

MD+ Creatine Advantage

version III

Creatine Advantage was formulated to Naturally Boost Energy, Decrease Fatigue, and Improve Body Composition and Mental and Physical Performance.

Creatine advantage information was updated September 14, 2021. By Mauro Di Pasquale, B.Sc. (Hons); M.D.



Creatine Advantage is the Ultimate Creatine Product and addresses several levels involved in maximizing energy and decreasing fatigue. The formulation contains dozens of additive and synergistic Ingredients for Maximizing the Body's Energy Systems, decreasing general and exercise induced fatigue, Improving Body Composition, and physical and mental performance.

To order go to <https://metabolicdiet.com/product/creatine-advantage/>

For information on my line of nutritional supplement products go to <https://metabolicdiet.com/shop/>

Creatine Advantage is manufacture in a GMP and NSF certified pharmaceutical grade facility.

The information below on the new Creatine Advantage version III is in a constant draft form as revisions are made as new information becomes available. This latest information will give you the flavor of just what Creatine Advantage will do for you in helping you achieve your health, body composition and physical and mental performance goals.

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Creatine Advantage version III Supplement Panel

Supplement Facts:		Serving Size 15 Grams			
		Servings Per Container: 35			
	Amount	% Daily			
	Per Serving	Value			
	Amount	% Daily			
	Per Serving	Value			
Calories	42		Creatine Monohydrate	3500 mg	*
Total Carbohydrates	2 g	1%	Glutamine Peptides (from Casein)	1500 mg	*
Vitamin C (as Ascorbic Acid)	50 mg	83%	Branched Chain Amino Acids	1000 mg	*
Vitamin B1 (as Thiamine Pyrophosphate)	30 mg	150%	(Leucine 600 mg, Valine 200 mg, Isoleucine 200 mg)		
Vitamin B2 (as Riboflavin)	30 mg	150%	L-Taurine	1000 mg	*
Vitamin B3 (as Niacin, Niacinamide and Inositol Hexanicotinate)	20 mg	100%	D-Ribose	800 mg	*
Vitamin B6 (as Pyridoxal-5-Phosphate)	5 mg	250%	Beta-Alanine	600 mg	*
Vitamin B12 (as Methylcobalamin)	200 mcg	3333%	L-Histidine	500 mg	*
Pantothenic Acid (as D-Calcium Pantothenate)	5 mg	50%	L-Inosine	400 mg	*
Biotin	300 mcg	100%	N-Acetyl Tyrosine	400 mg	*
Iron (as Ferrous Succinate)	3 mg	15%	N-Acetyl-Cysteine	400 mg	*
Calcium (as Calcium Phosphate)	150 mg	15%*	L-Histidine	350 mg	*
Magnesium (as Aspartate and Phosphate)	250 mg	62%	L-Carnitine Fumarate	350 mg	*
Potassium (as Phosphate and Succinate)	210 mg	6%*	L-Carnosine	300 mg	*
Phosphorus (as Calcium, Magnesium, Potassium Phosphate)	250 mg	25%	Citrulline Malate	300 mg	*
Manganese (as Manganese Aspartate)	2 mg	100%	Betaine (Trimethylglycine)	250 mg	*
Sodium (as Chloride)	25 mg	2%	Alpha Lipoic Acid	200 mg	*
Chromium (as CHROMEMATE™ Polynicotinate)	25 mcg	21%	Coenzyme Q10	40 mg	*
Zinc (as Monomethionine)	6 mg	40%	Creatine Advantage™ Complex - 820 mg*		
Selenium (as L-Selenomethionine)	25 mcg	35%	Calcium Pyruvate, Choline Bitartrate, L-Phenylalanine, AMP (Adenosine Monophosphate), ATP (Adenosine Triphosphate), NADH, Astaxanthin.		
Other Ingredients: Beet Powder, Natural Flavors, White Stevia Powder, and Erythritol.					
*Daily Value not established					
** Percent Daily Values are based on a 2000 calorie diet					

Introduction

The ergogenic as well as therapeutic effects of increasing muscle and body creatine by supplementation have been documented by studies spanning three decades. In those involved in exercise and sports, creatine supplementation has been shown to have ergogenic effects leading to improvements in athletic performance by increasing energy, strength and muscle mass, decreasing fatigue, and enhancing recover.^{12345,6,7,8,9,10,11121314151617}

A recent study concluded that creatine can maintain mitochondrial integrity, increase creatine phosphate resources, act as a cellular energy buffer, and protect two important cellular targets, mitochondrial DNA and RNA, from oxidative damage.¹⁸

Another recent study concluded that According to the available information, creatine has antioxidant properties and can be effective through direct and indirect mechanisms. It has a positive effect on oxidative stress and reduces ROS. Creatine can maintain mitochondrial integrity, increase CrP resources, act as a cellular energy buffer, and protect two important cellular targets, mtDNA and RNA, from oxidative damage.¹⁹

These and other beneficial effects of creatine supplementation, for example on the CNS, are enhanced in Creatine Advantage by stacking creatine with other ingredients.

Our formula not only contains the highest quality, pure crystalline creatine monohydrate so that it mixes instantly and leave's no chalky taste, but we've also added a host of other natural ingredients that make our formula much more effective and versatile than any other creatine products on the market

Creatine monohydrate is absorbed fairly well if just mixed with water. Using carbs increases insulin secretion and thus creatine utilization. However, by using the right formulation, as in Creatine Advantage, insulin levels are increased by the formulations' amino acids, which in turn maximizes creatine absorption. But as you'll discover, Creatine Advantage does much more than just raise creatine levels.

To understand why you need a number of synergistic ingredients besides creatine to maximize the energy systems in the body it's important to know some basics on creatine metabolism. Creatine is used by the body to make phosphocreatine, and the phosphocreatine is a high energy source that functions to replenish ATP (the primary energy source in the body) when it's depleted.

The body needs about 2 grams of creatine a day to account for the amount of creatine that is metabolized to creatinine irreversibly. The creatinine is then excreted in the body. Part of this turnover can be replaced through exogenous sources of creatine in foods, especially meat and fish, and of course by supplementing with creatine monohydrate or creatine phosphate (the two most common forms available in supplements with the monohydrate being by far the most widely available). The remainder is derived via endogenous synthesis from the precursors **arginine, glycine and**

methionine. Both the creatine and the creatine precursors (all three are in the glutamine peptides mix) are supplied in Creatine Advantage.

It's also important that you provide the body with the means to increase energy levels, preferably by breaking down and oxidizing body fat, so that phosphocreatine can be made from creatine plus phosphate. And it's important to simultaneously maximize the effects of insulin, GH, and IGF-I, which is difficult to do using carbs and sugars, not only to synergistically maximize the levels of these anabolic hormones, but also so that the creatine is most efficiently used.

Creatine Advantage doesn't overwhelm the body with creatine, since 3.5 grams a day is all that's needed to maximize creatine cellular levels - the usual doses of creatine used by athletes are mostly excreted²⁰ (as urinary creatine and a small amount of creatinine) and secondly the use of excessive amounts for long periods of time may be counterproductive as far as potential adverse effects.

An example of the usefulness of a steady lower dose of creatine is a recent study that found that lower dose Creatine supplementation had significant effects on body composition, muscle function, and body Creatine retention (see citation and abstract below).²¹

Low-dose creatine supplementation enhances fatigue resistance in the absence of weight gain.

[Rawson ES](#), [Stec MJ](#), [Frederickson SJ](#), [Miles MP](#). [Nutrition](#). 2011 Apr;27(4):451-5. Epub 2010 Jul 1.

Source

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Abstract

OBJECTIVE:

We examined the effects of 6 wk of low-dose creatine supplementation on body composition, muscle function, and body creatine retention.

METHODS:

Twenty healthy men and women (21 ± 2 y old) were randomized to receive creatine ($0.03 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$); $n = 10$, 4 women) or placebo ($n = 10$, 4 women) for 6 wk in a double-blind placebo-controlled fashion. Participants were tested on two occasions before supplementation to establish a reliable baseline, and then were retested after supplementation. Testing included body composition, maximal strength (three-repetition maximal concentric knee extension at 180 degrees/s), muscle fatigue (five sets of 30 concentric knee extensions at 180 degrees/s), and plasma creatine concentration.

RESULTS:

There were no significant differences in body mass, fat-free mass, fat mass, body fat percentage, total body water, or maximal strength in either group from before to after supplementation (all $P > 0.05$). After supplementation, plasma creatine increased significantly in the creatine group (+182%, $P = 0.03$), with no difference in the placebo group.

Compared with baseline values, creatine-supplemented volunteers were more resistant to fatigue during sets 2 (7%), 3 (9%), 4 (9%), and 5 (11%) (all $P < 0.05$). In placebo-supplemented participants, there was no improvement in fatigue resistance during sets 2 (0%), 3 (1%), 4 (0%), and 5 (-1%) (all $P > 0.05$).

CONCLUSION:

Ingesting a low dose ($\approx 2.3 \text{ g/d}$) of creatine for 6 wk significantly increased plasma creatine concentration and enhanced resistance to fatigue during repeated bouts of high-intensity contractions.

More Than Just Creatine

Using Creatine Advantage does more than just supply 3.5 grams of Creatine per serving. At the same time Creatine Advantage maximizes phosphocreatine and ATP production (the TCA cycle intermediates and the AMP), and protein synthesis (the amino acid content and glutamine peptides).

Added amino acids and dipeptides and other essential boosters allow an increase in the absorption and utilization of creatine and increase the volumizing, anticatabolic and anabolic effect of the Creatine Advantage formulation. The added energy ingredients and precursors make Creatine Advantage the ultimate creatine and energy mix, one that will maximize energy metabolism, muscle mass and performance.

But that's not all. Creatine Advantage, with its synergistic formulation, also has neuroprotective effects and may be useful for treating neurodegenerative diseases,^{22,23,24,25,26,27} likely due to its effects on phosphocreatine and ATP,²⁸ as well as protective and reparative effects on other cells and systems in the body.

For example, a study found that topical creatine has beneficial effects on skin damage because of its ability to recharge the energy mechanisms in these cells that deal with the protection and repair of skin damaged by free radicals.²⁹

Mitochondrial Effects

The effects of creatine are enhanced by stacking creatine with other ingredients. These added ingredients increase the use of creatine by the body, as well as increasing energy systems beyond just creatine phosphate, as well as providing extra cytoprotective and antioxidant protection.

For example, Creatine Advantage contains several ingredients, including creatine and alpha lipoic acid that have multiple functions, including ameliorating mitochondrial disorders.³⁰

As well, ingredients such as taurine, alpha lipoic acid, beta-alanine, L-carnitine fumarate, betaine, N-Acetyl-Cysteine, N-Acetyl-Tyrosine, and various amino acids, including histidine, and many other ingredients have potent cytoprotective, neuroprotective, antioxidant and fat burning effects on their own and work with the other ingredient to improve health, body composition and performance.

Coenzyme Q10 (ubiquinone-10, CoQ10)

Coenzyme Q10 (CoQ10), a coenzyme that is ubiquitous in animals, including humans, is a lipid-soluble antioxidant and acting as an electron carrier is a key component of the mitochondrial electron transport chain for adenosine triphosphate (ATP) production.³¹ It is also one of the key antioxidant nutrients that protect mitochondrial membrane lipids and proteins and mitochondrial DNA from free radical-induced oxidative damage.

As such it is necessary for proper energy metabolism. For example, myocardial CoQ₁₀ content is reduced by cardiac failure and aging. It is also reduced by statins, the popular cholesterol lowering drugs. Studies have suggested preventative supplementation of CoQ10 for cardiac health and for those on statins.^{32,33,34,35,36,37}

CoQ10 has been shown to decrease oxidative stress and mitochondrial damage leading to increases in mitochondrial mass in many tissues.^{38,39} As well, CoQ10 has been shown to affect the expression of genes involved in human cell signaling, metabolism and transport.

As such, since many neurodegenerative disorders, diabetes, cancer, and muscular and cardiovascular diseases have been associated with low CoQ10 levels, supplementation may be

beneficial in many conditions and diseases^{404142 434445} including alleviating intervertebral disc degeneration.⁴⁶

For example, CoQ10 supplementation has been shown to have anti-aging and beneficial effects on semen parameters, fertility, testicular damage, and reproductive hormones including testosterone.⁴⁷⁴⁸⁴⁹⁵⁰⁵¹⁵²⁵³⁵⁴⁵⁵ In a recent study CoQ10 while not found to directly increase testosterone, CoQ10 supplementation **“was found to ameliorate the reduction in testosterone induced by chemical reproductive toxicants, mainly by neutralizing the damaging effect of the generated free radicals.”**⁵⁶

CoQ10 has also been shown to have beneficial effects on oxidative stress, inflammation, the immune system, and on exercise performance.⁵⁷⁵⁸⁵⁹⁶⁰⁶¹⁶²⁶³⁶⁴⁶⁵⁶⁶⁶⁷

CoQ10 also regenerates and extends the action of vitamin E thus further protecting against membrane lipid peroxidation. Under the various forms of stress and inflammation, demand for coenzyme Q10 increases which must be met by dietary intake in order to optimize mitochondrial function.

As well, it has been shown that the reduced form of CoQ10 is an important physiological lipid-soluble antioxidant that scavenges free radicals generated chemically within liposomal membranes.^{68,69} It has also been shown that it reduces oxidative stress associated with strenuous exercise in rats, healthy adults and young athletes.⁷⁰⁷¹⁷²⁷³⁷⁴ As noted above, vitamin E and ubiquinone increase physical working capacity of experimental animals.⁷⁵

Generation of free radicals and subsequent lipid peroxidation have been proposed to contribute to delayed tissue damage. One study has found that ascorbate and ubiquinol levels were decreased after trauma.⁷⁶ In this study, changes in tissue levels of ubiquinol, but not ascorbate reflected the degree of trauma. The authors suggest that ubiquinol levels may provide a useful marker of the oxidative component of the secondary injury response.

A recent study found that CoQ10 supplementation **“significantly recovered mitochondrial function and concurrently decreased the generation of reactive oxygen species and lipid peroxides, inhibited the accumulation of lipid droplets and the formation of the NOD-like receptor family pyrin domain-containing three (NLRP3) inflammasome, and reduced interleukin-1 β release and cell death.”** Also, the authors concluded that their results clarified **“the causal role of CoQ10 in coupling the electron transport chain with β -oxidation”**.⁷⁷

Creatine Advantage also contains **L-carnitine**. Studies have shown that under certain conditions CoQ10 plus L-carnitine and in some cases L-carnitine alone, significantly increases total antioxidant, LH and testosterone levels as well as improving semen parameters.⁷⁸⁷⁹⁸⁰⁸¹⁸²⁸³⁸⁴⁸⁵⁸⁶

L-Carnitine

Creatine Advantage contains L-carnitine fumarate, with both parts of the ingredient involved in optimizing energy metabolism. The fumarate moiety increases the flux of the TCA cycle to increase ATP synthesis, as well as the potential to form glucose through gluconeogenesis.

L-carnitine is mainly known for shuttling fatty acid acyl units into mitochondria so that beta oxidation of these acyl units provides acetyl units to fuel the TCA cycle and through oxidative phosphorylation to increase ATP production. In this respect, L-carnitine functions much like a gas pump in that it puts fuel in the gas tank so that your car engine can use it to provide energy to run the car. LC also acts to maintain mitochondrial function and suppresses oleic acid-mediated MPT through acceleration of beta-oxidation.⁸⁷

But L-carnitine (LC) is much more than just the shuttle mechanism to get fatty acids into mitochondria, it also functions in the opposite direction when there's an overload of acyl and acetyl units in the mitochondria that can result in mitochondrial dysfunction and insulin resistance.⁸⁸ LC thus acts more like a regulator of mitochondrial function both by providing nutrients that can be used efficiently and removing nutrients that are clogging up the mitochondrial machinery. Studies have shown that the more fat is shuttled into the mitochondria and used as fuel, the more L-carnitine is needed. So, unless the body's metabolism is primed epigenetically to deal with utilizing fat as a primary fuel, and that also means a sufficient amount of LC to deal with the use of fat as a primary fuel (i.e. avoiding a relative carnitine insufficiency which can also be caused by aging and vegetarian diets), the result can be high rates of incomplete fat oxidation and intramuscular accumulation of fatty acylcarnitines, byproducts of lipid catabolism produced under conditions of metabolic stress including exercise.^{89,90}

Although it seems counter intuitive given LC role in fat metabolism, LC also increases insulin sensitivity and is a regulator of glucose metabolism and may be used to counter the metabolic syndrome and help treat type II diabetes.^{91,92}

A recent study found that the combination of LC, alpha lipoic acid, and betaine, all in Creatine Advantage, had beneficial effects on health and body composition.⁹³ As well,, LC is essential for proper muscle function and some studies have shown that carnitine supplementation improves exercise performance.⁹⁴

LC has antioxidant properties directly but also ramps up endogenous antioxidant systems including glutathione, catalase, and SOD. The dual action decreases the effects of ROS produced with higher intensity resistance and aerobic exercise. L-carnitine also decreases the production of some of the pro-inflammatory cytokines and has anti-inflammatory and immunomodulating effects.^{95,96,97}

Taurine

Taurine, a sulfur-containing amino acid and the second most abundant amino acid, and the most abundant free amino acid, found in skeletal muscle tissue, has many properties that can enhance the training effect, including its abilities to increase growth hormone, protect joints, and protect the liver, as well as its antioxidant and anabolic effects.⁹⁸ Taurine has also been shown to have insulin like effects and to help control cell volume. The volumizing effect on muscle cells is felt to lead to an increase in protein synthesis.

Over the years, oral taurine administration has been shown to help muscle cramping in patients with liver cirrhosis and myotonic dystrophy. Several studies have suggested that it may also help to alleviate muscle cramps occurring during and after exercise. But there's more to the story.

Taurine is considered a potent antioxidant and cytoprotective agent that may be useful for combating the adverse effects of physical and psychological stress, and aging.^{99,100,101,102}

A study in rats showed that taurine is useful for reducing physical fatigue, muscle damage, and exercise induced muscle injury during exercise training, presumably due to its antioxidant effects and the beneficial effects that taurine has on metabolism and on muscle and cardiac functions.¹⁰³

A recent study on rats has shown that oral taurine supplementation may increase muscle performance and reduce muscle injury caused by exercise.¹⁰⁴ The aim of the study was to determine if increasing muscle levels of taurine would decrease free radical damage after exercise-induced injury. The authors found that first of all taurine levels rose in muscle after supplementation, and secondly that running performance was improved by the taurine supplementation. Thus it appears taurine supplementation may facilitate exercise performance and reduce some of the counterproductive muscle injury caused by exercise.

A recent study found that taurine supplementation in patients with heart failure increases their exercise capacity.¹⁰⁵ Another recent study found that taurine decreases oxidative stress in skeletal muscle after eccentric exercise.¹⁰⁶ Another study found that taurine may attenuate exercise-induced DNA damage and enhance the capacity of exercise due to its cellular protective properties.¹⁰⁷

On a preventative level, taurine administration has been shown to increase taurine concentrations in skeletal muscles, reduce the decrease in taurine concentration in skeletal muscles on exercise, and up-regulates physical endurance.¹⁰⁸

There is some evidence to show that taurine may enhance training further by decreasing training induced fatigue. A recent paper has shown that Na⁺-K⁺-ATPase activity is depressed with fatigue, regardless of training state, suggesting that this may be an important determinant of fatigue.¹⁰⁹ Another recent paper associated fatigue and training with reduced Ca²⁺-ATPase activity.¹¹⁰ Previous studies have shown that taurine stimulates Na⁺-K⁺-ATPase activity and also the pumping rate of the Ca²⁺-activated ATPase pump.

One study found that taurine administration reduced the decrease in taurine in skeletal muscles in exercise, increased duration of running time in rats, and was considered to reduce exercise-induced muscle fatigue.¹¹¹ Also taurine supplementation has been shown to increase skeletal muscle force production, protects muscle function and reduce oxidative stress.¹¹²

While the evidence is circumstantial at present and a direct study linking the two research findings needs to be done, it's quite possible that supplemental taurine, besides all the positive effects we know it has, may also reduce exercise induced fatigue.

For more information go to my updated article on [Taurine](#).

Alpha Lipoic Acid

Alpha lipoic acid (ALA) has potent antioxidant properties intrinsically and secondary to its ability to increase levels of intra-cellular glutathione, and its ability to recycle other antioxidants such as vitamin C, vitamin E and glutathione.^{113,114,115,116,117} ALA and glutathione have been shown to have significant effects in decreasing mercury toxicity in the body.¹¹⁸

Alpha lipoic acid also has a number of useful and diverse properties. In a review¹¹⁹ the author states “LA improves glycemic control, polyneuropathies associated with diabetes mellitus, and effectively mitigates toxicities associated with heavy metal poisoning. As an antioxidant, LA directly terminates free radicals, chelates transition metal ions (e.g. iron and copper), increases cytosolic glutathione and vitamin C levels and prevents toxicities associated with their loss.”

ALA has significant anti-inflammatory properties and has been shown to inhibit IL-1, a proinflammatory cytokine and inhibit the synthesis of PGE2 by inhibiting COX-2 activity. This latter mode of action simulates the anti-inflammatory effects of the present class of NSAIDS such as Celebrex, Advil, Aleve, etc. As well, the anti-inflammatory effects of ALA are increased since it decreases both the pro-inflammatory cytokines^{120,121} and secondary cortisol elevations.

It has been shown to inhibit cross-linking among proteins, a process that contributes to the aging process in the body and especially in collagen-heavy tissues such as skin. Alpha-lipoic acid activates a collagen-regulating factor known as AP-1 that turns on enzymes that digest glycation-damaged collagen and thus make the skin more supple and youthful looking.

Besides having potent antioxidant and anti-inflammatory effects, ALA also has significant anabolic effects secondary to its beneficial effects on insulin sensitivity and growth hormone and IGF-I secretion, all factors involved in maintaining, repairing and regenerating musculoskeletal tissues.^{122,123,124,125}

ALA is also useful in reversing mitochondrial dysfunction, especially in aging mitochondria.^{126,127}

Astaxanthin

Astaxanthin, a powerful lipid based antioxidant complements and adds to the many beneficial effects of Creatine Advantage on energy metabolism, body composition, exercise performance and overall health.

Astaxanthin has been shown to have potential to improve health, enhance energy metabolism and exercise performance, increase fat metabolism during exercise, decrease oxidative stress and muscle injury, delay exhaustion, increasing improve body composition, enhance recovery, prevents redox imbalances, and attenuates muscle damage, counterproductive inflammation and fibrosis induced by rigorous physical training as well as immobilization.^{128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145}

Some of the benefits of Astaxanthin deserve special attention. For example, astaxanthin has a protective effect on mitochondria, the cellular powerhouses that produce the energy we need to live and function optimally. Protecting the mitochondria is especially important during exercise since destructive free radicals production increases almost exponentially and can damage not only the mitochondria, thus impairing energy systems, but also skeletal muscle as a whole impairing performance and recovery and increasing the chance of injury.¹⁴⁶

But that's not all because astaxanthin, through its effects on decreasing mitochondrial damage in other parts of the body such as the testes, also increases testosterone production and thus increases

the anabolic effects of exercise, and has also been shown to have positive effects on sperm parameters and fertility.¹⁴⁷

Unlike some other antioxidants, astaxanthin not only has intrinsic antioxidant and anti-inflammatory properties but it also increases the endogenous production of natural antioxidant defense mechanisms such as SOD and heme oxygenase-1.¹⁴⁸

As well, it works synergistically with other ingredients in Creatine Advantage. For example, in horses it's been shown that continuous dietary administration of astaxanthin and L-carnitine (both in Creatine Advantage) attenuates exercise-induced muscle damage.¹⁴⁹

For all these reasons astaxanthin plays a prominent part in the beneficial effects that Creatine Advantage has on all aspects of health, energy metabolism, nutrition, exercise, and anti-aging.

Other Amino Acids

Other amino acids that are a part of the glutamine peptides in Creatine Advantage contribute to overall health and repair in many ways. For example, proline and glycine are essential for collagen production. As well, the sulphur containing amino acids (also in the glutamine peptides) have significant antioxidant and other effects.¹⁵⁰

Increased Synthesis of PC and ATP

Creatine Advantage contains all the necessary products for the synthesis of both high energy phosphate compounds creatine phosphate and ATP, and for the efficient salvage of ATP after it's been metabolically degraded, including:

- **Inorganic phosphorus and phosphates – also important for normalizing and regulating thyroid hormone.**
- **Creatine**
- **Inosine**
- **Ribose**

For example, one study found that ribose supplementation acutely increased ATP resynthesis after high intensity exercise, and that that oral intake of ribose in humans after 1 wk of high-intensity training lead to higher resting ATP levels.¹⁵¹

It also contains the following nutrients to facilitate the glycolytic and TCA cycle energy processes:

- **Biotin** - a cofactor in many energy reactions involving glycogenolytic, glycolytic, TCA and anapleurotic enzymes.
- **Magnesium** - which has also been shown to increase energy systems, insulin sensitivity, protein synthesis and serum testosterone, GH and IGF-I levels.
- **Calcium** - which has been shown to facilitate muscle contraction and decreasing fatigue).
- **Potassium**, the transport of which is linked to aerobic glycolysis.

Increasing TCA Flux and ATP Synthesis

Creatine Advantage maximizes ATP production (as I mentioned above ATP is the main energy source in the body - the function of phosphocreatine is to replenish ATP, so it makes sense to increase ATP levels as well). It contains a proprietary blend of several ingredients that maximizes mitochondrial anapleurotic flux in the TCA cycle resulting in increased ATP production and increased energy availability for protein synthesis and other functions, including the formation of phosphocreatine.

These ingredients, including **coenzyme Q10** and several anapleurotic direct and indirect TCA cycle intermediates (such as **aspartate, citrate, malate, fumarate, succinate**, and the various anapleurotic and the various amino acids, including the **branched chain amino acids, glutamate, glutamine**, and other amino acids present in the **glutamine peptides** hydrolysate), impact on TCA Cycle (also known as the Citric Acid cycle and Krebs's Cycle) flux and maximize mitochondrial metabolism, increase aerobic ATP production, and enhance insulin and growth hormone/IGF-I secretion and formation.

The overall increase in anapleurotic flux produces an increase in aerobic energy production, insulin secretion, and protein synthesis, and results in an increased adaptive response, a surge in skeletal muscle cell growth, increased fat loss, and improved recovery.

Adenosine monophosphate (AMP), one of the ingredients in Creatine Advantage, activates AMPK (AMP-activated protein kinase). The AMPK pathway is active in sensing and regulating tissue energy metabolism, influencing fuel metabolism, especially fat, in tissues including muscle and liver, and increases insulin sensitivity in skeletal muscle,^{152 153154} AMPK also plays a part in decreasing the concentration of malonyl-coA in peripheral tissues, (as does exercise BTW) and thus decreases triglyceride accumulation and increases fatty acid oxidation.¹⁵⁵

The overall response to all of this is also an increase in energy output, which under conditions of energy deprivation, such as when you're trying to lose weight and/or body fat, increases fat oxidation further.

Insulin Boosting System

Creatine Advantage has a low carbohydrate based insulin boosting system (glutamine in the form of glutamine peptides - more stable in liquid form and more effective than free glutamine) and compounds to increase insulin sensitivity (**chromium, histidine** – which also provides intracellular buffering to stimulate anaerobic energy formation, **taurine**¹⁵⁶ – which also has significant antioxidant and protective effects, stimulates growth hormone secretion and increases cell volume, and racemic **alpha lipoic acid** (a combination of the two main enantiomers of ALA – ALA is also an excellent antioxidant) and thus make the insulin more effective.

All of these compounds increase the boosting effect that insulin has on intramuscular creatine phosphate levels. For example, a study found that co-ingestion of alpha-lipoic acid with creatine can enhance muscle total creatine content as compared to the ingestion of creatine and sucrose or creatine alone.¹⁵⁷

As well, there is a significant increase in insulin sensitivity and/or insulin secretion, when a protein hydrolysate, such as the **glutamine peptides**, is combined with creatine.¹⁵⁸ **Sodium** is also important for increasing creatine uptake in muscle and some studies has been found to be important for creatine uptake into relatively insulin insensitive muscles such as the soleus.¹⁵⁹

Creatine Advantage Also Contains:

Glutamine peptides (from casein rather than from wheat gluten so Creatine Advantage can be safely used by those with gluten sensitivity), which have anabolic (increases protein synthesis and muscle mass) and anticatabolic (decrease muscle breakdown) effects, above those normally associated with glutamine, as the peptides themselves have some physiological effects. Also the peptide form is better absorbed than free glutamine that is not peptide bonded.

As well, the glutamine in the glutamine peptides:

- Regulates protein synthesis and increases body composition and performance
- Increases both aerobic and anaerobic energy systems
- Has beneficial effects on the immune system
- Aids in the prevention and treatment of the overtraining syndrome.
- Increases insulin sensitivity when a protein hydrolysate is combined with creatine.¹⁶⁰

Glutamine has significant effects on body composition and performance as it favorably affects growth hormone and cortisol levels, protein synthesis, cell volume, muscle catabolism (inhibits it) and gastrointestinal and immune function.¹⁶¹¹⁶²¹⁶³¹⁶⁴¹⁶⁵ It's used for energy by most cells in the body but especially by the GI tract, liver, kidney and the immune system. The process for energy production is by successive deamination of glutamine to glutamate, then to alpha-ketoglutarate that enters the TCA/Krebs cycle and through the oxidative phosphorylation forms ATP, the main energy source on which the body functions.

Glutamine is also used as a basis for the synthesis of the ATP molecule itself, nucleic acids (DNA and RNA synthesis and repair), other amino acids and proteins, glucose through gluconeogenic pathways, carbamoylphosphate, and other metabolites. As well glutamine increases glutathione, a powerful endogenous antioxidant that mitigates the counter-productive effects of exercise on excessive muscle damage without affecting the positive effects of exercise.

The interconversions, reactions, pathways and signaling that glutamine is involved in are complex and impacts many metabolic processes that are beyond the means of this information piece. As an example, glutamate can be used (besides conversion to glutamine) in an alanine aminotransferase

reaction to produce alpha-ketoglutarate (AKG) and alanine or by the reverse reaction alpha-ketoglutarate can be aminated by ammonia or via a transamination reaction from other amino acids to form glutamate and pyruvate. The resulting alanine and pyruvate are involved in complex interactions and so the complexity of how glutamine affects metabolism soon increases exponentially.

A recent paper found that glutamine supplementation improves some parameters of sport and exercise performance, and chronic supplementation appears to be of special importance for

increasing tolerance to intermittent exercise, lowering feelings of fatigue, and optimizing recovery from muscle damage.¹⁶⁶ Glutamine may also act as a relevant resource for rehydration during strenuous and prolonged physical activity.

And glutamine plays well with other ingredients in Creatine Advantage. For example, a study found that a combination of creatine monohydrate plus glutamine together resulted in significantly increase muscle mass and strength.¹⁶⁷

Volumizing Ingredients

Creatine Advantage contains an advanced cell volumizing formula that results not only in increases in protein synthesis and an anabolic effect, but an increased transport of creatine inside muscle and other cells. This formula includes:

- **Glutamine**
- **Taurine**
- **Potassium**
- **Sodium**
- **Creatine** itself which has significant volumizing effects.

Branched Chain Amino Acids

Increased intracellular concentrations of branched chain amino acids (leucine, valine and isoleucine) stimulate formation of acetyl-coenzyme (CoA) and succinyl-CoA, thus increasing both glycolytic and anapleurotic flux and aerobic and anaerobic energy production. All three, but especially leucine, have a synergistic effect with creatine on increasing protein synthesis.

Beta-Alanine and Carnosine

Both Beta-alanine and Carnosine (beta-alanyl-L-histidine) were added to Creatine Advantage because of their powerful antioxidant, anti-inflammatory, and immune system effects, as well as their beneficial effects on physical and mental performance, healing and recovery.^{168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188}

Exercise is a catabolic process and unaided this catabolism isn't reversed right away even after you've finished training. Carnosine has an immediate effect on helping to change the catabolic state to one that's anabolic and aiding recovery in this and other ways. It also has beneficial effects on muscle damage and on increasing blood flow in muscle.¹⁸⁹

Carnosine has beneficial effects on exercise performance by helping to overcome muscle fatigue, likely due its effectiveness as a buffering agent, and perhaps its antioxidant, chelating, and enzyme regulating effects.¹⁹⁰

Carnosine levels tend to be higher in athletes such as sprinters^{191,192} and in bodybuilders¹⁹³ These studies also show that intramuscular carnosine may be an effective physiological H⁺ buffer and that there is a significant relationship between the carnosine concentration in human skeletal muscle and

high intensity exercise performance. A recent study found that beta-alanine supplementation increased muscle carnosine levels¹⁹⁴ and resulted in an improvement in exercise performance.¹⁹⁵

Since dietary carnosine is absorbed across intestinal epithelial cells, using carnosine itself would seem to be more useful than using beta-alanine. However, a recent study found that using carnosine and beta-alanine together results in a greater effect than using either one alone.¹⁹⁶ As such, I've included both in Creatine Advantage.

Ditto for the inclusion of Taurine as the combination of taurine and carnosine has been shown to be have protective properties towards testicular tissue and consequently for testosterone production.¹⁹⁷


The Journal of Sports Medicine and Physical Fitness 2020 Oct 22

DOI: [10.23736/S0022-4707.20.10887-9](https://doi.org/10.23736/S0022-4707.20.10887-9)

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language: English

Acute carnosine and β -alanine supplementation increases the compensated part of the ventilation vs work rate relationship during a ramp incremental cycle test in physically active men

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PDF

BACKGROUND: Chronic supplementation with carnosine and β -alanine (Carn- β A) has been proposed to improve muscle contractility and reduce muscle fatigue mainly through an increase in intracellular pH buffering capacity. However, the acute ergogenic effects of Carn- β A supplementation are poorly investigated. This study aimed at evaluating the acute effects of a single Carn- β A supplementation on the cardiorespiratory and metabolic response during a ramp cycle-ergometric test.

METHODS: This randomized, double-blind, placebo-controlled study, involved 10 healthy males (age 22.2 ± 1.9 years, body mass 72.5 ± 7.9 kg, stature 1.72 ± 0.08 m, body mass index, 24.47 ± 1.91 kg/m², mean \pm standard deviation). All the participants performed two maximal incremental ramp tests on a cycle ergometer, with a prior randomized assumption of 2.5 g L-carnosine plus 2.5 g β -alanine (Carn- β A) or placebo (PLA). During exercise, gas exchange parameters were measured breath-by-breath, heart rate was monitored by electrocardiography and rate perceived exertion was determined on Borg scales. From the ramp test, peak cardiorespiratory and metabolic parameters and ventilatory thresholds (VT1 and VT2) were calculated off-line.

RESULTS: No differences between the experimental conditions emerged at peak exercise. However, despite acute Carn- β A supplementation did not affect the single ventilatory thresholds, the compensated portion of the ramp test (i.e., the difference between VT2 and VT1) was significantly larger ($P = 0.043$) in Carn- β A.

CONCLUSIONS: These findings demonstrate a positive effect of acute Carn- β A supplementation on the compensated part of the exercise. This should be taken into account by nutritionists and athletes searching for nutritional supplements, when a quick effect based on an acute dose is required.

Citrulline Malate

Citrulline Malate (CM), a mixture of citrulline and malate, was added for several reasons. Citrulline has several effects, including increasing ammonia clearance, increasing bicarbonate, ornithine, arginine, and citrulline levels. Malate, a tricarboxylic acid cycle (TCA) intermediate, has beneficial effects on energy metabolism mainly by facilitating aerobic ATP production through anaplerotic reactions.

Overall, studies suggest that citrulline malate supplementation can boost athletic performance and enhance recovery by eliminating the amino acid breakdown products of protein metabolism and augmenting the detoxifying capacity of liver cells in removal of ammonium and lactate from the blood.¹⁹⁸¹⁹⁹²⁰⁰²⁰¹²⁰²²⁰³²⁰⁴

The bottom line is that CM supplementation has beneficial effects on energy metabolism, body composition, exercise performance, decreasing fatigue, and enhancing recovery short term by facilitating the shift from the catabolic training state to the post exercise anabolic state.²⁰⁵²⁰⁶²⁰⁷²⁰⁸

Biotin

Biotin is a water-soluble vitamin that acts a cofactor for several of the carboxylases involved in fatty acid synthesis, gluconeogenesis, and branched-chain amino acid (BCAA) metabolism.

The ketogenic phase of my diets and any ketogenic/low carb diet increases biotin bioavailability and consumption, and hence, promotes energy production by gluconeogenesis and branched-chain amino acid metabolism, which can result in biotin deficiency. A recent paper concluded that “It is suggested that individuals that consume the ketogenic diet have an increased biotin requirement.”²⁰⁹

Many other ingredients that increase the effectiveness of Creatine Advantage in maximizing energy metabolism, performance and body composition – see the complete nutrition panel below. Their function in enhancing the effects of Creatine Advantage in maximizing energy metabolism, performance and body composition will soon be added to this information piece.

What’s Not in Creatine Advantage

Almost as important as what’s in Creatine Advantage, is what’s not in it. For example, guanidinopropionic acid (GPA), an ingredient that is used in some creatine products, is not a useful ingredient as it seems that its use can decrease creatine levels in heart muscle cells and likely muscle cells.²¹⁰ As well, in keeping with a lower carb approach, which besides decreasing fat oxidation also decreases GH and IGF-I levels, Creatine Advantage only contains 1.5 grams of carbs per 10 grams serving - just enough to maximize creatine uptake into muscle cells, but not enough to have counter productive effects.

Safety of Long-Term Creatine Intake

Studies have shown that the long-term use of creatine does not have any significant side effects, such as an increase in muscle cramping or injuries, nor does it impact on the body’s ability to manufacture creatine endogenously once the creatine is discontinued.²¹¹²¹²²¹³²¹⁴ Muscle creatine levels usually return to normal within 4 weeks.²¹⁵

References

- ¹ Maughan RJ. Creatine supplementation and exercise performance. *Int J Sport Nutr*. 1995 Jun;5(2):94-101. doi: 10.1123/ijsn.5.2.94. PMID: 7670456.
- ² Harris RC, Söderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond)*. 1992 Sep;83(3):367-74. doi: 10.1042/cs0830367. PMID: 1327657.
- ³ Jones AM, Atter T, Georg KP. Oral creatine supplementation improves multiple sprint performance in elite ice-hockey players. *J Sports Med Phys Fitness*. 1999 Sep;39(3):189-96. PMID: 10573659.
- ⁴ Tarnopolsky MA, MacLennan DP. Creatine monohydrate supplementation enhances high-intensity exercise performance in males and females. *Int J Sport Nutr Exerc Metab*. 2000 Dec;10(4):452-63. doi: 10.1123/ijsnem.10.4.452. PMID: 11099372.
- ⁵ Chilibeck PD, Stride D, Farthing JP, Burke DG. Effect of creatine ingestion after exercise on muscle thickness in males and females. *Med Sci Sports Exerc*. 2004 Oct;36(10):1781-8.
- ⁶ Mendes RR, Pires I, Oliveira A, Tirapegui J. Effects of creatine supplementation on the performance and body composition of competitive swimmers. *J Nutr Biochem*. 2004 Aug;15(8):473-8.
- ⁷ Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. *Nutrition*. 2004 Jul-Aug;20(7-8):609-14.
- ⁸ Volek JS, Ratamess NA, Rubin MR, Gomez AL, French DN, McGuigan MM, Scheett TP, Sharman MJ, Hakkinen K, Kraemer WJ. The effects of creatine supplementation on muscular performance and body composition responses to short-term resistance training overreaching. *Eur J Appl Physiol*. 2004 May;91(5-6):628-37. Epub 2003 Dec 18.
- ⁹ Kilduff LP, Pitsiladis YP, Tasker L, Attwood J, Hyslop P, Dailly A, Dickson I, Grant S. Effects of creatine on body composition and strength gains after 4 weeks of resistance training in previously nonresistance-trained humans. *Int J Sport Nutr Exerc Metab*. 2003 Dec;13(4):504-20.
- ¹⁰ Kocak S, Karli U. Effects of high dose oral creatine supplementation on anaerobic capacity of elite wrestlers. *J Sports Med Phys Fitness*. 2003 Dec;43(4):488-92.
- ¹¹ Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. *J Strength Cond Res*. 2003 Nov;17(4):822-31.
- ¹² Hespel P, Derave W. Ergogenic effects of creatine in sports and rehabilitation. *Subcell Biochem*. 2007;46:245-59.
- ¹³ Cooke MB, Rybalka E, Williams AD, Cribb PJ, Hayes A. Creatine supplementation enhances muscle force recovery after eccentrically-induced muscle damage in healthy individuals. *J Int Soc Sports Nutr*. 2009 Jun 2;6:13. doi: 10.1186/1550-2783-6-13. PMID: 19490606; PMCID: PMC2697134.
- ¹⁴ Veggi K FT, Machado M, Koch AJ, Santana SC, Oliveira SS, Stec MJ. Oral creatine supplementation augments the repeated bout effect. *Int J Sport Nutr Exerc Metab*. 2013 Aug;23(4):378-87. doi: 10.1123/ijsnem.23.4.378. Epub 2013 Jan 23. PMID: 23349298.
- ¹⁵ Johannsmeyer S, Candow DG, Brahm's CM, Michel D, Zello GA. Effect of creatine supplementation and drop-set resistance training in untrained aging adults. *Exp Gerontol*. 2016 Oct;83:112-9. doi: 10.1016/j.exger.2016.08.005. Epub 2016 Aug 11. PMID: 27523919.
- ¹⁶ Mielgo-Ayuso J, Calleja-Gonzalez J, Marqués-Jiménez D, Caballero-García A, Córdova A, Fernández-Lázaro D. Effects of Creatine Supplementation on Athletic Performance in Soccer Players: A Systematic Review and Meta-Analysis. *Nutrients*. 2019 Mar 31;11(4):757. doi: 10.3390/nu11040757. PMID: 30935142; PMCID: PMC6520963.
- ¹⁷ Wax B, Kerksick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. *Nutrients*. 2021 Jun 2;13(6):1915. doi: 10.3390/nu13061915. PMID: 34199588; PMCID: PMC8228369.

- ¹⁸ Arazi H, Eghbali E, Suzuki K. Creatine Supplementation, Physical Exercise and Oxidative Stress Markers: A Review of the Mechanisms and Effectiveness. *Nutrients*. 2021 Mar 6;13(3):869. doi: 10.3390/nu13030869. PMID: 33800880; PMCID: PMC8000194.
- ¹⁹ Arazi H, Eghbali E, Suzuki K. Creatine Supplementation, Physical Exercise and Oxidative Stress Markers: A Review of the Mechanisms and Effectiveness. *Nutrients*. 2021 Mar 6;13(3):869. doi: 10.3390/nu13030869. PMID: 33800880; PMCID: PMC8000194.
- ²⁰ Vandenberghe K, Goris M, Van Hecke P, Van Leemputte M, Vangerven L, Hespel P. Long-term creatine intake is beneficial to muscle performance during resistance training. *J Appl Physiol*. 1997 Dec;83(6):2055-63.
- ²¹ Frederickson SJ, Miles MP. Low-dose creatine supplementation enhances fatigue resistance in the absence of weight gain. Rawson ES, Stec MJ, *Nutrition*. 2011 Apr;27(4):451-5.
- ²² Sullivan PG, Geiger JD, Mattson MP, Scheff SW. Dietary supplement creatine protects against traumatic brain injury. *Ann Neurol*. 2000 Nov;48(5):723-9.
- ²³ Ellis AC, Rosenfeld J. The role of creatine in the management of amyotrophic lateral sclerosis and other neurodegenerative disorders. *CNS Drugs*. 2004;18(14):967-80.
- ²⁴ Zhu S, Li M, Figueroa BE, et al., Prophylactic creatine administration mediates neuroprotection in cerebral ischemia in mice. *J Neurosci*. 2004 Jun 30;24(26):5909-12.
- ²⁵ Beal MF. Neuroprotective effects of creatine. *Amino Acids*. 2011 May;40(5):1305-13. doi: 10.1007/s00726-011-0851-0. Epub 2011 Mar 30. PMID: 21448659.
- ²⁶ Dolan E, Gualano B, Rawson ES. Beyond muscle: the effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. *Eur J Sport Sci*. 2019 Feb;19(1):1-14. doi: 10.1080/17461391.2018.1500644. PMID: 30086660.
- ²⁷ Roschel H, Gualano B, Ostojic SM, Rawson ES. Creatine Supplementation and Brain Health. *Nutrients*. 2021 Feb 10;13(2):586. doi: 10.3390/nu13020586. PMID: 33578876; PMCID: PMC7916590. Full text PDF is at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7916590/pdf/nutrients-13-00586.pdf>.
- ²⁸ Klivenyi P, Calingasan NY, Starkov A, et al. Neuroprotective mechanisms of creatine occur in the absence of mitochondrial creatine kinase. *Neurobiol Dis*. 2004 Apr;15(3):610-7.
- ²⁹ Lenz H, Schmidt M, Welge V, et al. The Creatine Kinase System in Human Skin: Protective Effects of Creatine Against Oxidative and UV Damage In Vitro and In Vivo. *J Invest Dermatol*. 2005 Feb;124(2):443-52.
- ³⁰ Marriage B, Clandinin MT, Glerum DM. Nutritional cofactor treatment in mitochondrial disorders. *J Am Diet Assoc*. 2003 Aug;103(8):1029-38.
- ³¹ Frei M, Kim C, Ames BN. Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. *Proc Natl Acad Sci* 1990; **87**:4879–83.
- ³² Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci* 1990; **87**:8931-34.
- ³³ Littarru GP, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical implications. *Mitochondrion*. 2007 Jun;7 Suppl:S168-74.
- ³⁴ Skarlovnik A, Janic M, Lunder M, Turk M, Šabovic M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. *Med Sci Monit*. 2014 Nov 6;20:2183-8.
- ³⁵ Wang LW, Jabbour A, Hayward CS, Furlong TJ, Girgis L, Macdonald PS, Keogh AM. Potential role of coenzyme Q10 in facilitating recovery from statin-induced rhabdomyolysis. *Intern Med J*. 2015 Apr;45(4):451-3.
- ³⁶ Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*. 2018 Oct 2;7(19):e009835. doi: 10.1161/JAHA.118.009835. PMID: 30371340.

- ³⁷ Lorza-Gil E, de Souza JC, García-Arévalo M, Vettorazzi JF, Marques AC, Salerno AG, Trigo JR, Oliveira HCF. Coenzyme Q10 protects against β -cell toxicity induced by pravastatin treatment of hypercholesterolemia. *J Cell Physiol.* 2019 Jul;234(7):11047-11059.
- ³⁸ Jing L, He MT, Chang Y, Mehta SL, He QP, Zhang JZ, Li PA. Coenzyme Q10 protects astrocytes from ROS-induced damage through inhibition of mitochondria-mediated cell death pathway. *Int J Biol Sci.* 2015 Jan 1;11(1):59-66.
- ³⁹ Noh YH, Kim KY, Shim MS, Choi SH, Choi S, Ellisman MH, Weinreb RN, Perkins GA, Ju WK. Inhibition of oxidative stress by coenzyme Q10 increases mitochondrial mass and improves bioenergetic function in optic nerve head astrocytes. *Cell Death Dis.* 2013 Oct 3;4:e820.
- ⁴⁰ Raygan F, Rezavandi Z, Dadkhah Tehrani S, Farrokhian A, Asemi Z. The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. *Eur J Nutr.* 2016 Dec;55(8):2357-2364.
- ⁴¹ Nasoohi S, Simani L, Khodagholi F, Nikseresht S, Faizi M, Naderi N. Coenzyme Q10 supplementation improves acute outcomes of stroke in rats pretreated with atorvastatin. *Nutr Neurosci.* 2019 Apr;22(4):264-272.
- ⁴² Chis BA, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. *Int J Vitam Nutr Res.* 2019 Mar 19;19:1-9.
- ⁴³ Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. *Biofactors.* 2003;18(1-4):101-11.
- ⁴⁴ Jorat MV, Tabrizi R, Kollahdoz F, Akbari M, Salami M, Heydari ST, Asemi Z. The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress in among coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Inflammopharmacology.* 2019 Apr;27(2):233-248.
- ⁴⁵ Andalib S, Mashhadi-Mousapour M, Bijani S, Hosseini MJ. Coenzyme Q10 Alleviated Behavioral Dysfunction and Bioenergetic Function in an Animal Model of Depression. *Neurochem Res.* 2019 May;44(5):1182-1191.
- ⁴⁶ Wang X, Meng Q, Qiu C, Li P, Qu R, Wang W, Wang Y, Liu L, Zhao Y. Potential therapeutic role of Co-Q10 in alleviating intervertebral disc degeneration and suppressing IL-1 β -mediated inflammatory reaction in NP cells. *Int Immunopharmacol.* 2018 Nov;64:424-431.
- ⁴⁷ Schmelzer C, Kubo H, Mori M, Sawashita J, Kitano M, Hosoe K, Boomgaarden I, Döring F, Higuchi K. Supplementation with the reduced form of Coenzyme Q10 decelerates phenotypic characteristics of senescence and induces a peroxisome proliferator-activated receptor- α gene expression signature in SAMP1 mice. *Mol Nutr Food Res.* 2010 Jun;54(6):805-15.
- ⁴⁸ Tian G, Sawashita J, Kubo H, Nishio SY, Hashimoto S, Suzuki N, Yoshimura H, Tsuruoka M, Wang Y, Liu Y, Luo H, Xu Z, Mori M, Kitano M, Hosoe K, Takeda T, Usami S, Higuchi K. Ubiquinol-10 supplementation activates mitochondria functions to decelerate senescence in senescence-accelerated mice. *Antioxid Redox Signal.* 2014 Jun 1;20(16):2606-20.
- ⁴⁹ Yan J, Fujii K, Yao J, Kishida H, Hosoe K, Sawashita J, Takeda T, Mori M, Higuchi K. Reduced coenzyme Q10 supplementation decelerates senescence in SAMP1 mice. *Exp Gerontol.* 2006 Feb;41(2):130-40.
- ⁵⁰ Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Fernández Vega A, de la Mata M, Delgado Pavón A, de Miguel M, Pérez Calero C, Villanueva Paz M, Cotán D, Sánchez-Alcázar JA. Coenzyme q10 therapy. *Mol Syndromol.* 2014 Jul;5(3-4):187-97.
- ⁵¹ Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. *J Urol.* 2009 Jul;182(1):237-48.
- ⁵² Fouad AA, Al-Sultan AI, Yacoubi MT. Coenzyme Q10 counteracts testicular injury induced by sodium arsenite in rats. *Eur J Pharmacol.* 2011 Mar 25;655(1-3):91-8.

- ⁵³ Walczak-Jedrzejowska R, Wolski JK, Slowikowska-Hilczer J. The role of oxidative stress and antioxidants in male fertility. *Cent European J Urol*. 2013;66(1):60-7.
- ⁵⁴ Safarinejad MR. The effect of coenzyme Q10 supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. *Int Urol Nephrol*. 2012 Jun;44(3):689-700.
- ⁵⁵ Banihani SA. Effect of Coenzyme Q10 Supplementation on Testosterone. *Biomolecules*. 2018 Dec 13;8(4). pii: E172. doi: 10.3390/biom8040172.
- ⁵⁶ Banihani SA. Effect of Coenzyme Q10 Supplementation on Testosterone. *Biomolecules*. 2018 Dec 13;8(4). pii: E172. doi: 10.3390/biom8040172.
- ⁵⁷ Onur S, Niklowitz P, Jacobs G, Nöthlings U, Lieb W, Menke T, Döring F. Ubiquinol reduces gamma glutamyltransferase as a marker of oxidative stress in humans. *BMC Res Notes*. 2014 Jul 4;7:427.
- ⁵⁸ Brauner H, Lüthje P, Grünler J, Ekberg NR, Dallner G, Brismar K, Brauner A. Markers of innate immune activity in patients with type 1 and type 2 diabetes mellitus and the effect of the anti-oxidant coenzyme Q10 on inflammatory activity. *Clin Exp Immunol*. 2014 Aug;177(2):478-82.
- ⁵⁹ Kaikkonen J, Kosonen L, Nyyssonen K, Porkkala-Sarataho E, Salonen R, Korpela H, Salonen JT. Effect of combined coenzyme Q10 and d-alpha-tocopheryl acetate supplementation on exercise-induced lipid peroxidation and muscular damage: a placebo-controlled double-blind study in marathon runners. *Free Radic Res*. 1998 Jul;29(1):85-92.
- ⁶⁰ Gokbel H, Gui I, Bleviranli M, et al. The effects of coenzyme Q10 supplementation on performance during repeated bouts of supramaximal exercise in sedentary men. *J Strength Cond Res*. 2010;24(1):97-102.
- ⁶¹ <https://jamanetwork.com/journals/jamaoncology/article-abstract/2732506> would suffice.
- ⁶² Sarmiento A, Diaz-Castro J, Pulido-Moran M, Kajarabille N, Guisado R, Ochoa JJ. Coenzyme Q10 Supplementation and Exercise in Healthy Humans: A Systematic Review. *Curr Drug Metab*. 2016;17(4):345-58.
- ⁶³ Chis BA, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. *Int J Vitam Nutr Res*. 2019 Mar 19:1-9.
- ⁶⁴ Mehrabani S, Askari G, Miraghajani M, Tavakoly R, Arab A. Effect of coenzyme Q10 supplementation on fatigue: A systematic review of interventional studies. *Complement Ther Med*. 2019 Apr;43:181-187.
- ⁶⁵ Komaki H, Faraji N, Komaki A, Shahidi S, Etaee F, Raoufi S, Mirzaei F. Investigation of protective effects of coenzyme Q10 on impaired synaptic plasticity in a male rat model of Alzheimer's disease. *Brain Res Bull*. 2019 Apr;147:14-21.
- ⁶⁶ Belviranli M, Okudan N. Effect of Coenzyme Q10 Alone and in Combination with Exercise Training on Oxidative Stress Biomarkers in Rats. *Int J Vitam Nutr Res*. 2019 Apr 30:1-11.
- ⁶⁷ Wang X, Meng Q, Qiu C, Li P, Qu R, Wang W, Wang Y, Liu L, Zhao Y. Potential therapeutic role of Co-Q10 in alleviating intervertebral disc degeneration and suppressing IL-1 β -mediated inflammatory reaction in NP cells. *Int Immunopharmacol*. 2018 Nov;64:424-431.
- ⁶⁸ Mortensen SA. Perspectives on therapy of cardiovascular diseases with coenzyme Q10 (ubiquinone). [Review] *Clinical Investigator* 1993;71(8 Suppl):S116-23.
- ⁶⁹ Beyer RE. An analysis of the role of coenzyme Q in free radical generation and as an antioxidant. *Biochemistry & Cell Biology* 1992;70(6):390-403.
- ⁷⁰ Chis BA, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. *Int J Vitam Nutr Res*. 2019 Mar 19:1-9.
- ⁷¹ Belviranli M, Okudan N. Effect of Coenzyme Q10 Alone and in Combination with Exercise Training on Oxidative Stress Biomarkers in Rats. *Int J Vitam Nutr Res*. 2019 Apr 30:1-11.
- ⁷² Sarmiento A, Diaz-Castro J, Pulido-Moran M, Moreno-Fernandez J, Kajarabille N, Chiroso I, Guisado IM, Javier Chiroso L, Guisado R, Ochoa JJ. Short-term ubiquinol supplementation reduces

- oxidative stress associated with strenuous exercise in healthy adults: A randomized trial. *Biofactors*. 2016 Nov 12;42(6):612-622.
- ⁷³ Pala R, Beyaz F, Tuzcu M, Er B, Sahin N, Cinar V, Sahin K. The effects of coenzyme Q10 on oxidative stress and heat shock proteins in rats subjected to acute and chronic exercise. *J Exerc Nutrition Biochem*. 2018 Sep 30;22(3):14-20.
- ⁷⁴ Orlando P, Silvestri S, Galeazzi R, Antonicelli R, Marcheggiani F, Cirilli I, Bacchetti T, Tiano L. Effect of ubiquinol supplementation on biochemical and oxidative stress indexes after intense exercise in young athletes. *Redox Rep*. 2018 Dec;23(1):136-145.
- ⁷⁵ Borisova IG, Seifulla RD, Zhuravlev AI. [Action of antioxidants on physical work capacity and lipid peroxidation in the body]. *Farmakol Toksikol* 1989;52(4):89-92.
- ⁷⁶ Lemke M, Frei B, Ames BN, Faden AI. Decreases in tissue levels of ubiquinol 9 and 10, ascorbate and alpha tocopherol following spinal cord impact trauma in rats. *Neurosci Lett* 1990;108(1-2):201-6.
- ⁷⁷ Chokchaiwong S, Kuo YT, Lin SH, Hsu YC, Hsu SP, Liu YT, Chou AJ, Kao SH. Coenzyme Q10 serves to couple mitochondrial oxidative phosphorylation and fatty acid β -oxidation, and attenuates NLRP3 inflammasome activation. *Free Radic Res*. 2018 Dec;52(11-12):1445-1455.
- ⁷⁸ Ghanbarzadeh S, Garjani A, Ziaee M, Khorrami A. Effects of L-carnitine and coenzyme q10 on impaired spermatogenesis caused by isoproterenol in male rats. *Drug Res (Stuttg)*. 2014 Sep;64(9):449-53.
- ⁷⁹ Ghanbarzadeh S, Garjani A, Ziaee M, Khorrami A. CoQ10 and L-carnitine attenuate the effect of high LDL and oxidized LDL on spermatogenesis in male rats. *Drug Res (Stuttg)*. 2014 Oct;64(10):510-5.
- ⁸⁰ Dokmeci D, Inan M, Basaran UN, Yalcin O, Aydogdu N, Turan FN, Uz YH. Protective effect of L-carnitine on testicular ischaemia-reperfusion injury in rats. *Cell Biochem Funct*. 2007 Nov-Dec;25(6):611-8.
- ⁸¹ Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology*. 2004 Apr;63(4):641-6.
- ⁸² Zare Z, Eimani H, Mohammadi M, Mofid M, Dashtnavard H. The effect of orally administered L-carnitine on testis tissue, sperm parameters and daily sperm production in adult mice. *Yakhteh Med J*. 2010;11:382–389.
- ⁸³ Sazegar G, Ebrahimi V, Boroujeni MJS, Mohammadi S, Salimnezhad R. Morphometric study of testis tissue and spermatogenesis following carnitine administration in diabetic rat induced with streptozotocin. *Iran J Diabetes Metab*. 2014;14:9–14.
- ⁸⁴ Kanter M, Topcu-Tarladacalisir Y, Parlar S. Antiapoptotic effect of L-carnitine on testicular irradiation in rats. *J Mol Histol*. 2010;41:121–128.
- ⁸⁵ Rezaei N, Mardanshahi T, Shafaroudi MM, Abedian S, Mohammadi H, Zare Z. Effects of L-Carnitine on the Follicle-Stimulating Hormone, Luteinizing Hormone, Testosterone, and Testicular Tissue Oxidative Stress Levels in Streptozotocin-Induced Diabetic Rats. *J Evid Based Integr Med*. 2018 Jan-Dec;23:2515690X18796053. doi: 10.1177/2515690X18796053.
- ⁸⁶ Elokil AA, Bhuiyan AA, Liu HZ, Hussein MN, Ahmed HI, Azmal SA, Yang L, Li S. The capability of L-carnitine-mediated antioxidant on cock during aging: evidence for the improved semen quality and enhanced testicular expressions of GnRH1, GnRHR, and melatonin receptors MT 1/2. *Poult Sci*. 2019 Apr 18. pii: pez201. doi: 10.3382/ps/pez201. [Epub ahead of print]
- ⁸⁷ Oyanagi E, Yano H, Kato Y, Fujita H, Utsumi K, Sasaki J. L-Carnitine suppresses oleic acid-induced membrane permeability transition of mitochondria. *Cell Biochem Funct*. 2008 Oct;26(7):778-86.
- ⁸⁸ Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, Lopaschuk GD, Muoio DM. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab*. 2008 Jan;7(1):45-56.

- ⁸⁹ Noland RC, Koves TR, Seiler SE, Lum H, Lust RM, Ilkayeva O, Stevens RD, Hegardt FG, Muoio DM. Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. *J Biol Chem*. 2009 Aug 21;284(34):22840-52.
- ⁹⁰ Stephens FB, Marimuthu K, Cheng Y, Patel N, Constantin D, Simpson EJ, Greenhaff PL. Vegetarians have a reduced skeletal muscle carnitine transport capacity. *Am J Clin Nutr*. 2011 Sep;94(3):938-44.
- ⁹¹ Ringseis R, Keller J, Eder K. Role of carnitine in the regulation of glucose homeostasis and insulin sensitivity: evidence from in vivo and in vitro studies with carnitine supplementation and carnitine deficiency. *Eur J Nutr*. 2012 Feb;51(1):1-18.
- ⁹² Molfino A, Cascino A, Conte C, Ramaccini C, Rossi Fanelli F, Laviano A. Caloric restriction and L-carnitine administration improves insulin sensitivity in patients with impaired glucose metabolism. *JPEN J Parenter Enteral Nutr*. 2010 May-Jun;34(3):295-9.
- ⁹³ Jang A, Kim D, Sung KS, Jung S, Kim HJ, Jo C. The effect of dietary α -lipoic acid, betaine, l-carnitine, and swimming on the obesity of mice induced by a high-fat diet. *Food Funct*. 2014 Jun 27. [Epub ahead of print]
- ⁹⁴ Neumann, G. Effects of L-carnitine on athletic performance. Seim, H. Loster, H. eds. *Carnitine: Pathophysiological Basics and Clinical Applications* 1996:61-71 Ponte Press Bochum, Germany.
- ⁹⁵ Manoli I, De Martino MU, Kino T, Alesci S. Modulatory effects of L-carnitine on glucocorticoid receptor activity. *Ann N Y Acad Sci*. 2004 Nov;1033:147-57.
- ⁹⁶ Famularo G, De Simone C, Trinchieri V, Mosca L. Carnitines and its congeners: a metabolic pathway to the regulation of immune response and inflammation. *Ann N Y Acad Sci*. 2004 Nov;1033:132-8.
- ⁹⁷ Pertosa G, Grandaliano G, Simone S, Soccio M, Schena FP. Inflammation and carnitine in hemodialysis patients. *J Ren Nutr*. 2005 Jan;15(1):8-12.
- ⁹⁸ Schaffer SW, Jong CJ, Ramila KC, Azuma J. Physiological roles of taurine in heart and muscle. *J Biomed Sci*. 2010 Aug 24;17 Suppl 1:S2.
- ⁹⁹ Cozzi R, Ricordy R, Bartolini F, Ramadori L, Perticone P and de Salvia R (1995). Taurine and ellagic acid: two differently acting natural antioxidants. *Environmental and Molecular Mutagenesis* 26, 248-254.
- ¹⁰⁰ Lourenco R, Camilo ME. Taurine: a conditionally essential amino acid in humans? An overview in health and disease. *Nutr Hosp*. 2002 Nov-Dec;17(6):262-70.
- ¹⁰¹ Schaffer S, Azuma J, Takahashi K, Mozaffari M. Why is taurine cytoprotective? *Adv Exp Med Biol*. 2003;526:307-21.
- ¹⁰² Bidri M, Choay P. Taurine: a particular amino acid with multiple functions. *Ann Pharm Fr*. 2003 Nov;61(6):385-91.
- ¹⁰³ Manabe S, Kurroda I, Okada K, Morishima M, Okamoto M, Harada N, Takahashi A, Sakai K, Nakaya Y. Decreased blood levels of lactic acid and urinary excretion of 3-methylhistidine after exercise by chronic taurine treatment in rats. *J Nutr Sci Vitaminol (Tokyo)*. 2003 Dec;49(6):375-80.
- ¹⁰⁴ Dawson Jr R, Biasetti M, Messina S, Dominy J. The cytoprotective role of taurine in exercise-induced muscle injury. *Amino Acids* 2002;22(4):309-24.
- ¹⁰⁵ Beyranvand MR, Kadkhodai Khalafi M, Roshan VD, Choobineh S, Parsa SA, Piranfar MA. Effect of taurine supplementation on exercise capacity of patients with heart failure. *J Cardiol*. 2011 Feb 18. [Epub ahead of print]
- ¹⁰⁶ Silva LA, Silveira PC, Ronsani MM, Souza PS, Scheffer D, Vieira LC, Benetti M, De Souza CT, Pinho RA. Taurine supplementation decreases oxidative stress in skeletal muscle after eccentric exercise. *Cell Biochem Funct*. 2011 Jan-Feb;29(1):43-9. doi: 10.1002/cbf.1716.
- ¹⁰⁷ Zhang M, Izumi I, Kagamimori S, Sokejima S, Yamagami T, Liu Z, Qi B. Role of taurine supplementation to prevent exercise-induced oxidative stress in healthy young men. *Amino Acids*. 2004 Mar;26(2):203-7.

- 108 Yatabe Y, Miyakawa S, Miyazaki T, Matsuzaki Y, Ochiai N. Effects of taurine administration in rat skeletal muscles on exercise. *J Orthop Sci.* 2003;8(3):415-9.
- 109 Fraser SF, Li JL, Carey MF, Wang XN, Sangkabutra T, Sostaric S, Selig SE, Kjeldsen K, McKenna MJ. Fatigue depresses maximal in vitro skeletal muscle Na(+)-K(+)-ATPase activity in untrained and trained individuals. *J Appl Physiol* 2002 Nov;93(5):1650-9.
- 110 Li JL, Wang XN, Fraser SF, Carey MF, Wrigley TV, McKenna MJ. Effects of fatigue and training on sarcoplasmic reticulum Ca(2+) regulation in human skeletal muscle. *J Appl Physiol* 2002;92(3):912-22.
- 111 Yatabe Y, Miyakawa S, Ohmori H, Mishima H, Adachi T. Effects of taurine administration on exercise. *Adv Exp Med Biol.* 2009;643:245-52.
- 112 Goodman CA, Horvath D, Stathis C, Mori T, Croft K, Murphy RM, Hayes A. Taurine supplementation increases skeletal muscle force production and protects muscle function during and after high-frequency in vitro stimulation. *J Appl Physiol.* 2009 Jul;107(1):144-54. Epub 2009 May 7.
- 113 Bast A, Haenen GR. Lipoic acid: a multifunctional antioxidant. *Biofactors.* 2003;17(1-4):207-13.
- 114 Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radic Biol Med.* 1995;19:227-250.
- 115 Jones W, Li X, Qu ZC, et al. Uptake, recycling, and antioxidant actions of alpha-lipoic acid in endothelial cells. *Free Radic Biol Med* 2002;33:83-93.
- 116 Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. *Free Radic Biol Med* 1997;22(1-2):359-78.
- 117 Podda M, Tritschler HJ, Ulrich H, et al. Alpha-lipoic acid supplementation prevents symptoms of vitamin E deficiency. *Biochem Biophys Res Commun.* 1994;204:98-104.
- 118 Patrick L. Mercury toxicity and antioxidants: Part 1: role of glutathione and alpha-lipoic acid in the treatment of mercury toxicity. *Altern Med Rev.* 2002;7(6):456-71.
- 119 Smith AR, Shenvi SV, Widlansky M, Suh JH, Hagen TM. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. *Curr Med Chem.* 2004 May;11(9):1135-46.
- 120 Packer L. Alpha lipoic acid: a metabolic antioxidant which regulates NF- kappaB signal transduction and protects against oxidative injury. *Drug Metab Rev* 1998;30:245-75.
- 121 Lee HA, Hughes DA. Alpha-lipoic acid modulates NF-kappaB activity in human monocytic cells by direct interaction with DNA. *Exp Gerontol.* 2002;37(2-3):401-10.
- 122 Faust A, Burkart V, Ulrich H, Weischer CH, Kolb H. Effect of lipoic acid on cyclophosphamide-induced diabetes and insulinitis in non-obese diabetic mice. *Int J Immunopharmacol.* 1994;16(1):61-6.
- 123 Burkart V, Koike T, Brenner HH, Imai Y, Kolb H. Dihydrolipoic acid protects pancreatic islet cells from inflammatory attack. *Agents Actions.* 1993;38(1-2):60-5.
- 124 Lateef H, Aslam MN, Stevens MJ, Varani J. Pretreatment of diabetic rats with lipoic acid improves healing of subsequently-induced abrasion wounds. *Arch Dermatol Res* 2005;297(2):75-83.
- 125 Thirunavukkarasu V, Nandhini AT, Anuradha CV. Fructose diet-induced skin collagen abnormalities are prevented by lipoic acid. *Exp Diabetes Res.* 2004;5(4):237-44.
- 126 Arivazhagan P, Ramanathan K, Panneerselvam C. Effect of DL-alpha-lipoic acid on mitochondrial enzymes in aged rats. *Chem Biol Interact.* 2001 Nov 28;138(2):189-98.
- 127 Palaniappan AR, Dai A. Mitochondrial ageing and the beneficial role of alpha-lipoic acid. *Neurochem Res.* 2007 Sep;32(9):1552-8.
- 128 Aoi W, Naito Y, Takanami Y, Ishii T, Kawai Y, Akagiri S, Kato Y, Osawa T, Yoshikawa T. Astaxanthin improves muscle lipid metabolism in exercise via inhibitory effect of oxidative CPT I modification. *Biochem Biophys Res Commun.* 2008 Feb 22;366(4):892-7.
- 129 Djordjevic B, Baralic I, Kotur-Stevuljevic J, Stefanovic A, Ivanisevic J, Radivojevic N, Andjelkovic M, Dikic N. Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players. *J Sports Med Phys Fitness.* 2012 Aug;52(4):382-92.

- 130 Earnest CP, Lupo M, White KM, Church TS. Effect of astaxanthin on cycling time trial performance. *Int J Sports Med.* 2011 Nov;32(11):882-8.
- 131 Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. *Mar Drugs.* 2011 Mar 21;9(3):447-65.
- 132 Ikeuchi M, Koyama T, Takahashi J, Yazawa K. Effects of astaxanthin supplementation on exercise-induced fatigue in mice. *Biol Pharm Bull.* 2006 Oct;29(10):2106-10.
- 133 Liu PH, Aoi W, Takami M, Terajima H, Tanimura Y, Naito Y, Itoh Y, Yoshikawa T. The astaxanthin-induced improvement in lipid metabolism during exercise is mediated by a PGC-1 α increase in skeletal muscle. *J Clin Biochem Nutr.* 2014 Mar;54(2):86-9.
- 134 Polotow TG, Vardaris CV, Mihaliuc AR, Gonçaves MS, Pereira B, Ganini D, Barros MP. Astaxanthin supplementation delays physical exhaustion and prevents redox imbalances in plasma and soleus muscles of Wistar rats. *Nutrients.* 2014 Dec 12;6(12):5819-38.
- 135 Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. *Mol Nutr Food Res.* 2011 Jan;55(1):150-65.
- 136 Maezawa T, Tanaka M, Kanazashi M, Maeshige N, Kondo H, Ishihara A, Fujino H. Astaxanthin supplementation attenuates immobilization-induced skeletal muscle fibrosis via suppression of oxidative stress. *J Physiol Sci.* 2016 Oct 6. [Epub ahead of print]
- 137 Kanazashi M, Tanaka M, Murakami S, Kondo H, Nagatomo F, Ishihara A, Roy RR, Fujino H. Amelioration of capillary regression and atrophy of the soleus muscle in hindlimb-unloaded rats by astaxanthin supplementation and intermittent loading. *Exp Physiol.* 2014 Aug;99(8):1065-77.
- 138 Aoi W, Naito Y, Yoshikawa T. Potential role of oxidative protein modification in energy metabolism in exercise. *Subcell Biochem.* 2014;77:175-87.
- 139 Choi HD, Kim JH, Chang MJ, Kyu-Youn Y, Shin WG. Effects of astaxanthin on oxidative stress in overweight and obese adults. *Phytother Res.* 2011 Dec;25(12):1813-8.
- 140 Choi HD, Youn YK, Shin WG. Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. *Plant Foods Hum Nutr.* 2011 Nov;66(4):363-9.
- 141 Baralic I, Djordjevic B, Dikic N, Kotur-Stevuljevic J, Spasic S, Jelic-Ivanovic Z, Radivojevic N, Andjelkovic M, Pejic S. Effect of astaxanthin supplementation on paraoxonase 1 activities and oxidative stress status in young soccer players. *Phytother Res.* 2013 Oct;27(10):1536-42.
- 142 Visioli F, Artaria C. Astaxanthin in cardiovascular health and disease: mechanisms of action, therapeutic merits, and knowledge gaps. *Food Funct.* 2017 Jan 25;8(1):39-63.
- 143 Kishimoto Y, Yoshida H, Kondo K. Potential Anti-Atherosclerotic Properties of Astaxanthin. *Mar Drugs.* 2016 Feb 5;14(2).
- 144 Wu H, Niu H, Shao A, Wu C, Dixon BJ, Zhang J, Yang S, Wang Y. Astaxanthin as a Potential Neuroprotective Agent for Neurological Diseases. *Mar Drugs.* 2015 Sep 11;13(9):5750-66.
- 145 Zhang L, Wang H. Multiple Mechanisms of Anti-Cancer Effects Exerted by Astaxanthin. *Mar Drugs.* 2015 Jul 14;13(7):4310-30.
- 146 Wolf AM, Asoh S, Hiranuma H, Ohsawa I, Iio K, Satou A, Ishikura M, Ohta S. Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress. *J Nutr Biochem.* 2010 May;21(5):381-9.
- 147 Comhaire FH, El Garem Y, Mahmoud A, Eertmans F, Schoonjans F. Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial. *Asian J Androl.* 2005 Sep;7(3):257-62.
- 148 Grimmig B, Kim SH, Nash K, Bickford PC, Douglas Shytle R. Neuroprotective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neurodegeneration. *Geroscience.* 2017 Feb;39(1):19-32.
- 149 Satoa F, Omuraa T, Ishimarua M, Endoa Y, Murasea H, Yamashitab E. Effects of Daily Astaxanthin and L-Carnitine Supplementation for Exercise-Induced Muscle Damage in Training

- Thoroughbred Horses Journal of Equine Veterinary Science Volume 35, Issue 10, October 2015, Pages 836–842
- 150 Atmaca G. Antioxidant effects of sulfur-containing amino acids. *Yonsei Med J.* 2004 Oct 31;45(5):776-88. Review.
- 151 Hellsten Y, Skadhaug L, Bangsbo J. Effect of ribose supplementation on resynthesis of adenine nucleotides after intense intermittent training in humans. *Am J Physiol Regul Integr Comp Physiol.* 2004 Jan;286(1):R182-8.
- 152 Ruderman NB, Cacicedo JM, Itani S, et al. Malonyl-CoA and AMP-activated protein kinase (AMPK): possible links between insulin resistance in muscle and early endothelial cell damage in diabetes. *Biochem Soc Trans.* 2003 Feb;31(Pt 1):202-6. Review.
- 153 Kraegen EW, Bruce C, Hegarty BD, Ye JM, Turner N, Cooney G. AMP-activated protein kinase and muscle insulin resistance. *Front Biosci.* 2009 Jan 1;14:4658-72.
- 154 Thomson DM, Winder WW. AMP-activated protein kinase control of fat metabolism in skeletal muscle. *Acta Physiol (Oxf).* 2009 May;196(1):147-54.
- 155 Ruderman NB, Saha AK, Kraegen EW. Minireview: malonyl CoA, AMP-activated protein kinase, and adiposity. *Endocrinology.* 2003 Dec;144(12):5166-71. Review.
- 156 Nandhini ATA & Anuradha CV. Taurine modulates kallikrein activity and glucose metabolism in insulin resistant rats. *Amino Acids* 2002; 222, 27-38.
- 157 Burke DG, Chilibeck PD, Parise G, Tarnopolsky MA, Candow DG. Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. *Int J Sport Nutr Exerc Metab.* 2003 Sep;13(3):294-302.
- 158 Derave W, Eijnde BO, Verbesssem P, Ramaekers M, Van Leemputte M, Richter EA, Hespel P. Combined creatine and protein supplementation in conjunction with resistance training promotes muscle GLUT-4 content and glucose tolerance in humans. *J Appl Physiol.* 2003 May;94(5):1910-6. Epub 2003 Jan 10.
- 159 Willott CA, Young ME, Leighton B, Kemp GJ, Boehm EA, Radda GK, Clarke K. Creatine uptake in isolated soleus muscle: kinetics and dependence on sodium, but not on insulin. *Acta Physiol Scand.* 1999 Jun;166(2):99-104.
- 160 Derave W, Eijnde BO, Verbesssem P, Ramaekers M, Van Leemputte M, Richter EA, Hespel P. Combined creatine and protein supplementation in conjunction with resistance training promotes muscle GLUT-4 content and glucose tolerance in humans. *J Appl Physiol.* 2003 May;94(5):1910-6. Epub 2003 Jan 10.
- 161161 Laviano A, Molino A, Lacaria MT, Canelli A, De Leo S, Preziosa I, Rossi Fanelli F. Glutamine supplementation favors weight loss in nondieting obese female patients. A pilot study. *Eur J Clin Nutr.* 2014 Nov;68(11):1264-6.
- 162 Legault Z, Bagnall N, Kimmerly DS. The Influence of Oral L-Glutamine Supplementation on Muscle Strength Recovery and Soreness Following Unilateral Knee Extension Eccentric Exercise. *Int J Sport Nutr Exerc Metab.* 2015 Oct;25(5):417-26.
- 163 Phillips GC. Glutamine: the nonessential amino acid for performance enhancement. *Curr Sports Med Rep* 2007; 6: 265-8.
- 164 Koo GH, Woo J, Kang S, Shin KO. Effects of Supplementation with BCAA and L-glutamine on Blood Fatigue Factors and Cytokines in Juvenile Athletes Submitted to Maximal Intensity Rowing Performance. *J Phys Ther Sci.* 2014 Aug;26(8):1241-6.
- 165 Cruzat VF, Bittencourt A, Scomazzon SP, Leite JS, de Bittencourt PI Jr, Tirapegui J. Oral free and dipeptide forms of glutamine supplementation attenuate oxidative stress and inflammation induced by endotoxemia. *Nutrition.* 2014 May;30(5):602-11.
- 166 Freitas HR. Glutamine in Sport and Exercise. *International Journal of Medical and Biological Frontiers* Hauppauge 2016; 22.4 :277-291.

- 167 Lehmkuhl M, Malone M, Justice B, Trone G, Pistilli E, Vinci D, Haff EE, Kilgore JL, Haff GG. The effects of 8 weeks of creatine monohydrate and glutamine supplementation on body composition and performance measures. *J Strength Cond Res.* 2003 Aug;17(3):425-38.
- 168 Saunders B, Elliott-Sale K, Artioli GG, Swinton PA, Dolan E, Roschel H, Sale C, Gualano B. β -alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. *Br J Sports Med.* 2017 Apr;51(8):658-669.
- 169 Saunders B, DE Salles Painelli V, DE Oliveira LF, DA Eira Silva V, DA Silva RP, Riani L, Franchi M, Gonçalves LS, Harris RC, Roschel H, Artioli GG, Sale C, Gualano B. Twenty-four Weeks of β -Alanine Supplementation on Carnosine Content, Related Genes, and Exercise. *Med Sci Sports Exerc.* 2017 May;49(5):896-906.
- 170 Blancquaert L, Baba SP, Kwiatkowski S, Stautemas J, Stegen S, Barbaresi S, Chung W, Boakye AA, Hoetker JD, Bhatnagar A, Delanghe J, Vanheel B, Veiga-da-Cunha M, Derave W, Everaert I. Carnosine and anserine homeostasis in skeletal muscle and heart is controlled by β -alanine transamination. *J Physiol.* 2016 Sep 1;594(17):4849-63.
- 171 Bellinger PM, Minahan CL. The effect of β -alanine supplementation on cycling time trials of different length. *Eur J Sport Sci.* 2016 Oct;16(7):829-36.
- 172 de Andrade Kratz C, de Salles Painelli V, de Andrade Nemezio KM, da Silva RP, Franchini E, Zagatto AM, Gualano B, Artioli GG. Beta-alanine supplementation enhances judo-related performance in highly-trained athletes. *J Sci Med Sport.* 2017 Apr;20(4):403-408.
- 173 Abbasoglu L, Kalaz EB, Soluk-Tekkesin M, Olgaç V, Dogru-Abbasoglu S, Uysal M. Beneficial effects of taurine and carnosine in experimental ischemia/reperfusion injury in testis. *Pediatr Surg Int.* 2012 Nov;28(11):1125-31.
- 174 Bellia F, Vecchio G, Cuzzocrea S, Calabrese V, Rizzarelli E. Neuroprotective features of carnosine in oxidative driven diseases. *Mol Aspects Med.* 2011 Aug;32(4-6):258-66.
- 175 Hipkiss AR, Cartwright SP, Bromley C, Gross SR, Bill RM. Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential? *Chem Cent J.* 2013 Feb 25;7(1):38.
- 176 Gross M, Boesch C, Bolliger CS, Norman B, Gustafsson T, Hoppeler H, Vogt M. Effects of beta-alanine supplementation and interval training on physiological determinants of severe exercise performance. *Eur J Appl Physiol.* 2014 Feb;114(2):221-34.
- 177 Szczesniak D, Budzen S, Kopec W, Rymaszewska J. Anserine and carnosine supplementation in the elderly: Effects on cognitive functioning and physical capacity. *Arch Gerontol Geriatr.* 2014 Sep-Oct;59(2):485-90.
- 178 Bellia F, Vecchio G, Cuzzocrea S, Calabrese V, Rizzarelli E. Neuroprotective features of carnosine in oxidative driven diseases. *Mol Aspects Med.* 2011 Aug;32(4-6):258-66.
- 179 Nagai K, Suda T. Immunoregulative effects of carnosine and beta-alanine. *J. Physiol. Soc Jap* 1986;48:564-571.
- 180 Boldyrev A, Johnson P. Carnosine and related compounds: antioxidant dipeptides. In: P. Johnson and A. Boldyrev, Editors, *Oxidative Stress at Molecular, Cellular and Organ Levels*, Res. Signpost 2002;101-114.
- 181 Hipkiss AR, Cartwright SP, Bromley C, Gross SR, Bill RM. Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential? *Chem Cent J.* 2013 Feb 25;7(1):38.
- 182 Nagai K, Suda T, Kawasaki K, Mathuura S. Action of carnosine and beta-alanine on wound healing. *Surgery.* 1986;100(5):815-21.
- 183 Wang AM, Ma C, Xie ZH, et al. Use of carnosine as a natural anti-senescence drug for human beings. *Biochemistry (Mosc)* 2000;65(7):869-71.
- 184 Zakharchenko MV, Temnov AV, Kondrashova MN. Effect of carnosine on self-organization of mitochondrial assemblies in rat liver homogenate. *Biochemistry (Mosc).* 2003;68(9):1002-5.

- 185 Hipkiss AR. On the enigma of carnosine's anti-ageing actions. *Exp Gerontol*. 2009 Apr;44(4):237-42.
- 186 Milioni F, de Poli RAB, Saunders B, Gualano B, da Rocha AL, Sanchez Ramos da Silva A, Muller PTG, Zagatto AM. Effect of beta-alanine supplementation during high-intensity interval training on repeated sprint ability performance and neuromuscular fatigue. *J Appl Physiol* (1985). 2019 Dec 1;127(6):1599-1610. doi: 10.1152/jappphysiol.00321.2019.
- 187 Dai Z, Lu XY, Zhu WL, Liu XQ, Li BY, Song L, Liu HF, Cai WW, Deng YX, Xu TT, Wang Q, Zhang SJ. Carnosine ameliorates age-related dementia via improving mitochondrial dysfunction in SAMP8 mice. *Food Funct*. 2020 Mar 1;11(3):2489-2497. doi: 10.1039/c9fo02453k. Epub 2020 Mar 5. PMID: 32134423
- 188 Limonta E, Invernizzi PL, Rampichini S, Bisconti AV, CÉ E, Longo S, Coratella G, Iaia MF, Esposito F. Acute carnosine and beta-alanine supplementation increases the compensated part of the ventilation vs work rate relationship during a ramp incremental cycle test in physically active men. *J Sports Med Phys Fitness*. 2020 Oct 22. doi: 10.23736/S0022-4707.20.10887-9. Online ahead of print. PMID: 33092320.
- 189 Stvolinsky SL, Dobrota D. Anti-ischemic activity of carnosine. *Biochemistry (Mosc)*. 2000; 65(7):849-55.
- 190 Begum G, Cunliffe A, Leveritt M. Physiological role of carnosine in contracting muscle. *Int J Sport Nutr Exerc Metab*. 2005 Oct;15(5):493-514. Links
- 191 Parkhouse WS, McKenzie DC, Hochachka PW, Ovalle WK. Buffering capacity of deproteinized human vastus lateralis muscle. *J Appl Physiol* 1985;58:14–17.
- 192 Susuki Y, Ito O, Takahashi H, Takamatsu K (2004) The effect of sprint training on skeletal muscle carnosine in humans. *Int J Sport Health Sci* 2: 105–110.
- 193 Tallon MJ, Harris RC, Boobis L, Fallowfield J, Wise JA (2005) The carnosine content of vastus lateralis is elevated in resistance trained bodybuilders. *J Strength Condit Res* 19: 725–729.
- 194 Harris RC, Tallon MJ, Dunnett M, Boobis L, Coakley J, Kim HJ, Fallowfield JL, Hill CA, Sale C, Wise JA. The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino Acids*. 2006;30(3):279-89.
- 195 Hill CA, Harris RC, Kim HJ, Harris BD, Sale C, Boobis LH, Kim CK, Wise JA. Influence of beta-alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. *Amino Acids*. 2007;32(2):225-33.
- 196 Effects of Acute Carnosine and β -Alanine on Isometric Force and Jumping Performance. Invernizzi PL, Limonta E, Riboli A, Bosio A, Scurati R, Esposito F. *Int J Sports Physiol Perform*. 2016 Apr;11(3):344-9.
- 197 Abbasoglu L, Kalaz EB, Soluk-Tekkesin M, Olgaç V, Dogru-Abbasoglu S, Uysal M. Beneficial effects of taurine and carnosine in experimental ischemia/reperfusion injury in testis. *Pediatr Surg Int*. 2012 Nov;28(11):1125-31.
- 198 Fornaris E, Vanuxem D, Dufлот JC, et al. Pharmacoclinical approach of citrulline malate activity: analysis of blood lactate during a standardized exercise. *Gazette Medicale* 1984;91:1-3.
- 199 Vanuxem D, Dufлот JC, Prevot H, et al. Influence of an anti-asthenia agent, citrulline malate, on serum lactate and ammonia kinetics during a maximum exercise test in sedentary subjects. *Séminaire des Hôpitaux de Paris* 1990; 66:477-81.
- 200 Wagenmakers AJ. Muscle amino acid metabolism at rest and during exercise: role in human physiology and metabolism. *Exerc Sport Sci Rev* 1998; 26:287-314.
- 201 Callis A, Magnan de Bornier B, Serrano JJ, Bellet H, Saumade R. Activity of citrulline malate on acid-base balance and blood ammonia and amino acid levels. Study in the animal and in man. *Arzneimittelforschung*. 1991; 41(6):660-3.

- 202 Briand J, Astoin J, Lavalmartin D, et al. Euglena, as a cellular model used in pharmacology for studying the effects of citrulline malate on lactate metabolism. *Comp Biochem Physiol* 1986; 85:553-8.
- 203 Gibala MJ, Tarnopolsky MA, Graham TE. Tricarboxylic acid cycle intermediates in human muscle at rest and during prolonged cycling. *Am J Physiol* 1997;35:E239-44.
- 204 Gibala MJ, Young ME, Taegtmeyer H. Anaplerosis of the citric acid cycle: role in energy metabolism of heart and skeletal muscle. *Acta Physiol Scand* 2000;168:657-65.
- 205 Giannesini B, Le Fur Y, Cozzone PJ, Verleye M, Le Guern ME, Bendahan D. Citrulline malate supplementation increases muscle efficiency in rat skeletal muscle. *Eur J Pharmacol*. 2011 Sep 30;667(1-3):100-4.
- 206 Wax B, Kavazis AN, Luckett W. Effects of Supplemental Citrulline-Malate Ingestion on Blood Lactate, Cardiovascular Dynamics, and Resistance Exercise Performance in Trained Males. *J Diet Suppl*. 2016;13(3):269-82.
- 207 Glenn JM, Gray M, Jensen A, Stone MS, Vincenzo JL. Acute citrulline-malate supplementation improves maximal strength and anaerobic power in female, masters athletes tennis players. *Eur J Sport Sci*. 2016 Nov;16(8):1095-103.
- 208 Glenn JM, Gray M, Wethington LN, Stone MS, Stewart RW Jr, Moyon NE. Acute citrulline malate supplementation improves upper- and lower-body submaximal weightlifting exercise performance in resistance-trained females. *Eur J Nutr*. 2017 Mar;56(2):775-784.
- 209 Yuasa M, Matsui T, Ando S, Ishii Y, Sawamura H, Ebara S, Watanabe T. Consumption of a low-carbohydrate and high-fat diet (the ketogenic diet) exaggerates biotin deficiency in mice. *Nutrition*. 2013 Oct;29(10):1266-70.
- 210 Boehm E, Chan S, Monfared M, Wallimann T, Clarke K, Neubauer S. Creatine transporter activity and content in the rat heart supplemented by and depleted of creatine. *Am J Physiol Endocrinol Metab*. 2003 Feb;284(2):E399-406.
- 211 Kreider RB. Species-specific responses to creatine supplementation. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R725–R726.
- 212 Greenwood M, Kreider RB, Melton C, Rasmussen C, Lancaster S, Cantler E, Milnor P, Almada A. Creatine supplementation during college football training does not increase the incidence of cramping or injury. *Mol Cell Biochem* 2003; 244: 83–88.
- 213 Dalbo VJ, Roberts MD, Stout JR, Kerksick CM. Putting to rest the myth of creatine supplementation leading to muscle cramps and dehydration. *Br J Sports Med*. 2008;42:567–73.
- 214 Cooper R, Naclerio F, Allgrove J, Jimenez A. Creatine supplementation with specific view to exercise/sports performance: an update. *Sports Nutr Rev J*. 2012;9:33.
- 215 Vandenberghe K, Goris M, Van Hecke P, Van Leemputte M, Vangerven L, Hespel P. Long-term creatine intake is beneficial to muscle performance during resistance training. *J Appl Physiol*. 1997 Dec;83(6):2055-63. Full paper in PDF format available at <https://journals.physiology.org/doi/pdf/10.1152/jappl.1997.83.6.2055>.