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Muscle quest:
Developing lean mass

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The many ways to muscle

Athletes are maestros of muscle. Their bodies bring together different systems, including circulation, brain and nerves, to repair and build muscle, then these muscles work in concert to perform a wide range of physical exercises. Sure, the range of athleticism spans amateur to professional, but the process of developing muscle is an elaborate symphony in everybody.

In this special sports nutrition muscle-focused digital issue, we go on a journey into how muscles are created, maintained, protected and repaired, highlighting nutritional tools along the way. First up is a detailed look at the science behind the body's mechanism related to muscle development, including how the central nervous system (CNS) and mitochondrial energy production interact with muscle structures and vital nutrients to spark lean mass growth from protein/amino acids.

We also focus on the mammalian target of rapamycin complex 1 (mTOR) pathway involved in anabolic (growth) and catabolic (breakdown) signaling in muscle. Triggering muscle protein synthesis (MPS) can involve amino acids, such as leucine, but many dietary ingredients are drawing attention in this hot area of muscle research for their ability to impact mTOR and MPS.

The hormone testosterone is anabolic and can drive muscle growth, but the exact mechanisms behind this benefit are still being researched, including possible influence on mTOR. We review the research behind popular natural testosterone boosters as well as key considerations involving safety and applicability.

Sleep affects testosterone levels, but the importance of slumber to muscle doesn't end there. We outline the mechanics of sleep, including where in the cycle muscle growth tends to occur and which dietary and lifestyle factors can help or hinder good sleep for muscle gains.

Also in this issue are articles on how certain nutrients may improve blood flow for increased nutrient delivery to the muscles, how broad banned substance list language challenges muscle-building formulation and certification, and how dietary management of inflammation can best protect muscle from harmful damage without hindering growth.

Finally, we talked to a neuromuscular researcher and expert about how nutrition can affect the brain's management of muscles, including the impact of certain deficiencies and the boost energizing ingredients such as creatine can provide the brain and muscles.

All in all, we designed this issue to pump you up with muscle knowledge and nutritional possibilities.

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The art and science of human muscle development

by Mark LeDoux

INSIDER's take

- The human body has cardiac, smooth and striated or skeletal muscles which vary in content and function.
- The protein efficiency ratio (PER) of a food or supplement impacts its effectiveness in supporting the human body.
- The need for adequate stores of water and metabolites is essential yet often overlooked when building muscle.

Two words come to mind when thinking about the complex relationship between two protein molecules associated with appropriate muscle development in humans: actin and myosin. Approximately 640 muscle groups exist in the human body, and each of them plays a significant role in holding together what constitutes an elegant and complicated organism known as a human being. The three main groups of muscles, which vary in content and function, are smooth, cardiac, and striated or skeletal.

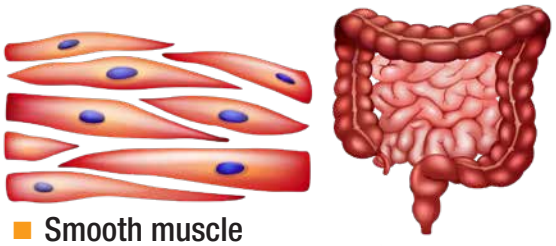
Smooth muscles are generally found in the alimentary tract and are involved with transporting food and orchestrating metabolism and elimination of body waste. Cardiac muscle is specialized and governed by a complex set of nutrient demands, while skeletal or striated muscles are responsible for skeletal function and human actions involving motion.

When it comes to building muscle, what is meant is enhancing the size and structure of a variety of tissues that make up those predominantly skeletal muscles tasked with normal daily function, such as picking up a pencil or walking up a flight of stairs.

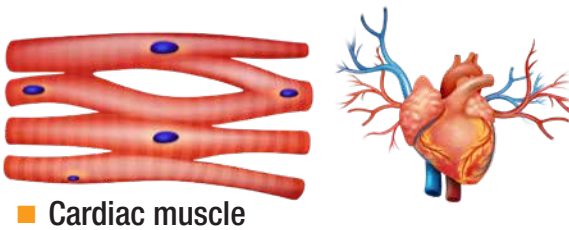
When looking at striated muscle, the type most commonly associated with visual muscular physique, it is important to understand that the entire muscle is wrapped in a layer of connective tissue called the epimysium, which is a Greek word translated into the English phrase “upon the muscle.” This muscle contains a collection of bundles of fascicles—a generally fibrous connecting tissue. Within the inner layer of the fascicles themselves are the tissues known as endomysium, tasked with surrounding and reinforcing every muscle fiber. In a strange paradox of human metabolism, in order to create new muscle, old fibers must be torn asunder through the stress of exercise, leading to the creation of even more fibers; this is the heart of the “no pain, no gain” adage.

Inside every muscle fiber is a collection of myofibril strands that bundle up to become muscle structures called sarcomeres, which consist of two basic proteins, actin and myosin. Sarcomeres are associated with muscle contraction. At a resting state, actin and myosin are essentially in a non-confrontive state. When a muscle

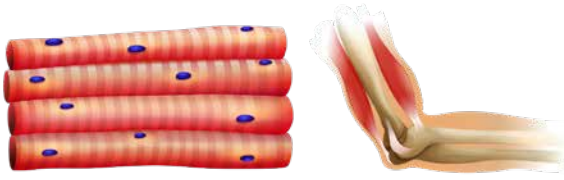
The three main groups of muscles, which vary in content and function



■ Smooth muscle



■ Cardiac muscle



■ Skeletal muscle

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is stressed during some form of activity, adenosine triphosphate (ATP) —the energy molecule—is utilized as a molecular accelerator to convert chemical energy into function. Within the muscle cells themselves are powerhouses of energy transformation known as mitochondria, but the entire fiber itself is protected by something called a sarcoplasmic reticulum, which is a group of cells loaded with molecular calcium pumps to load up the muscle warehouse with calcium ions.

When people talk about energy, they are talking about electrical impulses at a low level, which are tasked with initiating muscle movement commands generated in the human brain. Here, chemicals such as acetylcholine are targeted for release to communicate the need for metabolic channels to open, allowing sodium to enter the electric stimulus to instruct the muscle on next steps. When tubes within the actual muscle fibers receive the sodium stimulus, proteins are released from cells to permit calcium to enter the fray. When calcium is released through protein molecules, ever vigilant troponin binds with calcium. At that time, tropomyosin cleaves a phosphate from ATP, which providing energy for the muscle to contract and subsequently release. The additional result of this energy process is adenosine diphosphate (ADP).

In a choreographed symphony of metabolism, ATP and ADP are in a balanced, often accelerated, role of exchange, which leads to multiple contractions and release of the muscle fibers. Calcium is also in a constant state of flux as the entire muscle is looking to rearm itself for the next command to move in response to signals from the brain.

While the three different muscle groups are engaged in different functions simultaneously, cardiac, smooth and skeletal muscles create their movement through a sliding filament model of metabolic commands. While the striated or skeletal muscles are made up of bundles of protein fibers including actin and myosin myofilaments, it is the mineral calcium and the molecule of ATP that cause the binding and unbinding that make the sarcomeres contract and relax.

In a choreographed symphony of metabolism, ATP and ADP are in a balanced, often accelerated, role of exchange, which leads to multiple contractions and release of the muscle fibers.

To properly support muscle contraction and release, electrolytes play a dynamic role. Electrolytes are charged ions mixed with water, and the main five are calcium, chloride, magnesium, potassium and sodium. During extended exercise when the body is looking to maintain a homeostatic thermostat through perspiration, the two most important electrolytes lost through human sweat are potassium and sodium.

Glycogen found in muscle fibers is considered the most important energy source used by the human muscular system, so a diet rich in dense carbohydrate concentration is essential. But glycogen alone is insufficient to provide long-lasting results when seeking to nourish muscle cells. The reasons are manifestly associated with the high concentrations of proteins found in muscle fibers.

According to some experts, the amount of protein a human should consume to achieve and maintain optimum muscle activity is between 1 and 1.5 grams per kilogram of body weight. For example, if a person weighs 100 kilograms, or 220 pounds, the arithmetic calls for ingesting 100 to

150 grams of protein daily. Selecting the correct type of protein is also important, given that not all proteins are created equal.

Something to consider is the protein efficiency ratio (PER) of the food or supplement. Proteins with "compromised" levels of essential amino acids—those that must be ingested and which cannot be synthesized in the human gut for use—can have low levels of PER, while others that have a full complement in appropriate ratios of essential amino acids (e.g., human breast milk) are optimal.

Another consideration of building or maintaining healthy muscles is to not avoid dietary fats. Fats are essential for endocrine function (hormone balances), as well as enhancing the absorption and metabolism of nutrients that provide consistent energy sources through protracted periods of human exertion and exercise.

Most people who seek to preserve or enhance their muscle mass utilize repetitive motion activities such as walking, biking, rowing, swimming or weightlifting to not only stimulate muscle growth, but to achieve muscle density and concentration in certain areas of the musculoskeletal system. The rate-limiting factor to achieving long-term results from vigorous workouts is linked to metabolic fatigue, where the byproduct of repetitive muscle firing and contraction is the elevation of lactic acid. The presence of adequate levels of carnosine (usually achieved through supplementation) can extend the time to true muscle exhaustion.

Carnosine is a dipeptide molecule consisting of histidine (an amino acid) and beta-alanine (an amino acid), which has a variety of metabolic benefits beyond that of buffering lactic acid. Over the past decade, this area of science has been well studied with excellent outcomes.

Finally, adequate hydration, particularly before, during and after exercise, is mission critical. Through the sophisticated and elegant dance associated with muscle metabolism, energy creation and muscle destruction and subsequent repair, the need for adequate stores of water and metabolites—leading to enhanced elimination of waste components—is essential and often overlooked.

Additionally, the role of dietary anti-inflammatory agents that help block cyclooxygenase-2 (COX-2) expression cannot be overemphasized for muscle health and function. Recent studies continue to extol the virtues of properly extracted curcuminoids from turmeric (*J Diet Suppl*. 2019 Apr 26;1-14), proteolytic activities of bromelain from pineapple (*Med Sci Sports Exerc*. 2009 Oct;41[10]:1908-1914), and a host of other natural products. These should all be in the arsenal of professional athletes as well as weekend warriors, to make certain that their efforts to tone and shape their muscular structure and efficiency achieve the intended results. ✦

Mark A. LeDoux is chairman and CEO of Natural Alternatives International Inc. and chairman of the board of directors of the Natural Products Association.


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FUTURECEUTICALS

Caveat mTOR: Researched nutrients contributing to key muscle growth pathway

by Ralf Jäger, Ph.D.

INSIDER's take

- Muscle protein synthesis (MPS) is dependent on signaling by a protein kinase called the mechanistic target of rapamycin (mTOR).
- Supplements such as β-hydroxy-β-methylbutyrate (HMB) and phosphatidic acid (PA) can increase MPS via mTOR.
- Omega-3 fatty acids, including krill oil and its antioxidant constituent astaxanthin, can activate mTOR and stimulate muscle growth.

The total amount of muscle mass is the sum of muscle protein synthesis (MPS), and muscle protein breakdown (MPB). If MPS is greater than MPB, muscle mass increases.[1] A protein kinase called the mechanistic target of rapamycin (mTOR) has been widely recognized as a key regulator of muscle growth. Elevations in energy status, growth factors, amino acids and specific nutrients including β-hydroxy-β-methylbutyrate (HMB) and phosphatidic acid (PA) can increase MPS through an mTOR-dependent mechanism.[2]

Resistance exercise mechanically induces MPS increases through mTOR signaling, resulting in a hypertrophic response. Exercise has been shown to increase intracellular levels of the phospholipid PA, and PA activates mTOR signaling. Combining orally supplemented soy-derived PA (750 mg) with resistance exercise has been shown to significantly increase the responses in skeletal muscle hypertrophy, lean body mass and maximal strength compared to resistance exercise alone.[3]

Other phospholipids, such as phosphatidylinositol (PI), phosphatidylethanolamine (PE) and phosphatidylcholine (PC), and PA's metabolites diacylglycerol (DAG) and glycerol-3-phosphate (G3P) do not active mTOR, however, phosphatidylserine (PS) does.[3]

Resistance exercise and protein ingestion stimulate MPS, and are synergistic when protein consumption occurs before or after resistance exercise.[4] For building muscle mass and maintaining muscle mass through a positive muscle protein balance, an overall daily protein intake in the range of 1.4 to 2.0 g of protein/kg body weight/day (g/kg/d) of high-quality protein (complete or robust profile of amino acids) is sufficient for most exercising individuals. Optimal protein intake per serving for athletes to maximize MPS are dependent upon age and recent resistance exercise stimuli. General recommendations are 0.25 g of a high-quality protein per kg of body weight, or an absolute dose of 20 to 40 g.4 Total daily protein intake should ideally be evenly distributed, every three to four hours across the day, to optimize MPS.[4]

Protein consists of individual amino acids. When analyzing the effect of different amino acids on MPS, essential amino acids (EAAs) outperform

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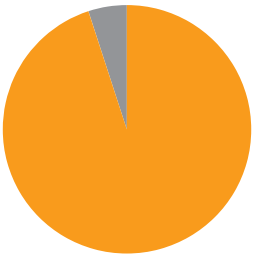
non-essential amino acids, and the branched chain amino acid (BCAA) leucine seems to play a key role. Therefore, an acute protein dose should contain up to 3,000 mg of leucine, in addition to a balanced array of the EAAs to optimally active MPS.[4]

HMB is a naturally occurring metabolite of EAA leucine. Similar to leucine, HMB increases mTOR signaling, with leucine's effect on MPS being more pronounced than HMB's (+110% vs. +70%, respectively), but HMB additionally reduces MPB by 57%.[5]

HMB induces acute muscle anabolism via a distinct, and/or additional mechanism to leucine. This ingredient works optimally when protein intake is suboptimal or during times of increased MPB (e.g., during calorie restriction, times of insufficient recovery or periods of overtraining). In untrained individuals, HMB combined with resistance training increased lean body mass in a dose-dependent manner: +0.4 kg (training alone), +0.8 kg (1.5 g of HMB) and +1.2 kg (3 g of HMB), establishing 3 g of HMB as the optimal dose.[6] In addition, HMB reduced exercise-induced muscle-damage in resistance and endurance athletes.

Krill oil is a marine source of the long-chain omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have been found to have positive effects on inflammation and recovery from exercise.[7] Research has shown EPA and DHA can increase the activation of the mTOR/p70s6k signaling pathway—a key protein in the initiation step of protein translation—in response to increased amino acid and insulin supply after eight weeks of PUFA supplementation, which leads to increase muscle mass in elderly men and women.[8]

Krill oil also contains astaxanthin, a red carotenoid pigment and strong antioxidant that naturally occurs in salmon, shrimp, krill, crustaceans and certain types of algae—it gives these organisms a reddish or pinkish color. Krill oil is a complex mixture of ingredients, with its PUFAs bound to phospholipids, mainly PC. While soy-derived PA and PS can stimulate a robust increase in mTOR signaling, soy-derived PC is not effective.[3] However, krill oil can activate mTOR signaling and, when combined with resistance exercise, 3 g of krill oil significantly increased lean body in young men.[9]



About 95%

of the body's creatine is stored in the muscles, and numerous studies have shown that creatine combined with resistance exercise increases muscle mass and athletic performance.

While young athletes can focus on increasing muscle protein synthesis to increase muscle mass, more mature active individuals must consider nutritional strategies to simultaneously prevent muscle protein breakdown.

Creatine is an ingredient commonly found in food, mainly in fish and meat, and is sold as a dietary supplement in markets around the world. Its use as an ergogenic aid and possible nutritional aid for certain neuromuscular disorders is well documented in scientific literature (see page 27 for more). Creatine monohydrate (CM), first marketed in the early 1990s, is the most researched form of creatine, with alternative forms being introduced in the late 1990s, in attempts to improve certain attributes such as solubility and efficacy. To date, no alternative form of creatine has been shown to be superior to CM.[10]

About 95% of the body's creatine is stored in the muscles, and numerous studies have shown that creatine combined with resistance exercise increases muscle mass and athletic performance. Creatine supplementation increases muscle phosphocreatine stores, which allow for increased recycling of the body's energy source ATP during high-intensity exercise.[10] However, creatine is also linked to mTOR. Creatine might activate mTOR parent mTOR complex 1 (mTORC1) by increasing IGF-I activity at rest, but it does not further potentiate mTORC1 signaling in the hours after exercise.[11]

Ursolic acid is a natural triterpene compound found in various fruits and vegetables, and has been shown to stimulate mTORC1 signaling in rat skeletal muscle.[12] When combined with resistance exercise, supplementation of 1,350 mg of ursolic acid from rosemary leaf extract was shown to increase strength in resistance-trained Korean men, but failed to increase muscle mass.[13] When ingested immediately following resistance exercise, 3g of UA had no effect on mTOR activity in resistance-trained young American men.[14]

While young athletes can focus on increasing MPS to increase muscle mass, more mature active individuals must consider nutritional strategies to simultaneously prevent MPB. Age-related loss of muscle mass, also called sarcopenia, is mainly driven by an increase in MPB. While strength training is an effective tool to combat age-related muscle loss, most elderly people do not train regularly due to multiple reasons, including the fear of injury.

HMB supplementation has been shown to improve muscle quality and strength without resistance training in a group of 65-year-old adults and older.[15] When combined with strength training, HMB supplementation increased strength, and increased fat loss in male and female subjects with an average age of 70 years.[16]

During energy restriction, muscle protein balance (MPS:MPB) becomes negative, resulting in a loss of muscle mass, particularly if rates of weight loss exceed 1.0% body mass loss per week.[4] Higher protein intakes (2.3 to 3.1 g/kg/d) may be needed to maximize the retention of lean body weight in resistance trained subject during hypocaloric periods. Specifically in weight cautious athletes, HMB might be the preferred nutrient to prevent MPB during calorie restriction.

Anabolic signaling mechanisms are complex, and it's hard to predict the long-term effectiveness of ingredients on muscle gains from acute activation of mTOR. In addition, mTOR can be activated by stimuli that do not result in muscle hypertrophy, such as cardiovascular workouts or inflammation. Any short-term in vitro, animal or even human anabolic signaling benefits need to be verified in long-term (eight to 12 week) controlled, human clinical studies using a resistance training program designed to induce muscle hypertrophy, while allowing to verify changes in lean body mass. ✦

Ralf Jäger, co-founder and partner of Increnovo LLC, is a certified sports nutritionist (CISSN), fellow of the International Society of Sports Nutrition (FISSN) and a member of the editorial board of the leading peer-reviewed *Journal of International Society of Sports Nutrition* (*JISSN*).

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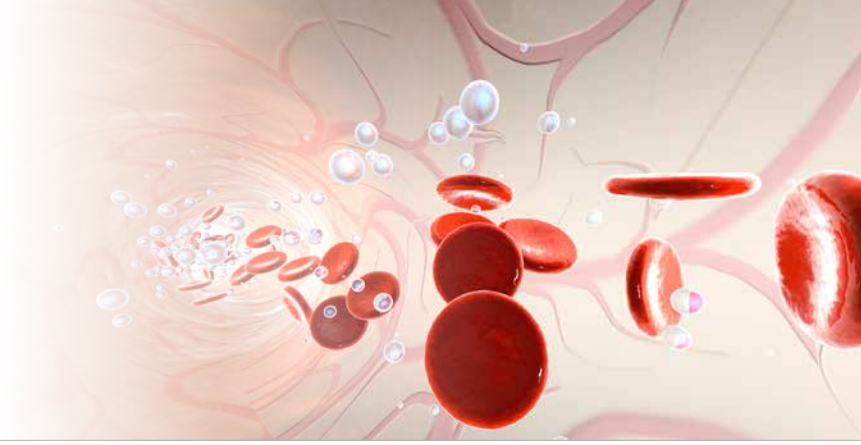

Boosting blood flow for muscle growth

by Susan Hewlings and Douglas Kalman

INSIDER's take

- Enhanced blood flow to an exercising muscle may delay fatigue and allow for increased training volumes and/or recovery.
- Ingredients that may enhance nitric oxide (NO)—and therefore vasodilation—have become popular in sports nutrition.
- Research is needed to explore the potential of multi-ingredients in contributing to muscular growth via enhanced blood flow.

When talking about muscle growth, people typically focus on protein turnover and the various aspects that influence both protein synthesis and breakdown. However, the importance of blood flow and the role it plays in muscle hypertrophy (muscle cell increase/growth) are often underemphasized and overlooked. Understanding the mechanics of how the body transports nutrients, and then how these nutrients interact with hormones and vasodilators to produce physiological change, is not easy. Examining some of the science surrounding blood flow and exercise as relates to and intersects with nutrition can provide meaningful background on what has become a category within sports nutrition.

After resistance exercise to failure (typically many repetitions), levels of energy-providing intramuscular adenosine triphosphate (ATP) and creatine phosphate (CP) become depleted, while adenosine diphosphate (ADP), adenosine monophosphate (AMP), adenosine, lactate and nitric oxide (NO) increase. These metabolites either directly or indirectly increase blood flow to the muscle. This contributes to muscle hypertrophy along with cellular swelling and changes in metabolites, referred to as "metabolic stress."[1,2] In addition, enhanced blood flow to an exercising muscle may delay fatigue and allow for increased training volumes and/or recovery, potentially leading to enhanced muscle growth and function indirectly. Due to the increased awareness of the role blood flow plays in muscle hypertrophy, several supplements have been marketed to enhance blood flow through various mechanisms.

Perhaps the most popular are the ingredients related to enhancing blood flow via NO, which stimulates vasodilation and is formed from L-arginine.[2] Therefore, supplementation with arginine is said to increase NO and thus, blood flow. Arginine supplementation has been shown to enhance exercise performance in athletes and active adults through an increased time to exhaustion,[3] improved recovery[4] and delayed muscular fatigue.[5,6]

The bioavailability of arginine has been questioned and therefore, in order to enhance absorption, inositol-stabilized arginine silicate (ASI, as Nitrosigine from Nutrition 21), a sports nutrition ingredient, has been tested and shown to increase blood levels of arginine and NO.[7] In healthy, minimally active males, 1,500 mg/d of ASI for four days significantly increased pre-workout energy levels, increased upper leg muscle size and reduced biomarkers of muscle damage during recovery from exercise.[8]

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Beetroot is recognized for its high levels of natural nitrates, which increase nitric oxide levels.

Supplementation with the non-protein amino acid L-citrulline has also been investigated as a way of overcoming the poor bioavailability of arginine because it helps to recycle L-arginine, and has been shown to increase plasma levels of L-arginine and thus NO bioavailability.[9,10] While it is rare in the food supply, it is concentrated in watermelon, which is often used as an extract.[11] A 2019 systematic review and meta-analysis of 13 studies with 198 subjects reported citrulline supplementation confers a significant benefit on strength and power outcomes in comparison to placebo.[12]

Another well-known ingredient, beetroot, is recognized for its high levels of natural nitrates, which increase NO levels.[13] Several studies have shown that beetroot juice supplementation has an ergogenic effect in runners, primarily through an increase in running economy[14,15,16] and time to exhaustion.[17] In the time-to-exhaustion study, supplementation with beetroot delayed muscle fatigue by reducing the exercise-induced impairments in contractile muscle function and lowered the perception of perceived effort and leg muscle pain during exercise. It has also been shown to improve sprint performance[18] and resistance exercise performance,[19] mainly through improvement in muscle contractility,[20] as well as muscular speed and power.[21] Over several training bouts, these improvements have been said to promote adaptive skeletal muscle remodeling that is synergistic to other processes stimulated by training that ultimately lead to muscular adaptations.[20] More research is needed to clearly identify the potential mechanisms by which beetroot supplementation may benefit exercise performance and muscular adaptations, but it shows promise.

Another natural ingredient said to increase NO levels is pomegranate. Pomegranate juice has a nitrate concentration of 12.93 mg/L.[22] It may illicit its effect not only by increasing NO levels, but by enhancing NO bioavailability and by protecting it against oxidation due to the fruit's high polyphenol content.[23,24] Supplementation of 1,000 mg of pomegranate extract 30 minutes before sprint and resistance exercise has been shown to enhance vessel diameter, blood flow and peak and average power output in resistance-trained males.[25] Similarly, ingestion of 100 mg of the extract 30 minutes before exercise increased vessel diameter and blood flow and delayed fatigue in active men and women.[26]

Numerous ingredients show promise for enhancing blood flow during exercise, primarily by increasing NO either directly or indirectly. These ingredients may support or enhance muscular growth and function in both athletes and non-athletes. More research should be conducted to explore the efficacy of multi-ingredient products to capitalize on the multiple mechanisms that contribute to muscular growth via enhanced blood flow. ✦

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Testosterone-boosting ingredients: Hidden potential

by Vince Kreipke

INSIDER's take

- Tongkat ali and D-aspartic acid were shown to support testosterone levels and provide related benefits.
- Many studies examining the potential of these ingredients were done in populations with low testosterone.
- Hormone boosters may influence the outcome of steroid and purity tests for professionals and athletes.

Testosterone has been an ever-growing topic of interest. And for good reason—it has been linked to superior physical performance.[1] Further, it is positively associated with body composition,[2] reaction time,[3] sexual function[4] and mood.[4]

With all these benefits, it is no wonder that many people, especially men, are continually searching for ways to boost their testosterone levels. Naturally, with age comes a decrease in testosterone levels.[5] But recently, it has been suggested that testosterone levels are decreasing across the U.S.,[6] independent of age, possibly as a result of poor health choices.[5]

As people attempt to correct lifestyle changes, they often look to resistance training and nutritional interventions to aid in promoting their natural testosterone levels. While some contradiction exists in the research about both of these methods, nutritional intervention may have potential in aiding individuals in their relentless quest.

Four key ingredients have gained popularity as nutritional testosterone boosters, *Tribulus terrestris*, tongkat Ali, D-aspartic acid and ashwagandha.

Tribulus terrestris

Tribulus terrestris is found on most continents and has been used in traditional medicine for centuries.

Animal studies are the main supporter of the potential benefits of T. terrestris, specifically improved endogenous testosterone concentrations.[7]

However, these results have been repeated in a pilot study of male patients with partial androgen deficiency, showing an increase in both free and total testosterone concentrations.[8]

Four key ingredients have gained popularity as nutritional testosterone boosters

Tribulus terrestris | Tongkat ali | D-aspartic acid | Ashwagandha

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These reported increases in testosterone levels have potential to manifest in meaningful results associated with T. terrestris supplementation, such as improvement in erectile dysfunction,[9] semen quality and markers of body composition.[10] Interestingly, T. terrestris supplementation has also improved symptoms and hormone levels associated with female sexual dysfunction.[11]

Though contested, research has suggested this ingredient may be effective for younger men, based on research involving 20- to 22-year old male athletes.[12] Notably, these increases were only seen the first 10 days of supplementation without any further increases at 20 days of supplementation, which may speak to limited potential of nutritional testosterone boosters.

Tongkat ali

Tongkat ali (also known as *Eurycoma longifolia*) is another herb with a long history in traditional medicine for sexual dysfunction, infertility and vitality.

In 2012, these claims were put to the test in men with late-onset hypogonadism. After one month of supplementation with tongkat ali, significant improvement was seen in testosterone concentrations.[13]

A year later, tongkat ali was shown to elicit improvements in mood in both men and women.[14] What's more, these improvements may be more than just the result of increased testosterone. The same study suggested tongkat ali may be able to decrease cortisol levels, a common stress hormone.

A small pilot study in healthy individuals suggested supplementation resulted in physical changes such as improvements in body composition and strength.[15]

Ashwangandha

Ashwagandha (*Withania somnifera*) has been held as a staple in ancient medicine. It has been shown to elicit benefits across multiple facets of life, and testosterone concentrations are no exception.[16]

Ashwagandha has shown promise in benefiting physical variables associated with increased testosterone, such as strength and body composition.[17] More importantly, these results were found in healthy men.

Additionally, supplementation has been shown to have positive effects on anxiety and stress.[18]

D-aspartic acid

Unlike the previously mentioned herbs, D-aspartic acid is an amino acid with testosterone-boosting potential.

Notably, this ingredient has been shown to raise testosterone levels in males in 12 days.[19]

Testosterone is essential to a healthy, long life, especially for men. Continuous maintenance is paramount in cultivating the vitality sought by so many.

D-aspartic acid has also shown promise in promoting physical benefits often seen with increases in testosterone. After 90 days of supplementation, it improved sperm quality in sub-fertile men.[20]

Nutritional testosterone boosters and steroid tests

Testosterone is a sticky topic, especially when it comes to boosting endogenous levels. Multiple organizations, especially those in sport, conduct strenuous tests to ensure the purity of their participants. These tests also stretch to servicemen and servicewomen, such as soldiers and police officers. And while they may benefit from the testosterone-boosting benefits of these ingredients, the potential risk of testing positive for exogenous testosterone administration (such as steroid use) can be deterring. Interestingly, tongkat ali[21] and T. terrestris[22] have not been shown to elicit a false positive on these tests.

Testosterone boosters are not for everyone

While some of these ingredients show promise in boosting testosterone concentrations, they are not for everyone. A common characteristic of numerous studies is that successes were found in individuals who were hypogonadal or on the lower end of the testosterone scale.

Although research indicates the potential of these ingredients, most of the research does not support changes in testosterone levels in healthy individuals, especially those who are resistance trained.[23] These findings have been further supported in "testosterone focused" multi-ingredient performance supplements consisting of a blend of these ingredients.[24]

Testosterone is essential to a healthy, long life, especially for men. Continuous maintenance is paramount in cultivating the vitality sought by so many. While further research is needed for these ingredients, nutritional intervention in combination with a healthy lifestyle seems to hold promise not only for raising testosterone concentrations, but also eliciting tangible outcomes seen in the real world. ✦

Vince Kreipke received his doctorate in exercise physiology with a focus in sports nutrition in 2016. During this time, he worked to determine the efficacy of many ingredients with a potential to benefit exercise performance and subsequent outcomes. Since then, he has been able to expand his focus to enhancing other aspects of daily living, such as cognitive performance and general health. Currently, Kreipke holds the position of scientific advisor at Onnit Labs Inc. where he continues his research into optimal human health and performance.

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Modifications to the WADA Prohibited List and impacts on sports nutrition

by Oliver Catlin

INSIDER's take

- Legitimate substances may experience negative consequences due to broad interpretations of the language used in the WADA Prohibited List.
- Despite widespread use in the natural product community, muscle building ecdysterone was added to the WADA monitoring program list in 2020.
- WADA states that "any preparation from cannabis" is prohibited, yet allows for CBD, which derives from the hemp form of cannabis.

The connections between the World Anti-Doping Agency (WADA) Prohibited List and products sold as dietary supplements are not often considered. Yet, history has proven that the WADA Prohibited List has been a source of inspiration for the darker side of the industry and has also been a harbinger of regulations to come. Modifications to the list language over the years have spawned new supplement categories and prompted regulatory attention as categories grow in prominence. As the 2020 WADA Prohibited List is poised to take effect, it's worth considering the past and present impacts modifications have had on the muscle-building and greater sports nutrition realm.

To understand the implications of the WADA Prohibited List, it pays to explore history to see the connections further. The prohormone era was going strong not more than 15 years ago. The substances used as active ingredients represented holes in both the U.S. regulatory language in place at the time and the WADA Prohibited List. Over time, the WADA list evolved to include more examples of prohormones, and as it did, regulatory language followed suit. The Anabolic Steroid Control Act of 2004 added language targeting prohormones, but ultimately it was not until the Anabolic Steroid Control Act of 2014 added significant penalties and made it easier for related substances to be considered under the regulations that prohormones were finally reduced to nuisance proportions.

But a new problem developed to take the place of prohormones. WADA had added selective androgen receptor modulators (SARMs) to the list in 2008, which drew attention to this new category. No SARMs were included as examples by name and the substances offered an alternative to prohormones that had yet to attract regulatory attention. This led to the exploitation of this developing category of drug as a new category of illegitimate dietary supplements.

The SARMs challenge has grown to enormous proportions, with trace amounts now frequently found as contaminants even in benign multivitamin supplements. UFC fighter Nate Diaz's recent positive for the SARM LGD- 4033 (aka Ligandrol) drew renewed attention to this concern. Industry groups are now taking action against SARMs and SARMs Control Act of 2018 has been proposed to address their presence.

Today the WADA Prohibited List includes Andarine, Ostarine, LGD-4033 and RAD 140 (Testolone) as examples of SARMs, and the proposed legislation includes nine examples. The Banned Substances Control Group (BSCG) lists 17 SARMs or related compounds on its BSCG dietary supplement ingredient advisory list. Andarine and Ostarine are perhaps the best known and have also been the first to slowly

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disappear from commerce. Other related substances often sold as SARMs, like GW-1516 (Cardarine) and SR9009 (Stenabolic), are categorized by WADA as metabolic modulators and are not mentioned in the proposed legislation. These continue to wiggle through the cracks and be exploited. One only needs to note the sale of SR9009 on Amazon to see that the issue with SARMs and their cousins persists and the confines of the WADA list often serve as a guide.

What is of greater concern to the supplement industry is not the illegitimate substances the WADA Prohibited List may inadvertently help popularize, but rather the legitimate substances that may get caught up in the broader interpretations of the language. Many WADA list categories include broad language to prohibit related substances, as in this clause: "and other substances with a similar chemical structure or similar biological effect(s)."

The muscle-building community need only consider recent adjustments to the language regarding myostatin inhibitors to see the possible implications. Myostatin inhibitors were previously prohibited as a category with few examples provided or clarification of what might be included. Modifications made in 2019 changed the category to specifically include "myostatin reducing agents" and "follistatin" as an example. These changes put epicatechins, which are common in green tea, and egg yolk-derived products that contain follistatin, at risk of being considered banned. These natural ingredients have become popular in sport nutrition products with some even certified for sport by third parties.

Many WADA list categories include broad language to prohibit related substances, as in this clause: "and other substances with a similar chemical structure or similar biological effect(s)."

The modifications to the WADA Prohibited List for 2020 may appear somewhat innocuous to the sports nutrition community at first glance, but some interesting things are worth noting.

Octodrine, otherwise known as DMHA or 1,5-dimethylhexylamine, was finally added to the WADA Prohibited List as an example. This completes the listing of the now infamous stimulant cousins that included DMAA (2009), DMBA (2018), and soon DMHA (2020). The timing of regulatory attention on these substances seems to coincide with the addition to the WADA Prohibited List. The FDA began to issue warning letters on DMAA in 2012, which persisted through 2017, while recently 11 DMHA warning letters were issued in April of 2019.

In the stimulant space, it should be noted that the WADA Prohibited List now includes "phenethylamine and its derivatives." This change was made in 2015 on the back of the stimulant revolution driven by DMAA and its cousins. The "Craze" supplement introduced dendrobium extract to sports nutrition as an alternative to DMAA, except the product really contained a close cousin to methamphetamine and amphetamine in the phenethylamine family. Unfortunately, the broad language used by WADA to address this concern could put common ingredients like cocoa extract at risk of being interpreted as banned for containing the less powerful parent substance phenethylamine itself.

The WADA 2020 Summary of Major Modification and Changes and Explanatory Notes outlines modifications to the cannabinoids wording, which was "updated for greater clarity." WADA created an uproar in 2018 when it removed CBD from the list. Here WADA states that "any preparation from cannabis" remains prohibited, while forgetting that CBD derives from the hemp form of cannabis. The language appears to both prohibit CBD and make an exception for it. Confusion remains as the minor cannabinoids commonly present in hemp and CBD products like CBN, CBG or others are still technically interpreted as prohibited. In practice, THC and synthetic cannabinoids are the targets of drug testing and only those will result in positive drug tests if relevant thresholds are breached.

It is wise to pay attention and consider what changes to the WADA Prohibited List might mean to the sports nutrition community.

Perhaps the biggest change of interest to the muscle-building community is the addition of ecdysterone to the WADA monitoring program list in 2020. The monitoring program is meant to "assess patterns and prevalence of misuse." The move opens up the possibility that ecdysteroids may be targeted more generally in the future. This action is likely based on the consideration that ecdysteroids may fill a demand for anabolic substances vacated by prohormones or SARMs. Understandable, but ecdysteroids are widespread in the natural product community and that should be considered as well.

A deeper dive on Examine.com finds that "Ecdysteroids are present in many plants (about 6% of plants in existence)." Plants that have higher levels of ecdysteroids include common ones like spinach, quinoa and yams, as well as other more unknown species like *Ajuga turkestanica*, *Rhaponticum carthamoides*, *Silene praemixta* or *Vitex scabra*.

The monitoring of ecdysterone itself could be the beginning of the WADA Prohibited List's inadvertently prohibiting an array of potentially legitimate ingredients, similar to the broad language used to address phenethylamine derivatives or myostatin-reducing agents.

As the WADA Prohibited List continues to expand and grow to include new product categories and examples, it is wise to pay attention and consider what those changes might mean to the sports nutrition community or the supplement brands that aim to provide products that meet the demand for performance enhancement while walking the fine line between prohibited and not. Further clarity can be explored in the WADA Prohibited List language to appropriately ban problematic substances while making room for legitimate ones. ✦

Oliver Catlin is president of Banned Substances Control Group (BSCG), an international third-party certification and testing provider specializing in banned substances in sport, label claims and contaminants, and GMP compliance. Originally an administrative director at the largest sport drug testing laboratory in the world, the UCLA Olympic Analytical Laboratory, Catlin has been a thought-leader in the anti-doping and dietary supplement communities for more than 15 years.

The cognitive-muscle connection

Nutrients can influence how the brain controls muscles

by Steve Myers

INSIDER's take

- The brain controls muscle movement via nerve signaling, and nutritional deficiencies can impact health and function along this brain-to-muscles axis.
- Energy in the brain is as important to muscle function as energy in muscle cells, thus energizing ingredients are important to neuromuscular function.
- In addition to diet, exercise is a top factor in neuromuscular function and premature aging, and can extend lifespan by several years.

Muscle movement is controlled by the brain and central nervous system (CNS), thus cognitive considerations exist for formulators and consumers interested in muscle function and performance. Much of what is known about this cognitive connection to muscle comes from research on muscle maladies, including sarcopenia (age-related muscle loss), and myopathies such as amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

Natural Products Insider talked to Mark Tarnopolsky, M.D., Ph.D., neurology professor, McMaster University, Ontario, Canada, about how the brain and CNS impact muscle function and how certain dietary supplement ingredients, including vitamins, minerals and creatine, may influence this connection.

Tarnopolsky has researched ingredients such as creatine and caffeine on neuromuscular signaling, performance and bioenergetics. He has also seen the impact of nutrition on his patients at the McMasters University Neuromuscular and Neurometabolic Clinic.

Natural Products Insider: Describe your experience with the brain-muscle connection, and what role, if any, nutrition plays in this relationship.

Tarnopolsky: I see lots of folks who have neuromuscular and different metabolic disorders. So, anywhere along what we call the neuraxis—from the brain, spinal cord, peripheral nerve and muscle—when someone comes with weakness or other features, we have to figure out where [along the axis] the lesion is. As part of this, we have to consider it could be a nutrition deficiency, because certain deficiencies can affect that whole transmission.

Natural Products Insider: How could such deficiencies affect a healthy, active consumer?

Tarnopolsky: Certainly, the big one is vitamin D. In the clinic, which I think is pretty reflective of the general population in North America, we find that 85% of patients are not meeting the current Canadian guidelines for vitamin D sufficiency—generally, the Canadian government is recommending that people should have 75 nanomoles per liter [nmol/L, a blood concentration unit], but I think this is more for optimal health. [Ed note: in the United States, the Institute of Medicine (IOM) has stated a level of 50 nmol/L is sufficient for more than 97% of the U.S. population.] You wouldn't notice you were lower until you get down around 25 nanomoles per liter, which is when we call it a deficiency state traditionally associated with a bone disease called rickets, which we don't see much anymore. What people didn't really recognize as much, because rickets looks so severe, is they get muscle weakness. And that's what we're seeing in the clinic.

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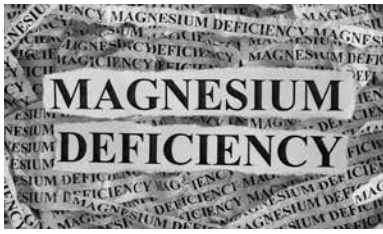
Natural Products Insider: Aren't modern consumers more aware of vitamin D deficiency?

Tarnopolsky: I think there's a lot of people out there who don't realize that their fatigue, their weakness, may be vitamin D deficiencies. It can affect muscle—there's a vitamin D receptor in muscle. When D levels are that low, we've had patients come in who look like they've got muscular dystrophy. They've got proximal muscle weakness, and their muscle enzyme, called the creatine kinase, is elevated—all the features that we see in both inflammatory muscle disease and some of our genetic disorders. Some of the folks said, "Oh, you're full of crap. It can't just be my vitamin D." But when we put them on [vitamin D supplementation], it's amazing how quickly they turn around. It's a big issue, I think, in North America, to get it checked if people are fatigued or tired. Certainly, if you're an athlete you want to make sure [D levels] are optimized, probably better than 75 nmol/L.

Natural Products Insider: What other nutrients are vital for neuromuscular health and function?

Tarnopolsky: Another big deficiency we see is vitamin B12. Deficiency frequency is higher in older adults, and we also see it in people who are vegan, vegetarian or have had, for example, gastric bypass surgery. With B12 deficiency, the first thing that people will probably notice, because it affects the peripheral nerve, is a numbness or tingling in their feet or a bit of gate instability—coordination and balance would be off. If it gets more severe, it can affect the spinal cord, the back part which [communicates] proprioception (knowing what the feet are doing). It can also affect the alpha motor neurons, which are the nerves that come from our spinal cord to our muscle. People can start getting weakness as well. If [B12 deficiency] left untreated, it affects the brain, and people can get demented. In our clinic, 13% of patients are deficient in vitamin B12.



Natural Products Insider: Minerals, such as calcium, sodium, potassium and magnesium, appear important to nerve transmission. Are mineral deficiencies common in patients you see?

Tarnopolsky: Severe copper deficiency, for example, is not that common because we have copper in water and various other food sources. But you do have to consider copper deficiency can also affect the spinal cord; people can have some stiffness and weakness of the legs. Iron deficiency, very common in females, is very important in muscle function. As for the others, there's no doubt that those are involved in the nerve and muscle transmission. But if those are out of whack, you've got some serious problems. That would not be something very common in society. You've got certain diseases such as Addison's or some salt wasting disorder, a kidney disease or similar, but those would be pretty unlikely to manifest in the general population. Even if you had a low calcium intake, your blood calcium levels are defended against quite vigorously. So even those stay pretty constant. Magnesium, if that gets really low it can affect nerve function and even neuromuscular transmission, but that's usually with a disease state where you see those things being deficient.

Magnesium, if that gets really low it can affect nerve function and even neuromuscular transmission, but that's usually with a disease state where you see those things being deficient.

Natural Products Insider: What about protein? It is well-known as crucial to muscle maintenance and building, but is there a cognitive connection?

Tarnopolsky: Being protein deficient is not the best situation, as we get older, for our muscles. It's hard to measure, but it probably has a negative effect even on your brain function if your amino acids are low and you're deficient in protein. Certainly, what we call the tea-and-toasters people, who are eating white bread with a bit of jam on it and tea or coffee, but not having good quality protein, are those most at risk for getting protein deficiency, which would manifest more as what we call sarcopenia or loss of muscle mass and weakness.

Natural Products Insider: Along with the signal transmission, energy plays a big role in this whole system, and we'd love to hear more about cognitive bioenergetics and how that pulls creatine into the mix.

Tarnopolsky: Creatine is a compound which is made in our body. Guanidinoacetate, which is made in the kidneys, is essentially a combination of arginine and glycine and eventually is converted into creatine in the liver. Creatine then is put out into the bloodstream and is taken up by creatine transporters into almost every tissue in our body—it goes into nerves, it goes into the brain. Most of it ultimately ends up in skeletal muscle because it's such a huge component of our total body mass.

Within skeletal muscle, creatine is part of the creatine-phosphocreatine system; it gets phosphorylated to become phosphocreatine, an energy store. At the onset of muscle contraction, for example, the phosphocreatine buffers the drop in [adenosine triphosphate (ATP)] for that phophoryl potential. The phosphocreatine re-phosphorylates [adenosine diphosphate (ADP)] back to ATP, and that gives you that buffer for the first nine to 10 seconds of muscle contraction, which is why sprinters were taking it.

What people have realized over the years is that optimal creatine and phosphocreatine stores are also important in nerve and brain. And there are deficiencies. For example, there's creatine transporter deficiency, where you can't bring creatine into the brain—creatine crosses the blood brain barrier but must be taken up into specific neurons. If you can't transport into the brain, kids have developmental delay and very severe disorder with seizures, as well. It shows the absolute necessity to have creatine and phosphocreatine in the body.

Natural Products Insider: Dietary sources of creatine are mostly animal, right, so what does this mean for those who eschew animal foods?

Tarnopolsky: The endogenous production by our kidneys and our livers is not sufficient to fully replenish our creatine stores. The only [dietary] sources are, essentially, eating the flesh of animals or mammals, which is where it's in really high levels. So, this means eating meat, and certainly fish—all fish have creatine and phosphocreatine, but some of the coldwater fish like herring have particularly high levels. There have been studies that have shown that vegans and vegetarians, because they're not also consuming exogenous creatine in their diet, can have lower levels of total [creatine] and phosphocreatine in muscle and the brain. There was one study that showed supplementation with creatine improved cognition in vegans, who had low levels to begin with.

Natural Products Insider: Vegans are known to monitor several key nutrients, but can creatine levels be monitored?

Tarnopolsky: Most know about B12 deficiency and making sure albumin is adequate, but creatine is not as well known or appreciated, that those levels are low. And the problem is that you can't do a blood measurement for it. I suppose a low creatinine level might be somewhat reflective of [creatine level], but it's just no substitute for doing a muscle biopsy and measuring it. Normally we have about 125 to 135 million moles per kg dry muscle mass of creatine and phosphocreatine (total creatine store). Vegans have anywhere from 95 to 105 [moles per kg], about a 25 to 30% reduction.

Natural Products Insider: What can you tell us about creatine mechanisms in the brain?

Tarnopolsky: One of its roles is to buffer this initial drop in ATP. If there was a threat to the brain—someone had a stroke, or they're having a seizure or something—that's where that energy is very important to buffer. But creatine does many other things. Studies have shown it has an antioxidant capacity. It's in such high concentrations that it quantitatively does have some antioxidant properties, if there's oxidative stress, which we know happens as we get older, or there's inflammation, for example. We also know that the creatine-phosphocreatine system helps to exchange energy more efficiently from the mitochondria (the powerhouse of your cells) out into the cytosol, which is the working part of your cells. This whole exchange system requires creatine and phosphocreatine. It's not absolutely dependent on function, but it certainly optimizes and improves that that shuttle system. There've also been studies showing some protection from low oxygen conditions, but it's hard to know exactly what the mechanism is. For example, if you had cerebral palsy and have decreased oxygen when coming out of the birth canal, there's some evidence that creatine supplementation can be helpful. The more common thing with stroke: there's a period where you have decreased oxygen supply to the brain, and some animal models have shown benefits. There are neurodegenerative disorders like Huntington's, amyotrophic lateral sclerosis (ALS) and Parkinson's disease, where some animal studies have shown that creatine can help to protect the brain under those stressful circumstances.

Natural Products Insider: Given these results, could creatine be useful in intense exercise situations, such as during oxygen deprivation from high altitude exercise?

Tarnopolsky: It's hard to say. With acute hypoxia, your buffering capacity is pretty short, a few seconds. If you're climbing a mountain, you're up there for days and days and days. Could there be some neuroprotective effect of creatine with prolonged altitude exposure? I don't know that anyone's done that study, but that's an interesting study that should be done.

Natural Products Insider: How do brain levels of creatine compare to muscle levels?

Tarnopolsky: Creatine is found in the brain, but the concentration is lower than in muscle. The brain is a lot harder to load. If you give somebody 3 g of creatine, the muscle will load, and you'll get about a 15 to 20% increase in muscle total creatine after a month. In the brain, most studies have shown that you've got to go to a fairly high level of intake. Some studies have used 20 g, and others of these 10 g to actually load brain. It takes a lot longer and the relative increase is less. The brain tends to be more resistant to creatine loading.

Natural Products Insider: Considering the role of neurotransmitters such as acetylcholine, is supplemental choline a factor in neuromuscular health?

Tarnopolsky: I really don't think that there's any evidence for that whatsoever. You know, people hand wave about choline supplementation, but there's no evidence that in a normal person neuromuscular junction (where neurons meet muscle fibers) function is in any way compromised with any type of activity. Even with fatigue, it's either central in the brain or is at the release of calcium from the sarcoplasmic reticulum or conduction block down the transverse tubule. In normal sports, we don't have neuromuscular junction fatigue.

Natural Products Insider: Anything else consumers can take or do to optimize neuromuscular function?

Tarnopolsky: The most important thing for all human beings, I think, is exercise. That's your number one thing that protects you against premature aging. It can give you an extra four-year lifespan extension (*PLoS Med*. 2012;9(11):e1001335) and, more importantly, it compresses aging. ✦

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Ingredients to help manage muscle damage, pain

by Marie Spano

INSIDER's take

- Tart cherries, curcumin, omega-3 fatty acids, MSM, enzymes, amino acids and CBD are popular solutions for minimizing muscle soreness.
- Although several ingredients are available to help support muscle recovery, many factors should be considered before developing products.
- Despite the increasing popularity of CBD, clinical research is needed to tie it to physical improvements in athletic populations.

Muscle soreness can hamper training and competition. Though the efficacious use of specific supplements can help get athletes back in the game, these products should be developed with caution. Tart cherries, curcumin, omega-3 fatty acids, methylsulfonylmethane (MSM), enzymes, amino acids and CBD are popular nutritional approaches for products that help consumers minimize muscle soreness.

How exercise affects muscle

A tough bout of training causes trauma to muscle cells. This triggers an immune system response to repair damage and remove waste products.[1] "Tissue injury leads to inflammation (to help aid healing), and this often leads to swelling, stiffness and pain receptors being sensitized—leading to pain," stated Richard Bloomer, Ph.D., dean of the School of Health Studies and the Center for Wellness and Fitness, University of Memphis. Blood supply increases, which brings immune cells in to clean up damaged muscle tissue, release free radicals (reactive oxygen species [ROS]) and produce proinflammatory cytokines which promote both injury and repair.[2,3]

"Acute exercise can lead to increased oxidative stress and inflamed tissue, particularly in untrained individuals," Bloomer said. Over time, the body adapts to recover more quickly, and a person is less sore after doing familiar exercise. Therefore, acute inflammation is not a major concern for most individuals. In fact, throwing anti-inflammatories into the mix to attenuate inflammation can do more harm than good by blunting training adaptations.

However, when soreness interferes with training or competition, consumers can look to supplemental ingredients to help minimize soreness.

Protecting muscles from excessive soreness

Tart cherry juice is rich in anthocyanins, powerful antioxidants that promote blood flow, support blood vessel functioning,[4] and block enzymes responsible for both acute and delayed inflammation.[5] In one study, two 12 oz. bottles of tart cherry juice taken daily decreased symptoms of eccentric exercise-induced muscle damage.[6] In the randomized, placebo-controlled study, those consuming a placebo experienced an exercise-induced loss of strength of 22% following a workout, while those drinking tart cherry juice lost 4% of their pre-workout strength.

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Curcumin shows promise in reducing muscle soreness, but more research is needed to determine an efficacious dose.

Tart cherry juice isn't for strength athletes only. In a randomized controlled trial, marathon runners given tart cherry juice twice daily for five days before a strenuous long-distance running event, on race day and for two days after their race, experienced significantly faster recovery of isometric strength and muscle function compared to a placebo group.[7]

Curcumin can lower inflammation by blocking several pathways, including cyclooxygenase-2 (COX-2), which is responsible for delayed inflammation. However, curcumin is poorly absorbed by the body and has very limited systemic bioavailability. Absorption and bioavailability can be enhanced with piperine or by incorporating curcumin into a lipid soluble supplement.[8] A double-blind, randomized study in young men found 1.5 g of curcumin given for 28 days prior to a muscle-damaging protocol led to lower levels of muscle soreness and lower levels of creatine kinase (CK, a marker of muscle damage) compared to placebo without affecting the natural inflammatory response.[9] In a randomized, crossover design, 2 g of curcumin combined with 20 mg of piperine or placebo was given three times per day 48 hours prior to exercise and 48 hours after a damaging bout of exercise. The supplement improved some aspects of muscle function 24 hours and 48 hours after exercise; however, it had no impact on muscle soreness.[10] Curcumin shows promise in reducing muscle soreness, but more research is needed to determine an efficacious dose.

Some research shows the omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), taken in doses ranging from 0.54 g EPA + DHA to 3.6 g EPA + DHA for two to eight weeks decreased muscle soreness in untrained individuals after a tough bout of training.[11-14] However, other studies show doses ranging from 0.36 g of EPA to 2 g DHA taken daily for three to four weeks did not effectively decrease muscle soreness in untrained individuals.[15-19] Little research has been conducted in trained individuals, though one study found large doses of EPA and DHA, 2.2 g each, taken for eight weeks prior to uphill running on a treadmill with a weight vest were ineffective in decreasing muscle soreness after a tough training bout.[20]

MSM taken daily at 3 g for 28 days prior to performing 10 sets of 10 eccentric knee extensions failed to produce any differences compared to a placebo.[21] Likewise, 3 g of MSM per day for three days before and two days after a half marathon didn't reduce markers of oxidative stress, muscle damage or pain from a half marathon.[22] One study showed study subjects experienced a decrease in muscle pain and discomfort following 3 g of MSM taken daily for 14 days prior to a bout of training. However, the study subjects performed an astounding 28 sets of leg extensions.[23]

The potential role of enzymes was highlighted in a paper looking at a multienzyme complex and delayed onset muscle soreness (DOMS).[24] In this randomized, double-blind, placebo-controlled study, 20 young healthy men were given a 50-mg multienzyme complex (alpha-amylase, cellulase, lipase, lactase and neutral protease), or placebo three times a day prior to running on a treadmill at a 10% incline for 30 minutes. Those taking the multienzyme complex found significant improvement in subjective pain and muscle tenderness. No significant difference was recorded in markers of inflammation, muscle damage or muscle flexion.

While CBD has become a popular pain reliever and anti-inflammatory with athletes as well as active and other consumers, no published research has examined CBD and muscle soreness after a bout of exercise. Scant evidence has linked CBD to chronic pain relief from a variety of conditions, with many studies using small sample sizes[25] and non-human populations[26] as well as varying types of pain experienced,[27,28,29] amount of CBD used (and at times THC was combined with CBD[30]), and method of CBD delivery[31] (patch, oral supplement, cream, etc.). According to the World Health Organization (WHO), "Bioavailability of CBD is erratic resulting in a variable pharmacokinetic profile." In addition, some indicators suggest a divide between responders and non-responders to CBD.[25]

If training sessions are diminishing in quality, recovery seems slow and an athlete is chronically fatigued, Bloomer suggested it may be best to back-off training and examine the nutrient quality of the athlete's diet. When training loads are high or an athlete performs an unaccustomed bout of exercise, tart cherry juice, curcumin and a multi-ingredient enzyme complex may be among the options to help minimize muscle soreness and aid in returning the player to activity sooner. ✦

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Gainzzzz:
The science of sleep and muscles

by Steve Myers

INSIDER's take

- Muscle growth tends to occur in late stage non-REM sleep, which is marked by slow brain waves.
- Testosterone levels rise during sleep and begin to fall upon waking, with peak levels usually around the onset of REM or deep sleep.
- Nutrients such as melatonin, theanine and protein can promote the sleep-muscle partnership, while alcohol consumption may be a dietary hindrance.

"Swoleness" (aka, developing large muscles) happens during sleep following resistance exercise. Not only is the body busy turning proteins into new muscle—muscle protein synthesis (MPS)—but it is also managing hormone levels important to muscle building. Further, lack of sleep or poor sleep quality can negatively impact the process of building new lean mass, also known as anabolism.

Sleep science

Sleep stages can be divided into one of two categories: rapid eye movement (REM) or non-REM (NREM) sleep. The body cycles through REM and NREM sleep throughout the night (or day, for some shift workers).

- **Stage 1: NREM** light transitional sleep during which the body relaxes, and both eye movement and brain waves slow.
- **Stage 2: NREM** is another period of light sleep when the heartbeat, breathing and muscle activities slow further, and body temperature drops as the body prepares for deep sleep.
- **Stage 3: NREM** is deep sleep marked by delta waves and relaxed muscles. It tends to start about 30 to 45 minutes after falling asleep. Blood flow increases, and growth hormone levels rise during this stage, helping to grow and repair tissues, including the muscles. During the November 2019 inaugural conference of the Society for NeuroSports, Jonathon Mike, Ph.D., professor of exercise science and sports performance, Grand Canyon University, Phoenix, noted the final "slow wave" stage of NREM sleep is when muscle gains and performance benefits are developed. He called sleep the "single most effective strategy for recovery from exercise."
- **Stage 4: REM** sleep often begins around 90 minutes after falling asleep. While the muscles are practically paralyzed, brain activity ramp back up to near wakefulness levels, respiration speeds up, and eyes move rapidly from side to side behind closed eyelids. This stage is when most dreams occur. When REM sleep spills into other stages of sleep, the conscious body can become aware of sleep paralysis that protects from acting out during REM sleep, but which can be alarming during wakefulness.

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Hormonal slumber

Research on muscle growth and testosterone, naturally occurring or supplemental, has been mixed. Testosterone and human growth hormone (HGH) are anabolic and rise after resistance or high-intensity exercise, but this short-term boost may not alter muscle building mechanics.[1]

"While testosterone is definitely anabolic, and promotes muscle growth in men and women at high doses, such as those used during steroid abuse, our findings show that naturally occurring levels of testosterone do not influence the rate of muscle protein synthesis," said researchers from McMasters University, Ontario, Canada, who looked for any differences in muscle growth between men with varying post-exercise levels of testosterone and HGH.[2]

The key to muscle growth sparked by anabolic hormones may be the number of androgen receptors in muscle tissue, as testosterone interacts with muscle via these receptors.[3]

Still, whether an athlete or consumer believes boosting testosterone will accelerate and amplify muscle growth, most would at least prefer to maintain and not reduce their normal testosterone stores. This is why good, regular sleep is important.

Testosterone levels rise during sleep and fall during wakefulness.[4] Peak testosterone levels occur around the onset of REM sleep, according to research reviewers, who noted decreases in both sleep efficiency and frequency of REM episodes lower concentrations of circulating testosterone, especially in older men.[5] Sleep apnea is another testosterone reducer, they reported. Other researchers reported disruption of slow-wave (aka delta) sleep, such as with chronic sleep problems, increases the risk of developing long-term androgen deficiency, according to research in young men.[6]

Sleep deprivation devastation

Beyond hormonal consequences, inadequate sleep may also alter cytokines (signaling molecules) involved in skeletal muscle recovery following resistance or eccentric exercise, according to published research online in August 2019.[7] A 2018 review of published research found, "sleep deprivation had little effect on muscle strength during resistance exercise, … [but] consecutive nights of sleep restriction could reduce the force output of multi-joint, but not single-joint movements."[8]

Cheri D. Mah, researcher at the Stanford Sleep Disorders Clinic and Research Laboratory, California, and her team conducted a series of studies on sleep restriction in athletes. They found three days of sleep restriction in elite athletes decreased maximal jump performance and impaired both joint coordination and reaction time, all of which increase injury risk.[9] On the other hand, sleep extension in athletes may improve cognitive and motor function, as their study of basketball players found adding a couple of hours of sleep each night improved reaction time, basketball skill performance and even mood.[10]

Beer muscles

Recent research detailed how chronic and binge alcohol consumption negatively alters circadian rhythm.[11] Further study on the neuromuscular impact of drinking found acute alcohol intake and just one night of sleep deprivation reduced quadriceps muscle activation, but had no significant influence on neuromuscular performance.[12]

Exercise and nutrition researcher Matthew Barnes, Ph.D., deputy head of the School of Sport, Exercise and Nutrition, Massey University, New Zealand, reported acute alcohol

consumption may impair exercise recovery and increase skeletal muscle injury risk by negatively altering normal protein synthesis, as well as blood flow and immunoendocrine function.[13]

"The impact alcohol has on recovery and sports performance is complicated and depends on many factors, including the timing of alcohol consumption post-exercise, recovery time required before recommencing training/competition, injury status and dose of alcohol being consumed," he concluded.

While Barnes referred to research in men, a University of North Texas, Denton, study on women found no such impact on recovery from acute alcohol consumption following resistance training, suggesting a gender difference.[14]

Another bit of evidence from this study team to consider: Post-exercise alcohol consumption can negatively affect resistance exercise-induced phosphorylation of the mTORC1 signaling pathway, which is a key mechanism of muscle building.[15] The kicker here, for male athletes, is the coed study found improved mTORC1 response in both genders following resistance exercise, but the negative effect of alcohol consumption may only impact muscular adaptions in men.

Sleep solutions

Several natural ingredients have shown promise as sleep support nutrition, including "clock-shifter" melatonin, soothing tea compound L-theanine, neurotransmitter gamma-aminobutyric acid (GABA) and the stress adaptogen ashwagandha. Likewise, the popular consumption of caffeine in beverages and pre-workout supplements can challenge sleep if taken too close to bedtime.

Protein taken before bed may increase MPS during sleep. Tim Snijders, Ph.D., assistant professor, and his team from Maastricht University, The Netherlands, reported in 2015 how healthy young men ingesting a protein supplement (27.5 g of protein, 15 g of carbohydrate and 0.1 g of fat) each night before bed had increased muscle mass and strength gains following resistance exercise, compared to a placebo group.[16]

This team subsequently found pre-sleep protein does not negatively impact the ability of protein ingested the following morning to stimulate MPS.[17] Compared to "fast acting" whey, casein is a "slow-acting" protein and ideal for pre-sleep ingestion. The Maastricht researchers showed healthy males ingesting 30 g of casein before sleep and following evening resistance exercise "improves whole body protein net balance and provides amino acids that are incorporated into myofibrillar protein during sleep."[18] However, adding free leucine to this pre-sleep protein supplementation did not increase MPS rates during post-exercise overnight recovery.

Several natural ingredients have shown promise as sleep support nutrition, including "clock-shifter" melatonin, soothing tea compound L-theanine, neurotransmitter GABA and the adaptogen ashwagandha.

Snooze button

The exploration of sleep and muscle development and performance is in early stages. As researchers find out more about how sleep and muscle mechanisms interact, as well as how nutrients and other dietary ingredients may promote improved sleep and bigger, stronger muscles, sports nutrition formulators will have more confidence in offering products to athletes and active consumers that support slumber and muscle. In the meantime, hitting the snooze button on this emerging area of sports nutrition research is not necessary, as consumers are increasingly tuned into the importance of sleep and are looking for products to catch more z's and gainz. ✦

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Chiseling away at the muscle supplement market

by Steve Myers

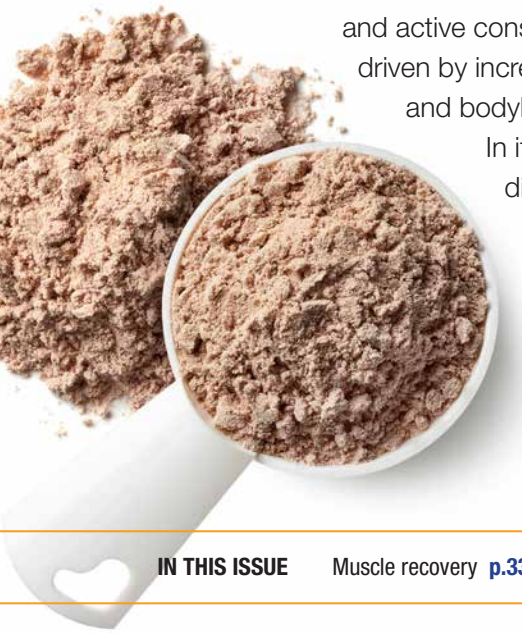
There are many ways to sculpt a muscular body. Following the Bronze Age, sculptors made human forms from marble. One of the most famous, Michelangelo, is credited with saying, "The sculpture is already complete within the marble block, before I start my work. It is already there, I just have to chisel away the superfluous material."

This is not always the literal case in humans, although some former athletes still have strong abs under fat. However, the template for building muscle is in each body just waiting for the right nutrition and exercise to free it from its imprisonment, a la Michelangelo.

As detailed in "The art and science of human muscle development" (page 6), liberating the muscle requires energy to move muscle fibers and amino acids to repair and build muscle stressed by exercise. Considering this foundation, dietary protein is the primary nutritional tool to supply the necessary amino acids to muscle, while creatine has emerged as a leading energy ingredient that can be stored or loaded in the muscle.

Dietary protein has enjoyed a surge in popularity in recent years, as consumers are more interested in body composition (fat vs. lean body mass), satiety and limiting other macronutrients such as carbohydrates.

"The demand for protein supplements from the young population is increasing mainly in athletes as they provide various benefits such as lowering cholesterol, building of muscles, increasing strength, fighting cancer, improving immunity and lowering blood pressure," reported Allied Market Research, in a 2019 report.



The market research firm further noted protein powder products, popular with athletes and active consumers, are expected to reach a market size of US$5.33 billion by 2025, driven by increased health consciousness as well as continuing demand from athletes and bodybuilders.

In its 2019 third-quarter global survey of active consumers, FMCG Gurus discovered that among the health issues consumers want to improve over the next 12 months, strength was No. 1, with 57% of respondents.

Body composition is a perennial health target for many people, and FMCG's survey found 50% are eager to improve their ratio of fat-to-lean mass (muscle), making it fifth on the survey's list; 44% of all respondents specifically called out lean body mass/muscle as a desired area to improve.

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Animal proteins, namely whey, still dominate the protein scene, with isolate a leading type and hydrolysates and concentrates also popular. Grand View Research reported the global whey protein market hit $7.4 billion in 2018 and should grow about 8.1% through 2025. As a fast protein, whey is commonly taken during short windows before and after exercise, whereas the slower acting casein protein is often taken at night.

Plant protein certainly is making a strong move in the sports nutrition market, estimated to reach $7.7 billion globally by 2025, according to Grand View, which predicted a 7.9% growth rate. "Rising concerns regarding the consumption of animal protein supplements has encouraged manufacturers to develop human nutrition products derived from soy, spirulina, pumpkin seed, hemp, pea, and rice among other plant-based sources," the firm noted.

While protein is popping up in all types of foods, ready-to-drink (RTD) beverages are a big deal in sports nutrition, and protein is starting to grab share in the sports drink market. At SupplySide East 2019, Holly McHugh, analyst with beverage consultant Imbibe Inc., said protein products and branched chain amino acid (BCAA) recovery beverages are popular for muscle gain and are popping up in mixes, shakes, waters, and various plant-based and dairy-based drinks, offering consumers many options.

On the plant front, she reported hemp protein is gaining popularity because of the general buzz about hemp and cannabidiol (CBD), as well as due to its other benefits such as high fiber content. "Overall it doesn't have as rich of an amino acid profile as pea and brown rice protein, so it's often used in combination with those [plants]," she noted.

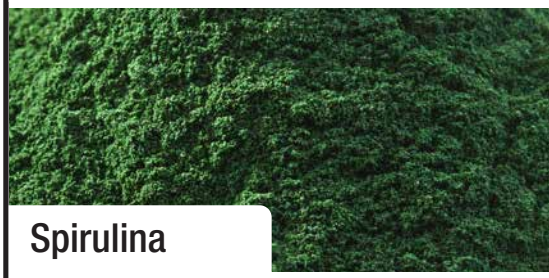
McHugh said other popular sports drink ingredients, including in muscle-focused formulations, are creatine, BCAAs and beta alanine, a precursor to muscle fatigue-inhibitor carnosine.

BCAAs are the essential amino acids (EAAs) leucine, isoleucine and valine, and they are touted for triggering muscle protein synthesis (MPS), the process of building new muscle. "When analyzing the effect of different amino acids on MPS, essential amino acids (EAAs) outperform nonessential amino acids, and the [BCAA] leucine seems to play a key role," wrote Ralf Jäger, co-founder of Increnovo (page 10).

Creatine is stored as a phosphate in the muscles. After adenosine triphosphate (ATP) loses a phosphate to create energy, creatine can provide the phosphate to regenerate ATP for continued energy, helping consumers work out longer and harder. As Jäger noted, however, there is some evidence creatine might activate the mechanistic target of rapamycin (mTOR) pathway that helps signal MPS (page 11).

Plant protein certainly is making a strong move in the sports nutrition market


Soy


Spirulina


Pumpkin seed


Hemp


Pea


Rice

Creatine is a triple threat, contributing not only muscle energy and growth, but also playing a role in the central nervous system's mission control of muscles. As neuromuscular expert Mark Tarnopolsky, M.D., Ph.D., a professor at McMasters University, Canada, explained (page 27), creatine is taken up by creatine transporters in almost every tissue in the body; most creatine goes into skeletal muscles, but it also enters the nerves and brain.

"Optimal creatine and phosphocreatine stores are also important in nerves and brain," he advised. "Creatine crosses the blood brain barrier but must be taken up into specific neurons." He said it is tougher to load the brain, compared to the muscle, so higher levels may be needed. A deficiency can contribute to neuromuscular and neurometabolic problems, he noted, adding vegans and vegetarians are especially at risk, as dietary creatine comes from animal foods and body levels aren't commonly or easily monitored.

Creatine's foray into RTDs has not been as easy or quick as for protein. According to McHugh, a consideration when formulating beverages with creatine is that it's usually sold in a powder because of challenges with solubility, but brands like Bang have successfully developed products with creatine in an RTD. "Our RTD team says that it takes some formulating work to keep it suspended in certain beverages and may have a sediment in the beverage," she noted.

Another trend with these ingredients in beverages is to formulate multiple benefits, not just muscle development. Benefits on body composition, energy and cognitive function are all complementary with muscle drinks. For example, McHugh highlighted LifeAid's FitAid drink, which combines BCAAs, omega-3s, coenzyme Q10 (CoQ10), magnesium, green tea and B-12, thus it helps with power/energy and muscle gain, focus and weight loss.

Vitamin B12 is another deficiency, along with vitamin D, that can spark neuromuscular problems, according to Tarnopolsky, while omega-3 fatty acids can promote muscle recovery from the stress of exercise.

The omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may help limit muscle soreness, although research using different doses has produced mixed results (page 31). Omega-3s are anti-inflammatory and join other dietary ingredients in targeting the inflammation and oxidative stress that needs to be managed properly to encourage muscle adaptations following exercise.

Curcumin is a popular anti-inflammatory but suffers bioavailability challenges, however enhancing formulas with piperine can boost muscle function benefits. Tart cherry is another anti-inflammatory with growing evidence for muscle recovery and protection, but the buzz leader CBD is still low on evidence in sports recovery, despite its widespread use for pain relief.

Good sleep is also a recovery solution. Sleep is restorative, and lack of sleep can curtail muscle recovery (page 33). Muscle enthusiasts may care that body levels of growth hormones, including testosterone, rise during the late stages of non-REM (rapid eye movement) and fall upon waking. Decreases in both sleep efficiency and REM (aka deep sleep) cycle frequency can lead to lower circulating hormone levels.

A trend in beverages is to formulate for multiple benefits, not just muscle development. Benefits on body composition, energy and cognitive function are all complementary with muscle drinks.

Sports nutrition and other consumers are tuning into this sleep issue, as the FMCG Gurus global survey revealed 47% of active consumers are looking to improve their quality of sleep. There are several promising supplements to promote sleep including "clock-shifter" melatonin, soothing tea compound L-theanine, neurotransmitter gamma-aminobutyric acid (GABA) and the stress adaptogen ashwagandha. However, caffeine and alcohol are possible detriments to sleep onset, quality and duration, thus could be a challenge for muscle building.

Hormones may be important to muscle development. Research shows testosterone interacts with insulin growth factor (IGF) to promote MPS (*J Clin Endocrin Metab.* 2000 April;85(4):1627-1633). Testosterone boosters are popular with some bodybuilders and other hardcore athletes, and some evidence shows testosterone can improve body composition and physical performance, as well as reaction time, sexual function and mood (page 17).

Tribulus terrestris, Tongkat ali (also known as *Eurycoma longifolia*), ashwagandha, D-aspartic acid and fenugreek are on the list of promising testosterone boosters, however research is mixed, and the strongest impact may be on specific populations, such as those with low hormone levels.

"Although research indicates the potential of these ingredients, most of the research does not support changes in testosterone levels in healthy individuals, especially those who are resistance trained," wrote Vince Kreipke, scientific advisor at Onnit Labs.

"Promise" is also the keyword for blood flow boosters, which are theorized to increase circulation and delivery of important muscle-building and -protecting ingredients. Increased blood flow promotes muscle hypertrophy and cellular swelling directly; it also may help delay fatigue and allow for increased training volumes and/or recovery, therefore potentially leading to enhanced muscle growth and function indirectly, explained Doug Kalman, Ph.D., R.D., and Susan Hewlings, Ph.D., R.D., of Nutrasource (page 14).

The root of vasodilation (opening of blood vessels) is nitric oxide (NO), which is made in the body from the amino acid arginine. As a supplement, arginine has suffered absorption issues, but novel solutions such as combining argine with inositol, silicon or citrulline are demonstrating an ability to raise arginine and NO levels in active consumers, leading to muscle-related benefits, Hewlings and Kalman noted.

Dietary nitrites and nitrates can also increase NO levels, and plants such as beetroot have been researched for improvements to muscle contraction, speed and power, as Kalman and Hewlings reported. They noted pomegranate has also shown promise in boosting blood flow and inhibiting fatigue in men and women, as well as boosting power output in resistance-trained men.

They concluded several such ingredients may support or enhance muscular growth and function in both athletes and nonathletes, however "more research should be conducted to explore the efficacy of multi-ingredient products in an effort to capitalize on the multiple mechanisms that contribute to muscular growth via enhanced blood flow."

Given these many approaches to chiseling a well-performing muscular physique, formulators have many ingredient tools to wield. Sports drinks are atop active consumers' wish lists, as shown in the FMCG Gurus survey, but some muscle-related ingredients can pose stiff challenges to making a tasty, aesthetically appealing beverage that offers numerous sports benefits. Bars and foods also present areas of opportunities, and powder-based supplements are steady performers. Another consideration for formulators in the muscle area is banned substance certification, which carries some weight even with athletes and consumers who are not in drug-tested sports.

As Oliver Catlin, president of the Banned Substance Control Group (BSCG), pointed out (page 21), the broad language used to establish the World Anti-Doping Agency (WADA) Prohibited List can bring negative consequences to otherwise legal dietary ingredients.

In the case of CBD, WADA prohibits "any preparation from cannabis," on one hand, but allows for CBD use on the other. For ecdysteroids, which are widely used in the sports nutrition market, the addition of muscle-building ecdysterone to the WADA monitoring program list in 2020 could spell trouble in the future for some plant-derived versions otherwise legitimate as dietary ingredients.

Finally, WADA is guilty of being too vague with describing prohibited classes of ingredients such as myostatin inhibitors—myostatin can limit muscle growth. Initially, WADA provided few examples of banned myostatin inhibitors, but its 2019 modifications highlighted "myostatin reducing agents" and follistatin among those banned from sport. Without further clarification, various legal dietary ingredients that contain follistatin or reduce myostatin may be at risk of being considered banned, such as egg yolk-derived products and epicatechins (e.g. tea, cocoa), respectively.

The bottom line is the market for muscle growth and function is full of potential, but also potholes. While a few ingredients like protein and creatine stand out as well researched, most of the ingredients promising to activate mTOR, flood muscles with nutrient-rich blood, beef up hormone levels, promote shut-eye for overnight gains, and protect muscles from inflammation and oxidative stress, all in the name of building muscle and improving muscle performance, are seeing mixed results and/or are in research infancy. Still, this is a market where consumers are looking for an edge and don't mind being out in front of the research curve, so brands can sell promise in this market. ✦

Inside Insider

Q. What are some of your health and nutrition strategies for building muscle?

A. A common strategy I have been using for many years is consuming whey protein post-workout to promote muscle growth. I have also recently added BCAAs to my pre-workout regimen.

Anthony Arteca
Senior account executive

A. When trying to build muscle, I lift weights three days a week—lower reps with heavier weight. I also drink protein (I use BPN Whey Protein) within 30 minutes after working out.

Cassie Jensen
Marketing specialist

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