

Natural Testosterone, Sex Drive Optimizer, and More



TestoBoost is a safe and effective way to significantly optimize your own natural testosterone production and spermatogenesis.

TestoBoost is by far the most powerful natural testosterone, libido, and sex drive optimizer on the market today. Because of its complex formulation, it offers beneficial effects on health, fertility, body composition, longevity, and physical and mental performance.

TestoBoost information updated December 16, 2023 by Mauro Di Pasquale, B.Sc. (Hons), M.D. <u>https://metabolicdiet.com/product/testoboost/</u>

All my nutritional supplement products are at https://metabolicdiet.com/shop/

TestoBoost is manufactured by GMP Laboratories in California, a GMP and NSF certified pharmaceutical grade facility.

Version VI of TestoBoost is the sixth reformulation of the original TestoBoost, which came out in February of 2002. Each version has been improved by considering new research, my own clinical work, and feedback from those who use it.

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

Table of Contents

TestoBoost and Covid-194
TestoBoost Version VI contains a unique formulation that will:
The TestoBoost Controversy5
The Use of TestoBoost Will Not Result in a Positive Drug Test!
Normal Testosterone Levels Are Not the Same for All Ages
What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old
Abstract
TestoBoost Imposters9
Just What Does TestoBoost Do?10
TestoBoost and Testosterone Replacement Therapy11
Nutrition Panel for TestoBoost version VI12
The Hypothalamic-Pituitary-Testicular Axis (HPTA)13
The Assault on Testosterone14
Who Uses TestoBoost?16
History of TestoBoost17
Why TestoBoost is Better than the Prohormones, Selective Androgen Modulators, Testosterone, and Anabolic Steroids18
Prohormones18
Replacement Therapy with Testosterone and Anabolic Steroids
The Relatively New Kids on the Block21
Why Using TestoBoost is Beneficial Even for Those on Exogenous Hormones
New Version of TestoBoost23
My reasons for reformulating include:23
Changes in TestoBoost Version VI24
Ingredients in TestoBoost version VI24
Vitamin A and Beta Carotene25
Vitamin B6 (Pyridoxine)26
Vitamin B12
Antioxidants
Vitamin D
Aromatase Inhibition by Vitamin D and Other ingredients in TestoBoost
Vitamin D and the Covid-19 Pandemic31

Magnesium31
Zinc
Manganese
Coenzyme Q10 (ubiquinone-10, CoQ10)34
Astaxanthin35
Boron
Saw Palmetto
Eurycoma Longifolia (Longjack, Tongkat Ali, Pasak Bumi)
Acetyl-L-Carnitine
5-Methyl Methoxy Isoflavone
Tribulus Terrestris Extract
Muira Puama
Phosphatidylserine40
Genistein40
Prickly Pear Extract *
Schisandra Chinensis41
Chrysin41
Cordyceps Sinensis41
Avena Sativa (Oat Wheat Straw)41
Curcumin
Alpha Lipoic Acid43
Bioperine43
The Advantages of Bioperine®43
Truth in ancient wisdom43
Arginine and Citrulline44
L-Citrulline Malate46
L-Arginine Alpha-Ketoglutarate46
Too Much Nitric Oxide Production Can Be Counter Productive47
Nitric oxide potently inhibits the rate-limiting enzymatic step in steroidogenesis
Testosterone-induced modulation of nitric oxide-cGMP signaling pathway and and and or solve and and and solve and and solve and so
Is steroid deficiency the cause of tolerance in nitrate therapy?

Decreased steroid hormone synthesis from inorganic nitrite and nitrate: studies in vitro and in vivo	51
D-Aspartic acid and nitric oxide as regulators of androgen production in boar testis5	2
D-Aspartate5	2
D-Aspartic acid stimulates steroidogenesis through the delay of LH receptor internalization in a mammalian Leydig cell line5	53
The role and molecular mechanism of D-aspartic acid in the release and synthesis of LH and testosterone in humans and rats5	54
D-Aspartic acid: an endogenous amino acid with an important neuroendocrine role5	4
Involvement of D-aspartic acid in the synthesis of testosterone in rat testes	5
What Can You Expect from TestoBoost version VI?5	6
Health Benefits and Protective Effects of TestoBoost5	7
NitAbol5	8
References5	8

TestoBoost and Covid-19

Recent studies have found that low testosterone levels could increase the chances of being infected and could be a cause for a poor prognosis following a positive SARS-CoV-2 test.¹²³⁴⁵⁶⁷

A recent study shows that COVID-19 itself depletes testosterone.⁸ Another recent study found that SARS-CoV-2, the virus that causes COVID-19, can infect the testes, and decrease levels of testosterone and affect fertility.⁹

In summary several studies have shown a correlation between low testosterone levels and increased morbidity and mortality.¹⁰ From all the studies it's apparent that normal levels of testosterone in men is paramount in fighting the present pandemic.

In my view it's a combination of the beneficial effects that testosterone imparts, including its obvious anabolic effects that strengthen the body overall and thus make it more resistant to disease. As well, testosterone has specific beneficial effects including, but not limited to, bolstering the immune system, anti-inflammatory effects, protective effects on the central nervous system and mitochondrial function, and neuroprotective effects.¹¹¹²¹³¹⁴

The bottom line is maintaining testosterone levels in the normal range for their age (see below under **Normal Testosterone Levels Are Not the Same for All Ages**) helps men to counter the testosterone lowering effects of SARS-CoV-2, both decrease the changes of getting infected, and decreasing the morbidity and mortality associated with the Coronavirus.

This is where TestoBoost comes in by optimizing testosterone levels naturally and keeping levels within the normal range regardless of the reasons your testosterone levels are compromised.

As well, many of the ingredients in TestoBoost have beneficial effects on morbidity and mortality. Some of these effects are also outlined below.

TestoBoost Version VI contains a unique formulation that will:

- Optimize both free and total testosterone, androgen receptors in skeletal muscle, brain, and other organs and tissues, and the binding of testosterone to the androgen receptor regardless of age, even in younger men¹⁵
- Provide a potent natural anabolic effect to improve body composition, muscle mass, strength, and physical and mental performance
- Optimize libido, sex drive, sexual performance, and fertility in both men and women
- Decrease, inappropriate, excessive estrogen production
- Decrease inappropriate, excessive production of dihydrotestosterone
- Promote improved health, energy, immunity, and well-being
- Help prevent lowered testosterone levels due to aging, stress, poor lifestyle choices, and parasitic, bacterial, and viral infections including coronaviruses such as the current SARS-CoV-2.
- Enhance prostate health
- Increase bone density
- Improve cognitive function and decrease mental and physical decline
- Decrease inflammation, a primary driver for metabolic and endocrine disruptions, and ill health

The TestoBoost Controversy

Before I go into more detail about the beneficial effects of TestoBoost on optimizing testosterone levels and doing much more to improve body composition, mental and physical performance, and health, there's a matter that's been festering around TestoBoost for more than a decade.

And it's still going on as WADA tries to prove allegations about Salazar and his medal winning IOC athletes Galen Rupp and Mo Farah. You can read about it at https://metabolicdiet.com/wp-content/uploads/2017/product_pdf/TestoBoost_Salazar.jpg. As an aside Salazar's athletes used my line of nutritional supplements for many years.

What I find ridiculous in this article is the statement by Dr. Rabin, referred to as the mosteminent expert in anti-doping, which BTW he's not. I started writing and being involved on all issues concerning drug use in sports before the 1976 Olympics in Montreal, Canada and was

writing articles and books and initiating drug testing programs in various sports before he was out of high school.

I was also a certified Medical Review Officer for several years (<u>https://www.mrocc.org/</u>) and even gave the presentation on ergogenic aids, including anabolic steroids and growth hormone, at one of my certification renewal symposiums over two decades ago.

Dr. Rabin states that my approach with TestoBoost, optimizing testosterone levels by negating any negative factors that are lowering both total and free testosterone in the body, and optimizing natural testosterone levels in both men and women is the "wrong approach."

He goes on to state "At WADA we say if you supplement these hormones, in particular testosterone, to bring it back to a level when you were 20 years old, this is cheating, because you are boosting your testosterone level and your muscles benefit from this boosting."

What he's saying is beyond ridiculous. First of all, who ever said that TestoBoost brought testosterone levels back to when you were 20 years old. What it does is optimize testosterone levels for whatever age group you're in and result in testosterone levels optimal for your current age group. It doesn't optimize testosterone levels of a 40-plus year-old to the raging levels of when he was decades younger.

What follows if we take his stance a bit further? Just how far can you go before the banned list becomes more of a farce than it already is when at present WADA bans compounds and methods for which they have no way of testing, and is unaware of some compounds and methods to enhance performance that are presently in use?

Supposedly, WADA and other drug testing agencies are put in place to create an even playing field. So, are they contemplating standardizing how much protein you're allowed to use to increase performance because of the same reasoning? How about advanced training techniques under knowledgeable coaches since other athletes don't have the resources to use them because of location and/or cost?

How about banning nitrate containing foods such as beets, spinach, and celery, or even extracts of these foods as nutritional supplements as they've been shown to enhance exercise performance? And what about banning some of the many dietary and lifestyle methods that can be used by aging athletes to offset some of the adverse effects of aging and/or poor prior lifestyles thus optimizing their performance?

A recent study found that the usual level used to determine testosterone deficiency shouldn't be one size fits all. Low normal levels in younger men may mean that they're testosterone deficient whereas the same levels in older men may be within the normal range.

But I digress.

The Use of TestoBoost Will Not Result in a Positive Drug Test!

Let me assure you that the use of TestoBoost is 100% legal under 2020 WADA/IOC guidelines (see <u>https://www.wada-</u> <u>ama.org/sites/default/files/wada_2020_english_prohibited_list_0.pdf</u> and <u>https://www.wada-</u> <u>ama.org/sites/default/files/wada_2020_english_summary_of_modifications.pdf</u>).

TestoBoost optimizes endogenous testosterone correcting anything that may be involved in decreasing natural optimal testosterone production usually through factors impacting on the hypothalamic-pituitary-testicular axis and androgen receptor number and binding. There are many factors that have a negative effect on natural testosterone production including pollution, stress, a lifestyle that may not be optimal, and tendencies towards recovery problems and injuries.

TestoBoost does not contain testosterone, any other hormones, peptides, SARMs, or any banned substance. It does not result in supraphysiological levels of testosterone or testosterone precursors. What it does is to allow your body to reach its natural and optimal potential for endogenous testosterone production.

I formulate my nutritional supplements, all of which are manufactured in a pharmaceutical grade laboratory that is both GMP and NSF certified, to produce certain desired effects that allows any athlete or anyone who exercises, or even wants to optimize health, and/or body composition and/or physical and mental performance, to be the best that they can be by dealing with any personal and even genetic issues (through epigenetic mechanisms) that may get in the way of their goals.

I consider my supplements as distinct and unlike any of the other nutritional supplements on the market today. My supplements can be considered as targeted super foods since each product in my supplement lineup contains several dozen evidence-based ingredients picked by me to work synergistically and additively, including many extracts that contain many ingredients on their own, to achieve specific results.

As far as positive doping violations, no drug tested athlete using TestoBoost, or any of my nutritional supplements, has never had a positive drug test and no athlete ever will.

There are several ways that I made sure that TestoBoost version VI and other nutritional supplements in my product line, are safe for drug tested athletes. The first is that I have TestoBoost, GHboost and all other supplements manufactured in a pharmaceutical level facility that is GMP and NSF certified. Each ingredient and the final product are tested to make sure they are safe to use and contain no contaminants that would result in a positive test.

Rather than have a third party check the final products, I use a more direct method by having a half dozen athletes use the product at or above suggested levels for two weeks and then have their urine and blood tested in a laboratory using WADA/IOC standards of detection. All

the results showed that all my products, including TestoBoost version VI are 100% safe for drug tested athletes.

As an aside I discovered from an acquaintance at WADA that TestoBoost, along with GHboost and the rest of my MD+ nutritional supplement products, have been tested by WADA/IOC in the past few years and their testing found no banned substances thus adding to the fact that all my supplements are completely safe to use for drug tested athletes.

Normal Testosterone Levels Are Not the Same for All Ages

Are normal testosterone levels applicable to all ages? The answer is no and what's normal for the elderly is not normal for those that are younger, especially in the first 40 years of life.

As such testosterone levels that fall within the accepted one size fits all range may not be normal in all age groups. For example, a younger athlete that has testosterone levels in the "normal range" may actually have lower levels of testosterone than is optimal for him or her. TestoBoost optimizes natural testosterone levels to levels that are normal for all age groups.

Zhu A, Andino J, Daignault-Newton S, Chopra Z, Sarma A, Dupree JM. What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old. J Urol. 2022 Dec;208(6):1295-1302. doi: 10.1097/JU.00000000002928. Epub 2022 Oct 25. PMID: 36282060.

What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old

<u>Alex Zhu 1</u>, <u>Juan Andino 1</u>, <u>Stephanie Daignault-Newton 1</u>, <u>Zoey Chopra 2</u>, <u>Aruna Sarma 1</u>, <u>James</u> <u>M Dupree 1</u> Affiliations expand

- PMID: 36282060
- DOI: <u>10.1097/JU.00000000002928</u>

Abstract

Purpose: There is an age-related decline in male testosterone production. It is therefore surprising that young men are evaluated for testosterone deficiency with the same cutoff of 300 ng/dL that was developed from samples of older men. Our aim is to describe normative total testosterone levels and age-specific cutoffs for low testosterone levels in men 20 to 44 years old.

Materials and methods: We analyzed the 2011-2016 National Health and Nutrition Examination Surveys, which survey nationally representative samples of United States residents. Men 20 to

44 years old with testosterone levels were included. Men on hormonal medications, with a history of testicular cancer or orchiectomy, and with afternoon/evening laboratory values were excluded. We separated men into 5-year intervals and evaluated the testosterone levels of each age group, and for all men 20 to 44 years old. We used the American Urological Association definition of a "normal testosterone level" (the "middle tertile") to calculate age-specific cutoffs for low testosterone levels.

Results: Our final analytic cohort contained 1,486 men. Age-specific middle tertile levels were 409-558 ng/dL (20-24 years old), 413-575 ng/dL (25-29 years old), 359-498 ng/dL (30-34 years old), 352-478 ng/dL (35-39 years old), and 350-473 ng/dL (40-44 years old). Age-specific cutoffs for low testosterone levels were 409, 413, 359, 352, and 350 ng/dL, respectively.

Conclusions: Diagnosis of testosterone deficiency has traditionally been performed in an ageindiscriminate manner. However, young men have different testosterone reference ranges than older men. Accordingly, age-specific normative values and cutoffs should be integrated into the evaluation of young men presenting with testosterone deficiency.

TestoBoost Imposters

My TestoBoost has been so successful and used over the last two plus decades by just about anyone who is interested in its beneficial health, anabolic, body composition, and physical and mental performance that over the years imposters by the hundreds have tried to usurp its mantle of success, primarily as a testosterone booster.

These feeble and useless imposters use names that are the same or almost identical to TestoBoost (for example making the B in lower case, putting the name all in capital letters, putting a space between Testo and Boost, putting the name all in capitals - TESTOBOOST), or simply marketing their ineffective products as testosterone boosters.

A real-world example you can try is to Google TestoBoost. When you do you won't find my TestoBoost in any of the results. There's a reason for that and it has to do with Google's greed with their monopoly on presenting the results that pays them the most money. I don't advertise through Google or use any other means to promote my products.

Unlike myself, nutritional supplement companies aggressively market these products in many ways beyond paying for their "space" in the Google machine, including phony before and after pictures, hyped up but false information, trumped up testimonials, and other devious ways to make their product look effective. For more info on how some supplement companies try to deceive have a look at my article <u>Lies</u>, <u>Lies</u>, <u>and Damn Lies</u>. Research to those pushing these imposters is merely a tool to be misused by tainting the results to suit their products. For more info have a look at an article I wrote several years ago and updated last year on testosterone boosters.

Just What Does TestoBoost Do?

TestoBoost (the latest version VI - see Nutritional Panel below) does just what its name suggests, it boosts or more accurately optimizes testosterone levels in both men and women. But it doesn't optimize testosterone levels by providing hormones or prohormones, it optimizes testosterone by natural mechanisms so that anyone can achieve their individual, unique, optimal testosterone levels and optimal androgen receptor number and binding.

TestoBoost works in many ways. One is by directly stimulating testosterone production to optimal levels for everyone regardless of their age or sex. It does this by downplaying negative influences that decrease the endogenous production of testosterone by their adverse effects on one or more areas in the hypothalamic-pituitary-gonadal axis (the hypothalamic-pituitary-testicular axis [HPTA] in men), the natural testosterone making machinery in both men and women.

TestoBoost does this by optimizing the release of gonadotropin releasing hormone and luteinizing hormone (LH), with the latter released by the pituitary to stimulate testosterone production by the gonads, testicles in men and ovaries in women. It also affects the feedback mechanisms that dictates when to increase or decrease testosterone production so that the direction of the HPTA encourages the increased production (the downward arrows in the illustration below) and discourages the feedback mechanisms (the upward arrows) that would decrease testosterone production.

TestoBoost counters the testosterone lowering effects of internal (lifestyle, diet choices, sleep disorders, overreaching and overtraining, and expected and unexpected stress) and environmental stressors including endocrine disrupting microelements and chemicals, indoor and outdoor air pollution, heavy metal exposure (for example Ginkgo biloba – in Joint Support - has been shown to help prevent lead testicular dysfunction¹⁶) and even exposure to Wi-Fi radiation.¹⁷¹⁸¹⁹²⁰

For example, studies have shown that resveratrol, and the B vitamins in TestoBoost, can counteract some of the detrimental effects of environmental pollution especially first, second, and third hand cigarette smoke and air pollution from several other sources including the burning of fossil fuels and organic material.²¹²²²³

TestoBoost also optimizes the peripheral production of testosterone. However, this machinery is more important in women than men since ovarian production of testosterone is low and as such peripheral testosterone production can be important, while in healthy men testicular production of testosterone can be said to account for essentially all their testosterone production.

But in many cases, it's not enough to simply optimize testosterone levels, it's also important that there is an efficient and productive binding of testosterone to the androgen receptor in order to get the maximum anabolic effect from the increased testosterone. Androgen receptor number and affinity for binding with testosterone are also optimized with the use of TestoBoost by helping to correct influences that decrease the number and weaken the binding of testosterone to the androgen receptor.

But TestoBoost is not a hormone or drug and doesn't increase testosterone levels right away. Like almost all effective nutritional supplements, TestoBoost works by optimizing the internal environment so that your body ramps up testosterone more slowly to levels that would ordinarily be optimal for your individual genetic makeup.

You usually won't see the full results until you've been diligently taking it for a few weeks and in some cases even more (although there are some exceptions with results felt within a few days). As well, as your body is influenced by the use of TestoBoost, you will also see beneficial effects on your health and well-being.

TestoBoost is useful for anyone who wants to naturally optimize their testosterone levels in order to increase muscle mass and strength and improve their sex drive. It's mainly useful for those who have lower than normal endogenous testosterone levels no matter what the cause.

TestoBoost is also used by those using or having used anabolic steroids and/or prohormones (obviously this doesn't include those that are drug tested), since both decrease the normal functioning of the HPTA (see below on why TestoBoost is superior to using anabolic steroids and prohormones).

Another plus with the use of TestoBoost rather than the use of exogenous testosterone and other exogenous hormones and drugs, is that there is no need for other medications such as finasteride, tamoxifen or various aromatase inhibitors to handle adverse effects from increased dihydrotestosterone and estrogen, since these are not problems encountered by the use of TestoBoost.

As well, the use of exogenous testosterone and other hormones and drugs causes the HPTA axis to shut down and atrophy making it difficult to reboot the axis if the exogenous substances are stopped. For example, athletes who use exogenous testosterone and/or anabolic steroids/SARMS and then want to stop using them, have a difficult time rebooting the HPTA and in some cases need testosterone replacement therapy as their endogenous testosterone steptosterone production never returns to normal.

I wrote a book almost four decades ago outlining the cause and possible cures for the management of adverse effects on the HPTA, including adverse effects on endogenous testosterone production and infertility, of stopping the use of anabolic androgenic steroids.²⁴ I also wrote an article several decades ago (<u>Getting Off the Anabolic Steroid Roller Coaster</u>) that I updated a few times and added some comments just recently.

It took a few decades before the full impact of what I wrote back then finally took hold, as seen in some recent studies and papers.²⁵²⁶²⁷²⁸²⁹³⁰³¹³²³³³⁴³⁵³⁶³⁷

TestoBoost and Testosterone Replacement Therapy

TestoBoost is also beneficial for those on testosterone replacement therapy (TRT) as it keeps the actual adverse effects of exogenous testosterone at bay. As well, TestoBoost keeps the endogenous testosterone pathways more intact and thus provide the benefits and advantages of testosterone precursors such as pregnenolone (the precursor of most steroid hormones, including the progestogens, androgens, estrogens, glucocorticoids and mineralocorticoids), androstenedione, and dehydroepiandrosterone (DHEA), as well as keeping the testosterone

producing machinery ready to go in producing endogenous testosterone if TRT is stopped.³⁸³⁹⁴⁰⁴¹⁴²

Nutrition Panel for TestoBoost version VI

Supplement I	acts:	Servin Servin	ng Size: 4 Tablets ngs Per Container: 30				
Ре	Amount r Serving	% Daily Value		Amount Per Serving	% Daily Value		
Vitamin A (as 71% Beta Carotene and 29% Palmitate)	7000 IU	140%	Tribulus Terrestris extract (fruit) Saponins 200 mg	500 mg	*		
Vitamin C (as Ascorbic Acid and Potassium Ascorbate)	200 mg	333%	Acetyl L-Carnitine HCL Nettle Extract (leaf)	300 mg 250 mg	*		
Vitamin D (as Cholecalciferol)	400 IU	100%	Alpha Lipoic Acid	150 mg	*		
Vitamin E (as d-alpha tocopheryl succinate)	200 IU	667%	Lycopene Astaxanthin	I0 mg 5 mg	*		
Niacin	10 mg	50%	TestoBoost Proprietary (Complex: 6390 m	ng*		
Vitamin B6 (as Pyridoxine HCL & Pyridoxal-5-Phosphate)	25 mg	250%	D-Aspartate, Citrulline Malate, Catuaba (bark), Muira Puama (bark), Saw Palmetto (berry), Suma (root) Calcium D-Glucarate, Chrysin,				
Vitamin BI2 (as Methylcobalamin)	200 mcg	3333%	Phosphatidylserine, Indole-3-Carbinol, Cordyceps Sinensis, Trans				
Folate	200 mcg	50%	Resveratrol, Processed Shilajit, Epimedium Grandiflorum, Ganoderma Lucidum, Damiana (leaf), Ipriflavone, Maca (root), Eurycoma Longifolia extract (root), Prickly Pear extract (leaf), 5-Methyl Methoxy Isoflavone, Coleus Forskholii extract (root), Schisandra (berry), Phosphorus, Quercetin Dihydrate, L-Arginine Alpha Ketoglutarate, Ginkgo Biloba extract, Grape Seed extract, Passionflower (herb), Ginger extract (root),				
Calcium (as Calcium Phosphate)	400 mg	40%					
Magnesium (as Magnesium Aspartate)	300 mg	75 %					
Zinc (as Zinc Monomethionine from Optizinc®) 15 mg	100%					
Manganese (as Manganese Chelate)	2 mg	100%					
Boron (as citrate)	3 mg	*	GLA (Gamma-linolenic acid from Borage	Seed Oil Powder),			
Bioperine®(Piper nigrum)(fruit)	5 mg	*	Chasteberry extract (Vitus agnus castus)	(fruit), Oat Straw (aeri	al parts),		
Coenzyme Q10	20 mg	*	Genistein.				
Other Ingredients: Cellulose, Croscarmellose Sodium, Hypromellose, Hydroxypropyl Cellulose.							
*Daily Value not established							

The Hypothalamic-Pituitary-Testicular Axis (HPTA)

(copyright Mauro Di Pasquale, M.D.)



The above illustration is of the HPTA in men. In women the Testicles would be substituted by the ovaries and the acronym would be the HPTO. If we generalized the axis to include both men and women, it would be the hypothalamic-pituitary-gonadal axis or the HPTG.

The Assault on Testosterone

In the past few decades there has been an exponential rise in the awareness of the importance of testosterone for men's general and sexual health and well-being. Along with this increased awareness is an increased interest in ways to restore testosterone levels either naturally or through testosterone replacement therapy. As well, although not as publicized, there has also been an increased awareness of the effects of low testosterone on women's general and sexual health and well-being.

And there are good reasons for all this increased concern since low serum testosterone can result in a myriad of symptoms including low libido, erectile and orgasmic dysfunction, increases in visceral fat, decreased muscle mass and bone mineral density, fatigue, depression, irritability, cognitive decline, and sleep disturbances, all of which can dramatically reduce wellbeing and quality of life.⁴⁷⁴⁸⁴⁹⁵⁰⁵¹⁵²⁵³⁵⁴⁵⁵⁵⁶⁵⁷

As we age, and in both men and women, testosterone levels decline.⁵⁸⁵⁹⁶⁰⁶¹ The reason for the decline include decreasing sensitivity to pituitary luteinizing hormone, decreases in the transporters of precursors such as cholesterol, and decreases in the steroidogenic enzymes of the mitochondria and smooth endoplasmic reticulum. Most of the changes that result in decreasing production of testosterone are thought to be due to oxidative damage that accumulates with time.

However, there's more to the story. For example, marriage and fatherhood result in declining testosterone levels in men although the reasons why are obscure.⁶²⁶³

In middle aged men free testosterone levels drop by up to a few percentage points each year after the age of 30 to 35 and even more in elderly men. The usual 1% drop in total testosterone translates into more of a drop in the free testosterone due to an increase in serum hormone binding globulin (SHBG) that binds with free testosterone leaving smaller amounts of the biologically active free testosterone. The drop in free testosterone by an increase in bound and thus inactive testosterone alone is enough to negatively affect our body composition and physical performance as we age.

But there's more than age involved as far as declining testosterone levels and that's one of the reasons for the increase in concern among men. Epidemiological studies have shown that both fertility and testosterone levels have declined in men compared to what they were even 20 years ago.⁶⁴⁶⁵⁶⁶⁶⁷⁶⁸

A meta-analysis published in March of 2023 outlined the crisis in men with decreased fertility and decreasing testosterone levels.⁶⁹ The authors state (giving citations) that "Furthermore, the decline in sperm count is paralleled by declines in testosterone and increases in testicular cancer and male genital anomalies (Skakkebæk et al., 2022). In fact, the decline in semen quality and male reproductive health has recently been described as a crisis". You can access the full paper in PDF format at this site -

https://academic.oup.com/humupd/article/29/2/157/6824414?login=false.

The reasons for this increased decline in testosterone levels and decrease in male fertility may be due to a variety of factors

including:⁷⁰⁷¹⁷²⁷³⁷⁴⁷⁵⁷⁶⁷⁷⁷⁸⁷⁹⁸⁰⁸¹⁸²⁸³⁸⁴⁸⁵⁸⁶⁸⁷⁸⁸⁸⁹⁹⁰⁹¹⁹²⁹³⁹⁴⁹⁵⁹⁶⁹⁷⁹⁸⁹⁹¹⁰⁰¹⁰¹¹⁰²¹⁰³¹⁰⁴¹⁰⁵¹⁰⁶¹⁰⁷¹⁰⁸¹⁰⁹¹¹⁰¹¹¹¹²¹¹³¹¹⁴¹¹⁵

- Lifestyle factors such as an increase in stress levels and sleep deprivation.
- Overtraining syndrome
- Eating patterns.
- Increase in obesity, truncal obesity, and waist circumference.
- Our changing diets are more and more dependent on processed foods.
- Decreased levels of vitamin D (see under vitamin D below).
- An increased exposure to environmental toxins and endocrine disruptors both through direct contact, and in our food, water, and air, as well as cell phone use.
- An increase in the use of medications, such as statins, narcotics, tranquilizers, antidepressants, some blood pressure medications and many others.
- An increase in the use of illicit drugs including anabolic-androgenic steroids (which depress the HPTA axis and endogenous testosterone production during and after use)¹¹⁸, marijuana, opioid narcotics, cocaine, and methamphetamines.
- And last, but becoming more important in today's society, is the ever-evolving male to female dynamics where men have to adjust to a more feminized world including spending more time with female influences, partaking in co-parenting, involved and attending births, sharing household chores, challenges to a male's traditional protective roles, pay disparities, etc.

Pollution, endocrine disrupters, and increased societal stress may be the major reasons for the drop in testosterone in all men, regardless of age and in women as well.¹¹⁹¹²⁰¹²¹ At present, we're surrounded by man-made endocrine disruptors that can push testosterone levels to low normal and even below normal levels, leaving men feeling less than a man both physically and functionally and women with lowered libido and increasing sexual dysfunction.

There are many pollutants and contaminants in our environment that act as endocrine disrupters, mainly from their toxicity and/or hormonal effects. These endocrine disruptors, which affect testosterone levels, semen quality, our health and feelings of well-being, are all around us including in our homes, in items we use every day in our food, water and air. Even pollutants that aren't the norm, such as noise pollution, besides having adverse cardiovascular effects and increasing the risk of type 2 diabetes, can lead to endocrine disruption especially decreased testosterone.¹²²

It's impossible to list them all but examples are pesticides, herbicides, synthetic fertilizers, parabens (in creams, lotions, sunscreens, shampoo, toothpaste), plastics that cover our food, and line cans used for both food and drink. They include dioxins, atrazine, phthalates, fire retardants, lead, mercury, non-stick cookware, organophosphates, glycol ethers, sprays and chemicals used to control pests, insects, and weeds, polycarbonate plastic, epoxy resins made from BPA, metals such as mercury, cadmium, and molybdenum, plant based phytoestrogens and fungi based mycoestrogens.¹²³

The plant-based phytoestrogens include the lignans and the natural phenolic compounds with the most common being the coumestans, prenylflavonoids and isoflavones (commonly found in soy and red clover).

For my recent updated article on pollution go to **Pollution as Devolution**.

Many of these endocrine disrupters affect us by increasing estrogen exposure and subsequently lowering testosterone, decreasing libido, and increasing sexual performance, including erectile dysfunction. Others affect the androgen receptor and decrease the binding of testosterone to the androgen receptor thus decreasing the beneficial effects of testosterone.

These endocrine disrupters work at many levels of the testosterone making machinery of our bodies, all the way from our brains, pituitary, adrenals and gonads, and many also affect binding to the androgen receptor. In men, they can have cumulative effects on the functioning of one or more levels of the hypothalamic-pituitary-testicular axis (HPTA) and the effects of testosterone.¹²⁴¹²⁵ The result is a decrease in testosterone levels and activity, and increasing estrogenic effects since many of the chemicals are endocrine disrupters which mimic estrogen (xenoestrogens and phytoestrogens).

It's also been shown that many medications, especially the statins used extensively to decrease cholesterol levels, that decrease testicular function and testosterone either by directly affecting Leydig cells in the testes or by inhibiting the hypothalamic-pituitary-testicular axis (HPTA).¹²⁶¹²⁷

The situation with the ubiquitous endocrine disruptors and the toxic effects they have on our hormonal systems is that without reparative actions it's possible that the conclusions of a recent study may well come true – a decrease in population by 2050. If this holds true, even given the expected expansion of medical intervention such as in vitro fertilization then the upcoming concerns about overpopulation and its dire consequences including having to double the quantity of food on the present arable land (which will be less as the years go by), increased pollution and climate warming, may no longer be the problem it's been made out to be.

Chronic inflammation, from a variety of sources, is a major factor involved not just in the lowering of testosterone levels, but also in increasing morbidity and biological aging. The many ingredients in TestoBoost with anti-inflammatory and antioxidant properties decreases chronic inflammation and thus has multiple beneficial effects.

TestoBoost counters inflammation and other disrupting influences as mentioned above, that keep your body from having your own natural optimal level of testosterone. As well, on top of countering negative epigenetic changes induced by our exposure to stress, drugs, pollutants, estrogenic endocrine disruptors and aging, it enhances positive epigenetic changes that allow our bodies to optimize our endogenous testosterone production and effects, and improve health, libido, sexual functioning, and fertility in both young and older adults.

Who Uses TestoBoost?

TestoBoost is used by both men and women who want to optimize their testosterone levels. Many users have lower testosterone levels and prefer optimizing their own natural testosterone production rather than using the various forms of exogenous testosterone (injections, pellets, gels, patches, sprays, etc.), all of which can carry significant adverse effects. TestoBoost is used by scores of drug tested athletes for two main reasons. Unlike the use of testosterone and anabolic steroids, TestoBoost doesn't shut down the Hypothalamic/Pituitary/Testicular axis (HPTA) and in fact optimizes it. As such, there are no adverse effects involved with the use of TestoBoost and none when it is discontinued.

TestoBoost, unlike the use of exogenous testosterone and anabolic steroids, also optimizes the endogenous precursors all the way from cholesterol to testosterone, including epitestosterone – all in a natural way with no changes in the ratio of metabolites or the process, including not increasing any metabolite above the normal range. What it does is ramp up testosterone production up to optimum levels for the individual and not to pharmacological levels.

TestoBoost is also used by many middle aged and older men and women as hormonal replacement therapy since unlike the use of exogenous testosterone products, TestoBoost doesn't shut down the HPTA and in fact optimizes it.

For drug tested athletes there are no banned substances in TestoBoost and because it optimizes natural testosterone production and never causes a positive drug test, unlike exogenous testosterone, anabolic steroids, prohormones, and selective androgen receptor modulators (SERMS). TestoBoost optimizes the endogenous precursors in the endogenous pathway from cholesterol to testosterone, including DHEA and epitestosterone – all in a natural way with no changes in the ratio of metabolites or the process, including not increasing any metabolite ratio or level above the normal range.

What TestoBoost does is to optimize the natural endogenous production of testosterone using all the natural pathways that lead to increased testosterone production. As such, this is the reason why the use of TestoBoost by athletes 100% won't and can't cause a positive drug test.

History of TestoBoost

The idea of and my original formulation for TestoBoost originated several decades ago. The first version of TestoBoost laid down the base for what I wanted to achieve for TestoBoost, a natural supplement that optimizes testosterone levels and sex drive in both men and women. The pathways that I targeted included normalizing all the relevant areas of the hypothalamic-pituitary-testicular axis (HPTA) through several independent mechanisms, and to decrease any potential side effects from endogenous increases in estrogen and dihydrotestosterone. Subsequent versions of TestoBoost, while keeping the base intact, added several ingredients that I felt would further optimize testosterone levels and sex drive, and further decrease any potential adverse effects.

The basis of the formula in TestoBoost, and in all the MD+ formulations, is to involve all possible pathways that lead to the desired effects, and to use multiple ingredients that work together to produce superior results. In the case of TestoBoost the desired effect was to remove blocks that inhibited natural and optimal testosterone levels in the body, a decrease in stressors that produce counterproductive elevations in cortisol, dihydrotestosterone and estrogen, and a salutary effect on overall health, libido and sex drive.

All of this is accomplished by using ingredients that are known or found likely to decrease factors that suppresses an individual's optimal testicular steroidogenesis (the formation of steroids by the testes, especially testosterone), and thus optimize natural sexual desire and physical and mental performance.

In order to do this, you must consider all the possible pathways that are involved in optimizing testosterone production, including:

- Optimizing hypothalamic and suprahypothalamic mechanisms to return luteinizing hormone (LH) production back to normal levels.
- Optimizing the effect of LH on testosterone production.
- Optimizing testicular steroidogenesis directly.
- Decreasing counter-productive inhibitors of steroidogenesis.
- Providing vitamins and minerals that might be frankly or marginally deficient and thus not allowing the full production of testosterone including magnesium, zinc, and vitamin B6.
- Optimizing peripheral formation of testosterone.
- Decreasing environmentally and stress induced counter-productive increases in the peripheral formation of dihydrotestosterone and estrogens.

As well, other compounds that have been shown to have effects on sexual desire and performance can be used in the mix. On top of this TestoBoost contains Bioperine, which significantly enhances the bioavailability of the many of the ingredients in TestoBoost by increasing their absorption.

The list of ingredients that could prove useful for optimizing testosterone levels is long and includes various vitamins such as vitamin A, B6, and D, minerals such as zinc, magnesium, manganese, and other ingredients such as arginine, boron, calcium-d-glucarate, catuaba bark, chasteberry (vitex agnus-castus), chrysin, citrulline malate, co-enzyme q10 (ubiquinone), forskohlin, damiana, 5-methyl methoxy isoflavone, Eurycoma longifolia, cordyceps sinensis, genistein, GLA, prickly pear extract, indole-3-carbinol, ipriflavone, maca root, muira puama, phosphatidylserine, quercetin dihydrate, saw palmetto, schisandra chinensis, stinging nettle extract and tribulus terrestris.

Other ingredients that have an indirect but still important effect on testosterone production includes various antioxidants such as vitamins C and E, alpha lipoic acid, grape seed extract (containing resveratrol), lycopene, and astaxanthin.

Why TestoBoost is Better than the Prohormones, Selective Androgen Modulators, Testosterone, and Anabolic Steroids

Prohormones

Over the last few decades prohormones and more so lately androgen receptor modulators have become more popular with athletes and those looking to enhance body composition and performance. At the same time the use of testosterone and anabolic steroids hasn't abated. All these substances were the fad for those who wanted anabolic steroid like effects at first

legally available in some nutritional supplements and now illegally obtained through the Internet.

While their use is declining the use of androgen receptor modulators has steadily climbed. have been used extensively but since in the past fifteen years the big push for those who want "anabolic steroid-like" effects were the prohormones. And even though many have been taken off the over the counter market in the US and other countries, they are still available in one form or another either in North America through the black market, or internationally over the Internet.

They range from androstenedione, to the more sophisticated ones that are supposed to be precursors to other anabolic steroids including nandrolone (Deca), boldenone, and even 1-testosterone compounds. The even include steroid like compounds that have various effects on either or both estrogen and testosterone.

The one exception is the legal availability of DHEA. However, while it may be useful for women, and for other purposes, it's useless for increasing endogenous testosterone levels in men. Most of the prohormones, including androstenedione, androstenediol, norandrostenediol, norandrostenedione, the boldenone and 1-testosterone precursors, and in fact any precursor prohormones are mostly ineffective at providing significant androgenic-anabolic effects, but can result in adverse effects, and will depress endogenous testosterone production.

The trend in these mostly useless and occasionally potent compounds, depending on what is used. For example, some of the prohormones are precursors to testosterone while others are weaker versions of the commercial anabolic steroids. The latter is the case with 1-testosterone and the 17-alpha methylated 1-testosterone, which in fact are weak anabolic steroids, with lower androgenic and anabolic effects than the more potent anabolic steroids that have been marketed over the years.

Basically, the ones being produced now and passed off as over the counter prohormones/steroids by unscrupulous companies, mainly overseas but also in North America, are the cast offs of the steroid producing drug industry. Of course, actual anabolic steroids are also available over the Internet and widely used.

The problem with most of the prohormones available over the past few decades is that while they have minimal androgenic and anabolic effects, they have significant side effects, both known and unknown. The prohormones that are being developed today to be used as a substitute for commercial anabolic steroids haven't adequately been investigated or studied for their potential short term or long-term side effects.

This is where the real problem with these compounds lies. We don't know what effects they have on various parts of the body including the liver, cardiovascular system, prostate, kidney, and especially on the hypothalamic-pituitary-testicular axis (HPTA). These products would never be allowed as prescription drugs because of the lack of proper animal and more importantly human trials. However, they're blatantly dumped on the market as nutritional supplements, when in fact they're drugs, or more correctly low level, and usually ineffective, anabolic steroids – with less efficacy than the commercial anabolic steroids, but with unknown, and potentially very harmful side effects.

While most of the prohormones and hormones that are available as nutritional supplements are of no use or marginally useful for body composition purposes, they can have significant side effects. One of the side effects that is most troubling is the effect they have on the hypothalamic-pituitary-testicular axis (HPTA), the pathway that's involved in endogenous testosterone production and control.

The worst-case scenario, and one that is common with the use of most of the prohormones, is that there is very little anabolic effect from the compounds themselves, but significant side effects, especially with a dampening effect on the HPTA, which in turn shuts off the production of endogenous testosterone. This HPTA shutdown also occurs with the use of exogenous testosterone and anabolic

steroids, and can sometimes result in permanent dysfunction of the normal HPTA, to the point where when these compounds are discontinued (as they invariably are) endogenous testosterone levels remain in the basement, and replacement therapy is sometimes the only solution to achieving normal systemic testosterone levels. In other words, they become either temporarily, or sometimes permanently eunuchoid, with a resulting need of testosterone replacement therapy.

Thus, the overall effect is a negative one in that the level of effective anabolic androgens in the body is decreased and the person thus has less anabolic hormones in their body. On top of that there are several possible side effects including a refractory HPTA, estrogen side effects, hepatoxicity, and adverse effects on cholesterol and the cardiovascular and immune system.

And if you're a drug-tested athlete, there is the very real possibility that you will test positive for the prohormones, especially with the norsteroid and boldenone precursor prohormones. A positive test, because of the difficulty of distinguishing the metabolites of the prohormones from the metabolites of the real anabolic steroids, leads to the same severe penalties, often a two to four-year ban, as a positive for anabolic steroids.

Replacement Therapy with Testosterone and Anabolic Steroids

Using testosterone and/or anabolic steroids to increase your levels of androgens in your body is also the wrong way to approach the problem of low systemic testosterone levels. For example, use of exogenous testosterone shuts down the hypothalamic-pituitary-testicular axis (HPTA) that controls testosterone production on the body.

Instead of helping stimulate testosterone production, the use of testosterone and anabolic steroids decreases the natural production of testosterone and basically shuts down your internal machinery for making testosterone. Once you go off the replacement therapy, your testosterone levels often end up lower than before you started taking the exogenous androgens.

In some cases, testosterone levels never even come close to recovering the pre androgen use levels, and the only alternative, if the system can't be "kick started" to produce testosterone, is to go back on replacement therapy with testosterone or anabolic steroids.

On the other hand, endogenous (developed within the body) hormone production avoids many of the problems associated with exogenous hormone use. By promoting the natural production of the hormone within the body, the regular feedback mechanisms are not bypassed and do not lead to many of the side effects associated with exogenous hormone use.

In fact the use of TestoBoost and other methods to increase endogenous testosterone production ramps up your natural testosterone producing machinery so that even if you stop taking it, your natural levels will be at least as high as before you started, and sometime higher as the body recognizes the higher level as normal and maintains that level naturally.

The bottom line is that whatever your reasons for wanting physiologically increased levels of testosterone, TestoBoost is the best way to go. Besides being more effective in increasing testosterone levels and providing an anabolic drive, the use of TestoBoost won't result in a positive drug test, as is the case with many of the prohormones, (for example the norsteroid ones), exogenous testosterone and anabolic steroids.

Even for those with below normal testosterone levels TestoBoost can be effective and is worth a try. However, in cases of HPTA dysfunction that necessitate testosterone replacement therapy there is

still some value in using TestoBoost since TestoBoost has so many other beneficial effects beyond boosting endogenous testosterone. And in some cases, TestoBoost may help keep the HPTA tuned so that the whole testosterone producing machinery doesn't totally shut down.

The Relatively New Kids on the Block

Testosterone and anabolic steroids, while potently anabolic, have undesirable androgenic and other adverse effects. The basis for the development of selective androgen receptor modulators (SARMs) is to provide anabolic effects on bone and skeletal muscle without the androgenic and other adverse effects. The degree in which this happens depends on the chemical structure of the various SARMS.

The use of selective androgen receptor modulators (SARMs) has escalated in the past few decade. One of the first SARMs is finasteride, patented in 1984 but not used to any extent until 20 years later. It's presently used mainly by men to treat an enlarged prostate or hair loss.

Finasteride may have some anabolic effects as it minimally increases testosterone. However, its true nature is that it's an anti-androgen which inhibits the formation of dihydrotestosterone. The significant adverse effects can include sexual dysfunction (which can persist after it's discontinued), gynecomastia, depression, anxiety, and suicidal ideation.¹²⁸¹²⁹¹³⁰

Lately more selective and anabolic SARMs unrelated to finasteride have been discovered that would be potentially useful for the treatment of breast cancer and cachexia but none have been approved by the FDA for any purpose.¹³¹ Of course those into increasing body composition and performance have already jumped on the SARMs bandwagon and they're widely used by bodybuilders and other athletes.

So far, no SARMs has been shown to be as anabolic as the anabolic steroids but because of their deceptively decreased adverse effects (all SARMS have adverse effects, in some cases more than the use of anabolic steroids) that are beginning to be documented¹³²)¹³³ their unregulated use has escalated over the past few decades. They are often used in combination with anabolic steroids and other anabolic/body composition/performance enhancing hormones, peptides and drugs such as growth hormone, IGF-1, growth hormone secretagogues, clenbuterol, insulin, thyroid hormone, stimulants, opioids, and many others.

However, while potentially safer in some ways to use than anabolic steroids they also cause similar side effects as anabolic steroids including reduced activity of the hypothalamic-pituitary-testicular axis and decreased production of testosterone even when they're discontinued, usually reversible over time but sometimes permanent and requiring testosterone replacement therapy.

As well, the use of the known SARMs will result in a positive drug test in drug tested athletes.¹³⁴¹³⁵¹³⁶ Over the years microdosing of testosterone and SARMS has become popular in drug tested athletes. Unfortunately for many athletes microdosing is both highly unresearched and incredibly imprecise, and therefore prone to all kinds of dosage mix-ups and mistakes on timing resulting in positive drug tests.

Given the new guidelines that a positive test for banned substances can be mitigated if the athlete can provide evidence that the intake was inadvertent, it's common for athletes using a banned substance and getting caught, to contaminate a nutritional supplement and use that as an excuse for a positive doping test.

The doping that is becoming common but is deflected falls on WADA/USADA who allow an athlete to skip or reduce the mandatory penalty for using banned substances such as SARMS if they can show it comes from unintentional use from a contaminated source. As such, the most common scapegoat is the adulteration of a nutritional supplements which does not contain banned substances but by contamination the product with the addition of a banned substance then becomes the accepted reason for the positive drug test.

As an example, one popular way of using SARMS such as andarine and ostarine, is to microdose them and if caught when drug tested then blaming a nutritional supplement. There are several easty wats for an athlete to contaminate say a vanilla protein powder, which does not contain the banned substances with a powdered banned substance, leaving no evidence that the product seal has been tampered with. WADA/USADA accept the false evidence and give the athlete a clean slate. To quote Forest Gump, "STUPID IS AS STUPID DOES."

Why Using TestoBoost is Beneficial Even for Those on Exogenous Hormones

For anyone using TRT or SARMs or prohormones, or in fact any exogenous therapy to increase testosterone levels it's critical to also use TestoBoost to optimize the effects but also to counter some of the adverse effects of exogenous use.

That's because the use of testosterone, anabolic steroids, SARMs and prohormones all have adverse effects to one degree or another and the use of TestoBoost minimizes these adverse effects.

TestoBoost is formulated to optimize your HPTA and as such, should you decide to go off the exogenous hormones, your system is still primed and as such the latency back to your normal testosterone production is dramatically lessened as the HPTA hasn't completely shut down.

TestoBoost also offers protection for increased levels of dihydrotestosterone (especially for those using topical testosterone in the form of patches, pumps, or gels (including Androgel, Testogel, and Testim and Axiron). that might cause adverse effects including erythrocytosis' prostatic hyperplasia and hair loss.^{137138 139}

It also offers protection from increased levels of estrogen so that estrogenic effects such as gynecomastia (colloquially referred to as bitch tits) and are less likely to happen.^{140 141}

As well, there are the various other beneficial effects that TestoBoost has on metabolism, body composition, mental and physical performance, and health.

New Version of TestoBoost

Research in nutrient metabolism and its effects on the body's hormonal and other systems is accumulating daily. The advancements made in the scientific and medical fields far outstrips the advancements made in computer chip technologies. However, although Intel puts out a new improved chip on a regular basis, most nutritional supplement products are rarely updated. Rather the norm is to put out another product with similar ingredients with some added superficial changes and announce that new product as a breakthrough of one sort of another.

As well, changes made to formulations are also made to remove a substance that has been either banned by the FDA or found harmful. In this case, the new formulations and renaming of the product aren't done for the sake of improving the formula but simply to stay compliant and thus to avoid any legal problems.

Examples of this are the new formulations of weight loss products that have removed ephedra and tried to fill the gap by introducing one or two other substances to make it look like they've improved the product rather than lessened it. These reworked products are a far cry from products, such as MD+ LipoFlush that are built from the ground up without even giving a thought to the use of ephedra.

Recycling formulations for economic gain is not new in the supplement business but I want no part of it. Hence the updated versions, improving with each new version, but the same name to the product.

My reasons for reformulating include:

- 1. The use of new evidence based scientific information.
- 2. The use of information from athletes who give me feedback and comments on the products and the ingredients found in them.

- 3. The use of information from personal use and the effects of pilot samples of updated product in a few dozen volunteers to fine tune the new formulation.
- 4. Feedback from colleagues and others who have used the product, including their subjective results and blood work.

Changes in TestoBoost Version VI

Several ingredients have been added to the TestoBoost formula. TestoBoost was already a very popular and effective supplement and very few of the original ingredients have been altered except to vary the concentrations of some of them.

As well new ingredients have been added.

New ingredients include:

Trans Resveratrol Processed Shilajit (Mumie) Epimedium Grandiflorum Citrulline Malate Ginkgo Biloba Lycopene Astaxanthin

The Proprietary Complex ingredient number and amounts were increased with the major change being the addition of citrulline malate, which now is the second most abundant ingredient in the complex. Both parts of the citrulline malate molecule are useful in TestoBoost because of beneficial effects on energy metabolism, protein synthesis and performance.

As well, the binders that are essential in having compressed tablets stay together in the bottle but make the ingredients available biologically, have been changed to reflect my focus on having my line of supplements free of artificial ingredients, colors, or preservatives.

Ingredients in TestoBoost version VI

TestoBoost contains several dozen ingredients which together optimize testosterone production either directly or by counteracting factors that tend to decrease natural testosterone production. Many of the ingredients in TestoBoost work additively and synergistically to produce beneficial effects beyond what a small number of ingredients can achieve.

But this information on TestoBoost is a work in progress and various aspects of it will be covered in future articles and blogs, as well as added to this info piece as new information is published, especially for the next version formulation.

Another important source for updating information and reformulating is the feedback I get from athletes, exercise enthusiasts, and men and women just looking for natural ways to optimize waning levels of testosterone and improving their health, vigor, well-being, and performance.

Vitamin A and Beta Carotene

There are a lot of misconceptions about vitamin A's functions, metabolism and toxicity, and about the role of carotenoids.

Vitamin A has multiple important functions in the body and is important in growth and both physical and mental development, maintenance of the immune system and vision, has antioxidant and anti-inflammatory activity, and increases insulin sensitivity.

Several studies have shown that vitamin A (retinal) and retinoic acid (the active metabolite of vitamin A) are required for growth and development and have vital functions in the body on health and metabolism, including the regulation of immune, gastrointestinal, musculoskeletal, and hormonal functioning, protein metabolism, energy homeostasis, insulin responses, and adipocyte and neuron differentiation and maintenance.¹⁴²,¹⁴³,¹⁴⁴,¹⁴⁵,¹⁴⁶,¹⁴⁷

Adequate levels of vitamin A are important for testicular, ovarian, pituitary, and adrenal function, and the production of testosterone and growth factors.¹⁴⁸¹⁴⁹¹⁵⁰ It is critical for the normal functioning of the testes, both in sperm production and the production of testosterone through effects on not only the testes but on the HPTA.¹⁵¹¹⁵²¹⁵³¹⁵⁴¹⁵⁵¹⁵⁶

Vitamin A has significant body composition effects and is instrumental in decreasing body fat. Vitamin A reduces lipid accumulation, induces lipolysis and fatty acid oxidation, and reduces the accumulation of body fat and decreases the number and size of fat cells.¹⁵⁷¹⁵⁸¹⁵⁹¹⁶⁰

Vitamin A is also important for growth and development as it acts in a hormonal way to influence cellular health in all organs and tissues, including the formation of all types of blood cells, enhancing the immune system and bone metabolism, and forming healthy skin. 161162163164165166167

Vitamin A has been recognized as a key regulator of adipose tissue and obesity.¹⁶⁸¹⁶⁹¹⁷⁰¹⁷¹¹⁷² As well, vitamin A alleviates some of the factors that decrease testosterone production.¹⁷³

Insufficient nutritional intake of vitamin A has been reported in 20–25% of adults and many more are not in the optimal range and as such may be limiting the beneficial effects of vitamin A. As such, vitamin A is included in TestoBoost to make sure sufficient amounts are available for its many important functions, including its essential role in testosterone production and spermatogenesis.

Increased levels of vitamin A are necessary under conditions that deplete vitamin A reserves, such as high protein diets and chronic physically demanding exercise (as seen in any elite athlete), and any polymorphisms that affect the absorption, metabolism and utilization of

vitamin A. There is also deficient intake in our society in those who diet to lose weight, minimize body fat, and maximize body composition.

Vitamin A toxicity is often misunderstood and while subclinical and clinical toxicities do occur, they're not common even at consistent long-term levels of 10,000 IU a day. Although vitamin A can cause liver damage, this damage typically occurs with daily doses of at least 25,000 units a day taken for several months. However, for both effectiveness and safety, TestoBoost contains over 2,000 IU of vitamin A and a healthy dose of the pre-cursor beta-carotene.

Beta carotene has several roles in the body. It is a potent antioxidant and anti-inflammatory, has beneficial effects on the immune system., and is useful in the prevention of obesity and excess fat accumulation. ¹⁷⁴¹⁷⁵¹⁷⁶ As well, beta-carotene has been found to have a protective effect on testicular toxicity, as has quercetin¹⁷⁷, which is also in TestoBoost, against testicular damage,.¹⁷⁸¹⁷⁹¹⁸⁰¹⁸¹ All of these properties help to enhance testosterone levels.

Beta-carotene can be converted into vitamin A, especially if there is a marginal or frank deficiency of vitamin A.¹⁸² Beta-carotene's conversion to vitamin A in the body is limited by a feedback system.¹⁸³

Supplementing the diet with beta-carotene does not produce any vitamin A toxicity despite its use in very high doses since it's only metabolized to vitamin A slowly and as needed. With adequate levels of vitamin A in the system the feedback mechanism markedly decreases the transformation of beta carotene into vitamin A, with the decrease being proportional to body levels of vitamin A.

Vitamin B6 (Pyridoxine)

Vitamin B6, a critical co-factor involved in macronutrient metabolism, GH and IGF-I secretion, tissue anabolism, and the production of neurotransmitters including dopamine, noradrenaline and serotonin, and is also involved in optimizing the function of the T-cell population, lymphocytes that are intimately involved in the immune response.¹⁸⁴¹⁸⁵

CD8+ T cells, also known as "killer cells", are cytotoxic - this means that they are able to directly kill virus-infected cells, something that is essential for decreasing the deadly effects of the Covid-19 pandemic.

As well, vitamin B6 is an essential co-factor necessary for the metabolism of protein and a useful supplement to take with any amino acid and/or protein product. Transamination of amino acids, important for many functions in the body including protein synthesis, anaplerosis, energy metabolism, is promoted by several enzymes among which are the aminotransferases, which are derivatives of vitamin B6. For example, in a deficiency of vitamin B6 the nonessential amino acids are synthesized only poorly and, therefore, protein synthesis cannot proceed normally.

Vitamin B6 and leucine have been shown to work together to increase fat oxidation and insulin sensitivity, improve body composition and reduce oxidative and inflammatory stress.¹⁸⁶¹⁸⁷ And the B vitamins in general, including those in TestoBoost have been shown to improve body composition and improve energy metabolism.¹⁸⁸

TestoBoost version VI has both pyridoxine (in the form of HCL) and pyridoxal-5-phosphate (P5P) in it. P5P is the metabolically active form of vitamin B6. Pyridoxine HCL, while as easily absorbed as P5P must be converted to P5P in the body in order to be used by the enzymes involved in protein metabolism and various hormonal processes.

P5P is the preferred form of vitamin B6 as it can be used directly in the body without relying on the liver's conversion of other forms of vitamin B6 into P5P. As well, less is needed to achieve the same cofactor effects. As such, half of the B6 is in P5P form, and if the body needs more, it can convert the pyridoxine HCL to P5P.

Vitamin B12

Vitamin B12 is metabolically involved in almost every cell in the body, including the synthesis and regulation of DNA and neurotransmitters. It is vital for normal brain and nervous system functioning and for the formation of red blood cells.

B12 is involved in fatty acid and amino acid metabolism, helping to regulate protein synthesis and lipolysis/lipogenesis, thus helping to improve body composition. As well, it helps to decrease serum levels of homocysteine, cholesterol and C-Reactive proteins, markers of heart disease and inflammation in the body. B12 is also involved in adrenal and testicular function including normalizing testosterone and cortisol levels, and spermatogenesis.

Vitamin B12 deficiency can lead to serious problems including anemia, and damage to the brain, central nervous system, and the reproductive axis. Even marginal deficiencies can cause symptoms including cognitive decline, fatigue, depression, lower testosterone production, decreased libido, and sexual and reproductive dysfunction.¹⁸⁹¹⁹⁰¹⁹¹¹⁹²¹⁹³¹⁹⁴¹⁹⁵¹⁹⁶¹⁹⁷¹⁹⁸

Vitamin B12 deficiency can occur secondary to low intake relative to need, such as can happen in vegetarians and especially vegans (vitamin B12 is essentially absent from plant sources), from deficient absorption due to certain intestinal disorders and problems with intrinsic factor, and from the use of certain medications, such metformin, a common diabetic medication.¹⁹⁹²⁰⁰²⁰¹²⁰²²⁰³²⁰⁴²⁰⁵²⁰⁶

Vitamin B12 (as methylcobalamin) in version VI of TestoBoost was increased from 100mcg to 200 mcg. TestoBoost contains enough B12 to make sure you receive all its benefits and none of the problems associated with low B12 levels.

Methylcobalamin is the biologically active form of B12, whereas cyanocobalamin, the form used in most supplements, is the synthetic form. As the body must change the cyanocobalamin into methylcobalamin, this process may be compromised in some people so using the metabolically active form is more efficient and improves bioavailability and function.

B12 helps to optimize macronutrient metabolism, maximize muscle mass and decrease body fat.²⁰⁷²⁰⁸ As well, it helps to decrease serum levels of homocysteine, cholesterol, TNF-alpha, and C-Reactive proteins, markers of heart CNS diseases and inflammation in the body.²⁰⁹²¹⁰ Decreasing inflammation helps to decrease cortisol levels and thus increase the anabolic effects of TestoBoost.

Antioxidants

Vitamin C is essential to proper collagen synthesis, and this is evident in the vitamin C deficiency disease scurvy, in which the collagen fibers synthesized in the body cannot form fibers properly, resulting in lesions, blood vessel fragility and poor wound healing.

Vitamin C has been shown to have some anticatabolic effects that likely involves decreasing exercise induced cortisol but may also have some effects through its antioxidant action. Conversely, some of the anticatabolic effects of antioxidants may be mediated through a decrease in cortisol.

Antioxidants may be of some use in training induced muscle ischemia and injury. Research shows that exercise can adversely affect muscle tissue by increasing the formation of free radicals. These free radicals can then lead to muscle fatigue, inflammation and muscular damage.²¹¹ During normal conditions free radicals are generated at a low rate and neutralized by antioxidant enzymes in the liver and skeletal muscle and other systems. Unfortunately, the increase in free radicals caused by exercise accompanies a simultaneous decrease in the supply of antioxidants to handle them.

Oxidant stress, from whatever source, be it environmental, exercise induced, or psychological stress, affects Leydig cells and results in decreased testosterone production. Antioxidant like vitamin C, and vitamin E have been shown to protect the body against stress induced damage. Supplementation with vitamin E alone or in combination with vitamin C prevents the reduction in testosterone and rise in corticosterone levels.²¹²

An early study showed that vitamin E has beneficial effects of the HPTA and can increase testosterone levels in both rats and humans.²¹³ Vitamin E has also been implicated in the prevention of ethanol toxicity in the HPTA and reproductive tissues.²¹⁴²¹⁵ As well, antioxidants such as vitamin C, vitamin E, lycopene, astaxanthin, zinc, and coenzyme Q10 have been shown to improve male fertility.²¹⁶

Antioxidants form a front-line defense against cell damage caused by free radicals, which are involved in damage to all systems in the body and in the aging process. As well, the antioxidants, immune stimulant, and other ingredients in MENS+, normalize and optimize the immune system to help deal with various problems and diseases. They are also effective in combating inflammation, free radicals, and other destructive processes that which are known to contribute towards aging and disease.

One of the most effective means of protecting ourselves from various endogenous and exogenous insults (including stress, free radicals, poor diet, and environmental chemicals and pollutants, including mercury and other heavy metals) is by using a complimentary combination of antioxidants.

In a review on antioxidants the author found that antioxidant vitamin and trace element intakes have been shown to be particularly important in the prevention of cancer, cardiovascular diseases, age related ocular diseases and in aging. In animal models, targeted interventions have been associated with reduction of tissue destruction is brain and myocardium ischemia-reperfusion models. In the critically ill antioxidant supplements have resulted in reduction of organ failure and of infectious complications.²¹⁷

Several ingredients in TestoBoost have antioxidant properties (including vitamin C, vitamin E, coenzyme Q10, alpha-lipoic acid, quercetin, lycopene, astaxanthin, and several of the herbal, amino acids, and other ingredients). These ingredients play an important role in reducing inflammation and decreasing tissue and organ damage.

There's been some adverse information published about the use of antioxidants and how they may decrease the anabolic and performance effects of exercise. These studies are misleading and done with blinders on. I'll be discussing this in detail in upcoming articles, blogs and podcasts, especially the ones I do and will be doing on SHR – <u>www.superhumanradio.org</u>.

Vitamin D

It's generally known that vitamin D, a fat-soluble vitamin, is essential for bone health and is important for augmenting calcium dynamics. It is needed for absorbing minerals such as calcium, iron, magnesium, and zinc, which are important for many metabolic effects, physical and mental.

Vitamin D plays key roles in cellular growth and immune function. Low levels of vitamin D are linked to lower moods and poor cognitive performance. Vitamin D has other important effects,²¹⁸ for example on insulin resistance,²¹⁹ inflammation²²⁰²²¹ and obesity²²²²²³.

But there's even more to vitamin D. Although getting adequate amounts of vitamin D is crucial to health, vitamin D deficiency is relatively common and in fact is the most widespread nutritional disorder in the world.²²⁴²²⁵²²⁶²²⁷ Several studies have shown that vitamin D corrects muscle dysfunction enhances protein synthesis and has specific anabolic effects especially in athletes who may be vitamin D deficient.

Studies in athletes have found that vitamin D has multiple functions on the musculoskeletal system that enhances both body composition and performance. For example, vitamin D may reduce stress fractures, total body inflammation, common infectious illnesses, help impaired muscle function, and may also aid in recovery from exercise and injury.²²⁸²²⁹²³⁰²³¹²³²²³³

Besides the effects of vitamin D on the musculoskeletal system, several studies have found that vitamin D has many other important functions, and that vitamin D deficiency may be involved in various body dysfunctions and diseases.

It's now recognized that vitamin D receptors (VDRs) are present on various nonmusculoskeletal organs and tissues, including in reproductive tissues, such as the testes, prostate, and human sperm. As such, vitamin D may be involved in regulating reproductive health, and sexual function, including testosterone levels.²³⁴²³⁵²³⁶²³⁷²³⁸

Two studies published in 2010 and 2011 found that vitamin D levels correlated with serum testosterone levels. The first study looked at the association of 25-hydroxyvitamin D [25(OH)D] levels with testosterone, free androgen index (FAI) and SHBG, as well as examining whether androgen levels show a similar seasonal variation to 25(OH)D.²³⁹

The authors found significant associations of 25(OH)D levels with testosterone, FAI and SHBG levels. As well, as would be expected by the availability of maximum sun exposure, 25(OH)D,

testosterone and FAI levels followed a similar seasonal pattern with the lowest points in March and peak levels in August.

The second study looked at healthy overweight men that had low vitamin D3 levels and testosterone levels in the lower reference range. One part of the group of men were given just over 3,000 IU of vitamin D3 over a 12-month period, while the other part was given a placebo. Vitamin D supplementation resulted in increased levels of circulating 25(OH)D concentrations while the placebo group showed no increase. As well, compared to baseline values, there was a significant increase in total testosterone levels, bioactive testosterone, and free testosterone levels in the vitamin D supplemented group but no change in the placebo group.²⁴⁰

Other recent studies have shown a connection between vitamin D and testosterone and fertility.²⁴¹ One study in Korean men found that the higher level of 25(OH)D was associated with higher total and free testosterone levels and that these associations persisted after adjusting for age, season, body composition, chronic disease, alcohol use, smoking, and exercise.²⁴²

A study presented May 17, 2015 at the American Urological Association (AUA) 2015 Annual Meeting (Abstract MP51-04) found that low levels of vitamin D are significantly and independently associated with low levels of testosterone in otherwise healthy middle-aged men.

Vitamin D3 is seemed to decrease mortality in elderly people living independently or in institutional care while vitamin D2, alfacalcidol and calcitriol had no statistically significant beneficial effects on mortality.²⁴³

Using vitamin D3 is also better for athletes as a recent study found that vitamin D2 can be counterproductive in that it amplifies muscle damage and while significantly increasing 25(OH)D2 it decreased 25(OH)D3, which is the more immediate substrate for biologically hormonally active form of vitamin D.²⁴⁴

A study published in 2023 concluded that a vitamin D deficiency/insufficiency increases the risk of muscle loss by 78% in older people.²⁴⁵ I would surmise that it would also apply to all ages to one extent or another since vitamin D deficiency/insufficiency is common (see above).

The bottom line is that supplementing with vitamin D, especially in the form of vitamin D3, is important to realize all the body composition, performance, and sexual functioning benefits that it has to offer in the many who are either marginally or frankly vitamin D deficient.

The problem with getting the vitamin D you need to escape a deficiency/insufficiency is that Humans only synthesize vitamin D when large areas of skin are exposed to sunlight, so everyone risks losing muscle strength if they don't get enough vitamin D by being exposed to the sun, eating food rich in vitamin D, or taking a supplement. To ensure adequate vitamin D levels TestoBoost and many other supplements in my lineup, especially <u>MVM</u>, contain vitamin D3.

Aromatase Inhibition by Vitamin D and Other ingredients in TestoBoost

Vitamin D is also involved in aromatase activity as it has been shown to downregulate aromatase so that less testosterone is converted to estrogen resulting in an increase in testosterone levels.²⁴⁶²⁴⁷

It's important that the right form of vitamin D is used for supplementation. Studies have found that vitamin D3 (cholecalciferol) is more effective at raising serum levels of 25(OH) and for longer periods of time than vitamin D2 (ergocalciferol) and thus is the preferred form of vitamin D supplementation.²⁴⁸²⁴⁹²⁵⁰

As well, several other ingredients in TestoBoost inhibit aromatase and thus lower estrogen including several of the antioxidants, grape seed extract, resveratrol (found in grape seed extract), stinging nettle have significant anti-aromatase activity.²⁵¹²⁵²²⁵³²⁵⁴²⁵⁵²⁵⁶²⁵⁷

And as you'll read below, astaxanthin, Eurycoma longifolia, and chrysin also inhibits aromatase.

Vitamin D and the Covid-19 Pandemic

Recent evidence has shown that optimizing and even going beyond optimum levels of vitamin D has potential in offering some protection against and treatment for the Covid-19 pandemic.

Even before any of the research came out citing the advantages of vitamin D, I was already taking at least 5000 units per day starting in early February of this year. My usual intake prior to then was in the 2000 to 4000 IU range. My vitamin D intake comes through my use of MVM, EFA+, TestoBoost, and several other supplements in my lineup that contain vitamin D.

My most recent test for vitamin D shows that my level is at the very high normal range, exactly where I want it to be.

As an aside, I don't just formulate the products in my nutritional supplement lineup, I use them exclusively every day and have been for decades.

Vitamin D has an immune-modulating effect and can lower inflammation. As well, vitamin D boosts immune function against viral diseases. In all vitamin D may be relevant to the cytokine storm and damaging respiratory response to COVID-19.In the past few months, several papers have been published on the beneficial effects of vitamin D, many advising higher daily doses, on the current Covid-19 pandemic.²⁵⁸²⁵⁹²⁶⁰²⁶¹²⁶²²⁶³²⁶⁴

For my full and regularly updated information on vitamin D, click here.

As well, other ingredients, present in TestoBoost, <u>MVM</u>, <u>Joint Support</u>, and others in my line of nutritional supplements, have beneficial effects on the immune system, giving a protective effect on a variety of stressors and infectious agents such as bacterial and viral infections, including Covid-19.

Magnesium

Magnesium, besides complementing the effects of calcium on bone health²⁶⁵ and obesity²⁶⁶ also has several other important functions. Magnesium deficiency, which has been on the rise

in the past few decades, results in significant adverse musculoskeletal, neurological, cardiovascular and metabolic effects.²⁶⁷

Magnesium is involved in numerous processes that affect muscle function including oxygen uptake, energy production, electrolyte balance, testicular function, and protein synthesis. Low levels of magnesium promote inflammation²⁶⁸²⁶⁹ and impact on the body's ability to handle stress.²⁷⁰ These functions are useful in alleviating the release of pro-inflammatory cytokines and decreasing both insulin resistance and inappropriate cortisol secretion.

There is evidence that marginal magnesium deficiency impairs exercise performance and increases oxidative stress. As well, strenuous exercise increases urinary and sweat losses that may increase magnesium requirements.²⁷¹

Recent surveys have shown that a significant number of individuals are magnesium deficient based on their intake. Athletes in sports with weight classes are especially vulnerable to magnesium deficiency due to their weight loss practices. As such, in these athletes, and others who are magnesium deficient or whose levels are marginal, magnesium supplementation would have beneficial effects on exercise performance.

Magnesium, because of its many functions has potential as an ergogenic aid.²⁷²²⁷³ A recent study found that magnesium supplementation improved alactic anaerobic metabolism, even though the athletes were not magnesium deficient.²⁷⁴ Another study found that magnesium supplementation increased strength performance.²⁷⁵ As well, magnesium may prove effective for muscle cramps²⁷⁶ and has a protective effect on muscle damage.²⁷⁷

Magnesium has been shown to influence testosterone levels as well as the anabolic peptide IGF-1.²⁷⁸²⁷⁹ One study found that supplementation with magnesium increases free and total testosterone values in sedentary and in athletes.²⁸⁰ In this study the increases were found to be higher in those who exercise than in sedentary individuals. As well, magnesium has been shown to work along with zinc and B6 (both of which are present in TestoBoost) to produce a significant anabolic effect.²⁸¹

Magnesium has also been shown to have significant benefits on immunity and overall health.

Magnesium Aspartate is used instead of the magnesium oxide as the aspartate salt has been shown to influence testosterone levels and is the ingredient that is in ZMA, along with zinc monomethionine and B6 (all of which are in TestoBoost).

Zinc

Zinc, a trace mineral, is a constituent of more than a hundred fundamentally important enzymes, so zinc deficiency has many negative effects on almost every body function.²⁸² As well, zinc deficiency can adversely affect the reproductive hormones adding another factor as to how it can impair athletic efforts.²⁸³ Zinc is also important for male fertility.²⁸⁴

Zinc is necessary for the immune system and is a potent inhibitor of various RNA viruses and may be beneficial for both prevention and treatment of the present COVID-19 pandemic.²⁸⁵²⁸⁶²⁸⁷²⁸⁸ It's interesting that like the Covid-19 virus, zinc deficiency can result in the loss of sense of smell and taste. It's possible that zinc deficiency may contribute to these

losses since zinc deficiency in humans is widespread²⁸⁹ and athletes may be particularly prone to lower plasma zinc levels.²⁹⁰

Exercise can lead to an increased need for certain nutrients. Problems can arise from exercise induced mineral loss, which is further enhanced by the finding that many of us don't consume adequate amounts of many essential minerals.

Studies have shown that many athletes, and female athletes in particular, consume diets that have been found to be inadequate for certain key minerals such as zinc, magnesium, copper, and iron. The combination of strenuous exercise and compromised mineral status ultimately leads to low endurance capacity, depressed immune function, and the development of a variety of disease conditions.

One study looked at the effects of zinc deficiency on physical performance and found that low dietary zinc was associated with impaired cardiorespiratory function and impaired metabolic responses during exercise.²⁹¹

Zinc deficiency adversely affects protein synthesis. In one study the effects of zinc deficiency in rats, on the levels of free amino acid in urine, plasma and skin extract were investigated.²⁹² Zinc deficiency adversely affected skin protein synthesis. Especially where a deficiency may be present, supplemental zinc has resulted in an increase the secretion of growth hormone and IGF-I,²⁹³ and testosterone²⁹⁴ and to raise plasma testosterone and sperm count.^{295,296}

A study looking at the effects of zinc supplementation on wrestlers found that the results obtained at the end of the study indicate that zinc supplementation (as well as several other ingredients in TestoBoost including NAC and ALA) prevents production of free radicals by activating the endogenous antioxidant system.²⁹⁷

This activation is important as it coincides with the effects of exercise, which also activates the endogenous antioxidant system and leads to increased endogenous antioxidants that enhance the beneficial effects of exercise on body composition and performance. The authors concluded that "physiologic doses of zinc supplementation to athletes may beneficially contribute to their health and performance."

It's been shown that there is an improvement in insulin resistance with zinc supplementation and that zinc is involved in controlling some of the aspects of obesity.²⁹⁸ Zinc also improves calcium metabolism and thus the beneficial effects that calcium has on fat metabolism.

As a show of their efficacy in protecting testicular toxicity, a recent study "recommended that synthetic antipsychotic drugs should be taken with Zinc and Ascorbate (both in TestoBoost) in order to help prevent reproductive toxicity associated with antipsychotic drugs.²⁹⁹

While some believe that high levels of zinc are needed for the multitude of benefits that it offers³⁰⁰ that is not the case in my experience. Increasing levels of zinc in TestoBoost above the RDA showed no improvements in the effects of TestoBoost on serum testosterone or aspects of fertility.

The amount of zinc in TestoBoost augments zinc found in several diverse foods to provide above RDA levels of bioabsorbable zinc. For example, lamb (3 ounces contains half the recommended daily value), beef, and pumpkin seeds, are rich in zinc content.

A recent study in mice found that the use of zinc enriched yeast improved testicular steroid production, antioxidant levels and spermatogenic dysfunction.³⁰¹ Using 3 different levels of zinc, the study found that the lowest dose of zinc supplementation had a better effect on improving testicular function.

Manganese

Manganese is necessary for the metabolism of proteins and fats. It's also vital for proper immune and central nervous systems functioning, increases insulin sensitivity, has antioxidant properties, and is involved in energy metabolism.³⁰²³⁰³

Manganese is a mineral that is required in small amounts to manufacture enzymes necessary for the metabolism of proteins and fats. It also supports the immune system, regulates blood sugar levels, and is involved in the production of cellular energy, reproduction, and bone growth.

Manganese supports blood clotting, aids in digestion, and as antioxidant, is a vital component of Sodium Oxide Dismutase, a large molecule that is the body's main front-line defense against damaging free radicals. Working with the B-complex vitamins, manganese help control the effects of stress while contributing to one's sense of wellbeing.

A deficiency in intake of manganese can retard growth, cause seizures, lead to poor bone formation, impair fertility, and cause birth defects. Researchers are also looking at new links between manganese deficiency and skin cancers.

Coenzyme Q10 (ubiquinone-10, CoQ10)

Coenzyme Q10 (CoQ10), a coenzyme that is ubiquitous in animals, including humans, is a lipid-soluble antioxidant and acting as an electron carrier is a key component of the mitochondrial electron transport chain for adenosine triphosphate (ATP) production.³⁰⁴ It is also one of the key antioxidant nutrients that protect mitochondrial membrane lipids and proteins and mitochondrial DNA from free radical-induced oxidative damage.

As such it is necessary for proper energy metabolism. For example, myocardial CoQ₁₀ content is reduced by cardiac failure and aging. It is also reduced by statins, the popular cholesterol lowering drugs. Studies have suggested preventative supplementation of CoQ10 for cardiac health and for those on statins.³⁰⁵³⁰⁶³⁰⁷³⁰⁸³⁰⁹³¹⁰

CoQ10 has been shown to decrease oxidative stress and mitochondrial damage leading to increases in mitochondrial mass in many tissues.³¹¹³¹² As well, CoQ10 has been shown to affect the expression of genes involved in human cell signaling, metabolism and transport.

As such, since many neurodegenerative disorders, diabetes, cancer, and muscular and cardiovascular diseases have been associated with low CoQ10 levels, supplementation may be beneficial in many conditions and diseases^{313314315 316317318} including alleviating intervertebral disc degeneration.³¹⁹

For example, CoQ10 supplementation has been shown to have anti-aging and beneficial effects on semen parameters, fertility, testicular damage, and reproductive hormones including testosterone.³²⁰³²¹³²²³²³³²⁴³²⁵³²⁶³²⁷³²⁸ In a recent study CoQ10 while not found to directly increase testosterone, CoQ10 supplementation "was found to ameliorate the reduction in testosterone induced by chemical reproductive toxicants, mainly by neutralizing the damaging effect of the generated free radicals."³²⁹

CoQ10 has also been shown to have beneficial effects on oxidative stress, inflammation, the immune system, and on exercise performance.³³⁰³³¹³³²³³³³⁴³³⁵³³⁶³³⁷³³⁸³³⁹³⁴⁰

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

As well, it has been shown that the reduced form of CoQ10 is an important physiological lipidsoluble antioxidant that scavenges free radicals generated chemically within liposomal membranes.^{341,342} It has also been shown that it reduces oxidative stress associated with strenuous exercise in rats, healthy adults and young athletes.³⁴³³⁴⁴³⁴⁵³⁴⁶³⁴⁷ As noted above, vitamin E and ubiquinone increase physical working capacity of experimental animals.³⁴⁸

Generation of free radicals and subsequent lipid peroxidation have been proposed to contribute to delayed tissue damage. One study has found that ascorbate and ubiquinol levels were decreased after trauma.³⁴⁹ In this study, changes in tissue levels of ubiquinol, but not ascorbate reflected the degree of trauma. The authors suggest that ubiquinol levels may provide a useful marker of the oxidative component of the secondary injury response.

A recent study found that CoQ10 supplementation "significantly recovered mitochondrial function and concurrently decreased the generation of reactive oxygen species and lipid peroxides, inhibited the accumulation of lipid droplets and the formation of the NOD-like receptor family pyrin domain-containing three (NLRP3) inflammasome, and reduced interleukin-1ß release and cell death." Also, the authors concluded that their results clarified "the causal role of CoQ10 in coupling the electron transport chain with ß-oxidation".³⁵⁰

TestoBoost also contains acetyl-l-carnitine, the acetyl form of L-carnitine which are interchangeable in the body with one forming the other as needed. While one forms from the other and have similar effects in the body, each also has specific effects. Studies have shown that under certain conditions CoQ10 plus L-carnitine and in some cases L-carnitine alone, significantly increases total antioxidant, LH and testosterone levels as well as improving semen parameters.³⁵¹³⁵²³⁵³³⁵⁴³⁵⁵³⁵⁶³⁵⁷³⁵⁸³⁵⁹

Astaxanthin

Astaxanthin, a powerful lipid-based antioxidant complements and adds to the many beneficial effects of TestoBoost on testosterone production, body composition, exercise performance, anti-aging, and overall health.³⁶⁰

Astaxanthin has been shown to have potential to improve health, decrease morbidity (for example a recent study found that astaxanthin significantly improves gastric and intestinal

ulcers and cancers)³⁶¹, enhance exercise performance, increase fat metabolism during exercise, decrease oxidative stress and muscle injury, delay exhaustion, improve body composition, enhance recovery, prevents redox imbalances, decrease obesity related disease, and attenuates muscle damage, counterproductive inflammation and fibrosis induced by rigorous physical training as well as

immobilization.³⁶²³⁶³³⁶⁴³⁶⁵³⁶⁶³⁶⁷³⁶⁸³⁶⁹³⁷⁰³⁷¹³⁷²³⁷³³⁷⁴³⁷⁵³⁷⁶³⁷⁷³⁷⁸³⁷⁹³⁸⁰

Some of the benefits of Astaxanthin deserve special attention. For example, astaxanthin has a protective effect on mitochondria, the cellular powerhouses that produce the energy we need to live and function optimally. Protecting the mitochondria is especially important during exercise since destructive free radical production increases almost exponentially and can damage not only the mitochondria, thus impairing energy systems, but also skeletal muscle as a whole impairing performance and recovery and increasing the chance of injury.³⁸¹

But that's not all because astaxanthin, through its effects on decreasing mitochondrial damage in other parts of the body such as the testes, also increases testosterone production and thus increases the anabolic effects of exercise and has also been shown to have positive effects on sperm parameters and fertility.³⁸²

As far as testosterone production it's been found that mitochondrial function is paramount for the optimal functioning of Leydig cells, the cells in the testes that produce testosterone.³⁸³ Oxidative stress, for example from exposure to hydrogen peroxide, acts directly on testicular Leydig cells impairs mitochondrial functioning and decreases steroidogenesis and thus impairs testosterone production.³⁸⁴ Astaxanthin rescues Leydig cells from oxidative stress and thus restores normal testosterone production.³⁸⁵

It's also been shown that astaxanthin acts as an aromatase inhibitor, and thus decreases the effects of estrogen on the HPTA and thus acts to further increase testosterone levels. In one study a combination of astaxanthin and saw palmetto (both ingredients are in TestoBoost) increased serum testosterone, and decreased estrogen and dihydrotestosterone (DHT) production.³⁸⁶ The end result is increased testosterone levels as there is less testosterone being metabolized to estrogen and DHT.

Unlike some other antioxidants, astaxanthin not only has intrinsic antioxidant and antiinflammatory properties but it also increases the endogenous production of natural antioxidant defense mechanisms such as SOD and heme oxygenase-1.³⁸⁷

As well it works synergistically with other ingredients in TestoBoost. For example, in horses it's been shown that continuous dietary administration of astaxanthin and L-carnitine attenuates exercise-induced muscle damage.³⁸⁸ Also the combination of astaxanthin and saw palmetto has also been shown as an effective ancillary treatment for prostate cancer.³⁸⁹

For all these reasons astaxanthin plays a prominent part in the beneficial effects that TestoBoost has on all aspects of health, nutrition, exercise, body composition and anti-aging.

Boron

All of the ingredients in TestoBoost have a part in the effects of TestoBoost. For example, boron which is often not normally considered an ingredient of importance in boosting
testosterone does in fact have protective effects that can be involved in optimizing testosterone levels.

Turkez H, Yıldırım S, Sahin E, Arslan ME, Emsen B, Tozlu OO, Alak G, Ucar A, Tatar A, Hacimuftuoglu A, Keles MS, Geyikoglu F, Atamanalp M, Saruhan F, Mardinoglu A. Boron Compounds Exhibit Protective Effects against Aluminum-Induced Neurotoxicity and Genotoxicity: In Vitro and In Vivo Study. Toxics. 2022 Jul 28;10(8):428. doi: 10.3390/toxics10080428. PMID: 36006107; PMCID: PMC9413983.

Abstract

Genetic, neuropathological and biochemical investigations have revealed meaningful relationships between aluminum (AI) exposure and neurotoxic and hematotoxic damage. Hence, intensive efforts are being made to minimize the harmful effects of Al. Moreover, boron compounds are used in a broad mix of industries, from cosmetics and pharmaceuticals to agriculture. They affect critical biological functions in cellular events and enzymatic reactions, as well as endocrinal and mineral metabolisms. There are limited dose-related data about boric acid (BA) and other boron compounds, including colemanite (Col), ulexite (UX) and borax (BX), which have commercial prominence. In this study, we evaluate boron compounds' genetic, cytological, biochemical and pathological effects against aluminum chloride (AICl₃)induced hematotoxicity and neurotoxicity on different cell and animal model systems. First, we perform genotoxicity studies on in vivo rat bone marrow cells and peripheric human blood cultures. To analyze DNA and chromosome damage, we use single cell gel electrophoresis (SCGE or comet assay) and micronucleus (MN) and chromosome aberration (CA) assays. The nuclear division index (NDI) is used to monitor cytostasis. Second, we examine the biochemical parameters (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), total antioxidant capacity (TAC) and total oxidative status (TOS)) to determine oxidative changes in blood and brain. Next, we assess the histopathological alterations by using light and electron microscopes. Our results show that Al increases oxidative stress and genetic damage in blood and brain in vivo and in vitro studies. All also led to severe histopathological and ultrastructural alterations in the brain. However, the boron compounds alone did not cause adverse changes based on the abovestudied parameters. Moreover, these compounds exhibit different levels of beneficial effects by removing the harmful impact of AI. The antioxidant, antigenotoxic and cytoprotective effects of boron compounds against Al-induced damage indicate that boron may have a high potential for use in medical purposes in humans. In conclusion, our analysis suggests that boron compounds (especially BA, BX and UX) can be administered to subjects to prevent neurodegenerative and hematological disorders at determined doses.

Saw Palmetto

Saw palmetto (Serenoa repens) has been shown to increase levels of testosterone and decrease levels of dihydrotestosterone and estrogen.³⁹⁰ Because of this inhibition it increases testosterone levels by inhibiting conversion to dihydrotestosterone, a hormone that in adults is responsible for male pattern baldness, prostate hypertrophy, and even acne, and to a lesser level estrogen that is counterproductive in males. As far as dihydrotestosterone, Saw palmetto inhibits the enzyme 5-alpha-reductase, which produces dihydrotestosterone from testosterone.

By means of its ability to decrease the formation of dihydrotestosterone, saw palmetto has been shown to be useful in preventing and treating prostate problems including prostate hyperplasia.³⁹¹³⁹²³⁹³³⁹⁴³⁹⁵³⁹⁶³⁹⁷

As well, saw palmetto enhances erectile responses by inhibition of phosphodiesterase 5 activity and increase in inducible nitric oxide synthase messenger ribonucleic acid expression in the penile corpus cavernosum, and may also increase sexual activity.³⁹⁸³⁹⁹

Saw palmetto may also have benefits on hair regrowth including androgenic and other forms of hair loss.⁴⁰⁰⁴⁰¹⁴⁰²

Beta sitosterol is a plant sterol ester found in saw palmetto berries (present in TestoBoost). While beta sitosterol, used mainly for people with prostate problems,⁴⁰³ also has immune system, cortisol controlling and anti-inflammatory effects.⁴⁰⁴⁴⁰⁵⁴⁰⁶ In one study a mixture of beta sitosterols were tested on marathon runners. The supplemented group, but not the placebo group, showed increased immune cell numbers, decreased inflammation, and decreased cortisol levels.⁴⁰⁷

Eurycoma Longifolia (Longjack, Tongkat Ali, Pasak Bumi)

Eurycoma longifolia, also known as 'Malaysian ginseng', Longjack, Tongkat ali, and pasak bumi) is reported to have aphrodisiac and testosterone enhancing effects and has a long history of use in South-East Asia to decrease stress and improve physical strength and psychological resilience.⁴⁰⁸⁴⁰⁹

Several studies on murine models have shown that Longjack increased free serum testosterone and DHEA levels, muscle strength, and sexual drive and performance.⁴¹⁰⁴¹¹⁴¹²⁴¹³

More importantly, more recent studies in humans have shown that Eurycoma longifolia increases testosterone levels and libido, shows ergogenic effects and acts as an aromatase inhibitor in both men and women, as well as increasing erectile function, fertility and spermatogenesis, and quality of life.⁴¹⁴⁴¹⁵⁴¹⁶⁴¹⁷⁴¹⁸⁴¹⁹⁴²⁰⁴²¹⁴²²⁴²³⁴²⁴ The increase in free testosterone in women is thought to be due to the significant decline in sex hormone-binding globulin concentrations.

As such, it works synergistically with other ingredients in TestoBoost that work in similar ways, including acetyl-L-carnitine, catuaba bark, maca root, coleus forskohlii (forskolin), muira puama, chasteberry (vitex agnus-castus), suma root, schisandra chinensis, cordyceps sinensis, and avena sativa.

Acetyl-L-Carnitine

For example, one study found that carnitines including acetyl-L-carnitine (ALCAR) worked as well as replacement testosterone therapy in improving sexual dysfunction, depressed mood, and fatigue in aging men.⁴²⁵

As well, ALCAR seems to have an effect on the hypothalamic-pituitary-testicular axis. Studies have shown that ALC prevented the decrease in plasma testosterone levels after chronic swimming⁴²⁶, and that ALC stimulates testosterone production⁴²⁷.

Studies have shown that ALCAR have positive effects on male infertility.428429

5-Methyl Methoxy Isoflavone

Methoxy Isoflavone has been shown to increase protein synthesis in animal models, including livestock, with no significant side effects. Anecdotal evidence over the past year has shown that it may exhibit some mild anabolic and anti-cortisol effects.

Tribulus Terrestris Extract

Tribulus terrestris (TT) saponins were used successfully by Eastern European athletes to enhance body composition, strength, and performance. Tribulus works by increasing LH and testosterone levels. It also has been shown to have some effects on sex drive and sexual function. Several recent studies have found that TT increases testosterone levels and has other beneficial effects including neuroprotection and enhancing male fertility as well as showing no toxicity. ⁴³⁰⁴³¹⁴³²⁴³³

For example a study found that TT extract increased blood testosterone levels, strength and athletic performance.⁴³⁴ Another study found that the use of TT does not result in a positive drug test.⁴³⁵ Several studies have shown positive effects of TT extracts on rats and other animals, including increased levels of testosterone, increased libido, and positive effects on erectile dysfunction.⁴³⁶,⁴³⁷,⁴³⁸

TT has also been shown to not only elevate testosterone levels but also to increase androgen receptors and testosterone-androgen receptor binding.⁴³⁹ The same study found that TT increased IGF-1 levels and the IGF-1 receptors. The authors of this study concluded that "The present study provided preliminary evidence supporting the use of TT extracts as a dietary supplement for the promotion of skeletal muscle mass increase and the enhancement of athletic performance in humans performing high intensity exercise."

Other recent studies found that TT had positive effects on anaerobic performance in boxers and alleviated muscle damage⁴⁴⁰ and that TT increased performance, body mass, and gastrocnemius mass of rats undergoing overtraining, which might be attributed to the changes in androgen-AR axis and IGF-1R signaling.⁴⁴¹

Muira Puama

There have been few clinical studies on muira puama although anecdotally this herb is best known for its aphrodisiac qualities. In 1990, at the Institute of Sexology in Paris, France, a clinical study with 262 men complaining of lack of sexual desire demonstrated muira puama extract to be effective. Those with loss of libido claimed that the treatment was helpful.⁴⁴²

In 2000, researchers at the Institute of Sexology published another study assessing the effectiveness of muira puama and ginkgo biloba using 202 healthy women who complained

about low libido and sexual dysfunction. The study found that the combination resulted in increased libido and sexual activity, as well as increased sexual satisfaction, orgasm quantity and quality, and thoughts about sex.⁴⁴³

Recently, muira puama has gained more of a following and is used for several problems such as PMS and sexual dysfunction. It's also used to relieve stress and for anti-aging.

Phosphatidylserine

phosphatidylserine (PS) has several important regulatory functions within mammalian cells,⁴⁴⁴ including inhibiting the production of proinflammatory cytokines⁴⁴⁵,⁴⁴⁶ inducing antiinflammatory responses,⁴⁴⁷,⁴⁴⁸ and inhibiting immune responses at the site of inflammation.⁴⁴⁹

As well, in vitro studies have shown antioxidant effects with the ability of PS to protect cells against oxygen-derived free radicals and suppress iron-dependent lipid peroxidation.⁴⁵⁰,⁴⁵¹

PS administrations may be useful for treating the neurochemical and behavioral changes that occur with aging and for improving learning and memory.^{452,453,454,455,456,⁴⁵⁷ Studies have shown that PS is produced less with age and appears to beneficially affect brain function through interacting with brain neurotransmitters. In one study PS induced consistent improvement of depressive symptoms, memory and behavior in a group of 10 elderly women with depressive disorders.⁴⁵⁸}

Thus because of the potential role of PS in neuroendocrine-immune communications,⁴⁵⁹ PS is one of the agents proposed for the treatment of various disorders including Alzheimer's disease.^{460,461}

Several research papers have indicated that PS supplementation attenuates the serum cortisol response to acute exercise stress, increases the testosterone to cortisol ratio, decreases oxidative stress, and increases exercise capacity.⁴⁶²⁴⁶³⁴⁶⁴⁴⁶⁵

For all these reasons PS provides significant benefits and is an important ingredient in TestoBoost.

Genistein

Genistein (4',5,7-trihydroxyisoflavone), a major isoflavone in soybeans and a specific inhibitor of protein tyrosine kinase, acts to decrease estrogen in the body. A recent study has shown that there is a synergistic anti-estrogenic effect of indole-3-carbinol and genistein.⁴⁶⁶ As well as these two ingredients, TestoBoost also contains other anti-estrogenic compounds including calcium-d-glucarate,⁴⁶⁷ chrysin,⁴⁶⁸ ginkgo biloba extract,⁴⁶⁹ and ipriflavone.⁴⁷⁰⁴⁷¹ The addition of piperine as Bioperine increases the absorption of these and other ingredients increasing the biological synergistic effects of the combination of ingredients on lowering estrogen effects.

Prickly Pear Extract *

This extract is felt to have neuroprotective and antioxidant effects. Also has insulin like effects and has been shown to have a favorable effect on cholesterol in the body. There is some anecdotal evidence that the use of prickly pear acts as an adaptogen, boosting recovery via an anti-cortisol action. As such it works with other ingredients in TestoBoost to boost recovery and decrease counterproductive cortisol levels.

Schisandra Chinensis

Schizandra is a woody vine with clusters of red berries that is found in northern and northeastern China and adjacent regions in Russia and Korea. It is used to treat a variety of medical conditions and is widely known as a longevity herb and aphrodisiac. Athletes have used schisandra in the belief that it will increase endurance and combat fatigue under physical stress.⁴⁷² It is also felt to have liver protective effects.

Chrysin

Chrysin has been shown to increase testosterone directly and indirectly as an aromatase inhibitor.⁴⁷³⁴⁷⁴⁴⁷⁵

Cordyceps Sinensis

Cordyceps sinensis, a fungus grown in the high mountain ranges of the Himalayas and Tibetan plateau, is parasitic on caterpillars, using the caterpillar's body as a host. It has been used for centuries in the Orient as a medicine for numerous ailments and an aphrodisiac. It is particularly valued for its beneficial effects on libido and sexual performance. Although research in humans is lacking, cordyceps has been shown to raise testosterone levels in rats and mice.⁴⁷⁶⁴⁷⁷⁴⁷⁸⁴⁷⁹⁴⁸⁰⁴⁸¹

Cordyceps is also used by athletes for performance enhancement. It became popular when it was reported that it was used by the female Chinese runners when they won several track events in 1993. Although the coach said that their performance was due to a tonic from caterpillar fungus, it was later shown that it was due to the use of anabolic steroids (between 1990 and 1998 28 Chinese swimmers tested positive for anabolic steroids, amounting to half of all the positive drug tests worldwide in that period of time) and other performance enhancing drugs.

While not an anabolic steroid, cordyceps does have some anti-inflammatory, metabolic, and antioxidant effects that could make it useful for enhancing exercise performance and health. 482483484485486487

Avena Sativa (Oat Wheat Straw)

Avena sativa has been shown to have many effects on health and sexual functioning. Because of anti-inflammatory, antioxidant, immunological, cardioprotective, cognitive enhancing, and other properties, it's felt to be a therapeutic agent in the prevention and treatment of various conditions and diseases.⁴⁸⁸⁴⁸⁹⁴⁹⁰⁴⁹¹⁴⁹²⁴⁹³

Avena sativa is also considered to be an aphrodisiac and able to enhance sexual functioning.⁴⁹⁴

Crit Rev Food Sci Nutr. 2013;53(2):126-44. doi: 10.1080/10408398.2010.526725.

Avena sativa (Oat), a potential neutraceutical and therapeutic agent: an overview.

Singh R, De S, Belkheir A.

Abstract

The aim of the present review article is to summarize the available information related to the availability, production, chemical composition, pharmacological activity, and traditional uses of Avena sativa to highlight its potential to contribute to human health. Oats are now cultivated worldwide and form an important dietary staple for the people in number of countries. Several varieties of oats are available. It is a rich source of protein, contains a number of important minerals, lipids, ß-glucan, a mixed-linkage polysaccharide, which forms an important part of oat dietary fiber, and also contains various other phytoconstituents like avenanthramides, an indole alkaloid-gramine, flavonoids, flavonolignans, triterpenoid saponins, sterols, and tocols. Traditionally oats have been in use since long and are considered as stimulant, antispasmodic, antitumor, diuretic, and neurotonic. Oat possesses different pharmacological activities like antioxidant, anti-inflammatory, wound healing, immunomodulatory, antidiabetic, anticholesterolaemic, etc. A wide spectrum of biological activities indicates that oat is a potential therapeutic agent.

Curcumin

The active constituent in turmeric, known as curcumin, is a potent antioxidant with antiinflammatory properties and has a wide range of therapeutic effects.⁴⁹⁵ Turmeric exhibits marked anti-inflammatory action and has been shown to be as effective as some antiinflammatory drugs and as a plus has fewer adverse effects.⁴⁹⁶⁴⁹⁷. For example, in a doubleblinded trial, post-surgical patients receiving curcumin experienced reductions in stiffness and joint swelling comparable to the effects of phenylbutazone, a potent anti-inflammatory drug.⁴⁹⁸

Of all the spices and herbal preparations, it seems that only the spice turmeric has any antiinflammatory effects. This was the conclusion of a study of a variety of Ayurvedic and herbal preparations, which was presented at the 9th Asia Pacific League of Associations for Rheumatology Congress. In this study, a variety of herbal and Ayurvedic preparations were tested in rats. The rats were fed oral doses of the varied herbal and Ayurvedic recipes. Only turmeric showed anti-inflammatory effects when tested on irritated paws of the rats.

It works by inhibiting cyclooxgenase and lipoxygenase enzymes that catalyze the formation of inflammatory prostaglandins.

Several studies have shown the effectiveness of curcumin, especially when coupled with piperine which increases absorption of curcumin (both are in TestoBoost) on exercise

induced muscle damage and soreness, and recovery as well as on improving body composition and exercise performance. ⁴⁹⁹⁵⁰⁰⁵⁰¹⁵⁰²⁵⁰³⁵⁰⁴⁵⁰⁵ In one study the combination of curcumin and piperine resulted in an improvement of in sprint mean power output 24 hours post-exercise.⁵⁰⁶

As well, other studies have shown the value of curcumin in the prevention and treatment of neurological dysfunction such as Alzheimer's disease and other neurological diseases.⁵⁰⁷⁵⁰⁸

Since testosterone levels are compromised by acute and chronic inflammation, the antiinflammatory effects of turmeric, along with the other potent antioxidants in TestoBoost, such as vitamin C and E, resveratrol (in grape seed extract), alpha lipoic acid, lycopene, astaxanthin, and other ingredients in TestoBoost, relieves the effects of inflammation on testosterone secretion and thus results in increased Testosterone levels in the body.

Alpha Lipoic Acid

Besides having potent antioxidant properties, likely secondary to increasing levels of intracellular glutathione, ALA also increases insulin sensitivity. Alpha lipoic acid (ALA), a potent antioxidant⁵⁰⁹⁵¹⁰⁵¹¹ that can recycle other antioxidants such as vitamin C, vitamin E and glutathione.⁵¹²⁵¹³ ALA can be used to increase testosterone secretion and insulin functioning and sensitivity⁵¹⁴⁵¹⁵ by its actions on the pro-inflammatory cytokines⁵¹⁶⁵¹⁷ and because of its effects on decreasing secondary cortisol elevations.

Bioperine

TestoBoost contains piperine marketed as Bioperine,⁵¹⁸ which significantly enhances the bioavailability of supplemented nutrients through increased absorption and decreased metabolic inactivation.⁵¹⁹⁵²⁰⁵²¹⁵²²

The Advantages of Bioperine®

Bioperine® is the only product sourced out of piperine to obtain a patented status for its ability to increase the bioavailability of nutritional compounds. Secondly, it is the only source from piperine to have undergone clinical studies in the U.S. to substantiate its safety and efficacy for nutritional use.

The subtle, yet potent properties of Bioperine® have been measured in several clinical studies with healthy volunteers in the U.S. These studies measured the absorption of three distinct categories of products. The categories evaluated with and without Bioperine® were fat-soluble (beta-carotene), water-soluble (vitamin B 6) and a mineral (selenium, in the form of selenomethionine).

Gastrointestinal absorption of all the studied nutrients, as measured by amounts present in the blood, increased dramatically when administered with Bioperine® as compared to the control group receiving the nutrient alone. Selenium levels increased by 30%, beta-carotene increased by 60%, and the vitamin B 6 increase was slightly higher than beta-carotene.

Truth in ancient wisdom

A recognized feature of the 6000-year-old practice of Ayurveda is its preoccupation with the proper functioning of the digestive tract, specifically the digestion and absorption of nutrients. Nearly two-thirds of all traditional Ayurvedic formulas contain a special blend of ingredients, which includes black pepper, for this purpose.

There are various reasons discussed in scientific literature for the unfavorable nutritional status of a given population, but the focus essentially comes down to one single problemnutrient bioavailability. By far, the greatest factors that reduce the bioavailability of nutrients are those that diminish the intestine's absorption capacity. Even today, there is a growing consensus among nutritionists that the obstacle to better nutrition clearly lies in the efficient delivery of nutrients to the body. It is not what you eat that counts, it is what you absorb.

Bioperine improves bioavailability of ingredients in TestoBoost but it also has several other beneficial properties, including thermogenic effects, reducing cholesterol and protecting against neurodegeneration and cognitive impairment. As well, it has been shown that it may have immunomodulatory, antioxidant, anti-asthmatic, anti-carcinogenic, anti-inflammatory, anti-ulcer, and anti-amoebic properties.⁵²³⁵²⁴⁵²⁵⁵²⁶⁵²⁷⁵²⁸⁵²⁹

For current information on the beneficial effects of piperine as the trademark Bioperine go to **https://www.bioperine.com/index.php/aboutbioperine**.

Arginine and Citrulline

Arginine, citrulline (alone and converted to arginine), and the BCAAs and other ingredients in TestoBoost, increase GH, IGF-I and insulin secretion and response, thus providing a synergistic anabolic effect on muscle and canceling out insulin's lipogenic and anti-lipolytic effects. In other words, you get all the good anabolic and fat burning effects from the synergism and none of the bad.

Arginine and citrulline also increase nitric oxide formation, which is felt to have a beneficial effect on blood flow in muscle and thus enhance nutrient and oxygen delivery, buffering and the clearing of metabolic by products, and increasing protein synthesis.

Arginine has beneficial effects on exercise performance, protein synthesis, the immune system, increasing growth hormone and IGF-1 levels, increasing insulin sensitivity, and serving as substrates for other amino acids, creatine, and polyamines.⁵³⁰

As well, arginine (and thus citrulline) has been shown to increase the anabolic effects of testosterone⁵³¹ and work in concert with the BCAAs to improve performance.⁵³²,

On a whole-body basis, synthesis of arginine occurs principally via the intestinal-renal axis, wherein epithelial cells of the small intestine, which produce citrulline primarily from glutamine and glutamate, collaborate with the proximal tubule cells of the kidney, which extract citrulline from the circulation and convert it to arginine, which is returned to the circulation. As a consequence, impairment of small bowel or renal function can reduce endogenous arginine synthesis, thereby increasing the dietary requirement.

Citrulline is made from ornithine and carbamoyl phosphate in one of the central reactions in the urea cycle. It is also produced from arginine as a byproduct of the enzymatic production of nitric oxide from the amino acid arginine, catalyzed by nitric oxide synthase.

Citrulline has several effects, including increasing ammonia clearance, increasing bicarbonate, ornithine, and arginine levels. However, it may have benefits that the other amino acids do not have and that are independent of its conversion to arginine.

Citrulline does have some advantages over arginine in that citrulline possesses a highly specific metabolism that bypasses splanchnic extraction because it is not used by the intestine or taken up by the liver. As such the absorption of citrulline from diet or supplementation, as well as the citrulline synthesized de novo in the kidneys and endothelial and immune cells, reaches higher levels in the body than if arginine is used. It's estimated that less than 40% of dietary arginine reaches the systemic circulation compared to over 60 percent of citrulline.

As such oral citrulline can be used to deliver arginine to the systemic circulation and thus may provide all the benefits or oral arginine. As well, it's recently been shown that citrulline, while not used in the formation of proteins, stimulates protein synthesis in skeletal muscle through the mammalian target of rapamycin signaling pathway.⁵³³

Overall, studies suggest that citrulline supplementation (along with asparagine, which is in TestoBoost and is metabolized to malate thus giving the advantages of citrulline malate, which is also in TestoBoost) can boost athletic performance and enhance recovery in a number of ways. First and foremost is its ability to raise extracellular and intracellular levels of arginine.

By eliminating the amino acid breakdown products of protein metabolism and augmenting the detoxifying capacity of liver cells in removal of ammonium and lactate from the blood citrulline decreases fatigue, enhances recovery and facilitates the shift from the catabolic training state to the post exercise anabolic state.⁵³⁴⁵³⁵⁵³⁶⁵³⁷⁵³⁸⁵³⁹⁵⁴⁰

However, even though citrulline has been praised in internet articles as superior to the use of arginine, that is not necessarily the case.

- One of the problems with using citrulline as against arginine in that energy is needed to synthesize arginine. Arginine is synthesized from citrulline in arginine and proline metabolism by the sequential action of the cytosolic enzymes argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL). In terms of energy, this is costly, as the synthesis of each molecule of argininosuccinate requires hydrolysis of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), i.e., two ATP equivalents. In essence, taking an excess of arginine gives more energy by saving ATPs that can be used elsewhere, including fueling exercise.
- Citrulline on its own is unable to affect plasma insulin or growth hormone levels, a different story to that of increased arginine or ornithine.
- The use of arginine results in higher spikes of arginine in the body, giving increased biological effects, while citrulline results in more constant but lower levels of arginine in the body.

So, what's the answer? It seems that using both citrulline and arginine in TestoBoost allows the best of both worlds as far as the beneficial effects of arginine and citrulline, within certain limits.

L-Citrulline Malate

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

Overall, studies suggest that citrulline malate supplementation can boost power and endurance athletic performance, enhance recovery by various pathways including direct effects on skeletal muscle function and contractile force, decreasing post-exercise muscle soreness, eliminating the amino acid breakdown products of protein metabolism and augmenting the detoxifying capacity of liver cells in removal of ammonium and lactate from the blood.⁵⁴¹⁵⁴²⁵⁴³⁵⁴⁴⁵⁴⁵⁵⁴⁶⁵⁴⁷⁵⁴⁸⁵⁴⁹⁵⁵⁰⁵⁵¹⁵⁵²⁵⁵³⁵⁵⁴⁵⁵⁵ These actions decrease fatigue, enhance recovery and facilitate the shift from the catabolic training state to the post exercise anabolic state.

Adding to the effect on energy metabolism is the presence of arginine, glycine and methionine in Amino. That's because creatine can be produced endogenously via a two-step process involving these three amino acids.

As well, the combination of arginine and glycine, along with the ketoisocaproic acid (GAKIC) that is formed from leucine, make up a trio that has been found to be a useful combination if used after exercise, and before doing any further exercise.⁵⁵⁶

L-Arginine Alpha-Ketoglutarate

There's 250 mg of L-Arginine alpha-ketoglutarate in TestoBoost. There is evidence that alphaketoglutarate preserves muscle mass and acts as an efficient anticatabolic compound.^{557,558} Addition of alpha-ketoglutarate to postoperative total parenteral nutrition prevented the decrease in muscle protein synthesis and free glutamine that usually occurs after surgery.⁵⁵⁹ One study has found that an alpha-ketoglutarate-pyridoxine complex may have some beneficial effects on human maximal aerobic and anaerobic performance.⁵⁶⁰

Thus, by ingesting AKG in sufficient quantities, the demand for muscle glutamine might ultimately be spared to some degree, thereby allowing muscle protein synthesis to proceed unhindered (e.g. such as during the muscle hypertrophic response which follows a resistance training workout) and reducing the catabolism of muscle tissue.

Studies have shown that:

1. AKG reduces the decline in muscle free glutamine that is associated with reductions in protein synthesis.⁵⁶¹

2. The use of AKG, instead of glutamine, prevents the decline in protein anabolism observed following surgery.⁵⁶²

AKG seems to exert anti-catabolic effects by preserving muscle glutamine.⁵⁶³ These results are not surprising in that the carbon skeleton of BCAAs can be used to synthesize glutamine after the transamination reaction of BCAAs, and ketoglutarate is the immediate carbon donor for glutamine synthesis. The utilization of arginine and ornithine as a carbon source for glutamine synthesis is also a possibility.

A recent study looked at the effects of L-arginine alpha-ketoglutarate (AAKG) on measures of body composition and performance.⁵⁶⁴ Two separate studies were conducted to assess the pharmacokinetic profile of ingesting two forms of AAKG, timed released and non-timed release, in the

blood (study 1) and the effects of dietary supplementation of AAKG on training adaptations in resistance-trained men (study 2).

The study found that the 2 formulations have different pharmacokinetic patterns that may affect arginine release, uptake, and/or physiologic effect over time. As well, the L-arginine alpha-

ketoglutarate (AAKG) in both formulations positively influenced strength (as measured by one rep maximum bench press) and Wingate peak power performance.

Arginine also has several beneficial health effects. If used in lower doses studies have shown that it does not increase nitric oxide (NO) but still has beneficial effects on protein synthesis, the immune system, increasing growth hormone levels, increasing insulin sensitivity, and serving as substrates for other amino acids, creatine, and polyamines.

Too Much Nitric Oxide Production Can Be Counter Productive

Recent research has shown the ergogenic effects of Increasing nitric oxide in the body. As used by bodybuilders and other athletes the use of nitric oxide inducing supplements and ingredients has some benefits in improving exercise tolerance and performance, as well as providing more of a pump when training. The overall impression given by the studies and articles is that increasing nitric oxide production over both the short and long term provides significant ergogenic effects.

its detrimental effects on testosterone makes the use of nitric oxide supplements containing one or more of large amounts of L-arginine, L-arginine precursors such as citrulline, nitrates and nitrites counterproductive for muscle hypertrophy, body composition and athletic performance.

The amount of arginine and citrulline taken by supplementation is critical for its beneficial effects. Too much of arginine/citrulline/nitrites/nitrates can be counterproductive as long-term use of supplements that have excessive amounts of these nitric oxide producing ingredients leads to larger increases in nitric oxide in the testes, which results in decreased testosterone levels.

In higher doses, and especially if combined with nitrate/nitrite, arginine and citrulline increase NO formation and facilitates vasodilation, improves sexual functioning, and helps keep you cool during exercise. ⁵⁶⁵, ⁵⁶⁶

But there is an important caveat. The ability of arginine/citrulline in higher doses, and especially if coupled with nitrates/nitrites, to increase nitric oxide is one of the reasons that TestoBoost contains only 200 mg of arginine and 500 mg of L-citrulline in the form of citrulline malate.

That's because excessive production of nitric oxide, whether through the exogenous use of significant amounts of one or more of arginine, citrulline, and nitrates/nitrites can result in both a decrease in muscle contraction and myotoxicity (negative effect on skeletal muscle),⁵⁶⁷,⁵⁶⁸ and more importantly a lowering of endogenous testosterone production since nitric oxide inhibits testicular Leydig cell steroidogenesis.⁵⁶⁹⁵⁷⁰

Since there is a hierarchy of effects depending on the substrate availability for NO production and the amount of NO produced, excessive amounts of substrates go beyond the beneficial endothelial effects (increasing blood flow, oxygen, and nutrients to muscles thus increasing clearance of waste products and increasing protein synthesis) and result in long term counterproductive effects.

The nitric oxide (NO) signaling pathway has also been identified in testicular Leydig cells (the cells that produce testosterone) and is coupled to cGMP production.⁵⁷¹⁵⁷²⁵⁷³ This signaling system appears to act in opposition to modulate testicular steroidogenesis, providing stimulation at lower concentrations of nitric oxide and inhibition at higher concentrations mediated by the direct effect of nitric oxide on the activities of steroidogenic enzymes.⁵⁷⁴⁵⁷⁵⁵⁷⁶ Thus, lower levels of testicular nitric oxide can be beneficial for testosterone production, but higher levels are detrimental.

The reasons behind nitric oxides effects on testicular steroidogenesis are complex and this is not the place to go into all the details. However, we'll be devoting an entire article on this subject in the near future.

There's no doubt that increasing nitric oxide can lead to short term improvements in exercise tolerance and performance, as well as producing more of a pump when training. These effects that users feel when using the high dose NO products make for good marketing but bad science.

The overall impression given by supplement companies with NO products, and articles on the Internet, including some studies, is that significantly increasing nitric oxide production over both the short and long term provides anabolic and performance enhancing effects.

The bottom line, however, is that the detrimental effects of long term excessive nitric oxide on skeletal muscle and especially on testosterone makes the use of nitric oxide supplements containing one or more of large amounts of L-arginine, L-arginine precursors such as citrulline, nitrates and nitrites counterproductive for muscle hypertrophy, body composition and athletic performance.

It's also been shown that nitric oxide and D-aspartate are factors in the control of testosterone production in the testes, with D-aspartate increasing and nitric oxide decreasing testosterone production.⁵⁷⁷⁵⁷⁸

Normally I simply cite the references as endnotes but in the case of nitric oxide and Daspartate I thought it would be useful for you to actually see not only the citations but the abstracts as well. As such I've included several from PubMed about both ingredients so you can see why I limit arginine/citrulline and increase the amount of d-aspartate in TestoBoost version VI.

Mol Cell Endocrinol. 2002 Aug 30;194(1-2):39-50.

Nitric oxide potently inhibits the rate-limiting enzymatic step in steroidogenesis.

Drewett JG, Adams-Hays RL, Ho BY, Hegge DJ.

Department of Pharmacology, Physiology and Therapeutics, University of North Dakota School of Medicine and Health Sciences, 501 North Columbia Road, 58203, Grand Forks, ND 58203, USA. james.drewett@uc.edu

Abstract

This study tested the hypothesis that nitric oxide (NO) inhibits the rate-limiting catalytic step in steroidogenesis, cytochrome P450 cholesterol side-chain cleaving enzyme (CYP11A1), independent of soluble guanylyl cyclase (GC-S) stimulation. To assess CYP11A1 activity, pregnenolone levels were quantified in murine adrenocortical Y1 cells in the presence of the 3beta-hydroxy-Delta(5)-steroid dehydrogenase inhibitor, 2alpha-cyano-17beta-hydroxy-4,4',17alpha-trimethylandrost-5-ene-3-one. The NO donor, (Z)-1-[2-(2-aminoethyl-N-(2-ammonioethyl)amino]diazen-1-ium-1,2-diolate(deta nonoate), inhibited vasoactive intestinal peptide-, forskolin- and 22alpha-hydroxycholesterol (22HC)-facilitated pregnenolonogenesis in the absence of GC-S activation and in the presence of a GC-S inhibitor, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ). CYP11A1 was also heterologously expressed in monkey COS7 cells. Deta nonoate inhibited 22HC-facilitated activity of the over-expressed enzyme in the absence of GC-S activation and in the presence of ODQ. The NO-independent, GC-S agonist, 1-benzyl-3-(5'-hydroxymethyl-2'-furyl)indazole did not inhibit steroidogenesis. The IC(50) for effects of free NO on CYP11A1 was potent and in the 0.4-2 microM range. These results support the hypothesis that NO inhibits the rate-limiting enzyme in steroidogenesis independent of GC-S activation.

Biol Reprod. 2010 Sep;83(3):434-42. Epub 2010 May 12.

Testosterone-induced modulation of nitric oxide-cGMP signaling pathway and androgenesis in the rat Leydig cells.

Andric SA, Janjic MM, Stojkov NJ, Kostic TS.

Reproductive Endocrinology and Signaling Group, Department of Biology and Ecology, Faculty of Sciences, University of Novi Sad, Novi Sad, Serbia.

Abstract

Testosterone, acting as a systemic and local factor, is one of the major regulatory molecules that initiate and maintain testicular function. In the present study, different experimental approaches were used to evaluate the role of testosterone in regulation of the nitric oxide (NO)-cGMP pathway in Leydig cells derived from normal and hypogonadotropic male rats treated with testosterone for 24 h and 2 wk. Realtime quantitative PCR and Western blot analysis revealed increased inducible NO synthase (NOS2) expression followed by increased NO secretion from Levdig cells ex vivo after continuous treatment with testosterone for 2 wk in vivo. The cGMP-specific phosphodiesterases Pde5, Pde6, and Pde9 were upregulated, whereas PRKG1 protein was decreased after a 2-wk testosterone treatment. Induction of Nos2 and Pde5 in Leydig cells was blocked by androgen receptor antagonist. In experimental hypogonadotropic hypogonadism, expression of NOS2 was significantly reduced, and treatment with testosterone increased NOS2 expression above control levels. PDE5 protein level was unchanged in hypogonadal rats, whereas treatment of hypogonadal rats with testosterone significantly increased it. In contrast, hypogonadism and testosterone replacement reduced PRKG1 protein in Leydig cells. In vitro treatment with testosterone caused gradually increased Nos2 gene expression followed by increased nitrite and cGMP production by purified Levdig cells. In summary, testosterone up-regulated NO signaling via increased NOS2 expression and contributed to down-regulation of cGMP signaling in Leydig cells. Thus, testosterone-induced modulation of NO-cGMP signaling may serve as a potent autocrine regulator of testicular steroidogenesis.

Med Hypotheses. 2000 Oct;55(4):310-3.

Is steroid deficiency the cause of tolerance in nitrate therapy?

Panesar NS.

Department of Chemical Pathology, the Chinese University of Hong Kong, Shatin, New Territories, Hong Kong. nspanesar@cuhk.edu.hk

Abstract

The award of the Nobel Prize in Physiology and Medicine for 1998 bears witness to the 'explosive' field of nitric oxide (NO), and who would have thought the explosive nitroglycerin owed its therapeutic effectiveness to this little molecule? NO is also involved in causing penile erection, which has brought sildenafil to the aid of patients with erectile dysfunction. However, emerging evidence in animals and in

vitro studies indicates that NO also inhibits steroidogenesis, which may have repercussions in humans. The decrease in androgen secretion may impact on secondary sexual characteristics, including penile size. The tolerance to the nitrate therapy in angina, characterized by volume expansion and not due to sodium retention, may also be related to steroid hormone deficiency. Decreased cortisol secretion may impair water excretion, resulting in volume expansion. Impaired aldosterone secretion would cause hyponatraemia with resultant raised renin. I hypothesize that continuous therapy with nitrates and sildenafil will result in diminished levels of steroid hormones with predicted sequelae.

Toxicol Appl Pharmacol. 2000 Dec 15;169(3):222-30.

Decreased steroid hormone synthesis from inorganic nitrite and nitrate: studies in vitro and in vivo.

Panesar NS, Chan KW.

Department of Chemical Pathology, The Chinese University of Hong Kong, Shatin, New Territories, SAR China. nspanesar@cuhk.edu.hk

Abstract

Nitrites and nitrates are consumed nonchalantly in diet. Organic nitrates are also used as vasodilators in angina pectoris, but the therapy is associated with tolerance whose mechanism remains elusive. Previously, we found inorganic nitrate inhibited steroidogenesis in vitro. Because adrenocorticoids regulate water and electrolyte metabolism, tolerance may ensue from steroid deficiency. We have studied the effects of nitrite and nitrate on in vitro synthesis and in vivo blood levels of steroid hormones. In vitro, nitrite was more potent than nitrate in inhibiting human chorionic gonadotropin (hCG)-stimulated androgen synthesis by Mouse Leydig Tumor cells. At concentrations above 42 mM, nitrite completely inhibited androgen synthesis, and, unlike nitrate, the inhibition was irreversible by increasing hCG concentration. The cAMP production remained intact but reduced with both ions. The nitric oxide (NO) scavenger, 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxy-3-oxide (c-PTIO) significantly increased hCG- or cAMP-stimulated androgen synthesis in all buffers, suggesting that NO is a chemical species directly involved in the nitrite/nitrate-induced inhibition. This is further supported by c-PTIO countering the inhibitory action of methylene blue on androgen synthesis. Rats given distilled water containing 50 mg/L NaNO(2) or NaNO(3) for 4 weeks drank significantly less daily. At the end, their blood corticosterone and testosterone levels were significantly decreased. The adrenocortical histology showed bigger lipid droplets, which are pathogonomic of impaired steroidogenesis. Nitrite and nitrate are metabolized to NO, which binds heme in cytochrome P450 enzymes, thereby inhibiting steroidogenesis. Therapeutic nitrates likewise may decrease adrenal (and gonadal) steroidogenesis. Cortisol deficiency would impair water excretion causing volume expansion, and aldosterone deficiency would cause sodium loss and raised renin. Paradoxically, volume expansion without sodium retention and raised renin has all been reported in tolerance.

D-Aspartic acid and nitric oxide as regulators of androgen production in boar testis.

Lamanna C, Assisi L, Vittoria A, Botte V, Di Fiore MM.

Department of Life Sciences, Second University of Naples, via Vivaldi 43, 81100 Caserta, Italy.

Abstract

D-Aspartic acid (D-Asp) and nitric oxide (NO) are two biologically active molecules playing important functions as neurotransmitters and neuromodulators of nerve impulse and as regulators of hormone production by endocrine organs. We studied the occurrence of D-Asp and NO as well as their effects on testosterone synthesis in the testis of boar. This model was chosen for our investigations because it contains more Leydig cells than other mammals. Indirect immunofluorescence applied to cryostat sections was used to evaluate the co-localization of D-Asp and of the enzyme nitric oxide synthase (NOS) in the same Leydig cells. D-Asp and NOS often co-existed in the same Leydig cells and were found, separately, in many other testicular cytotypes. D-Asp level was dosed by an enzymatic method performed on boar testis extracts and was 40+/-3.6 nmol/g of fresh tissue. NO measurement was carried out using a biochemical method by NOS activity determination and expressed as quantity of nitrites produced: it was 155.25+/-21.9 nmol/mg of tissue. The effects of the two molecules on steroid hormone production were evaluated by incubating testis homogenates, respectively with or without D-Asp and/or the NO-donor Larginine (L-Arg). After incubation, the testosterone presence was measured by immunoenzymatic assay (EIA). These in vitro experiments showed that the addition of D-Asp to incubated testicular homogenates significantly increased testosterone concentration, whereas the addition of L-Arg decreased the hormone production. Moreover, the inclusion of L-Arg to an incubation medium of testicular homogenates with added D-Asp, completely inhibited the stimulating effects of this enantiomer. Our results suggest an autocrine action of both D-Asp and NO on the steroidogenetic activity of the Leydig cell.

D-Aspartate

D-aspartate (D-Asp) was increased to 1.2 grams per dose for two reasons. First of all, aspartate has been shown to increase reproductive function and testosterone production in murine and human models.⁵⁷⁹⁵⁸⁰⁵⁸¹⁵⁸²⁵⁸³⁵⁸⁴ A study set up to see if a relationship exists between the presence of D-Asp and the hormonal activity⁵⁸⁵ had the following results:

1) Both D-Asp and testosterone are synthesized in rat testes in two periods of the animal's life: before birth, about the 17th day after fertilization and, after birth, at sexual maturity.

2) Immunocytochemical studies have demonstrated that this enantiomer is localized in Leydig and Sertoli cells.

3) In vivo experiments, consisting of i.p. injection of D-Asp to adult male rats, demonstrated that this amino acid accumulates in pituitary and testis (after 5 h, the accumulation was of 12 and 4-fold over basal values, respectively); simultaneously, luteinizing hormone, testosterone and progesterone significantly increased in the blood.

4) Finally, in vitro experiments, consisting of the incubation of D-Asp with isolated testes also demonstrated that this amino acid induces the synthesis of testosterone.

Recent studies have shown that D-Asp has similar effects in man in that it has a role in the regulation and physiological levels of luteinizing hormone and testosterone.⁵⁸⁶ For the full PDF version of the latter study go to <u>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774316/pdf/1477-7827-7-120.pdf</u>.

D-aspartate also increases growth hormone levels and has significant metabolic effects, including AMP production, improving the salvage of ATP from in muscle cells, and acts as an anaplerotic precursor and thus increases TCA flux and ATP formation. This aids in the synthesis of hormones, including testosterone and growth hormone.⁵⁸⁷

<u>J Endocrinol Invest.</u> 2016 Feb;39(2):207-13. doi: 10.1007/s40618-015-0333-4. Epub 2015 Jun 28. D-Aspartic acid stimulates steroidogenesis through the delay of LH receptor internalization in a mammalian Leydig cell line. Di Nisio A¹, De Toni L¹, Ferigo M², Rocca MS¹, Speltra E¹, Ferlin A¹, Foresta C³.

Abstract

PURPOSE:

Recent experimental evidence on non-mammalian animal models showed that D-Aspartic acid (d-Asp) administration increases testosterone levels through upregulation of StAR in Leydig cells. In this study, we aimed to investigate in vitro the signaling pathway associated with d-Asp stimulation in MA-10 murine Leydig cells.

METHODS:

MA-10 cells were stimulated with different concentrations of d-Asp, in presence or absence of hCG. Then total testosterone (T) levels in the culture medium were evaluated by electrochemiluminescence immunoassay, and StAR and LHR protein expressions were quantified by the means of Western blotting. LHR cellular localization after hormonal stimulation was assessed by immunofluorescence. RESULTS:

Stimulation with the sole d-Asp did not induce any relevant increase of T release from cultured cells. On the other hand, stimulation with hCG induced significant increase of T (P = 0.045). Concomitant stimulation with hCG and d-Asp, at the concentration of 0.1 and 1 nM, induced additional and significant increase of released T (P = 0.03 and P = 0.04, respectively). StAR protein levels increased after concomitant stimulation

with hCG and d-Asp 0.1 nM, compared with stimulation with the sole hCG (P = 0.02), whereas no variation in LHR protein expression was observed. Finally, d-Asp attenuated displacement of LHR staining, from cell membrane to cytoplasm, subsequent to hCG stimulation.

CONCLUSIONS:

In this study, we confirmed a steroidogenic role for d-Asp, in concert with hCG, on murine Leydig cells, which is mediated by an increase in StAR protein levels. In addition, we showed that the possible mechanism subtending the effect of d-Asp could rely on the modulation of LHR exposure on the cell membrane.

Reprod Biol Endocrinol. 2009 Oct 27;7:120.

The role and molecular mechanism of D-aspartic acid in the release and synthesis of LH and testosterone in humans and rats.

Topo E, Soricelli A, D'Aniello A, Ronsini S, D'Aniello G.

Source

1Stazione Zoologica Anton Dohrn, 80121, Villa Comunale, 80121, Napoli, Italy. enza.topo@szn.it

Abstract

BACKGROUND:

D-aspartic acid is an amino acid present in neuroendocrine tissues of invertebrates and vertebrates, including rats and humans. Here we investigated the effect of this amino acid on the release of LH and testosterone in the serum of humans and rats. Furthermore, we investigated the role of D-aspartate in the synthesis of LH and testosterone in the pituitary and testes of rats, and the molecular mechanisms by which this amino acid triggers its action.

METHODS:

For humans: A group of 23 men were given a daily dose of D-aspartate (DADAVIT) for 12 days, whereas another group of 20 men were given a placebo. For rats: A group of 10 rats drank a solution of either 20 mM D-aspartate or a placebo for 12 days. Then LH and testosterone accumulation was determined in the serum and D-aspartate accumulation in tissues. The effects of D-aspartate on the synthesis of LH and testosterone were gauged on isolated rat pituitary and Leydig cells. Tissues were incubated with D-aspartate, and then the concentration (synthesis) of LH and cGMP in the pituitary and of testosterone and cAMP in the Leydig cells was determined. RESULTS:

In humans and rats, sodium D-aspartate induces an enhancement of LH and testosterone release. In the rat pituitary, sodium D-aspartate increases the release and synthesis of LH through the involvement of cGMP as a second messenger, whereas in rat testis Leydig cells, it increases the synthesis and release of testosterone and cAMP is implicated as second messenger. In the pituitary and in testes D-Asp is synthesized by a D-aspartate racemase which convert L-Asp into D-Asp. The pituitary and testes possesses a high capacity to trapping circulating D-Asp from hexogen or endogen sources.

CONCLUSION:

D-aspartic acid is a physiological amino acid occurring principally in the pituitary gland and testes and has a role in the regulation of the release and synthesis of LH and testosterone in humans and rats.

Brain Res Rev. 2007 Feb;53(2):215-34. Epub 2006 Nov 21.

D-Aspartic acid: an endogenous amino acid with an important neuroendocrine role.

Source

Laboratory of Neurobiology, Stazione Zoologica A Dohrn, Villa Comunale 1, 80121 Napoli, Italy. daniello@szn.it Abstract

D-Aspartic acid (d-Asp), an endogenous amino acid present in vertebrates and invertebrates, plays an important role in the neuroendocrine system, as well as in the development of the nervous system. During the embryonic stage of birds and the early postnatal life of mammals, a transient high concentration of d-Asp takes place in the brain and in the retina. d-Asp also acts as a neurotransmitter/neuromodulator. Indeed, this amino acid has been detected in synaptosomes and in synaptic vesicles, where it is released after chemical (K(+) ion, ionomycin) or electric stimuli. Furthermore, d-Asp increases cAMP in neuronal cells and is transported from the synaptic clefts to presynaptic nerve cells through a specific transporter. In the endocrine system, instead, d-Asp is involved in the regulation of hormone synthesis and release. For example, in the rat hypothalamus, it enhances gonadotropin-releasing hormone (GnRH) release and induces oxytocin and vasopressin mRNA synthesis. In the

pituitary gland, it stimulates the secretion of the following hormones: prolactin (PRL), luteinizing hormone (LH), and growth hormone (GH) In the testes, it is present in Leydig cells and is involved in testosterone and progesterone release. Thus, a

hypothalamus-pituitary-gonads pathway, in which d-Asp is involved, has been formulated. In conclusion, the present work is a summary of previous and current research done on the role of d-Asp in the nervous and endocrine systems of invertebrates and vertebrates, including mammals.

Life Sci. 1996;59(2):97-104.

Involvement of D-aspartic acid in the synthesis of testosterone in rat testes.

D'Aniello A, Di Cosmo A, Di Cristo C, Annunziato L, Petrucelli L, Fisher G.

Source

Department of Biochemistry, Zoological Station of Naples, Italy.

Abstract

D-Aspartic acid (D-Asp) is an endogenous amino acid which occurs in many marine and terrestrial animals. In fetal and young rats, this amino acid occurs prevalently in nervous tissue, whereas at sexual maturity it occurs in endocrine glands and above all in pituitary and testes. Here, we have studied if a relationship exists between the presence of D-Asp and the hormonal activity. The following results were obtained: 1) Both D-Asp and testosterone are synthesized in rat testes in two periods of the animal's life: before birth, about the 17th day after fertilization and, after birth, at sexual maturity. 2) Immunocytochemical studies have demonstrated that this enantiomer is localized in Leydig and Sertoli cells. 3) In vivo experiments, consisting of i.p. injection of D-Asp to adult male rats, demonstrated that this amino acid accumulates in pituitary and testis (after 5 h, the accumulation was of 12 and 4-fold over basal values, respectively); simultaneously, luteinizing hormone, testosterone and progesterone significantly increased in the blood (1.6-fold, p < 0.05; 3.0-fold, p < 0.01 and 2.9-fold, p < 0.01, respectively). 4) Finally, in vitro experiments, consisting of the incubation of D-Asp with isolated testes also demonstrated that this amino acid induces the synthesis of testosterone. These results suggest that free D-Asp is involved in the steroidogenesis.

What Can You Expect from TestoBoost version VI?

First, let me be clear about what you can't expect from using TestoBoost version VI and that's the same effect as using moderate to high doses of anabolic steroids, including exogenous testosterone. The use of these hormones will raise the level of androgenic-anabolic hormones significantly above physiological levels, while at the same time shutting down the production of endogenous testosterone. TestoBoost won't do that.

What TestoBoost will do is ramp up your testosterone production from the ground up so that all normal pathways are accentuated, and none are shut down. We've already covered the ways that TestoBoost will do this. What we haven't discussed is what you can expect from its use.

The new TestoBoost version VI can double levels of free testosterone in those who have levels that are in the low normal range. Those who have testosterone levels in the high normal range generally get less of an effect, in many cases only increasing free testosterone levels by 15% or less. There are exceptions and I've seen TestoBoost increase testosterone levels to 10-20% above the upper limit of the normal range, but supraphysiological levels, while they occur are not the norm.

TestoBoost is especially effective in those who have depressed testosterone levels for a variety of reasons, including stress, training intensity and duration (see two abstracts below), and illness.

Considering all the testing I've done/supervised in the past fifteen plus years on people using TestoBoost this is what can be expected from its use.

- Men with low or below normal levels can expect an increase in free testosterone that can put them up as far as the mid normal range the increase can be anywhere from 15% to 200% depending on the initial levels.
- Men with mid-range testosterone levels can usually expect a 15 to 50% increase in free testosterone levels.
- Men in the high normal range can expect up to a 15% increase in free testosterone levels.
- In men with testosterone levels below the normal range the results are extremely variable, from no effect at all to raising free testosterone levels up to the mid normal range. The variability results from the many reasons that testosterone levels can plummet below normal levels.
- In women, the results are also extremely variable and can result in minimal effects (5-10% increase) up to a doubling of free testosterone levels.

A recent study found that the usual level used to determine testosterone deficiency shouldn't be one size fits all. Low normal levels in younger men may mean that they're testosterone deficient whereas the same levels in older men may be within the normal range.⁵⁸⁸ Thus in younger men with low but what is considered normal testosterone levels, TestoBoost will raise testosterone levels to what would going by this study actually be normal in the younger age group.

Health Benefits and Protective Effects of TestoBoost

Although TestoBoost is formulated to increase testosterone levels and enhance anabolism, it's also formulated to provide substantial health benefits. For example, it has several ingredients, including saw palmetto (serenoa repens), zinc, quercetin, GLA (in borage oil) and stinging nettle that enhance prostate health in males, and provide anti-inflammatory effects in both males and females.

Some of these ingredients also decrease the formation of dihydrotestosterone from testosterone,⁵⁸⁹ thus maximizing testosterone levels while at the same time decreasing the adverse effects of higher systemic and tissue levels of dihydrotestosterone, which includes adverse effects on the prostate and hair loss.⁵⁹⁰

TestoBoost also contains several potent antioxidants, such as alpha lipoic acid, beta carotene, vitamin C, vitamin E, Coenzyme Q10, turmeric, lycopene, and astaxanthin, which act to improve pituitary and testicular/ovarian function, and decrease the adverse effects of free radicals on the hypothalamic-pituitary-testicular/ovarian axis, and the associated pathways that are responsible for maximizing endogenous testosterone production.

For example, one study has found that vitamin E and vitamin C protect the testes from damage secondary to oxidant damage.⁵⁹¹ Alpha lipoic acid (ALA), because it is a Sulphur compound, can bind and help eliminate heavy metals such as copper, iron, mercury and cadmium, all of which can cause oxidant damage to the gonads (testes and ovaries).

Alpha lipoic acid (ALA) has a double antioxidant effect as it has significant antioxidant properties on its own, but also regenerates glutathione, the most important endogenous antioxidant. ALA and glutathione have been shown to have significant effects in decreasing mercury toxicity in the body.⁵⁹²

Forskolin alone and the combination of forskolin and antioxidants in TestoBoost impact on Leydig cell function (these are the testicular cells that make testosterone) and result in combating the normal decrease in testosterone seen with various toxins, aging and stress.⁵⁹³⁵⁹⁴⁵⁹⁵ Forskolin, along with increasing serum testosterone has also has been shown to help lose body fat and improve body composition.⁵⁹⁶

TestoBoost also contains several other vitamins, minerals and nutrients that are important for optimizing testosterone levels. These include vitamin A, vitamin B6, vitamin B12, niacin, calcium, magnesium, manganese, boron, zinc, ginger and Coenzyme Q10.

The bottom line is that TestoBoost version VI is the most effective testosterone booster on the market today. And although it doesn't contain any prohormones, which can have significant side effects, it surpasses any prohormone formulation in increasing testosterone levels and in providing several benefits including potent anabolic, anticatabolic and fat burning effects. As well it has significant effects in improving health, decreasing morbidity and enhancing healthy and productive lifespan.

NitAbol

If increasing your anabolic drive and maximizing muscle mass while minimizing body fat is important to you, check out <u>NitAbol</u>, the nighttime anabolic, fat burning combo that combines <u>TestoBoost</u> with <u>GHboost</u> and <u>Myosin Protein</u>.

NitAbol is also perfect for those who want to lose weight but would prefer to maintain the muscle they have and strictly lose body fat. In this case, I'd also recommend that you use <u>LipoFlush</u> as the ultimate fat loss supplement. Information on all these supplements can be found on my website at <u>https://metabolicdiet.com/shop/</u>.

References

- 1 Rastrelli G, Di Stasi V, Inglese F, Beccaria M, Garuti M, Di Costanzo D, Spreafico F, Greco GF, Cervi G, Pecoriello A, Magini A, Todisco T, Cipriani S, Maseroli E, Corona G, Salonia A, Lenzi A, Maggi M, De Donno G, Vignozzi L. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology. 2020 May 20:10.1111/andr.12821. doi: 10.1111/andr.12821. Online ahead of print. PMID: 32436355. Full text in PDF format available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/andr.12821.
- 2 Salciccia S, Del Giudice F, Gentile V, Mastroianni CM, Pasculli P, Di Lascio G, Ciardi MR, Sperduti I, Maggi M, De Berardinis E, Eisenberg ML, Sciarra A. Interplay between male testosterone levels and the risk for subsequent invasive respiratory assistance among COVID-19 patients at hospital admission. Endocrine. 2020 Oct 8:1-5. doi: 10.1007/s12020-020-02515-x. Online ahead of print. PMID: 33030665.
- 3 Lanser L, Burkert FR, Thommes L, Egger A, Hoermann G, Kaser S, Pinggera GM, Anliker M, Griesmacher A, Weiss G, Bellmann-Weiler R. Testosterone Deficiency Is a Risk Factor for Severe COVID-19. Front Endocrinol (Lausanne). 2021 Jun 18;12:694083. doi: 10.3389/fendo.2021.694083. PMID: 34226825; PMCID: PMC8253686.
- 4 Papadopoulos V, Li L, Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone? Andrology. 2020 Jul 18:10.1111/andr.12868. doi: 10.1111/andr.12868. Epub ahead of print. PMID: 32681716; PMCID: PMC7404939.
- 5 Infante M, Pieri M, Lupisella S, D'Amore L, Bernardini S, Fabbri A, Iannetta M, Andreoni M, Morello M. Low testosterone levels and high estradiol to testosterone ratio are associated with hyperinflammatory state and mortality in hospitalized men with COVID-19. Eur Rev Med Pharmacol Sci. 2021 Oct;25(19):5889-5903. doi: 10.26355/eurrev_202110_26865. PMID: 34661247.
- 6 Zheng S, Zou Q, Zhang D, Yu F, Bao J, Lou B, Xie G, Lin S, Wang R, Chen W, Wang Q, Teng Y, Feng B, Shen Y, Chen Y. Serum level of testosterone predicts disease severity of male COVID-19 patients and is related to T-cell immune modulation by transcriptome analysis. Clin Chim Acta. 2021 Nov 12:S0009-8981(21)00389-2. doi: 10.1016/j.cca.2021.11.006. Epub ahead of print. PMID: 34774827; PMCID: PMC8585551.
- 7 Vena W, Pizzocaro A, Maida G, Amer M, Voza A, Di Pasquale A, Reggiani F, Ciccarelli M, Fedeli C, Santi D, Lavezzi E, Lania AG, Mazziotti G; Humanitas COVID19 Task Force. Low testosterone predicts hypoxemic respiratory insufficiency and mortality in patients with COVID-19 disease: another piece in the COVID puzzle. J Endocrinol Invest. 2021 Nov 18:1–10. doi: 10.1007/s40618-021-01700-7. Epub ahead of print. PMID: 34792796; PMCID: PMC8600346.

- 8 Çayan S, Uguz M, Saylam B, Akbay E. Effect of serum total testosterone and its relationship with other laboratory parameters on the prognosis of coronavirus disease 2019 (COVID-19) in SARS-CoV-2 infected male patients: a cohort study. Aging Male. 2020 Sep 3:1-11. doi: 10.1080/13685538.2020.1807930. Online ahead of print. PMID: 32883151.
- 9 Campos RK, Camargos VN, Azar SR, Haines CA, Eyzaguirre EJ, Rossi SL. SARS-CoV-2 Infects Hamster Testes. Microorganisms. 2021; 9(6):1318. https://doi.org/10.3390/microorganisms9061318.
- 10 Morgentaler A, Traish A, Barua RS, Dandona P, Dhindsa S, Khera M, Saad F. Recognizing the True Value of Testosterone Therapy in Health Care. Androg Clin Res Ther. 2022 Dec 28;3(1):217-223. doi: 10.1089/andro.2022.0021. PMID: 36643964; PMCID: PMC9814113.
- 11 Ghanim H, Dhindsa S, Batra M, Green K, Abuaysheh S, Kuhadiya ND, Makdissi A, Chaudhuri A, Dandona P. Effect of Testosterone on FGF2, MRF4, and Myostatin in Hypogonadotropic Hypogonadism: Relevance to Muscle Growth. J Clin Endocrinol Metab. 2019 Jun 1;104(6):2094-2102. doi: 10.1210/jc.2018-01832. PMID: 30629183; PMCID: PMC6481910.
- 12 Toro-Urrego N, Garcia-Segura LM, Echeverria V, Barreto GE. Testosterone protects mitochondrial function and regulates neuroglobin expression in astrocytic cells exposed to glucose deprivation. Front Aging Neurosci. 2016;8:152.
- 13 Berg WT, Miner M. Hypogonadism and metabolic syndrome: review and update. Curr Opin Endocrinol Diabetes Obes. 2020 Dec;27(6):404-410.
- 14 Dandona P, Dhindsa S, Ghanim H, Saad F. Mechanisms underlying the metabolic actions of testosterone in humans: A narrative review. Diabetes Obes Metab. 2020 Sep 29. doi: 10.1111/dom.14206. Online ahead of print. PMID: 32991053.
- 15 Zhu A, Andino J, Daignault-Newton S, Chopra Z, Sarma A, Dupree JM. What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old. J Urol. 2022 Oct 25:101097JU000000000002928. doi: 10.1097/JU.000000000002928. Epub ahead of print. PMID: 36282060.
- 16 Asiwe JN, Ekene EN, Agbugba LC, Moke EG, Akintade AV, Ben-Azu B, Eruotor H, Daubry TME, Anachuna KK, Oyovwi MO. Ginkgo biloba supplement abates lead-induced endothelial and testicular dysfunction in Wistar rats via up-regulation of Bcl-2 protein expression, pituitary-testicular hormones and down-regulation of oxido-inflammatory reactions. J Trace Elem Med Biol. 2023 Sep;79:127216. doi: 10.1016/j.jtemb.2023.127216. Epub 2023 May 19. PMID: 37224746.
- 17 Rosati MV, Sancini A, Tomei F, Sacco C, Traversini V, De Vita A, De Cesare DP, Giammichele G, De Marco F, Pagliara F, Massoni F, Ricci L, Tomei G, Ricci S. Correlation between benzene and testosterone in workers exposed to urban pollution. Clin Ter. 2017 Nov-Dec;168(6):e380-e387.
- 18 Jaffar FHF, Osman K, Ismail NH, Chin KY, Ibrahim SF. Adverse Effects of Wi-Fi Radiation on Male Reproductive System: A Systematic Review. Tohoku J Exp Med. 2019 Jul;248(3):169-179.
- 19 Ren J, Cui J, Chen Q, Zhou N, Zhou Z, Zhang GH, Wu W, Yang H, Cao J. Low-level lead exposure is associated with aberrant sperm quality and reproductive hormone levels in Chinese male individuals: Results from the MARHCS study low-level lead exposure is associated with aberrant sperm quality. Chemosphere. 2019 Nov 26;244:125402.
- 20 Maciejewski R, Radzikowska-Büchner E, Flieger W, Kulczycka K, Baj J, Forma A, Flieger J. An Overview of Essential Microelements and Common Metallic Nanoparticles and Their Effects on Male Fertility. Int J Environ Res Public Health. 2022 Sep 4;19(17):11066. doi: 10.3390/ijerph191711066. PMID: 36078782; PMCID: PMC9518444.
- 21 Xuan L L, Shi J, Yao C S, Bai J Y, Qu F, Zhang J L, et al. Vam3, a resveratrol dimer, inhibits cigarette smoke-induced cell apoptosis in lungs by improving mitochondrial function[J]. Acta Pharmacol Sin, 2014, 35(6):779±791.
- 22 Zhong J, Trevisi L, Urch B, Lin X, Speck M, Coull BA, Liss G, Thompson A, Wu S, Wilson A, Koutrakis P, Silverman F, Gold DR, Baccarelli AA. B-vitamin Supplementation Mitigates Effects of Fine Particles on Cardiac Autonomic Dysfunction and Inflammation: A Pilot Human Intervention Trial. Sci Rep. 2017 Apr 3;7:45322.

- 23 Alamo A, Condorelli RA, Mongioì LM, Cannarella R, Giacone F, Calabrese V, La Vignera S, Calogero AE. Environment and Male Fertility: Effects of Benzo-α-Pyrene and Resveratrol on Human Sperm Function In Vitro. J Clin Med. 2019 Apr 25;8(4):561. doi: 10.3390/jcm8040561. PMID: 31027257; PMCID: PMC6518055.
- 24 Di Pasquale Mauro. Anabolic Steroid Side Effects Facts, Fiction and Treatment. (1989) MGD Press. ISBN 0-9692235-0-3.
- 25 Coward RM, Rajanahally S, Kovac JR, Smith RP, Pastuszak AW, Lipshultz LI.Anabolic steroid induced hypogonadism in young men. J Urol. 2013 Dec;190(6):2200-5.
- 26 Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism: diagnosis and treatment. Fertil Steril. 2014 May;101(5):1271-9.
- 27 Karavolos S, Reynolds M, Panagiotopoulou N, McEleny K, Scally M, Quinton R.Clin Endocrinol (Oxf). Male central hypogonadism secondary to exogenous androgens: a review of the drugs and protocols highlighted by the online community of users for prevention and/or mitigation of adverse effects. 2015 May;82(5):624-32.
- 28 Hengevoss J, Piechotta M, Müller D, Hanft F, Parr MK, Schänzer W, Diel P.J Steroid Biochem Mol Biol. Combined effects of androgen anabolic steroids and physical activity on the hypothalamicpituitary-gonadal axis. 2015 Jun;150:86-96.
- 29 Kanayama G, Hudson JI, DeLuca J, Isaacs S, Baggish A, Weiner R, Bhasin S, Pope HG Jr. Prolonged hypogonadism in males following withdrawal from anabolic-androgenic steroids: an under-recognized problem. Addiction. 2015 May;110(5):823-31.
- 30 Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, Gustafsson F, Faber J, Juul A, Kistorp C.PLoS One. Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. 2016 Aug 17;11(8):e0161208. doi: 10.1371/journal.pone.0161208. eCollection 2016.PMID: 27532478.
- 31 Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S.Sports Med. Effects of Anabolic Androgenic Steroids on the Reproductive System of Athletes and Recreational Users: A Systematic Review and Meta-Analysis. 2017 Sep;47(9):1869-1883.
- 32 Stárka L, Dušková M, Kolátorová L, Lapcík O. [Anabolic steroid induced hypogonadism in men: overview and case report]. Vnitr Lek. Fall 2017;63(9):598-603.
- 33 Vorona E, Nieschlag E. Adverse effects of doping with anabolic androgenic steroids in competitive athletics, recreational sports and bodybuilding. Minerva Endocrinol. 2018 Dec;43(4):476-488. doi: 10.23736/S0391-1977.18.02810-9. Epub 2018 Feb 19. PMID: 29463075.
- 34 Habous M, Giona S, Tealab A, Aziz M, Williamson B, Nassar M, Abdelrahman Z, Remeah A, Abdelkader M, Binsaleh S, Muir G. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. BJU Int. 2018 Nov;122(5):889-897.
- 35 Vilar Neto JO, da Silva CA, Lima AB, Caminha JSR, Pinto DV, Alves FR, Araújo JS, Daher EF. Disorder of hypothalamic-pituitary-gonadal axis induced by abusing of anabolic-androgenic steroids for short time: A case report. Andrologia. 2018 Nov;50(9):e13107. doi: 10.1111/and.13107. PMID: 30039560.
- 36 Alibegovic A. Testicular morphology in hypogonadotropic hypogonadism after the abuse of anabolic steroids. Forensic Sci Med Pathol. 2018 Dec;14(4):564-567.
- 37 Tatem AJ, Beilan J, Kovac JR, Lipshultz LI. Management of Anabolic Steroid-Induced Infertility: Novel Strategies for Fertility Maintenance and Recovery. World J Mens Health. 2019 Mar 26.
- 38 Vallée M, Mayo W, Le Moal M. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging. Brain Res Brain Res Rev. 2001 Nov;37(1-3):301-12. doi: 10.1016/s0165-0173(01)00135-7. PMID: 11744095.
- 39 Li L, Yao Y, Zhao J, Cao J, Ma H. Dehydroepiandrosterone protects against hepatic glycolipid metabolic disorder and insulin resistance induced by high fat via activation of AMPK-PGC-1a-NRF-1

and IRS1-AKT-GLUT2 signaling pathways. Int J Obes (Lond). 2020 May;44(5):1075-1086. doi: 10.1038/s41366-019-0508-8. Epub 2020 Jan 7. PMID: 31911660.

- 40 Li L, Yao Y, Zhao J, Cao J, Ma H. Dehydroepiandrosterone protects against hepatic glycolipid metabolic disorder and insulin resistance induced by high fat via activation of AMPK-PGC-1a-NRF-1 and IRS1-AKT-GLUT2 signaling pathways. Int J Obes (Lond). 2020 May;44(5):1075-1086. doi: 10.1038/s41366-019-0508-8. Epub 2020 Jan 7. PMID: 31911660.
- 41 Barbiero I, Bianchi M, Kilstrup-Nielsen C. Therapeutic potential of pregnenolone and pregnenolone methyl ether on depressive and CDKL5 deficiency disorders: Focus on microtubule targeting. J Neuroendocrinol. 2022 Feb;34(2):e13033. doi: 10.1111/jne.13033. Epub 2021 Sep 8. PMID: 34495563; PMCID: PMC9286658.
- 42 Zhang X, Xiao J, Liu T, He Q, Cui J, Tang S, Li X, Liu M. Low Serum Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate Are Associated With Coronary Heart Disease in Men With Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne). 2022 Jun 27;13:890029. doi: 10.3389/fendo.2022.890029. PMID: 35832423; PMCID: PMC9271610.
- 43 Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves wellbeing, mood, and sexual function in premenopausal women. Menopause. 2003;10:390–8.
- 44 Kingsberg SA, Woodard T. Female sexual dysfunction: focus on low desire. Obstet Gynecol. 2015 Feb;125(2):477-86.
- 45 Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. Expert Opin Pharmacother. 2015 Apr;16(6):875-87.
- 46 Jayasena CN, Alkaabi FM, Liebers CS, Handley T, Franks S, Dhillo WS. A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women. Clin Endocrinol (Oxf). 2019 Mar;90(3):391-414.
- 47 Beattie MC, Adekola L, Papadopoulos V, Chen H, Zirkin BR. Leydig cell aging and hypogonadism. Exp Gerontol. 2015 Feb 18. pii: S0531-5565(15)00076-5.
- 48 Tsujimura A. The Relationship between Testosterone Deficiency and Men's Health. World J Mens Health. 2013 Aug;31(2):126-35.
- 49 Chantada Abal V, Vázquez-Martul Pazos D, Portela Pereira P, Aller Rodriguez M, Barreiro Mallo A, Sánchez Vázquez A. [Testosterone deficit syndrome in the old male]. Arch Esp Urol. 2013 Sep;66(7):684-8.
- 50 Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab. 2006;91:2509–13.
- 51 Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007;92:4241–5.
- 52 Matsumoto AM. Andropause: Clinical implications of the decline in serum testosterone level with aging in men. J Gerontol A Biol Sci Med Sci. 2002;57:M76–99.
- 53 Seidman SN, Weiser M. Testosterone and mood in aging men. Psychiatr Clin North Am. 2013 Mar;36(1):177-82.
- 54 Basaria S. Reproductive aging in men. Endocrinol Metab Clin North Am. 2013 Jun;42(2):255-70.
- 55 Basaria S. Male hypogonadism. Lancet. 2014 Apr 5;383(9924):1250-63.
- 56 Schreiber G1, Ziemer M.The aging male--diagnosis and therapy of late-onset hypogonadism. J Dtsch Dermatol Ges. 2008 Apr;6(4):273-9.
- 57 McHenry Martin C. Testosterone deficiency in older men: a problem worth treating. Consult Pharm. 2012 Mar;27(3):152-63.
- 58 Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31.
- 59 Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf) 2003;58:710–7.

- 60 Fabbri E, An Y, Gonzalez-Freire M, Zoli M, Maggio M, Studenski SA, Egan JM, Chia CW, Ferrucci L. Bioavailable Testosterone Linearly Declines Over A Wide Age Spectrum in Men and Women From The Baltimore Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci. 2016 Sep;71(9):1202-9.
- 61 Liu Z, Liu J, Shi X, Wang L, Yang Y, Tao M, Fu Q. Comparing calculated free testosterone with total testosterone for screening and diagnosing late-onset hypogonadism in aged males: A cross-sectional study. J Clin Lab Anal. 2017 Sep;31(5).
- 62 Gettler LT, McDade TW, Agustin SS, Feranil AB, Kuzawa CW. Do testosterone declines during the transition to marriage and fatherhood relate to men's sexual behavior? Evidence from the Philippines. Horm Behav. 2013 Nov;64(5):755-63.
- 63 Holmboe SA, Priskorn L, Jørgensen N, Skakkebaek NE, Linneberg A, Juul A, Andersson AM. Influence of marital status on testosterone levels-A ten year follow-up of 1113 men. Psychoneuroendocrinology. 2017 Jun;80:155-161.
- 64 Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab. 2007 Jan;92(1):196-202.
- 65 Bhasin S (2007) Secular decline in male reproductive function: Is manliness threatened? J Clin Endocrin & Metab 92: 44–45
- 66 Perheentupa A, Mäkinen J, Laatikainen T, Vierula M, Skakkebaek NE, Andersson AM, Toppari J. A cohort effect on serum testosterone levels in Finnish men. Eur J Endocrinol. 2013 Jan 17;168(2):227-33.
- 67 Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002; 87:589–598
- 68 Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006 Jul;60(7):762-9.
- ⁶⁹ Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Jolles M, Pinotti R, Swan SH. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod Update. 2023 Mar 1;29(2):157-176. doi: 10.1093/humupd/dmac035. PMID: 36377604.
- 70 Mazur A, Westerman R, Mueller U. Is rising obesity causing a secular (age-independent) decline in testosterone among American men? PLoS One. 2013 Oct 16;8(10):e76178. doi: 10.1371/journal.pone.0076178. eCollection 2013.
- 71 Travison TG, Áraujo AB, Kupelian V, O'Donnell AB, McKinlay JB. Relative contribution of aging, health, and life-style factors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007;92:549–55.
- 72 Zhao YT, Qi YW, Hu CY, Chen SH, Liu Y. Advanced glycation end products inhibit testosterone secretion by rat Leydig cells by inducing oxidative stress and endoplasmic reticulum stress. Int J Mol Med. 2016 Aug;38(2):659-65.
- 73 Wang L, Hu W, Xia Y, Wang X. Associations between urinary polycyclic aromatic hydrocarbon metabolites and serum testosterone in U.S. adult males: National Health and nutrition examination survey 2011-2012. Environ Sci Pollut Res Int. 2017 Mar;24(8):7607-7616.
- 74 Klinefelter GR, Laskey JW, Amann RP. Statin drugs markedly inhibit testosterone production by rat Leydig cells in vitro: implications for men. Reprod Toxicol. 2014 Jun;45:52-8.
- 75 Medras M, Kubicka E, Józkow P, Slowinska-Lisowska M, Trzmiel-Bira A, Filus A. Treatment with statins and testosterone levels in men. Endokrynol Pol. 2014;65(6):464-8.
- 76 Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. J Androl. 2012 Jul-Aug;33(4):515-28. doi: 10.2164/jandrol.110.011874.
- 77 Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician. 2012 Jul;15(3 Suppl):ES145-56.

- 78 Singh P. Andropause: Current concepts. Indian J Endocrinol Metab. 2013 Dec;17(Suppl 3):S621-9.
- 79 Cook PS, Notelovitz M, Kalra PS, Kalra SP. Effect of diazepam on serum testosterone and the ventral prostate gland in male rats. Arch Androl. 1979;3(1):31-5.
- 80 Watanabe K, Motoya E, Matsuzawa N, Funahashi T, Kimura T, Matsunaga T, Arizono K, Yamamoto I. Marijuana extracts possess the effects like the endocrine disrupting chemicals. Toxicology. 2005 Jan 31;206(3):471-8.
- 81 Mandal TK, Das NS. Testicular toxicity in cannabis extract treated mice: association with oxidative stress and role of antioxidant enzyme systems. Toxicol Ind Health. 2010 Feb;26(1):11-23.
- 82 Hallinan R, Byrne A, Agho K, McMahon CG, Tynan P, Attia J. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. Int J Androl. 2009 Apr;32(2):131-9.
- 83 Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. Clin Endocrinol (Oxf). 2006; 65:125–131.
- 84 Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. Eur J Endocrinol. 2006 Sep;155(3):443-52.
- 85 Svartberg J, von Mühlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromsø study. Eur J Epidemiol. 2004;19(7):657-63.
- 86 Niskanen L, Laaksonen DE, Punnonen K, Mustajoki P, Kaukua J, Rissanen A. Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. Diabetes Obes Metab. 2004 May;6(3):208-15.
- 87 Ozata M, Oktenli C, Bingol N, Ozdemir IC. The effects of metformin and diet on plasma testosterone and leptin levels in obese men. Obes Res. 2001 Nov;9(11):662-7.
- 88 Gettler LT, McKenna JJ, McDade TW, Agustin SS, Kuzawa CW. Does cosleeping contribute to lower testosterone levels in fathers? Evidence from the Philippines. PLoS One. 2012;7(9):e41559.
- 89 Storey AE, Ziegler TE. Primate paternal care: Interactions between biology and social experience. Horm Behav. 2016 Jan;77:260-71.
- 90 Mascaro JS, Hackett PD, Rilling JK. Testicular volume is inversely correlated with nurturingrelated brain activity in human fathers. Proc Natl Acad Sci U S A. 2013 Sep 24;110(39):15746-51.
- 91 Gettler LT, McDade TW, Agustin SS, Feranil AB, Kuzawa CW. Do testosterone declines during the transition to marriage and fatherhood relate to men's sexual behavior? Evidence from the Philippines. Horm Behav. 2013 Nov;64(5):755-63.
- 92 Kohtz AS, Walf AA, Frye CA. Effects of non-contingent cocaine on 3alpha-androstanediol. I. Disruption of male sexual behavior. Physiol Behav. 2019 May 1;203:120-127.
- 93 Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician. 2012 Jul;15(3 Suppl):ES145-56.
- 94 O'Rourke TK Jr, Wosnitzer MS. Opioid-Induced Androgen Deficiency (OPIAD): Diagnosis, Management, and Literature Review. Curr Urol Rep. 2016 Oct;17(10):76.
- 95 Hsieh A, DiGiorgio L, Fakunle M, Sadeghi-Nejad H. Management Strategies in Opioid Abuse and Sexual Dysfunction: A Review of Opioid-Induced Androgen Deficiency. Sex Med Rev. 2018 Oct;6(4):618-623.
- 96 Coluzzi F, Billeci D, Maggi M, Corona G.Testosterone deficiency in non-cancer opioid-treated patients. J Endocrinol Invest. 2018 Dec;41(12):1377-1388.
- 97 Nathalie V. Goletiani, Jack H. Mendelson, Michelle B. Sholar, Arthur J. Siegel, Nancy K. Mello. Opioid and Cocaine Combined effect on Cocaine-Induced Changes in HPA and HPG Axes Hormones In Men Pharmacol Biochem Behav. Author manuscript; available in PMC 2010 May 12.
- 98 Alibegovic A. Testicular morphology in hypogonadotropic hypogonadism after the abuse of anabolic steroids. Forensic Sci Med Pathol. 2018 Dec;14(4):564-567.

- 99 Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S. Effects of Anabolic Androgenic Steroids on the Reproductive System of Athletes and Recreational Users: A Systematic Review and Meta-Analysis. Sports Med. 2017 Sep;47(9):1869-1883.
- 100 Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, Gustafsson F, Faber J, Juul A, Kistorp C. Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. PLoS One. 2016 Aug 17;11(8):e0161208.
- 101 Vilar Neto JO, da Silva CA, Lima AB, Caminha JSR, Pinto DV, Alves FR, Araújo JS, Daher EF. Disorder of hypothalamic-pituitary-gonadal axis induced by abusing of anabolic-androgenic steroids for short time: A case report. Andrologia. 2018 Nov;50(9):e13107.
- 102 Pirola I, Cappelli C, Delbarba A, Scalvini T, Agosti B, Assanelli D, Bonetti A, Castellano M. Anabolic steroids purchased on the Internet as a cause of prolonged hypogonadotropic hypogonadism. Fertil Steril. 2010 Nov;94(6):2331.e1-3.
- 103 Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism: diagnosis and treatment. Fertil Steril. 2014 May;101(5):1271-9.
- 104 Bhasin S, Gagliano-Jucá T, Huang G, Basaria S. Age-Related Changes in the Male Reproductive System. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. 2018 Dec 14.
- 105 Fui MN, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. Asian J Androl. 2014 Mar-Apr;16(2):223-31.
- 106 Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S. Risks and benefits of testosterone therapy in older men. Nat Rev Endocrinol. 2013 Jul;9(7):414-24.
- 107 Shimon I, Lubina A, Gorfine M, Ilany J. Feedback inhibition of gonadotropins by testosterone in men with hypogonadotropic hypogonadism: comparison to the intact pituitary-testicular axis in primary hypogonadism. J Androl. 2006 May-Jun;27(3):358-64.
- 108 Gettler LT, Kuo PX, Bechayda SA. Fatherhood and psychobiology in the Philippines: Perspectives on joint profiles and longitudinal changes of fathers' estradiol and testosterone. Am J Hum Biol. 2018 Nov;30(6):e23150.
- 109 Holmboe SA, Priskorn L, Jørgensen N, Skakkebaek NE, Linneberg A, Juul A, Andersson AM. Influence of marital status on testosterone levels-A ten year follow-up of 1113 men. Psychoneuroendocrinology. 2017 Jun;80:155-161.
- 110 Gettler LT, Sarma MS, Gengo RG, Oka RC, McKenna JJ. Adiposity, CVD risk factors and testosterone: Variation by partnering status and residence with children in US men. Evol Med Public Health. 2017 Feb 11;2017(1):67-80.
- 111 Gettler LT, Oka RC. Are testosterone levels and depression risk linked based on partnering and parenting? Evidence from a large population-representative study of U.S. men and women. Soc Sci Med. 2016 Aug;163:157-67.
- 112 Lord C, Sekerovic Z, Carrier J. Sleep regulation and sex hormones exposure in men and women across adulthood. Pathol Biol (Paris). 2014 Oct;62(5):302-10.
- 113 Cadegiani FA, Kater CE. Novel causes and consequences of overtraining syndrome: the EROS-DISRUPTORS study. BMC Sports Sci Med Rehabil. 2019 Sep 18;11:21.
- 114 He M, Zhou W, Liu K, Wang X, Liu C, Shi F, Cao J, Chen Q. The prevalence of male rotating shift work correlates with reduced total fertility rate: an ecological study of 54,734 reproductive-aged males in 35 European countries between 2000 and 2015. Chronobiol Int. 2021 Jul;38(7):1072-1082.
- 115 Maluin SM, Osman K, Jaffar FHF, Ibrahim SF. Effect of Radiation Emitted by Wireless Devices on Male Reproductive Hormones: A Systematic Review. Front Physiol. 2021 Sep 24;12:732420. doi: 10.3389/fphys.2021.732420. PMID: 34630149; PMCID: PMC8497974.

- 116 Chu KY, Khodamoradi K, Blachman-Braun R, Dullea A, Bidhan J, Campbell K, Zizzo J, Israeli J, Kim M, Petrella F, Ibrahim E, Ramasamy R. Effect of Radiofrequency Electromagnetic Radiation Emitted by Modern Cellphones on Sperm Motility and Viability: An In Vitro Study. Eur Urol Focus. 2023 Jan;9(1):69-74. doi: 10.1016/j.euf.2022.11.004. Epub 2022 Nov 12. PMID: 36379868; PMCID: PMC9928907.
- 117 Chu KY, Petrella F, Bidhan J. Mobile cell phone use and impact on male fertility potential-an environmental pollutant that needs more research. Fertil Steril. 2023 Dec;120(6):1171-1172. doi: 10.1016/j.fertnstert.2023.10.019. Epub 2023 Oct 14. PMID: 37839725.
- 118 Di Pasquale MG. Anabolic Steroid Side Effects Facts, Fiction and Treatment., Drugs in Sports Series Book Number Two. MGD Press. Copyright 1989 by Mauro G. Di Pasquale.
- 119 Zhang S, Mo J, Wang Y, Ni C, Li X, Zhu Q, Ge RS. Endocrine disruptors of inhibiting testicular 3ß-hydroxysteroid dehydrogenase. Chem Biol Interact. 2019 Apr 25;303:90-97.
- 120 Al-Saleh I, Coskun S, Al-Doush I, Al-Rajudi T, Abduljabbar M, Al-Rouqi R, Palawan H, Al-Hassan S. The relationships between urinary phthalate metabolites, reproductive hormones and semen parameters in men attending in vitro fertilization clinic. Sci Total Environ. 2019 Mar 25;658:982-995. doi: 10.1016/j.scitotenv.2018.12.261.
- 121 Sobolewski M, Anderson T, Conrad K, Marvin E, Klocke C, Morris-Schaffer K, Allen JL, Cory-Slechta DA. Developmental exposures to ultrafine particle air pollution reduces early testosterone levels and adult male social novelty preference: Risk for children's sex-biased neurobehavioral disorders. Neurotoxicology. 2018 Sep;68:203-211.
- 122 Dzhambov A, Dimitrova D. Chronic noise exposure and testosterone deficiency -- meta-analysis and meta-regression of experimental studies in rodents. Endokrynol Pol. 2015;66(1):39-46.
- 123 Wielogórska E, Elliott CT, Danaher M, Connolly L. Endocrine disruptor activity of multiple environmental food chain contaminants. Toxicol In Vitro. 2015 Feb;29(1):211-20.
- 124 Orton F, Ermler S, Kugathas S, Rosivatz E, Scholze M, Kortenkamp A. Mixture effects at very low doses with combinations of anti-androgenic pesticides, antioxidants, industrial pollutant and chemicals used in personal care products. Toxicol Appl Pharmacol. 2014 Aug 1;278(3):201-8.
- 125 Kortenkamp A. Ten years of mixing cocktails: a review of combination effects of endocrinedisrupting chemicals. Environ Health Perspect. 2007 Dec;115 Suppl 1:98-105.
- 126 Baspinar O, Bayram F, Korkmaz S, Aksu M, Kocer D, Dizdar OS, Simsek Y, Toth PP. The effects of statin treatment on adrenal and sexual function and nitric oxide levels in hypercholesterolemic male patients treated with a statin. J Clin Lipidol. 2016 Nov Dec;10(6):1452-1461.
- 127 Samplaski MK, Nangia AK. Adverse effects of common medications on male fertility. Nat Rev Urol. 2015 Jul;12(7):401-13.
- 128 Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5a-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. J Sex Med. 2011 Mar;8(3):872-84.
- 129 Hirshburg JM, Kelsey PA, Therrien CA, Gavino AC, Reichenberg JS. Adverse Effects and Safety of 5-alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review. J Clin Aesthet Dermatol. 2016 Jul;9(7):56-62.
- 130 Wei L, Lai EC, Kao-Yang YH, Walker BR, MacDonald TM, Andrew R. Incidence of type 2 diabetes mellitus in men receiving steroid 5a-reductase inhibitors: population based cohort study. BMJ. 2019 Apr 10;365:I1204.
- 131 Solomon ZJ, Mirabal JR, Mazur DJ, Kohn TP, Lipshultz LI, Pastuszak AW. Selective Androgen Receptor Modulators: Current Knowledge and Clinical Applications. Sex Med Rev. 2019 Jan;7(1):84-94.
- 132 Mohideen H, Hussain H, Dahiya DS, Wehbe H. Selective Androgen Receptor Modulators: An Emerging Liver Toxin. J Clin Transl Hepatol. 2023 Feb 28;11(1):188-196. doi: 10.14218/JCTH.2022.00207. Epub 2022 Nov 4. PMID: 36479151; PMCID: PMC9647117.

- 133 Arayangkool C, Gozun M, Tanariyakul M, Techasatian W, Leesutipornchai T, Nishimura Y. Bile Cast Nephropathy Because of Acute Liver Injury Associated With Selective Androgen Receptor Modulators. ACG Case Rep J. 2023 Jul 26;10(7):e01105. doi: 10.14309/crj.000000000001105. PMID: 37501938; PMCID: PMC10371315.
- 134 Garg N, Hansson A, Knych HK, Stanley SD, Thevis M, Bondesson U, Hedeland M, Globisch D. Structural elucidation of major selective androgen receptor modulator (SARM) metabolites for doping control. Org Biomol Chem. 2018 Jan 31;16(5):698-702.
- 135 Thevis M, Schänzer W. Detection of SARMs in doping control analysis. Mol Cell Endocrinol. 2018 Mar 15;464:34-45.
- 136 Zierau O, Kolodziejczyk A, Vollmer G, Machalz D, Wolber G, Thieme D, Keiler AM. Comparison of the three SARMs RAD-140, GLPG0492 and GSK-2881078 in two different in vitro bioassays, and in an in silico androgen receptor binding assay. J Steroid Biochem Mol Biol. 2019 Feb 27;189:81-86.
- 137 Borst SE, Shuster JJ, Zou B, Ye F, Jia H, Wokhlu A, Yarrow JF. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. BMC Med. 2014 Nov 27;12:211.
- 138 Cervi A, Balitsky AK. Testosterone use causing erythrocytosis. CMAJ. 2017 Oct 16;189(41):E1286-E1288.
- 139 Aghazadeh M, Pastuszak AW, Johnson WG, McIntyre MG, Hsieh TM, Lipshultz LI. Elevated Dihydrotestosterone is Associated with Testosterone Induced Erythrocytosis. J Urol. 2015 Jul;194(1):160-5.
- 140 Rhoden EL, Morgentaler A. Treatment of testosterone-induced gynecomastia with the aromatase inhibitor, anastrozole. Int J Impot Res. 2004 Feb;16(1):95-7.
- 141 Tan RS, Cook KR, Reilly WG. High estrogen in men after injectable testosterone therapy: the low T experience. Am J Mens Health. 2015 May;9(3):229-34.
- 142 Maden M. Retinoic acid in the development, regeneration and maintenance of the nervous system. Nat Rev Neurosci 2007; 8:755–765. Vitamin A and the epigenome
- 143 Theodosiou M, Laudet V, Schubert M. From carrot to clinic: an overview of the retinoic acid signaling pathway. Cell Mol Life Sci. 2010 May;67(9):1423-45.
- 144 Amann PM, Eichmüller SB, Schmidt J, Bazhin AV. Regulation of gene expression by retinoids. Curr Med Chem. 2011;18(9):1405-12.
- 145 Noy N. Non-classical Transcriptional Activity of Retinoic Acid. Subcell Biochem. 2016;81:179-199.
- 146 Bar-El Dadon S, Reifen R. Vitamin A and the epigenome. Crit Rev Food Sci Nutr. 2017 Jul 24;57(11):2404-2411.
- 147 Mahmoudi MJ, Saboor-Yaraghi AA, Zabetian-Targhi F, Siassi F, Zarnani AH, Eshraghian MR, Shokri F, Rezaei N, Kalikias Y, Mahmoudi M. Vitamin A Decreases Cytotoxicity of Oxidized Low-Density Lipoprotein in Patients with Atherosclerosis. Immunol Invest. 2016;45(1):52-62.
- 148 Vieira AV. Retinoid endocrinology from metabolism to cellular signaling. Subcell Biochem. 1998;30:29-51.
- 149 Clagett-Dame M, Knutson D. Vitamin A in reproduction and development. Nutrients. 2011;3:385– 428.
- 150 Livera G, Rouiller-Fabre V, Pairault C, Levacher C, Habert R. Regulation and perturbation of testicular functions by vitamin A. Reproduction. 2002 Aug;124(2):173-80.
- 151 Livera G, Rouiller-Fabre V, Pairault C, Levacher C, Habert R. Regulation and perturbation of testicular functions by vitamin A. Reproduction. 2002 Aug;124(2):173-80.
- 152 Appling DR, Chytil F. Evidence of a role for retinoic acid (vitamin A-acid) in the maintenance of testosterone production in male rats. Endocrinology. 1981 Jun;108(6):2120-4.
- 153 Chaudhary LR, Hutson JC, Stocco DM. Effect of retinol and retinoic acid on testosterone production by rat Leydig cells in primary culture. Biochem Biophys Res Commun. 1989 Jan 31;158(2):400-6.

- 154 Huang HS, Dyrenfurth I, Gunsalus GL, Hembree WC. Effect of vitamin A deficiency upon gonadotropin response to gonadotropin-releasing hormone. Biol Reprod. 1985 Dec;33(5):1176-87.
- 155 Hogarth CA, Griswold MD. The key role of vitamin A in spermatogenesis. J Clin Invest. 2010 Apr;120(4):956-62.
- 156 Hogarth CA, Griswold MD. Retinoic acid regulation of male meiosis. Curr Opin Endocrinol Diabetes Obes. 2013 Jun;20(3):217-23.
- 157 Noy N. The one-two punch: Retinoic acid suppresses obesity both by promoting energy expenditure and by inhibiting adipogenesis. Adipocyte. 2013 Jul 1;2(3):184-7.
- 158 Berry DC, DeSantis D, Soltanian H, Croniger CM, Noy N. Retinoic acid upregulates preadipocyte genes to block adipogenesis and suppress diet-induced obesity. Diabetes. 2012 May;61(5):1112-21.
- 159 Wang B, Yang Q, Harris CL, Nelson ML, Busboom JR, Zhu MJ, Du M. Nutrigenomic regulation of adipose tissue development role of retinoic acid: A review. Meat Sci. 2016 Oct;120:100-6.
- 160 Berry DC, Noy N. All-trans-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor beta/delta and retinoic acid receptor. Mol Cell Biol. 2009 Jun;29(12):3286-96.
- 161 Cassani B, Villablanca EJ, De Calisto J, Wang S, Mora JR. Vitamin A and immune regulation: role of retinoic acid in gutassociated dendritic cell education, immune protection and tolerance. Mol Aspects Med 2012; 33 : 63-76.
- 162 Tiruvalluru M, Ananthathmakula P, Ayyalasomayajula V, Nappanveettil G, Ayyagari R, Reddy GB. Vitamin A supplementation ameliorates obesity-associated retinal degeneration in WNIN/Ob rats. Nutrition 2013; 29 : 298-304.
- 163 Jeyakumar SM, Vijaya Kumar P, Giridharan NV, Vajreswari A. Vitamin A improves insulin sensitivity by increasing insulin receptor phosphorylation through protein tyrosine phosphatase 1B regulation at early age in obese rats of WNIN/ Ob strain. Diabetes Obes Metab 2011; 13 : 955-8.
- 164 Ribeiro Nogueira C, Ramalho A, Lameu E, Da Silva Franca CA, David C, Accioly E. Serum concentrations of vitamin A and oxidative stress in critically ill patients with sepsis. Nutr Hosp. 2009 May-Jun;24(3):312-7.
- 165 Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol 2008; 8 : 685-98.
- 166 Márquez M, Yépez CE, Sútil-Naranjo R, Rincón M. Basic aspects and measurement of the antioxidant vitamins A and E. Invest Clin. 2002 Sep;43(3):191-204.
- 167 Brown CC, Noelle RJ. Seeing through the dark: New insights into the immune regulatory functions of vitamin A. Eur J Immunol. 2015 May;45(5):1287-95.
- 168 Jeyakumar SM, Vajreswari A. Vitamin A as a key regulator of obesity & its associated disorders: Evidences from an obese rat model. Indian J Med Res. 2015 Mar;141(3):275-84.
- 169 Yasmeen R, Jeyakumar SM, Reichert B, Yang F, Ziouzenkova O. The contribution of vitamin A to autocrine regulation of fat depots. Biochim Biophys Acta. 2012 Jan;1821(1):190-7.
- 170 Jeyakumar SM, Vajreswari A, Giridharan NV. Chronic dietary vitamin A supplementation regulates obesity in an obese mutant WNIN/Ob rat model. Obesity (Silver Spring). 2006 Jan;14(1):52-9.
- 171 Zulet AM, Puchau B, Hermsdorff HHM, Navarro C, Martinz JA. Vitamin A intake is inversely related with adiposity in healthy young adults. J Nutr Sci Vitaminol (Tokyo) 2008; 54 : 347-52.
- 172 Yasmeen R, Jeyakumar SM, Reichert B, Yang F, Ziouzenkova O. The contribution of vitamin A to autocrine regulation of fat depots. Biochim Biophys Acta 2012; 1821 : 190-7.
- 173 Takumi N, Shirakawa H, Ohsaki Y, Ito A, Watanabe T, Giriwono PE, Sato T, Komai M. Dietary vitamin K alleviates the reduction in testosterone production induced by lipopolysaccharide administration in rat testis. Food Funct. 2011 Jul;2(7):406-11.
- 174 Kawata A, Murakami Y, Suzuki S, Fujisawa S. Anti-inflammatory Activity of ß-Carotene, Lycopene and Tri-n-butylborane, a Scavenger of Reactive Oxygen Species. In Vivo. 2018 Mar-Apr;32(2):255-264.

- 175 Bonet ML, Canas JA, Ribot J, Palou A. Carotenoids and their conversion products in the control of adipocyte function, adiposity and obesity. Arch Biochem Biophys. 2015 Apr 15;572:112-125.
- 176 Bonet ML, Canas JA, Ribot J, Palou A. Carotenoids in Adipose Tissue Biology and Obesity. Subcell Biochem. 2016;79:377-414.
- 177 Xia LZ, Jiang MZ, Liu LL, Wu Y, Zhang YL, Yang LX, Shen XY, Zhang QY, Lin M, Gao HT. Quercetin inhibits testicular toxicity induced by the mixture of three commonly used phthalates in rats. J Sci Food Agric. 2023 Feb;103(3):1541-1549. doi: 10.1002/jsfa.12251. Epub 2022 Oct 18. PMID: 36197122.
- 178 Orazizadeh M, Khorsandi L, Absalan F, Hashemitabar M, Daneshi E. Effect of beta-carotene on titanium oxide nanoparticles-induced testicular toxicity in mice. J Assist Reprod Genet. 2014 May;31(5):561-8.
- 179 Khorsandi L, Orazizadeh M, Moradi-Gharibvand N, Hemadi M, Mansouri E. Beneficial effects of quercetin on titanium dioxide nanoparticles induced spermatogenesis defects in mice. Environ Sci Pollut Res Int. 2017 Feb;24(6):5595-5606.
- 180 Tvrdá E, Kovác J, Ferenczyová K, Kalocayová B, Duracka M, Benko F, Almášiová V, Barteková M. Quercetin Ameliorates Testicular Damage in Zucker Diabetic Fatty Rats through Its Antioxidant, Anti-Inflammatory and Anti-Apoptotic Properties. Int J Mol Sci. 2022 Dec 16;23(24):16056. doi: 10.3390/ijms232416056. PMID: 36555696; PMCID: PMC9781092.
- 181 Xia LZ, Jiang MZ, Liu LL, Wu Y, Zhang YL, Yang LX, Shen XY, Zhang QY, Lin M, Gao HT. Quercetin inhibits testicular toxicity induced by the mixture of three commonly used phthalates in rats. J Sci Food Agric. 2023 Feb;103(3):1541-1549. doi: 10.1002/jsfa.12251.
- 182 Kawata A, Murakami Y, Suzuki S, Fujisawa S. Anti-inflammatory Activity of ß-Carotene, Lycopene and Tri-n-butylborane, a Scavenger of Reactive Oxygen Species. In Vivo. 2018 Mar-Apr;32(2):255-264.
- 183 von Lintig J. Provitamin A metabolism and functions in mammalian biology. Am J Clin Nutr. 2012 Nov;96(5):1234S-44S.
- 184 Parra M, Stahl S, Hellmann H. Vitamin B6 and Its Role in Cell Metabolism and Physiology. Cells. 2018 Jul 22;7(7):84. doi: 10.3390/cells7070084.
- 185 Bingjun Qian, Shanqi Shen, Jianhua Zhang, Pu Jing Effects of Vitamin B6 Deficiency on the Composition and Functional Potential of T Cell Populations J Immunol Res. 2017; 2017: 2197975. Published online 2017 Mar 6. doi: 10.1155/2017/2197975
- 186 Zemel MB, Bruckbauer A. Effects of a leucine and pyridoxine-containing nutraceutical on fat oxidation, and oxidative and inflammatory stress in overweight and obese subjects. Nutrients. 2012 Jun;4(6):529-41.
- 187 Zemel MB, Bruckbauer A. Effects of a leucine and pyridoxine-containing nutraceutical on body weight and composition in obese subjects. Diabetes Metab Syndr Obes. 2013 Aug 23;6:309-15.
- 188 Zheng Y, Ma AG, Zheng MC, Wang QZ, Liang H, Han XX, Schouten EG. B Vitamins Can Reduce Body Weight Gain by Increasing Metabolism-related Enzyme Activities in Rats Fed on a High-Fat Diet. Curr Med Sci. 2018 Feb;38(1):174-183.
- 189 Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014 Sep 4;349:g5226.
- 190 Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, Ueland PM, Yajnik C. Vitamin B12 deficiency. Nat Rev Dis Primers. 2017 Jun 29;3:17040.
- 191 Gräsbeck R. Hooked to vitamin B12 since 1955: a historical perspective. Biochimie. 2013 May;95(5):970-5.
- 192 Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev 2003;(3):CD004326.
- 193 Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. Nutr Rev 1996;54:382-90.

- 194 Boxmeer JC, Smit M, Weber RF, Lindemans J, Romijn JC, Eijkemans MJ, Macklon NS, Steegers-Theunissen RP. Seminal plasma cobalamin significantly correlates with sperm concentration in men undergoing IVF or ICSI procedures. J Androl. 2007 Jul-Aug;28(4):521-7.
- 195 Watanabe T, Ohkawa K, Kasai S, Ebara S, Nakano Y, Watanabe Y. The effects of dietary vitamin B12 deficiency on sperm maturation in developing and growing male rats. Congenit Anom (Kyoto). 2003 Mar;43(1):57-64.
- 196 Kawata T, Tamiki A, Tashiro A, Suga K, Kamioka S, Yamada K, Wada M, Tanaka N, Tadokoro T, Maekawa A. Effect of vitamin B12-deficiency on testicular tissue in rats fed by pair-feeding. Int J Vitam Nutr Res. 1997;67(1):17-21.
- 197 Kawata T, Takada T, Morimoto F, Fujimoto N, Tanaka N, Yamada K, Wada M, Tadokoro T, Maekawa A. Effects of vitamin B12-deficiency on testes tissue in rats. J Nutr Sci Vitaminol (Tokyo). 1992 Aug;38(4):305-16.
- 198 Jatoi S, Hafeez A, Riaz SU, Ali A, Ghauri MI, Zehra M. Low Vitamin B12 Levels: An Underestimated Cause Of Minimal Cognitive Impairment And Dementia. Cureus. 2020 Feb 13;12(2):e6976. doi: 10.7759/cureus.6976. PMID: 32206454.
- 199 Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol. 2010 Jan;148(2):195-204.
- 200 Kozyraki R, Cases O. Vitamin B12 absorption: mammalian physiology and acquired and inherited disorders. Biochimie. 2013 May;95(5):1002-7.
- 201 Buvat DR. Use of metformin is a cause of vitamin B12 deficiency. Am Fam Physician 2004;69:264.
- 202 Kapadia CR. Vitamin B12 in health and disease: part I--inherited disorders of function, absorption, and transport. Gastroenterologist. 1995 Dec;3(4):329-44.
- 203 Woo KS, Kwok TC, Celermajer DS. Vegan diet, subnormal vitamin B-12 status and cardiovascular health. Nutrients. 2014 Aug 19;6(8):3259-73.
- 204 Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014 Sep 4;349:g5226.
- 205 Venderley AM, Campbell WW. Vegetarian diets: nutritional considerations for athletes. Sports Med. 2006;36(4):293-305.
- 206 Herrmann M, Obeid R, Scharhag J, Kindermann W, Herrmann W. Altered vitamin B12 status in recreational endurance athletes. Int J Sport Nutr Exerc Metab. 2005 Aug;15(4):433-41.
- 207 Baltaci D, Kutlucan A, Turker Y, Yilmaz A, Karacam S, Deler H, Ucgun T, Kara IH. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas (Zenica). 2013 Aug;10(2):203-10.
- 208 Knight BA, Shields BM, Brook A, Hill A, Bhat DS, Hattersley AT, Yajnik CS. Lower Circulating B12 Is Associated with Higher Obesity and Insulin Resistance during Pregnancy in a Non-Diabetic White British Population. PLoS One. 2015 Aug 19;10(8):e0135268. doi:
- 10.1371/journal.pone.0135268. eCollection 2015.
- 209 Al-Daghri NM, Rahman S, Sabico S, Yakout S, Wani K, Al-Attas OS, Saravanan P, Tripathi G, McTernan PG, Alokail MS. Association of Vitamin B12 with Pro-Inflammatory Cytokines and Biochemical Markers Related to Cardiometabolic Risk in Saudi Subjects. Nutrients. 2016 Sep 6;8(9).
- 210 Shen L, Ji HF. Associations between Homocysteine, Folic Acid, Vitamin B12 and Alzheimer's Disease: Insights from Meta-Analyses. J Alzheimers Dis. 2015;46(3):777-90.
- 211 Sjodin B, Hellsten Westing Y, Apple FS. Biochemical mechanisms for oxygen free radical formation during exercise. Sports Med 1990;10(4):236-54.
- 212 Lodhi GM, Latif R, Hussain MM, Naveed AK, Aslam M. Effect of ascorbic acid and alpha tocopherol supplementation on acute restraint stress induced changes in testosterone, corticosterone and nor epinephrine levels in male Sprague Dawley rats. J Ayub Med Coll Abbottabad. 2014 Jan-Mar;26(1):7-11.

- 213 Umeda F, Kato K, Muta K, Ibayashi H. Effect of vitamin E on function of pituitary-gonadal axis in male rats and human subjects. Endocrinol Jpn. 1982 Jun;29(3):287-92. doi: 10.1507/endocri1954.29.287. PMID: 6816576.
- 214 Zhu Q, Emanuele MA, LaPaglia N, Kovacs EJ, Emanuele NV. Vitamin E prevents ethanolinduced inflammatory, hormonal, and cytotoxic changes in reproductive tissues. Endocrine. 2007 Aug;32(1):59-68. doi: 10.1007/s12020-007-9010-5. Epub 2007 Oct 16. PMID: 17992603.
- 215 Shirpoor A, Norouzi L, Khadem-Ansari MH, Ilkhanizadeh B, Karimipour M. The Protective Effect of Vitamin E on Morphological and Biochemical Alteration Induced by Pre and Postnatal Ethanol Administration in the Testis of Male Rat Offspring: A Three Months Follow-up Study. J Reprod Infertil. 2014 Jul;15(3):134-41. PMID: 25202670; PMCID: PMC4138419.
- 216 Mora-Esteves C, Shin D. Nutrient supplementation: improving male fertility fourfold. Semin Reprod Med. 2013 Jul;31(4):293-300.
- 217 Berger MM. Can oxidative damage be treated nutritionally? Clin Nutr. 2005; 24(2):172-83.
- 218 Nagpal S, Na S, Rathnachalam R. Non-Calcemic Actions of Vitamin D Receptor Ligands. Endocr Rev. 2005 Mar 29;
- 219 Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and ß cell dysfunction. Am J Clin Nutr 2004;79:820–5.
- 220 Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380–5.
- 221 Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380–5.
- 222 Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, Yanovski J 2004 The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 89:1196–1199.
- 223 Arunabh S, Pollack S, Yeh J, Aloia JF 2003 Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endocrinol Metab 88:157–161.
- 224 Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. J Intern Med 2000;247:260–8.
- 225 Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338:777–83
- 226 Weaver CM, Fleet JC. Vitamin D requirements: current and future. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1735S-9S.
- 227 Alkharfy KM, Al-Daghri NM, Ahmed M, Yakout SM. Effects of vitamin D treatment on skeletal muscle histology and ultrastructural changes in a rodent model. Molecules. 2012 Jul 31;17(8):9081-9.
- 228 von Hurst PR1, Beck KL. Vitamin D and skeletal muscle function in athletes. Curr Opin Clin Nutr Metab Care. 2014 Nov;17(6):539-45.
- 229 Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int. 2013 Feb;92(2):151-62.
- 230 Shuler FD, Wingate MK, Moore GH, Giangarra C. Sports health benefits of vitamin d. Sports Health. 2012 Nov;4(6):496-501.
- 231 von Hurst PR, Beck KL. Vitamin D and skeletal muscle function in athletes. Curr Opin Clin Nutr Metab Care. 2014 Nov;17(6):539-45.
- 232 Ceglia L. Vitamin D and skeletal muscle tissue and function. Mol Aspects Med. 2008 Dec;29(6):407-14. doi: 10.1016/j.mam.2008.07.002.
- 233 Larson-Meyer E. Vitamin D supplementation in athletes. Nestle Nutr Inst Workshop Ser. 2013;75:109-21.

- 234 Morley JE. Scientific overview of hormone treatment used for rejuvenation. Fertil Steril. 2013 Jun;99(7):1807-13.
- 235 Aquila S, Guido C, Perrotta I, Tripepi S, Nastro A, et al. Human sperm anatomy: ultrastructural localization of 1alpha, 25-dihydroxyvitamin D receptor and its possible role in the human male gamete. J Anat 2008; 213: 555-64.
- 236 Nimptsch K, Platz EA, Willett WC, Giovannucci E. Association between plasma 25-OH vitamin D and testosterone levels in men. Clin Endocrinol (Oxf) 2012; 77: 106-12.
- 237 Foresta C, Selice R, Di Mambro A, Strapazzon G. Testiculopathy and vitamin D insufficiency. Lancet. 2010 Oct 16;376(9749):1301.
- 238 Lee DM, Tajar A, Pye SR, Boonen S, Vanderschueren D, Bouillon R, O'Neill TW, Bartfai G, Casanueva FF, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Pendleton N, Punab M, Wu FC; EMAS study group. Association of hypogonadism with vitamin D status: the European Male Ageing Study. Eur J Endocrinol. 2012 Jan;166(1):77-85.
- 239 Wehr E, Pilz S, Boehm BO, März W, Obermayer-Pietsch B. Association of vitamin D status with serum androgen levels in men. Clin Endocrinol (Oxf). 2010 Aug;73(2):243-8.
- 240 Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, Wehr E, Zittermann A. Effect of vitamin D supplementation on testosterone levels in men. Horm Metab Res. 2011 Mar;43(3):223-5.
- 241 Özkaya F, Demirel A. Vitamin D deficiency in infertile patients. Arch Esp Urol. 2018 Dec;71(10):850-855.
- 242 Tak YJ, Lee JG, Kim YJ, Park NC, Kim SS, Lee S, Cho BM, Kong EH, Jung DW, Yi YH. Serum 25-hydroxyvitamin D levels and testosterone deficiency in middle-aged Korean men: a cross-sectional study. Asian J Androl 2015;17:324-8.
- 243 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2014 Jan 10;1:CD007470.
- 244 Nieman DC, Gillitt ND, Shanely RA, Dew D, Meaney MP, Luo B. Vitamin D2 supplementation amplifies eccentric exercise-induced muscle damage in NASCAR pit crew athletes. Nutrients. 2013 Dec 20;6(1):63-75.
- 245 Delinocente MLB, Luiz MM, de Oliveira DC, de Souza AF, Ramírez PC, de Oliveira Máximo R, Soares NC, Steptoe A, de Oliveira C, da Silva Alexandre T. Are Serum 25-Hydroxyvitamin D Deficiency and Insufficiency Risk Factors for the Incidence of Dynapenia? Calcif Tissue Int. 2022 Dec;111(6):571-579. doi: 10.1007/s00223-022-01021-8. Epub 2022 Sep 15. PMID: 36109388; PMCID: PMC9613743.
- 246 Capellino S1, Straub RH, Cutolo M. Aromatase and regulation of the estrogen-to-androgen ratio in synovial tissue inflammation: common pathway in both sexes. Ann N Y Acad Sci. 2014 May;1317:24-31.
- 247 Lundqvist J1, Norlin M, Wikvall K. 1a,25-Dihydroxyvitamin D3 exerts tissue-specific effects on estrogen and androgen metabolism. Biochim Biophys Acta. 2011 Apr;1811(4):263-70.
- 248 Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans J. Clin. Endocrinol. Metab., 89 (2004), pp. 5387–5391
- 249 Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months. Br J Nutr. 2013 Mar 28;109(6):1082-8.
- 250 Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hyppönen E, Berry J, Vieth R, Lanham-New S. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr. 2012 Jun;95(6):1357-64.
- 251 Wang Y, Lee KW, Chan FL, Chen S, Leung LK. The red wine polyphenol resveratrol displays bilevel inhibition on aromatase in breast cancer cells. Toxicol Sci. 2006 Jul;92(1):71-7.

- 252 Wang Y, Leung LK. Pharmacological concentration of resveratrol suppresses aromatase in JEG-3 cells. Toxicol Lett. 2007 Sep 28;173(3):175-80.
- 253 Kijima I, Phung S, Hur G, Kwok SL, Chen S. Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression. Cancer Res. 2006 Jun 1;66(11):5960-7. doi: 10.1158/0008-5472.CAN-06-0053. PMID: 16740737.
- 254 Gansser D, Spiteller G. Aromatase inhibitors from Urtica dioica roots. Planta Med. 1995 Apr;61(2):138-40. doi: 10.1055/s-2006-958033. PMID: 17238068.
- 255 Baravalle R, Ciaramella A, Baj F, Di Nardo G, Gilardi G. Identification of endocrine disrupting chemicals acting on human aromatase. Biochim Biophys Acta Proteins Proteom. 2018 Jan;1866(1):88-96.
- 256 Wang Y, Pan P, Li X, Zhu Q, Huang T, Ge RS. Food components and environmental chemicals of inhibiting human placental aromatase. Food Chem Toxicol. 2019 Mar 25;128:46-53.
- 257 Jenzer H, Sadeghi-Reeves L. Nutrigenomics-Associated Impacts of Nutrients on Genes and Enzymes With Special Consideration of Aromatase. Front Nutr. 2020 Apr 9;7:37. doi: 10.3389/fnut.2020.00037. PMID: 32328497; PMCID: PMC7161344.
- 258 Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020 Apr 2;12(4). pii: E988. doi: 10.3390/nu12040988.
- 259 McCartney DM, Byrne DG. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J. 2020 Apr 3;113(4):58.
- 260 Caccialanza R, Laviano A, Lobascio F, Montagna E, Bruno R, Ludovisi S, Corsico AG, Di Sabatino A, Belliato M, Calvi M, Iacona I, Grugnetti G, Bonadeo E, Muzzi A, Cereda E. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. Nutrition. 2020 Apr 3:110835. doi: 10.1016/j.nut.2020.110835. [Epub ahead of print]
- 261 Panarese A, Shahini E. Letter: Covid-19, and vitamin D. Aliment Pharmacol Ther. 2020 May;51(10):993-995. doi: 10.1111/apt.15752. Epub 2020 Apr 12.
- 262 Jakovac H. COVID-19 and vitamin D-Is there a link and an opportunity for intervention? Am J Physiol Endocrinol Metab. 2020 May 1;318(5):E589. doi: 10.1152/ajpendo.00138.2020.
- 263 Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav Immun. 2020 Apr 22. pii: S0889-1591(20)30589-4. doi:
 - 10.1016/j.bbi.2020.04.046. [Epub ahead of print]
- 264 Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020 May 6. doi: 10.1007/s40520-020-01570-8. [Epub ahead of print]
- 265 Belluci MM, de Molon RS, Rossa C Jr, Tetradis S, Giro G, Cerri PS, Marcantonio E Jr, Orrico SRP. Severe magnesium deficiency compromises systemic bone mineral density and aggravates inflammatory bone resorption. J Nutr Biochem. 2019 Nov 26;77:108301. doi: 10.1016/j.jnutbio.2019.108301. [Epub ahead of print]
- 266 Lelovics Z. Relation between calcium and magnesium intake and obesity. Asia Pac J Clin Nutr. 2004;13(Suppl):S144.
- 267 Razzaque MS. Magnesium: Are We Consuming Enough? Nutrients. 2018 Dec 2;10(12).
- 268 Rayssiguier Y, Mazur A. R [Magnesium and inflammation:lessons from animal models.] Clin Calcium. 2005;15(2):245-248.
- 269 Maier JA, Malpuech-Brugere C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis. Biochim Biophys Acta. 2004 May 24;1689(1):13-21.
- 270 Seelig MS. Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review). J Am Coll Nutr. 1994 Oct;13(5):429-46.
- 271 Nielsen FH, Lukaski HC.Update on the relationship between magnesium and exercise. Magnes Res. 2006 Sep;19(3):180-9.
- 272 Volpe SL. Magnesium and the Athlete. Curr Sports Med Rep. 2015 Jul-Aug;14(4):279-83. doi: 10.1249/JSR.000000000000178. PMID: 26166051.
- 273 Maggio M, De Vita F, Lauretani F, Nouvenne A, Meschi T, Ticinesi A, Dominguez LJ, Barbagallo M, Dall'aglio E, Ceda GP. The Interplay between Magnesium and Testosterone in Modulating Physical Function in Men. Int J Endocrinol. 2014;2014:525249. doi: 10.1155/2014/525249. Epub 2014 Mar 3. PMID: 24723948; PMCID: PMC3958794.
- 274 Setaro L, Santos-Silva PR, Nakano EY, Sales CH, Nunes N, Greve JM, Colli C.Magnesium status and the physical performance of volleyball players: effects of magnesium supplementation. J Sports Sci. 2014;32(5):438-45.
- 275 Santos DA, Matias CN, Monteiro CP, Silva AM, Rocha PM, Minderico CS, Bettencourt Sardinha L, Laires MJ. Magnesium intake is associated with strength performance in elite basketball, handball and volleyball players. Magnes Res. 2011 Dec;24(4):215-9.
- 276 Garrison SR, Allan GM, Sekhon RK, Musini VM, Khan KM. Magnesium for skeletal muscle cramps. Cochrane Database Syst Rev. 2012 Sep 12;9:CD009402.
- 277 Córdova A, Mielgo-Ayuso J, Roche E, Caballero-García A, Fernandez-Lázaro D. Impact of Magnesium Supplementation in Muscle Damage of Professional Cyclists Competing in a Stage Race. Nutrients. 2019 Aug 16;11(8). pii: E1927.
- 278 Maggio M, De Vita F, Lauretani F, Nouvenne A, Meschi T, Ticinesi A, Dominguez LJ, Barbagallo M, Dall'aglio E, Ceda GP. The Interplay between Magnesium and Testosterone in Modulating Physical Function in Men. Int J Endocrinol. 2014;2014:525249.
- 279 Maggio M, Ceda GP, Lauretani F, Cattabiani C, Avantaggiato E, Morganti S, Ablondi F, Bandinelli S, Dominguez LJ, Barbagallo M, Paolisso G, Semba RD, Ferrucci L. Magnesium and anabolic hormones in older men. Int J Androl. 2011 Dec;34(6 Pt 2):e594-600.
- 280 Cinar V, Polat Y, Baltaci AK, Mogulkoc R. Effects of magnesium supplementation on testosterone levels of athletes and sedentary subjects at rest and after exhaustion. Biol Trace Elem Res. 2011 Apr;140(1):18-23. doi: 10.1007/s12011-010-8676-3. Epub 2010 Mar 30. PMID: 20352370.
- 281 Koehler K, Parr MK, Geyer H, Mester J, Schänzer W. Serum testosterone and urinary excretion of steroid hormone metabolites after administration of a high-dose zinc supplement. Eur J Clin Nutr. 2009 Jan;63(1):65-70.
- 282 Kieffer F. (Trace elements: their importance for health and physical performance.) Deutsche Zeitschrift fuer Sportmedizin 1986;37(4):118-123.
- 283 Oteiza PI, Olin KL, Fraga CG, Keen CL. Zinc deficiency causes oxidative damage to proteins, lipids and DNA in rat testes. J Nutr 1995;125(4):823-9.
- 284 Fallah A, Mohammad-Hasani A, Colagar AH. Zinc is an Essential Element for Male Fertility: A Review of Zn Roles in Men's Health, Germination, Sperm Quality, and Fertilization. J Reprod Infertil.
 2018 Apr-Jun;19(2):69-81. PMID: 30009140; PMCID: PMC6010824.
- 285 Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev. 2015 Apr;14(4):277-85.
- 286 Maares M, Haase H. Zinc and immunity: An essential interrelation. Arch Biochem Biophys. 2016 Dec 1;611:58-65.
- 287 Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav Immun. 2020 Apr 22. pii: S0889-1591(20)30589-4. doi:
 - 10.1016/j.bbi.2020.04.046. [Epub ahead of print]
- 288 Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, Svistunov AA, Petrakis D, Spandidos DA, Aaseth J, Tsatsakis A, Tinkov AA. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). Int J Mol Med. 2020 Apr 14. doi: 10.3892/ijmm.2020.4575. [Epub ahead of print]

- 289 Prasad AS. Zinc deficiency in women, infants and children. Journal of the American College of Nutrition 1996;15(2):113-20.
- 290 Cordova A, Alvarez-Mon M. Behaviour of zinc in physical exercise: a special reference to immunity and fatigue. Neuroscience & Biobehavioral Reviews 1995;19(3):439-45.
- 291 Lukaski HC: Low dietary zinc decreases erythrocyte carbonic anhydrase activities and impairs cardiorespiratory function in men during exercise. Am J Clin Nutr 2005; 81: 1045-1051.
- 292 Hsu JM. Zinc deficiency and alterations of free amino acid levels in plasma, urine and skin extract. Progress in Clinical & Biological Research 1977;14:73-86.
- 293 Dorup I, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. British Journal of Nutrition 1991;66(3):505-21.
- 294 Ghavami-Maibodi SZ, Collipp PJ, Castro-Magana M, Stewart C and Chen SY. Effect of oral zinc supplements on growth, hormonal levels and zinc in healthy short children. Ann Nutr Metab 1983;273:214-219.
- 295 Hartoma TR, Nahoul K, Netter A. Zinc, plasma androgens and male sterility. Lancet 1977;2:1125-1126.
- 296 Hunt CD, Johnson PE, Herbel J, Mullen LK. Effects of dietary zinc depletion on seminal volume of zinc loss, serum testosterone concerntrations and sperm morphology in young men. Am J Clin Nutr 1992;56(1):148-157.
- 297 Kara E, Gunay M, Cicioglu I, Ozal M, Kilic M, Mogulkoc R, Baltaci AK. Effect of zinc supplementation on antioxidant activity in young wrestlers. Biol Trace Elem Res. 2010 Apr;134(1):55-63.
- 298 Marreiro DN, Geloneze B, Tambascia MA, Lerario AC, Halpern A, Cozzolino SM. [Participation of zinc in insulin resistance] Arq Bras Endocrinol Metabol. 2004;48(2):234-9.
- 299 Opeyemi A, Adeoye O, Adebanji A, Olawumi J. CREM, PRM I and II gene expression in Wistar rats testes treated with antipsychotic drugs: Chlorpromazine, Rauwolfia vomitoria and co-administration of reserpine, zinc and ascorbic acid. JBRA Assist Reprod. 2021 Feb 2;25(1):97-103. doi: 10.5935/1518-0557.20200058. PMID: 32960520; PMCID: PMC7863111.
- 300 Santos HO, Teixeira FJ. Use of medicinal doses of zinc as a safe and efficient coadjutant in the treatment of male hypogonadism. Aging Male. 2020 Dec;23(5):669-678. doi: 10.1080/13685538.2019.1573220. Epub 2019 Feb 15. PMID: 30767598.
- 301 Zhang Z, Cheng Q, Liu Y, Peng C, Wang Z, Ma H, Liu D, Wang L, Wang C. Zinc-Enriched Yeast May Improve Spermatogenesis by Regulating Steroid Production and Antioxidant Levels in Mice. Biol Trace Elem Res. 2021 Oct 18. doi: 10.1007/s12011-021-02970-1. Epub ahead of print. PMID: 34664181.
- 302 Baly DL, Keen CL, Hurley LS. Pyruvate carboxylase and phosphoenolpyruvate carboxykinase activity in developing rats: effect of manganese deficiency. J Nutr. 1985 Jul;115(7):872-9.
- 303 Prohaska JR. Functions of trace elements in brain metabolism. Physiol Rev. 1987 Jul;67(3):858-901.
- 304 Frei M, Kim C, Ames BN. Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci 1990; 87:4879–83.
- 305 Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci 1990; 87:8931-34.
- 306 Littarru GP, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical implications. Mitochondrion. 2007 Jun;7 Suppl:S168-74.
- 307 Skarlovnik A, Janic M, Lunder M, Turk M, Šabovic M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. Med Sci Monit. 2014 Nov 6;20:2183-8.

- 308 Wang LW, Jabbour A, Hayward CS, Furlong TJ, Girgis L, Macdonald PS, Keogh AM. Potential role of coenzyme Q10 in facilitating recovery from statin-induced rhabdomyolysis. Intern Med J. 2015 Apr;45(4):451-3.
- 309 Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2018 Oct 2;7(19):e009835. doi: 10.1161/JAHA.118.009835. PMID: 30371340.
- 310 Lorza-Gil E, de Souza JC, García-Arévalo M, Vettorazzi JF, Marques AC, Salerno AG, Trigo JR, Oliveira HCF. Coenzyme Q10 protects against ß-cell toxicity induced by pravastatin treatment of hypercholesterolemia. J Cell Physiol. 2019 Jul;234(7):11047-11059.
- 311 Jing L, He MT, Chang Y, Mehta SL, He QP, Zhang JZ, Li PA. Coenzyme Q10 protects astrocytes from ROS-induced damage through inhibition of mitochondria-mediated cell death pathway. Int J Biol Sci. 2015 Jan 1;11(1):59-66.
- 312 Noh YH, Kim KY, Shim MS, Choi SH, Choi S, Ellisman MH, Weinreb RN, Perkins GA, Ju WK. Inhibition of oxidative stress by coenzyme Q10 increases mitochondrial mass and improves bioenergetic function in optic nerve head astrocytes. Cell Death Dis. 2013 Oct 3;4:e820.
- 313 Raygan F, Rezavandi Z, Dadkhah Tehrani S, Farrokhian A, Asemi Z. The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. Eur J Nutr. 2016 Dec;55(8):2357-2364.
- 314 Nasoohi S, Simani L, Khodagholi F, Nikseresht S, Faizi M, Naderi N. Coenzyme Q10 supplementation improves acute outcomes of stroke in rats pretreated with atorvastatin. Nutr Neurosci. 2019 Apr;22(4):264-272.
- 315 Chis BA, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. Int J Vitam Nutr Res. 2019 Mar 19:1-9.
- 316 Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors. 2003;18(1-4):101-11.
- 317 Jorat MV, Tabrizi R, Kolahdooz F, Akbari M, Salami M, Heydari ST, Asemi Z. The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress in among coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Inflammopharmacology. 2019 Apr;27(2):233-248.
- 318 Andalib S, Mashhadi-Mousapour M, Bijani S, Hosseini MJ. Coenzyme Q10 Alleviated Behavioral Dysfunction and Bioenergetic Function in an Animal Model of Depression. Neurochem Res. 2019 May;44(5):1182-1191.
- 319 Wang X, Meng Q, Qiu C, Li P, Qu R, Wang W, Wang Y, Liu L, Zhao Y. Potential therapeutic role of Co-Q10 in alleviating intervertebral disc degeneration and suppressing IL-1ß-mediated inflammatory reaction in NP cells. Int Immunopharmacol. 2018 Nov;64:424-431.
- 320 Schmelzer C, Kubo H, Mori M, Sawashita J, Kitano M, Hosoe K, Boomgaarden I, Döring F, Higuchi K. Supplementation with the reduced form of Coenzyme Q10 decelerates phenotypic characteristics of senescence and induces a peroxisome proliferator-activated receptor-alpha gene expression signature in SAMP1 mice. Mol Nutr Food Res. 2010 Jun;54(6):805-15.
- 321 Tian G, Sawashita J, Kubo H, Nishio SY, Hashimoto S, Suzuki N, Yoshimura H, Tsuruoka M, Wang Y, Liu Y, Luo H, Xu Z, Mori M, Kitano M, Hosoe K, Takeda T, Usami S, Higuchi K. Ubiquinol-10 supplementation activates mitochondria functions to decelerate senescence in senescenceaccelerated mice. Antioxid Redox Signal. 2014 Jun 1;20(16):2606-20.
- 322 Yan J, Fujii K, Yao J, Kishida H, Hosoe K, Sawashita J, Takeda T, Mori M, Higuchi K. Reduced coenzyme Q10 supplementation decelerates senescence in SAMP1 mice. Exp Gerontol. 2006 Feb;41(2):130-40.
- 323 Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Fernández Vega A, de la Mata M, Delgado Pavón A, de Miguel M, Pérez Calero C, Villanueva Paz M, Cotán D, Sánchez-Alcázar JA. Coenzyme q10 therapy. Mol Syndromol. 2014 Jul;5(3-4):187-97.

- 324 Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. J Urol. 2009 Jul;182(1):237-48.
- 325 Fouad AA, AI-Sultan AI, Yacoubi MT. Coenzyme Q10 counteracts testicular injury induced by sodium arsenite in rats. Eur J Pharmacol. 2011 Mar 25;655(1-3):91-8.
- 326 Walczak-Jedrzejowska R, Wolski JK, Slowikowska-Hilczer J. The role of oxidative stress and antioxidants in male fertility. Cent European J Urol. 2013;66(1):60-7.
- 327 Safarinejad MR. The effect of coenzyme Q10 supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. Int Urol Nephrol. 2012 Jun;44(3):689-700.
- 328 Banihani SA. Effect of Coenzyme Q10 Supplementation on Testosterone. Biomolecules. 2018 Dec 13;8(4). pii: E172. doi: 10.3390/biom8040172.
- 329 Banihani SA. Effect of Coenzyme Q10 Supplementation on Testosterone. Biomolecules. 2018 Dec 13;8(4). pii: E172. doi: 10.3390/biom8040172.
- 330 Onur S, Niklowitz P, Jacobs G, Nöthlings U, Lieb W, Menke T, Döring F. Ubiquinol reduces gamma glutamyltransferase as a marker of oxidative stress in humans. BMC Res Notes. 2014 Jul 4;7:427.
- 331 Brauner H, Lüthje P, Grünler J, Ekberg NR, Dallner G, Brismar K, Brauner A. Markers of innate immune activity in patients with type 1 and type 2 diabetes mellitus and the effect of the anti-oxidant coenzyme Q10 on inflammatory activity. Clin Exp Immunol. 2014 Aug;177(2):478-82.
- 332 Kaikkonen J, Kosonen L, Nyyssonen K, Porkkala-Sarataho E, Salonen R, Korpela H, Salonen JT. Effect of combined coenzyme Q10 and d-alpha-tocopheryl acetate supplementation on exercise-induced lipid peroxidation and muscular damage: a placebo-controlled double-blind study in marathon runners. Free Radic Res. 1998 Jul;29(1):85-92.
- 333 Gokbel H, Gui I, Bleviranl M, et al. The effects of coenzyme Q10 supplementation on performance during repeated bouts of supramaximal exercise in sedentary men. J Strength Cond Res. 2010;24(1):97-102.
- 334 https://jamanetwork.com/journals/jamaoncology/article-abstract/2732506 would suffice.
- 335 Sarmiento A, Diaz-Castro J, Pulido-Moran M, Kajarabille N, Guisado R, Ochoa JJ. Coenzyme Q10 Supplementation and Exercise in Healthy Humans: A Systematic Review. Curr Drug Metab. 2016;17(4):345-58.
- 336 Chis BÁ, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. Int J Vitam Nutr Res. 2019 Mar 19:1-9.
- 337 Mehrabani S, Askari G, Miraghajani M, Tavakoly R, Arab A. Effect of coenzyme Q10 supplementation on fatigue: A systematic review of interventional studies. Complement Ther Med. 2019 Apr;43:181-187.
- 338 Komaki H, Faraji N, Komaki A, Shahidi S, Etaee F, Raoufi S, Mirzaei F. Investigation of protective effects of coenzyme Q10 on impaired synaptic plasticity in a male rat model of Alzheimer's disease. Brain Res Bull. 2019 Apr;147:14-21.
- 339 Belviranli M, Okudan N. Effect of Coenzyme Q10 Alone and in Combination with Exercise Training on Oxidative Stress Biomarkers in Rats. Int J Vitam Nutr Res. 2019 Apr 30:1-11.
- 340 Wang X, Meng Q, Qiu C, Li P, Qu R, Wang W, Wang Y, Liu L, Zhao Y. Potential therapeutic role of Co-Q10 in alleviating intervertebral disc degeneration and suppressing IL-1ß-mediated inflammatory reaction in NP cells. Int Immunopharmacol. 2018 Nov;64:424-431.
- 341 Mortensen SA. Perspectives on therapy of cardiovascular diseases with coenzyme Q10 (ubiquinone). [Review] Clinical Investigator 1993;71(8 Suppl):S116-23.
- 342 Beyer RE. An analysis of the role of coenzyme Q in free radical generation and as an antioxidant. Biochemistry & Cell Biology 1992;70(6):390-403.
- 343 Chis BA, Chis AF, Muresan A, Fodor D. Q10 Coenzyme Supplementation can Improve Oxidative Stress Response to Exercise in Metabolic Syndrome in Rats. Int J Vitam Nutr Res. 2019 Mar 19:1-9.

- 344 Belviranli M, Okudan N. Effect of Coenzyme Q10 Alone and in Combination with Exercise Training on Oxidative Stress Biomarkers in Rats. Int J Vitam Nutr Res. 2019 Apr 30:1-11.
- 345 Sarmiento A, Diaz-Castro J, Pulido-Moran M, Moreno-Fernandez J, Kajarabille N, Chirosa I, Guisado IM, Javier Chirosa L, Guisado R, Ochoa JJ. Short-term ubiquinol supplementation reduces oxidative stress associated with strenuous exercise in healthy adults: A randomized trial. Biofactors. 2016 Nov 12;42(6):612-622.
- 346 Pala R, Beyaz F, Tuzcu M, Er B, Sahin N, Cinar V, Sahin K. The effects of coenzyme Q10 on oxidative stress and heat shock proteins in rats subjected to acute and chronic exercise. J Exerc Nutrition Biochem. 2018 Sep 30;22(3):14-20.
- 347 Orlando P, Silvestri S, Galeazzi R, Antonicelli R, Marcheggiani F, Cirilli I, Bacchetti T, Tiano L. Effect of ubiquinol supplementation on biochemical and oxidative stress indexes after intense exercise in young athletes. Redox Rep. 2018 Dec;23(1):136-145.
- 348 Borisova IG, Seifulla RD, Zhuravlev AI. [Action of antioxidants on physical work capacity and lipid peroxidation in the body]. Farmakol Toksikol 1989;52(4):89-92.
- 349 Lemke M, Frei B, Ames BN, Faden AI. Decreases in tissue levels of ubiquinol 9 and 10, ascorbate and alpha tocopherol following spinal cord impact trauma in rats. Neurosci Lett 1990;108(1-2):201-6.
- 350 Chokchaiwong S, Kuo YT, Lin SH, Hsu YC, Hsu SP, Liu YT, Chou AJ, Kao SH. Coenzyme Q10 serves to couple mitochondrial oxidative phosphorylation and fatty acid ß-oxidation, and attenuates NLRP3 inflammasome activation. Free Radic Res. 2018 Dec;52(11-12):1445-1455.
- 351 Ghanbarzadeh S, Garjani A, Ziaee M, Khorrami A. Effects of L-carnitine and coenzyme q10 on impaired spermatogenesis caused by isoproterenol in male rats. Drug Res (Stuttg). 2014 Sep;64(9):449-53.
- 352 Ghanbarzadeh S, Garjani A, Ziaee M, Khorrami A. CoQ10 and L-carnitine attenuate the effect of high LDL and oxidized LDL on spermatogenesis in male rats. Drug Res (Stuttg). 2014 Oct;64(10):510-5.
- 353 Dokmeci D, Inan M, Basaran UN, Yalcin O, Aydogdu N, Turan FN, Uz YH. Protective effect of Lcarnitine on testicular ischaemia-reperfusion injury in rats. Cell Biochem Funct. 2007 Nov-Dec;25(6):611-8.
- 354 Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004 Apr;63(4):641-6.
- 355 Zare Z, Eimani H, Mohammadi M, Mofid M, Dashtnavard H. The effect of orally administered lcarnitine on testis tissue, sperm parameters and daily sperm production in adult mice. Yakhteh Med J. 2010;11:382–389.
- 356 Sazegar G, Ebrahimi V, Boroujeni MJS, Mohammadi S, Salimnezhad R. Morphometric study of testis tissue and spermatogenesis following carnitine administration in diabetic rat induced with stereptozotocin. Iran J Diabetes Metab. 2014;14:9–14.
- 357 Kanter M, Topcu-Tarladacalisir Y, Parlar S. Antiapoptotic effect of I-carnitine on testicular irradiation in rats. J Mol Histol. 2010;41:121–128.
- 358 Rezaei N, Mardanshahi T, Shafaroudi MM, Abedian S, Mohammadi H, Zare Z. Effects of I-Carnitine on the Follicle-Stimulating Hormone, Luteinizing Hormone, Testosterone, and Testicular Tissue Oxidative Stress Levels in Streptozotocin-Induced Diabetic Rats. J Evid Based Integr Med. 2018 Jan-Dec;23:2515690X18796053. doi: 10.1177/2515690X18796053.
- 359 Elokil AA, Bhuiyan AA, Liu HZ, Hussein MN, Ahmed HI, Azmal SA, Yang L, Li S. The capability of L-carnitine-mediated antioxidant on cock during aging: evidence for the improved semen quality and enhanced testicular expressions of GnRH1, GnRHR, and melatonin receptors MT 1/2. Poult Sci. 2019 Apr 18. pii: pez201. doi: 10.3382/ps/pez201. [Epub ahead of print]
- ³⁶⁰ Kidd P. Astaxanthin, cell membrane nutrient with diverse clinical benefits and anti-aging potential. Altern Med Rev. 2011 Dec;16(4):355-64.

361 Lee J, Kim MH, Kim H. Anti-Oxidant and Anti-Inflammatory Effects of Astaxanthin on Gastrointestinal Diseases. Int J Mol Sci. 2022 Dec 7;23(24):15471. doi: 10.3390/ijms232415471. PMID: 36555112; PMCID: PMC9779521.

362 Aoi W, Naito Y, Takanami Y, Ishii T, Kawai Y, Akagiri S, Kato Y, Osawa T, Yoshikawa T. Astaxanthin improves muscle lipid metabolism in exercise via inhibitory effect of oxidative CPT I modification. Biochem Biophys Res Commun. 2008 Feb 22;366(4):892-7.

- 363 Djordjevic B, Baralic I, Kotur-Stevuljevic J, Stefanovic A, Ivanisevic J, Radivojevic N, Andjelkovic M, Dikic N. Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players. J Sports Med Phys Fitness. 2012 Aug;52(4):382-92.
- 364 Earnest CP, Lupo M, White KM, Church TS. Effect of astaxanthin on cycling time trial performance. Int J Sports Med. 2011 Nov;32(11):882-8.
- 365 Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. Mar Drugs. 2011 Mar 21;9(3):447-65.
- 366 Ikeuchi M, Koyama T, Takahashi J, Yazawa K. Effects of astaxanthin supplementation on exercise-induced fatigue in mice. Biol Pharm Bull. 2006 Oct;29(10):2106-10.
- 367 Liu PH, Aoi W, Takami M, Terajima H, Tanimura Y, Naito Y, Itoh Y, Yoshikawa T. The astaxanthin-induced improvement in lipid metabolism during exercise is mediated by a PGC-1a increase in skeletal muscle. J Clin Biochem Nutr. 2014 Mar;54(2):86-9.
- 368 Polotow TG, Vardaris CV, Mihaliuc AR, Gonçalves MS, Pereira B, Ganini D, Barros MP.Astaxanthin supplementation delays physical exhaustion and prevents redox imbalances in plasma and soleus muscles of Wistar rats. Nutrients. 2014 Dec 12;6(12):5819-38.
- 369 Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. Mol Nutr Food Res. 2011 Jan;55(1):150-65.
- 370 Maezawa T, Tanaka M, Kanazashi M, Maeshige N, Kondo H, Ishihara A, Fujino H. Astaxanthin supplementation attenuates immobilization-induced skeletal muscle fibrosis via suppression of oxidative stress. J Physiol Sci. 2017 Sep;67(5):603-611.
- 371 Kanazashi M, Tanaka M, Murakami S, Kondo H, Nagatomo F, Ishihara A, Roy RR, Fujino H. Amelioration of capillary regression and atrophy of the soleus muscle in hindlimb-unloaded rats by astaxanthin supplementation and intermittent loading. Exp Physiol. 2014 Aug;99(8):1065-77.
- 372 Aoi W, Naito Y, Yoshikawa T. Potential role of oxidative protein modification in energy metabolism in exercise. Subcell Biochem. 2014;77:175-87.
- 373 Choi HD, Kim JH, Chang MJ, Kyu-Youn Y, Shin WG. Effects of astaxanthin on oxidative stress in overweight and obese adults. Phytother Res. 2011 Dec;25(12):1813-8.
- 374 Choi HD, Youn YK, Shin WG. Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. Plant Foods Hum Nutr. 2011 Nov;66(4):363-9.
- 375 Baralic I, Djordjevic B, Dikic N, Kotur-Stevuljevic J, Spasic S, Jelic-Ivanovic Z, Radivojevic N, Andjelkovic M, Pejic S. Effect of astaxanthin supplementation on paraoxonase 1 activities and oxidative stress status in young soccer players. Phytother Res. 2013 Oct;27(10):1536-42.
- 376 Visioli F, Artaria C. Astaxanthin in cardiovascular health and disease: mechanisms of action, therapeutic merits, and knowledge gaps. Food Funct. 2017 Jan 25;8(1):39-63.
- 377 Kishimoto Y, Yoshida H, Kondo K. Potential Anti-Atherosclerotic Properties of Astaxanthin.Mar Drugs. 2016 Feb 5;14(2).
- 378 Wu H, Niu H, Shao A, Wu C, Dixon BJ, Zhang J, Yang S, Wang Y. Astaxanthin as a Potential Neuroprotective Agent for Neurological Diseases. Mar Drugs. 2015 Sep 11;13(9):5750-66.
- 379 Zhang L, Wang H. Multiple Mechanisms of Anti-Cancer Effects Exerted by Astaxanthin. Mar Drugs. 2015 Jul 14;13(7):4310-30.
- 380 Radice RP, Limongi AR, Viviano E, Padula MC, Martelli G, Bermano G. Effects of astaxanthin in animal models of obesity-associated diseases: A systematic review and meta-analysis. Free Radic Biol Med. 2021 Aug 1;171:156-168. doi: 10.1016/j.freeradbiomed.2021.05.008. Epub 2021 May 8. PMID: 33974978.

- 381 Wolf AM, Asoh S, Hiranuma H, Ohsawa I, Iio K, Satou A, Ishikura M, Ohta S. Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress. J Nutr Biochem. 2010 May;21(5):381-9.
- 382 Comhaire FH, El Garem Y, Mahmoud A, Eertmans F, Schoonjans F. Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial. Asian J Androl. 2005 Sep;7(3):257-62.
- 383 Hales DB, Allen JA, Shankara T, Janus P, Buck S, Diemer T, Hales KH. Mitochondrial function in Leydig cell steroidogenesis. Ann N Y Acad Sci. 2005 Dec;1061:120-34.
- 384 Tsai SC1, Lu CC, Lin CS, Wang PS. J Cell Biochem. 2003 Dec 15;90(6):1276-86. Antisteroidogenic actions of hydrogen peroxide on rat Leydig cells.
- 385 Wang JY, Lee YJ, Chou MC, Chang R, Chiu CH, Liang YJ, Wu LS. Astaxanthin protects steroidogenesis from hydrogen peroxide-induced oxidative stress in mouse Leydig cells. Mar Drugs. 2015 Mar 16;13(3):1375-88.
- 386 Angwafor F 3rd, Anderson ML. An open label, dose response study to determine the effect of a dietary supplement on dihydrotestosterone, testosterone and estradiol levels in healthy males. J Int Soc Sports Nutr. 2008 Aug 12;5:12.
- 387 Grimmig B, Kim SH, Nash K, Bickford PC, Douglas Shytle R. Neuroprotective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neurodegeneration. Geroscience. 2017 Feb;39(1):19-32.
- 388 Satoa F, Omuraa T, Ishimarua M, Endoa Y, Murasea H, Yamashitab E. Effects of Daily Astaxanthin and L-Carnitine Supplementation for Exercise-Induced Muscle Damage in Training Thoroughbred Horses Journal of Equine Veterinary Science Volume 35, Issue 10, October 2015, Pages 836–842
- 389 Anderson ML: A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro. J Herb Pharmacother 2005, 5(1):17-26.
- ³⁹⁰ Angwafor F 3rd, Anderson ML. An open label, dose response study to determine the effect of a dietary supplement on dihydrotestosterone, testosterone and estradiol levels in healthy males. J Int Soc Sports Nutr. 2008 Aug 12;5:12. doi: 10.1186/1550-2783-5-12. PMID: 18700016; PMCID: PMC2525623.
- 391 Minutoli L, Bitto A, Squadrito F, Marini H, Irrera N, Morgia G, Passantino A, Altavilla D. Serenoa Repens, lycopene and selenium: a triple therapeutic approach to manage benign prostatic hyperplasia. Curr Med Chem. 2013;20(10):1306-12.
- 392 Geavlete P, Multescu R, Geavlete B. Serenoa repens extract in the treatment of benign prostatic hyperplasia. Ther Adv Urol. 2011 Aug;3(4):193-8.
- 393 Gordon AE, Shaughnessy AF. Saw palmetto for prostate disorders. Am Fam Physician. 2003 Mar 15;67(6):1281-3.
- 394 Veltri RW, Marks LS, Miller MC, Bales WD, Fan J, Macairan ML, Epstein JI, Partin AW. Saw palmetto alters nuclear measurements reflecting DNA content in men with symptomatic BPH: evidence for a possible molecular mechanism. Urology. 2002 Oct;60(4):617-22.
- 395 Habib FK, Ross M, Ho CK, Lyons V, Chapman K. Serenoa repens (Permixon) inhibits the 5alpha-reductase activity of human prostate cancer cell lines without interfering with PSA expression. Int J Cancer. 2005 Mar 20;114(2):190-4.
- 396 Sudeep HV, Thomas JV, Shyamprasad K. A double blind, placebo-controlled randomized comparative study on the efficacy of phytosterol-enriched and conventional saw palmetto oil in mitigating benign prostate hyperplasia and androgen deficiency. BMC Urol. 2020 Jul 3;20(1):86. doi: 10.1186/s12894-020-00648-9. PMID: 32620155; PMCID: PMC7333342.
- ³⁹⁷ Saponaro M, Giacomini I, Morandin G, Cocetta V, Ragazzi E, Orso G, Carnevali I, Berretta M, Mancini M, Pagano F, Montopoli M. Serenoa repens and Urtica dioica Fixed Combination: In-Vitro

Validation of a Therapy for Benign Prostatic Hyperplasia (BPH). Int J Mol Sci. 2020 Dec 2;21(23):9178. doi: 10.3390/ijms21239178. PMID: 33276425; PMCID: PMC7730996.

- 398 Yang S1, Chen C, Li Y, Ren Z, Zhang Y, Wu G, Wang H, Hu Z, Yao M. Saw palmetto extract enhances erectile responses by inhibition of phosphodiesterase 5 activity and increase in inducible nitric oxide synthase messenger ribonucleic acid expression in rat and rabbit corpus cavernosum. Urology. 2013 Jun;81(6):1380.e7-13.
- 399 Fernández LC, Mas R, Fernández J, Mendoza S, Gámez R, Pardo B. Effects of D-004, a lipid extract of the fruit of the Cuban royal palm (Roystonea regia) or the lipidosterolic extract of saw palmetto (Serenoa repens) on the sexual activity in male rats: A controlled, experimental study. Curr Ther Res Clin Exp. 2008 Feb;69(1):65-74.
- 400 Zhu HL, Gao YH, Yang JQ, Li JB, Gao J. Serenoa repens extracts promote hair regeneration and repair of hair loss mouse models by activating TGF-ß and mitochondrial signaling pathway. Eur Rev Med Pharmacol Sci. 2018 Jun;22(12):4000-4008. doi: 10.26355/eurrev_201806_15285. PMID: 29949176.
- 401 Evron E, Juhasz M, Babadjouni A, Mesinkovska NA. Natural Hair Supplement: Friend or Foe? Saw Palmetto, a Systematic Review in Alopecia. Skin Appendage Disord. 2020 Nov;6(6):329-337. doi: 10.1159/000509905. Epub 2020 Aug 23. PMID: 33313047; PMCID: PMC7706486.
- 402 York K, Meah N, Bhoyrul B, Sinclair R. A review of the treatment of male pattern hair loss. Expert Opin Pharmacother. 2020 Apr;21(5):603-612. doi: 10.1080/14656566.2020.1721463. Epub 2020 Feb 17. PMID: 32066284.
- 403 Berges RR, et al. Randomized, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Lancet 1995;345:1529-32.
- 404 Bouic PJ, Lamprecht JH. Plant sterols and sterolins: a review of their immune-modulating properties. Altern Med Rev. 1999 Jun;4(3):170-7.
- 405 Kurano M, Hasegawa K, Kunimi M, Hara M, Yatomi Y, Teramoto T, Tsukamoto K. Sitosterol prevents obesity-related chronic inflammation. Biochim Biophys Acta Mol Cell Biol Lipids. 2018 Feb;1863(2):191-198.
- 406 Hidayathulla S, Shahat AA, Ahamad SR, Al Moqbil AAN, Alsaid MS, Divakar DD. GC/MS analysis and characterization of 2-Hexadecen-1-ol and beta sitosterol from Schimpera arabica extract for its bioactive potential as antioxidant and antimicrobial. J Appl Microbiol. 2018 May;124(5):1082-1091.
- 407 Bouic PJ, Clark A, Lamprecht J, Freestone M, Pool EJ, Liebenberg RW, Kotze D, van Jaarsveld PP. The effects of B-sitosterol (BSS) and B-sitosterol glucoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation. Int J Sports Med. 1999 May;20(4):258-62.
- 408 Talbott SM, Talbott JA, George A, Pugh M. Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. J Int Soc Sports Nutr. 2013 May 26;10(1):28.
- 409 Henkel RR, Wang R, Bassett SH, Chen T, Liu N, Zhu Y, Tambi MI. Tongkat Ali as a potential herbal supplement for physically active male and female seniors--a pilot study. Phytother Res. 2014 Apr;28(4):544-50.
- 410 Ang HH, Lee KL, Kiyoshi M. Eurycoma longifolia Jack enhances sexual motivation in middleaged male mice. J Basic Clin Physiol Pharmacol. 2003;14(3):301-8.
- 411 Ang HH, Ngai TH, Tan TH. Effects of Eurycoma longifolia Jack on sexual qualities in middle aged male rats. Phytomedicine. 2003;10(6-7):590-3.
- 412 Chinnappan SM, George A, Pandey P, Narke G, Choudhary YK. Effect of Eurycoma longifolia standardised aqueous root extract-Physta® on testosterone levels and quality of life in ageing male subjects: a randomised, double-blind, placebo-controlled multicentre study. Food Nutr Res. 2021 May 19;65. doi: 10.29219/fnr.v65.5647. PMID: 34262417; PMCID: PMC8254464.

- 413 Leisegang K, Finelli R, Sikka SC, Panner Selvam MK. Eurycoma longifolia (Jack) Improves Serum Total Testosterone in Men: A Systematic Review and Meta-Analysis of Clinical Trials. Medicina (Kaunas). 2022 Aug 4;58(8):1047. doi: 10.3390/medicina58081047. PMID: 36013514; PMCID: PMC9415500.
- 414 Low BS, Das PK, Chan KL. Standardized quassinoid-rich Eurycoma longifolia extract improved spermatogenesis and fertility in male rats via the hypothalamic-pituitary-gonadal axis. J Ethnopharmacol. 2013 Feb 13;145(3):706-14. doi: 10.1016/j.jep.2012.11.013. Epub 2012 Dec 20. PMID: 23261482.
- 415 Tambi MI1, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? Andrologia. 2012 May;44 Suppl 1:226-30.
- 416 Henkel RR, Wang R, Bassett SH, Chen T, Liu N, Zhu Y, Tambi MI. Tongkat Ali as a Potential Herbal Supplement for Physically Active Male and Female Seniors-A Pilot Study. Phytother Res. 2013 Jun 11.
- 417 Chen CK, Mohamad W2, Ooi FK, Ismail SB, Abdullah MR, George A. Supplementation of Eurycoma longifolia Jack Extract for 6 Weeks Does Not Affect Urinary Testosterone: Epitestosterone Ratio, Liver and Renal Functions in Male Recreational Athletes. Int J Prev Med. 2014 Jun;5(6):728-33.
- 418 George A, Henkel R. Phytoandrogenic properties of Eurycoma longifolia as natural alternative to testosterone replacement therapy. Andrologia. 2014 Sep;46(7):708-21.
- 419 Low BS, Choi SB, Abdul Wahab H, Das PK, Chan KL. Eurycomanone, the major quassinoid in Eurycoma longifolia root extract increases spermatogenesis by inhibiting the activity of phosphodiesterase and aromatase in steroidogenesis. J Ethnopharmacol. 2013 Aug 26;149(1):201-7.
- 420 Henkel RR, Wang R, Bassett SH, Chen T, Liu N, Zhu Y, Tambi MI. Tongkat Ali as a potential herbal supplement for physically active male and female seniors--a pilot study. Phytother Res. 2014 Apr;28(4):544-50.
- 421 Leitão AE, Vieira MCS, Pelegrini A, da Silva EL, Guimarães ACA. A 6-month, double-blind, placebo-controlled, randomized trial to evaluate the effect of Eurycoma longifolia (Tongkat Ali) and concurrent training on erectile function and testosterone levels in androgen deficiency of aging males (ADAM). Maturitas. 2021 Mar;145:78-85. doi: 10.1016/j.maturitas.2020.12.002. Epub 2020 Dec 10. PMID: 33541567.
- 422 Talbott SM1, Talbott JA, George A, Pugh M. Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. J Int Soc Sports Nutr. 2013 May 26;10(1):28.
- 423 Chan KQ, Stewart C, Chester N, Hamzah SH, Yusof A. The effect of Eurycoma Longifolia on the regulation of reproductive hormones in young males. Andrologia. 2021 May;53(4):e14001. doi: 10.1111/and.14001. Epub 2021 Feb 9. PMID: 33559971.
- 424 Chinnappan SM, George A, Pandey P, Narke G, Choudhary YK. Effect of *Eurycoma longifolia* standardised aqueous root extract-Physta[®] on testosterone levels and quality of life in ageing male subjects: a randomised, double-blind, placebo-controlled multicentre study. Food Nutr Res. 2021 May 19;65. doi: 10.29219/fnr.v65.5647. PMID: 34262417; PMCID: PMC8254464.
- 425 Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004 Apr;63(4):641-6.
- 426 Bidzinska B. Petraglia F. Angioni S. Genazzani AD. Criscuolo M. Ficarra G. Gallinelli A. Trentini GP. Genazzani AR. Effect of different chronic intermittent stressors and acetyl-l-carnitine on hypothalamic beta-endorphin and GnRH and on plasma testosterone levels in male rats. Neuroendocrinology. 57(6):985-90, 1993 Jun.

- 427 Palmero S. Leone M. Prati M. Costa M. Messeni Leone M. Fugassa E. De Cecco L. The effect of L-acetylcarnitine on some reproductive functions in the oligoasthenospermic rat. Hormone & Metabolic Research. 22(12):622-6, 1990 Dec.
- 428 Zhou X, Liu F, Zhai S. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. Asia Pac J Clin Nutr. 2007;16 Suppl 1:383-90. PMID: 17392136.
- 429 Wei G, Zhou Z, Cui Y, Huang Y, Wan Z, Che X, Chai Y, Zhang Y. A Meta-Analysis of the Efficacy of L-Carnitine/L-Acetyl-Carnitine or N-Acetyl-Cysteine in Men With Idiopathic Asthenozoospermia. Am J Mens Health. 2021 Mar-Apr;15(2):15579883211011371. doi: 10.1177/15579883211011371. PMID: 33906513; PMCID: PMC8108089.
- 430 Ranjithkumar R, Alhadidi Q, Shah ZA, Ramanathan M. Tribulusterine containing Tribulus terrestris extract exhibited neuroprotection through attenuating stress kinases mediated inflammatory mechanism: in vitro and in vivo studies. Neurochem Res. 2019;12:1–5.
- 431 Ranjithkumar R, Alhadidi Q, Shah ZA, Ramanathan M. Tribulusterine containing Tribulus terrestris extract exhibited neuroprotection through attenuating stress kinases mediated inflammatory mechanism: in vitro and in vivo studies. Neurochem Res. 2019;12:1–5.
- 432 Fernández-Lázaro D, Mielgo-Ayuso J, Del Valle Soto M, Adams DP, González-Bernal JJ, Seco-Calvo J. The Effects of 6 Weeks of *Tribulus terrestris* L. Supplementation on Body Composition, Hormonal Response, Perceived Exertion, and CrossFit[®] Performance: A Randomized, Single-Blind, Placebo-Controlled Study. Nutrients. 2021 Nov 7;13(11):3969. doi: 10.3390/nu13113969. PMID: 34836225; PMCID: PMC8623187.
- 433 Salahshoor MR, Abdolmaleki A, Faramarzi A, Jalili C, Shiva R. Does *Tribulus terrestris* improve toxic effect of Malathion on male reproductive parameters? J Pharm Bioallied Sci. 2020 Apr-Jun;12(2):183-191. doi: 10.4103/jpbs.JPBS_224_19. Epub 2020 Apr 10. PMID: 32742118; PMCID: PMC7373104.
- 434 Milasius K, Dadeliene R, Skernevicius J. The influence of the Tribulus terrestris extract on the parameters of the functional preparedness and athletes' organism homeostasis. Fiziol Zh. 2009;55(5):89-96.
- 435 Saudan C, Baume N, Emery C, Strahm E, Saugy M. Short term impact of Tribulus terrestris intake on doping control analysis of endogenous steroids. Forensic Sci Int. 2008 Jun 10;178(1):e7-10.
- 436 Gauthaman K, Adaikan PG, Prasad RN. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci. 2002 Aug 9;71(12):1385-96.
- 437 El-Tantawy WH, Temraz A, El-Gindi OD. Free serum testosterone level in male rats treated with Tribulus alatus extracts. Int Braz J Urol. 2007 Jul-Aug;33(4):554-8; discussion 558-9.
- 438 Gauthaman K, Ganesan AP. The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction--an evaluation using primates, rabbit and rat. Phytomedicine. 2008 Jan;15(1-2):44-54.
- 439 Wu Y, Yang H, Wang X. The function of androgen/androgen receptor and insulin growth factor-1/insulin growth factor-1 receptor on the effects of Tribulus terrestris extracts in rats undergoing high intensity exercise. Mol Med Rep. 2017 Sep;16(3):2931-2938.
- 440 Ma Y, Guo Z, Wang X. Tribulus terrestris extracts alleviate muscle damage and promote anaerobic performance of trained male boxers and its mechanisms: Roles of androgen, IGF-1, and IGF binding protein-3. J Sport Health Sci. 2017 Dec;6(4):474-481.
- 441 Yin L, Wang Q, Wang X, Song LN. Effects of Tribulus terrestris saponins on exercise performance in overtraining rats and the underlying mechanisms. Can J Physiol Pharmacol. 2016 Nov;94(11):1193-1201.
- 442 Waynberg, J. Aphrodisiacs: Contributions to the Clinical Validation of the Traditional Use of Ptychopetalum guyanna. Presented at the First International Congress on Ethnopharmacology, Strasbourg, France, June 5–9, 1990.

- 443 Waynberg J, Brewer S. Effects of Herbal vX on libido and sexual activity in premenopausal and postmenopausal women. Adv Ther. 2000 Sep-Oct;17(5):255-62.
- 444 Blokland, A., W. Honig, F. Browns, and J. Jolles. Cognition-enhancing properties of subchronic phosphatidylserine (ps) treatment in middle-aged rats: comparison of bovine cortex ps with egg ps and soybean ps. Nutrition 1999;15:778-783.
- 445 Gilbreath, M. J., D. L. Hoover, C. R. Alving, G. M. Swartz, and M. S. Metzer. Inhibition of lymphokine-induced macrophage microbicidal activity against leishmania major by liposomes: characterization of the physicochemical requirements for liposome inhibition. J. Immunol. 1986;137:1681-1687.
- 446 Aramaki, Y., R. Matsuno, F. Nitta, H. Arima, and S. Tsuchiya. Negatively charged liposomes inhibit tyrosine phosphorylation of 41-kda protein in murine macrophages stimulated with lps. Biochem. Biophys. Res. Commun. 231:827-830, 1997.
- 447 Huynh, M. L., V. A. Fadok, and P. M. Henson. Phosphatidylserine-dependent ingestion of apoptotic cells promotes tgf-[beta]1 secretion and the resolution of inflammation. J. Clin. Invest. 109:41-50, 2002.
- 448 Monastra, G., and A. Bruni. Decreased serum level of tumor necrosis factor in animals treated with lipopolysaccharide and liposomes containing phosphatidylserine. Lymphokine Cytokine Res. 11:39-43, 1992.
- 449 Hoffmann, P. R., J. A. Kench, A. Vondracek, et al. Interaction between phosphatidylserine and the phosphatidylserine receptor inhibits immune responses in vivo. J. Immunol. 174:1393-1404, 2005.
- 450 Latorraca, S., P. Piersanti, G. Tesco, S. Piacentini, L. Amaducci, and S. Sorbi. Effect of phosphatidylserine on free radical susceptibility in human diploid fibroblasts. J. Neural Transm. Park. Dis. Dement. Sect. 6:73-77, 1993.
- 451 Dacaranhe, C. D., and J. Terao. A unique antioxidant activity of phosphatidylserine on ironinduced lipid peroxidation of phospholipid bilayers. Lipids 36:1105-1110, 2001.
- 452 Nunzi-MG, Milan-F, Guidolin-D, Polato-P, Toffano-G. Effects of phosphatidylserine administration of aged-related structural changes in the rat hippocampus and septal complex. Pharmacopsychiatry 1989;22(Suppl 2):125-8.
- 453 Valzelli L, Kozak W, Zanotti A, Toffano G. Activity of phosphatidylserine on memory retrieval and on exploration in mice. Methods & Findings in Experimental & Clinical Pharmacology 1987;9(10):657-60.
- 454 Calderini G, Aporti F, Bellini F, Bonetti AC, Teolato S. Zanotti A. Toffano G. Pharmacological effect of phosphatidylserine on age-dependent memory dysfunction. Annals of the New York Academy of Sciences 1985;444:504-6.
- 455 Gianotti C, Porta A, De Graan PN, Oestreicher AB, Nunzi MG. B-50/GAP-43 phosphorylation in hippocampal slices from aged rats: effects of phosphatidylserine administration. Neurobiology of Aging 1993;14(5):401-6.
- 456 Crook TH, Tinklenberg J, Yesavage J, et al. Effects of phosphatidylserine in age-associated memory impairment. Neurology 1991;41(5):644-9.
- 457 Jorissen BL, Brouns F, Van Boxtel MP, et al. Safety of soyphosphatidylserine liposomes. Nature 1976;260: 331-3 derived phosphatidylserine in elderly people. Nutr Neurosci 2002;5: 337-43
- 458 Maggioni M, Picotti GB, Bondiolotti GP, Panerai A. Cenacchi T. Nobile P. Brambilla F. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. Acta Psychiatrica Scandinavica 1990; 81(3):265-70.
- 459 Scapagnini U, Guarcello V, Triolo G, Cioni M. Morale MC. Farinella Z. Marchetti B. Therapeutic perspectives in psychoneuroendocrinimmunology (PNEI): potential role of phosphatidylserine in neuroendocrine-immune communications. International Journal of Neuroscience 1990;51(3-4):299-301.

- 460 Amaducci L, Crook TH, Lippi A, et al. Use of phosphatidylserine in Alzheimer's disease. Annals of the New York Academy of Sciences 1991;640:245-9.
- 461 Soares JC, Gershon S. Advances in the pharmacotherapy of Alzheimer's disease [published erratum appears in Eur Arch Psychiatry Clin Neurosci 1995;245(2):128]. European Archives of Psychiatry & Clinical Neuroscience 1994. 244(5):261-71.
- 462 Starks MA1, Starks SL, Kingsley M, Purpura M, Jäger R. The effects of phosphatidylserine on endocrine response to moderate intensity exercise. J Int Soc Sports Nutr. 2008 Jul 28;5:11.
- 463 Starks MA, Starks SL, Kingsley M, Purpura M, Jäger R. The effects of phosphatidylserine on endocrine response to moderate intensity exercise. J Int Soc Sports Nutr. 2008 Jul 28;5:11.
- 464 Kingsley MI, Wadsworth D, Kilduff LP, McEneny J, Benton D. Effects of phosphatidylserine on oxidative stress following intermittent running. Med Sci Sports Exerc. 2005 Aug;37(8):1300-6.
- 465 Kingsley MI, Miller M, Kilduff LP, McEneny J, Benton D. Effects of phosphatidylserine on exercise capacity during cycling in active males. Med Sci Sports Exerc. 2006 Jan;38(1):64-71.
- 466 Auborn KJ, Fan S, Rosen EM, Goodwin L, Chandraskaren A, Williams DE, Chen D, Carter TH. Indole-3-carbinol is a negative regulator of estrogen. J Nutr. 2003 Jul;133(7 Suppl):2470S-2475S. 467 Calcium-D-glucarate. Altern Med Rev. 2002 Aug;7(4):336-9.
- 468 Iannone M, Botrè F, Cardillo N, de la Torre X. Synthetic isoflavones and doping: A novel class of aromatase inhibitors? Drug Test Anal. 2019 Feb;11(2):208-214.
- 469 Park YJ, Choo WH, Kim HR, Chung KH, Oh SM. Inhibitory Aromatase Effects of Flavonoids from Ginkgo Biloba Extracts on Estrogen Biosynthesis. Asian Pac J Cancer Prev. 2015;16(15):6317-25.
 470 Chen S, Kao YC, Laughton CA. Binding characteristics of aromatase inhibitors and
- phytoestrogens to human aromatase. J Steroid Biochem Mol Biol. 1997 Apr;61(3-6):107-15.
- 471 Jeong HJ, Shin YG, Kim IH, Pezzuto JM. Inhibition of aromatase activity by flavonoids. Arch Pharm Res. 1999 Jun;22(3):309-12.
- 472 Ahumada F. Et al (1989) Studies on the effect of Schisandra chinensis extract on horses submitted to exercise and maximum effort. Phytotherapy Res. 3(5):175.
- 473 Jana K, Yin X, Schiffer RB, Chen JJ, Pandey AK, Stocco DM, Grammas P, Wang X. Chrysin, a natural flavonoid enhances steroidogenesis and steroidogenic acute regulatory protein gene expression in mouse Leydig cells. J Endocrinol. 2008 May;197(2):315-23.
- 474 Darwish HA, Arab HH, Abdelsalam RM. Chrysin alleviates testicular dysfunction in adjuvant arthritic rats via suppression of inflammation and apoptosis: comparison with celecoxib. Toxicol Appl Pharmacol. 2014 Sep 1;279(2):129-40.
- 475 Iannone M, Botrè F, Cardillo N, de la Torre X. Synthetic isoflavones and doping: A novel class of aromatase inhibitors? Drug Test Anal. 2019 Feb;11(2):208-214.
- 476 Pao HY, Pan BS, Leu SF, Huang BM. Cordycepin stimulated steroidogenesis in MA-10 mouse Leydig tumor cells through the protein kinase C Pathway. J Agric Food Chem. 2012 May 16;60(19):4905-13.
- 477 Leu SF, Poon SL, Pao HY, Huang BM. The in vivo and in vitro stimulatory effects of cordycepin on mouse leydig cell steroidogenesis. Biosci Biotechnol Biochem. 2011;75(4):723-31.
- 478 Chang Y, Jeng KC, Huang KF, Lee YC, Hou CW, Chen KH, Cheng FY, Liao JW, Chen YS. Effect of Cordyceps militaris supplementation on sperm production, sperm motility and hormones in Sprague-Dawley rats. Am J Chin Med. 2008;36(5):849-59.
- 479 Wong KL, So EC, Chen CC, Wu RS, Huang BM. Regulation of steroidogenesis by Cordyceps sinensis mycelium extracted fractions with (hCG) treatment in mouse Leydig cells. Arch Androl. 2007 Mar-Apr;53(2):75-7.
- 480 Hsu CC, Huang YL, Tsai SJ, Sheu CC, Huang BM. In vivo and in vitro stimulatory effects of Cordyceps sinensis on testosterone production in mouse Leydig cells. Life Sci. 2003 Sep 5;73(16):2127-36.
- 481 Huang BM, Hsu CC, Tsai SJ, Sheu CC, Leu SF. Effects of Cordyceps sinensis on testosterone production in normal mouse Leydig cells. Life Sci. 2001 Oct 19;69(22):2593-602.

- 482 Wang Y, Wang Y, Liu D, Wang W, Zhao H, Wang M, Yin H. Cordyceps sinensis polysaccharide inhibits PDGF-BB-induced inflammation and ROS production in human mesangial cells. Carbohydr Polym. 2015 Jul 10;125:135-45.
- 483 Yan F, Wang B, Zhang Y. Polysaccharides from Cordyceps sinensis mycelium ameliorate exhaustive swimming exercise-induced oxidative stress. Pharm Biol. 2014 Feb;52(2):157-61.
- 484 Rossi P, Buonocore D, Altobelli E, Brandalise F, Cesaroni V, Iozzi D, Savino E, Marzatico F. Improving Training Condition Assessment in Endurance Cyclists: Effects of Ganoderma lucidum and Ophiocordyceps sinensis Dietary Supplementation. Evid Based Complement Alternat Med. 2014;2014:979613.
- 485 Kumar R, Negi PS, Singh B, Ilavazhagan G, Bhargava K, Sethy NK. Cordyceps sinensis promotes exercise endurance capacity of rats by activating skeletal muscle metabolic regulators. J Ethnopharmacol. 2011 Jun 14;136(1):260-6.
- 486 Chen S, Li Z, Krochmal R, Abrazado M, Kim W, Cooper CB. Effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy older subjects: a double-blind, placebo-controlled trial. J Altern Complement Med. 2010 May;16(5):585-90.
- 487 Colson SN, Wyatt FB, Johnston DL, Autrey LD, FitzGerald YL, Earnest CP. Cordyceps sinensisand Rhodiola rosea-based supplementation in male cyclists and its effect on muscle tissue oxygen saturation. J Strength Cond Res. 2005 May;19(2):358-63.
- 488 Singh R, De S, Belkheir A. Avena sativa (Oat), a potential neutraceutical and therapeutic agent: an overview. Crit Rev Food Sci Nutr. 2013;53(2):126-44.
- 489 Othman RA, Moghadasian MH, Jones PJ. Cholesterol-lowering effects of oat ß-glucan. Nutr Rev. 2011 Jun;69(6):299-309.
- 490 Richman E. The safety of oats in the dietary treatment of coeliac disease. Proc Nutr Soc. 2012 Nov;71(4):534-7.
- 491 Andersson KE, Hellstrand P. Dietary oats and modulation of atherogenic pathways. Mol Nutr Food Res. 2012 Jul;56(7):1003-13.
- 492 Chu YF, Wise ML, Gulvady AA, Chang T, Kendra DF, Jan-Willem van Klinken B, Shi Y, O'Shea M. In vitro antioxidant capacity and anti-inflammatory activity of seven common oats. Food Chem. 2013 Aug 15;139(1-4):426-31.
- 493 Dimpfel W, Storni C, Verbruggen M. Ingested oat herb extract (Avena sativa) changes EEG spectral frequencies in healthy subjects. J Altern Complement Med. 2011 May;17(5):427-34.
- 494 Malviya N, Jain S, Gupta VB, Vyas S. Recent studies on aphrodisiac herbs for the management of male sexual dysfunction--a review. Acta Pol Pharm. 2011 Jan-Feb;68(1):3-8.
- 495 Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). J Altern Complement Med. 2003;9(1):161-8.
- ⁴⁹⁶ Wang Z, Singh A, Jones G, Winzenberg T, Ding C, Chopra A, Das S, Danda D, Laslett L, Antony B. Efficacy and Safety of Turmeric Extracts for the Treatment of Knee Osteoarthritis: a Systematic Review and Meta-analysis of Randomised Controlled Trials. Curr Rheumatol Rep. 2021 Jan 28;23(2):11. doi: 10.1007/s11926-020-00975-8. PMID: 33511486.
- ⁴⁹⁷ Zeng L, Yu G, Hao W, Yang K, Chen H. The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis. Biosci Rep. 2021 Jun 25;41(6):BSR20210817. doi: 10.1042/BSR20210817. PMID: 34017975; PMCID: PMC8202067.
- 498 Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. Int J Clin Pharmacol Ther Toxicol. 1986;24(12):651-4.
- 499 Alappat L, Awad AB. Curcumin and obesity: evidence and mechanisms. Nutr Rev. 2010 Dec;68(12):729-38.
- 500 Nicol LM, Rowlands DS, Fazakerly R, Kellett J. Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS). Eur J Appl Physiol. 2015 Aug;115(8):1769-77.

- 501 McFarlin BK, Venable AS, Henning AL, Sampson JN, Pennel K, Vingren JL, Hill DW. Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin. BBA Clin. 2016 Feb 18;5:72-8.
- 502 Davis JM, Murphy EA, Carmichael MD, Zielinski MR, Groschwitz CM, Brown AS, Gangemi JD, Ghaffar A, Mayer EP. Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. Am J Physiol Regul Integr Comp Physiol. 2007 Jun;292(6):R2168-73.
- 503 Delecroix B, Abaïdia AE, Leduc C, Dawson B, Dupont G. Curcumin and Piperine Supplementation and Recovery Following Exercise Induced Muscle Damage: A Randomized Controlled Trial. J Sports Sci Med. 2017 Mar 1;16(1):147-153.
- 504 McFarlin BK, Venable AS, Henning AL, Sampson JN, Pennel K, Vingren JL, Hill DW. Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin. BBA Clin. 2016 Feb 18;5:72-8.
- 505 Phan TT, See P, Lee ST, Chan SY. Protective effects of curcumin against oxidative damage on skin cells in vitro: its implication for wound healing. J Trauma. 2001;51(5):927-31.
- 506 Delecroix B, Abaïdia AE, Leduc C, Dawson B, Dupont G. Curcumin and Piperine Supplementation and Recovery Following Exercise Induced Muscle Damage: A Randomized Controlled Trial. J Sports Sci Med. 2017 Mar 1;16(1):147-153.
- 507 Goozee KG, Shah TM, Sohrabi HR, Rainey-Smith SR, Brown B, Verdile G, Martins RN. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. Br J Nutr. 2016 Feb 14;115(3):449-65.
- 508 Dey A, Bhattacharya R, Mukherjee A, Pandey DK. Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. Biotechnol Adv. 2017 Mar -Apr;35(2):178-216.
- 509 Packer L, Witt EH, Tritschler HJ. Alpha–lipoic acid as a biological antioxidant. Free Radic Biol Med. 1995;19:227–250.
- 510 Jones W, Li X, Qu ZC, et al. Uptake, recycling, and antioxidant actions of alpha-lipoic acid in endothelial cells. Free Radic Biol Med 2002;33:83-93.
- 511 Bast A, Haenen GR. Lipoic acid: a multifunctional antioxidant. Biofactors. 2003;17(1-4):207-13.
- 512 Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. Free Radic Biol Med 1997;22(1-2):359-78.
- 513 Podda M, Tritschler HJ, Ulrich H, et al. Alpha–lipoic acid supplementation prevents symptoms of vitamin E deficiency. Biochem Biophys Res Commun. 1994;204:98–104.
- 514 Faust A, Burkart V, Ulrich H, Weischer CH, Kolb H. Effect of lipoic acid on cyclophosphamideinduced diabetes and insulitis in non-obese diabetic mice. Int J Immunopharmacol. 1994;16(1):61-6.
- 515 Burkart V, Koike T, Brenner HH, Imai Y, Kolb H. Dihydrolipoic acid protects pancreatic islet cells from inflammatory attack. Agents Actions. 1993;38(1-2):60-5.
- 516 Packer L. Alpha lipoic acid: a metabolic antioxidant which regulates NF- kappaB signal transduction and protects against oxidative injury. Drug Metab Rev 1998;30:245–75.
- 517 Lee HA, Hughes DA. Alpha-lipoic acid modulates NF-kappaB activity in human monocytic cells by direct interaction with DNA. Exp Gerontol. 2002;37(2-3):401-10.
- 518 https://bioperine.com/index.php/researchhighlight.
- 519 Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998 May;64(4):353-6.
- 520 Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. Indian J Med Res. 2010 May;131:682-91.
- 521 Badmaev V, Majeed M, Prakash L, Norkus EP. Piperine. An Alkaloid Derived From Black Pepper, Increases Serum Response Of Beta-Carotene During 14-Days Of Oral Beta-Carotene Supplementation Nutrition Research (1999) 19(3) 381-388.

- 522 Badmaev V, Majeed M, Prakash L. Piperine derived from black pepper increases the plasma levels of coenzyme Q10 following oral supplementation. J Nutr Biochem. 2000 Feb;11(2):109-13.
- 523 Duangjai A, Ingkaninan K, Praputbut S, Limpeanchob N. Black pepper and piperine reduce cholesterol uptake and enhance translocation of cholesterol transporter proteins. J Nat Med. 2013 Apr;67(2):303-10.
- 524 Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. Phytomedicine. 2002 Apr;9(3):224-31.
- 525 Vijayakumar RS, Surya D, Nalini N. Antioxidant efficacy of black pepper (Piper nigrum L.) and piperine in rats with high fat diet induced oxidative stress. Redox Rep. 2004;9(2):105-10.
- 526 Park UH, Jeong HS, Jo EY, Park T, Yoon SK, Kim EJ, Jeong JC, Um SJ. Piperine, a component of black pepper, inhibits adipogenesis by antagonizing PPAR? activity in 3T3-L1 cells. J Agric Food Chem. 2012 Apr 18;60(15):3853-60.
- 527 Meghwal M, Goswami TK.Piper nigrum and piperine: an update. Phytother Res. 2013 Aug;27(8):1121-30.
- 528 Srinivasan K.Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Crit Rev Food Sci Nutr. 2007;47(8):735-48.
- 529 Chonpathompikunlert P, Wattanathorn J, Muchimapura S. Piperine, the main alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease. Food Chem Toxicol. 2010 Mar;48(3):798-802.
- 530 Álvares TS, Meirelles CM, Bhambhani YN, Paschoalin VM, Gomes PS. L-Arginine as a potential ergogenic aid in healthy subjects. Sports Med. 2011 ;41(3):233-48.
- 531 Cremades A, Ruzafa C, Monserrat F, Lopez-Contreras AJ, Penafiel R. Influence of dietary arginine on the anabolic effects of androgens. J Endocrinol. 2004 Nov;183(2):343-51.
- 532 Chang CK, Chang Chien KM, Chang JH, Huang MH, Liang YC, Liu TH. Branched-chain amino acids and arginine improve performance in two consecutive days of simulated handball games in male and female athletes: a randomized trial. PLoS One. 2015 Mar 24;10(3):e0121866.
- 533 Bahri S1, Zerrouk N, Aussel C, Moinard C, Crenn P, Curis E, Chaumeil JC, Cynober L, Sfar S. Citrulline: from metabolism to therapeutic use. Nutrition. 2013 Mar;29(3):479-84.
- 534 Fornaris E, Vanuxem D, Duflot JC, et al. Pharmacoclinical approach of citrulline malate activity: analysis of blood lactate during a standardized exercise. Gazette Medicale 1984;91:1-3.
- 535 Vanuxem D, Duflot JC, Prevot H, et al. Influence of an anti-asthenia agent, citrulline malate, on serum lactate and ammonia kinetics during a maximum exercise test in sedentary subjects. Séminaire des Hôpitaux de Paris 1990; 66:477-81.
- 536 Wagenmakers AJ. Muscle amino acid metabolism at rest and during exercise: role in human physiology and metabolism. Exerc Sport Sci Rev 1998; 26:287-314.
- 537 Callis A, Magnan de Bornier B, Serrano JJ, Bellet H, Saumade R. Activity of citrulline malate on acid-base balance and blood ammonia and amino acid levels. Study in the animal and in man. Arzneimittelforschung. 1991; 41(6):660-3.
- 538 Briand J, Astoin J, Lavalmartin D, et al. Euglena, as a cellular-model used in pharmacology for studying the effects of citrulline malate on lactate metabolisation. Comp Biochem Physiol 1986; 85:553-8.
- 539 Gibala MJ, Tarnopolsky MA, Graham TE. Tricarboxylic acid cycle intermediates in human muscle at rest and during prolonged cycling. Am J Physiol 1997;35:E239-44.
- 540 Gibala MJ, Young ME, Taegtmeyer H. Anaplerosis of the citric acid cycle: role in energy metabolism of heart and skeletal muscle. Acta Physiol Scand 2000;168:657-65.
- 541 Fornaris E, Vanuxem D, Duflot JC, et al. Pharmacoclinical approach of citrulline malate activity: analysis of blood lactate during a standardized exercise. Gazette Medicale 1984;91:1-3.

- 542 Vanuxem D, Duflot JC, Prevot H, et al. Influence of an anti-asthenia agent, citrulline malate, on serum lactate and ammonia kinetics during a maximum exercise test in sedentary subjects. Séminaire des Hôpitaux de Paris 1990; 66:477-81.
- 543 Wagenmakers AJ. Muscle amino acid metabolism at rest and during exercise: role in human physiology and metabolism. Exerc Sport Sci Rev 1998; 26:287-314.
- 544 Callis A, Magnan de Bornier B, Serrano JJ, Bellet H, Saumade R. Activity of citrulline malate on acid-base balance and blood ammonia and amino acid levels. Study in the animal and in man. Arzneimittelforschung. 1991; 41(6):660-3.
- 545 Briand J, Astoin J, Lavalmartin D, et al. Euglena, as a cellular-model used in pharmacology for studying the effects of citrulline malate on lactate metabolisation. Comp Biochem Physiol 1986; 85:553-8.
- 546 Gibala MJ, Tarnopolsky MA, Graham TE. Tricarboxylic acid cycle intermediates in human muscle at rest and during prolonged cycling. Am J Physiol 1997;35:E239-44.
- 547 Gibala MJ, Young ME, Taegtmeyer H. Anaplerosis of the citric acid cycle: role in energy metabolism of heart and skeletal muscle. Acta Physiol Scand 2000;168:657-65.
- 548 Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, Cozzone PJ. Citrulline/malate promotes aerobic energy production in human exercising muscle. Br J Sports Med. 2002 Aug;36(4):282-9.
- 549 Pérez-Guisado J, Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. J Strength Cond Res. 2010 May;24(5):1215-22.
- 550 Sureda A, Córdova A, Ferrer MD, Pérez G, Tur JA, Pons A. L-citrulline-malate influence over branched chain amino acid utilization during exercise. Eur J Appl Physiol. 2010 Sep;110(2):341-51.
- 551 Giannesini B, Le Fur Y, Cozzone PJ, Verleye M, Le Guern ME, Bendahan D. Citrulline malate supplementation increases muscle efficiency in rat skeletal muscle. Eur J Pharmacol. 2011 Sep 30;667(1-3):100-4.
- 552 Wax B, Kavazis AN, Weldon K, Sperlak J. Effects of supplemental citrulline malate ingestion during repeated bouts of lower-body exercise in advanced weightlifters. J Strength Cond Res. 2015 Mar;29(3):786-92.
- 553 Wax B, Kavazis AN, Luckett W. Effects of Supplemental Citrulline-Malate Ingestion on Blood Lactate, Cardiovascular Dynamics, and Resistance Exercise Performance in Trained Males. J Diet Suppl. 2016;13(3):269-82.
- 554 Glenn JM, Gray M, Jensen A, Stone MS, Vincenzo JL. Acute citrulline-malate supplementation improves maximal strength and anaerobic power in female, masters athletes tennis players. Eur J Sport Sci. 2016 Nov;16(8):1095-103.
- 555 Glenn JM, Gray M, Wethington LN, Stone MS, Stewart RW Jr, Moyen NE. Acute citrulline malate supplementation improves upper- and lower-body submaximal weightlifting exercise performance in resistance-trained females. Eur J Nutr. 2017 Mar;56(2):775-784.
- 556 Buford BN, Koch AJ. Glycine-arginine-alpha-ketoisocaproic acid improves performance of repeated cycling sprints. Med Sci Sports Exerc. 2004 Apr;36(4):583-7.
- 557 Hammarqvist F, Wernerman J, von der Decken A, Vinnars E. Alpha-ketoglutarate preserves protein synthesis and free glutamine in skeletal muscle after surgery. Surgery 1991; 109(1):28-36.
- 558 Roth E, Karner J, Roth-Merten A, Winkler S; Valentini L; Schaupp K. Effect of alpha-ketoglutarate infusions on organ balances of glutamine and glutamate in anaesthetized dogs in the catabolic state. Clin Sci 1991; 80(6):625-631.
- 559 Wernerman J, Hammarqvist F, Vinnars E. Alpha-ketoglutarate and postoperative muscle catabolism. Lancet 1990; 335(8691):701-703.
- 560 Marconi C, Sassi G, Cerretelli P. The effect of an alpha-ketoglutarate-pyridoxine complex on human maximal aerobic and anaerobic performance. Eur J Appl Physiol 1982; 49(3):307-17.

- 561 Hammarqvist F, Wernerman J. Ali R. Vinnars E. Effect of an amino acid solution enriched with branched chain amino acid or ornithine-ketoglutarate on the post-operative intracellular amino acid concentration of muscle. British Journal of Surgery 1990; 77(2):214-218.
- 562 Wernerman, J Hammarqvist-F; Vinnars-E. Alpha-ketoglutarate and postoperative muscle catabolism. Lancet 1980; 335:701.
- 563 Blomqvist BI, Hammarqvist F, von der Decken A, et al. Glutamine and alpha-ketoglutarate prevent the decrease in muscle free glutamine concentration and influence protein synthesis after total hip replacement. Metabolism 1995; 44:1215-1222.
- 564 Campbell B, Roberts M, Kerksick C, Wilborn C, Marcello B, Taylor L, Nassar E, Leutholtz B, Bowden R, Rasmussen C, Greenwood M, Kreider R. Pharmacokinetics, safety, and effects on exercise performance of I-arginine alpha-ketoglutarate in trained adult men. Nutrition. 2006 Sep;22(9):872-81.
- 565 Huynh NN, Chin-Dusting J. Amino acids, arginase and nitric oxide in vascular health. Clin Exp Pharmacol Physiol. 2006 Jan-Feb;33(1-2):1-8.
- 566 Lacerda AC, Marubayashi U, Coimbra CC. Nitric oxide pathway is an important modulator of heat loss in rats during exercise. Brain Res Bull. 2005 Sep 30;67(1-2):110-6.
- 567 Richmonds CR, Kaminski HJ. Nitric oxide myotoxicity is age related. Mech Ageing Dev. 2000 Feb 15;113(3):183-91.
- 568 Perkins WJ, Han YS, Sieck GC. Skeletal muscle force and actomyosin ATPase activity reduced by nitric oxide donor. J Appl Physiol. 1997 Oct;83(4):1326-32.
- 569 Drewett JG, Adams-Hays RL, Ho BY, Hegge DJ. Nitric oxide potently inhibits the rate-limiting enzymatic step in steroidogenesis. Mol Cell Endocrinol. 2002;194(1–2):39–50.
- 570 Del Punta K, Charreau EH, Pignataro OP. Nitric oxide inhibits Leydig cell steroidogenesis. Endocrinology. 1996;137(12):5337–5343.
- 571 Andric SA, Janjic MM, Stojkov NJ, Kostic TS. Protein kinase G-mediated stimulation of basal Leydig cell steroidogenesis. Am J Physiol Endocrinol Metab. 2007;293(5):E1399–E1408.
- 572 Andric SA, Janjic MM, Stojkov NJ, Kostic TS. Testosterone-induced modulation of nitric oxidecGMP signaling pathway and androgenesis in the rat Leydig cells. Biol Reprod. 2010;83(3):434– 442.
- 573 Gambaryan S, Butt E, Marcus K, et al. cGMP-dependent protein kinase type II regulates basal level of aldosterone production by zona glomerulosa cells without increasing expression of the steroidogenic acute regulatory protein gene. J Biol Chem. 2003;278(32):29640–29648.
- 574 Del Punta K, Charreau EH, Pignataro OP. Nitric oxide inhibits Leydig cell steroidogenesis. Endocrinology. 1996;137(12):5337–5343.
- 575 Drewett JG, Adams-Hays RL, Ho BY, Hegge DJ. Nitric oxide potently inhibits the rate-limiting enzymatic step in steroidogenesis. Mol Cell Endocrinol. 2002;194(1–2):39–50.
- 576 Mondillo C, Pagotto RM, Piotrkowski B, Reche CG, Patrignani ZJ, Cymeryng CB, Pignataro OP. Involvement of nitric oxide synthase in the mechanism of histamine-induced inhibition of Leydig cell steroidogenesis via histamine receptor subtypes in Sprague-Dawley rats. Biol Reprod. 2009 Jan;80(1):144-52.
- 577 Di Fiore MM, Lamanna C, Assisi L, Botte V. Opposing effects of D-aspartic acid and nitric oxide on tuning of testosterone production in mallard testis during the reproductive cycle. Reprod Biol Endocrinol. 2008;6:1.
- 578 Lamanna C, Assisi L, Vittoria A, Botte V, Di Fiore MM. D-Aspartic acid and nitric oxide as regulators of androgen production in boar testis. Theriogenology. 2007 Jan 15;67(2):249-54.
- 579 D'Aniello G, Ronsini S, Notari T, Grieco N, Infante V, D'Angel N, et al. d-Aspartate, a key element for the improvement of sperm quality. Adv Sex Med. 2012;2:47–53.
- 580 Nagata Y, Homma H, Lee JA, Imai K. D-Aspartate stimulation of testosterone synthesis in rat Leydig cells. FEBS Lett. 1999 Feb 12;444(2-3):160-4.

- 581 Raucci F, D'Aniello A, Di Fiore MM. Stimulation of androgen production by D-aspartate through the enhancement of StAR, P450scc and 3β-HSD mRNA levels in vivo rat testis and in culture of immature rat Leydig cells. Steroids. 2014;84:103–110.
- 582 Burrone L, Raucci F, Di Fiore MM. Steroidogenic gene expression following D-aspartate treatment in frog testis. Gen Comp Endocrinol. 2012 Jan 1;175(1):109-17.
- 583 Di Nisio A, De Toni L, Ferigo M, Rocca M, Speltra E, Ferlin A, et al. d-Aspartic acid stimulates steroidogenesis through the delay of LH receptor internalization in a mammalian Leydig cell line. J Endocrinol Invest. 2015;39:207–213.
- 584 Di Nisio A, De Toni L, Ferigo M, Rocca MS, Speltra E, Ferlin A, Foresta C. D-Aspartic acid stimulates steroidogenesis through the delay of LH receptor internalization in a mammalian Leydig cell line. J Endocrinol Invest. 2016 Feb;39(2):207-13.
- 585 D'Aniello A, Di Cosmo A, Di Cristo C, Annunziato L, Petrucelli L, Fisher G, Involvement of Daspartic acid in the synthesis of testosterone in rat testes. Life Sciences 1996; 59(2):97-104.
- 586 Topo E, Soricelli A, D'Aniello A, Ronsini S, D'Aniello G. The role and molecular mechanism of Daspartic acid in the release and synthesis of LH and testosterone in humans and rats. Reprod Biol Endocrinol. 2009 Oct 27;7:120.
- 587 D'Aniello A. D-Aspartic acid: an endogenous amino acid with an important neuroendocrine role. Brain Res Rev. 2007 Feb;53(2):215-34.
- 588 Zhu A, Andino J, Daignault-Newton S, Chopra Z, Sarma A, Dupree JM. What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old. J Urol. 2022 Oct 25:101097JU000000000002928. doi: 10.1007/JU.00000000002028. Epub aboad of print. DMID: 26282060.
- 10.1097/JU.000000000002928. Epub ahead of print. PMID: 36282060.
- 589 Pham H, Ziboh VA. 5 alpha-reductase-catalyzed conversion of testosterone to dihydrotestosterone is increased in prostatic adenocarcinoma cells: suppression by 15-lipoxygenase metabolites of gamma-linolenic and eicosapentaenoic acids. J Steroid Biochem Mol Biol. 2002 Nov;82(4-5):393-400.
- 590 Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. J Altern Complement Med. 2002 Apr;8(2):143-52.
- 591 Sen Gupta R, Sen Gupta E, Dhakal BK, Thakur AR, Ahnn J. Vitamin C and vitamin E protect the rat testes from cadmium-induced reactive oxygen species. Mol Cells. 2004 Feb 29;17(1):132-9.
- 592 Patrick L. Mercury toxicity and antioxidants: Part 1: role of glutathione and alpha-lipoic acid in the treatment of mercury toxicity. Altern Med Rev. 2002 Dec;7(6):456-71.
- 593 Girish BP, Reddy PS. Forskolin ameliorates mancozeb-induced testicular and epididymal toxicity in Wistar rats by reducing oxidative toxicity and by stimulating steroidogenesis. J Biochem Mol Toxicol. 2018 Feb;32(2).
- 594 Godard MP, Johnson BA, Richmond SR. Body composition and hormonal adaptations associated with forskolin consumption in overweight and obese men. Obes Res. 2005 Aug;13(8):1335-43.
- 595 Girish BP, Reddy PS. Forskolin ameliorates mancozeb-induced testicular and epididymal toxicity in Wistar rats by reducing oxidative toxicity and by stimulating steroidogenesis. J Biochem Mol Toxicol. 2018 Feb;32(2). doi: 10.1002/jbt.22026. PMID: 29283200.
- 596 Chen H, Liu J, Luo L, Zirkin BR. Dibutyryl cyclic adenosine monophosphate restores the ability of aged Leydig cells to produce testosterone at the high levels characteristic of young cells.

