, Abstract

"It is concluded that oral treatment with a G. biloba extract (Gibidyl Forte®) is able to dilate forearm blood vessels causing increments in regional blood flow without changing blood pressure levels in healthy subjects." "...16 healthy subjects (nine females and seven males) with a median age of 32 years (range: 21-47 years)."
Mehslen 2002, Summary & p.375

"The therapeutic mechanisms of EGb 761® can be attributed to its individual constituents whose differing mechanisms of action may lead to a pharmacological synergy within the formulation."
Nash, p1

"In microvascular terms, it [Ginkgo] has several beneficial effects, namely its vasodilator and endothelial-protecting activities."
Raposo 2021, p.16

"Our results show that six weeks' supplementation with Ginkgo biloba extract in physically active young men may provide some marginal improvements in their endurance performance expressed as VO2max and blood antioxidant capacity, as evidenced by specific biomarkers, and elicit somewhat better neuroprotection through increased exercise-induced production of BDNF."
Sadowska-Krepa 2017, Abstract

"After treatment, the experimental group [Ginkgo biloba] showed a reduction in blood viscosity, improved cerebral perfusion in specific areas and improved global cognitive functioning."
Santos 2003, Abstract
[Note: Subjects were 48 normal, healthy males 60-70 years.]

"GK501 improves memory function in the hours following a single dose, with 120 mg the optimal dose."
Scholey 2013, p.144
[Note: A serving of MultiV provides 120 mg of an analogous extract as that used by Scholey.]

"First, the EGb treatment improves memory processes, particularly working memory and memory consolidation. ... Second, this improvement in functioning was clearly evident to participants throughout the trial indicating that the changes were not only statistically significant but of a magnitude that could be subjectively noticed by the participants despite the double blinding of the study."
Stough 2001, p.133
[Note: Participants were "...young healthy adults ranging in age from 18 to 40 yr."]

"...it is important to explore other bioactive flavonoids of G. biloba and the interaction between different flavonoids of G. biloba."
Tao 2022, p.7

6. SPECTRA® TOTAL ORAC5 ANTIOXIDANT BLEND

Why Antioxidant Blend for Endurance Exercise?
MultiV-PRO provides the full, clinically-studied dose of SPECTRA® Total ORAC5 Antioxidant Blend with broad-spectrum antioxidant benefits that do not interfere with training adaptation or recovery, simulating antioxidant benefits from a healthy diet rich in fruits, spices and vegetables.

Antioxidants & Excercise Research Conundrum
At present, there is an ongoing back-and-forth dialogue in the world of research about exercise and antioxidant supplementation. On one hand, there is plenty of evidence to show derangements of antioxidant function from strenuous exercise. For example, extreme long-distance running (Marathon of Sands) led to decreases in blood levels of antioxidant vitamins and enzymes 72 hours after the race was over – a severe deficiency of normal antioxidants. Blood markers of oxidative damage (TBARS) were also still elevated 72 hours after the race (Machefer 2004). At first, after it was found that strenuous exercise also increased oxidative species (free radicals, etc.) that cause physical damage to tissues and triggered inflammatory markers, the rush was on to defeat this mechanism and thus prolong performance and speed recovery. A lot of free radicals are generated by exercise, so a lot of antioxidants were given to try to prevent exercise damage to extend performance. Sure enough, free radicals and even some damage can be prevented by ingesting more antioxidants – so far, so good.

After a decade or more of ambivalent results from ever-increasing doses of antioxidants (Yes! ... Hold on, wait... Maybe! er, um, ... No?), the consensus pendulum has swung towards not using large doses of antioxidants during exercise. Squelching oxidants also squelches the release of normal inflammatory signals that are now known to initiate the normal post-exercise recovery and repair processes in muscle. High antioxidant intakes also showed slower adaptation to training effects, and sometimes even poorer exercise performance and longer recovery times – an antioxidant backfire. Antioxidants and exercise studies have not panned out from the original findings of need. So what's the deal with antioxidants and exercise?

Without spewing pages of scientific gobbledy-gook, here is the very short version. Most antioxidant and exercise studies used single antioxidant nutrients like Vitamin C, Vitamin E or the combination, at ever-increasing dosages. Then sulfhydryl antioxidants (L-Cysteine, N-Acetyl-L-Cysteine [NAC], Methionine and Glutathione [GSH]) had their turns with the escalating dose syndrome typical of short-term, single-agent, pharmaceutical-style studies but ill-advised for making sense from a multi-factorial, multi-system issue – nutrient effects on exercise performance. Many other antioxidants were applied singly with underwhelming results to help performance and/or recovery. Same story – there is a zone of inadequate intake and status for these antioxidants that worsens exercise performance and recovery, then a zone of amounts that has some positive effects (adequacy), then excessive doses that worsen exercise performance and recovery – the Antioxidant Conundrum.

Citations for Antioxidants & Exercise Conundrum: Elkington 2015; Henriquez-Olguin 2020; Knez 2007; Machefer 2004; Neubauer 2008, 2015; Lewis 2015; Pinho 2010; Sachdev 2008; Vina 2000

Antioxidant Research on Excercise has been Shortsighted
There have been fatal flaws in antioxidants and exercise research from the beginning. First and foremost has been the utterly dumb idea of giving a big amount of a single or even a few antioxidants and expecting benefits. Dumb? Yes, very dumb. Why? Our bodies have a network of antioxidant systems to counteract the many types of free radicals and oxidative agents. Does a spider use one strand or an entire web to catch flies? You get the picture.

In fact, supplementing high doses of one or a few antioxidants imbalances the networked system, and because of what oxygen and antioxidants are, that causes more problems than solutions. Here's an allegory: you have a roomful of people undergoing happy conversations, and all of a sudden, one of them breaks out their electric guitar with amp and shreds at 150 decibels – communication and happy conversations are gone and bad things ensue.

Another big issue has been the ignorance of what antioxidants really are. An axiom about antioxidants is that they are molecular double-edged swords. Free radicals/oxidative species are constantly formed because we breathe and burn oxygen (O2), which is a diradical itself. Free radicals and oxidative species are super reactive chemically and permanently alter and destroy the molecules that make up you, and they live on as a string of damaged molecules until they either run into an antioxidant, which takes the molecular hit, sacrificing its molecular structure for you, or they obliterate themselves on one of your structural molecules like collagen, enzymes, proteins or cell phospholipid membranes fatty acids, or worse, DNA or RNA.

In low doses antioxidants break the chain of free radicals to prevent cell damage. Most antioxidants, especially the nutritional ones like Vitamin C, E, Coenzyme Q10 (ubiquinone) and selenium/glutathione are rechargeable to live to fight another millisecond. Antioxidants enzymes are some of the fastest-reacting enzymes known, able to take out hundreds of thousands of free radicals per second. Relatively few antioxidants work strongly on each of many types of free radicals, thus slowing or stopping the damage wreaked by free radicals.

But those antioxidants that took the free radical hit are often damaged, and some can morph into pro-oxidants if not converted to a safer molecular form. Damaged antioxidants are either quickly recharged, repaired or removed from the body by an elegant systems network that culminates in using energy metabolism (i.e., calories) to fully make free radicals completely disappear. However, at high megadoses, antioxidants cannot be recharged, repaired or removed fast enough, and they behave as pro-oxidants, becoming free radicals or oxidative species themselves, and overwhelm other parts of the antioxidant system network, causing damage – but again, that's only at excessive doses of the antioxidant in question. This is why less is more for antioxidant dosing.

Another issue with antioxidant research is how to measure oxidative and antioxidative effects. Usually, only a few markers per study were looked at, and the big systems network picture was lost – and so were most pieces for putting together the antioxidant/exercise puzzle. Even worse is the ultra-complicated chemistry of free radicals when they alter a fatty acid, carbohydrate, protein or DNA/RNA base. There are literally millions of molecular possibilities and then on top of that, molecular rearrangements happen quickly. Some of the most common rearrangements are used as biomarkers of damage, but still miss the bulk of what is going on. If you are taking a survey about who will win the next election, would you interview three random persons or hundreds? It's not easy being an antioxidant researcher. Like the seven blind men feeling different parts of an elephant, all sorts of myopic conclusions have been published based on incomplete data being poorly interpreted. At least we do know the basics about what free radicals can do to us – everybody that lives long enough to age experiences the outcomes. Today, we know that pumping up Vitamin C or Vitamin E or Selenium or NAC or any single antioxidant too much is as bad as not having enough – maybe worse. Bottom line – being high normal range with intakes of as many antioxidants as possible is the best way to go.

Citations Antioxidants & Research: *Henriquez-Olguin 2020; Klotz 2014; McLeay 2017; Neubauer 2008, 2015*

Think of antioxidants as money. You are King of the World, but your people suffer from starvation and predation (free radicals as wolves, for instance). So you provide an antioxidant fix that feeds and protects by giving a very few people a million dollars. You expect that to work for everyone. Depending on where you look (your few beneficiaries or the population as a whole), you can claim success or utter failure. But if you spread those millions around to everyone, then starvation and predation is better counteracted countrywide and everybody is healthier and resistant. So it goes with antioxidant research, necessitating careful interpretation of context of each individual scientific report. Keep the big picture in mind when it comes to antioxidant research findings. What's the focus and intent?

Redox State

The redox state (balance of free radicals and antioxidants) influences your energy metabolism, which uses molecular oxygen (O2), which itself is a diradical. Yes, vital oxygen has two unpaired electrons (aka free radicals) all the time and is the root of all redox evil. Can't live without it, can't live with it. Oxygen's normal diradical state makes it easy to generate metabolic energy and water in mitochondria so you can exercise, think, and live. To illustrate the importance of staying alive by actively taking up free radicals, how long can you live without oxygen? Minutes. Without water? Days to weeks. Without food? Weeks to months. So, as you live and breathe is due to handling free radicals. The ubiquity of oxygen as a double free radical is why oxidative damage is synonymous with free radical damage – it's the biggest source of free radicals in our bodies.

Exercise consumes more oxygen (heard of VO2max?) and thus generates more free radicals that your body compensates for, but to what extent? Pushing yourself to past the point of exhaustion and getting normal delayed onset muscle soreness is all about oxidative stress.

Also, almost all antioxidants are more than just about suicide bombing by free radicals. They send clear and actionable messages with their sacrifice. Antioxidants and their breakdown products also are signaling molecules themselves to your tissues and your microbiome – so your body can sense and try to rectify an imbalance by increasing or decreasing enzyme antioxidants or energy metabolism – something your body can control without an instant dietary intake of the right antioxidants.

Citations Redox & Exercise Research: Henriquez-Olguin 2020; Klotz 2014; Lewis 2015; Margaritelis 2020

How antioxidants work is complicated, many-splendored, but well controlled and constantly adjusting to keep you running, cellularly and literally:

"In any case, when discussing cellular responses to a given signal, the idea of a signaling cascade embedded in an entire network of sensors, checkpoints, controls, response elements, and feedback mechanisms and loops needs to be taken seriously." Klotz 2014, p.128

Blueprint for Benefits from Antioxidants

By interpreting and understanding well-researched findings about antioxidants and health from other research areas (like mortality), it is obvious there is a sweet spot of having enough of many kinds of antioxidants, without too many or too much of any one kind, to derive max benefits from antioxidants. Which is why healthy diets rich in all sorts of antioxidants (mostly from plant

foods) is associated with less mortality and better health. It's about balance and networking – communications and conversations going on inside your body.

Taking a cue from the lessons learned by human studies on antioxidants and health, benefits are from increased fruit and vegetable intakes in healthy, diverse diets, not from massive doses of supplemental Vitamin C or E or Beta Carotene or any other single antioxidant. This means that hundreds of different kinds of antioxidants at a collective moderate intake of each – and more than most people normally consume – is the blueprint for antioxidant benefits, along with ensuring normal, adequate antioxidant actions from the nutritionally essential vitamin and mineral antioxidants (which is what MultiV-PRO does with Vitamins C & E, Beta Carotene, and trace minerals that run antioxidant enzymes – Copper, Iron, Manganese, Selenium, Zinc). These and other vitamins and minerals operate your energy metabolism to fuel antioxidation, cell repair, exercise performance and overall health.

Citations Antioxidants & Exercise Blueprint: Aune 2019; Jayedi 2018; Neubauer 200, 2015; Sheng 2022; Visioli 2015

Antioxidant Answer – SPECTRA® TOTAL ORAC5 Blend

One way to optimize your redox state is to get enough amounts and types of antioxidants from real foods. Over and over, healthy diets are associated with lower free radical damage and higher – but not excessive – intakes of a plethora of antioxidants. That's exactly what SPECTRA® TOTAL ORAC5 Blend (SPECTRA) has done. Developed by VDF Futureceuticals®, a leader in scientifically-researched food extracts and concentrates, SPECTRA is a blend of 29 different food sources of concentrates and extracts with hundreds of different types of antioxidants from fruits, vegetables, seeds, herbs, and spices – matching a healthy diet rich in fruits, vegetables, herbs and spices.

Check out the antioxidant-rich food concentrates in SPECTRA – and ask yourself how many of those foods you actually eat each and every day. By taking SPECTRA, you can say all of them!

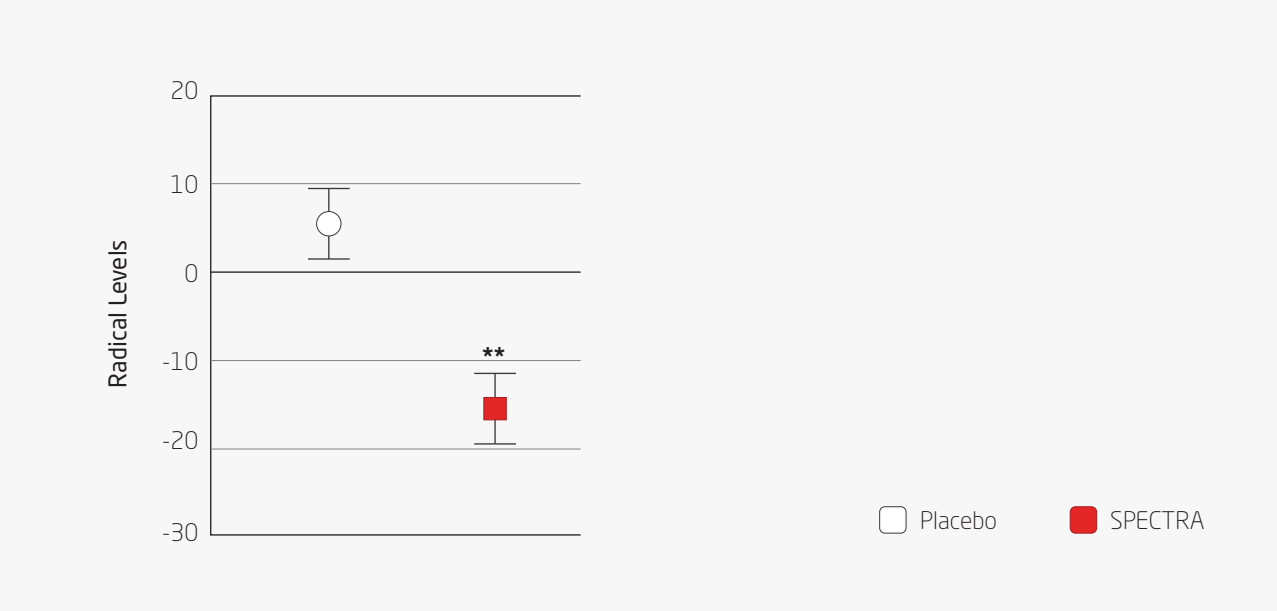
SPECTRA® TOTAL ORAC5 Blend Composition

Coffea arabica Extract, Green Tea Extract, Broccoli Sprout Concentrate, Onion Extract, Apple Extract, Quercetin, Tomato Concentrate, Broccoli Concentrate, Camu Camu Concentrate, Maltodextrin, Acerola Extract, Acai Concentrate, Turmeric Concentrate, Garlic Concentrate, Basil Concentrate, Oregano Concentrate, Cinnamon Concentrate, Carrot Concentrate, Elderberry Concentrate, Mangosteen Concentrate, Blackcurrant Extract, Blueberry Extract, Sweet Cherry Concentrate, Raspberry Concentrate, Spinach Concentrate, Chokeberry Concentrate, Kale Concentrate, Blackberry Concentrate, Silicon Dioxide, Bilberry Extract, Brussels Sprout Concentrate, Sunflower Lecithin.

Does SPECTRA® TOTAL ORAC5 Blend work in real life?

The next trick is to show that SPECTRA actually has antioxidant activity in humans at a reasonable dose. VDF Futureceuticals has done this too. Two separate human studies of healthy adults at a dose of 100 mg per day (the same dose in a daily serving of MultiV-PRO) found significant broad-spectrum antioxidant effects. First, free radical levels in serum were reduced significantly ($P<0.005$) (see Figure below). Next, each of the five major oxidative species were effectively quenched in vitro by SPECTRA supplementation, and those antioxidant effects, especially nitrosative effects, were significantly improved in circulating blood by SPECTRA supplementation. Antioxidant effects were significant after one hour and continued for three hours (Nemzer 2014 647, 2014 828). SPECTRA showed significant decreases of oxidative biomarkers at lower levels of intake (100mg) compared to 4 grams or more of other fruit/vegetable blends.

% Change in Fee Radical levels in serum after one hour



Adapted from Nemzer 2014 p. 652
** Significantly different from placebo

A series of studies from other FV blends in pill form on smokers, overweight persons and healthy subjects found improvements in uptake and activity of antioxidants. Activities showing improvements were: better circulation, increased cognitive functions, reduced systemic inflammation, immune support, reduced serum homocysteine and lower measures of oxidative damage. These are helpful attributes, but how does that affect exercising individuals known to have more oxidative damage?

Exercising subjects taking other FV blends found lowered biomarkers of oxidative damage (protein carbonyls, malondialdehyde, oxidized glutathione, total oxidative stress) without worsening DOMS symptoms (Bloomer 2006; Goldfarb 2007; Lamprecht 2007; 2009, 2012; 2015). An important finding was continued improvement of activities with longer periods of studies, up to 24 weeks. In other words, the antioxidant blends do not lose their effectiveness over time (just like a healthy diet), and results get better and better.

Other human studies of endurance athletes with different intakes of total dietary antioxidants (food and supplements) have found benefits for exercise physiology and performance. For example, a recent publication correlated total dietary antioxidant intake with antioxidant actions and oxidative stress by a treadmill test to exhaustion in 24 ultramarathoners/triathletes – 12 women, 12 men (Devrim-Lanpir 2020). Interestingly, coffee intake accounted for 1/3-1/2 of the total antioxidant intake from diet by the FRAP test, but it was excluded from the FRAP score because of questions about whether roasted coffee antioxidants get absorbed into the body. The non-coffee total dietary antioxidant score was moderate-to-high for all subjects, and was compared to measurements from the exhaustive treadmill exercise. More total dietary antioxidant intake led to lower oxidative damage markers and higher blood antioxidant status. Men, but not women, showed better lactate clearance with higher blood antioxidant status. The researchers concluded that total dietary antioxidant intake positively improved exercise performance and post-exercise recovery.

Thus, SPECTRA is a minimal-volume, high-performance antioxidant mixture with comprehensive antioxidant benefits, buoyed by similar positive findings from other fruit/vegetable blends. The advantage of SPECTRA is a smaller amount to swallow for equal or better antioxidant actions, and a larger number of plant concentrates. It is clear that balanced FV blends provide benefits without compromising training adaptations or recovery.

Citations Spectra Antioxidant Effects: Ali 2011; Arcusa 2021; Bamonti 2013; Bloomer 2006; Bresciani 2017; Carrillo 2021; Chambers 1996; Del Rio 2017; Devrim-Lanpir 2020; Esfahani 2011; Harasym 2014; Kawashima 2007; Kiefer 2004; Lamprecht 2007, 2009, 2012, 2013; 2015; Lorenzoni 2019; Nantz 2006; Nemzer 2014 647, 2014 828; Novembrino 2011; Panunzio 2003; Plotnick 2003; Romain 2022; Samman 2003; Williams 2017

Antioxidants & Exercise Summary

A lot of antioxidant/redox water has gone under the research bridge, and the take-home message is to get a decent but not excessive amount of as many types of antioxidants from healthy plant foods as possible, along with ensuring adequate status of essential vitamins and minerals. Large amounts of Vitamin C & E are associated with detriments in exercise training and performance, which has generated a backlash against any and all antioxidants in general – a conclusion not based on facts. By using SPECTRA, a plant-based, balanced, concentrated mixture of many antioxidants, at a daily dose shown to improve resistance to all types of pro-oxidants, MultiV-PRO adds the right mix of total dietary antioxidants supported by human clinical research to provide antioxidant functions and benefits, maintaining training and recovery benefits.

Literature Quotes for Antioxidants, Excercise & SPECTRA ®

"Dietary antioxidant intake including antioxidant and polyphenolic content may positively improve both exercise performance and post-exercise recovery..."
Devrim-Lanper 2020, p.12

"In any case, it is clear considering the positive and negative effects of free radicals, and that the right balance between these and antioxidants is necessary for health and optimal training effectiveness. ... Meanwhile, few practical recommendations can be made, other than to realise that, at least for endurance athletes, antioxidant supplementation is not a case of 'the more, the better'."
Gross 2015, p.119

"A number of studies have shown, however, that consuming less common fruits and vegetables contributes much more to the reduction of free-radical processes, most likely because they contain a large amount of non-vitamin antioxidants, such as polyphenols and anthocyanins."
Harasym 2014, Abstract

"Users of antioxidant supplements in both the half and full Ironman races had significantly ($P < 0.05$) elevated MDA after races compared with nonsupplementers."
Knez 2007, Abstract

"A well-balanced mixture of phytonutrients, vitamins, minerals and other bioactives from a variety of FV may lead to additive and synergistic interactions in human metabolism that result in health benefits. Hence, to bring as many as possible of these FV bioactives together in one supplement might be superior to supplements containing only vitamins, phytochemicals, juice or powder from just one or a few fruits and/or vegetables."
Lamprecht 2015, p.184
[NOTE: FV = Fruits & Vegetables, as in SPECTRA]

"In summary, the evidence to date points to biomarkers of ARH showing a moderate to strong relationship with several measures of performance in athletes."
Lewis 2015, p.403
[NOTE: ARH = Alterations in Redox Homeostasis – normalizing biomarkers showed better performance]

"Moderately dosed and timely limited antioxidant supplementation and/or the use of specialized sports products (e.g. beverages, carbohydrate-rich bars, gels, etc.) fortified with antioxidants may be warranted in specific situations such as during acute bouts of intense endurance exercise lasting several hours and in the early recovery period (within ca. 24 hours) thereafter, or during energy restriction/weight loss programs. However, high dosed antioxidant supplementation, i.e. >>100% of the recommended dietary allowance (RDA)/dietary reference intake (DRI), in addition to the dietary intake of antioxidants, should be avoided."
Neubauer 2015, p.56

"In conclusion, the IR [Ironman triathlon Race] induces changes in oxidative damage biomarkers and in the antioxidant enzymes."
Pinho 2010, p.310

"Diet with a higher antioxidant capacity in midlife was associated with a lower risk of all-cause, cardiovascular and respiratory disease mortality in the Singapore Chinese population, supporting the public health recommendation of consuming more plant-based foods that are rich in antioxidant nutrients."
Sheng 2022, Abstract

"In other words, we do not have sufficient experimental evidence to suggest the intake of pharma-nutrition preparations based on antioxidants. In fact, the converse might be true and we probably should discourage their use. However, epidemiological studies are quite clear: higher intakes of antioxidants (vitamins, but also polyphenols) are associated with better prognosis."
Visioli 2015, p.104

7. BORON

Why Boron for endurance excercise?

Why Boron for endurance exercise? Do you like strong bones and joints, and more efficient use of steroid hormones, including Vitamin D? Thought you would! Boron maintains long-term integrity of bones, joints, steroid hormone levels, Vitamin D actions and more. Dietary intakes are typically about half needed to exhibit boron's health benefits, and those intakes are dependent on where you live, where your drinking water comes from, and where your food is grown.

MultiV-PRO has the ultimate Boron compound – FruiteX-B® (Calcium Fructoborate), one of the many plant forms of chelated Boron, with patented synthesis and uses. FruiteX-B® has advantages over the more common forms of inorganic Boron (Sodium Tetraborate) and other Boron chelates. FruiteX-B® has an increasing number of human studies that touch on topics important for endurance exercises, like musculoskeletal health and hormonal health, with wide-ranging benefits for endurance.

Boron is subtle but not boring

Boron is a weird element, very unlike any others, even the elements nearest it in the Periodic Table of Elements (Carbon, Aluminum, Silicon). Boron is a metalloid solid in pure form, and it likes to make very specific polyhedral (pyramid-shaped) bonds with oxygen (as in Sodium Tetraborate and Calcium Fructoborate, aka FruiteX-B® in MultiV-PRO) and with cis diol groups (hydroxy groups) on other molecules, like polyphenols, steroid hormones, hormone receptors and sugars (obviously this is important for what it does to you – read on).

Part of the problem with understanding Boron is that how it works has been figured out, but nobody except the leading researchers in the field (Borologists – and yes, that's a real word) are studying human effects of Boron in a way that looks for its strengths. But Boron has been a victim of its own success – confusing regulatory agencies with too many ways to be essential, with a unique mechanism of action not appreciated even by most scientists, and with not curing a single boron-specific deficiency disease, like scurvy by Vitamin C. In fact, that's because Boron affects many areas of health. Boron has much more data on how it is essential compared to other trace minerals already listed as essential – chromium, for example. So far, attempts to have Boron recognized as an essential nutrient have not become official because it is so weird and mysterious to regulators, and difficult to measure. But your body knows what to do with Boron.

Citations - Boron Is Not Boring: Bita 2022; Bolanos 2004; Cordova-Chavez 2023; Devirian 2003; Donoiu 2018; Expert Group 2002; Hunt 1999, 2007, 2012; Hunter 2019; Khaliq 2018; Meacham 2010; Miljkovic 2004, 2009; Mogosanu 2016; Nielsen 1990 45, 1990 319, 1991 274, 1991 2661, 1998 319, 2006, 2008, 2011, 2014, 2017, 2020; ODS 2020; Oancea 2018; Pizzorno 2015; Rondanelli 2020; Scorei 2011 315, 2011 1223; Weber 2022; WHO 1996; Wimmer 2009, 2019

How Boron works - It's a molecular slipstitch

Boron's super unique atomic bonding possibilities make it useful (and essential) for a seemingly unconnected variety of uses. Boron makes heat-resistant borosilicate glass (e.g., Pyrex) by stitching together the silica chains, preventing expansion with heat or compression with cold. Boron is essential for vascular plants to build their hard structures. Borate salts form unique, pyramid-shaped molecules that are essential for building cell walls in vascular plants (i.e., grow and repair structures like roots, stems, leaves, tree trunks, etc.). During formation or repair of plant tissues, Boron literally loosely connects growing plant structures on a molecular level to form the scaffold that gets finalized quickly thereafter – like a quick slipstitch that holds together sewing or quilting fabric pieces before the tight stitching is done.

This attribute of Boron gives it several super-powers for mammals too (humans included). Boron, by its unique, non-metallic, bonding chemistry, slipstitches Vitamin D and steroid hormones to their receptors longer than usual, causing more signaling to a cell, and more hormone effects (but not too much). This slipstitch effect means a greater Vitamin D/hormone effect without changing levels in blood or tissues. Boron does not increase amounts of hormones by itself, it increases their potency – within normal biological limits, without danger of hormonal excesses. This allows your body to use its normal hormonal feedback loops to normalize hormone levels, not merely increase or decrease them. In real life, this helps lower-than-normal hormone levels get closer to functionality by making a hormone deficiency less deficient. The steroidal hormones most affected are Vitamin D, estrogen and testosterone (others are less well studied).

Human steroid hormone receptors (including Vitamin D forms which are really secosteroids) use this same molecular connection to make a steroid molecule stay longer on its receptor, generating a larger signal, and thus, more effect if needed (the crucial feedback part has been misunderstood by much research). Your cells carefully monitor hormone receptors, so Boron effects don't get out of control.

Another slipstitch effect of borates is interaction with enzymes involved in cellular energy production. The slipstitch effect makes these important enzymes a little faster, facilitating the constant grabbing and releasing of substrates/outputs. We all want more energy on demand.

Citations Boron - How It Works: Bolanos 2004; Khaliq 2018; Nielsen 1991 274; 1991 2661, 1998 319, 2011, 2014, 2017, 2020; Pizzorno 2015; Scorei 2013

Getting more Boron

The goal with Boron nutriture is first, prevent a deficiency. Not only does calcium & magnesium status suffer, but also Vitamin D activity is decreased when Boron intakes are below 1 mg daily. MultiV-PRO uses a longer lasting, plant form of Boron – FruiteX-B® Calcium Fructoborate at a daily dose of 1 mg Boron per serving. MultiV-PRO added to Boron intakes from food and water closes the gap between typical intakes and clinically studied doses of 2.5-6 mg/day, preventing deficiencies.

A lot of overlooked research has found an average intake in US adults of Boron as ~1 mg daily, about half as Borate salts and half as plant chelate forms. Boron intakes in US women and men show most are not getting an adequate intake (at least 1 mg/day). Fortunately, Boron intakes of 2 mg or more daily are considered by experts to be a healthy intake for adults.

In plants, borate forms of Boron complex with sugars, amino acids and organic acids in plants to form a number of Boron complexes. This is why food sources of Boron are plant foods and not animal foods. Raisins, grapes, nuts, seeds, plums, fruits and wine are top sources for dietary Boron. Drinking water adds borate forms of Boron, but intakes are very location-specific, meaning getting Boron from drinking water is unreliable. Plant boron sources are also dependent on the local water content of Boron, but plants concentrate available Boron and convert it into chelated forms, one of which is FruiteX-B® (Calcium Fructoborate).

Research in humans has shown that plant Boron compounds are a time-release form of borate salts in the bloodstream. Both Borate salt and Boron compounds work similarly, but plant Boron compounds have longer-lasting effects at lower doses since Borate is so soluble it gets lost into urine quickly. This means that, compared to Boron chelates, a higher daily intake of Borate is necessary for Boron to exert its full effects. And it means that the Boron chelates in FruiteX-B® in MultiV-PRO easily repletes most persons, even those with a low Boron dietary intake.

Citations - Getting More Boron: *Hunt 2012; Hunter 2019; Khaliq 2018; Meacham 2010; Nielsen 1987, 1988, 1990 319, 1991 274, 1991 2661, 1998 319, 2006, 2008, 2011, 2014, 2017, 2020; ODS 2020; Pizzorno 2015; Rainey 1999; Simsek 2003; Sutherland 1998; WHO 1996*

Boron & Exercise

What was missed by many from the epiphanic 1987 study results for hormones and bone health (Nielsen 1987) were the positive effects of Boron for retaining calcium and magnesium bodywide – this is vital for muscular performance and exercise recovery, but even more so for connective tissues – bones especially.

Given its role with steroid hormones and Vitamin D, Boron is an indirect potentiator for endurance exercise physiology and recovery. Using boron supplements to increase steroid hormone levels predictably failed in strength athletes, but endurance athletes are unstudied for boron effects, except for one study that found serum Boron levels in professional Spanish athletes were similar to sedentary controls (Maynar 2017). MultiV-PRO uses a boron chelate found in plant foods (FruiteX-B®), which acts as a time-release borate, extending the utility of boron supplementation.

Although there is a paucity of human studies on Boron for endurance exercise performance, there are studies showing that Boron dietary or supplement intakes of ~2 mg daily or more benefit factors that are important for exercise performance. These include: 1) increased levels and/or efficiency of steroid hormones; 2) improved Vitamin D functions; 3) improved retention of calcium and magnesium; 4) improved cardiometabolic measures such as CRP and biomarkers of heart health. The data on reducing biomarkers of stress (like CRP) is in older adults, but it has been consistent with how Boron works. Also, by enhancing active Vitamin D levels (calcitriol), another normal mechanism is operative – Vitamin D also has a strong effect on muscle repair and recovery. Boron works with Vitamin D to sooth overworked muscles.

One exercise performance study, using FruiteX-B® in combination with other known ergogenic aids (creatine, coffee fruit extract and Vitamin D) found significantly improved golf drive distances vs. placebo (Ziegenfuss 2015), even though 1-RM bench press and body mass changes were not different between groups. The other ingredients mean that performance improvements in golf swing cannot be attributed solely to the Boron compound, and golf as a sport is less relevant to endurance exercise performance.

Citations - Boron & Exercise: *BBita 2022; Bolanos 2004; Chiang 2017; Dzik 2019; Ghozali 2022; Heffernan 2019; Hunt 1998, 1999; Maynar 2017; Moran 2013; Naghii 1997, 1999; Nielsen 1987, 2006; Pietrzkowski 2013; Pizzorno 2015; Tomlinson 2015; Weber 2022; Ziegenfuss 2015*

Boron - A hormone helper

This means that your normal hormonal responses to exercise are optimized by Boron. Your hormone levels keep their usual changes in blood levels, except that your receptors work more efficiently. These steroid hormones include the following series: 1) corticosteroids; 2) estrogens/progesterones; 3) androgens (testosterone); 4) mineralocorticoids; and 5) calciferols (Vitamin D). The net effect of normal hormonal responses being optimized is to reduce normal, exercise-induced inflammation, thus improve recovery and adaptation from intense exercise, and assist calcium and magnesium redistribution.

Yes, an early study on Boron given to postmenopausal women found small but significant increases in blood levels of estrogen and testosterone after weeks of supplementation, but the experimental setting carefully controlled diet and activity to pinpoint Boron effects (Nielsen 1987). Nevertheless, this finding was taken out of context and for a short period, Boron was being touted for building muscle mass via more testosterone. These product promoters did not realize that these women also showed increased estrogen (estradiol), which is anathema to bodybuilding (but good for amenorrheic, oligomenorrheic or postmenopausal women). Needless to say, later studies did not find muscle-building effects in men with even large doses of boron salts, perhaps because of

an increase in estrogens. Boron supplementation to normal, healthy males led to significant increases in blood levels of estrogen (estradiol), with a statistical trend for an increase in testosterone.

Another study of sodium tetraborate Boron (10 mg) supplemented for seven days showed opposite results in eight healthy male volunteers (academic staff and students, obviously sedentary) (Naghii 2011) in a placebo-controlled, crossover study. Six hours after the first Boron dose, rapid decreases in sex hormone binding globulin (SHBG) were observed. C-Reactive Protein (hsCRP) and TNF-alpha were also significantly decreased, with a trend for cortisol lowering. Testosterone, free testosterone, estradiol and Vitamin D levels were unchanged. These analytes did not change during the placebo period. After seven days, free testosterone was significantly increased along with free/total testosterone, free/estradiol and total/estradiol ratios. Estradiol levels were significantly decreased. hsCRP, IL6, TNF-alpha showed trends for decreased levels. Vitamin D levels did not change. Thus, in healthy young males, a higher Boron dose may achieve similar effects as 3 mg doses in postmenopausal and elderly subjects. This study illustrates the importance of performing dose-response and time curves instead of random intakes at a time when the pharmacokinetics are not known – a sound research practice seldom encountered with nutrients. Thus, there is strong evidence that a high Boron dose in young, sedentary men has beneficial effects on hormones and biomarkers of normal inflammation.

To bring home the known effects of Boron on hormones into real life, a human study of over 100 collegiate women with primary dysmenorrhea (PMS) were given placebo or 10 mg of sodium tetraborate from two days before the end of their cycle until the third day of menstrual flow for five days (Nikkah 2015). Boron reduced pain severity by ~20% compared to 7-9% for the placebo group. These results fit both the hormonal and low magnesium mechanisms of causations for PMS pain that Boron affects.

Boron has exhibited several Mechanisms of Action to assist making steroid hormones and Vitamin D more active, within normal ranges – not excessive. Human clinical findings give evidence for the known Mechanisms of Action for hormones and cytokine mediators having biological benefits from Boron supplementation.

Citations - Boron, Hormones & Vitamin D: Bello 2018; Benderdour 1998; Eskin 2015; Ferrando 1993; Green 1994; Hunt 2012; Khaliq 2018; Meacham 2010; Naghii 1993, 1997, 1999, 2011; Nikkah 2015; Nielsen 1987, 1990 319, 1991 274; 1991 2661, 1998 319, 2006, 2008, 2011, 2014, 2017, 2020; ODS 2020; Pizzorno 2015; Scorei 2013; Ziegenfuss 2015

Boron & Musculoskeletal health

In humans, bone has the highest concentration of Boron. The link between Boron and calcium, magnesium and Vitamin D enhancements has shown that Boron plays an important role in maintaining healthy bone mass at all ages. Short-term studies (relevant to the one-year bone turnover time) have shown improvements that predict better bone health. Also, people with higher bone levels of Boron show higher bone mass – a direct correlation between more Boron = more bone.

Comparing effects of Boron supplementation in college-age sedentary and athletic women for ten months found minor changes in blood and urine levels of calcium, magnesium and phosphorus with exercisers showing lower blood levels of magnesium and phosphorus. Bone density increased, but given the subjects' ages, bone growth is normally increasing. This study had several other confounders – small subject numbers per group (5-10) coupled with large variability and less sensitive bone mass measurement (lumbar spine), meaning it was underpowered (Meacham 1994, 1995).

Boron supplementation to postmenopausal women reproducibly showed benefits for bone mass and status of calcium and magnesium. Similarly, several studies have found improvements in older persons with everyday joint discomfort from FruiteX-B®, even in relatively short time periods (eight weeks). The consensus of these two lines of research is that Boron has beneficial effects on bone and joint health in older persons, but the relevancy to younger women and men is promising but not well known as of yet.

Citations - Boron & Musculoskeletal Health: *Bita 2022; Bolanos 2004; Devirian 2003; Eskin 2015; Ghivercea 2004; Hunt 1999, 2012; Hunter 2019; Khaliq 2018; Mahmood 2016; Meacham 1994, 1995, 2010; Miljkovic 2004; Naghii 1993, 2011; Newnham 1994; Nielsen 1987, 1990 45, 1990 319, 1991 274; 1991 2661, 1992, 1998 319, 2006, 2008, 2011, 2014, 2017, 2020; ODS 2020; Pizzorno 2015; Price 2012; Rondanelli 2020; Scorei 2013; Volpe 1993*

Boron & Exercise Summary

Boron clearly has long-range health benefits for maintaining musculoskeletal system health. Boron does this in many-splendored ways, such as specific and unique roles supporting healthy levels and functions of steroid hormones and Vitamin D, positively affecting calcium and magnesium status. Supplementation with Boron showed positive results in healthy young women with PMS. There are hints of other metabolic roles and repairing tissue damage, which would be handy for exercise recovery. However, no studies specifically studied endurance exercise performance effects of Boron in persons of any age. Judging from the unique mechanisms of action for boron, it is an optimizer to overall health rather than a stimulator regardless of condition (like caffeine is). One clear finding is that Boron intakes of 2 mg or more daily, which is what MultiV-PRO is designed to assure with FruiteX-B®, have long-term benefits for bone health and other musculoskeletal systems, including joints and muscles. Since endurance athletes often have low Vitamin D status and intakes, and are prone to musculoskeletal stress, ensuring an adequate Boron intake is a healthy way to support the musculoskeletal system to help maintain continued exercise performance.

Literature Quote for Boron & Exercise

"Boron may have a beneficial effect on the function of such hormones as vitamin D, estrogen, thyroid hormone, insulin, and progesterone. ... Boron clearly plays many important roles in enhancing human health..."
Eskin 2015, p.1

"Mounting evidence suggests that boron is essential to human beings."
Expert Group on Vitamins and Minerals 2002, p.2

"We applaud the previous and ongoing efforts of fellow scientists who have so passionately contributed to the advancement of B-related research and knowledge; we militantly challenge the current misconceptions related to B toxicity; finally, we encourage the world to recognize the clearly important human and animal health benefits inherent in these various B-containing molecules, benefits that have been hiding in plain sight within our plant-based diets since the very beginning of time."
Hunter 2019, p.21

"In vertebrates, the borates are essential for their unique bonding and structural characteristics. ... Furthermore, it is beneficial for different organs, because of its interactions with calcium, vitamin D, and magnesium."
Khaliq 2018, p.31

"Recent findings have reinforced the significance to health of adequate boron status. The effects of boron are multiple and versatile. ... When administered at an effective dose, boron shows remarkable properties, and its nutritional value cannot be underestimated.
Khaliq 2018, pp.44-5

"Current research implicates boron as an essential nutrient in humans demonstrating healthful effects in cellular functions.... Proposed mechanisms of action implicate that boron, found in cells as boric acid, participates in important membrane functions and intracellular signaling cascades."
Meacham 2010, Abstract

"The formation of steroid hormones from precursors involve one or more hydroxylations of the steroid structures and it is hypothesized that boron enhances the rate of hydroxylation. It appears that enhancement in the rate of hydroxylation by boron followed by the increase in the hormone levels support the proposal."
Naghii 1999, pp.35-7

"...a considerable number of people consume less than 1 mg boron per day."
Oancea 2018, p.5

"The findings support the contention that boron has a biological function that affects calcium metabolism, and thus bone formation and maintenance in humans. ... The findings suggest that boron is an essential trace element for humans."
Nielsen 1990, pp.52-3

"As indicated in the preceding, the two human experiments described yielded a bewildering and surprising array of significant findings when it is considered that boron apparently has a biochemical role so subtle that it was considered unimportant in nutrition until the 1980s. However, if one closely analyzes the findings, the results from the first two human experiments indicate that boron affected many variables affected by calcium, and suggest that the similarity between the effects of boron and calcium occurred because they affected a similar system, or systems, which indirectly affect many variables."
Nielsen 1991 274, p.279

"Recent findings indicate that a significant number of people do not consistently consume more than 1 mg B/d; this suggests that B could be a practical nutritional or clinical concern."
Nielsen 1998 319, Abstract

"Now that the opinion about the nutritional importance of boron is changing, a question that has come to the fore is: Why wasn't this recognized sooner? A reasonable answer to that question is that boron apparently has a biochemical function that is very subtle. Moreover, this role apparently is one that allows optimal functioning of other nutrients or hormones and thus is overlooked as attention is directed toward altering the intake of the substance whose suboptimal metabolism is directly involved in a pathologic consequence (e.g., calcium supplementation to prevent bone loss)."
Nielsen 2000, p.512
[NOTE: The inability of calcium supplementation with or without Vitamin D to actually build bone mass in older persons just screams the need for more boron and magnesium! This has relevance for bone mass maintenance in endurance athletes too.]

"Growing evidence from a variety of experimental models shows that boron is a bioactive and beneficial (perhaps essential) element for humans."
Nielsen 2011, Abstract

"Evidence that boron is a beneficial bioactive trace element is substantial. The evidence has come from numerous laboratories that have used a variety of experimental models, including humans. In nutritional amounts, boron promotes bone health and brain function, modulates the immune or inflammatory response, and influences the response to oxidative stress. Boron apparently has diverse effects through influencing a cell signaling system or the formation and/or activity of an entity involved in many biochemical processes. Based on findings from both animal and human experiments, an intake of boron near 1.0 mg/day would be a reasonable suggestion for an adequate intake that would assure the benefits provided by boron."
Nielsen 2017, Abstract

"Because boron may be bioactive through forming diester complexes with phosphoinositides, glycoproteins, and glycolipids that contain cis-hydroxyl groups in membranes, recent research has examined whether these boroesters influence membrane receptors and signal transduction and may thus be the basis for boron enhancement of insulin, vitamin D, and progesterone effects."
Nielsen 2020, p.462

"Interestingly, in the same study, it was found that treatment with CFB increased blood levels of endogenous calcitriol, an active form of vitamin D. ... This activity could be beneficial for muscles damaged due to overtraining and remaining under inflammatory conditions."
Pietrzkowski 2013, p. 483

"Physicians are less likely to be aware that dietary insufficiencies of magnesium, silicon, Vitamin K, and boron are also widely prevalent, and each of these essential nutrients is an important contributor to bone health."
Price 2012, Abstract

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