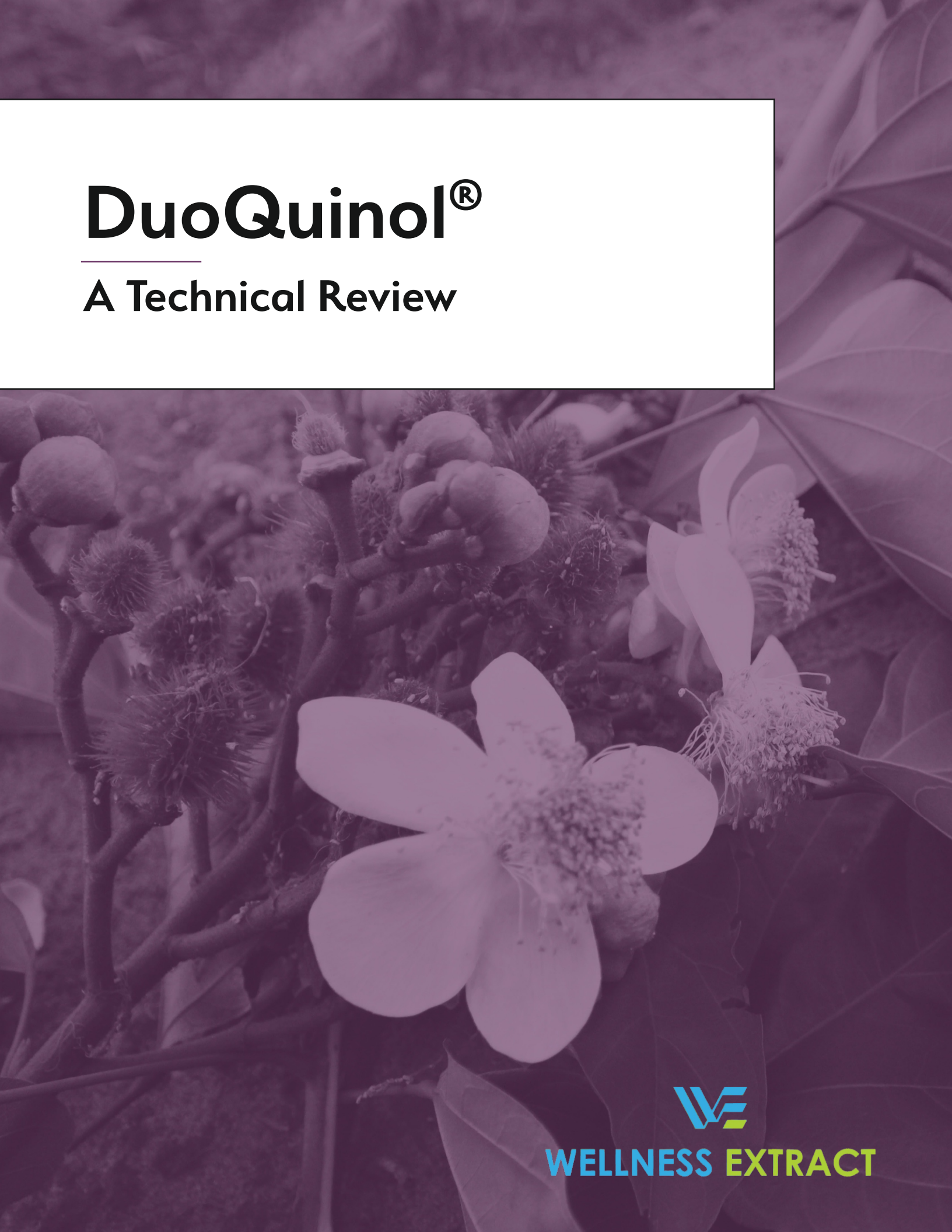
DuoQuinol®

A Technical Review



WELLNESS EXTRACT

What is DuoQuinol®?

Created through a nature-identical redox reaction process powered by fat-solubilized vitamin C, DuoQuinol® offers a unique combination of ubiquinol and geranylgeraniol. As the active form of CoQ10, ubiquinol is a key player in cellular energy production, while geranylgeraniol – a building block of CoQ10 – further supports mitochondrial and skeletal muscle health. In short, DuoQuinol® is ubiquinol with a functionally distinctive edge.

An Introduction to Coenzyme Q10

Scientists at Liverpool's Morton laboratory caught a first glimpse at ubiquinone in 1955[1,2], but it was not until 1957 that Frederick Crane famously isolated CoQ10 from beef hearts.[3] The discovery launched an investigation into one of today's most well-known and widely-studied nutrients.

Since then, researchers have found that CoQ10 declines with age[4,5], and coincides with a variety of chronic conditions, including heart disease, type 2 diabetes, and cancer.[6] Clinical trials demonstrated that supplemental CoQ10 can be extremely beneficial for heart patients[6-9], and Japan was the first to approve the nutrient for treatment of congestive heart failure in 1974.[10]

Shortly after the first CoQ10 trials began in the 1980s, the first of a range of statin drugs entered the US market in 1986. The medicine – while being revolutionary in the treatment of hypercholesterolemia – came with a cost. Patients reported feeling side effects such as fatigue and muscle pain. A 1990 study by Drs. Folker and Langsjoen – both pioneers in the CoQ10 field – revealed that statin decreased CoQ10 levels in humans, appearing to be responsible for some of the side effects experienced by statin users.[11] Replenishing CoQ10 levels through supplementation can help. Today, approximately 45% of cardiologists recommend CoQ10 to their patients – more than double that of other supplements[12] – a testament that reflects the nutrient's proven track record of safety and efficacy.

The Difference Between Ubiquinone and Ubiquinol

Ubiquinone and ubiquinol are the two faces of CoQ10, and both are present in the electron transport chain that produces the body's energy currency, ATP. The CoQ10 forms interconvert via redox reactions, and hence enable a flow of electrons that creates the energy needed to produce ATP. Ubiquinone is the oxidized form of CoQ10, and is able to accept electrons from other molecules in the transport chain. By accepting an electron, ubiquinone becomes reduced to ubiquinol, the antioxidant form of CoQ10. In turn, ubiquinol can donate electrons, thereby returning to its oxidized ubiquinone state. By maintaining this inter-conversion, CoQ10 seals its role as the body's ultimate biochemical energy provider.

At first glance, the interchangeability of CoQ10 makes choosing between its two forms for supplementation may seem irrelevant. There are, however, clear advantages to using ubiquinol, which is the only fat-soluble antioxidant naturally produced in humans[13,14], and is the predominant CoQ10 form present in the body.[15,16] One benefit is ubiquinol's greater bioavailability, found to be up to 70% better than that of ubiquinone.[17] Ubiquinol's two alcohol groups are more hydrophilic than ubiquinone's two keto groups, allowing greater water

solubility in the fat-water mixed micelle matrix of the GI tract. This allows ubiquinol better villi access for systemic absorption. Outside the GI tract, differences in bioavailability between the two CoQ10 forms were shown to be even more dramatic in an aging model of human skin. In this study, ubiquinol was absorbed much more efficiently than ubiquinone, with an approximate 40-fold increase in cellular uptake, and 70-fold increase in mitochondrial uptake.[96]

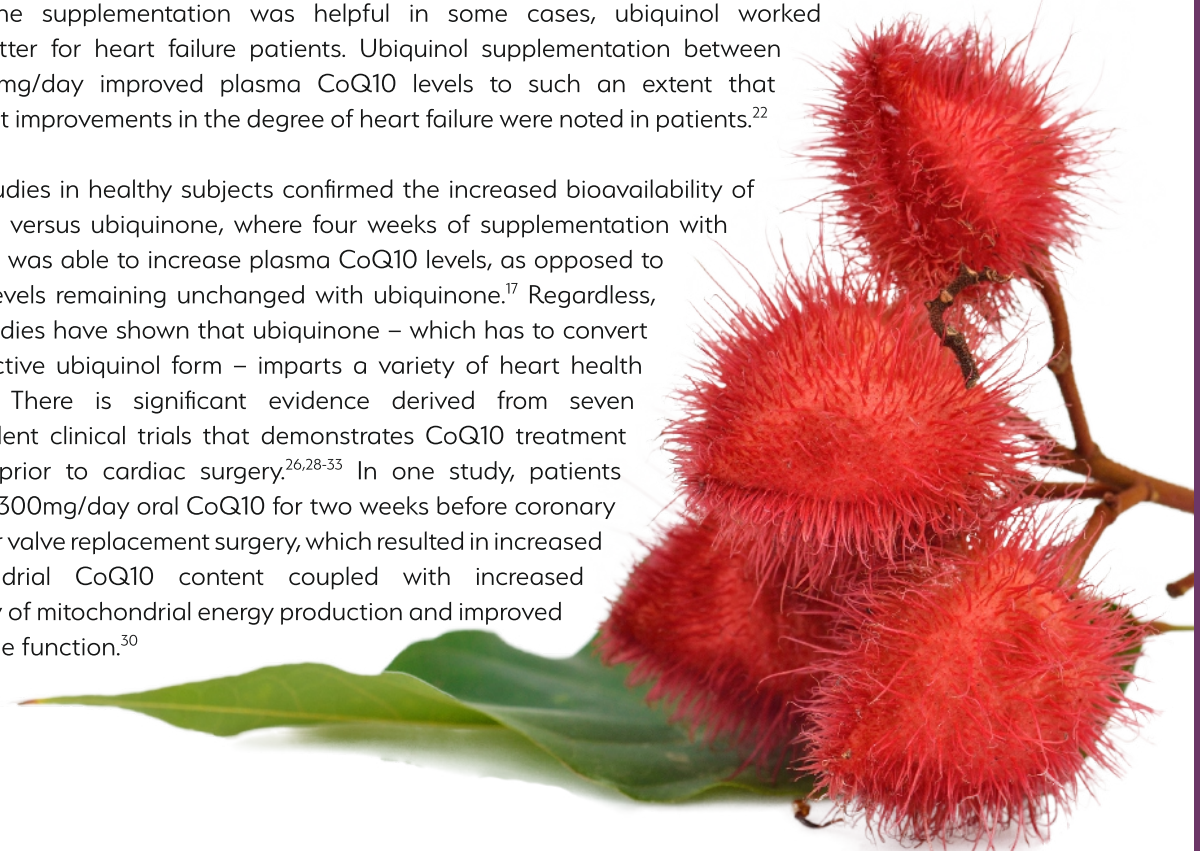
Another benefit of supplemental ubiquinol addresses age-related deficiencies. Unfortunately, as we age it becomes harder for the body to convert ubiquinone to ubiquinol.[4,5] The ability to convert ubiquinone to ubiquinol may also carry a genetic component, where a polymorphism of the main enzyme involved in conversion could affect 5-20% of the population, depending on ethnicity.[18,19] Research has shown that the ratio of ubiquinone over ubiquinol increased steadily with age, especially after age 40, providing less of the active form of CoQ10.[20] One study further suggests that the body's CoQ10 production declines at a rate of 10% per decade.[21] Because of this, and since ubiquinol contributes to energy production, it is the preferred choice for supplementation. In fact, human studies have established that ubiquinol supplementation can improve the CoQ10 ratio and maintain levels in chronic conditions that are typically associated with deficiencies.[22]

Ubiquinol's Cardiovascular Benefits

Ubiquinol is the only natural antioxidant made by the human body.[13] As a lipid-soluble molecule, ubiquinol exerts its antioxidant benefits in fat-rich cell membranes and LDL particles, but also within the mitochondria.[14] As a large lipid, CoQ10's role as an antioxidant is somewhat "residential". It is well-known that ubiquinol dwells in LDL particles. LDL is "bad" cholesterol, but it is oxidized LDL (oxLDL) that is particularly atherogenic.[23] Ubiquinol's presence in LDL particles ensures that progression to oxLDL is prevented. Beyond its antioxidant capabilities, vital role in cellular energy production, and advanced bioavailability, numerous research studies support ubiquinol supplementation for heart health.[24,25]

The inability of mitochondria to adequately supply the myocardium with ATP is central to the loss of contractile function in heart failure, and results in sometime fatal energy deprivation of the cell.[26] Early studies have demonstrated that heart failure patients had a lower than average plasma CoQ10 level, and the degree of CoQ10 deficiency correlated directly with the severity of heart failure.[22,27] While ubiquinone supplementation was helpful in some cases, ubiquinol worked much better for heart failure patients. Ubiquinol supplementation between 450-600mg/day improved plasma CoQ10 levels to such an extent that significant improvements in the degree of heart failure were noted in patients.[22]

Other studies in healthy subjects confirmed the increased bioavailability of ubiquinol versus ubiquinone, where four weeks of supplementation with ubiquinol was able to increase plasma CoQ10 levels, as opposed to CoQ10 levels remaining unchanged with ubiquinone.[17] Regardless, many studies have shown that ubiquinone – which has to convert to the active ubiquinol form – imparts a variety of heart health benefits. There is significant evidence derived from seven independent clinical trials that demonstrates CoQ10 treatment benefits prior to cardiac surgery.[26,28-33] In one study, patients received 300mg/day oral CoQ10 for two weeks before coronary bypass or valve replacement surgery, which resulted in increased mitochondrial CoQ10 content coupled with increased efficiency of mitochondrial energy production and improved contractile function.[30]



The effects of CoQ10 were also studied in two double-blind placebo-controlled trials in patients with ischemic heart disease, where treated patients presented with reduced angina, improved exercise tolerance, and decreased ischemic changed on echocardiogram.[34,35] These benefits may be related to increased efficiency in myocardial mitochondrial energy production, as demonstrated in another trial following CoQ10-treated patients.[26,30] Put together, CoQ10 – and particularly ubiquinol – improves overall cardiac functions.

Further adding to cardiovascular health, CoQ10 was shown to have hypotensive effects.[36-39] One study showed that CoQ10 lowered blood pressure in type 2 diabetes patients[37], while in another study, CoQ10 improved endothelial function and lowered blood pressure in both patients with diabetes and dyslipidemia.[40] The effect of CoQ10 on hypertension is significant, and has been shown to reduce blood pressure by 17mmHg systolic and 10mmHg diastolic.[26,41] Interestingly, the hypotensive effect of CoQ10 was found to be specific to states of oxidative stress, and was not seen in normotensive humans and animals.[26,41] It has been proposed that CoQ10 acts via vasodilation, having a direct effect on the endothelium and vascular smooth muscle, which leads to a reduction in peripheral resistance and ultimately lowers blood pressure.[41-43] Remarkably, 50% of subjects in one study were able to cease at least one of their hypertensive medications following CoQ10 supplementation.[44]

Among its many perks, CoQ10's demonstrated effects for heart health are striking. With benefits ranging from heart failure treatment to blood pressure improvement, CoQ10 supplementation – particularly using its active and more bioavailable form ubiquinol – is a must for cardiovascular well-being.

GG: Beyond CoQ10

What is GG?

Geranylgeraniol (GG) is synthesized endogenously in the human body via the mevalonate pathway—the same biochemical pathway by which cholesterol, vitamin K2, steroid hormones and CoQ10 are synthesized. As a central membrane-situated molecule, GG plays a critical role in tissue systems and metabolic processes throughout the body, including healthy mitochondrial function and energy production. GG is an essential building block that supports various functions, among the most important include maintenance of skeletal muscles and CoQ10 synthesis. Similar to CoQ10, production of GG declines naturally during aging and is inhibited by use of certain pharmaceutical drugs, including statins. By replenishing natural levels, GG can protect from age-related physical decline (e.g. sarcopenia), support the body's CoQ10 synthesis and energy production, and revoke skeletal muscle fatigue.

GG Source

GG is present in a variety of foods, but the majority of it is made endogenously. As a building block of various natural color components, GG's presence is visually apparent in both plants and mammals. In plants, GG assists the production of both carotenoids and chlorophyll, which can be seen in red and green colors of leaves, seeds, and fruits. In mammals, GG aids the production of hemoglobin precursor heme, imparting a maroon color to organ vasculature, while in crustaceans, it produces a red color –astaxanthin – in the animals' exoskeletons. The GG in DuoQuinol® is purified from the South American rainforest plant *Bixa orellana* – commonly known as annatto – that has been used for centuries in the coloring of foods and cosmetics. 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. As a common denominator between plants and animals, GG is an endogenous nutrient that is ubiquitous everywhere in nature.

GG in the Mevalonate Pathway

GG shares a common biosynthesis pathway with CoQ10, known as the mevalonate pathway. This ancient metabolic pathway is also responsible for the production of other important nutrients, with GG being directly involved in the synthesis of skeletal muscle proteins, vitamin K2 (specifically MK4) and CoQ10.

As has been found with CoQ10, the body's capacity to maintain the mevalonate pathway remains stable throughout young adulthood, but its activity changes during the aging process.[46] This inadvertently results in GG depletion and subsequent aging hallmarks such as decreased energy and reduced protein production. Furthermore, prescription drugs such as statins can lead to GG decimation, resulting in reduced synthesis of its downstream metabolic products and associated complications.

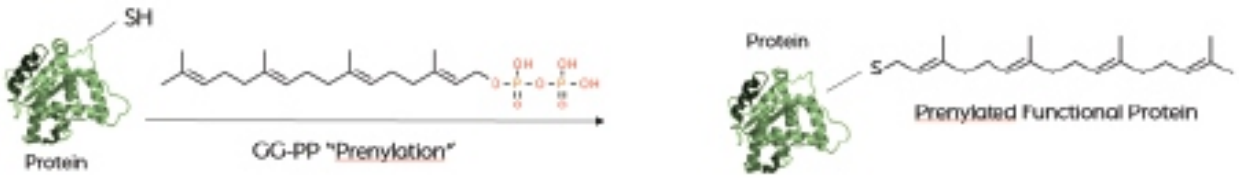
GG Benefits

Evidence supports GG's benefits in conditions characterized by depletion of essential biological micronutrients. Through its role as a structural component of endogenous molecules, GG is able to correct deficiencies and restore optimal health.

Promotes Muscle Function and Strength

Age-related loss 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 and myopathy. Fortunately, research suggests that replenishing GG exogenously can satisfactorily restore these processes.

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.[47] They later explored GG's physiological relevance through experiments with HMG CoA reductase inhibitors.[48] Whereas these inhibitors blocked GG biosynthesis resulting in loss of protein prenylation (a mechanism by which isoprenoids such as GG donate their structure to build proteins and allow them to anchor to cell membranes), adding back GG exogenously restored such protein synthesis.[48] Similarly, GG-dependent proteins were restored by supplementing the nutrient in statin-treated pulmonary smooth muscle cells.[49]



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.[50] The focus of this study was to examine GG's effect on exertion muscles 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.[50] 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 those on statin medications.

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

Activates CoQ10 Production

As a crucial component to mitochondrial health, CoQ10's status and availability to the body is of utmost importance. 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 to mitigate statin side effects, restore mitochondrial functioning, and protect muscles in a synchronous approach.[45,51]

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.[52-54] CoQ10 levels were found to be consistently low in fibromyalgia patients and supplementation improved symptoms.[55-57] Whereas true CoQ10 deficiency is rare, gradually declining levels of the quinone during the aging process are a common occurrence[4,5], as is CoQ10's noted drop alongside several chronic and age-related illnesses such as type 2 diabetes, cancer, and congestive heart failure.[58]

Studies corroborate GG as an intermediate in the synthesis of ubiquinone through radio-labelling, which showed GG as a building block.[59] GG is also an essential component in the prenylation of CoQ10 in Golgi membranes, which is catalyzed by the protein-coding gene UBIAD1.[60,61] CoQ10 depletion and its subsequent fatigue manifestation and poor lipid antioxidant status may be remedied by GG supplementation.

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.[62] CoQ10 has specific cardiotonic advantages besides its cardiovascular benefits. It is one of the very few endogenous non-protein antioxidants the body makes for its lipid protection, and relies heavily on GG to function as needed.[63]

Absorption Benefits

DuoQuinol®'s unique absorption technology utilizes GG as a natural solubilizer to increase bioavailability of the enabling ubiquinol form (the ubiquinone form of CoQ10 is less hydrophilic, and therefore has lower bioavailability). The natural GG solubilizer resists ubiquinol from recrystallizing, keeping the mixture amorphous. Overall, DuoQuinol® renders its ubiquinol bioaccessible for optimum absorption.

GG-Gold®

GG-Gold® is a multi-patented ingredient produced by American River Nutrition for use in supplements, foods & beverages, and cosmetic products, and is a main component of DuoQuinol®. American River Nutrition produces GG-Gold® in the USA, at their state-of-art 24,000 sq. ft. GMP facility in Hadley, Massachusetts, 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 of the aging population.

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

DuoQuinol® as a Statin Companion

Heart disease is the leading cause of death in the US, with more than 600,000 Americans succumbing to the illness each year. A major factor contributing to cardiovascular disease progression is elevated cholesterol, which is ailing more than 30 percent of the US population. As a result, 40 million Americans are currently taking prescription drugs – called statins – in an effort to keep cholesterol under control. What's more, a recent 10 year retrospective study on statin use determined that the drug not only mitigates chronic inflammation, but also reduced cardiovascular disease mortality and all-cause mortality by 20% and 25%, respectively.[64] This Harvard study is extraordinary as it covered more than 300,000 seniors (>75 years old), whereas almost all earlier statin trials use patients in their 40s and 50s. Besides the 40 million on statins, the American Diabetes Association recommends that 35 million diabetics should be on statins. Should the American Heart Association recommend the elderly – constituting another 40 million – take the cholesterol reducer as well, then the total statin prescription number would easily exceed the most common acetaminophen NSAID medication. The relevance to DuoQuinol® adjunctive statin companionship will reach universality.

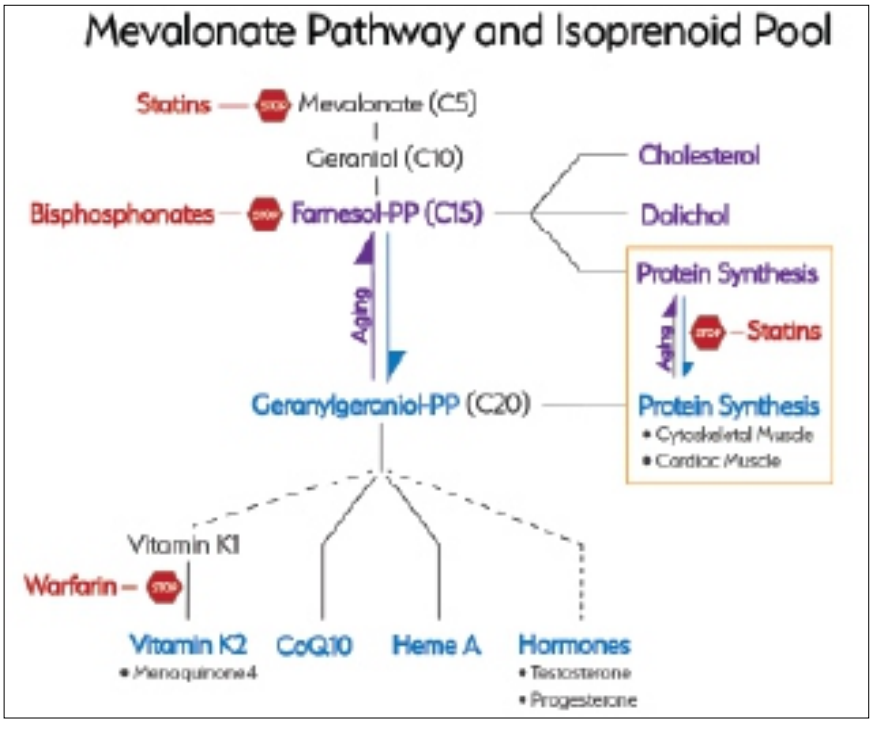
Although statins are highly effective in lowering cholesterol, side effects are common and include loss of energy and muscle pain. These side effects occur because statins not only lower cholesterol, but also two other important nutrients the body makes in a shared metabolic pathway: GG and CoQ10. For this reason, doctors often recommend that patients on a statin regimen supplement with CoQ10, which can restore the body's natural reserves and prevent occasional fatigue. One thing CoQ10 can't always correct is statin-induced muscle pain (myalgia) and weakness (myopathy), which develops due to GG decimation.[51,65,66] GG is an important substrate to produce skeletal muscle protein, so when GG levels are depleted by statins, muscle symptoms develop. DuoQuinol® not only helps boost energy metabolism, but provides support for the unique nutritional requirements of statin users to promote healthy muscle function and strength.[45,51,67]

What Causes Statin Side Effects?

Statin drugs exert their effects early 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 neuromyotoxicity and mitochondrial toxicity.[68,69] 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 biochemical strangulation of GG synthesis due to statins, which is responsible for a drop in CoQ10, and a decline in proteins necessary to maintain muscle mass.

A commonly reported problem by statin users is muscle pain and weakness. The exact mechanisms behind myopathy and myotoxicity statin users experience are not fully understood, 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.[70-72] While some studies have shown that supplemental CoQ10 can reduce muscle pain and weakness [73-76], others demonstrated that supplemental CoQ10 alone could not rescue muscle cells from statin-associated myopathy, suggesting that decreased CoQ10 synthesis in the presence of statins was not always symptomatic to muscle vulnerability.[51,65,66] 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.[51]

Statins are widely prescribed to Americans. They are powerful cholesterol-reducing drugs, but they are "not specific". Instead, statins are indiscriminate cholesterol reducers. GG corrects these indiscriminate statin features. 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 membrane-bound nutrients, including proteins and CoQ10. Moreover, GG is an indispensable adjuvant to CoQ10 supplementation, covering the other requirements of statin users.



Replenishing Energy with Ubiquinol and GG

Loss of energy and fatigue were identified as two of statin's common complaints. One study in over 1,000 adults showed that patients on statin medications were significantly more likely to suffer impaired energy and fatigue with exertion relative to a placebo group.[77] Statins have also been shown to decrease mitochondrial oxidation, resulting in dysfunction that may be linked to reduced ubiquinone.[78] CoQ10 supplementation in statin users was shown to improve energy in a small clinical trial [79], and it is well known that CoQ10 is instrumental to the body's energy metabolism.[63]

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.[80] 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.[45] 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."[45]

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.[66,81,82] 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[45] and prevented muscle damage.[67,83]

Restoring Skeletal Muscle Health with GG

Statin-associated muscle-related adverse effects are a common occurrence in statin users.[84] Studies among professional athletes have shown that only 20% of top sports performers were able to tolerate statin treatment without side effect.[85] 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.[51,67] Other researchers noted that GG was able to repair and rescue cellular functions that prevent statin-associated muscle cell damage.[45]

One specific gene indicated in the development of muscle atrophy is atrogin-1, which was found to be induced in statin-related muscle wasting.[83] Atrogin-1 is induced earlier in the atrophy process and precedes the loss of muscle weight.[86] Expression of atrogin-1 on a clinical level was confirmed to be significantly higher in muscle samples from symptomatic statin-treated patients.[87] This statin-induced atrogin-1 expression and muscle damage was revoked by GG in both cultured mouse myotubes and zebrafish.[83] Whereas statin led to visible muscle damage in zebrafish, co-supplementation of GG reduced atrogin-1 and consequent muscle fiber damage. In a mouse model testing GG's effect on atrophied muscle regeneration, atrogin-1 was suppressed by supplementation. GG treatment also increased myotube thickness and skeletal muscle fiber size, suggesting that the nutrient was able to rescue muscle atrophy via suppression of atrogin-1.[88]

The loss of GG-dependent protein 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,[48] and multiple studies show that GG co-supplementation with statins was able to restart cell growth in human arterial and bronchial smooth muscle cells,[89,90] and to restore DNA synthesis and cell division.[48,91,92]

GG clearly has a central role in protein activation. Researchers pointed to GG "as the principal target of statin-dependent myotoxicity,"[67] further noting that statin-induced muscle damage "is the result of a geranylgeranylation defect"[83] — due to GG deprivation.

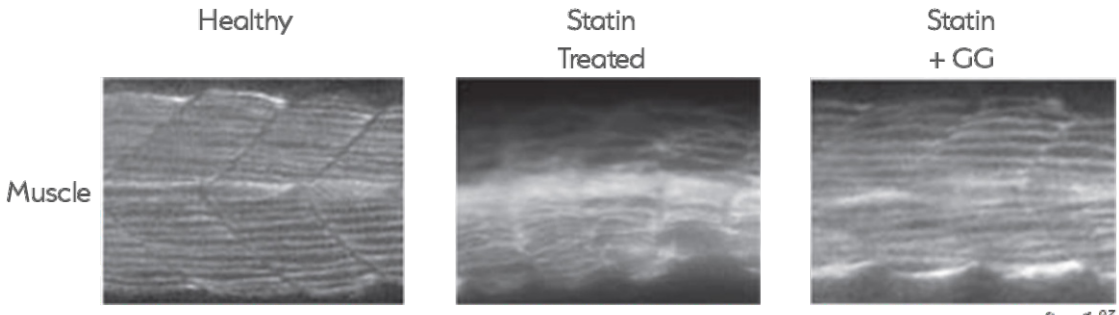


fig. 1 [83]

Statin destroyed led to visible muscle damage. GG reduced fiber damage in myotubes.

The DuoQuinol® Advantage

Well-Understood Benefits of Ubiquinol

As the reduced form of Coenzyme Q10 and the main component of DuoQuinol®, ubiquinol is a powerful antioxidant, the only one known to be made naturally by the body.[13,93,94] As an antioxidant with extra electrons, ubiquinol efficiently protects the mitochondria from oxidative stress, and is a key electron carrier in the respiratory chain responsible for ATP energy production.[13,95] Cellular energy is particularly important for organs with high metabolic activity, such as the heart. This in part is why ubiquinol is beneficial to the heart, protecting not only from lipid peroxidation, but also improving heart function directly.[15,22,50]

Activates Natural CoQ10 Production

One of the main attributes that sets DuoQuinol® apart is its ability to stimulate endogenous CoQ10 production via a molecule called geranylgeraniol (GG). The GG molecule is built into the same pathway the body uses to produce energy, and is an actual building block of CoQ10.[45,59]

Enhances Cellular Absorption

DuoQuinol®'s unique absorption technology utilizes GG as a natural solubilizer to increase bioavailability of the enabling ubiquinol (the ubiquinone form of CoQ10 is less hydrophilic, and therefore has lower bioavailability). The natural GG solubilizer resists ubiquinol from recrystallizing, keeping the mixture amorphous.

Promotes Muscle Function and Strength

GG, DuoQuinol®'s unique ingredient, is not only a building block for CoQ10, but is also essential in the production of proteins the body uses to build and maintain skeletal muscle.[50] In experiments where both GG and CoQ10 were depleted, resulting in muscle damage, only GG was able to reverse muscle damage and restore muscle function.[45,51,67]

References

1. Festenstein, G.N., et al., A constituent of the unsaponifiable portion of animal tissue lipids (lambda max. 272 m mu). Biochem J, 1955. 59(4): p. 558-66.
2. Olson, R.E. and H. Rudney, Biosynthesis of ubiquinone. Vitam Horm, 1983. 40: p. 1-43.
3. Crane, F.L., et al., Isolation of a quinone from beef heart mitochondria. Biochim Biophys Acta, 1957. 25(1): p. 220-1.
4. Ernster, L. and G. Dallner, Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta, 1995. 1271(1): p. 195-204.
5. Kalen, A., E.L. Appelkvist, and G. Dallner, Age-related changes in the lipid compositions of rat and human tissues. Lipids, 1989. 24(7): p. 579-84.
6. Zozina, V.I., et al., Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem. Curr Cardiol Rev, 2018. 14(3): p. 164-174.
7. DiNicolantonio, J.J., et al., Coenzyme Q10 for the treatment of heart failure: a review of the literature. Open Heart, 2015. 2(1): p. e000326.
8. Huang, C.H., et al., High plasma coenzyme Q10 concentration is correlated with good left ventricular performance after primary angioplasty in patients with acute myocardial infarction. Medicine (Baltimore), 2016. 95(31): p. e4501.
9. Mortensen, S.A., et al., The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail, 2014. 2(6): p. 641-9.
10. Khatta, M., et al., The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med, 2000. 132(8): p. 636-40.
11. Folkers, K., et al., Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci U S A, 1990. 87(22): p. 8931-4.
12. Schultz, H. Cardiologists recommend CoQ10, but some aren't sure why, survey finds. NutraIngredients USA, 2015.
13. Ernster, L. and P. Forsmark-Andree, Ubiquinol: an endogenous antioxidant in aerobic organisms. Clin Investig, 1993. 71(8 Suppl): p. S60-5.
14. Forsmark-Andree, P. and L. Ernster, Evidence for a protective effect of endogenous ubiquinol against oxidative damage to mitochondrial protein and DNA during lipid peroxidation. Mol Aspects Med, 1994. 15 Suppl: p. s73-81.
15. Mohr, D., V.W. Bowry, and R. Stocker, Dietary supplementation with coenzyme Q10 results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoprotein to the initiation of lipid peroxidation. Biochim Biophys Acta, 1992. 1126(3): p. 247-54.
16. Bhagavan, H.N. and R.K. Chopra, Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. Mitochondrion, 2007. 7 Suppl: p. S78-88.
17. Langsjoen, P.H. and A.M. Langsjoen, Comparison study of plasma coenzyme Q10 levels in healthy subjects supplemented with ubiquinol versus ubiquinone. Clin Pharmacol Drug Dev, 2014. 3(1): p. 13-7.
18. Kelsey, K.T., et al., Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. Br J Cancer, 1997. 76(7): p. 852-4.
19. Mantle, D. and A. Dybring, Bioavailability of Coenzyme Q10: An Overview of the Absorption Process and Subsequent Metabolism. Antioxidants (Basel), 2020. 9(5).
20. Wada, H., et al., Redox status of coenzyme Q10 is associated with chronological age. J Am Geriatr Soc, 2007. 55(7): p. 1141-2.
21. Schniertshauer, D., D. Gebhard, and J. Bergemann, Age-Dependent Loss of Mitochondrial Function in Epithelial Tissue Can Be Reversed by Coenzyme Q10. J Aging Res, 2018. 2018: p. 6354680.
22. Langsjoen, P.H. and A.M. Langsjoen, Supplemental ubiquinol in patients with advanced congestive heart failure. Biofactors, 2008. 32(1-4): p. 119-28.
23. Carr, A.C., B.Z. Zhu, and B. Frei, Potential antiatherogenic mechanisms of ascorbate (vitamin C) and alpha-tocopherol (vitamin E). Circ Res, 2000. 87(5): p. 349-54.
24. Mollace, V., et al., Pathophysiological Basis for Nutraceutical Supplementation in Heart Failure: A Comprehensive Review. Nutrients, 2021. 13(1).
25. Ghavami, A., et al., Effects of Coenzyme Q10 Supplementation on Anthropometric Indices in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Prev Med, 2020. 11: p. 181.
26. Pepe, S., et al., Coenzyme Q10 in cardiovascular disease. Mitochondrion, 2007. 7 Suppl: p. S154-67.
27. Folkers, K., S. Vadhanavikit, and S.A. Mortensen, Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. Proc Natl Acad Sci U S A, 1985. 82(3): p. 901-4.
28. Chello, M., et al., Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. Ann Thorac Surg, 1994. 58(5): p. 1427-32.
29. Judy, W.V., W.W. Stogsdill, and K. Folkers, Myocardial preservation by therapy with coenzyme Q10 during heart surgery. Clin Investig, 1993. 71(8 Suppl): p. S155-61.
30. Rosenfeldt, F., et al., Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. J Thorac Cardiovasc Surg, 2005. 129(1): p. 25-32.
31. Shiguma, S., et al., [The protective effect of coenzyme Q10 on myocardial metabolism and hemodynamics in open heart surgery]. Kyobu Geka, 1983. 36(4): p. 268-71.
32. Sunamori, M., et al., Clinical experience of coenzyme Q10 to enhance intraoperative myocardial protection in coronary artery revascularization. Cardiovasc Drugs Ther, 1991. 5 Suppl 2: p. 297-300.
33. Tanaka, J., et al., Coenzyme Q10: the prophylactic effect on low cardiac output following cardiac valve replacement. Ann Thorac Surg, 1982. 33(2): p. 145-51.
34. Kamikawa, T., et al., Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. Am J Cardiol, 1985. 56(4): p. 247-51.
35. Schardt, F., et al., Effect of CoQ10 on ischemia-induced ST-segment depression: a double-blind, placebo controlled, crossover study., in Biochemical and Clinical Aspects of CoQ10, K. Folkers and Y. Yamamura, Editors. 1985, Elsevier: Amsterdam. p. 385-394.
36. Burke, B.E., R. Neuenschwander, and R.D. Olson, Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. South Med J, 2001. 94(11): p. 1112-7.
37. Hodgson, J.M., et al., Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr, 2002. 56(11): p. 1137-42.
38. Singh, R.B., et al., Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. J Hum Hypertens, 1999. 13(3): p. 203-8.
39. Yamagami, T., N. Shibata, and K. Folkers, Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension. Res Commun Chem Pathol Pharmacol, 1975. 11(2): p. 273-88.
40. Watts, G.F., et al., Coenzyme Q(10) improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. Diabetologia, 2002. 45(3): p. 420-6.
41. Rosenfeldt, F.L., et al., Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum Hypertens, 2007. 21(4): p. 297-306.
42. Digiesi, V., et al., Coenzyme Q10 in essential hypertension. Mol Aspects Med, 1994. 15 Suppl: p. s257-63.
43. Folkers, K., et al., Bioenergetics in clinical medicine. XVI. Reduction of hypertension in patients by therapy with coenzyme Q10. Res Commun Chem Pathol Pharmacol, 1981. 31(1): p. 129-40.
44. Langsjoen, P., R. Willis, and K. Folkers, Treatment of essential hypertension with coenzyme Q10. Mol Aspects Med, 1994. 15 Suppl: p. S265-72.
45. Campia, I., et al., Geranylgeraniol prevents the cytotoxic effects of mevastatin in THP-1 cells, without decreasing the beneficial effects on cholesterol synthesis. Br J Pharmacol, 2009. 158(7): p. 1777-86.
46. Tonini, C., M. Segatto, and V. Pallottini, Impact of Sex and Age on the Mevalonate Pathway in the Brain: A Focus on Effects Induced by Maternal Exposure to Exogenous Compounds. Metabolites, 2020. 10(8).

47. Crick, D.C., C.J. Waechter, and D.A. Andres, Utilization of geranylgeraniol for protein isoprenylation in C6 glial cells. Biochem Biophys Res Commun, 1994. 205(1): p. 955-61.
48. Crick, D.C., D.A. Andres, and C.J. Waechter, Novel salvage pathway utilizing farnesol and geranylgeraniol for protein isoprenylation. Biochem Biophys Res Commun, 1997. 237(3): p. 483-7.
49. Finder, J.D., 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, 1997. 272(21): p. 13484-8.
50. Irwin, J.C., A.S. Fenning, and R.K. Vella, Geranylgeraniol prevents statin-induced skeletal muscle fatigue without causing adverse effects in cardiac or vascular smooth muscle performance. Transl Res, 2020. 215: p. 17-30.
51. Jaskiewicz, A., et al., Diverse Action of Selected Statins on Skeletal Muscle Cells-An Attempt to Explain the Protective Effect of Geranylgeraniol (GGOH) in Statin-Associated Myopathy (SAM). J Clin Med, 2019. 8(5).
52. Hargreaves, I.P., Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol, 2014. 49: p. 105-11.
53. Quinzii, C.M., S. DiMauro, and M. Hirano, Human coenzyme Q10 deficiency. Neurochem Res, 2007. 32(4-5): p. 723-7.
54. Quinzii, C.M., M. Hirano, and S. DiMauro, CoQ10 deficiency diseases in adults. Mitochondrion, 2007. 7 Suppl: p. S122-6.
55. Cordero, M.D., et al., Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q(1)(0) effect on clinical improvement. PLoS One, 2012. 7(4): p. e35677.
56. Cordero, M.D., et al., Oral coenzyme Q10 supplementation improves clinical symptoms and recovers pathologic alterations in blood mononuclear cells in a fibromyalgia patient. Nutrition, 2012. 28(11-12): p. 1200-3.
57. Cordero, M.D., et al., Coenzyme Q10 distribution in blood is altered in patients with fibromyalgia. Clin Biochem, 2009. 42(7-8): p. 732-5.
58. Rodick, T.C., et al., Potential role of coenzyme Q10 in health and disease conditions. Nutr Diet Supp, 2018. 10: p. 1-11.
59. Stoffel, W. and C. Martius, Zur Synthese der K-Vitamine und Ubichinone. Angew Chem, 1960. 72(17): p. 627-627.
60. Hirota, Y., et al., Functional characterization of the vitamin K2 biosynthetic enzyme UBIAD1. PLoS One, 2015. 10(4): p. e0125737.
61. Huang, H., et al., Structure of a membrane-embedded prenyltransferase homologous to UBIAD1. PLoS Biol, 2014. 12(7): p. e1001911.
62. Sharma, A., et al., Coenzyme Q10 and Heart Failure: A State-of-the-Art Review. Circ Heart Fail, 2016. 9(4): p. e002639.
63. Saini, R., Coenzyme Q10: The essential nutrient. J Pharm Bioallied Sci, 2011. 3(3): p. 466-7.
64. Orkaby, A.R., et al., Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. JAMA, 2020. 324(1): p. 68-78.
65. Laaksonen, R., et al., Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther, 1995. 57(1): p. 62-6.
66. Marcoff, L. and P.D. Thompson, The role of coenzyme Q10 in statin-associated myopathy: a systematic review. J Am Coll Cardiol, 2007. 49(23): p. 2231-7.
67. Jaskiewicz, A., et al., Geranylgeraniol Prevents Statin-Dependent Myotoxicity in C2C12 Muscle Cells through RAP1 GTPase Prenylation and Cytoprotective Autophagy. Oxid Med Cell Longev, 2018. 2018: p. 6463807.
68. Baker, S.K. and M.A. Tarnopolsky, Statin-associated neuromyotoxicity. Timely Top Med Cardiovasc Dis, 2005. 9: p. E26.
69. Marshall, T.M., New insights into the statin-cholesterol controversy. Journal of American Physicians and Surgeons, 2014. 19(2): p. Summer.
70. Tan, J.T. and A.R. Barry, Coenzyme Q10 supplementation in the management of statin-associated myalgia. Am J Health Syst Pharm, 2017. 74(11): p. 786-793.
71. Taylor, B.A., Does Coenzyme Q10 Supplementation Mitigate Statin-Associated Muscle Symptoms? Pharmacological and Methodological Considerations. Am J Cardiovasc Drugs, 2018. 18(2): p. 75-82.
72. Zaleski, A.L., B.A. Taylor, and P.D. Thompson, Coenzyme Q10 as Treatment for Statin-Associated Muscle Symptoms-A Good Idea, but. Adv Nutr, 2018. 9(4): p. 519S-523S.
73. Fedacko, J., et al., Coenzyme Q(10) and selenium in statin-associated myopathy treatment. Can J Physiol Pharmacol, 2013. 91(2): p. 165-70.
74. Qu, H., et al., Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc, 2018. 7(19): p. e009835.
75. Skarlovnik, A., et al., Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. Med Sci Monit, 2014. 20: p. 2183-8.
76. Zlatohlavek, L., et al., The effect of coenzyme Q10 in statin myopathy. Neuro Endocrinol Lett, 2012. 33 Suppl 2: p. 98-101.
77. Golomb, B.A., et al., Effects of Statins on Energy and Fatigue With Exertion: Results From a Randomized Controlled Trial. Arch Intern Med, 2012. 172(15): p. 1180-1182.
78. De Pinieux, G., et al., Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. Br J Clin Pharmacol, 1996. 42(3): p. 333-7.
79. Reidenberg, M.M., Statins, lack of energy and ubiquinone. Br J Clin Pharmacol, 2005. 59(5): p. 606-7.
80. Marcuzzi, A., et al., Geranylgeraniol and Neurological Impairment: Involvement of Apoptosis and Mitochondrial Morphology. Int J Mol Sci, 2016. 17(3): p. 365.
81. Johnson, T.E., et al., Statins induce apoptosis in rat and human myotube cultures by inhibiting protein geranylgeranylation but not ubiquinone. Toxicol Appl Pharmacol, 2004. 200(3): p. 237-50.
82. Levy, H.B. and H.K. Kohlhaas, Considerations for supplementing with coenzyme Q10 during statin therapy. Ann Pharmacother, 2006. 40(2): p. 290-4.
83. Cao, P., et al., Statin-induced muscle damage and atrogin-1 induction is the result of a geranylgeranylation defect. FASEB J, 2009. 23(9): p. 2844-54.
84. Cham, S., et al., Statin-associated muscle-related adverse effects: a case series of 354 patients. Pharmacotherapy, 2010. 30(6): p. 541-53.
85. Sinzinger, H. and J. O'Grady, Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. Br J Clin Pharmacol, 2004. 57(4): p. 525-8.
86. Gomes, M.D., et al., Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proc Natl Acad Sci U S A, 2001. 98(25): p. 14440-5.
87. Hanai, J., et al., The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. J Clin Invest, 2007. 117(12): p. 3940-51.
88. Miyawaki, A., et al., Oral Administration of Geranylgeraniol Rescues Denervation-induced Muscle Atrophy via Suppression of Atrogin-1. In Vivo, 2020. 34(5): p. 2345-2351.
89. Corsini, A., et al., Relationship between mevalonate pathway and arterial myocyte proliferation: in vitro studies with inhibitors of HMG-CoA reductase. Atherosclerosis, 1993. 101(1): p. 117-25.
90. Vigano, T., et al., Mevalonate pathway and isoprenoids regulate human bronchial myocyte proliferation. Eur J Pharmacol, 1995. 291(2): p. 201-3.
91. Crick, D.C., C.J. Waechter, and D.A. Andres, Geranylgeraniol restores cell proliferation to lovastatin treated C6 glial cells. SAAS Bull Biochem Biotechnol, 1996. 9: p. 37-42.
92. Vogt, A., et al., Protein geranylgeranylation, not farnesylation, is required for the G1 to S phase transition in mouse fibroblasts. Oncogene, 1996. 13(9): p. 1991-9.
93. Frei, B., M.C. Kim, and B.N. Ames, Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci U S A, 1990. 87(12): p. 4879-83.
94. Littarru, G.P. and L. Tiano, Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. Mol Biotechnol, 2007. 37(1): p. 31-7.
95. Dominiak, K. and W. Jarmuszkiewicz, [Different faces of the mitochondrial coenzyme Q]. Postepy Biochem, 2020. 65(4): p. 271-277.
96. Marcheggiani F, Kordes S, Cirilli I, Orlando P, Silvestri S, Vogelsang A, et al. Anti-ageing effects of ubiquinone and ubiquinol in a senescence model of human dermal fibroblasts. Free radical biology & medicine. 2021;165:282-8. Epub 2021/01/23.

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