



COMPOUNDING PHARMACY

OWNER SUMMIT

MARCH 19-21, 2026 | AUSTIN, TEXAS

From Dispensing to Supporting: The Pharmacist's Role in Restoring Nutrients, Reducing Side Effects, and Driving Revenue Through Nutrient-Depletion and Cofactor Protocols

Dr. Cheryl Burdette

Protecting The Pharmacy With Practitioner Only Products

In today's omni-channel marketplace, patients can easily bypass the pharmacy.

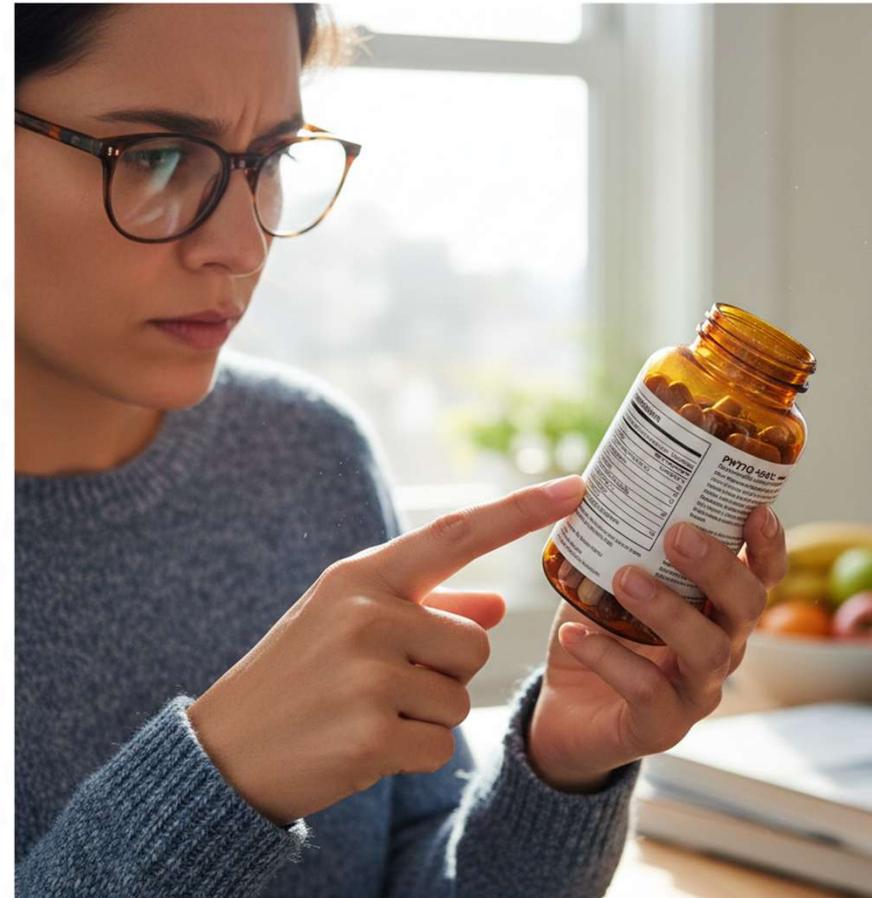
A simple test:

- Take a photo of a Supplement Facts panel
- Run it through Google Lens
- Instantly locate identical or similar products online

Even private-labeled supplements often trace back to:

- Amazon
- Fullscript
- Big-box retailers
- Direct-to-consumer websites

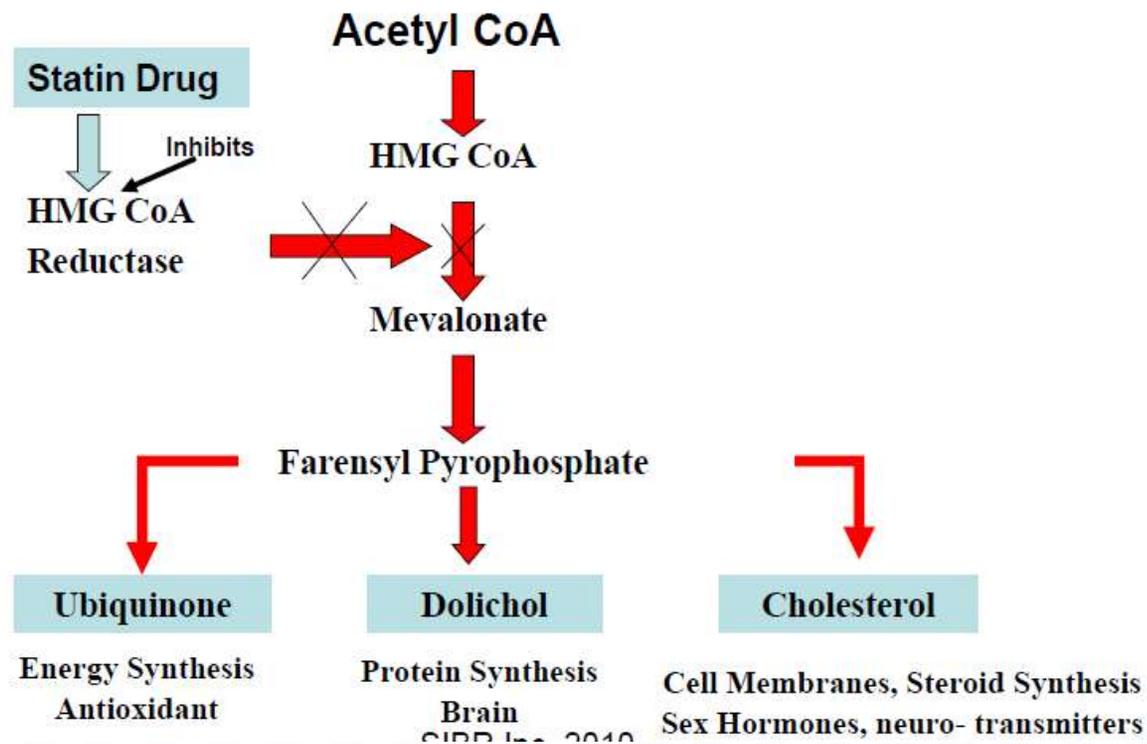
When products are searchable, they are shoppable.



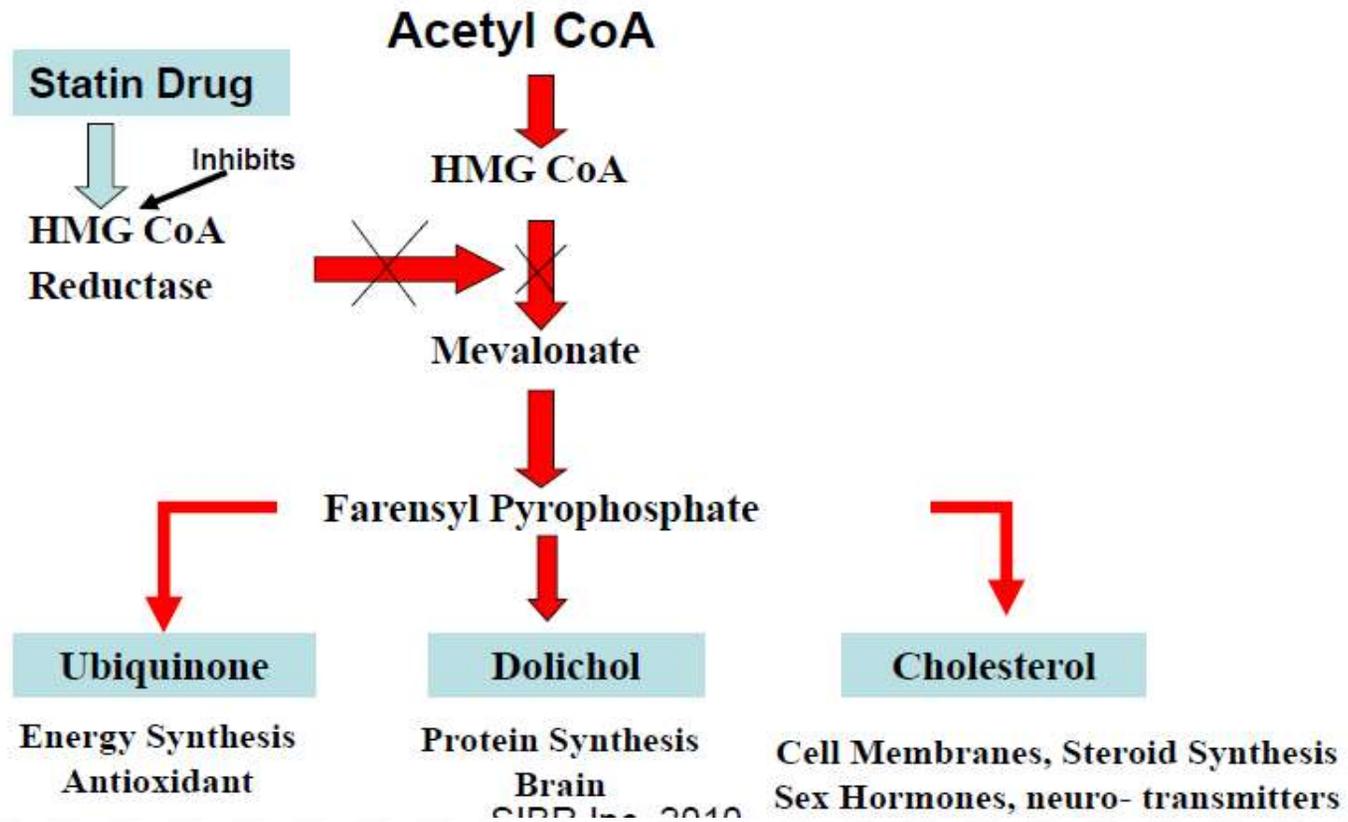
Most Common Drugs Used In The US

- **Atorvastatin (Lipitor):** For high cholesterol and cardiovascular disease prevention.
- **Metformin (Glucophage):** For Type 2 diabetes management.
- **Levothyroxine (Synthroid):** For thyroid hormone replacement (hypothyroidism).
- **Lisinopril (Prinivil, Zestril):** For high blood pressure and heart failure.
- **Amlodipine (Norvasc):** For high blood pressure and angina.
- **Metoprolol (Lopressor):** For hypertension and heart issues.
- **Albuterol (Ventolin):** For asthma and breathing problems.
- **Omeprazole (Prilosec):** For acid reflux and gastrointestinal issues.
- **Losartan (Cozaar):** For hypertension.
- **Gabapentin (Neurontin):** For nerve pain and seizures.

Biosynthetic Pathway to Cholesterol, Ubiquinone, and Dolichol



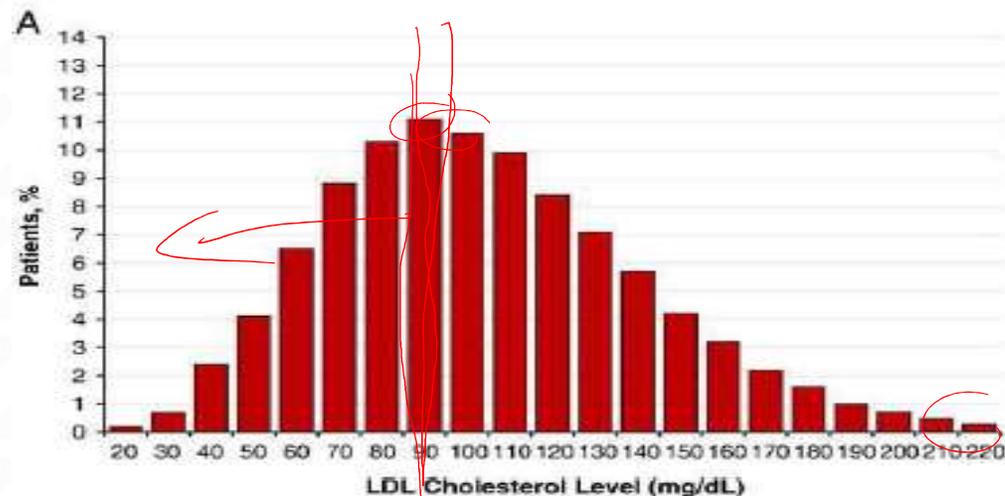
Synthesis of CoQ10



Nutrition 101, The Statin Controversy

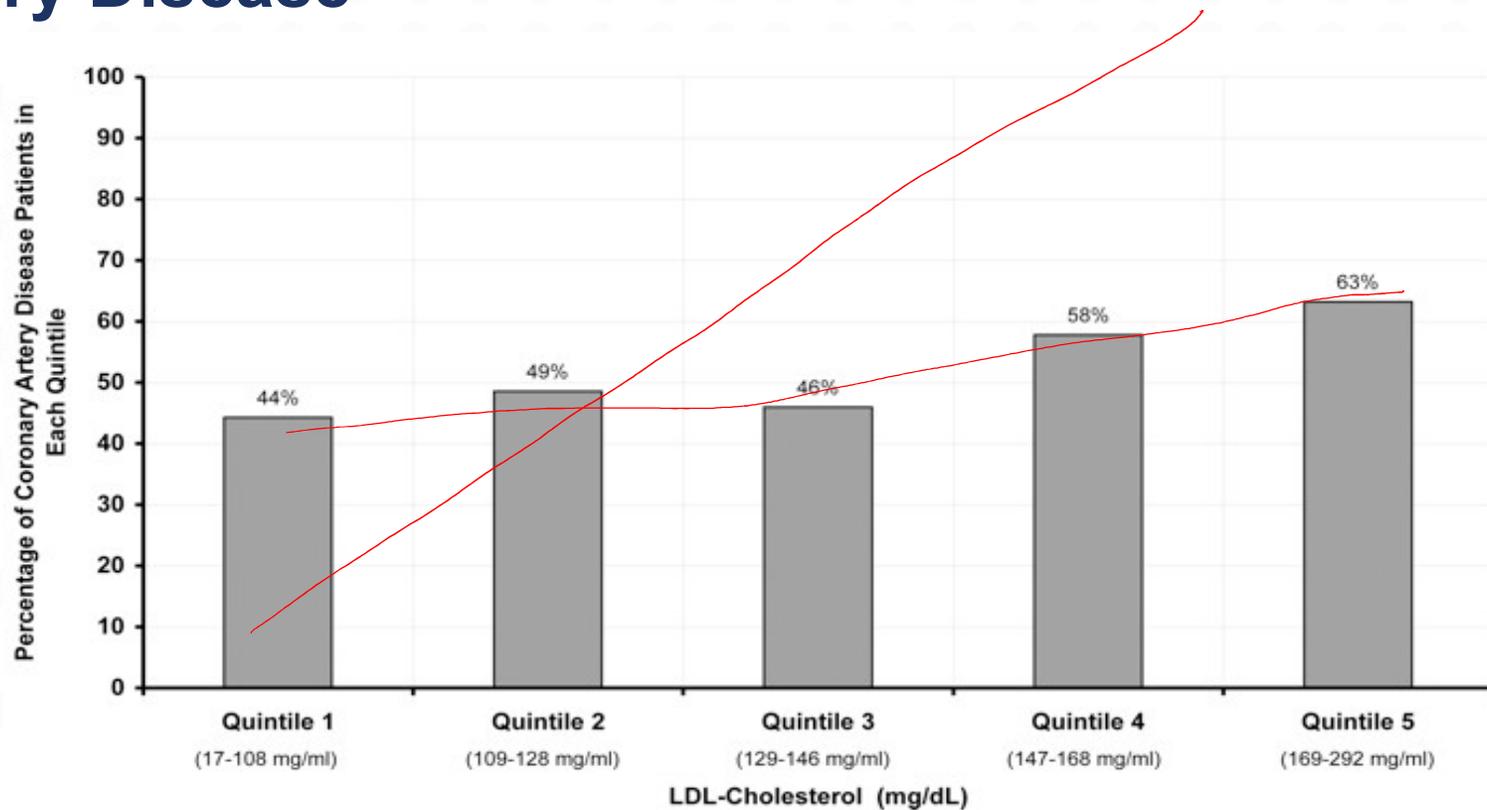
- Statins suppress HMG-CoA Reductase
- This not only blocks production of cholesterol, but production of CoQ10 as well
- While lowering lipids, there is an increase in CHF as well as increase risk of liver cancer
- Are lipids even the right end point?

Coronary Artery Disease (CAD) is Often Associated with *Normal Levels* of LDL-Cholesterol

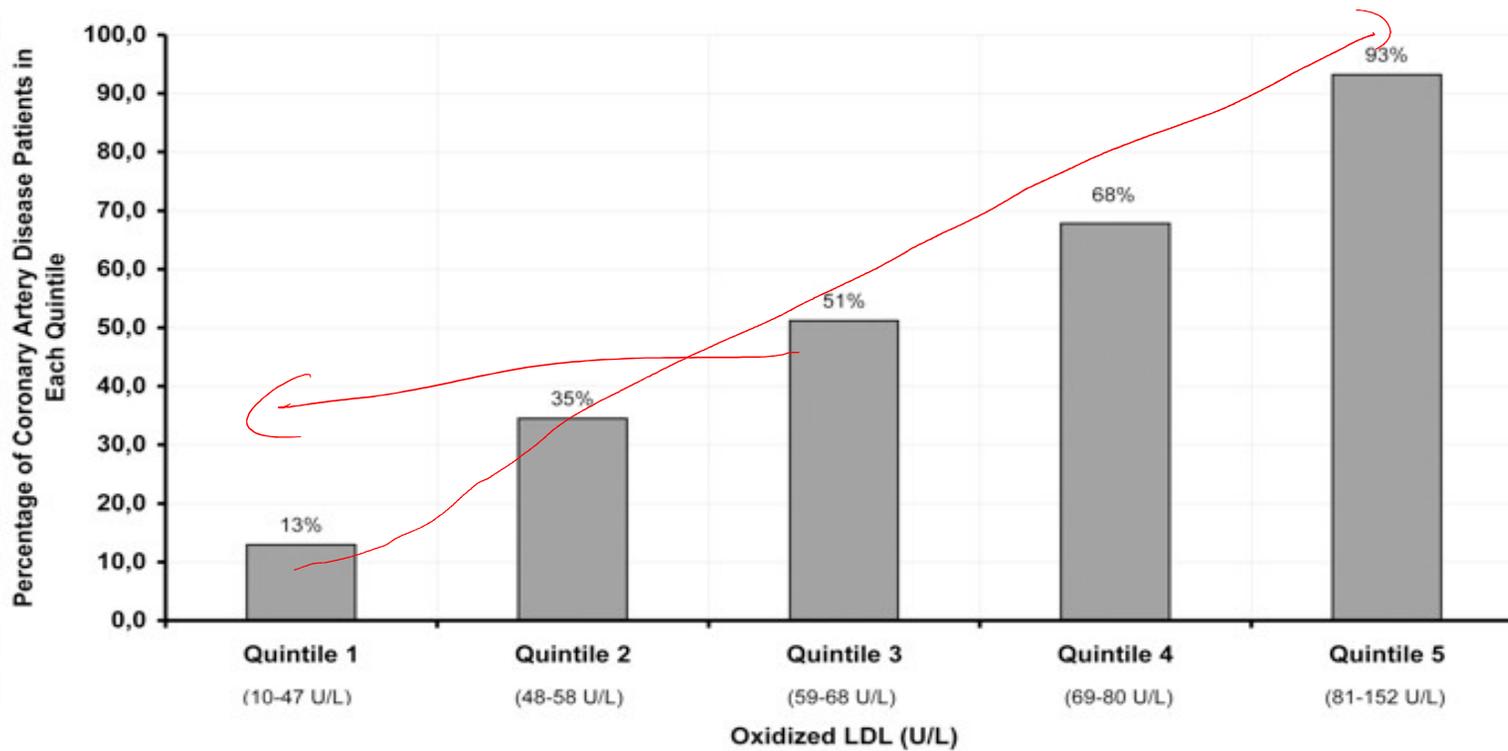


- Data from *Get with the Guidelines Study* (Sponsored by AHA, Dallas, TX)
- Lipid data within 24 hour of admission from patients hospitalized with CAD
 - n = 136,905
 - 50% had admission LDL-Chol <100 mg/dl
 - 17.6% had admission LDL-Chol <70 mg/dl
 - 23% had admission LDL-Chol > 130 mg/dl
 - Conclusion: **Other risk factors must exist**

Relationship Between LDL-Cholesterol and Coronary Artery Disease



Relationship Between Oxidized LDL and Coronary Artery Disease

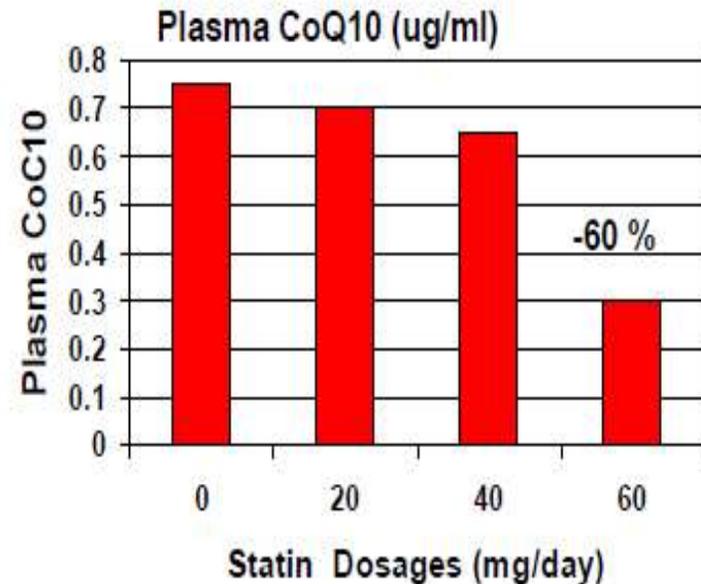
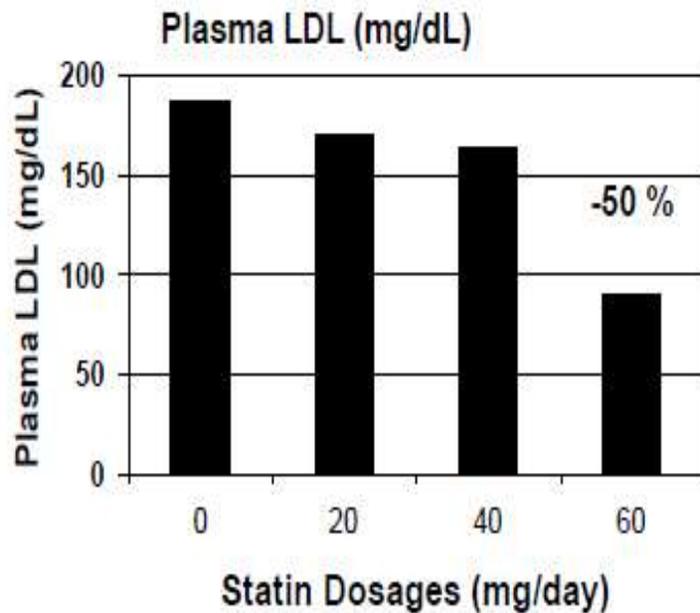


Testing Starting Point

- oxLDL as a launching point
- More extensive cardiac work up in those with significant history or family history

Hong CG, Florida E, Li H, Parel PM, Mehta NN, Sorokin AV. Oxidized low-density lipoprotein associates with cardiovascular disease by a vicious cycle of atherosclerosis and inflammation: A systematic review and meta-analysis. *Front Cardiovasc Med.* 2023 Jan 16;9:1023651. doi: 10.3389/fcvm.2022.1023651. PMID: 36727024; PMCID: PMC9885196.

Statin Drugs and LDL and CoQ10



Statin Drug Side Effects

- Myalgia
- Low Energy
- Muscle Cramps
- Muscle Fatigue
- Muscle Wasting
- Heart Failure
- Cataracts
- Dementia
- Myopathy
- Neuropathy
- Reduced Immunity
- Cancers

CoQ10 Improvement of Statin Drug Adversities

	Plasma CoQ10 (ug/ml)	
	2.5 ug/ml	5.0 ug/ml
• Myalgia	35 %	80 %
• Fatigue	30	75
• Myopathy	25	80
• Muscle Cramps	35	85
• Dementia	20	60
• Reduced Immunity	38	79
• Exercise Tolerance	28	85

SUMMARY

- Higher bloods CoQ10 levels are more clinically effective than low blood levels
- CoQ10 reduces the severity of Congestive Heart Failure
- CoQ10 reduces cardiac arrhythmia's
- CoQ10 protects the myocardium after a heart attack
- CoQ10 will reduce the adverse side effects of Statin drugs

Berberine

- Amplifies exercise through AMPKinase
- GLP-1
- Akkermansia
- Improving lipids which shifts postmenopause (estrogen and HDL)
- Improving glucose tolerance

Berberine preserves eNOS

- In both cultured endothelial cells and blood vessels isolated from rat aorta, berberine concentration dependently enhanced phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser1177 and promoted the association of eNOS with heat shock protein 90 (HSP90), leading to an increased production of nitric oxide.
- Berberine attenuated high glucose-induced generation of reactive oxygen species, cellular apoptosis, nuclear factor-kappaB activation, and expression of adhesion molecules, thus suppressing monocyte attachment to endothelial cells.
- Berberine elicited endothelium-dependent vasodilatations and alleviated high glucose-mediated endothelial dysfunction. All these beneficial effects of berberine on the endothelium were abolished by either pharmacological inhibition of adenosine monophosphate-activated protein kinase (AMPK) or adenovirus-mediated overexpression of a dominant negative version of AMPK.
- Berberine protects against endothelial injury and enhances the endothelium-dependent vasodilatation, which is mediated in part through activation of the AMPK signalling cascade. Berberine or its derivatives may be useful for the treatment and/or prevention of endothelial dysfunction associated with diabetes and cardiovascular disease.

Berberine prevents hyperglycemia-induced endothelial injury and enhances vasodilatation via adenosine monophosphate-activated protein kinase and endothelial nitric oxide synthase. Cardiovasc Res. 2009 Jun 1;82(3):484-9

Berberine decreases attachment of oxLDL, preserving oxygen diffusion to tissue

- A spectrum of factors lead to endothelial dysfunction, which results in the expression of endothelial-leukocyte adhesion molecules [e.g., vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and endothelial-leukocyte adhesion molecule-1], secreted chemokines [e.g., monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8)] and other effector proteins ([Gimbrone and Garcia-Cardena, 2016](#)).
- BBR was reported to dramatically decrease oxLDL-stimulated adhesion of monocytes to human umbilical vein endothelial cells (HUVECs) by suppressing the expression of VCAM-1 and ICAM-1 ([Huang et al., 2013](#)).

Berberine and Its Effects On Nitric Oxide Production

- Neuronal NOS, eNOS, and inducible NOS are related to the production of NO. Neuronal NOS and eNOS function as anti-atherosclerosis factors, whereas inducible NOS is likely to play a pro-atherosclerosis role ([Li et al., 2014](#)). BBR showed atheroprotective effects by affecting the NO signaling pathway.
- It was demonstrated that phosphorylation of eNOS at Ser1177 was enhanced by BBR dose-dependently, leading to an increased eNOS protein expression and NO production ([Wang et al., 2009b](#)). [Zhang et al. \(2013\)](#) reported that BBR considerably upregulated eNOS expression and NO levels in palmitate-treated HUVECs and ameliorated endothelial dysfunction.
- Bu-Shen-Ning-Xin Decoction, a Chinese herbal compound containing BBR, upregulated NO synthesis via estrogen receptor β pathway. Subsequently, NO suppressed apoptosis and NF- κ B activity in endothelial cells and inhibited atherosclerosis progression ([Wang et al., 2013](#)).
- Elevated circulating endothelial microparticles (EMPs) are tightly linked to endothelial dysfunction. The diminished eNOS protein expression mediated by EMPs was markedly inhibited by BBR in HUVECs.
- Furthermore, BBR-induced decline in circulating CD31⁺/CD42⁻ microparticles (necessary for platelet/endothelial interaction) contributed to the improvement of endothelial function in healthy subjects ([Wang et al., 2009a](#); [Cheng et al., 2013](#)).

Metformin and berberine, two versatile drugs in treatment of common metabolic diseases.

- In a three months trial, 36 patients with T2DM were randomly assigned with berberine or metformin. It was found that hypoglycemic effect of berberine is comparable to that of metformin. The level of hemoglobin A1c (HbA1c), fasting and postprandial glucose decreased by 7.5%, 6.9% and 11.1% respectively at the end of the trial. Similar findings were reported in a clinical study of Zhang et al [28].
- A meta-analysis of 21 clinical trials revealed that berberine has therapeutic effects on T2DM, hyperlipidemia and hypertension, comparable to other therapeutic regimes [29].
- Studies have indicated that, similarly to metformin, berberine executes its functions by regulating a variety of effectors including AMPK, MAPK, PKC, PPAR α , PPAR γ [28, 30].
- To be noteworthy, via activation of AMPK, berberine can stimulate glucose uptake in muscle, liver and adipose, and inhibit gluconeogenesis in liver by downregulation of gluconeogenic enzymes (phosphoenolpyruvate carboxyl kinase and glucose-6-phosphatase) [31].

Oncotarget. 2017 Sep 11;9(11):10135-10146

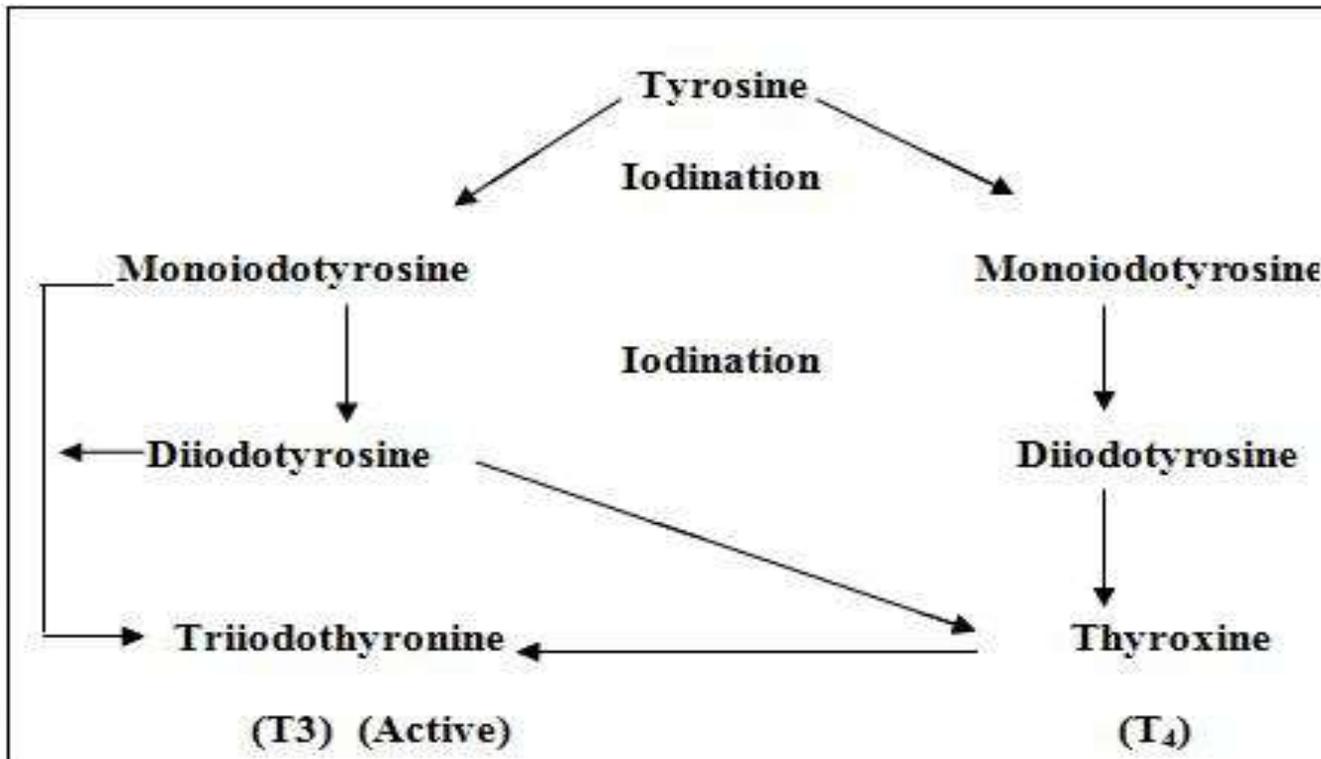
Levothyroxine, right direction but...

- Its just T4, and T3 is 10x more active – and sadly not usually measured
- But people will just convert, right?
- Calcium depletion?

Metformin Drug Depletions

- Decreases B vitamins – decrease B6 increases xanthanuric acid which creates resistance in the insulin receptor
- Dumps bile in the gut, so can be irritating
- B12
- CoQ10

Thyroid pathway



Complete Thyroid Profile

- TSH <2.5 to even <1.0 =
One of the most
underdiagnosed treatments
out there
- Free and total T3
- Free and total T4
- Reverse T3
- Thyroglobulin Antibodies
- TPO Antibodies

Symptoms of Low Thyroid

Fatigue

Weight Gain

Cold Hands and Feet

Changes in Hair and Nails

Hormonal Imbalance: PCOS, infertility

Constipation

Histaminosis

Metabolic Shut Down

Headaches

Often taxed by chronic infection

Decreased Conversion

- Nutrient Deficiency: Zinc and Selenium
- Cadmium Toxicity (Chelators)
- Liver Congestion (ALA, Selenium, NAC, Milk Thistle)
- Cortisol (Ashwaganda, Theanine)
- Oxidative Stress (Nrf2 Activation)

• T4  T3

The Role of Glutathione Peroxidase

T4  T3



Glutathione Peroxidase
Markers of Oxidative Stress: 8-OHdG, F2-Isoprostane
Glutathione Level

Hypertension



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Half the List of Top Drugs Are For HTN

- **Lisinopril (Prinivil, Zestril):** For high blood pressure and heart failure, Zinc depletion.
- **Amlodipine (Norvasc):** For high blood pressure and angina, CoQ 10 depletion
- **Metoprolol (Lopressor):** For hypertension and heart issues, CoQ10 and Melatonin!
- **Losartan (Cozaar):** For hypertension, increased depletion of electrolytes and Zinc

Jin K. A Microcirculatory Theory of Aging. Aging Dis. 2019 Jun 1;10(3):676-683.

- Aging is the progressive decline of physiological functions necessary for survival and reproduction. In gaining a better understanding of the inevitable aging process, the hope is to preserve, promote, or delay healthy aging through the treatment of common age-associated diseases.
- Although there are theories that try to explain the aging process, none of them seem to fully satisfy.
- The main functions of the microcirculation are the delivery of oxygen and nutrients and the removal of CO₂, metabolic debris, and toxins. The microcirculatory impairment or dysfunction over time will result in the accumulation of toxic products and CO₂ and loss of nutrition supplementation and O₂ in corresponding tissue systems or internal organs, which eventually affect normal tissue and organ functions, leading to aging. T
- Therefore, I propose a microcirculatory theory of aging: aging is the process of continuous impairment of microcirculation in the body.

MicroCirculatory Conditions, The Importance of Capillaries

Diabetes

Erectile Dysfunction

Cardiovascular Disease

Dementia

Cancer and increased metastasis

Chronic Conditions & Fatigue

Covid, Organ Failure

Hypertension

Age Related Capillary Loss

- There is a substantial number of studies presenting strong evidence of decreased vessel density with age, indicating an age-associated failure of vascular recovery in organs such as the brain in animals and humans alike.
- In studies involving aged rodents: healthy senescent rats (29 months) experienced a loss of about 40% of arteriolar density on the cortical surface compared with young adult rats (13 months) [18]. There was also 39% fewer arterioles penetrating the cortex and cortical surface [18-21].
- Arteriole-arteriole anastomoses and venules were also subject to similar decreases, indicating that aging can affect vessels found on the surface and even the deeper cortical layers of the brain.
- In the hippocampus of aged rats, there was a 20% decrease in capillary number, 3% decrease in capillary length, and 24% increase in intercapillary distance [22].

Nitric Oxide As A Longevity Molecule

- Aging is associated with a decline in physiological function and exercise performance. These effects are mediated, at least in part, by an age-related decrease in the bioavailability of nitric oxide (NO), a ubiquitous gasotransmitter and regulator of myriad physiological processes.
- The decrease in NO bioavailability with aging is especially apparent in sedentary individuals, whereas older, physically active individuals maintain higher levels of NO with advancing age.
- Strategies which enhance NO bioavailability (including nutritional supplementation) have been proposed as a potential means of reducing the age-related decrease in physiological function and enhancing exercise performance and may be of interest to a range of older individuals including those taking part in competitive sport.
- In this brief review we discuss the effects of aging on physiological function and endurance exercise performance, and the potential role of changes in NO bioavailability in these processes.

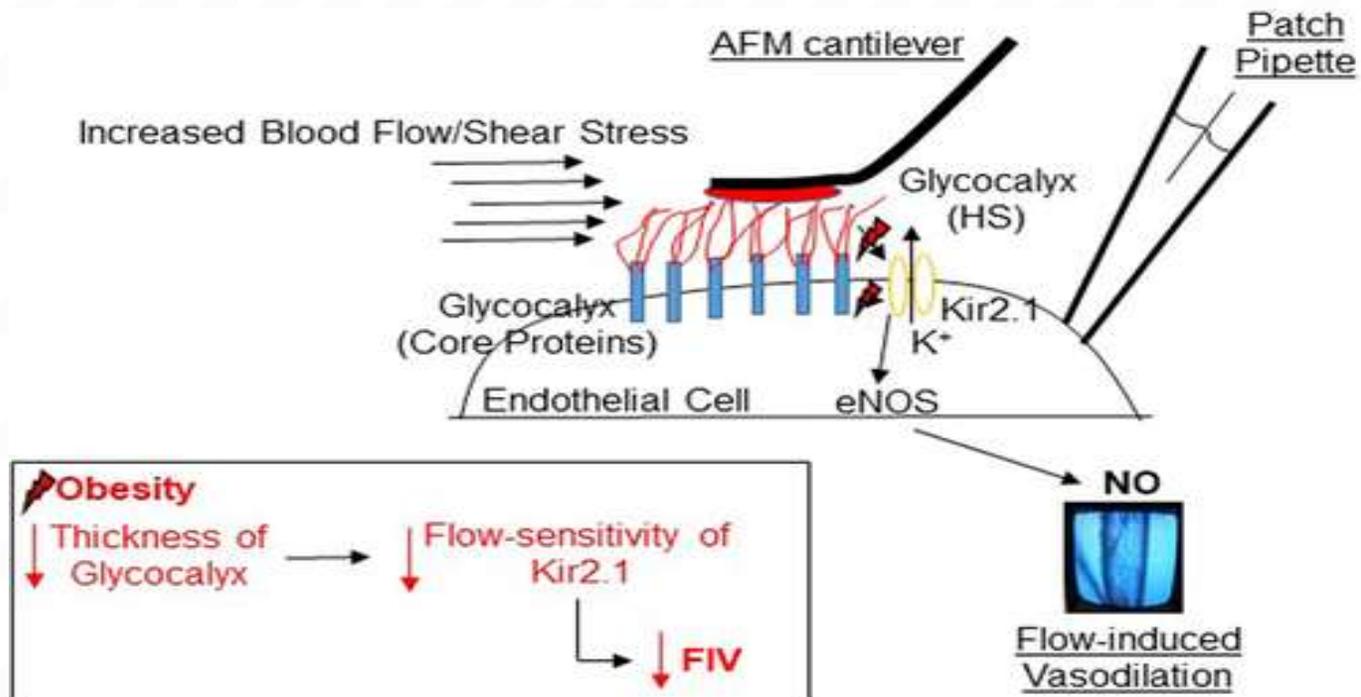
Nitric oxide, aging and aerobic exercise: Sedentary individuals to Master's athletes, Nitric Oxide, Volumes 125–126, 2022, Pages 31-39,

Dietary supplements for improving nitric-oxide synthesis. J Prev Med Hyg. 2022 Oct 17;63(2 Suppl 3):E239-E245.

- Nitric oxide (NO) is an essential component of the human body, involved in blood vessel dilation, stimulation of hormone release, signaling and regulation of neurotransmission. Nitric oxide is synthesized by nitric-oxide-synthase-dependent and -independent pathways. Nitric oxide supplementation improves cardiac health, enhances performance during exercise, reduces high blood pressure during pregnancy, reduces erectile dysfunction and improves healing processes and respiratory response.
- Nitric-oxide-associated benefits are mostly apparent in untrained or moderately trained individuals. L-arginine and L-citrulline supplementation contributes to nitric oxide levels because L-arginine is directly involved in NO synthesis, whereas L-citrulline acts as an L-arginine precursor that is further converted to NO by a reaction catalyzed by NO synthase.
- L-arginine supplements increase respiratory response and enhance performance during exercise, while L-citrulline with malate and other molecules increase working capacity. Various studies involving beetroot juice have reported a significant increase in plasma nitrite levels, regarded as markers of NO, after intake of beetroot juice.

Enzymes and Proteins of the Vascular Wall/Glycocalyx

- Endothelial nitric oxide synthase (endothelial NOS)
- Extracellular superoxide dismutase (SOD3)
- Angiotensin converting enzyme
- Antithrombin-III (decreases coagulation)
- Lipoprotein lipase (degrades LDL)
- Apolipoproteins (proteins that bind lipids)
- Growth factors
- Chemokines



Ibra S. Fancher. Arteriosclerosis, Thrombosis, and Vascular Biology. Impairment of Flow-Sensitive Inwardly Rectifying K⁺ Channels via Disruption of Glycocalyx Mediates Obesity-Induced Endothelial Dysfunction, Volume: 40, Issue: 9, Pages: e240-e255, DOI: (10.1161/ATVBAHA.120.314935)

Ebong, Eno Essien, David C. Spray, and John M. Tarbell. Glycocalyx Core Proteins Selectively Mediate Endothelial NOS activation and Cell Alignment in Response to Shear Stress. The FASEB Journal 27.1_MeetingAbstracts (2013): 379-3

Magnesium and Smooth Muscle

JCI The Journal of Clinical Investigation

Magnesium relaxes arterial smooth muscle by decreasing intracellular Ca^{2+} without changing intracellular Mg^{2+} .

E K D'Angelo, ... , H A Singer, C M Rembold

J Clin Invest. 1992;**89**(6):1988-1994. <https://doi.org/10.1172/JCI115807>.

Research Article

Elevations in extracellular $[\text{Mg}^{2+}]$ ($[\text{Mg}^{2+}]_o$) relax vascular smooth muscle. We tested the hypothesis that elevated $[\text{Mg}^{2+}]_o$ induces relaxation through reductions in myoplasmic $[\text{Ca}^{2+}]$ and myosin light chain phosphorylation without changing intracellular $[\text{Mg}^{2+}]$ ($[\text{Mg}^{2+}]_i$). Histamine stimulation of endothelium-free swine carotid medial tissues was associated with increases in both Fura 2- and aequorin-estimated myoplasmic $[\text{Ca}^{2+}]$, myosin phosphorylation, and force. Elevated $[\text{Mg}^{2+}]_o$ decreased myoplasmic $[\text{Ca}^{2+}]$ and force to near resting values. However, elevated $[\text{Mg}^{2+}]_o$ only transiently decreased myosin phosphorylation values: sustained $[\text{Mg}^{2+}]_o$ -induced decreases in myoplasmic $[\text{Ca}^{2+}]$ and force were associated with inappropriately high myosin phosphorylation values. The elevated myosin phosphorylation during $[\text{Mg}^{2+}]_o$ -induced relaxation was entirely on serine 19, the Ca^{2+} /calmodulin-dependent myosin light chain kinase substrate. Myoplasmic $[\text{Mg}^{2+}]$ (estimated with Mag-Fura 2) did not significantly increase with elevated $[\text{Mg}^{2+}]_o$. These results are consistent with the hypothesis that increased $[\text{Mg}^{2+}]_o$ induces relaxation by decreasing myoplasmic $[\text{Ca}^{2+}]$ without changing $[\text{Mg}^{2+}]_i$. These data also demonstrate dissociation of myosin phosphorylation from myoplasmic $[\text{Ca}^{2+}]$ and force during Mg^{2+} -induced relaxation. This finding suggests the presence of a phosphorylation-independent (yet potentially Ca^{2+} -dependent) mechanism for regulation of force in vascular smooth muscle.

Clinical Relevance

- Magnesium – 250-750 mg, clinical reference range for Hypertension and other Cardiac issues (arrhythmia, status post MI, CHF)
- Relaxes smooth muscle that creates shear force
- Smooth muscle constricts secondary to Magnesium loss caused by inflammation, inflammation increased with any infection and leaky vessel

Magnesium!!!!

- Patients take the wrong type and not enough
- Forms from spirulina are a breakthrough in delivery
- Overcomes absorption issues while providing additional peptides with side benefit

Capros amla extract (*Phyllanthus emblica*)

Indian gooseberry



Taxon: *Phyllanthus emblica* L.

Heterotypic synonym:

Emblica officinalis Gaertn.

Mirobalanus embilica Burm.

Common names:

- **emblic** (Source: [World Econ Pl](#)) - English
- **emblic myrobalan** (Source: [Dict Rehm](#)) - English
- **Indian gooseberry** (Source: [Dict Rehm](#)) - English
- **groseillier de Ceylan** (Source: [Dict Rehm](#)) - French
- **myrobalan emblic** (Source: [Dict Rehm](#)) - French
- **amblabaum** (Source: [Dict Rehm](#)) - German
- **amla** (Source: [Econ Bot](#)) - India
- **aonla** (Source: [CultTropS](#)) - India
- **mirobalano** (Source: [Dict Rehm](#)) - Spanish
- **nelí** (Source: [Dict Rehm](#)) - Spanish
- **emblika** (Source: [Kulturvaxtdatabas](#)) - Swedish

History

Amla, or Indian gooseberry, is entwined with the culture and history of India. The bright yellow-green fruit comes from the *Phyllanthus emblica* tree. Its connection to people goes so far back that it's hard to know exactly when we began to find ways of using this plant. Ayurveda health system texts mention the Ayurvedic name of the fruit as amalaki. For Hindus, the tree is worshipped on the holy day Amalaka Ekadashi. Amla is revered by the Hindu religion because of the belief that the deity Vishnu lives within it, and part of this tree's wonder is found in the health value associated with it.



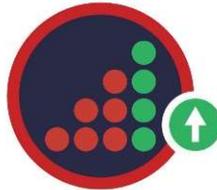
Capros[®] improves

Biomarker Optimization



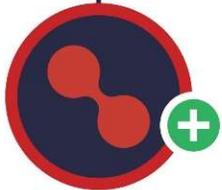
Modulates hsCRP
(biomarker of metabolic health)

Performance



Improves energy & endurance
by boosting nitric oxide

Heart Health



Supports healthy lipid
levels in the normal range



Improves blood flow
by supporting healthy
endothelial function

Endothelial Function



Boosts nitric oxide
and glutathione

Capros

Phyllanthus emblica Berry Extract

- Human clinical studies show that Capros improves endothelial function, lipid profile, and blood flow and increases production of nitric oxide.
- Capros showed significant effects in modulating markers of metabolic health.
- A clinical trial found that *P. emblica* mitigated the effects of stress-induced cardiovascular changes in healthy volunteers.
- VEGAN, certified organic
- HTN, Lipid Lowering, Modulates Oxidative Stress

Usharani 2017

- **Statistically significant results, 12 healthy volunteers**
 - Decrease in aortic augmentation pressure from 6.6 ± 2.15 to 4.6 ± 2.02 ($P < 0.01$)
 - Decrease in augmentation index (AIx) from 120.1 ± 12.80 to 116.2 ± 12.63 ($P < 0.05$)
- Data from a study evaluating the effect of Capros *Phyllanthus emblica* (amla) extract supplementation at 500 mg/day on mental stress-induced changes to cardiovascular parameters
- *“Acute mental stress results in temporary increase in arterial stiffness and wave stiffness. Standardized Emblica officinalis fruit extract decreased the mental stress-induced changes on aortic wave reflections in normal healthy subjects. These results suggest the beneficial effect of Emblica officinalis in mitigating the effects of stress, thereby reducing the risk of acute cardiovascular morbidity.”*

Usharani et al. *Int J Pharm Sci Rev Res.* 2017;8(10):4138-4146. doi:10.13040/IJPSR.0975-8232.8(10).4138-46.



Bergamot Extract

Citrus bergamia



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Bergamot Polyphenolic Fraction (BPF) Studied for Efficacy

- Hyperlipidemia
- Hyperglycemia
- Hypercholesterolemia
- Cardiovascular disease
- HDL/LDL imbalance
- Non-alcoholic fatty liver disease (NAFLD)
- Metabolic syndrome (MS/MetS) ...

*The brilliant
performance of BPF
on MS and
dyslipidemia is
astonishing ...”*

~ Janda et al

Janda et al. Molecular mechanisms of lipid-and glucose-lowering activities of bergamot flavonoids. *PharmaNutrition*. 2016 Oct;4(suppl):S8-S18.
doi:10.1016/j.phanu.2016.05.001.

Bergamot Polyphenolic Fraction

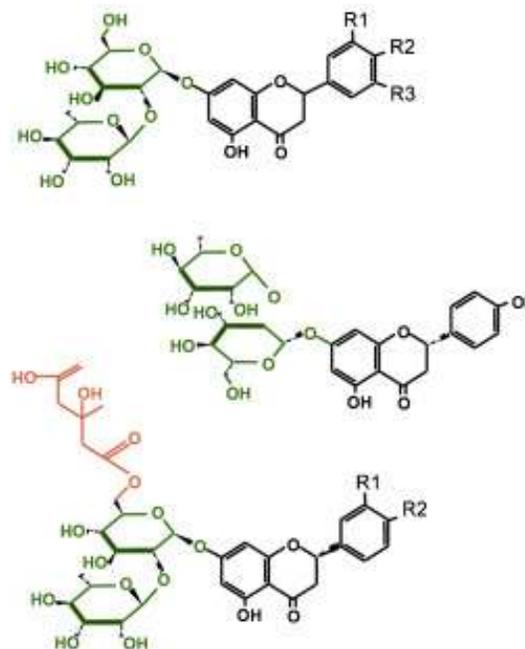
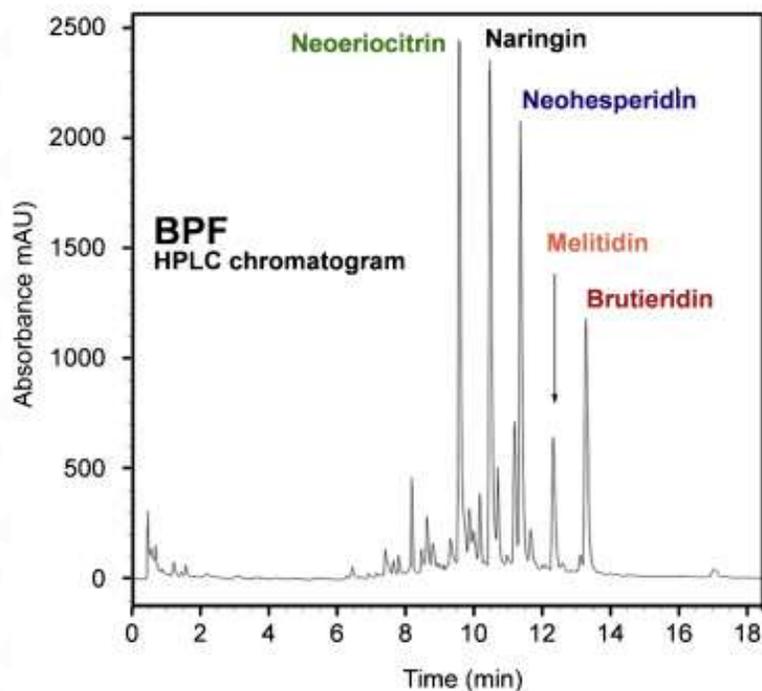
Mechanisms



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Flavonoids in the Bergamot Polyphenolic Fraction



Neohesperidin
 R1=OCH₃
 R2=H
 R3=OH

Neeriocitrin
 R1=OH
 R2=OH

Naringin

Brutieridin
 R1=OH
 R2=OCH₃

Melitidin
 R1=H
 R2=OH

Janda et al. Molecular mechanisms of lipid-and glucose-lowering activities of bergamot flavonoids. *PharmaNutrition*. 2016 Oct;4(suppl):S8-S18. doi:10.1016/j.phanu.2016.05.001.

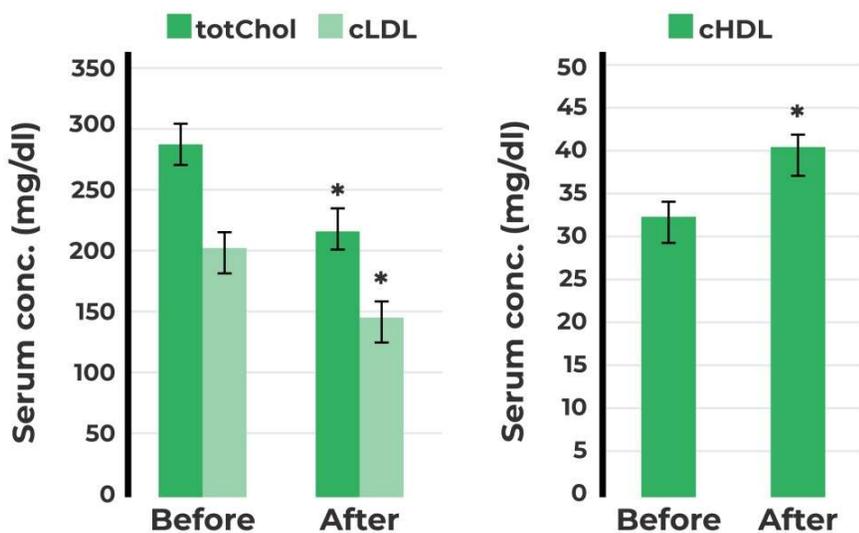
Flavonoids in the Bergamot Polyphenolic Fraction Influence Molecular Pathways

- Naringin and neohesperidin activate AMPK
- Brutieridin and melitidin are known HMG-CoA reductase inhibitors, exhibiting statin-like properties
- Neeriocitrin is theorized to inhibit phosphodiesterase 3B (PDE3B)

Janda et al. Molecular mechanisms of lipid-and glucose-lowering activities of bergamot flavonoids. *PharmaNutrition*. 2016 Oct;4(suppl):S8-S18.
doi:10.1016/j.phanu.2016.05.001.

BPF Clinical Outcome - Mollace 2011, 237 patients

Statin-Intolerant Cohort



Mollace et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. *Fitoterapia*. 2011 Apr;82(3):309-316. doi:10.1016/j.fitote.2010.10.014.

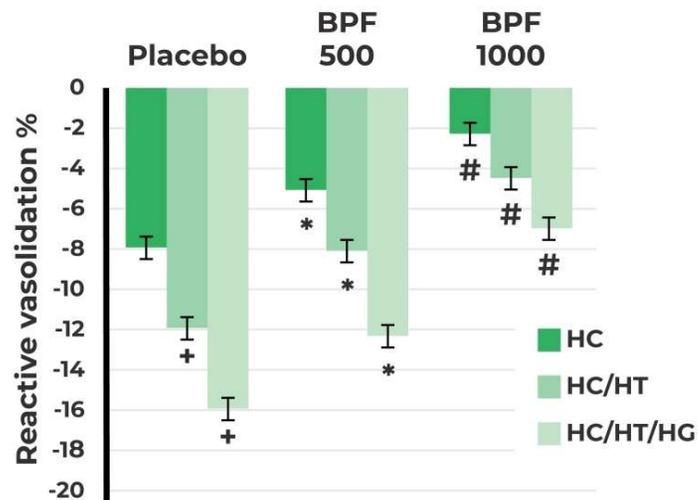
Patients with Statin Intolerance

- Reduced total cholesterol
- Reduced LDL cholesterol
- Raised HDL cholesterol

BPF Clinical Outcome - Mollace 2011

Vasodilation

Measured from brachial artery diameter during reactive hyperemia



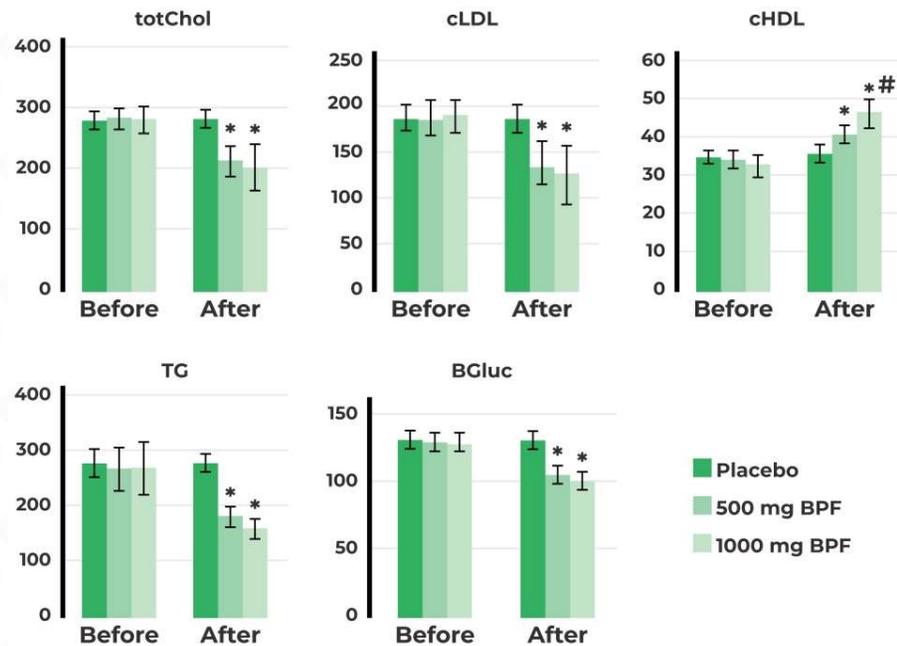
Effects of BPF at 500 or 1000 mg/day in Patients with:

- Hypercholesterolemia (HC)
- Hypertriglyceridemia (HT)
- Hyperglycemia (HG)
- Mixed hyperlipidemia (HC/HT)
- Associated hyperglycemia (HC/HT/HG)

Significant improvement in vasodilation response compared to placebo

Mollace et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. *Fitoterapia*. 2011 Apr;82(3):309-316. doi:10.1016/j.fitote.2010.10.014.

BPF Clinical Outcome - Mollace 2011



Patients with Metabolic Syndrome

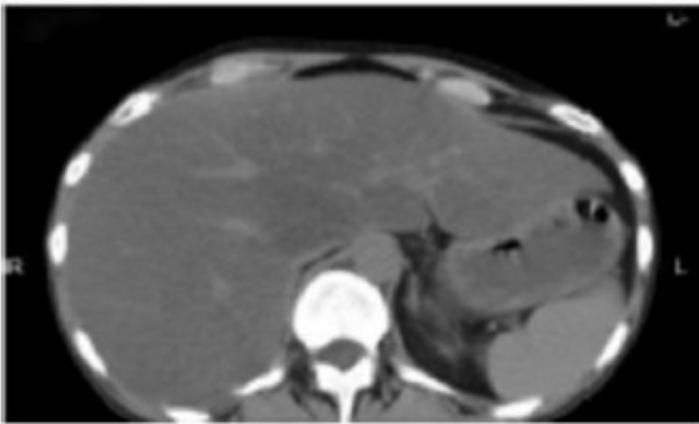
- Reduced total cholesterol
- Reduced LDL cholesterol
- Raised HDL cholesterol
- Reduced triglycerides
- Reduced blood glucose levels

Mollace et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. *Fitoterapia*. 2011 Apr;82(3):309-316. doi:10.1016/j.fitote.2010.10.014.

BPF Clinical Outcome – Gliozzi 2016

Bergamot polyphenols reduced accumulation of fat in the liver resulting in overall improvement of liver function

A



B



Image of liver section before (A) and after (B) BPF treatment

Nitric Oxide



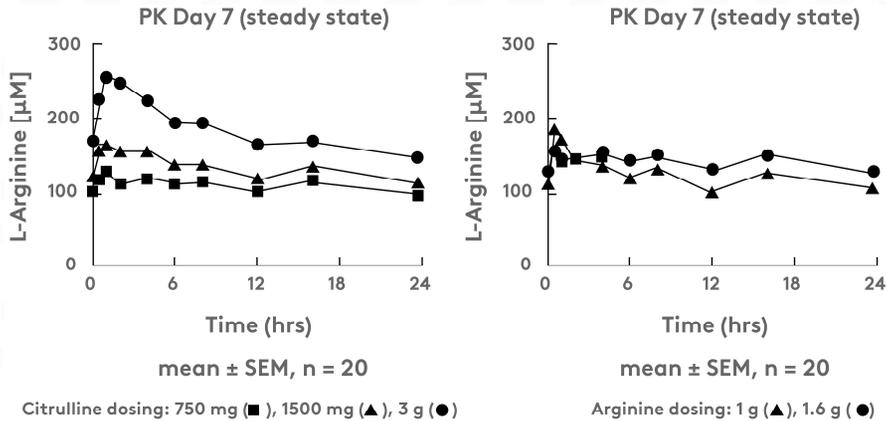
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L-CITRULLINE

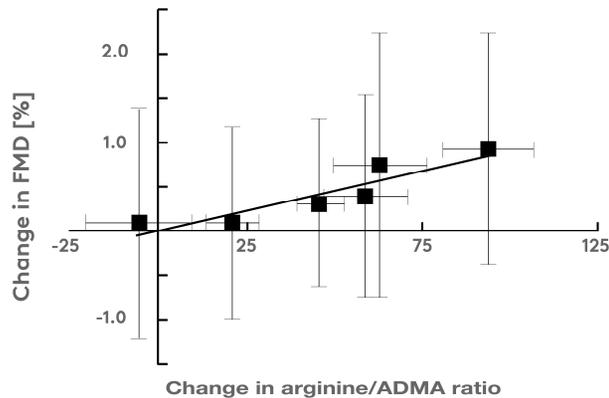


- A nonessential amino acid and precursor to L-arginine
- It readily permeates the intestinal wall and enters the bloodstream
- Foods rich in L-citrulline, such as watermelon, and dietary supplements may increase plasma arginine availability for NO synthesis

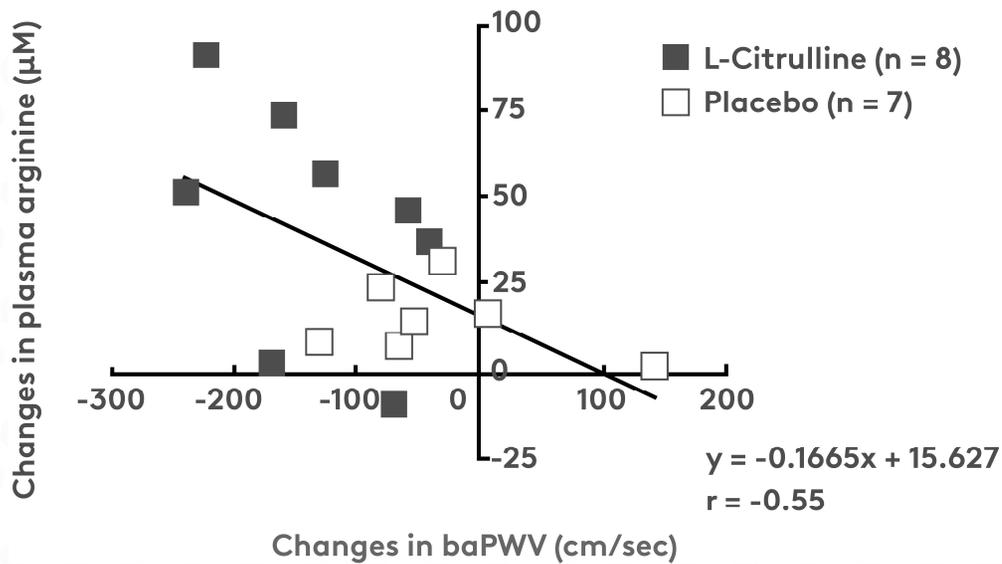


ORAL L-CITRULLINE MAY BENEFIT ENDOTHELIAL FUNCTION

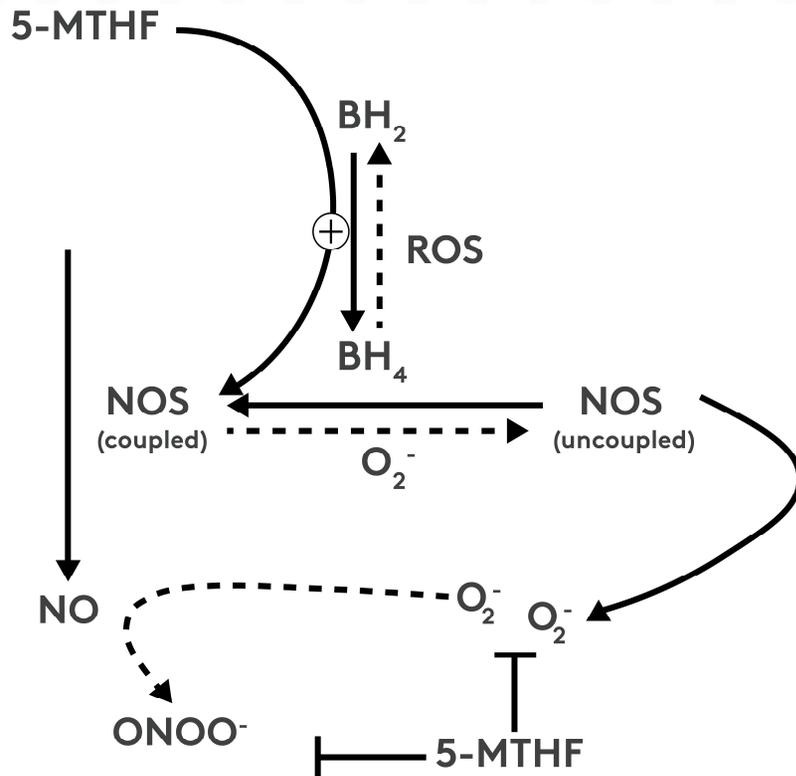
- Oral L-citrulline may lead to higher plasma arginine levels than arginine supplements.
- In subjects (N = 20) with impaired NO activity and elevated ADMA, L-arginine and L-citrulline were assessed for pharmacokinetic and pharmacodynamic effects over a 7-day period.
- 3 g of L-citrulline twice daily most efficiently increased arginine plasma and NO-dependent signaling to benefit endothelial function.
- Pooled analysis of data for all treatments revealed a correlation between plasma L-arginine/ADMA ratio and flow-mediated vasorelaxation (FMD).



L-CITRULLINE MAY IMPACT ARTERIAL STIFFNESS



- L-citrulline increases plasma arginine and positively influences NO, contributing to vascular function.
- L-citrulline (5.6 g/d for 7 days) significantly affected arterial stiffness in healthy volunteers (N = 15).
- Measurement was via brachial-ankle pulse wave velocity (baPWV), a noninvasive method for measuring arterial stiffness.
- Research with a larger population group, at varying doses, is needed to determine the optimal dose for arterial benefit.



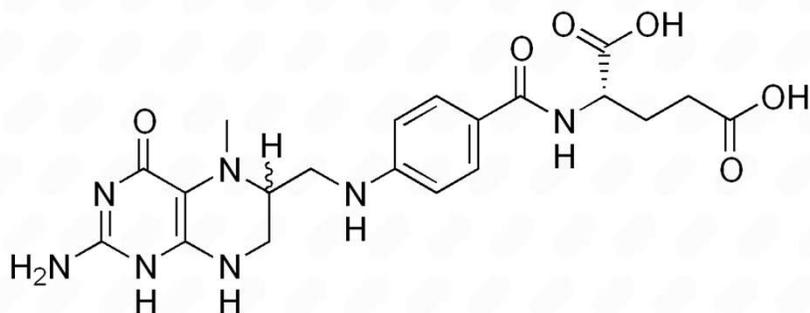
Proposed mechanisms by which 5-MTHF may increase NO synthesis and bioavailability.

FOLATE

- Folic acid and its principal circulating metabolite 5-methyltetrahydrofolate (5-MTHF) positively influence vascular function and oxidative stress by regulating NO synthesis.
- Folate affects the coupling of endothelial NOS and its cofactor tetrahydrobiopterin (BH₄), enhancing NO bioavailability.
- Folate also has a demonstrated role in moderating homocysteine levels; a high level can impair the bioavailability of NO.



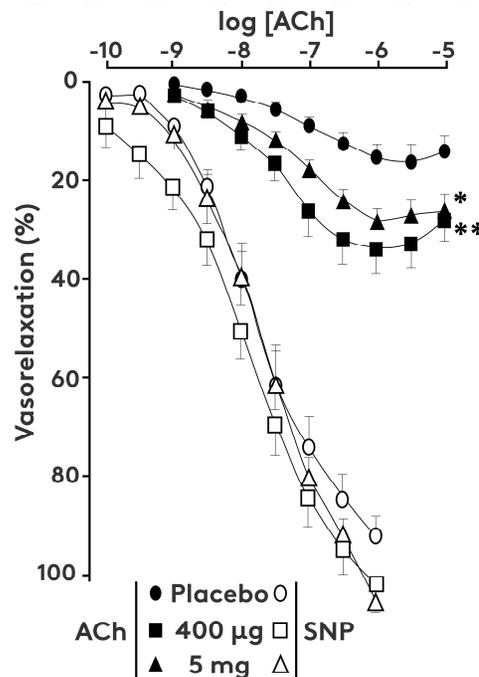
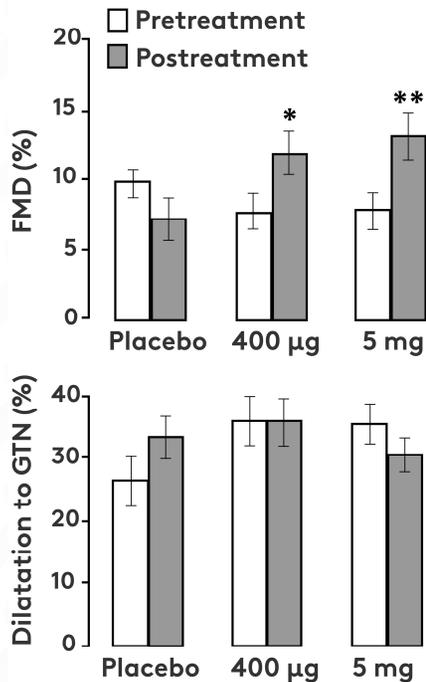
Folic Acid



5-methyltetrahydrofolate

SUPPLEMENTAL FOLIC ACID AND 5-MTHF EQUALLY REDUCE HOMOCYSTEINE (Hcy) LEVELS

- In a study of healthy older adults (N = 40) with normal serum folate, 400 mcg of folic acid, and the equimolar amount of 5-MTHF effectively lowered lowering Hcy over a 4-week treatment period.
- A study comparing the Hcy-lowering potential of 5-MTHF (416 mcg, 208 mcg) to folic acid (400 mcg) in female subjects (N = 144) over a 24-week period found that both doses of 5-MTHF were adequate alternatives to folic acid for reducing Hcy.
- Although these studies suggest folic acid and 5-MTHF as equivalent, the bioavailability of folic acid is impaired in those with a 5,10-methylenetetrahydrofolate reductase (MTHFR) genetic polymorphism, rendering 5-MTHF necessary to alter Hcy levels in those individuals.



FOLATE AND VASCULAR FUNCTION

- Before coronary artery bypass, subjects (N = 56) were given 400 mcg of folic acid, 5 mg of folic acid, or placebo daily for 7 weeks to assess the effect on blood vessels.
- Improved vascular function was observed and equal in both low- and high-dose groups.
- Beneficial effect was attributed to improved availability of BH4 for NOS and reduced vascular oxidative stress.



FOLATE IMPROVES VASCULAR FUNCTION IN OLDER ADULTS

- Older adults have lower vascular endothelial function, attributed to an age-related decrease in vasodilator mechanisms, including attenuated NO-dependent vasodilatation.
- In 2 studies comparing young subjects (N = 11, ~age 22) with older subjects (N = 11, ~age 71), subjects in both groups were given intradermal 5-MTHF and oral folic acid.
- Results indicated an increased vasodilatation response, locally for intradermal application and systemically, through 6 weeks of oral (5 mg/d) folic acid supplementation in only the older individuals.
- Response was attributed to a boost to the NO-dependent mechanism of vasodilatation, suggesting oral folic acid as a viable intervention for improved microvascular function in older adults.



HAWTHORN AND VASCULAR HEALTH

- Traditional use indicates a benefit for blood pressure, blood flow, and heart rhythm.
- Animal and laboratory research suggests vasodilatory properties may be attributed to increased blood flow and the activation of endothelial NOS.
- A randomized, double-blind study in subjects (N = 92) with mild hypertension who were given 20 drops of hawthorn extract 3 times daily significantly decreased systolic and diastolic blood pressure after 3 months.
- Additional trials are needed to further elicit the benefit and effective dose to support endothelial health.

Asher GN, Viera AJ, Weaver MA, Dominik R, Caughey M, Hinderliter AL. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: a randomized, controlled cross-over trial. *BMC Complement Altern Med.* 2012;12:26. Published 2012 Mar 29. doi:10.1186/1472-6882-12-26

- Hawthorn (*Crataegus* spp.) is a thorny shrub that grows commonly in northern temperate regions around the world. Typically the leaf and flower, berry, or a combination of all three are consumed as a powder, tea, or liquid extract. Its therapeutic use is reported as early as the 1st century BCE, and references to its use in cardiovascular diseases date to the 1600's [1].
- The chemical constituents considered to be the primary bioactive components of hawthorn are the flavonoids and oligomeric procyanidins (OPCs) [2]. Hawthorn extracts have been shown to enhance release of nitric oxide (NO) from vascular endothelium causing vasodilation, which appears to be associated with the OPC-rich fraction of hawthorn extract [3-5].

Asher GN, Viera AJ, Weaver MA, Dominik R, Caughey M, Hinderliter AL. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: a randomized, controlled cross-over trial. *BMC Complement Altern Med*. 2012;12:26. Published 2012 Mar 29. doi:10.1186/1472-6882-12-26

- Exogenous intake of nitrate in humans is converted by commensal bacteria to nitrite, which can then be reduced to NO [35]. However, the reduction process catalyzed by nitrite reductase is particularly inefficient [36].
- Zand, et al. screened over 100 botanicals and found hawthorn to have the highest nitrate reductase activity. They then tested a combination supplement that was both rich in natural nitrate (beetroot) and nitrite reductase activity (hawthorn) and found that the supplement produced sustained *in vitro* NO release with a $t_{1/2}$ of about 60 minutes and rapid and sustained human plasma NO levels (~1.4 μM) after a single dose *in vivo*.
- Steady state human plasma nitrite concentrations rose from 0.10 μM to 0.28 μM after taking the supplement for 30 days, which was statistically significantly greater than placebo, while plasma nitrite concentrations decreased in the placebo group. Finally, mildly hypertensive participants (systolic BP 135 - 160 mm Hg, n = 9) experienced a mean 7 mm Hg systolic and 2.7 mm Hg diastolic blood pressure reduction.

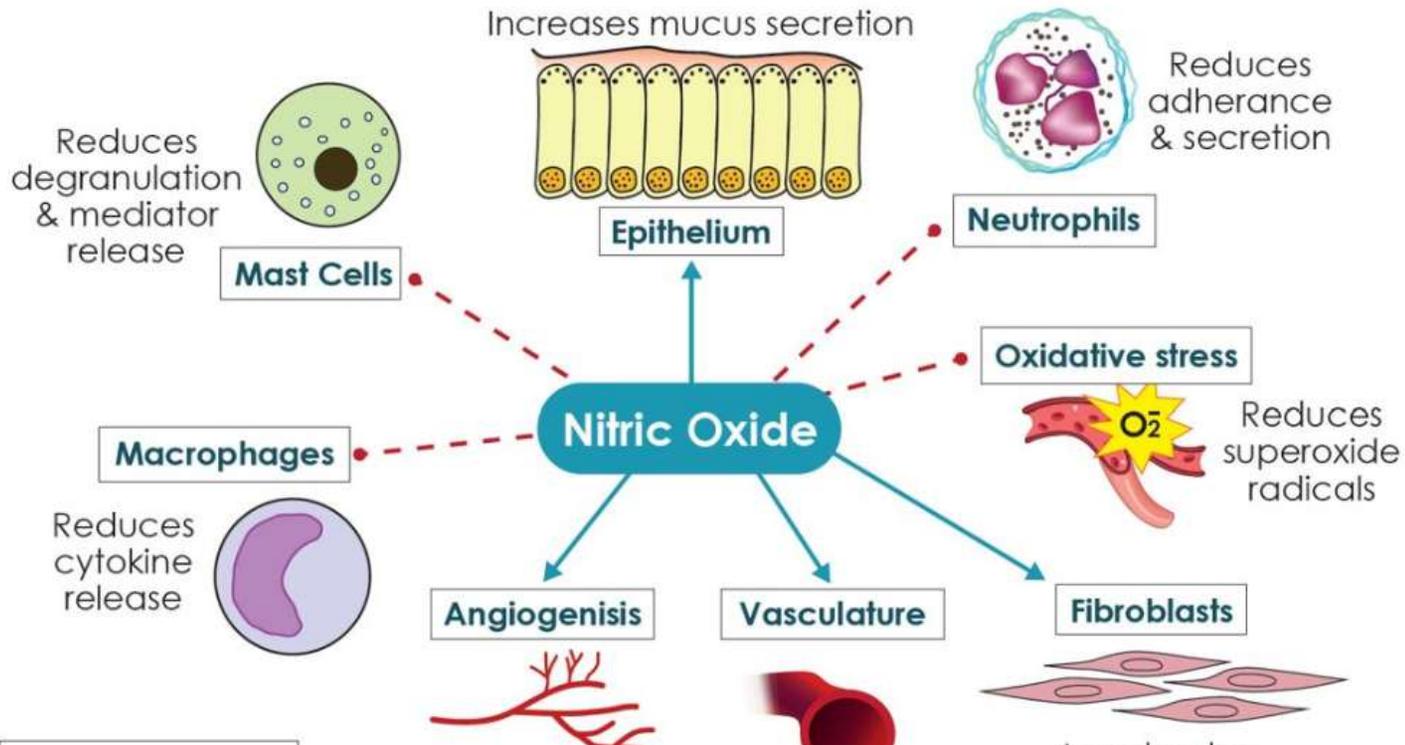
PPIs Create Atrophy

Conclusions:

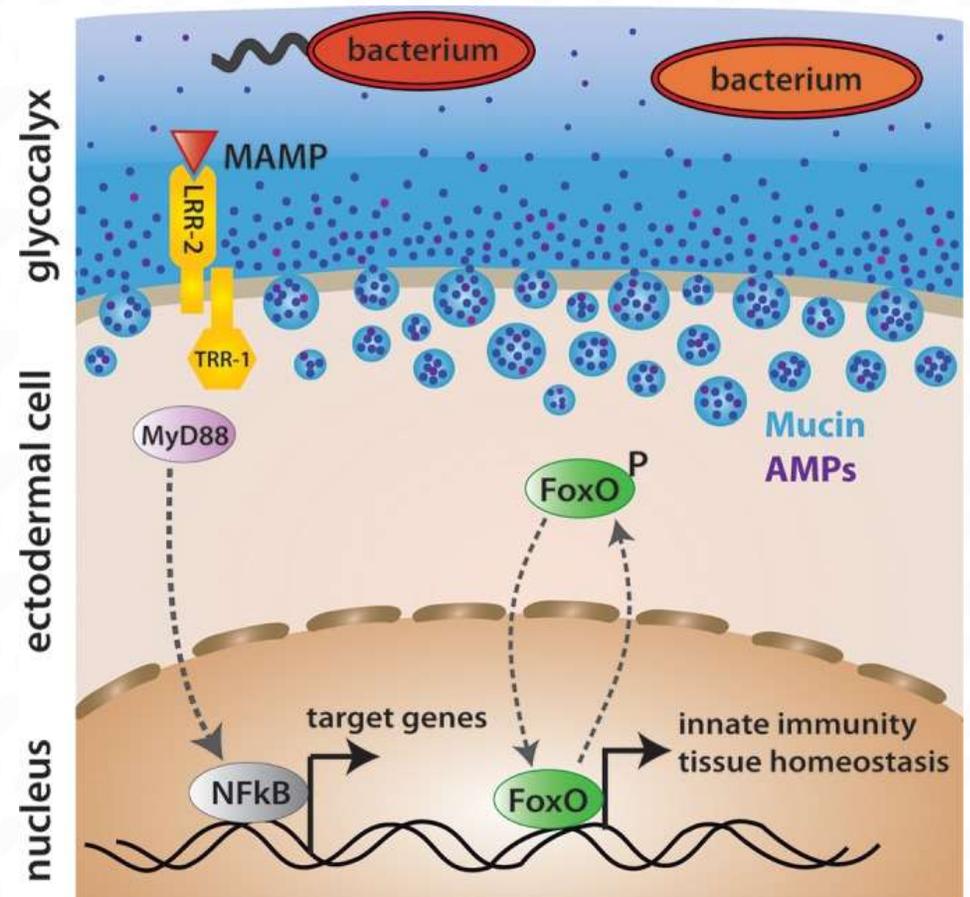
- The pooled data suggest that long-term PPI use is associated with increased rates of gastric atrophy. Large-scale multicenter studies should be conducted to further investigate the relationship between acid suppressants and precancerous diseases.
- Increases ADMA, decrease NO production in the gut

Li Z, Wu C, Li L, Wang Z, Xie H, He X, Feng J. Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis. Saudi J Gastroenterol. 2017 Jul-Aug;23(4):222-228. doi: 10.4103/sjg.SJG_573_16. PMID: 28721975; PMCID: PMC5539675.

Major beneficial actions of NO in the mechanism of gastrointestinal mucosal defense



NO and Gut Lining



NO and Gut Lining

- The concept of GI cytoprotection was introduced by Andre Robert in 1968, referring to the ability of prostaglandins (PGs), in minute amounts, to greatly increase the resistance of the stomach to injury induced by a wide range of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), ethanol, high concentrations of acid and bile salts (Robert et al., 1968).

Side Effects Are Expansive – Call to Deprescribe

- Proton Pump Inhibitors are used widely to manage many gastric acid-related conditions such as gastroesophageal disease, gastritis, esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome, peptic ulcer disease, nonsteroidal anti-inflammatory drug-associated ulcers, and *Helicobacter pylori* eradication, around the globe.
- Adverse effects associated with the long-term use of proton pump inhibitors including renal disorders (acute interstitial nephritis, acute kidney injury, chronic kidney disease, and end-stage renal disease), cardiovascular risks (major adverse cardiovascular events, myocardial infarction, stent thrombosis, and stroke), fractures, infections (*Clostridium difficile* infection, community-acquired pneumonia, and Coronavirus disease 2019), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, hypokalemia), hypergastr
- inemia, cancers (gastric cancer, pancreatic cancer, colorectal cancer, hepatic cancer), hepatic encephalopathy, and dementia. Clinicians including prescribers and pharmacists should be aware of the adverse effects of taking proton pump inhibitors for an extended period of time.
- In addition, the patients taking proton pump inhibitors for long-term should be monitored for the listed adverse effects. The American Gastroenterological association recommends a few non-pharmacological measures and the use of histamine 2 blockers to lessen gastrointestinal symptoms of gastroesophageal reflex disease and the utilization of proton pump inhibitors treatment if there is a definitive indication. Additionally, the American Gastroenterological association's Best Practice Advice statements emphasize deprescribing when there is no clear indication for proton pump inhibitors therapy.
- Maideen NMP. Adverse Effects Associated with Long-Term Use of Proton Pump Inhibitors. Chonnam Med J. 2023 May;59(2):115-127. doi: 10.4068/cmj.2023.59.2.115. Epub 2023 May 25. PMID: 37303818; PMCID: PMC10248387.

NO produced in the Gut

- As in other tissues, NO can be produced by three **NOS** enzymes in the GI tract.
- **Neuronal NOS (nNOS)** also known as NOS1) is the ‘cytokine-inducible’, neuron-associated form of the enzyme, primarily contributing to regulation of smooth muscle function and pain.
- **Inducible NOS (iNOS)** also known as NOS2) is the ‘inducible’ form of the enzyme, primarily involved in responses to inflammation and injury.
- **Endothelial NOS (eNOS)** also known as NOS3) is the ‘endothelial’ form of the enzyme, which plays particularly important roles in the GI tract in regulating mucosal defence from injury and vasodilation.

GASTROINTESTINAL DISORDERS

Nitric oxide can kick-start the gut lining to fight inflammation

Naveed Saleh, MD, MS, for MDLinx | July 17, 2018

- To this end, the researchers promoted NO synthesis in enterocytes by upregulating ASL and complementing its substrates using citrulline and fisetin nutraceutical supplements. (Citrulline is naturally found in watermelon, spinach, and beets; fisetin is found in apples, persimmons, and strawberries.)
- Consequently, this induction of endogenous NO production by enterocytes fortified epithelial integrity of the gut lining and decreased inflammation secondary to colitis. Moreover, because inflammation aggravates colon cancer, colon tumors in the mouse models shrank in size and number.

GASTROINTESTINAL DISORDERS

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- On a related note, the team found that NO derived from immune cells is linked to activation of macrophages, and thus more inflammation. By contrast, NO derived from enterocytes keeps these activated macrophages at bay, and inhibits macrophage infiltration and tissue damage.
- “We show here that boosting the metabolic ability of the enterocytes to synthesize and adjust the level and localization of NO to the exact amount and place where it is needed is the most beneficial treatment for reducing colitis severity,” the researchers concluded. “Because the duration, severity, and extent of colitis have all been shown to increase the risk for colon cancer development, not surprisingly, our combination of citrulline/fisetin also decreased inflammation-associated colon cancer.”

GASTROINTESTINAL DISORDERS

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- Additionally, the investigators showed the greater metabolic benefit of supplementing substrates and upregulating metabolic enzymes versus that of administering therapy straight-up with molecules that are deficient.
- “We trusted the body to make use of its own healing mechanisms,” reflected Dr. Stettner. “We provided it with the building blocks and let it manufacture NO in the right amount and exactly in the right place.”

Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2(Suppl 2):S4.

- Nitric oxide (NO) is known to have a protective effect on the gastrointestinal tract. In preclinical studies NO was shown to help maintain gastric mucosal integrity, to inhibit leukocyte adherence to the endothelium, and to repair NSAID-induced damage.
- In addition, epidemiologic studies have shown that the use of NO-donating agents with NSAIDs or aspirin resulted in reduced risk for gastrointestinal bleeding.
- Recent studies have shown that cyclo-oxygenase inhibiting NO-donating drugs (CINODs), in which a NO molecule is chemically linked to an NSAID, are effective anti-inflammatory agents and may result in less gastrointestinal damage than is associated with NSAID use.

Kubes P, Wallace JL. Nitric oxide as a mediator of gastrointestinal mucosal injury?-Say it ain't so. Mediators Inflamm. 1995;4(6):397-405.

- Nitric oxide (NO) appears to be one of the most important signals for mucus secretion as it is the mediator responsible for cholinergic-stimulated mucus release.³
- NO increases mucosal blood flow, which acts to dilute toxic substances, neutralize them, and remove them before they accumulate to damaging concentrations.³
- Supporting the nitrate to nitrite to NO pathway increases mucosal blood flow and vasodilation, increases mucus production and thickness, modulates mucosal immune response, prevents acute peptic ulceration, and can even repair NSAID damage to the intestinal tract.³

Rocha BS, et al. Inorganic nitrate prevents the loss of tight junction proteins and modulates inflammatory events induced by broad-spectrum antibiotics: A role for intestinal microbiota? Nitric Oxide. 2019;88:27-34.

- Tight junction proteins play a vital role in epithelial transport and are responsible for barrier integrity of the intestinal tract. Loss of tight junction proteins results in the breakdown of the intestinal barrier called leaky gut. There is decreased gastric expression of the tight junction proteins occludin and claudin 5 during dysbiosis.
- However, following nitrate consumption, both protein levels rebound.⁴

Coleman JW. Nitric oxide: a regulator of mast cell activation and mast cell-mediated inflammation. Clin Exp Immunol. 2002;129(1):4-10.

- Furthermore, nitrite and NO can regulate the activity of mast cells.¹¹ Mast cells are white blood cells that are part of the immune system and function as a bridge between the immune and nervous system.
- Mast cells modulate the inflammatory processes in depression, anxiety, brain fog, and insomnia.¹² Mast cells become activated in the absence of NO production, and increased superoxide production contributes to mast cell activation.¹¹
- Conversely, nitrites and NO are an effective inhibitor of mast cell dependent inflammatory events. Nitrites and NO suppress antigen-induced degranulation and mediator release, including histamine and cytokine expression.¹¹
- In addition, nitrites and NO inhibit leukocyte endothelial cell attachment and inhibit generation of ROS by mast cells.¹¹

Coming off of a PPI

- Low and Slow
- Increase atrophy of the gut lining
- Increase Osteoporosis
- Increase allergies
- Increases atrophy
- Start with demulcents and build gut lining, while giving enzymes at every meal
- Slowly decrease PPI – have a strategy for break through pain (increase DGL or Slippery Elm), start with just pancreatic enzymes
- When doing well, add HCL. Start at a low dose 300 mg of HCL, and increase at largest meal, until just a small amount of burning, then back down amount taken the day before.
- Can give enzymes and PPIs at same time to off-set what PPI does

Navigating The Nuances

- Rule of Thumb: If you are more than 2 drugs, you are likely experiencing nutritional deficiencies. Multivitamin is non-negotiable
- Add additional support where need
- Encourage a movement to diet and lifestyle interventions, and the rest will improve

Dr. Cheryl Burdette