Annatto-GG™ 150

designs for health®

*Unique compound to support healthy aging and cellular energy generation**

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Annatto-GG™ 150 is a unique product that provides 150 mg geranylgeraniol (GG), a compound that plays a critical role in numerous biological processes. Annatto-GG™ 150 features American River Nutrition's GG-Gold™, a patented form of GG extracted from annatto seeds. Since GG is required for protein synthesis, it may be prudent to include GG supplementation in a regimen intended to support building and maintaining muscle mass, particularly in older individuals.

Geranylgeraniol occurs naturally in annatto, flaxseed, sunflower and olive oils, tomatoes, and select medicinal herbs.[1] It is synthesized endogenously in humans but endogenous production may not always be adequate to support the body's needs. Synthesis of GG declines naturally during aging and is inhibited by use of certain pharmaceutical drugs (namely, cholesterol-lowering statins and the bisphosphonates for osteoporosis), potentially resulting in a need for supplementation.

While there are numerous applications for Annatto-GG™ 150 (see box at right), the primary area of focus is supporting healthy aging—specifically, supporting muscle protein synthesis, bone health and cellular energy generation.

Geranylgeraniol is required for:*

- Protein synthesis & modification
- Cellular growth, differentiation, survival and apoptosis
- Synthesis of CoQ10, heme A, dolichol and prenylated proteins
- Conversion of vitamin K1 to K2

Annatto-GG™ 150 may help support:*

- Endogenous synthesis of CoQ10
- Prevention/reversal of sarcopenia, muscle wasting or cachexia
- Maintenance of healthy bone density
- Endogenous synthesis of vitamin K2
- Metabolic health (metabolic syndrome, type 2 diabetes, obesity)
- Antinociception (pain reduction)
- Skin health (acne, psoriasis, aging)

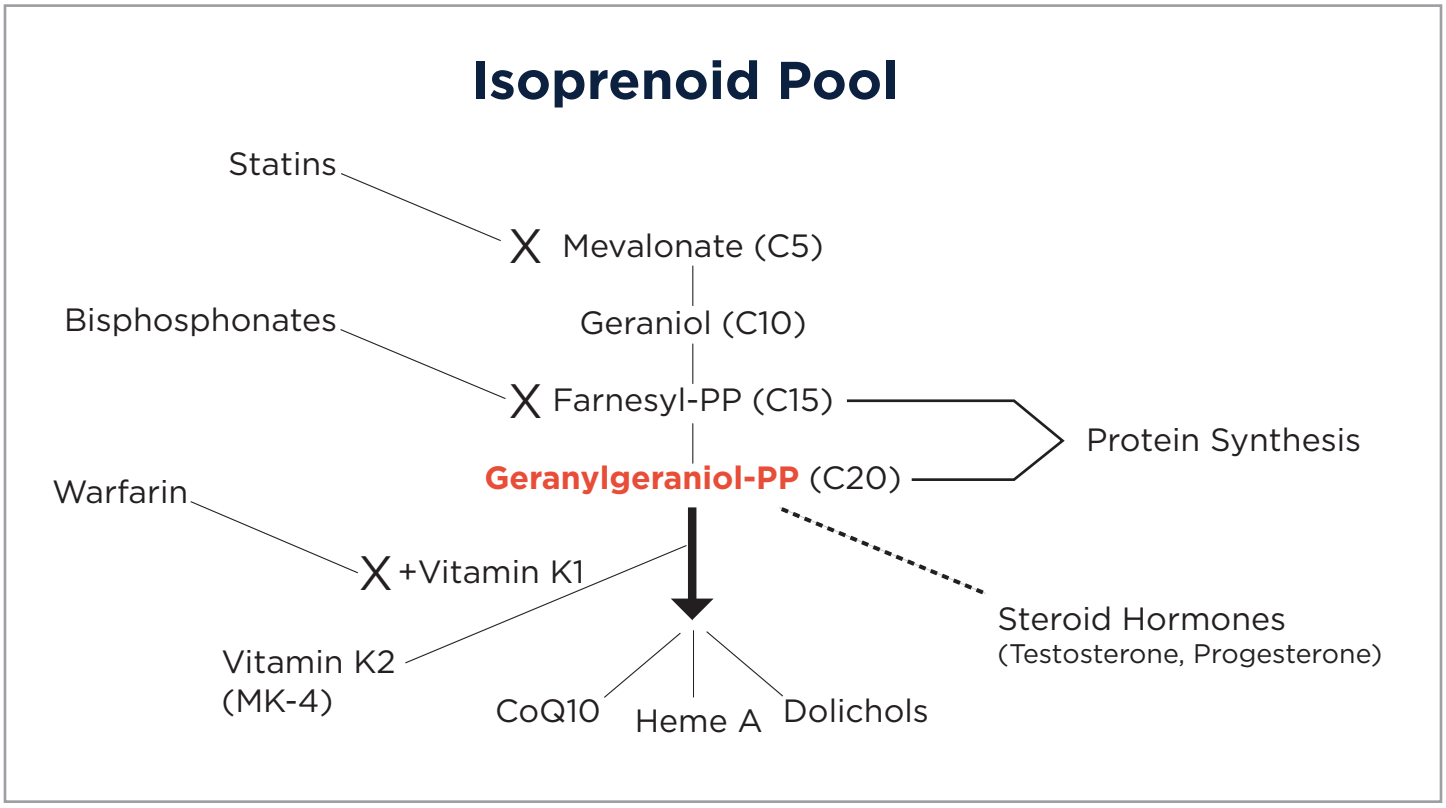
Sarcopenia Prevention/Reversal

Sarcopenia is an extremely common issue in aging and compromises mobility, independence and quality of life. Owing to the role of GG in protein synthesis and post-translational modification, the natural decline in GG synthesis during aging—particularly if coupled with use of pharmaceutical agents that inhibit synthesis—may contribute to the undesirable loss of muscle mass.

Researchers believe myogenesis requires modification of certain proteins by GG (a process called geranylgeranylation). GG was shown to reduce expression of muscle atrophy-related genes and enhance myogenic differentiation in murine skeletal muscle myoblasts.[2] Increasing the supply of GG with Annatto-GG™ 150 may help support muscle protein synthesis. Additionally, evidence suggests that compared to younger individuals, older individuals have a reduced anabolic response to dietary protein and may require a higher protein intake than is commonly recommended in order to build or maintain muscle mass. The frequent recommendation for 0.8 g/kg/d may not be sufficient to maintain nitrogen balance and researchers recommend increasing the minimum protein intake to 1.0 g/kg/d as a minimum, with intakes of 1.3 g/kg/d possibly being needed to remain in nitrogen balance, and potentially more for increasing muscle mass.[3-8] Higher protein intakes, especially from high-quality complete protein sources, are associated with reduced risk for frailty in older adults.[9-11] Since GG is required for protein synthesis, it may be prudent to include GG supplementation in a regimen intended to support building and maintaining muscle mass, particularly in older individuals.

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

CoQ10 Synthesis – Cellular Energy
A decline in synthesis of ubiquinone (CoQ10) during aging may play a role in mitochondrial dysfunction and decreased cellular energy generation, which may cascade into reduced physical activity and therefore loss of muscle mass and strength as well as general malaise.



GG is synthesized endogenously via the mevalonate pathway—the same biochemical pathway by which cholesterol, CoQ10 and other essential compounds are synthesized. Statin drugs exert their effects early in this pathway (via inhibition of the enzyme HMG-CoA reductase), far upstream of where GG and these other compounds are produced. Synthesis of all compounds produced after this step is inhibited, which likely underlies the neuromyotoxicity and mitochondrial toxicity of statins.[12,13]

The exact mechanisms behind the myopathy and myotoxicity many statin users experience is not known for certain but it's possible they result from inadequate synthesis of CoQ10 and/or GG.[14,15] Researchers have stated that GG is "the principal target of statin-dependent myotoxicity,"[16] and statin-induced muscle damage "is the result of a geranylgeranylation defect"[17]—potentially due to an inadequate pool of GG.

Animal models and cell studies show that given in combination with statins, GG increases mitochondrial respiration and restores ubiquinone synthesis without negatively impacting the cholesterol-lowering effects of statins. 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.[18] In human monocytes and liver cells, GG reversed mevastatin-induced reductions in ubiquinone synthesis and mitochondrial electron transport that typically lead to cell death without impeding the drug's cholesterol-lowering property for those who may benefit from that.[19] Notably, addition of GG was more effective than addition of 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."[19]

Vitamin K2 Synthesis – Bone Health

Osteoporosis is another major concern during aging that often goes hand-in-hand with sarcopenia. Vitamin K2 plays a crucial role in supporting bone mass by regulating calcium trafficking—facilitating calcium deposition in bones and teeth and inhibiting deposition in soft tissue such as blood vessels and joints.[20-24] Although vitamin K1 accounts for > 90% of dietary vitamin K, the K2 form menaquinone-4 (MK-4) makes up > 90% of tissue vitamin K stores. GG is needed for synthesis of K2, so a decreased supply of GG may result in reduced bone mineralization, increased risk for soft tissue calcification, and – especially in chronic kidney disease – kidney stones.[25] In a mouse model of type 2 diabetes-induced osteoporosis, GG administered at a human dose equivalent to 160 mg/d significantly improved bone turnover and protected bone microstructure and quality in the femur and trabecular bone tissue.[26] Fermentation vitamin K2 products (such as MK-7 through MK-11) are also menaquinones of longer isoprenoid tails. Interestingly, gut microbes do not produce MK-4; the only known MK-4 in the human body is synthesized via GG.

Supplementation with GG may help mitigate the effects of bisphosphonate drugs. Used to treat osteopenia and osteoporosis, these drugs interfere with endogenous synthesis of GG through the mevalonate pathway via inhibition of farnesyl pyrophosphate synthase, involved in the steps immediately preceding GG synthesis. (They target the same pathway as statins but exert their effects on a different enzyme.) A common result of nitrogen-containing bisphosphonate (NBP) use is osteonecrosis of the jaw (ONJ). Effective treatments for this are lacking, and GG has been identified as a potential preventive and therapeutic agent.[27] GG was shown to reverse the effects of NBPs on reduced angiogenesis, which is speculated to be one of many mechanisms contributing to ONJ.[27,28] GG has also been shown to reverse the negative effects of NBPs in human fibroblasts, osteogenic cells and HUVEC cells.[29] 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. Researchers concluded that systemic or local GG treatment could be a therapeutic strategy for ONJ.[30] Similar results have been demonstrated for GG reversing the negative effects of NBP on human alveolar osteoblasts, periodontal ligament fibroblasts and oral keratinocytes.[31-33]

Considering the critical role of vitamin K2 in supporting bone mass, it is ironic that NBPs may result in reduced vitamin K2 synthesis. These drugs may indirectly induce the opposite of their intended effect.

Steroidogenesis

Steroid hormone synthesis naturally declines with age. This reduction in hormones critical for vitality and quality of life is exacerbated by the use of pharmaceutical drugs that impair synthesis of cholesterol, the building block for testosterone, progesterone and estrogen. A systematic review and meta-analysis of randomized controlled trials on the effect of statins on testosterone in men and women found that statins have a mild testosterone-lowering effect, but the clinical significance of this may differ among individual patients.[34]

The average reduction was low, but individual patients may experience larger decreases, potentially resulting in reduced libido,[35] erectile dysfunction (ED)[36] and other complications, particularly in older men and those with existing cardiovascular risk factors.[37] Overall, however, research in this area is mixed.[38,39] One systematic review and meta-analysis found that statins, alone or in combination with sildenafil, improved ED[40] and a retrospective cohort analysis found no significant association between statin use and increased risk for male sexual dysfunction.[41]

Supplementing with GG as raw material or cofactor in hormone synthesis has the potential to ameliorate the negative effects of statins on testosterone levels. GG has been shown to increase production of both testosterone and progesterone in murine Leydig tumor cells.[42] Rats supplemented with vitamin K2 MK-4 (the synthesis of which requires GG) showed increased plasma and testicular levels of testosterone. MK-4 may be involved in testosterone synthesis in the testes, leading researchers to speculate that supplementation may positively impact the natural decline in this hormone during aging.[43,44] Vitamin K1 was not shown to have this effect, suggesting that K2—specifically, MK-4—is needed for this process.

Pain Reduction
Brazilian folk medicine has traditionally employed seeds from the plant Pterodon pubescens Benth (also called Sucupira branca) for their medicinal properties. Modern laboratory assays have determined that this plant is a source of GG, and these extracts have been shown to be anti-inflammatory, analgesic, muscle-relaxing, anti-rheumatic and hypoglycemic.[45-47]

Rodent models employing oral administration of GG show that the analgesic effects can take place as quickly as within minutes (for immediate pain relief and reduction of pain from skin burn, heat burn and gastritis). Anti-nociceptive effects for edema and pressure pain took hours, and pain reduction for rheumatoid arthritis was observed within 2 weeks.[47-49]

Supplement Facts

Serving Size 1 softgel

Amount Per Serving		% Daily Value
Trans-Geranylgeraniol (as GG-Gold™)	150 mg	*

*Daily Value not established.

Other Ingredients: Bovine gelatin, purified water, glycerine.

GG-Gold™ is a trademark of American River Nutrition, LLC.
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Recommended Use:
Take one softgel per day, or as directed by your health care practitioner.

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