



Geranylgeraniol (GG) Overview

Introduction

Geranylgeraniol (GG) is a substance that is made in the human body via a biochemical pathway called the mevalonate pathway. This is the same biochemical pathway that makes cholesterol, CoQ10, dolichol and Heme A.

The mevalonate pathway plays a critical role in numerous cellular processes throughout the body. For example, it keeps our mitochondria healthy and generates ATP - the energy that all cells use.

GG is an important part of the mevalonate pathway. GG supports CoQ10 synthesis, muscle health, bone health and also hormone regulation.

In the body, GG is converted to the 'activated' form called geranylgeranyl pyrophosphate (GGPP). When taken orally, GG is activated by the body and incorporated into the mevalonate pathway.

Unfortunately, as we age, our levels of GG decline. Certain medications also inhibit the mevalonate pathway, namely statins and bisphosphonates (the latter are prescribed to treat osteoporosis). By inhibiting the mevalonate pathway, these medicines also inhibit GG and CoQ10.

Scientific evidence shows that it is the reduction in GG that is responsible for many of the common side effects experienced by those taking statins, namely, muscle aches and pains and muscle weakness.

Supplementation with GG may help mitigate the side effects of statins, and may support healthy aging more broadly.

GG Source

GG is ubiquitous in nature. It is a precursor to carotenoids, certain vitamins and chlorophyll. Hence, when you see a yellow/orange/red colour in plants, you know that GG is present! Notably, GG is also found in edible oils such as olive, linseed and sunflower oils.

One of the most abundant sources of GG is the South American Annatto plant (*Bixa orellana*). You may be familiar with the Annatto plant, it has been used for centuries to colour foods and cosmetics.

Here at Xtend-Life, we always choose the most premium ingredients. Our GG

is a multi-patented ingredient called GG-Gold™. It is made in a GMP facility in Massachusetts, USA using a clean, physical extraction process from the Annatto plant. There are no chemicals used during extraction. Once extracted, GG-Gold™ undergoes extensive quality control and testing at Xtend-Life before being released in GG PURE.

GG, Proteins and Cellular Function

GG is used by the body for both protein synthesis and another process called post-translational modification of proteins. Post-translational modification means modification of the protein once it is synthesized in cells. This process affects what proteins can do.

When it comes to GG and its smaller sibling Farnesyl (a precursor to GG), their specific post-translational modification is a process called protein prenylation. The proteins that are modified in this way are known as isoprenoid-modified proteins or prenylated proteins.

In mammals, isoprenoid-modified (or prenylated) proteins make up 1-2% of all cellular proteins and GG is the main contributor to this process. While this might sound like a low percentage, a shortage of GG results in serious problems and harm to the body.

Numerous essential intracellular proteins undergo prenylation. Some examples include:

- Most members of the small GTPase superfamily of proteins
- Heterotrimeric G proteins
- Nuclear lamins.

These proteins are involved in regulating a plethora of cellular processes and functions including signal transduction (how cells understand what's going on outside the cell), protein synthesis, regulation of the creation, growth and movement of cells, placement of proteins into membranes and structure of membranes, to name a few! As you can see, protein prenylation by GG is essential to the normal function of cells!

GG for Statin-Induced Muscle-Related Side Effects

Muscle pain and weakness is the most common side effect among statin users. Research points to reduced GG as the primary cause, with lowered levels of CoQ10 likely as a lesser contributing factor.

In biochemistry experiments, statins induced muscle damage and adding GG prevented that muscle damage. This was mediated by GG's effect on a gene called atrogin-1 which is responsible for muscle atrophy¹.

Several other cell-based studies have confirmed this finding. In these studies, researchers added GG to statin-treated muscle cells and in doing so, restored the viability of muscle cells^{2,3}. Other researchers noted that GG was able to repair and rescue cellular functions that prevent statin-induced muscle damage⁴.

The loss of GG-dependent protein prenylation caused by statins affects muscle cells in particular and other cells in general. Multiple studies show that co-administration of GG with statins restores cell growth in muscle cells and restores DNA synthesis and cell division^{5,6,7}.

Researchers have pointed to GG as "the principal target of statin-dependent myotoxicity"⁸ and have concluded that statin-induced muscle damage "is the result of a geranylgeranylation defect"¹. Fortunately, supplementation with GG provides a simple means to restore protein generated from GG⁹.

GG and CoQ10

CoQ10 is an essential part of the electron transport chain - the process whereby cells' mitochondria produce energy. Levels of CoQ10 drop as we age¹⁰ and low levels of CoQ10 are a hallmark of several age-related illness such as type II diabetes and cancer¹¹.

GG is a precursor for the synthesis of CoQ10¹² in the mevalonate pathway. Statin treatment directly inhibits the mevalonate pathway to decrease cholesterol. An unintended side-effect is that statins also inhibit CoQ10 production and affect mitochondrial function.

One of the most studied side effects of statins is the decrease in CoQ10 and associated mitochondrial impairment.

In cell-based experiments, statins reduced GG and CoQ10, impairing mitochondrial function and cell proliferation, and increasing cell death. Adding GG reversed the ill-effects of the statin, without affecting the statins ability to reduce cholesterol. Notably, adding GG was more effective than adding CoQ10 at eliminating the ill-effects of the statin¹³.

Lowered cellular energy production is most problematic for heart muscles, since unlike skeletal muscles, our heart muscles are always working. Hence adding CoQ10 supplementation while taking statins is a popular strategy for supporting cellular energy production.

GG, Vitamin K and Calcium

Vitamin K is best known for its role in blood clotting, but it is also very important for healthy bones and teeth. Vitamin K, particularly the K2 form is like a traffic controller directing calcium where to go in the body. Vitamin K2 is also known as menaquinone.

We want calcium directed into our bones and teeth, but not our soft tissues such as blood vessels, kidney or joints. Calcium in these areas can cause problems such as arterial calcification, kidney stones and arthritis.

Way back in 1960 scientists discovered that GG is needed to make Vitamin K2. This has been confirmed by many scientific studies since then and it is now recognised that GG is required for the conversion of Vitamin K1 to Vitamin K2¹⁴.

Statins reduce Vitamin K2 by inhibiting GG through the mevalonate pathway. Lowered levels of Vitamin K2 accelerate calcification of arteries in those taking statins¹⁵. In cell culture and animal studies, adding GG restores Vitamin K2 levels in the presence of statins^{16,17}.

Based on years of scientific studies dating back to 1960, research suggests supplementing with GG may be an effective strategy to ensure healthy Vitamin K2 and calcium trafficking for those taking statins.

GG and Testosterone

Population-based studies show that testosterone levels in men decrease with age¹⁸. Low testosterone levels cause infertility and sexual dysfunction in men and have been linked with a range of chronic diseases .

Testosterone is produced in the Leydig cells of the testicles and is derived from cholesterol, which, as we know, is produced through the mevalonate pathway.

In cell culture experiments, GG stimulated the production of testosterone and its precursor progesterone. The same research paper reported results from animal studies which suggests a human equivalent dose of 66mg/day is sufficient to increase plasma testosterone levels²⁰. The mechanism is still being worked out but involves GG and Vitamin K2 interacting directly.

Hence GG may support healthy testosterone levels for aging men.

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