CoQnol™

*A Revolutionary Concept in Combining Extracellular with Intracellular Delivery of Ubiquinol**

designs for health®

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CoQnol™ 100 and CoQnol™ 200 feature a unique combination of ubiquinol and geranylgeraniol (GG), two physiologically essential molecules with complementary and synergistic actions. GG complements the actions of ubiquinol due to its unique ability to boost endogenous CoQ10 synthesis and promote efficient cellular permeability.

The innovation: The ubiquinol in this product is produced from ubiquinone through a novel patented process, in the presence of GG and ascorbyl palmitate, without the use of petrochemicals.

Ubiquinol is the reduced form of coenzyme Q10 (CoQ10) and is provided as DuoQuinol™, an innovative, patent-pending form of this molecule from American River Nutrition (ARN).

Geranylgeraniol (GG) is an important endogenous molecule in human physiology — it is a precursor in the synthesis of ubiquinol and many other functional cell metabolites and signaling molecules. GG is a naturally occurring terpenoid in a variety of plants and serves as a precursor to essential components such as carotenoids. The GG in CoQnol™ is GG-Gold™, a patented form also from ARN.

Available in 100 and 200 mg Dosage Options

Supplement Facts

Serving Size 1 softgel

Amount Per Serving		% Daily Value
Ubiquinol (as DuoQuinol™)	100 mg	*
Trans-Geranylgeraniol (as GG-Gold™)	60 mg	*

*Daily Value not established.

Other Ingredients: Bovine gelatin, medium chain triglycerides, purified water, glycerine, quillaja extract, annatto (color).
Contains fish (cod).

Supplement Facts

Serving Size 1 softgel

Amount Per Serving		% Daily Value
Ubiquinol (as DuoQuinol™)	200 mg	*
Trans-Geranylgeraniol (as GG-Gold™)	125 mg	*

*Daily Value not established.

Other Ingredients: Bovine gelatin, medium chain triglycerides, purified water, glycerine, quillaja extract, annatto (color).
Contains fish (cod).

Unique Physical Properties of CoQnol™ Softgels: The proprietary blend of ubiquinol, GG, ascorbyl palmitate, quillaja extract, medium-chain triglycerides, and glycerine creates a stable solution that prevents crystallization and oxidation of ubiquinol, and is a natural patent-pending formulation from ARN. Quillaja is an extract from the bark of the *Quillaja saponaria* tree, commonly used as an emulsifier in foods.

The unique composition of CoQnol formula in a softgel enables ubiquinol absorption to be approximately 100% higher than the individual compound and 18% to 19% higher than other leading brands of solubilized ubiquinol. Gastrointestinal (GI) absorption is determined by the following factors: (1) bioaccessibility, which estimates the percent of the nutrient solubilized/micellized for absorption in the GI cells, (2) transport coefficient in the GI cells, and (3) transport coefficient into the general circulation, which accounts for loss due to liver metabolism.[1] Bioaccessibility of ubiquinol in the DuoQuinol™ matrix was estimated at 1.73%, with a protocol defined by McClements, et. al,[1] which uses three processing chambers with distinct environments specific to human digestion in the mouth, stomach, and intestine.

Inclusion of GG May Overcome Limitations of Supplementing with CoQ10 Alone

Research has highlighted the challenges posed by CoQ10 supplementation, as either ubiquinone or ubiquinol, in achieving efficient transport through cell membranes and inside cells. Other than providing antioxidant function in the blood for cells and lipoproteins, and for cellular membranes, the other key clinical application is to deliver CoQ10 inside the mitochondria in support of energy production. The only modality utilized to date that can achieve this goal has been to use high doses of CoQ10 to increase plasma CoQ10 as much as eight times higher than the normal range.[2] The ensuing difference in the CoQ10 concentration between blood and tissues encourages intracellular transport of CoQ10. However, in vitro studies have shown that transfer of CoQ10 through cell membranes is low.[3-7] CoQ10 is a large molecule, and its transfer is limited by receptors/transporters that do not adapt to moving large quantities of CoQ10 from the outside to the inside of cells.[4-7] This is the opposite direction from how the body normally supplies endogenous CoQ10 (see Fig. 1). Human studies have used doses of 30 mg to 3,000 mg of CoQ10 (both forms) in various emulsifying formulations.[2] However, CoQ10 delivery in many tissues,[7,8] such as brain or muscle,[9] appears to be low and reaches a plateau following these doses.[10] This may explain the lackluster clinical benefit obtained for interventions in certain conditions.[4,8] Fortunately, GG supplementation provides the perfect complementary solution to this problem.

Supplemental GG increases body stores of CoQ10 in the opposite direction compared with exogenous CoQ10 by boosting endogenous production of CoQ10.

GG is well absorbed in the GI tract, possibly at 44%. In vitro studies have characterized GG as "cell permeable[11] and readily diffusable[3]," which has been proven to easily penetrate outer and inner cell membranes, as its molecular weight is one-third that of CoQ10. Supplemental GG provides building blocks and upregulates by mass action the metabolic pathways that synthesize ubiquinone[3] and other essential cell-signaling molecules (see Fig. 1).[11]

Endogenous Synthesis and Dietary Intake of CoQ10
CoQ10 is synthesized as ubiquinone in peroxisomes and possibly other organelles, depending on the cell type. This process utilizes downstream metabolites from GG and tyrosine (or phenylalanine), along with vitamin B6 as a cofactor (see Fig. 1).[8] Many Americans have suboptimal protein intake and, as a result, also of tyrosine and its precursor, phenylalanine. Total endogenous production of ubiquinone has been estimated at approximately 500 mg/day (depending on body size) with a turnover of 4 days.[4] Total ingested CoQ10 from eating food averages 5 mg/day.[4]

Tissue Content of CoQ10 and GG Declines with Aging and Certain Conditions
A 10% decline in aerobic cellular respiration has been observed every decade, possibly due to the natural decline in ubiquinol synthesis and increased degradation due to aging.[8] In part, this may explain the difficulty in maintaining a healthy weight and physical activity. The following aerobic cellular respiration declines were observed at age 80 versus age 20: heart (−58%), pancreas (−83%), adrenal (−50%), liver (−17%), kidney (−45%) and skin (−75%). A severe deficiency was found in individuals with diabetes (−65%), pancreatic cancer (−30%) and those treated with statins (−20% to −26%).[12] The decline in CoQ10 levels is likely an indicator of reduced endogenous production of its precursor, GG.

Advantages of Supplementing CoQ10 as Ubiquinol versus Ubiquinone
Supplemental CoQ10, whether in the form of ubiquinol or ubiquinone, is absorbed from the GI tract and transferred into lymph, where it is transported by chylomicrons. Subsequently, CoQ10 is delivered to the bloodstream and transported to the liver, where it is transferred to lipoproteins and returned to the blood circulation.[4] CoQ10 distribution in the blood seems relatively stable, with approximately 80% to 98% as ubiquinol, and the rest coming from ubiquinone.[8,13]

Figure 1 illustrates the conversions that take place for ubiquinol and ubiquinone during absorption. These conversions emphasize the potential superiority of supplemental ubiquinol versus ubiquinone, as it contributes to the body's antioxidant reserve rather than depleting it.[4,13] This occurs because the majority of ubiquinol (80% to 98%) is absorbed unchanged, with only a small portion getting oxidized (2% to 20%) while recycling other antioxidants. In contrast, the majority of ubiquinone (80% to 98%) is reduced, thus decreasing the body's antioxidant reserve. This difference may be especially beneficial in states of high oxidative stress (aging, diabetes, exercise, and excessive toxin load) or in those whose gut cells need greater antioxidant protection. As depicted in Figure 1, the two forms of CoQ10 (ubiquinone and ubiquinol) are interconverting while supporting various metabolic pathways until they are metabolized for excretion. Thus, all the benefits observed in clinical trials with the ubiquinone form would likely be obtained when supplementing with ubiquinol, too, when the total amount of CoQ10 absorbed was the same. It is also possible that additional benefits may be observed due to ubiquinol's contribution to the body's antioxidant reserve.

Supplementation with CoQ10 may have numerous applications[8,10,12-24]:*

- Helps raise plasma CoQ10 in healthy and statin-treated individuals
- Shown to potentially reduce all-cause mortality
- Helps improve quality of life, especially in the elderly
- Supports healthy aging and may help slow senescence
- Supports a healthy immune response
- Neurological/cognitive support
- Supports a healthy inflammatory response
- Enables adenosine triphosphate (ATP) production
- Supports healthy metabolic rate and fat metabolism through thermogenesis
- Promotes exercise performance
- May reduce exercise-induced oxidative stress
- Supports healthy cardiovascular function
- Supports nitric oxide metabolism for healthy endothelial function
- Supports normal glucose metabolism
- May play a role in cancer risk reduction by reducing oxidative stress
- Supports kidney health
- May help promote a normal response to pain
- Supports liver health
- May benefit bone metabolism
- Supports eye health
- Supports healthy skin cell function
- Supports normal sperm motility

Biological actions of CoQ10[4,8,22]:

a. Ubiquinone may be reduced to ubiquinol by alpha-lipoic acid or glutathione reductase or as part of the following reactions:

- Participation in the mitochondrial electron transport chain, where 95% of the body's ATP is produced
- As a cofactor for nicotinamide adenine dinucleotide (NAD+) plus hydrogen (NADH)-oxidase regulation of the cytosolic ratio of NAD+/NADH and ascorbate reduction involved in the regulation of cell growth and differentiation

b. Ubiquinone is required for activation of mitochondrial uncoupling proteins, which are responsible for fat metabolism and thermogenesis.

c. Ubiquinone regulates mitochondrial permeability transition pores, which affect apoptosis and DNA damage.

d. Ubiquinol is the only endogenous lipid-soluble antioxidant and it occurs in all body cells. It protects lipids, proteins, nuclear and especially mitochondrial DNA, which has poor repair mechanisms. It recycles vitamins E and C while converting to ubiquinone.

e. Ubiquinone and ubiquinol contribute to the control of membrane fluidity, as they intersperse in cell and organelle membranes.

f. CoQ10 exerts multiple anti-inflammatory effects by initiating the release of mediators from lymphocytes and monocytes into the blood, which subsequently modify expression of NFjB1-dependent genes in a variety of tissues.

g. CoQ10 affects more than a hundred genes, including those involved in mitochondrial biogenesis,[14] which stimulates SIRT1, SIRT3 and PGC-1alpha

h. CoQ10 is involved in mitochondrial calcium homeostasis.[25]

GG complements CoQ10 supplementation as a precursor and stimulator of metabolic pathways to support essential cellular and physiological functions.

GG is a precursor in the endogenous synthesis of CoQ10 and it complements CoQ10 supplementation due to its involvement in a variety of biochemical pathways.[3,11] In vitro studies have shown that GG can boost CoQ10 synthesis by mass action.[3] GG supplementation may compensate for the age-related decline in CoQ10 synthesis, which affects mitochondrial respiration rate, thus lowering metabolic rate. GG has the potential to boost ATP production, potentially increasing physical and mental performance at any age.* In addition, GG is a building block and may boost synthesis of various metabolites involved in cell signaling. Examples include the Rho GTPase family (RhoA, Rac1, and Cdc42), which coordinates cell function and communication, cellular growth, survival and apoptosis, protein synthesis/modification, and their intracellular movement.[3,11]

GG supports a normal response to inflammation[26,27] and pain,[28,29] which may be especially relevant to statin-related symptoms in the muscles. GG supports immune health,[30] synthesis of testosterone/progesterone,[31-33] and has potential anti-viral properties through its metabolite, geranylgeranyl acetone.[34-35]

GG can mitigate the statin-related downregulation of CoQ10 synthesis and many additional statin side effects by replenishing physiologically important metabolites created upstream from CoQ10 synthesis.

Numerous side effects of statins have been reported: muscle pain/dysfunction, increased inflammation, cognitive problems, and liver toxicity.[36-40] Statins have also been shown to lower plasma and intracellular levels of CoQ10 and GG, leading to mitochondrial dysfunction and changes in mitochondrial morphology/density, all of which contribute to lower ATP synthesis.[41,42] This may lead to a myriad of physiological dysfunctions, impaired physical and mental function, and a lowered metabolic rate. Supplementation with ubiquinol or ubiquinone helps increase plasma CoQ10 in statin-treated individuals, even above normal levels, but is unable to completely mitigate all medication-induced adverse effects. This is because CoQ10 supplementation is unable to enhance the synthesis of metabolites created upstream from CoQ10 entry in the mevalonate pathway (see Fig. 1).[41,42] Statin drugs exert their effects early in this pathway (via inhibition of the enzyme HMG-CoA reductase), upstream of where GG and these other compounds are produced. Thus, it is not surprising that not all individuals who take CoQ10 experience a reversal of statin-associated muscle symptoms and markers of muscle damage (as evidenced by creatine kinase).[43] Metabolites affected by statins or bisphosphonates are highlighted in yellow in Figure 1. Supplementation with ubiquinol or ubiquinone does not completely mitigate the side effects caused by these medications, both of which inhibit enzymatic actions downstream from mevalonate. As illustrated in Figure 1, GG supplementation may replenish downstream metabolites, all of which are critical for healthy physiology.

A study looked at the effects of supplementing with 300 mg/day ubiquinol in individuals treated with 30 mg/day of simvastatin. In the first 4 weeks of statin treatment, plasma CoQ10 dropped from 773 mmol/L to 539 mmol/L.[42] After supplementation with 300 mg/day ubiquinol for 4 subsequent weeks, while continuing the statin, plasma CoQ10 was raised to 2,305 mmol/L, which is approximately three times higher than the baseline CoQ10 level observed without the statin.[42] However, in spite of this impressive increase in plasma CoQ10, exogenous supplementation was only able to partially reverse the mitochondrial dysfunction caused by the statin use.[42] These results show that there is a need for additional interventions to further improve mitochondrial function for patients using statins, and they suggest that GG supplementation may be efficacious, as evidenced by reduced mitochondrial damage and maintenance of healthy mitochondrial structure/function in vitro.[26] In human monocytes and hepatocytes, GG reversed mevastatin-induced reductions in ubiquinone synthesis and mitochondrial electron transport and respiration that typically lead to cell death without impeding the drug's cholesterol-lowering property.[3] Notably, addition of GG was more effective than addition of exogenous CoQ10 for attenuating these adverse effects. An in vitro study concludes, "geranylgeraniol may be a more useful and practical means of limiting the toxicities of statins without reducing their efficacy as cholesterol-lowering agents."[3] A deficiency of mevalonate metabolites, which is the result of the statin's actions, has been shown to increase inflammation, as evidenced by elevated NLRP3 inflammasome and interleukin 6 (IL-6).[44] Another in vitro study showed that administration of GG to statin-treated human neurons decreased the expression of NLRP3 inflammasome and IL-6.[26] This effect of GG may be relevant to patients with novel viral infections of the respiratory tract, as recent studies show that expression of NLRP3 inflammasome and levels of CRP and IL-6 are elevated in certain stages of the disease process.[45]

Critical Role of GG in Muscle Metabolism in Healthy Physiology and Under Statin Use

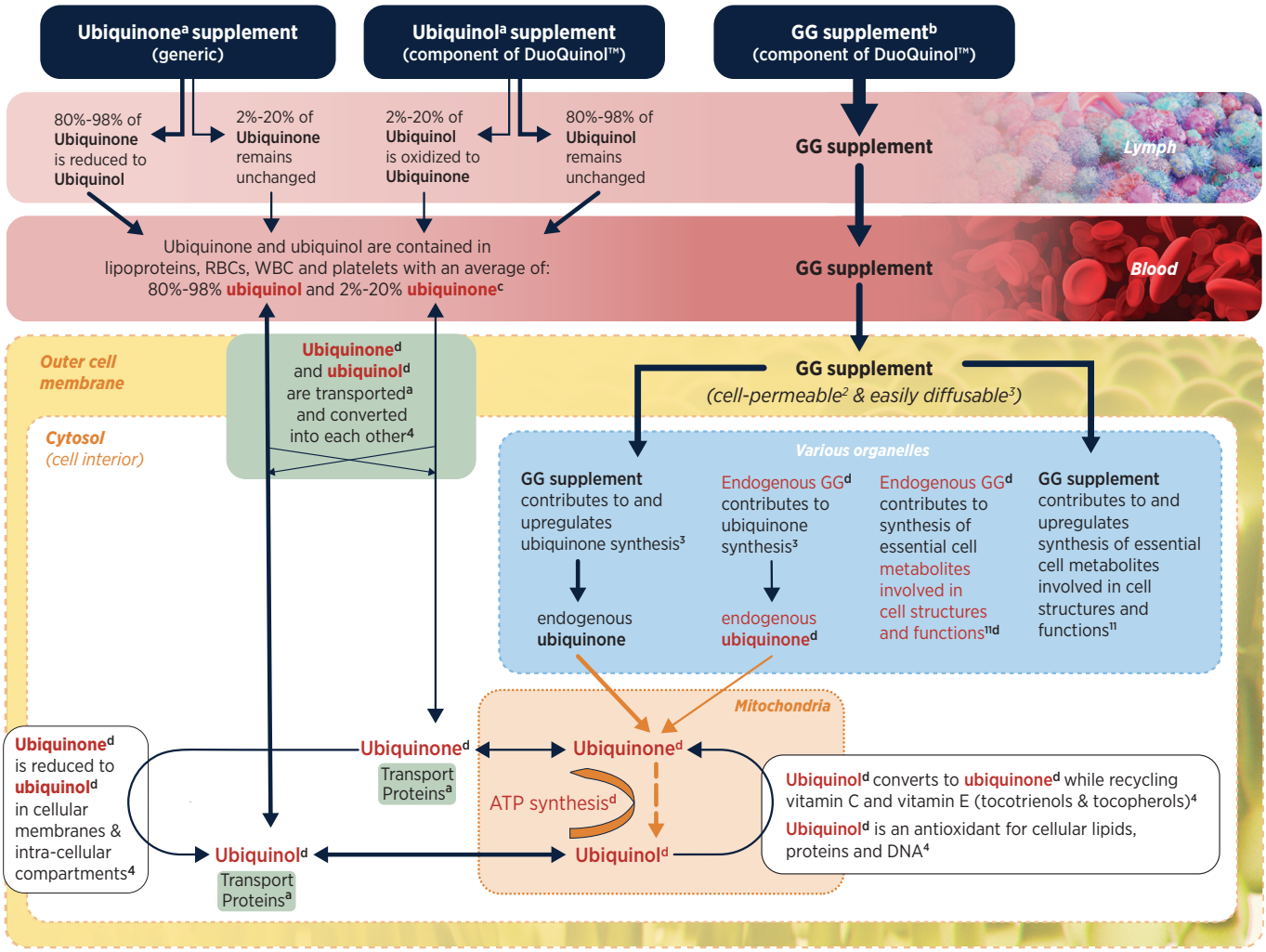
Myogenesis requires modification of certain skeletal muscle proteins by GG (a process called geranylgeranylation). Researchers conclude that GG is "the principal target of statin-dependent myotoxicity,"[11] and that statin-induced muscle damage "is the result of a geranylgeranylation defect"[46] — potentially due to the decimation of the GG pool. GG was shown to reduce expression of muscle atrophy-related genes and enhance myogenic differentiation in murine skeletal muscle myoblasts.[47] A family of Rho proteins derived from GG are used for intracellular trafficking and signaling, skeletal myogenesis and differentiation, and muscle contraction and relaxation. GG depletion was associated with skeletal muscle fiber damage. GG is utilized for skeletal proteins to perform universal contraction function. Supplementation with GG was shown to prevent statin-induced myopathy.[48]

A 2019 animal study investigated the effects of 15 mg GG/kg body weight supplementation on muscle structure and function, administered alone or with a statin.[49] The study concluded that GG and GG + statin groups (compared to control and statin only groups) performed significantly better in shinbone muscle force production, skeletal muscle fatigue reversal, and cardiac muscle contraction/relaxation.[49] GG also improved endothelium-dependent relaxation in mesenteric (muscular) arteries.[49] The animal dose used in this study is equivalent to a human dose of 2.4 mg/kg body weight, which translates into 168 mg for 70 kg body weight.[49]

GG has an essential role in the metabolism of vitamin K, bone strength, and reduction of arterial calcification.

Vitamin K2 (menaquinone-4 [MK-4]) contains GG in its structure, which contributes to vitamin K2 (MK-4) formation and storage in body tissues.[50] GG supplementation may mitigate the increased risk of arterial calcification associated with statin use.[51,52] Doses of 30 mg to 160 mg GG may support reduced bone resorption. Supplementation with GG may help alleviate some of the effects of bisphosphonate drugs.* (For more details, refer to the DuoQuinol™ White Paper.)

Fig. 1 DuoQuinol™, a synergistic combination of geranylgeraniol (GG) & ubiquinol to maximize energy & support healthy aging



[a] Transfer of CoQ10 (ubiquinol + ubiquinone) through cell membranes and inside cells is limited because it is controlled by transporters/receptors and passive diffusion. These are influenced by the difference in CoQ10 concentrations between blood and cell compartments, which limits how much CoQ10 can be transferred.[4-7]

[b] GI absorption of GG and intracellular delivery is efficient since it is a cell-permeable and a readily diffusible molecule through cell membranes and organelles.[3,11] This is due to its structure and having a third the molecular weight of CoQ10. GG is converted to its active form geranylgeraniol pyrophosphate and metabolized similar to endogenous GG.[3,11]

[c] Blood content of ubiquinol and ubiquinone is derived from supplementation and endogenous synthesis.[8,13]

[d] The levels of metabolites **highlighted in red** are diminished by actions from statins, bisphosphonates, aging and chronic conditions.[3,11] Endogenous GG levels may also decline with aging.

ATP = adenosine triphosphate; CoQ10 = coenzyme Q10; GI = gastrointestinal tract; GG = geranylgeraniol; RBCs = red blood cells; WBCs = white blood cells.

Recommended Use: Take one softgel per day with a meal, or as directed by your healthcare practitioner. **Note:** This formula is best absorbed with a meal. For maximum bioavailability, multiple doses should be taken at different times of the day.

Synergistic formulas recommended for support of mitochondrial function, bone and arterial health:* Annatto-E, Annatto-E-GG, Designs for Health formulas containing vitamins D & K, Tri-K™, Mitochondrial NRG™, Mito-PQQ™, OsteoForce™, OsteoForce™ Supreme and Osteoben®

For a list of references cited in this document, please visit:

https://www.designsforhealth.com/techsheet-references/cognol-references.pdf

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Health care practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

To contact Designs for Health, please call us at (860) 623-6314, or visit us on the web at www.designsforhealth.com.