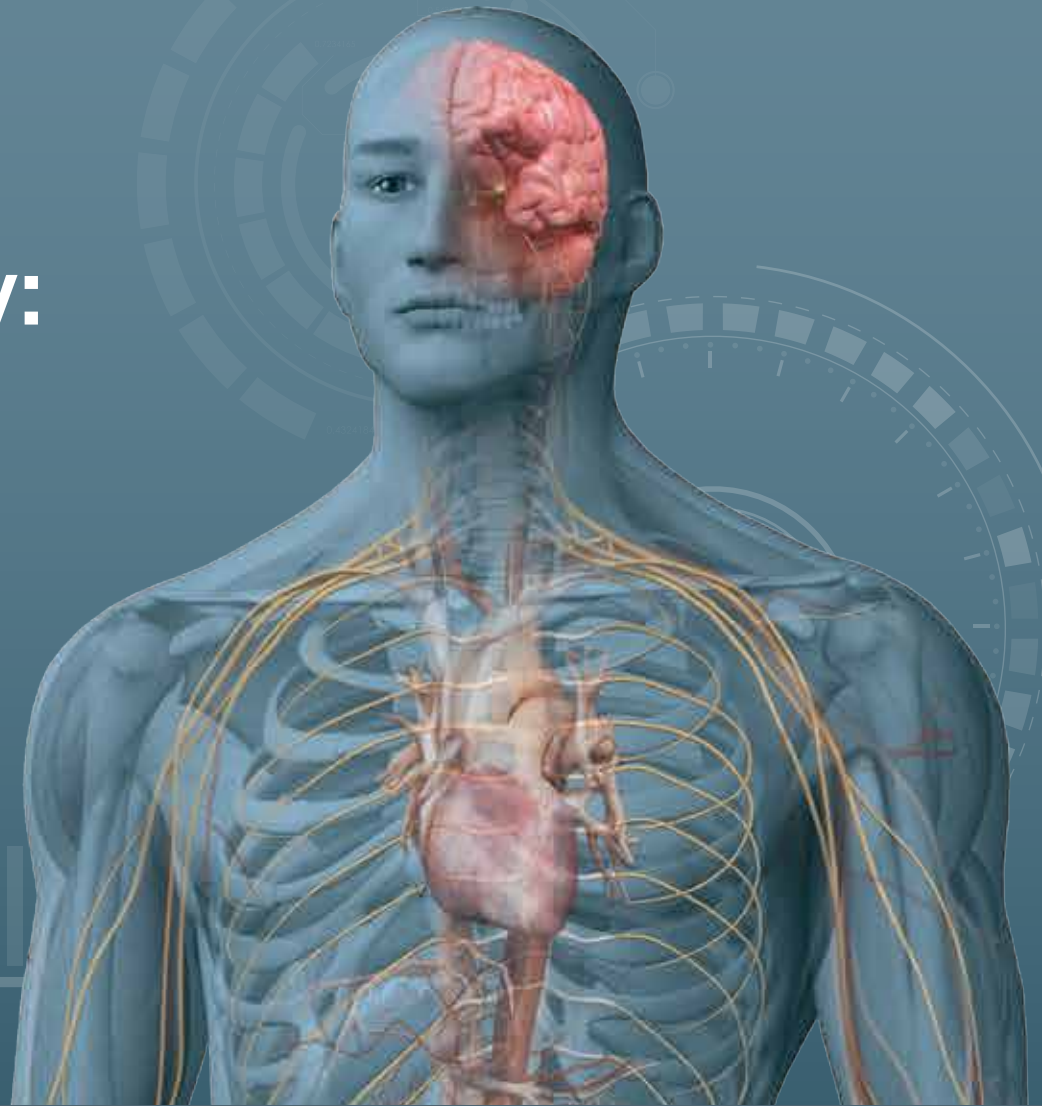
The Mevalonate Pathway:

Key to Mitochondrial Health



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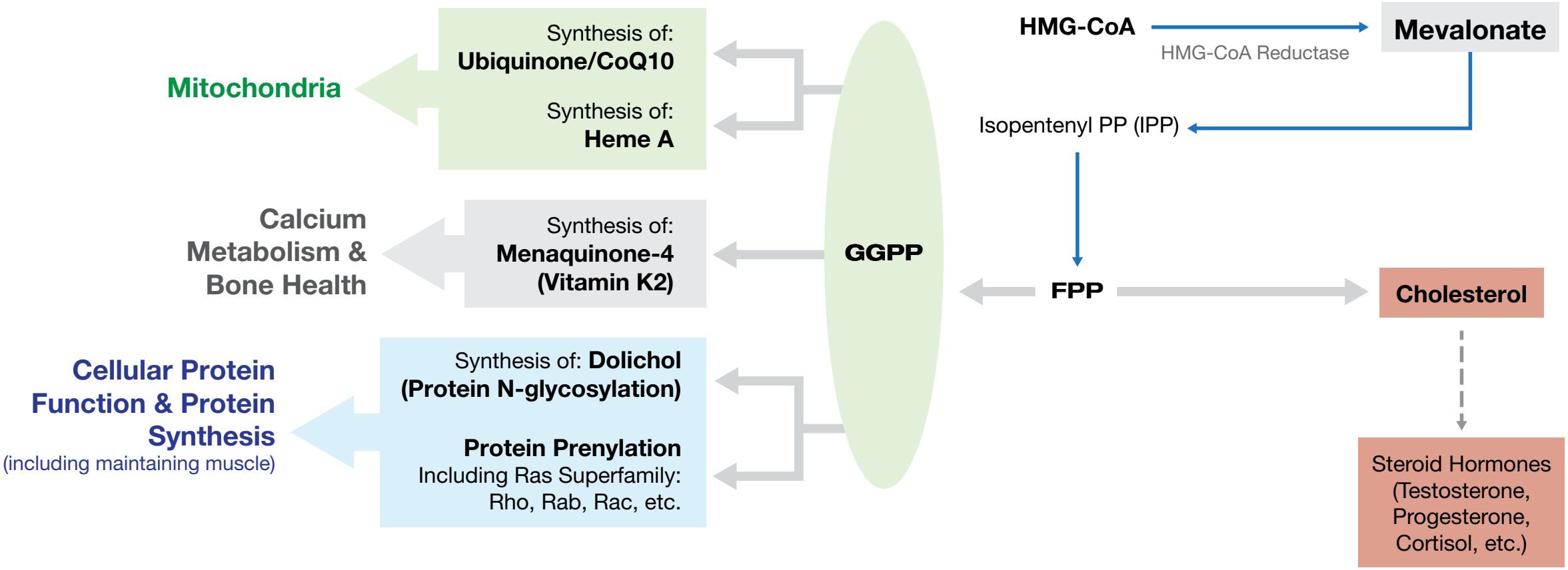
Workshop Presentation for Healthcare Practitioners Only

Introduction to the Mevalonate Pathway

Especially important in the **musculoskeletal, cardiovascular, and nervous systems**



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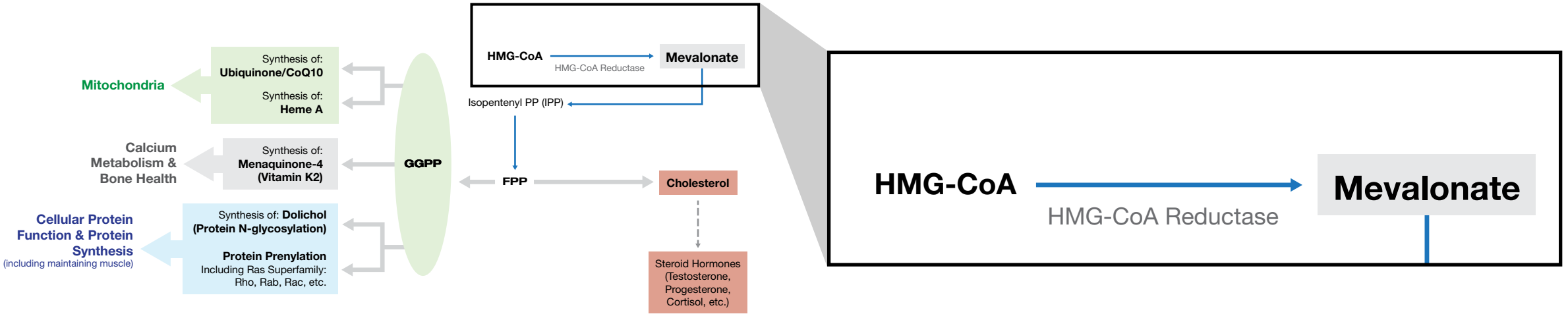
The Mevalonate Pathway

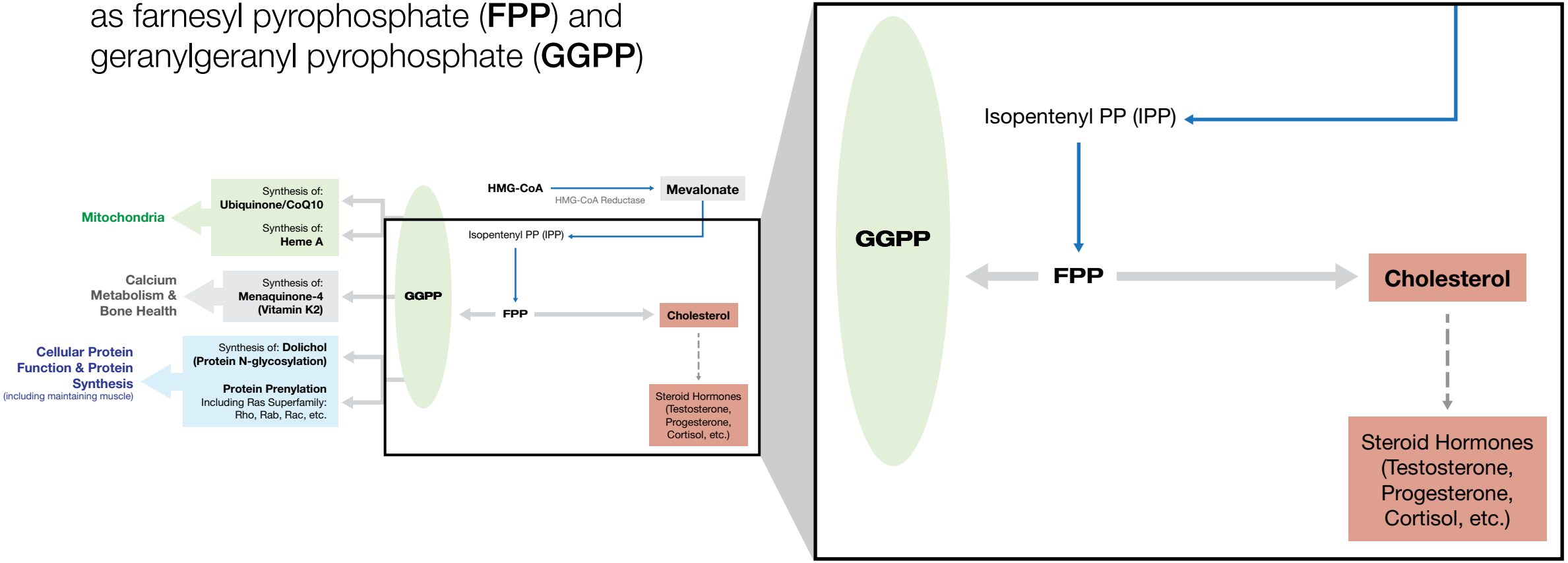
Starts with **formation of mevalonate** from HMG-CoA



The research information presented is not a claim regarding any product or its ingredients.

The Mevalonate Pathway

- Provides requirements for **cholesterol biosynthesis**
- Produces important molecules, such as farnesyl pyrophosphate (**FPP**) and geranylgeranyl pyrophosphate (**GGPP**)



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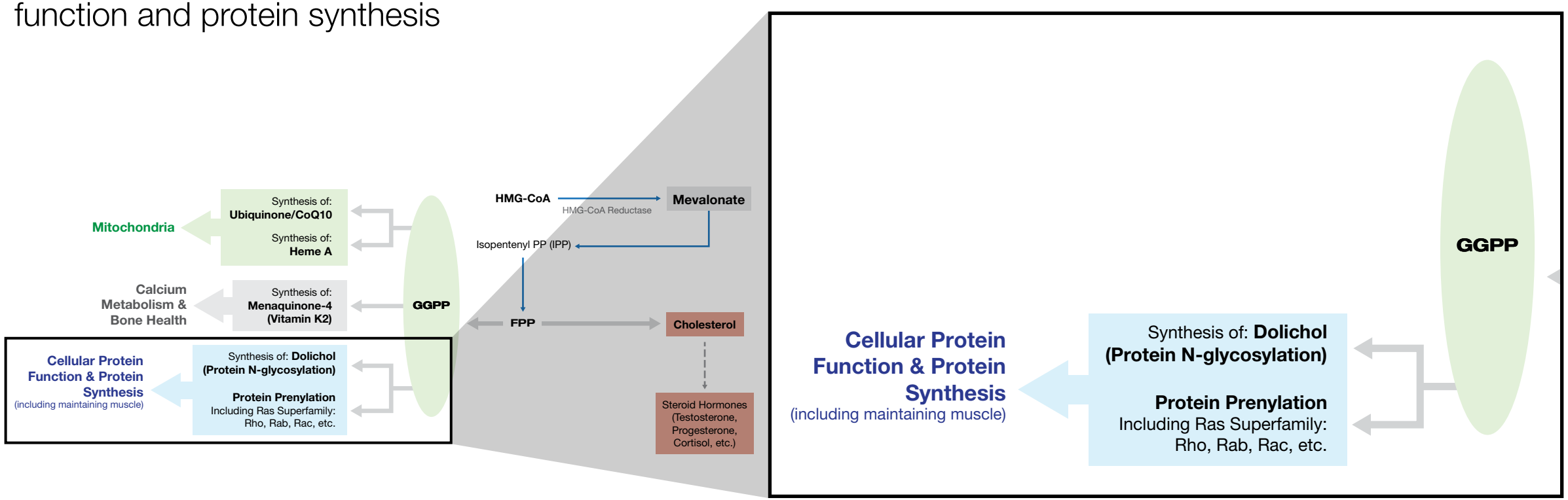
The Mevalonate Pathway

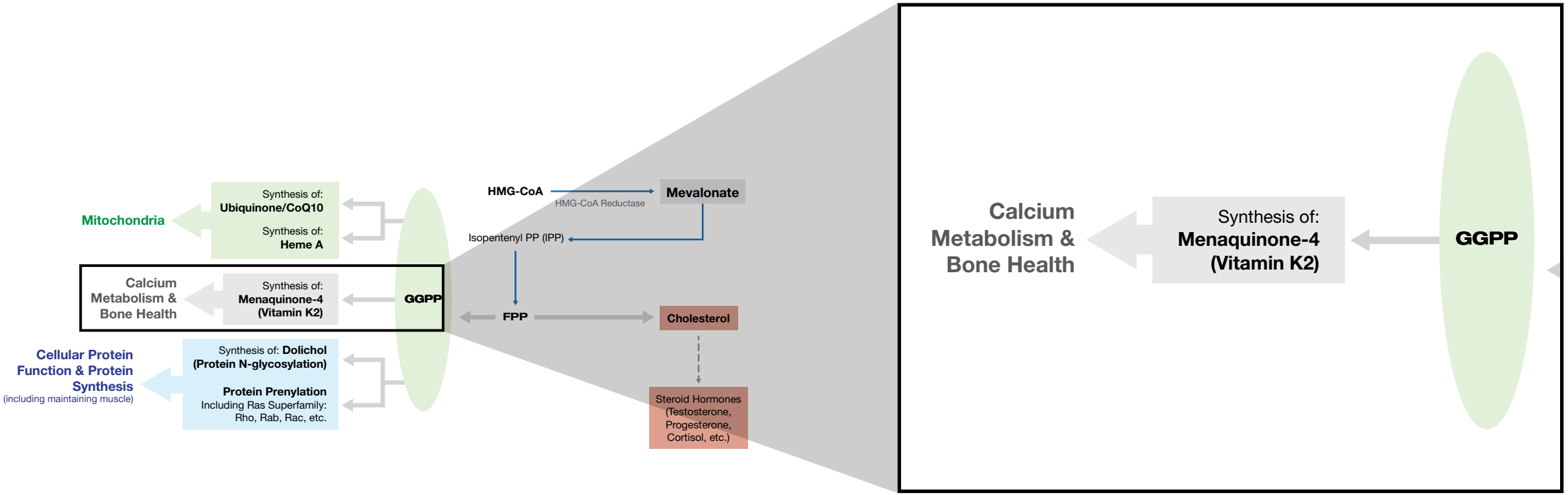
Important in protein glycosylation and protein prenylation, which are modifications affecting cellular protein function and protein synthesis



The research information presented is not a claim regarding any product or its ingredients.

The Mevalonate Pathway

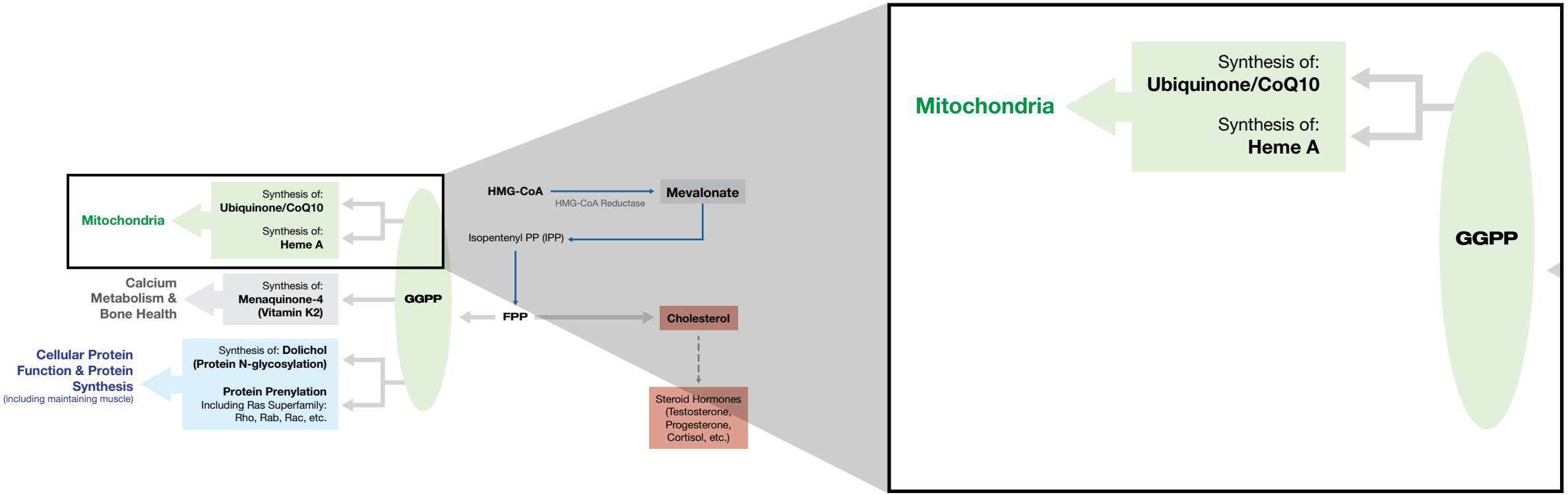
Pathway for synthesis of MK-4 (vitamin K2)



The research information presented is not a claim regarding any product or its ingredients.

The Mevalonate Pathway

Pathway for synthesis of ubiquinone and heme A, which are important for the mitochondrial electron transport chain (ETC)



Baker S. *Integrative Medicine*. 2024;22(6):54-7.
Tricarico PM, et al. *Int J Mol Sci*. 2015 Jul 15;16(7):16067-84.

The research information presented is not a claim regarding any product or its ingredients.

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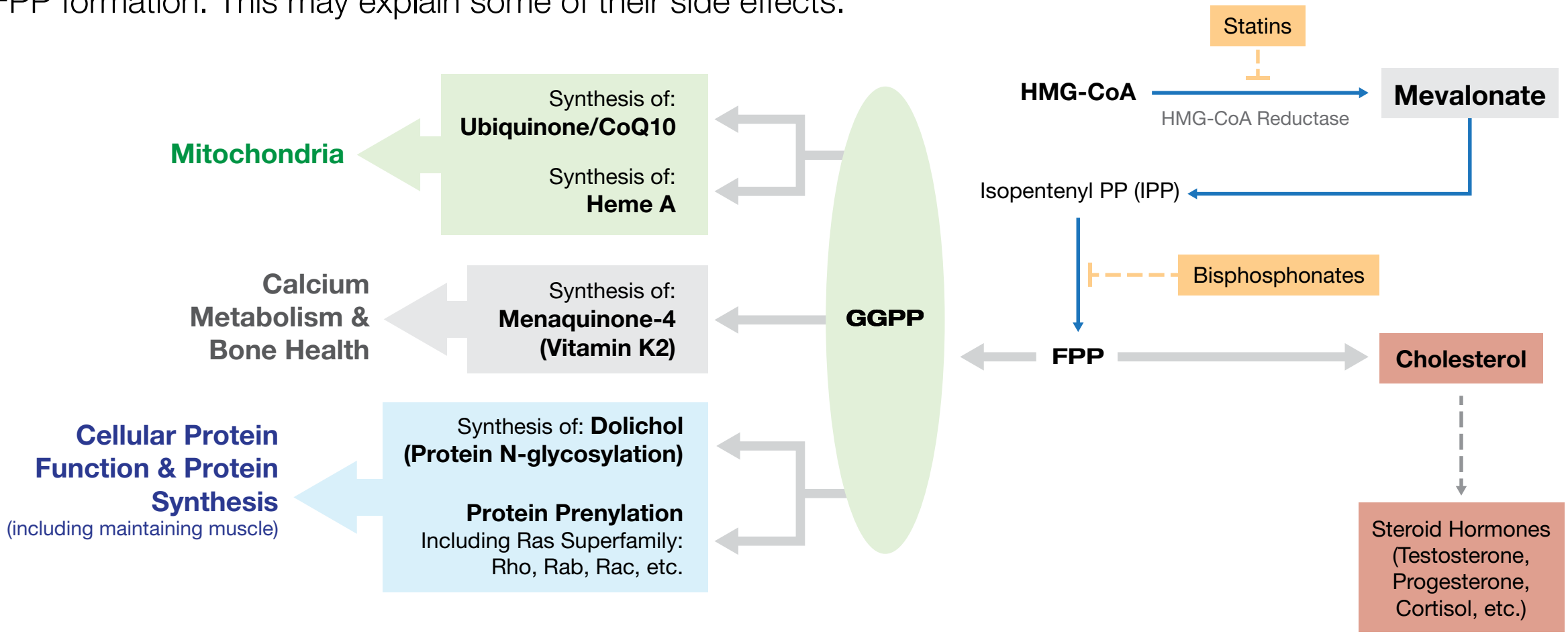
Mevalonate Pathway Is Affected by Certain Medications

Statins inhibit mevalonate formation, and bisphosphonates inhibit FPP formation. This may explain some of their side effects.



Baker. *S Integrative Med.* 2024;22(6):54-057.
Cui Y, et al. *Free Radic Biol Med.* 2023;206:33-49. doi: 10.1016/j.freerabiomed.2023.06.022.

Mollazadeh H, et al. *J Cachexia Sarcopenia Muscle.* 2021;12(2):237-251. doi:10.1002/jcsm.12654
Tricarico PM, et al. *Int J Mol Sci.* 2015 Jul 15;16(7):16067-84.

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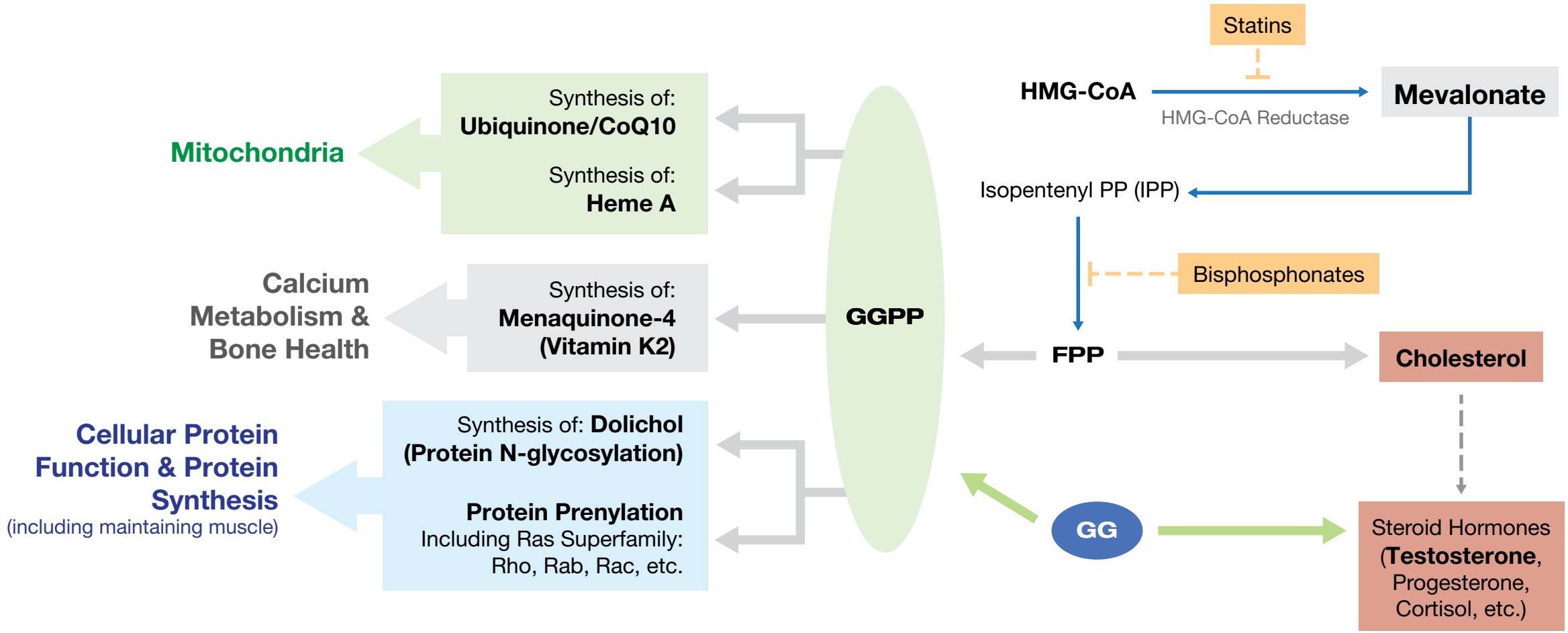
Newly Available Geranylgeraniol (GG), Key to Mevalonate Pathway



Baker S. *Integrative Med.* 2024;22(6):54-7.

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Geranylgeraniol (GG)

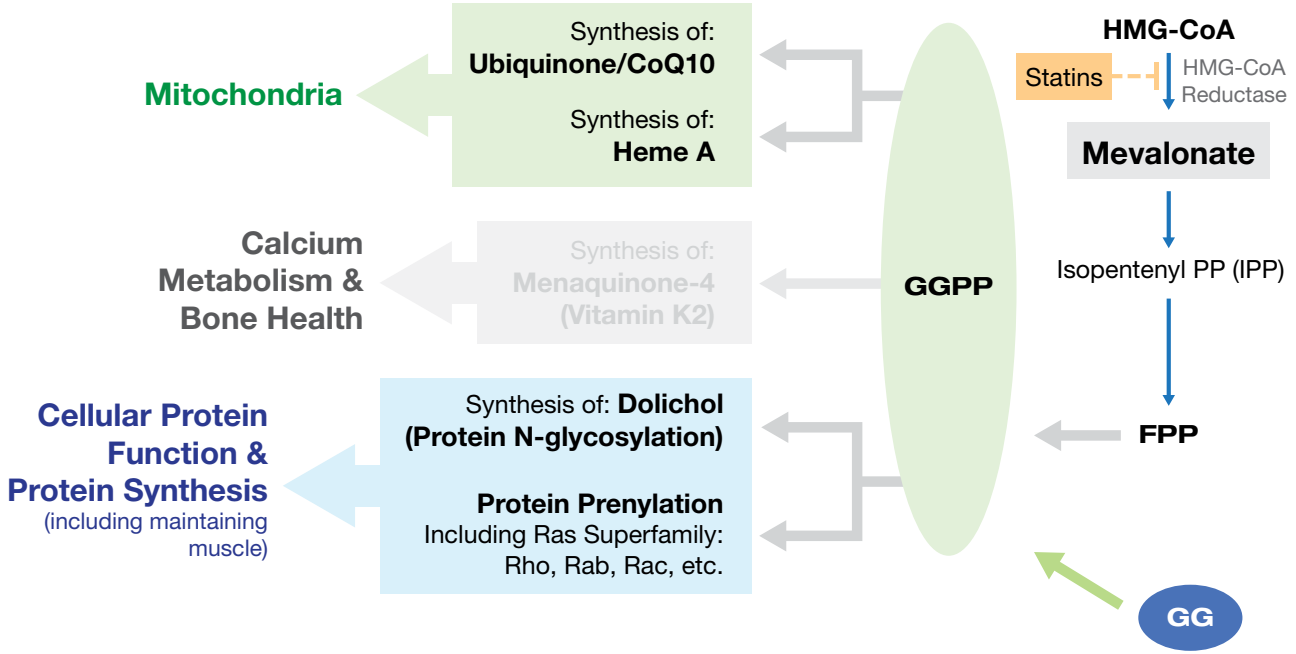
- GG supports the Mevalonate Pathway through GGPP.
- GG is a building block of CoQ10.
- GG levels decline with age.
- GG may help protect against age-related declines in mitochondria, muscle mass, testosterone, etc.
- GG has potential for protecting mitochondria against certain medications (statins and bisphosphonates), toxins, age, etc.
- In vitro studies suggest GG **may help reverse the effects of statins** on mitochondrial function in certain pathways more **effectively than CoQ10**.

Baker S. *Integrative Medicine.* 2024;22(6):54-7.
Campia I, et al. *British J Pharm.* 2009 Dec;158(7):1777-86.
Geeth R, et al. *Nutraceuticals.* 2023 Dec 12;3(4):605-18.
Jiwan NC, et al. *In Vivo.* 2022;36(6):2638-2649. doi:10.21873/invivo.12998
Paul C, et al. Townsend Letter. *The Examiner of Alternative Medicine.* Accessed September 30, 2024. https://townsendletter.com/geranylgeraniol-boosts-endogenous-synthesis-of-cq10-paul-et-al/

The research information presented is not a claim regarding any product or its ingredients.

Why Statin Users May Further Benefit From GG Plus CoQ10

- Research shows that CoQ10 supplementation increases **plasma** CoQ10 in statin-treated individuals.
- CoQ10 supplementation **does not** completely mitigate other adverse effects in statin-treated individuals, particularly myopathy.
- The adverse effects of statins on muscle may be through **inhibition of GG-related protein** synthesis rather than CoQ10 suppression alone.



Tan B, et al. *Front Physiol.* 2023;14:1246589. doi:10.3389/fphys.2023.1246589
Paul C, et al. Townsend Letter. *The Examiner of Alternative Medicine.* Accessed September 30, 2024. https://townsendletter.com/geranylgeraniol-boosts-endogenous-synthesis-of-cq10-paul-et-al/

The research information presented is not a claim regarding any product or its ingredients.

GG Had Broader Protective Effects Against Cytotoxicity of Statins Than Exogenous Ubiquinone

In this study…

- This was an in vitro study performed using human cells to demonstrate the effects of Mevastatin and GG.
- Mevastatin reduced:
  - » Synthesis of cholesterol, GGPP, and ubiquinone
  - » Mitochondrial electron transport
  - » Enzymes that regulate cell processes
- Mevastatin increased:
  - » Cell death
- **GG reversed all of these effects** of Mevastatin, without affecting its ability to reduce cholesterol synthesis.
- Incubation of the cells with **GG alone increased the synthesis of ubiquinone**.
- GG had **broader effectiveness** than exogenous ubiquinone.

In Vitro of Human

Geranylgeraniol Prevents the Cytotoxic Effects of Mevastatin in THP-1 Cells, Without Decreasing the Beneficial Effects on Cholesterol Synthesis

Campia I, et al. *British J Pharm.* 2009 Dec;158(7): 1777-86.

The research information presented is not a claim regarding any product or its ingredients.

Lipophilic Statin Use and Risk of Dementia in Early Mild Cognitive Impairment

In this study...

- 96-month prospective, longitudinal analysis of PET scan data in 157 early mild cognitive impairment (eMCI) subjects with below-median cholesterol
- Subjects stratified by statin type (lipophilic vs. other) and non-statin users
- **Lipophilic statin users had a 2.4x higher conversion rate to dementia** vs. non-users (24% vs. 10%, p=0.04) over eight years.
  - » Conversion rate of other-statin (ie., water-soluble statin) subjects did not significantly differ from non-statin subjects
- Posterior cingulate metabolic decline, a hallmark of early Alzheimer's progression, was identified among lipophilic statin users. No significant decline occurred among other-statin and non-statin subjects.

Human Study

Lipophilic Statins in Subjects With Early Mild Cognitive Impairment: Associations with Conversion To Dementia and Decline In Posterior Cingulate Brain Metabolism in a Long-Term Prospective Longitudinal Multi-Center Study

Padmanabham P, et al. *J Nuclear Med.* 2021: 62(1):102.

The research information presented is not a claim regarding any product or its ingredients.

Statin Effect in Neuronal Cell Line Improved by GG

In this study…

- Statins blocked the Mevalonate Pathway in a neuronal cell line.
- This increased inflammasome gene expression and programmed cell death related to mitochondrial dysfunction.
- Co-administration of **GG reduced the inflammatory marker** and the damage to mitochondria.

In Vitro of Human

Geranylgeraniol and Neurological Impairment: Involvement of Apoptosis and Mitochondrial Morphology

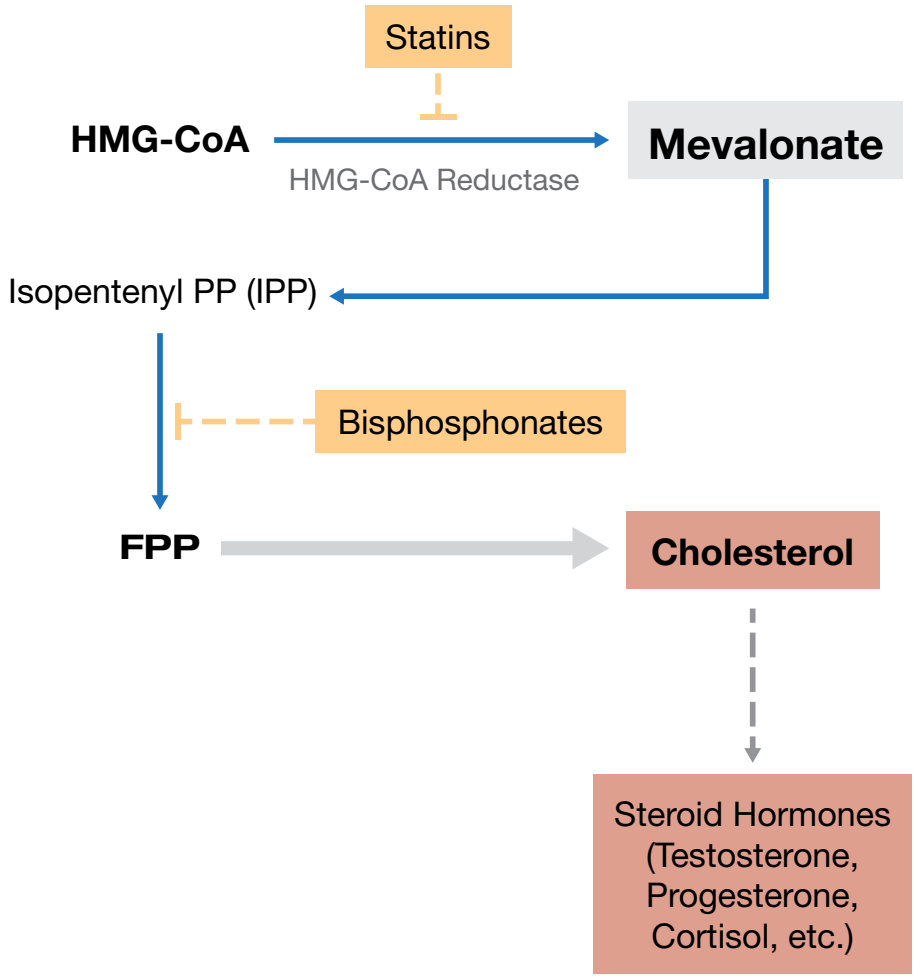
Marcuzzi A, et al. *Int J Mol Sci.* 2016 Mar 11;17(3):365.

GG & Testosterone

The research information presented is not a claim regarding any product or its ingredients.

Mevalonate Pathway & Testosterone Synthesis

Testosterone is derived from cholesterol in the Mevalonate Pathway



The research information presented is not a claim regarding any product or its ingredients.

GG Regulates Testosterone Production

In this study...

- *In vitro* research suggests GG regulates the steroidogenesis pathway and enhances testosterone and progesterone (its precursor) through the cAMP/PKA pathway, independent of luteinizing hormone stimulation.
- The role of GG in steroidogenesis may bring new possibilities.
- GG could be useful in the treatment of men with late-onset hypogonadism.

Review

A Novel Function of Geranylgeraniol in Regulating Testosterone Production

Ho HJ, et al. *Biosci Biotechnol Biochem.* 2018;82(6):956-962.

The research information presented is not a claim regarding any product or its ingredients.

GG Increases Testosterone in Males with Lower Testosterone

In this study...

- 8-week randomized, placebo-controlled, dose-escalation trial using 150–300 mg/d of GG
- 66 healthy adults (ages 30–49)
- Assessed blood safety markers (CBC, metabolic panel) and sex hormones
- No significant changes in blood chemistry, hematology, or sex hormones in general population.
- A subgroup of males with testosterone below the 3rd quartile (males <700 ng/dL) showed significant increases in total testosterone (+7.5%), free testosterone (+15.0%), and bioavailable testosterone (+14.8%).
- GG was well-tolerated with no adverse effects on safety markers.

Human Study

The Effects of Geranylgeraniol on Blood Safety and Sex Hormone Profiles in Healthy Adults: A Dose-Escalation, Randomized, Placebo-Controlled Trial

Gheith R, et al. *Nutraceuticals*. 2023 Dec 12;3(4):605-18.

The research information presented is not a claim regarding any product or its ingredients.

GG & Bone

The research information presented is not a claim regarding any product or its ingredients.

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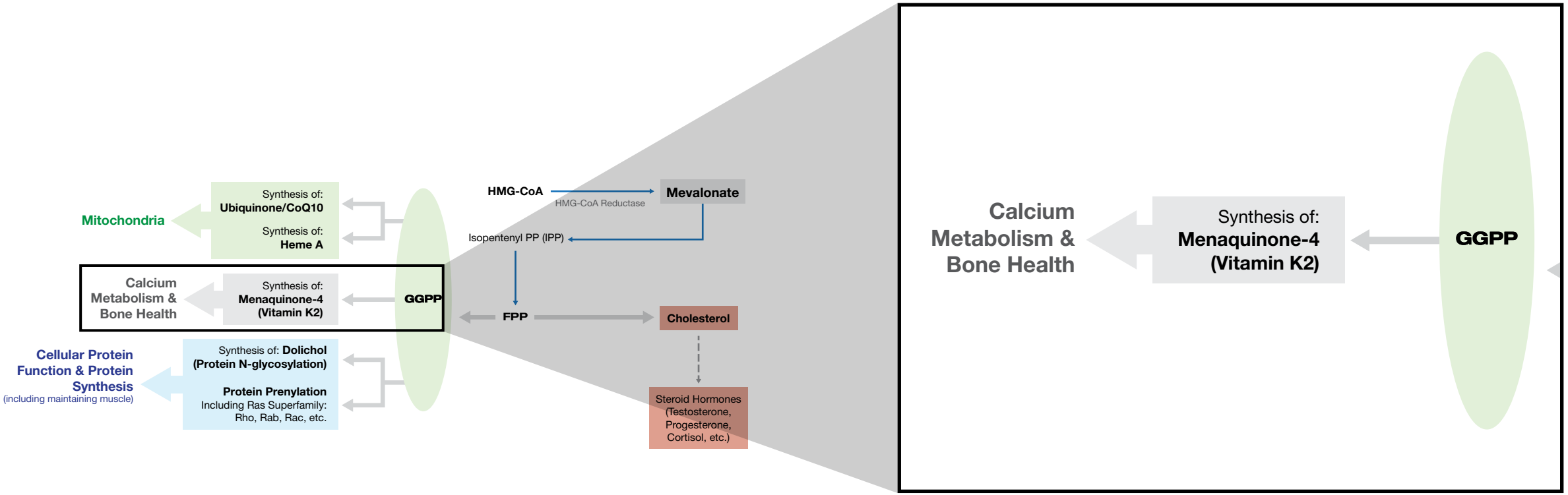
GG's Connection to MK-4 (Vitamin K2) & Bone



The research information presented is not a claim regarding any product or its ingredients.

GG May Mitigate Osteonecrosis of the Jaw (ONJ)

In this study…

- Bisphosphonate-related ONJ (BRONJ) is the most prevalent condition associated with bisphosphonate use in cancer and osteoporosis treatment.
- Nitrogen-containing bisphosphonates disrupt mevalonate pathway substrates needed for GTPase prenylation.
- GG is a promising approach to mitigate BRONJ, because GG is a substrate for GTPase prenylation.

Review

The Role of Geranylgeraniol in Managing Bisphosphonate-Related Osteonecrosis of the Jaw

Chin KY, et al. *Front Pharmacol*. 2022;13:878556.

GG's Influence on Bone Microstructure

In this study...

- Obesity and T2DM produce detrimental effects on bone health.
- Relative to the HFD group, HFD + GG:
  - » Improved glucose homeostasis
  - » Mitigated bone microarchitecture deterioration and improved bone quality
  - » Reduced pro-inflammatory adipokines
  - » Favorably modified taxonomic profiles
- GG improves glucose homeostasis and bone microstructure in obese mice, probably via suppression of pro-inflammation and modification of microbiome composition.

in Vivo of Animal

Beneficial Effect of Dietary Geranylgeraniol on Glucose Homeostasis and Bone Microstructure in Obese Mice Is Associated with Suppression of Proinflammation and Modification of Gut Microbiome

Chung E, et al. *Nutr Res.* 2021;93:27-37.

The research information presented is not a claim regarding any product or its ingredients.

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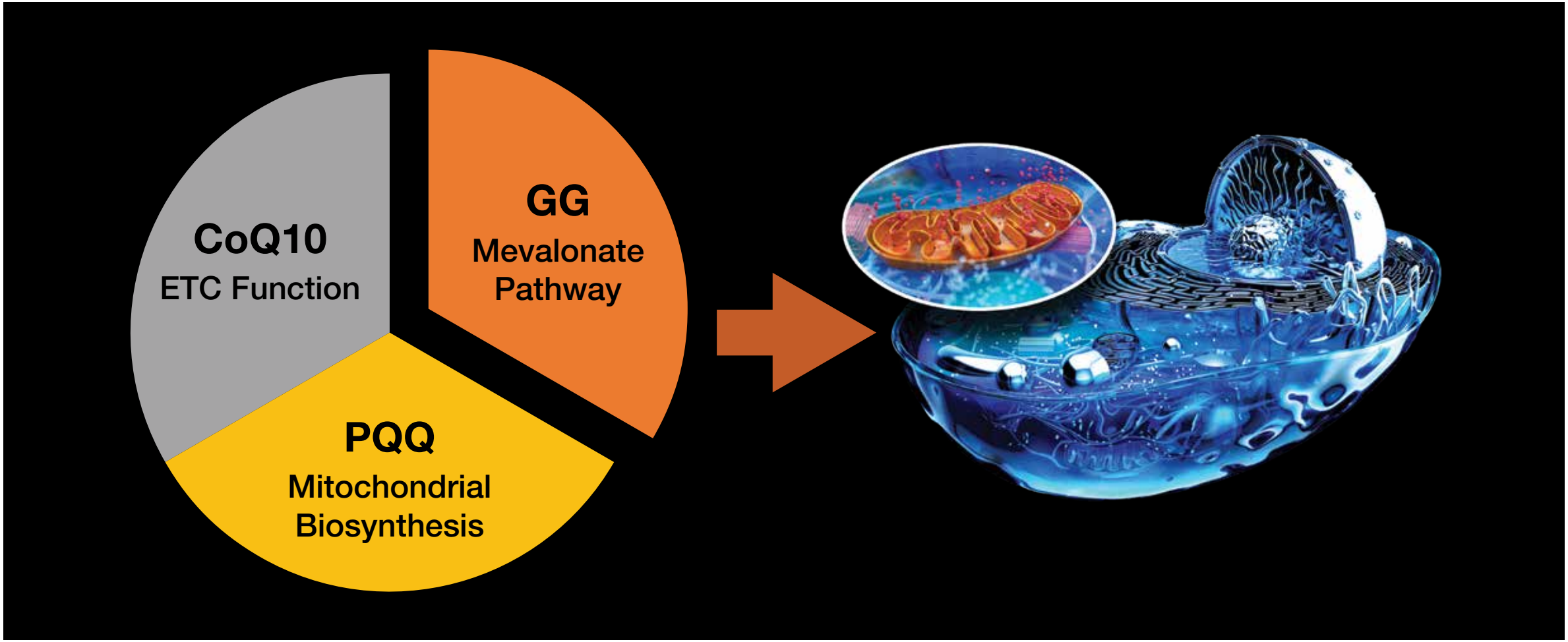
Super-Charging Mitochondria with Complementary Nutrients for Better Cardiovascular & Cognitive Results



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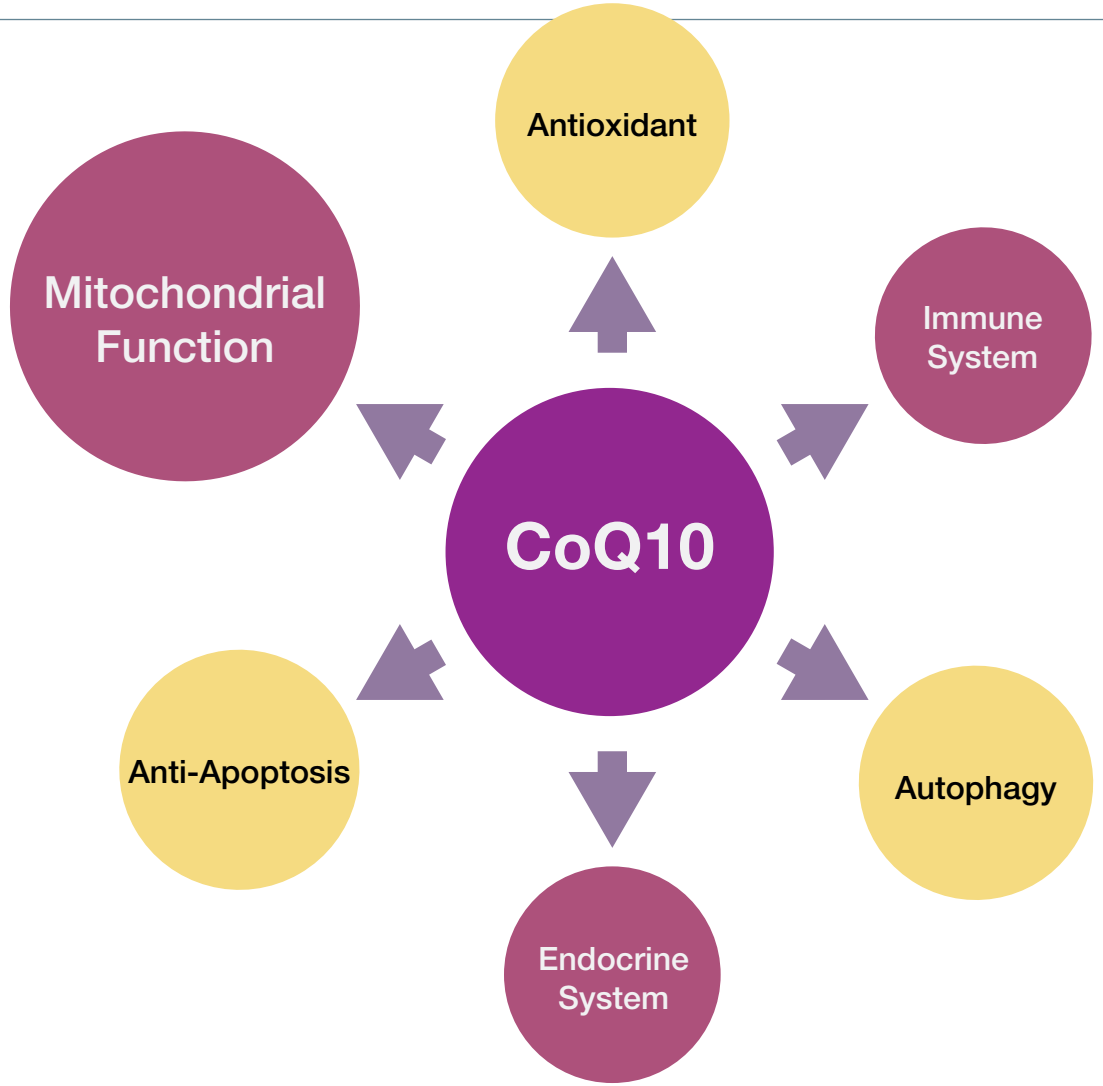
Coenzyme Q10 (CoQ10) Health Benefits

CoQ10 levels are highest in organs with high rates of metabolism and mitochondria, such as the heart and brain.

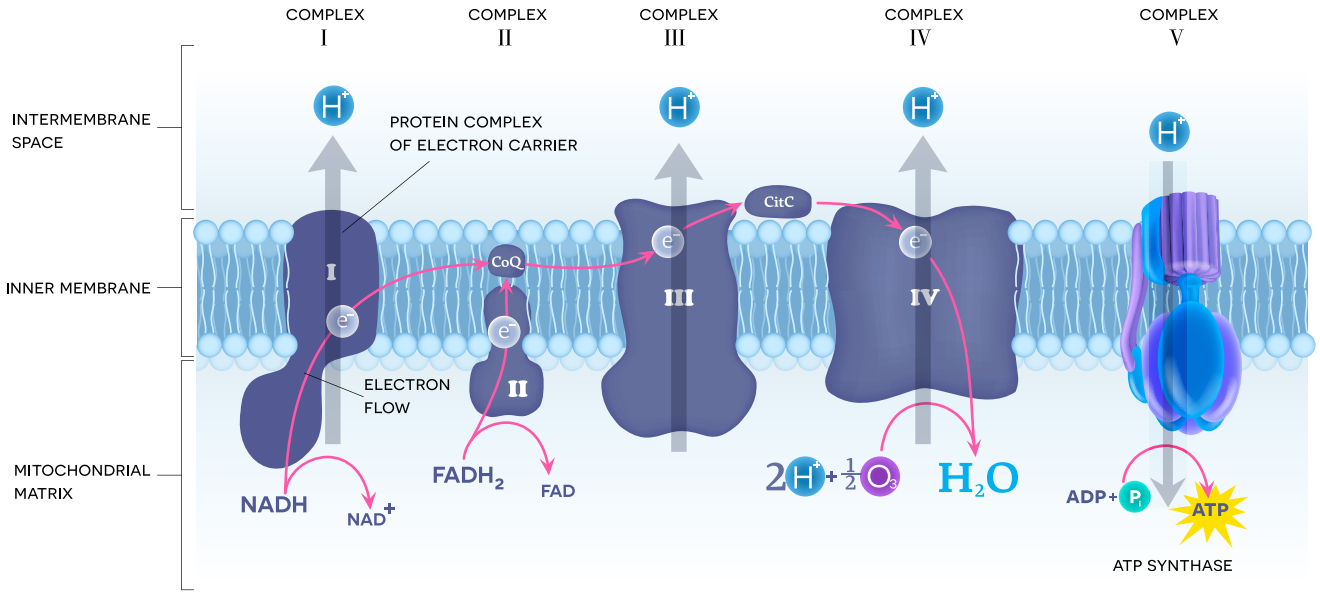


de la Bella-Garzón R, et al. *Antioxidants* (Basel). 2022;11(2):279. 29. doi:10.3390/antiox11020279
Hargreaves I, et al. *Int J Mol Sci.* 2020;21(18):6695. doi:10.3390/ijms21186695
Manzar H, et al. *Int J Mol Sci.* 2020;21(23):9299. doi:10.3390/ijms21239299

The research information presented is not a claim regarding any product or its ingredients.

CoQ10: Essential to Mitochondrial Function

- CoQ10 is an essential biological cofactor of the ETC.
- It carries electrons from complexes I and II to complex III, thus participating in ATP production.
- It also functions as an important endogenous lipophilic antioxidant in mitochondrial cell membranes.

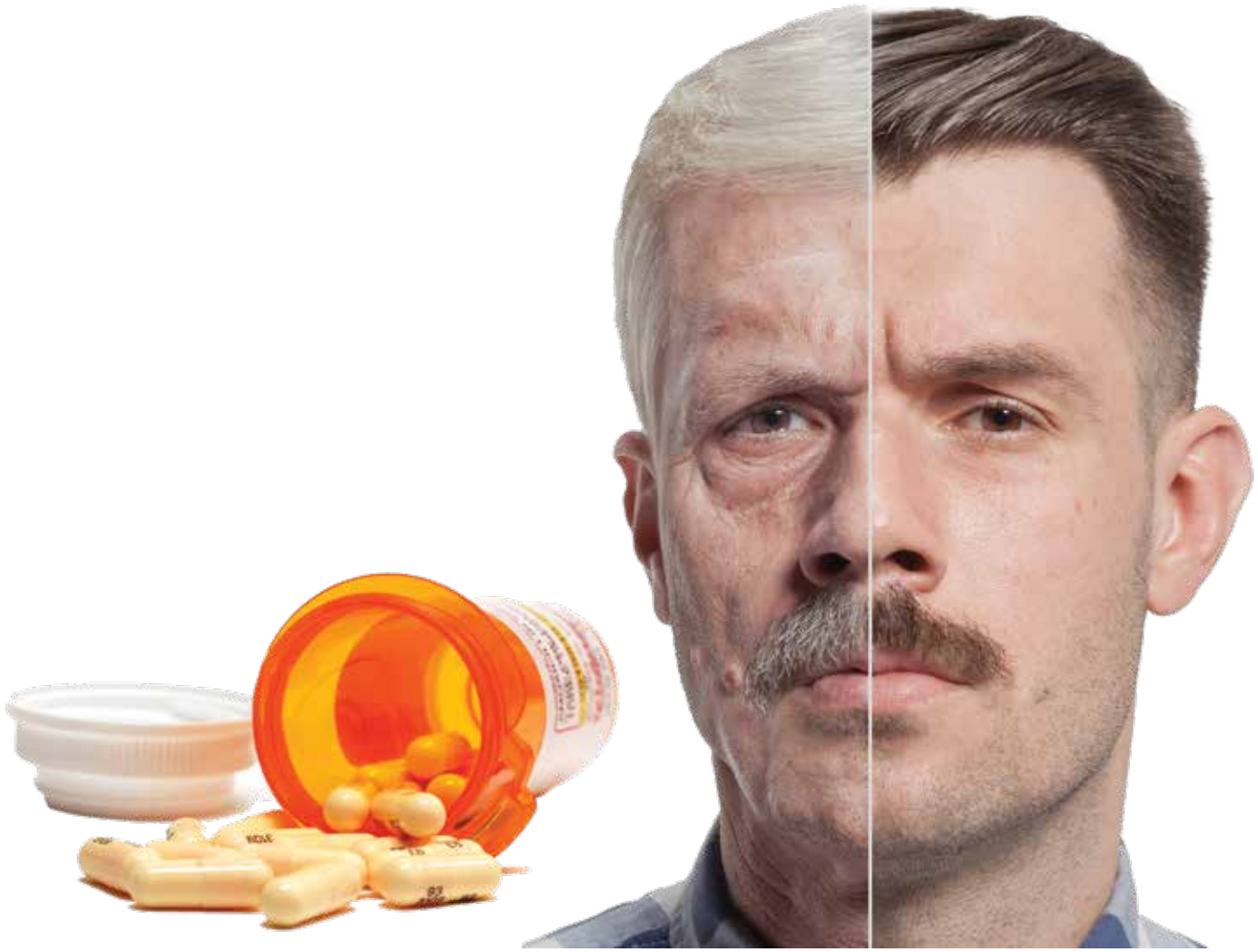


Hargreaves I, et al. *Int J Mol Sci.* 2020;21(18):6695. doi:10.3390/ijms21186695
Wipf P, et al. *J Huntingtons Dis.* 2022;11(1):3-15. doi:10.3233/JHD-210510

The research information presented is not a claim regarding any product or its ingredients.

Reasons For Increased CoQ10 Demand

- Chronic, degenerative diseases
- Impaired biosynthesis
- Certain medications
- Increased usage by the body
  - » High physical/muscular activity
  - » Stress (mental, physical)
- Environmental exposures
- Increased oxidative stress
- Aging
  - » Production at age 65 is about 50% of that at age 25.



Gutierrez-Mariscal FM, et al. *Antioxidants* (Basel). 2021;10(6):906. doi:10.3390/antiox10060906
Hargreaves I, et al. *Int J Mol Sci.* 2020;21(18):6695. doi:10.3390/ijms21186695
Manzar H, et al. *Int J Mol Sci.* 2020;21(23):9299. doi:10.3390/ijms21239299

The research information presented is not a claim regarding any product or its ingredients.

CoQ10 Is Critical for Cardiovascular Health

- Needed for mitochondrial ETC function in cells of heart and cardiovascular system
- Antioxidant effect in the endothelial and vascular system, which influence cardiovascular health
- Supports improvement of lipid profiles
- Improves vascular smooth muscle activity, counteracting vasoconstriction and lowering blood pressure

Review

Coenzyme Q10 and Cardiovascular Diseases

Gutierrez-Mariscal FM, et al. *Antioxidants* (Basel). 2021;10(6):906. doi:10.3390/antiox10060906.

The research information presented is not a claim regarding any product or its ingredients.

CoQ10: Systematic Review of 14 Studies

In this study...

- 1067 participants: predominantly older adult males with heart failure and ischemic heart disease; patients scheduled for cardiac surgery
- CoQ10 supplementation, 60–300 mg/d:
  - » Increased serum CoQ10 concentrations
  - » Led to fewer major adverse cardiovascular events
  - » Had quantifiable effects on inflammatory markers in patients with ischemic heart disease
  - » Improved myocardial hemodynamics before cardiac surgery
  - » Improved functional capacity

Systematic Review

Coenzyme Q10 as Adjunctive Therapy for Cardiovascular Disease and Hypertension: A Systematic Review

Sue-Ling CB, et al. *J Nutr.* 2022 Jul 1;152(7):1666-74.

The research information presented is not a claim regarding any product or its ingredients.

Pyrroloquinoline Quinone (PQQ): Emerging as a "Longevity Vitamin"

- Vitamin-like compound and enzyme cofactor
- Enhances **mitochondrial biogenesis**
- Has antioxidant and anti-inflammatory properties
  - » Helps protects nerves from the degradation caused by neurotoxins
- May lower the risk of disease during aging
- The absence of PQQ from nutrient sources produces "broad abnormalities."

Review

Pyrroloquinoline-Quinone is More Than an Antioxidant: A Vitamine-Like Accessory Factor Important in Health and Disease Prevention

Jonscher KR, et al. *Biomolecules*. 2021;11(10):1441. doi:10.3390/biom11101441.

The research information presented is not a claim regarding any product or its ingredients.

PQQ Improved Brain Function in Adults

In this study…

- Double-blind, placebo-controlled trial
- 20 mg/d of PQQ for 12 weeks in 62 young and older adults
- After 8 weeks, adults aged 20–40 years had improved cognitive flexibility, processing speed, and execution speed.
- After 12 weeks, older adults (41–65 years) showed improvements in complex and verbal memory.

Human Study

Pyrroloquinoline Quinone Disodium Salt Improves Brain Function in Both Younger and Older Adults

Tamakoshi M, et al. *Food Funct.* 2023 Mar 6;14(5):2496-2501. doi:10.1039/d2fo01515c.

The research information presented is not a claim regarding any product or its ingredients.

PQQ Supported Cognitive Functions in Elderly

In this study…

- Randomized, double-blind, placebo-controlled, parallel-group study
- 20 mg/d of PQQ for 12 weeks in 41 elderly
- PQQ increased cerebral blood flow in the prefrontal cortex.
- Administration of various cognitive tests (Stroop, visual-spatial, etc.) indicated that PQQ can prevent reduction of brain function in aged persons, especially in attention and working memory.

Human Study

Effect of the Antioxidant Supplement Pyrroloquinoline Quinone Disodium Salt (BioPQQ™) on Cognitive Functions

Itoh Y, et al. *Adv Exp Med Biol.* 2016;876:319-325. doi:10.1007/978-1-4939-3023-4_40.

The research information presented is not a claim regarding any product or its ingredients.

PQQ Increased Mitochondrial Biogenesis

In this study…

- 20 mg/d PQQ or placebo in 23 men for six weeks
- PQQ group showed a significant increase in an important biomarker (PGC-1α) for mitochondrial biogenesis, after six weeks of endurance training.

Human Study

Effects of Pyrroloquinoline Quinone (PQQ) Supplementation on Aerobic Exercise Performance and Indices of Mitochondrial Biogenesis in Untrained Men

Hwang, PS., et al. *J Am Coll Nutr.* 2020;39(6): 547-556. doi:10.1080/07315724.2019.1705203.

The research information presented is not a claim regarding any product or its ingredients.

PQQ Improved Cholesterol

In this study…

- Randomized, double-blind, placebo-controlled study
- 20 mg/d of PQQ for 12 weeks in 29 healthy adult men
- PQQ caused a marginally significant decrease in the mean LDL-chol (from 136.1 to 127.0 mg/dL) by 12 weeks.
- In a stratification analysis of the high LDL-chol (≥140mg/dL) subgroup, **mean LDL-chol levels decreased significantly from the baseline** in the PQQ group.

Human Study

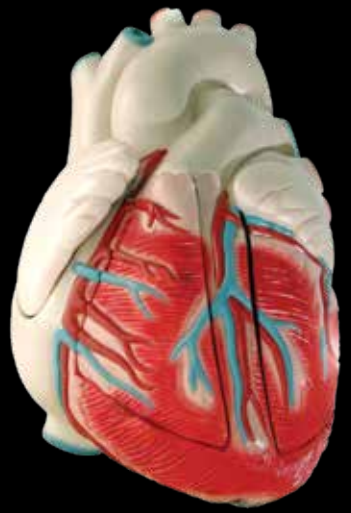
Effects of Pyrroloquinoline Quinone Salt Intake on the Serum Cholesterol Levels of Healthy Japanese Adults

Nakano M, et al. *J Nutr Sci Vitaminol* (Tokyo). 2015;61(3):233-40. doi: 10.3177/jnsv.61.233.

The research information presented is not a claim regarding any product or its ingredients.

Gain a Clinical Edge with GG Plus PQQ and CoQ10

Cardiovascular



Mitochondria

Brain

Musculoskeletal, Energy, Bone, etc.

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Ubiquinol vs. Ubiquinone

- “Several clinical studies have reported no significant difference in the relative bioavailability of ubiquinone and ubiquinol supplements.”
- “In summary, on the basis of the evidence reviewed above, the concept of the superior bioavailability of supplemental ubiquinol compared to ubiquinone would appear to be mistaken.”
- “This concept, widely disseminated on the Internet, seems in part to have originated from an inappropriate comparison between bioavailability data from studies by Shults et al. in 1998 [24] and Hosoe et al. in 2007 [25]. The older study involved the use of a dry powdered crystalline form of ubiquinone, which is poorly absorbed but was the only formulation available at the time.”

Human Study

Bioavailability of Coenzyme Q_{10}: An Overview of the Absorption Process and Subsequent Metabolism

Mantle D, et al. *Antioxidants* (Basel). 2020;9(5):386. doi:10.3390/antiox9050386.

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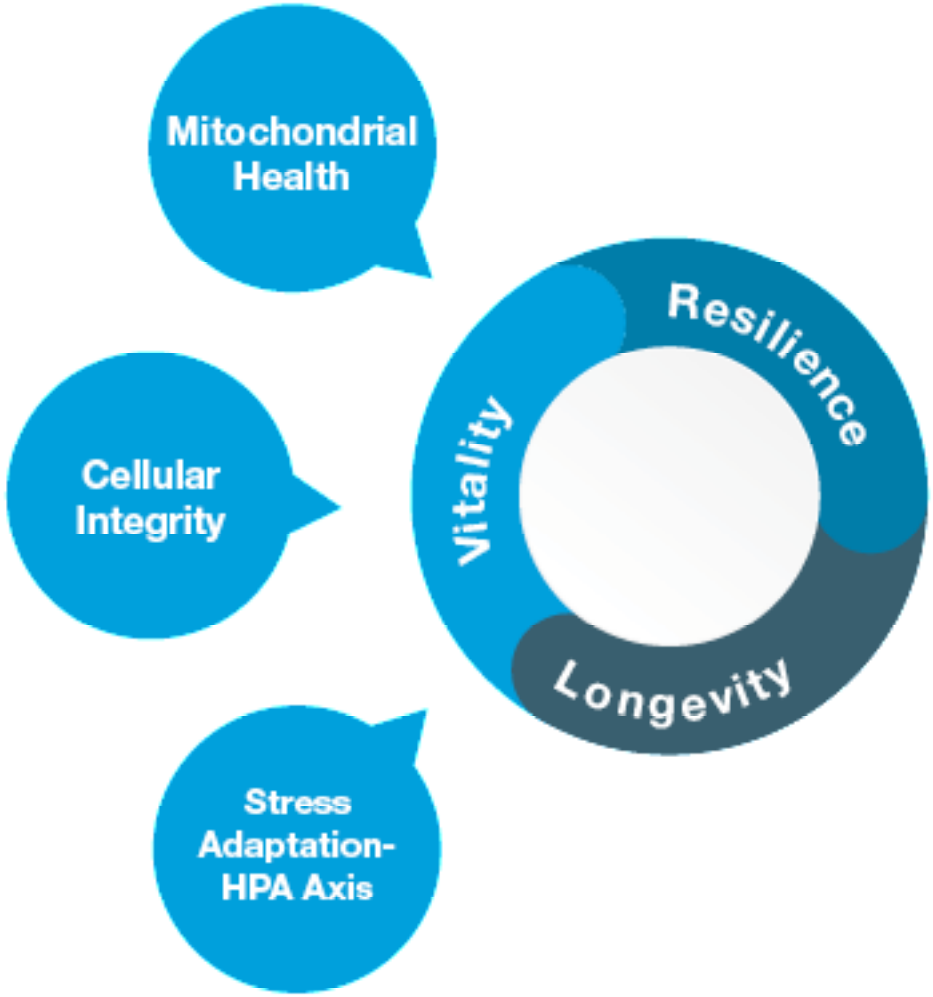
Utilize Today's Science in a Results-Based Vitality Strategy

Supporting 3 Key Pillars of Vitality



Scan to learn more.

To experience the difference, join us at our booth.