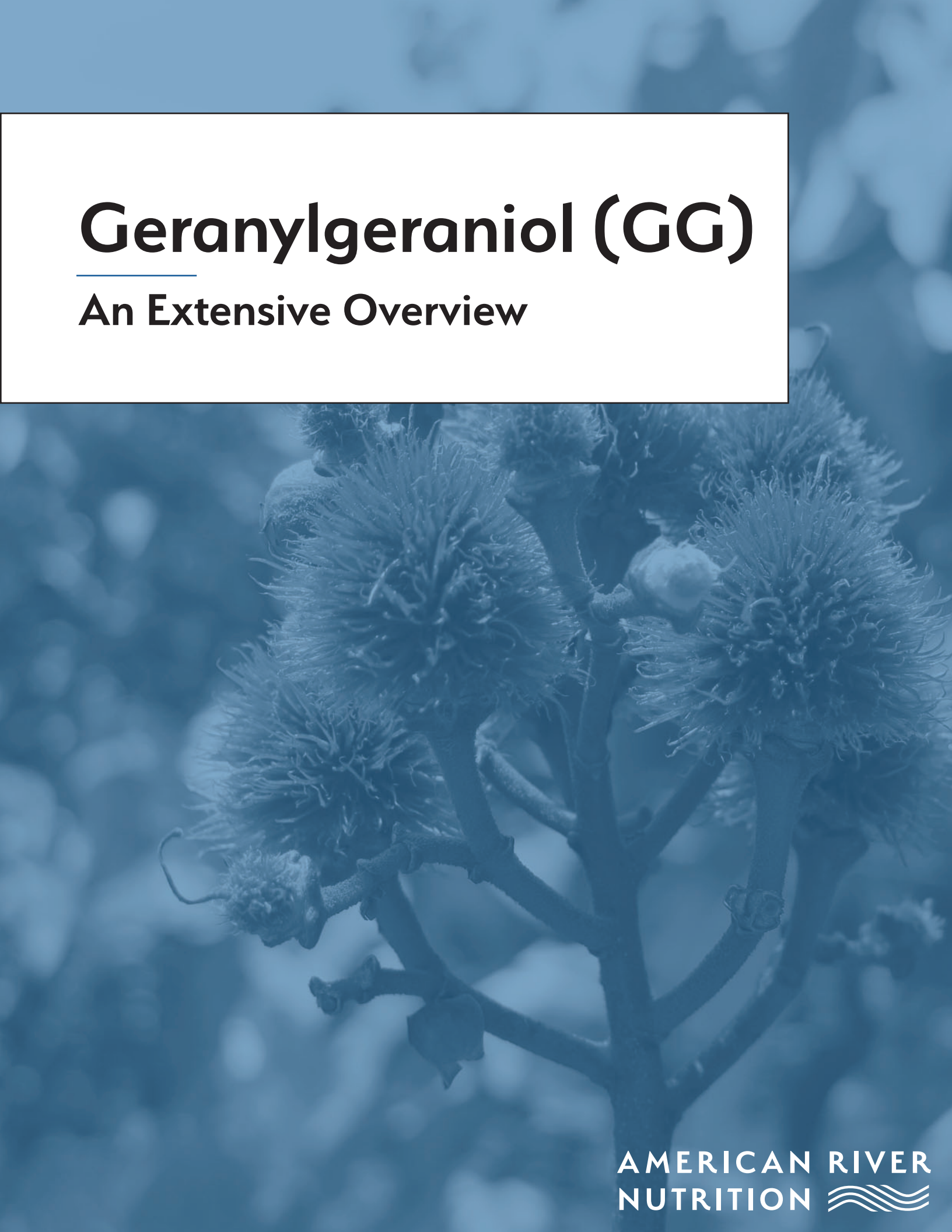
Geranylgeraniol (GG)

An Extensive Overview



AMERICAN RIVER NUTRITION

Introduction

Geranylgeraniol (GG) is a compound synthesized endogenously in the human body via the mevalonate pathway—the same biochemical pathway by which cholesterol, vitamin K2, steroid hormones and ubiquinone (CoQ10) are synthesized. As such, it plays a critical role in tissue systems and metabolic processes throughout the body, including healthy mitochondrial function and the generation of ATP, the currency of energy in all mammals including humans. GG occurs naturally in various foods, but the majority is synthesized endogenously. GG is an essential building block that supports muscle health, bone health, hormone regulation and CoQ10 synthesis. Production of GG declines naturally during aging and is inhibited by use of certain pharmaceutical drugs, namely, statins and bisphosphonates. By replenishing natural levels, GG can protect from age-related physical decline, maintain structural support for the body and revoke skeletal muscle fatigue.

Characteristics of GG

History

GG was first synthesized in 1939 as a base molecule of diterpenes[1], and was isolated from linseed oil through a USDA-sponsored study in 1966[2], at which point it was already known to be responsible for photosynthetic pigment synthesis[3]. GG is thought to be located at the crossroads of the biosynthesis pathways for chlorophyll and chloroplastic carotenoids, where it is a precursor to carotene and lutein in leaves[4]. The diterpene has also been shown to transform into phytol, lycopene, and other carotenoids[5]. Whereas phytol then mainly goes on to produce vitamin E tocopherol and phylloquinol (vitamin K1), tocotrienol – a compound of the vitamin E family with an unsaturated side chain – is directly converted from GG[3].

Universal Presence

If you see any carotenoid color (typically yellow/orange/red/maroon) in the roots, leaves, fruits or seeds of any plant, you know that GG is present. Likewise, the heme color (typically red) in organs and the vasculature of animals – warm- or cold-blooded – indicates the presence of GG. Intuitively, the color of plants and the blood of animals announces the presence of GG everywhere.

Source: Annatto

As a precursor to carotenoids, certain vitamins and chlorophyll, GG can be found in a variety of plants[2,3]. Higher concentrations of geranylgeraniol can be found in edible oils such as olive, linseed, and sunflower[6-9].

One of the most abundant sources of GG can be found in Bixa orellana, a South American plant

commonly known as annatto that has been used for centuries in the coloring of foods and cosmetics[10]. GG is responsible for annatto's coloring component called bixin, as well as the vitamin E antioxidant tocotrienol that the plant produces to protect its signature carotenoid from oxidation.

Ancient medicinal uses of annatto[11] as a cardiotonic, hypotensive, antibiotic, and anti-inflammatory agent provided clues that the plant would one day play an important role in modern healthcare. Today, GG-Gold™ – a pure geranylgeraniol extract from annatto – is the first product to bring these age-old benefits to health-conscious consumers.

GG-Gold™

GG-Gold™ is a multi-patented ingredient produced by American River Nutrition for use in supplements, foods & beverages, and cosmetic products. American River Nutrition produces GG-Gold™ in the USA, at their state-of-art 24,000 sq. ft. GMP facility in Hadley, MA, using a clean, purely physical extraction process. The novelty of GG-Gold™ as a unique ingredient for inclusion in dietary supplements and other commercial applications provides a point of differentiation that can be leveraged in various markets. Its efficacy in supporting biological processes that wane with advanced years and in the face of medication-induced deficiency provide opportunity for it to be positioned in an ever-growing market segment within aging populations.

Exploring the specific mechanisms of action by which GG supports human physiology helps highlight its ubiquitous influence on health.

Mechanisms of Action

GG and other isoprenoids are produced in humans through the mevalonate pathway, an ancient metabolic pathway present in both plants and mammals.[12] This pathway is also instrumental for the production of cholesterol and other sterols, ubiquinone, dolichol, hemes, vitamin K2, vitamin D, proteins, and the sex hormones.[13] GG is involved in the body's production of proteins, vitamin K2, ubiquinone, testosterone, and progesterone.[14-19] To achieve this synthesis, the body primarily utilizes GG in the activated pyrophosphate (GGPP), but studies have shown that GG can be activated by the body and incorporated into the mevalonate pathway.[14,17,18,20,21]

Although the body's capacity to maintain the mevalonate pathway remains fairly stable throughout young adulthood, its activity can change during the aging process, resulting in GG depletion and subsequent aging hallmarks such as decreased energy and reduced protein production. This occurs through the downstream effects on GG's metabolic products, whose synthesis drop as the levels of GG substrate decrease. Furthermore, certain prescription drugs, particularly statins and bisphosphonates, decimate the "isoprenoid pool".

Supplementation with GG can replenish the isoprenoid pool and facilitate endogenous production of essential nutrients and metabolites. As such, introduction of exogenous GG through dietary supplementation may ameliorate certain health conditions that are, either through aging or medication, related to the decline of vital nutrients our body makes.

GG Benefits

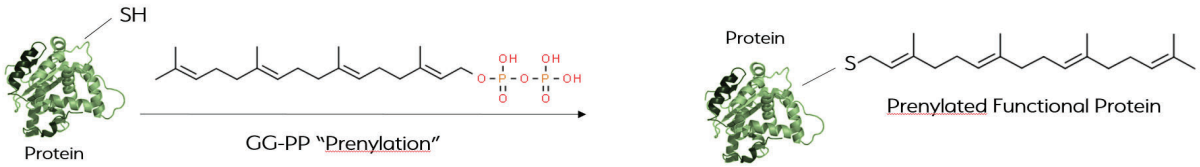
Evidence supports GG's benefits in a variety of conditions characterized by depletion of essential biological micronutrients. These biological outcomes may be attributed to GG's role as a structural component of endogenous molecules.

Musculoskeletal Function, Viability & Activity

Age-related losses of muscle mass and strength are major contributors to reduced quality of life and loss of independence for older individuals. Used for protein synthesis and post-translational modification, GG is essential for growth, differentiation, and survival of cells. Downregulation of this process, be it age-related or drug-induced, may lead to a range of muscular conditions, including muscle wasting, sarcopenia, and myopathy. Fortunately, research suggests that replenishing GG exogenously can satisfactorily restore these processes.

Proteins direct virtually all activities of cells[22], forming what we know as the framework of life. There are four basic types of proteins that perform a variety of functions; fibrous[23], globular[24], membrane[25] and disordered[26] proteins. There are several thousand different proteins in each cell[22], and proteins occupy about 25% of the cell volume.[27] In mammals, isoprenoid-modified (or prenylated) proteins comprise 1-2% of cellular proteins[15], and geranylgeraniol is the predominant isoprenoid found on cellular proteins.[15,28-30] While this is a small percentage of proteins made from isoprenoids – especially GG – they wreak global harm to the body if diminished.

Protein prenylation is a way to make protein via protein modification using a prosthetic isoprenoid.[31] GG is the prosthetic arm that anchors into the membrane. This isoprenoid-enabled prenylation of proteins is essential for their association with membranes and interactions to allow proteins to traffic between membranes in the cytosol (a crucial step for signal transduction).[30,31]



The first study to thoroughly investigate GG's involvement in protein synthesis was carried out in 1994, when scientists radiolabeled GG and showed that it was incorporated into protein fractions.[15] The researchers simultaneously found that they could utilize free GG (supplemented) versus the activated GGPP form as a metabolic source for protein prenylation. They later labeled this supplemental GG as the "salvage pathway", and explored its physiological relevance through experiments with HMG CoA reductase inhibitors.[20] Whereas these inhibitors caused a block in FPP and GGPP biosynthesis resulting in loss of protein prenylation, adding back GG exogenously restored such protein synthesis.[20] Similarly, GGPP proteins were restored by supplemental GG in statin-treated pulmonary smooth muscle cells.[32]

There is an extensive list of geranylgeranylated proteins, including small GTP-binding proteins that are involved in the control of cytoskeletal-membrane interactions.[15] When observing GG behavior in model membranes, researchers demonstrated structural isoprenoid-rich microdomains, suggesting that the isoprenyl group is a

protein anchor to enhance protein clustering and to ensure membrane interaction.[33] Other GGPP proteins, such as GTPases (enzymes responsible for the binding of proteins to GTP) function in both protein biosynthesis and signal transduction. These include Ras, which ensures cytoskeletal integrity and cell proliferation, and Rho, which involves cellular function and differentiation.[21,34] In skeletal muscle, RAP GTPase is known to be exclusively formed by GG.[35]

One study investigated the role of GG in rescuing Ras protein prenylation function, cholesterol synthesis, and cell morphology. While GG did not affect cholesterol synthesis, it did reverse changes in the cell's shape caused by statin inhibition on GG biosynthesis, a restorative benefit of GG on Rho protein (a subfamily of the Ras protein superfamily).[34]

Although many studies have shown GG's rescue of muscle function in the presence of statins, one study went further to confirm that GG is beneficial for muscle building in the absence of statin.[36] The focus of this study was to examine GG's effect on exertion muscles – including gastrocnemius, soleus, and tibialis anterior – in young, healthy rats. The GG dosage used was equivalent to 170mg/d for a 70kg human. Results showed that GG increased force production of muscles and prevented skeletal muscle fatigue, and these improvements were not associated with adverse changes in heart function, hence confirming GG's safe use. Moreover, GG improved vascular health by increasing endothelium-dependent relaxation in muscular arteries, which was likely due to enhanced nitric oxide associated with GG supplementation. In the same study, researchers also tested the adverse effects of statins on shinbone muscles, confirming that statins reduced force production in these muscles.[36] Importantly, co-supplementation with GG completely abrogated statin's ill effects on the muscles, thus preventing statin-induced muscle fatigue. Whereas statins reduced normal functions of contraction and relaxation of the thoracic aorta and mesenteric artery muscles, GG, when added, consistently contracted and relaxed muscles better, suggesting that GG corrects cardiac muscle contractility and improves vasorelaxation. Taken together, the results of this study advocate for the use of GG in both young athletes and those on statin medications.

GG is a building block for protein synthesis and skeletal structure of the cell. GG demonstrates significant influence on muscle health, its potential in age-related muscle decline, enzyme activity, protein trafficking, and connective tissue integrity.

Bone Integrity and Composition

Vitamin K is be best known for its blood clotting abilities, but to a lesser known extent, it is also a crucial contributor to healthy bone mass. Vitamin K—particularly the K2 form—is needed for proper functioning of proteins that deposit calcium into bones and teeth while inhibiting calcification of soft tissues such as blood vessels, kidney, gall and joints. There are several causes of vitamin K deficiency, ranging from dietary insufficiency and malabsorption to drug inhibition. For vitamin K-deficient individuals, supplementation with GG may be a helpful strategy to replenish stores of this essential vitamin and ensure the preservation of its arterial and bone health benefits.

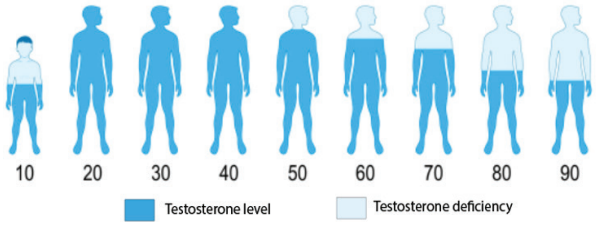
Vitamin K in the form of phylloquinone (vitamin K1) was first identified in 1935, when it was shown to be essential for normal blood coagulation.[37] Later, in 1939, researchers found another type of vitamin K in putrefied (fermented) fish meal, which became known as menaquinone or vitamin K2.[38,39] Biologically, vitamin K is a required cofactor for gamma-glutamyl carboxylase, which converts glutamic acid residues into γ-carboxyglutamic acid residues in proteins involved in blood clotting and bone metabolism and calcification.[16,40] Vitamin K also functions as a mitochondrial electron carrier during ATP production and regulates protein kinase A signalling that is essential in basic processes such as energy metabolism, muscle contraction, membrane transport and gene expression.[40,41] Isomers of vitamin K are essential for the carboxylation of vitamin K-dependent proteins involved in blood coagulation and regulation of calcification, and are required for the synthesis of calcium-binding proteins.[40]

Whereas plant-derived phylloquinone contains a saturated phytyl chain, menaquinone (vitamin K2) contains a number of isoprenoid unsaturated side chains, with the two common forms containing 4 and 7 side chains (menaquinone-4 or MK-4, and menaquinone-7 or MK-7, respectively). MK-4 is the most abundant menaquinone in the body. The unequivocal and indispensable factor to complete MK-4 synthesis is GG, and many studies have now confirmed GG is obligatory in the synthesis of MK-4.[16,18,40,42,43] It was noted as early as 1960 through radiolabeling experiments that GG is an intermediate building block of vitamin K2 synthesis.[19]

MK-7 (and longer menaquinones) are produced by fermentation bacteria in the colon "outside" the body, and understanding of their absorption is unknown. MK-4 manages calcium transport throughout the body, especially to the bone where >90% of calcium is found. Since MK-4 is synthesized in the body, its role in bone mineralization is of physiologic importance.

Hormone Regulation

Population-based studies show that testosterone levels in men decrease with age[44], and this decline has been linked with chronic diseases and shortened life expectancy.[45-50]



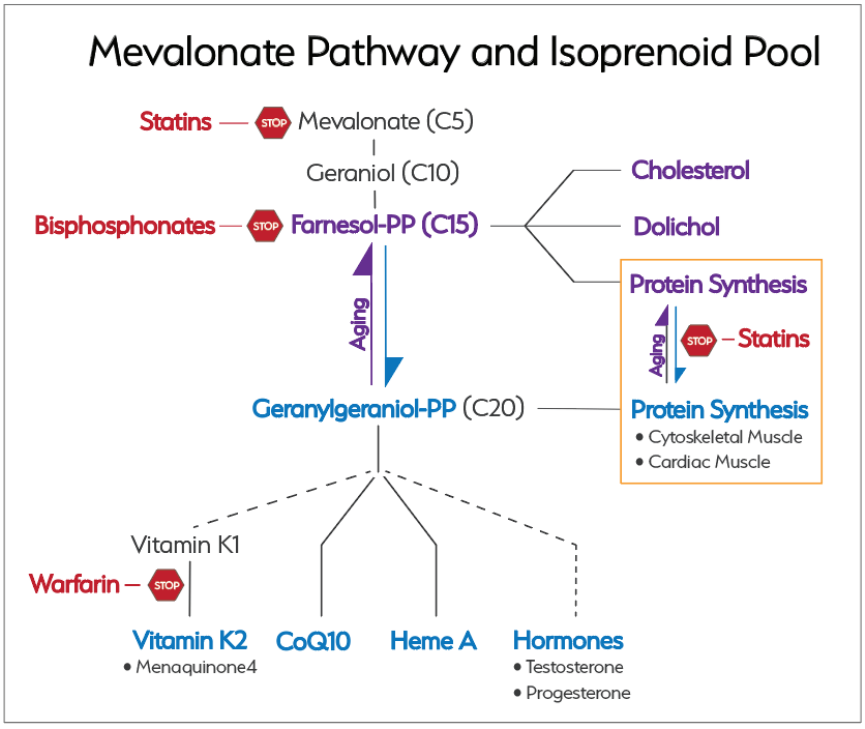
Testosterone in men is produced by the Leydig cells in testicles, sharing the common origin of cholesterol through the mevalonate pathway.[18] As a central part of the mevalonate pathway, GG is crucial in regulating testosterone production. In testis-derived cells, GG was shown to regulate the steroidogenesis pathway, enhancing not only testosterone synthesis, but also synthesis of its precursor, progesterone.[17] MK-4 and GG are intricately connected, and were shown to stimulate testosterone

production by increasing cAMP levels via protein kinase A activity, an important messenger the body uses to signal various biological processes.[18,51] From animal studies, it is known that a human equivalent dose of 66mg/d GG significantly elevated plasma testosterone levels.[17] Interestingly, GG was shown to interact directly with MK-4 in regulating testosterone production.[17,18]

GG – a key factor in testosterone synthesis – may be useful in reversing testosterone decline in aging men, thereby improving their ability to thrive.

CoQ10 Synthesis

CoQ10 is an important compound that has been shown to improve symptoms associated with mitochondrial disorders. Statin treatment, which directly targets the mevalonate pathway to decrease cholesterol, decreases CoQ10 (unintended) and was shown to be a myopathy biomarker. GG can act in concert as a building block to increase CoQ10 levels in statin users and older adults, and to restore mitochondrial functioning and protect muscles in a synchronous approach.[14,52]



CoQ10 was discovered by Frederick Crane in the 1950s as an essential component to the electron transport chain.[53,54] Small amounts occur naturally in certain foods, but the majority of plasma and cellular CoQ10 is synthesized endogenously. CoQ10 is critical for electron transfer in mitochondrial membranes for respiratory chain activity and, as a lipid-soluble antioxidant, to protect biological membranes from oxidative damage.[40]

Deficiency in CoQ10 can primarily be traced back to genetic mutations that become apparent in childhood, but cases of adult-onset deficiency associated with cerebellar ataxia, mitochondrial disorders,

and myopathy have also been reported.[55-57] CoQ10 levels were found to be consistently low in fibromyalgia patients and supplementation improved symptoms.[58-60] Whereas true CoQ10 deficiency is rare, gradually declining levels of the quinone during the aging process are a common occurrence[61,62], as is CoQ10's noted drop alongside several chronic and age-related illnesses such as type 2 diabetes, cancer, and congestive heart failure.[63]

Studies corroborate GG as an intermediate in the synthesis of ubiquinone through radio-labelling, which showed GG as a building block.[19] GG is also an essential component in the prenylation of CoQ10 in Golgi membranes, which is catalyzed by the protein-coding gene UBIAD1.[40,42]

GG is needed to synthesize CoQ10 in the cell.[19] CoQ10 is part of the respiratory chain to produce energy as ATP in the cell, and because the heart never sleeps, heart muscles are most sensitive to CoQ10 requirement.[64] CoQ10 has specific cardiotonic benefits besides its cardiovascular benefits. It is one of the very few endogenous non-protein antioxidants the body makes for its lipid protection.[65]

GG and Drug Intervention

Statins

Statin drugs exert their effects much earlier in the mevalonate pathway (via inhibition of the enzyme HMG-CoA reductase), far upstream from where GG and its downstream crucial products are synthesized. Statin therapy leads to the desired drop in cholesterol and indiscriminately reduces the synthesis of all downstream compounds, contributing to the noted drug side effects of neuromyotoxicity and mitochondrial toxicity.[66,67] Among the most common side-effects studied is the decreased synthesis of CoQ10, which may result in depressed cellular energy generation via impaired mitochondrial respiration, with cascading effects on numerous tissue systems. At stake is a fundamental problem - the biologic strangulation of GG synthesis due to statins, which is responsible not only for a drop in CoQ10, but also a decline in proteins necessary to maintain muscle mass. Further affected is the endogenous vitamin K2 production, which plays a role in vascular calcification and, paradoxically, atherosclerosis.[68]

A commonly reported problem by statin users is muscle pain and weakness. The exact mechanisms behind myopathy and myotoxicity statin users experience are not known for certain, but published results point to GG compellingly and to CoQ10 secondarily. Although CoQ10 has been shown to deplete as a result of statin therapy, leading to decreased energy production in muscles, its direct connection with myopathy remains controversial.[69-71] Studies have shown that supplemental CoQ10 alone could not rescue muscle cells from statin-associated myopathy, suggesting that reduced CoQ10 synthesis in the presence of statins was not symptomatic to muscle vulnerability.[52,72,73] As opposed to ubiquinone, GG plays a central role in the mevalonate pathway that statins inhibit, justifying GG's unique ability to restore mitochondria and protect muscle cells.[52]

Animal models and cell studies abundantly show that GG reduces statin side effects both independently and by aiding ubiquinone synthesis. When given in combination with statins, GG increases mitochondrial respiration and restores ubiquinone synthesis without negatively impacting statins' ability to lower cholesterol. Administration of GG to statin-treated human neurons decreased expression of inflammatory markers and reduced mitochondrial damage, facilitating maintenance of proper mitochondrial structure and function.[74] In human monocytes and liver cells, GG reversed mevastatin-induced reductions in ubiquinone synthesis and

mitochondrial electron transport that typically lead to cell death, also without impeding the drug's cholesterol-lowering property.[14] Notably, GG was more effective than exogenous CoQ10 for attenuating these adverse effects, leading researchers to state that compared to ubiquinone, "Geranylgeraniol may be a more useful and practical means of limiting the toxicities of statins, without reducing their efficacy as cholesterol lowering agents."[14]

A review of these collective works shows that although lower levels of CoQ10 may impair energy metabolism of muscles and lead to muscle damage, statin toxicity is not fully prevented by the restoration of normal ubiquinone levels.[73,75,76] GG on the other hand, which functions upstream of CoQ10 synthesis in the mevalonate pathway, increased not only the synthesis of ubiquinone in the presence of statins, but also enhanced mitochondrial function[14] and prevented muscle damage.[21,77]

One of GG's perhaps most important tasks is in building muscle. To demonstrate how indispensable GG is to muscle health, researchers added the isoprenoid to statin-treated muscle cells, and were able to restore RAP1 prenylation and cell viability.[21,52] Other researchers noted that GG was able to repair and rescue cellular functions that prevent statin-associated muscle cell damage.[14]

One specific gene indicated in the development of muscle atrophy is atrogin-1, which was found to be induced in statin-related muscle wasting.[77] Atrogin-1 is induced earlier in the atrophy process and precedes the loss of muscle weight.[78] Expression of atrogin-1 on a clinical level was confirmed to be significantly higher in muscle samples from symptomatic statin-treated patients.[79] This statin-induced atrogin-1 expression and muscle damage was revoked by GG in both cultured mouse myotubes and zebrafish.[77] Whereas statin led to visible muscle damage in zebrafish, co-supplementation of GG reduced atrogin-1 and consequent muscle fiber damage.

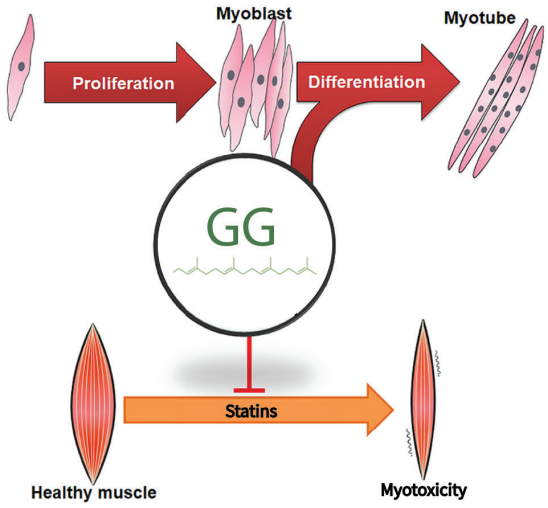


Figure based on: Hsieh, Sheng-Kuo, et al. "Promotion of Myotube Differentiation and Attenuation of Muscle Atrophy in Murine C2C12 Myoblast Cells Treated with Teaghrelin." Chemico-Biological Interactions, vol. 315, 2020, p. 108893., doi:10.1016/j.cbi.2019.108893.

The loss of GG-dependent protein prenylation caused by statins affects muscle cells in particular and other cells in general. Fortunately, addition of exogenous GG provides a simple means to restore protein generated from GG,[20] and multiple studies show that GG co-supplementation with statins was able to restart cell growth in human arterial and bronchial smooth muscle cells,[80,81] and to restore DNA synthesis and cell division.[20,82,83]

GG clearly has a central role in protein activation. Researchers pointed to GG "as the principal target of statin-dependent myotoxicity,"[21] further noting that statin-induced muscle damage "is the result of a geranylgeranylation defect"[77] — due to a constricted supply of GG.

Inhibition of key enzymes in the mevalonate pathway reduce conversion of vitamin K1 to the K2 form, the latter being instrumental in bone mineralization with important implications for calcium scores in

atherosclerosis.[84] Vitamin K2-dependent enzymes play essential roles in calcium trafficking, and a deficit of enzyme activity may contribute to reduced bone mineralization with concurrent vascular and soft tissue calcification—a phenomenon called the "calcium paradox."[85,86] Bringing GG and K2 into the mix, this is no longer paradoxical, but rather is precisely expected when synthesis of this critical compound is reduced. K2 is a cofactor for matrix Gla protein, which researchers have described as "the strongest inhibitor of tissue calcification presently known."[84] K2 is needed for carboxylation of matrix Gla protein as well as bone Gla protein (a.k.a. osteocalcin). Elevated levels of undercarboxylated osteocalcin are associated with osteoporosis, while higher circulating levels of undercarboxylated matrix Gla protein have been shown to predict cardiovascular disease and mortality.[87] An insufficient supply of fully carboxylated matrix Gla protein may explain the atherosclerosis observed among some statin users—another phenomenon that seems paradoxical on the surface, but which is mechanistically explained by statin-induced reduction in K2 synthesis.[68]

Studies using statins were able to further elucidate GG's importance for vitamin K2 biosynthesis. Statins are known to interfere with the conversion of phylloquinone to menaquinone, which in turn lead to increased risk of arterial calcification.[68] One study showed that statins – through a reduction of GGPP in the mevalonate pathway – decreased MK-4 levels dose-dependently, whereas exogenous addition of GGPP enhanced MK-4 production.[40] This study also found that the interactions between GG levels, UBIAD1, and cholesterol synthesis are indelibly linked: When UBIAD1 was removed and accompanied by lower MK-4 levels, cholesterol synthesis increased.[40]

Another study corroborated these results, showing that in the presence of statins, MK-4 levels were low, and GG was shunted toward cholesterol synthesis.[16] These researchers found statins to inhibit biosynthesis of isoprenoid intermediates, including GGPP, thereby reducing conversion of dietary phylloquinone to MK-4 through limited GGPP availability. Supplementing with GGPP rescued MK-4 production.[16] Importantly, statins were associated with a significant reduction in kidney levels of MK-4, which may be clinically relevant because low levels of MK-4 have been associated with calcification in chronic kidney disease, and low vitamin K is implicated in renal disease.[16]

Statins are widely prescribed and used by Americans. They are powerful cholesterol-reducing drugs, but they are "not specific". There is a large array of unwanted effects exhibited by statins on the vital mevalonate metabolic pathway and their corresponding pathological manifestations, and GG provides the corrective steps in ameliorating these impacts. Supplemental GG may serve as a viable intervention to reduce the risk of statin-associated myotoxicity, and to bolster production of key nutrients, including proteins, CoQ10 and vitamin K2.

Bisphosphonates

Bisphosphonate drugs are another category of pharmaceuticals that interfere with endogenous synthesis of GG. Nitrogen-containing bisphosphonates (NBPs) also exert their effects via the mevalonate pathway, but the enzyme target of these drugs is farnesyl pyrophosphate synthase (FPPS) downstream from mevalonate, so the mechanism is different from that of statins. FPPS is involved in the steps preceding GG synthesis. A noted adverse effect of NBP use is osteonecrosis of the jaw (ONJ). There is no current treatment for ONJ, and GG has been identified as a potential preventive and therapeutic agent.[88]

Regarding a potential role for GG in mitigating the adverse effects of NBPs, GG was shown to reverse the effects of these drugs by reduced angiogenesis,[88] which has been hypothesized as one of several mechanisms contributing to ONJ.[89] GG has also been shown to reverse the negative effects of NBPs in human fibroblasts, osteogenic cells and HUVEC cells.[90] Endothelial progenitor cells (EPC) co-treated with NBPs and GG showed significantly increased cell viability, migration ability and increased EPC colony density (decreased apoptosis) compared to non-GG-treated controls, effectively reversing the negative effects of NBPs. Similar results have been demonstrated for GG reversing the negative effects of NBP on human alveolar osteoblasts, periodontal ligament fibroblasts and oral keratinocytes.[91-93]

GG presents a treatment for an unusual side effect of a popular anti-osteoporosis drug in protecting the gum and jaw. This condition, if left unattended, presents obvious risk of opportunistic infections.

Conclusion

Geranylgeraniol is a multifunctional molecule that serves numerous critical functions throughout the body, including supporting muscle and bone health, steroid hormone regulation, ATP generation, and synthesis of another crucial energetic and antioxidant compound, CoQ10. GG's biochemical role as an integral component of proteins and MK-4 also lend to its critical role at an endogenous cellular level and in healthy physiology. Collectively, this multitude of biological influences demonstrate its ability to mitigate age-related decline and support healthy aging. These benefits become chronically important as GG declines with age. The value of exogenously-supplied GG is further emphasized due to common prescriptions known to impair GG synthesis. GG supplementation may be warranted for aging individuals to regulate hormonal production to improve zest, and for those who are taking statin and bisphosphonate medications. With an increasingly aging population and high proportion of polypharmacy among patients, GG exhibits an exceptional safeguard in supporting mitochondrial health, cellular vitality, and overall healthy aging.

References

1.Ruzicka L, Firmenich G. Zur Kenntnis der Diterpene (37. Mitteilung). Synthese des aliphatischen Diterpenalkohols Geranyl-geraniol. Helv. 1939;22(1):392-396.
2. Fedeli E, Capella P, Cirimele M, Jacini G. Isolation of geranyl geraniol from the unsaponifiable fraction of linseed oil. Journal of lipid research. May 1966;7(3):437-441.
3. Gutbrod K, Romer J, Dormann P. Phytol metabolism in plants. Progress in lipid research. Apr 2019;74:1-17.
4. Costes C. Biosynthèse du phytol des chlorophylles et du squelette tétraterpénique des caroténoïdes dans les feuilles vertes. Phytochemistry. 1966;5(3):311-324.
5. Wagner-Jauregg T. Synthesen von Terpenen aus Isopren. Ann Chem. 1932;52(496):52-77.
6. Biedermann M, Haase-Aschoff P, Grob K. Wax ester fraction of edible oils: Analysis by on-line LC-GC-MS and GC x GC-FID. Eur J Lipid Sci Technol. 2008;110:1084-1094.
7. Muraguchi T, Okamoto K, Mitake M, Ogawa H, Shidoji Y. Polished rice as natural sources of cancer-preventing geranylgeranoic acid. Journal of clinical biochemistry and nutrition. Jul 2011;49(1):8-15.
8. Ranalli A, Modesti G, Patumi M, Fontanazza G. The compositional quality and sensory properties of virgin olive oil from a new olive cultivar Ð I-77. Food Chem. 2000;69(2000):37-46.
9. Reiter B, Lorbeer E. Analysis of the Wax Ester Fraction of Olive Oil and Sunflower Oil by Gas Chromatography and Gas Chromatography–Mass Spectrometry. JAOCS. 2001;78(9):881-888.
10. Jondiko IJO, Pattenden G. Terpenoids and apocarotenoid from seeds of Bixa orrellana. Phytochem. 1989;28(11):3159-3162.
11. de Araujo Vilar D, de Araujo Vilar MS, de Lima e Moura TFA, et al. Traditional uses, chemical constituents, and biological activities of Bixa orellana L.: A review. Sci Wor J. 2014;2014:857292.
12. Lange BM, Rujan T, Martin W, Croteau R. Isoprenoid biosynthesis: the evolution of two ancient and distinct pathways across genomes. Proc Natl Acad Sci U S A. Nov 21 2000;97(24):13172-13177.
13. Holstein SA, Hohl RJ. Isoprenoids: remarkable diversity of form and function. Lipids. Apr 2004;39(4):293-309.
14. Campia I, Lussiana C, Pescarmona G, Ghigo D, Bosia A, Riganti C. Geranylgeraniol prevents the cytotoxic effects of mevastatin in THP-1 cells, without decreasing the beneficial effects on cholesterol synthesis. British journal of pharmacology. Dec 2009;158(7):1777-1786.
15. Crick DC, Waechter CJ, Andres DA. Utilization of geranylgeraniol for protein isoprenylation in C6 glial cells. Biochem Biophys Res Commun. Nov 30 1994;205(1):955-961.
16. Harshman SG, Shea MK, Fu X, et al. Atorvastatin Decreases Renal Menaquinone-4 Formation in C57BL/6 Male Mice. J Nutr. Mar 1 2019;149(3):416-421.
17. Ho HJ, Shirakawa H, Giriwono PE, Ito A, Komai M. A novel function of geranylgeraniol in regulating testosterone production. Bioscience, biotechnology, and biochemistry. Jun 2018;82(6):956-962.
18. Ho HJ, Shirakawa H, Yoshida R, et al. Geranylgeraniol enhances testosterone production via the cAMP/protein kinase A pathway in testis-derived I-10 tumor cells. Bioscience, biotechnology, and biochemistry. 2016;80(4):791-797.
19. Stoffel W, Martius C. Zur Synthese der K-Vitamine und Ubichinone. Angew Chem. 1960;72(17):627-627.
20. Crick DC, Andres DA, Waechter CJ. Novel salvage pathway utilizing farnesol and geranylgeraniol for protein isoprenylation. Biochem Biophys Res Commun. Aug 28 1997;237(3):483-487.
21. Jaskiewicz A, Pajak B, Litwiniuk A, Urbanska K, Orzechowski A. Geranylgeraniol Prevents Statin-Dependent Myotoxicity in C2C12 Muscle Cells through RAP1 GTPase Prenylation and Cytoprotective Autophagy. Oxidative medicine and cellular longevity. 2018;2018:6463807.
22. Cooper GM, ed The Molecular Composition of Cells. Sunderland (MA): Sinauer Associates; 2000. The Cell: A Molecular Approach.
23. Squire JM, Parry DA. Fibrous Protein Structures: Hierarchy, History and Heroes. Sub-cellular biochemistry. 2017;82:1-33.
24. Travaglini-Allocatelli C, Ivarsson Y, Jemth P, Gianni S. Folding and stability of globular proteins and implications for function. Current opinion in structural biology. Feb 2009;19(1):3-7.
25. Cournia Z, Allen TW, Andricioaei I, et al. Membrane Protein Structure, Function, and Dynamics: a Perspective from Experiments and Theory. The Journal of membrane biology. Aug 2015;248(4):611-640.
26. Dyson HJ. Making Sense of Intrinsically Disordered Proteins. Biophysical journal. Mar 8 2016;110(5):1013-1016.
27. Brown GC. Total cell protein concentration as an evolutionary constraint on the metabolic control distribution in cells. Journal of theoretical biology. Nov 21 1991;153(2):195-203.
28. Farnsworth CC, Gelb MH, Glomset JA. Identification of geranylgeranyl-modified proteins in HeLa cells. Science. Jan 19 1990;247(4940):320-322.
29. Rilling HC, Breunger E, Epstein WW, Crain PF. Prenylated proteins: the structure of the isoprenoid group. Science. Jan 19 1990;247(4940):318-320.
30. Zhang FL, Casey PJ. Influence of metal ions on substrate binding and catalytic activity of mammalian protein geranylgeranyltransferase type-I. The Biochemical journal. Dec 15 1996;320 (Pt 3):925-932.
31. Palsuledesai CC, Distefano MD. Protein prenylation: enzymes, therapeutics, and biotechnology applications. ACS chemical biology. Jan 16 2015;10(1):51-62.
32. Finder JD, Litz JL, Blaskovich MA, et al. Inhibition of protein geranylgeranylation causes a superinduction of nitric-oxide synthase-2 by interleukin-1beta in vascular smooth muscle cells. J Biol Chem. May 23 1997;272(21):13484-13488.
33. Funari SS, Prades J, Escriba PV, Barcelo F. Farnesol and geranylgeraniol modulate the structural properties of phosphatidylethanolamine model membranes. Molecular membrane biology. Jul-Aug 2005;22(4):303-311.
34. Ownby SE, Hohl RJ. Farnesol and geranylgeraniol: prevention and reversion of lovastatin-induced effects in NIH3T3 cells. Lipids. Feb 2002;37(2):185-192.
35. Mullen PJ, Luscher B, Scharnagl H, Krahenbuhl S, Brecht K. Effect of simvastatin on cholesterol metabolism in C2C12 myotubes and HepG2 cells, and consequences for statin-induced myopathy. Biochemical pharmacology. Apr 15 2010;79(8):1200-1209.
36. Irwin JC, Fenning AS, Vella RK. Geranylgeraniol prevents statin-induced skeletal muscle fatigue without causing adverse effects in cardiac or vascular smooth muscle performance. Translational research : the journal of laboratory and clinical medicine. Jan 2020;215:17-30.
37. Dam H. The antihaemorrhagic vitamin of the chick. The Biochemical journal. Jun 1935;29(6):1273-1285.
38. McKee RW, Binkley SB, Thayer SA, MacCorquodale DW, Doisy EA. The isolation of vitamin K2. J Biol Chem. 1939;131:327-344.
39. Sommer P, Kofler M. Physicochemical Properties and Methods of Analysis of Phylloquinones, Menaquinones, Ubiquinones, Plastoquinones, Menadione, and Related Compounds. Vitamins & Hormones. 1967;24:349-399.
40. Hirota Y, Nakagawa K, Sawada N, et al. Functional characterization of the vitamin K2 biosynthetic enzyme UBIAD1. PloS one. 2015;10(4):e0125737.
41. Shabb JB. Physiological substrates of cAMP-dependent protein kinase. Chemical reviews. Aug 2001;101(8):2381-2411.
42. Huang H, Levin EJ, Liu S, Bai Y, Lockless SW, Zhou M. Structure of a membrane-embedded prenyltransferase homologous to UBIAD1. PLoS biology. Jul 2014;12(7):e1001911.
43. Schumacher MM, Jun DJ, Jo Y, Seemann J, DeBose-Boyd RA. Geranylgeranyl-regulated transport of the prenyltransferase UBIAD1 between membranes of the ER and Golgi. Journal of lipid research. Jul 2016;57(7):1286-1299.
44. Okamura K, Ando F, Shimokata H. Serum total and free testosterone level of Japanese men: a population-based study. International journal of urology : official journal of the Japanese Urological Association. Sep 2005;12(9):810-814.
45. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis. May 2010;210(1):232-236.
46. Beatrice AM, Dutta D, Kumar M, et al. Testosterone levels and type 2 diabetes in men: current knowledge and clinical implications. Diabetes, metabolic syndrome and obesity : targets and therapy. 2014;7:481-486.
47. Huhtaniemi I. Late-onset hypogonadism: current concepts and controversies of pathogenesis, diagnosis and treatment. Asian journal of andrology. Mar-Apr 2014;16(2):192-202.
48. Ma RC, Tong PC. Testosterone levels and cardiovascular disease. Heart. Nov 2010;96(22):1787-1788.

49.Pye SR, Huhtaniemi IT, Finn JD, et al. Late-onset
hypogonadism and mortality in aging men. The Journal of clinical endocrinology and metabolism. Apr 2014;99(4):1357-1366.
50. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Archives of internal medicine. Aug 14-28 2006;166(15):1660-1665.
51. Ito A, Shirakawa H, Takumi N, et al. Menaquinone-4 enhances testosterone production in rats and testis-derived tumor cells. Lipids in health and disease. Sep 13 2011;10:158.
52. Jaskiewicz A, Pajak B, Labieniec-Watala M, Palma C, Orzechowski A. Diverse Action of Selected Statins on Skeletal Muscle Cells-An Attempt to Explain the Protective Effect of Geranylgeraniol (GGOH) in Statin-Associated Myopathy (SAM). Journal of clinical medicine. May 16 2019;8(5).
53. Crane FL. Discovery of ubiquinone (coenzyme Q) and an overview of function. Mitochondrion. Jun 2007;7 Suppl:S2-7.
54. Crane FL, Hatefi Y, Lester RL, Widmer C. Isolation of a quinone from beef heart mitochondria. Biochim Biophys Acta. Jul 1957;25(1):220-221.
55. Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. The international journal of biochemistry & cell biology. Apr 2014;49:105-111.
56. Quinzii CM, DiMauro S, Hirano M. Human coenzyme Q10 deficiency. Neurochemical research. Apr-May 2007;32(4-5):723-727.
57. Quinzii CM, Hirano M, DiMauro S. CoQ10 deficiency diseases in adults. Mitochondrion. Jun 2007;7 Suppl:S122-126.
58. Cordero MD, Cano-Garcia FJ, Alcocer-Gomez E, De Miguel M, Sanchez-Alcazar JA. Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q(1)(0) effect on clinical improvement. PloS one. 2012;7(4):e35677.
59. Cordero MD, Cotan D, del-Pozo-Martin Y, et al. Oral coenzyme Q10 supplementation improves clinical symptoms and recovers pathologic alterations in blood mononuclear cells in a fibromyalgia patient. Nutrition. Nov-Dec 2012;28(11-12):1200-1203.
60. Cordero MD, Moreno-Fernandez AM, deMiguel M, et al. Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clinical biochemistry. May 2009;42(7-8):732-735.
61. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. May 24 1995;1271(1):195-204.
62. Kalen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. Lipids. Jul 1989;24(7):579-584.
63. Rodick TC, Seibels DR, Babu JR, Huggins KW, Ren G, Mathews ST. Potential role of coenzyme Q10 in health and disease conditions. Nutr Diet Supp. 2018;10:1-11.
64. Sharma A, Fonarow GC, Butler J, Ezekowitz JA, Felker GM. Coenzyme Q10 and Heart Failure: A State-of-the-Art Review. Circulation. Heart failure. Apr 2016;9(4):e002639.
65. Saini R. Coenzyme Q10: The essential nutrient. Journal of pharmacy & bioallied sciences. Jul 2011;3(3):466-467.
66. Baker SK, Tarnopolsky MA. Statin-associated neuromyotoxicity. Timely topics in medicine. Cardiovascular diseases. Sep 1 2005;9:E26.
67. Marshall TM. New insights into the statin-cholesterol controversy. Journal of American Physicians and Surgeons. 2014;19(2):Summer.
68. Okuyama H, Langsjoen PH, Hamazaki T, et al. Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. Expert review of clinical pharmacology. Mar 2015;8(2):189-199.
69. Tan JT, Barry AR. Coenzyme Q10 supplementation in the management of statin-associated myalgia. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. Jun 1 2017;74(11):786-793.
70. Taylor BA. Does Coenzyme Q10 Supplementation Mitigate Statin-Associated Muscle Symptoms? Pharmacological and Methodological Considerations. American journal of cardiovascular drugs : drugs, devices, and other interventions. Apr 2018;18(2):75-82.
71. Zaleski AL, Taylor BA, Thompson PD. Coenzyme Q10 as Treatment for Statin-Associated Muscle Symptoms-A Good Idea, but. Adv Nutr. Jul 1 2018;9(4):519S-523S.
72. Laaksonen R, Jokelainen K, Sahi T, Tikkanen MJ, Himberg JJ. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clinical pharmacology and therapeutics. Jan 1995;57(1):62-66.
73. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. Journal of the American College of Cardiology. Jun 12 2007;49(23):2231-2237.
74. Marcuzzi A, Piscianz E, Zweyer M, et al. Geranylgeraniol and Neurological Impairment: Involvement of Apoptosis and Mitochondrial Morphology. International journal of molecular sciences. Mar 11 2016;17(3):365.
75. Johnson TE, Zhang X, Bleicher KB, et al. Statins induce apoptosis in rat and human myotube cultures by inhibiting protein geranylgeranylation but not ubiquinone. Toxicol Appl Pharmacol. Nov 1 2004;200(3):237-250.
76. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q10 during statin therapy. The Annals of pharmacotherapy. Feb 2006;40(2):290-294.
77. Cao P, Hanai J, Tanksale P, Imamura S, Sukhatme VP, Lecker SH. Statin-induced muscle damage and atrogin-1 induction is the result of a geranylgeranylation defect. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. Sep 2009;23(9):2844-2854.
78. Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proc Natl Acad Sci U S A. Dec 4 2001;98(25):14440-14445.
79. Hanai J, Cao P, Tanksale P, et al. The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. The Journal of clinical investigation. Dec 2007;117(12):3940-3951.
80. Corsini A, Mazzotti M, Raiteri M, et al. Relationship between mevalonate pathway and arterial myocyte proliferation: in vitro studies with inhibitors of HMG-CoA reductase. Atherosclerosis. Jun 1993;101(1):117-125.
81. Vigano T, Hernandez A, Corsini A, et al. Mevalonate pathway and isoprenoids regulate human bronchial myocyte proliferation. European journal of pharmacology. Oct 15 1995;291(2):201-203.
82. Crick DC, Waechter CJ, Andres DA. Geranylgeraniol restores cell proliferation to lovastatin treated C6 glial cells. SAAS bulletin, biochemistry and biotechnology. 1996;9:37-42.
83. Vogt A, Qian Y, McGuire TF, Hamilton AD, Sebti SM. Protein geranylgeranylation, not farnesylation, is required for the G1 to S phase transition in mouse fibroblasts. Oncogene. Nov 7 1996;13(9):1991-1999.
84. Cranenburg EC, Schurgers LJ, Vermeer C. Vitamin K: the coagulation vitamin that became omnipotent. Thrombosis and haemostasis. Jul 2007;98(1):120-125.
85. Flore R, Ponziani FR, Di Rienzo TA, et al. Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis. European review for medical and pharmacological sciences. Sep 2013;17(18):2433-2440.
86. Maresz K. Proper Calcium Use: Vitamin K2 as a Promoter of Bone and Cardiovascular Health. Integr Med (Encinitas). Feb 2015;14(1):34-39.
87. Vermeer C, Theuwissen E. Vitamin K, osteoporosis and degenerative diseases of ageing. Menopause international. Mar 2011;17(1):19-23.
88. Pabst AM, Kruger M, Sagheb K, et al. The influence of geranylgeraniol on microvessel sprouting after bisphosphonate substitution in an in vitro 3D-angiogenesis assay. Clinical oral investigations. Apr 2017;21(3):771-778.
89. Pabst AM, Kruger M, Blatt S, et al. Angiogenesis in the Development of Medication-Related Osteonecrosis of the Jaws: An Overview. Dentistry journal. Dec 26 2016;5(1).
90. Ziebart T, Koch F, Klein MO, et al. Geranylgeraniol - a new potential therapeutic approach to bisphosphonate associated osteonecrosis of the jaw. Oral oncology. Mar 2011;47(3):195-201.
91. Pabst AM, Kruger M, Ziebart T, Jacobs C, Sagheb K, Walter C. The influence of geranylgeraniol on human oral keratinocytes after bisphosphonate treatment: An in vitro study. Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery. Jun 2015;43(5):688-695.
92. Williams C, Johnson B, Svrcina H, Kawsky B, Jones D. Use of geranylgeraniol to rescue osteoblasts and periodontal ligament fibroblasts from zoledronate-induced apoptosis. The FASEB Journal. April 2014;663.16.
93. Zafar S, Coates DE, Cullinan MP, Drummond BK, Milne T, Seymour GJ. Zoledronic acid and geranylgeraniol regulate cellular behaviour and angiogenic gene expression in human gingival fibroblasts. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. Oct 2014;43(9):711-721.

†These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent disease.

American River Nutrition™

333 Venture Way, Hadley, MA 01035 | 413-253-3449 | arn@american-river.com | www.americanrivernutrition.com