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Natural Support for Lipid Metabolism and Cardiovascular Health

Cardiovascular disease remains the leading cause of death in the United States, driven by a decades-long process, with dyslipidemia at its core.[1] While statins remain the cornerstone of lipid-lowering therapy, approximately 15% of patients prescribed statins do not refill their initial prescriptions, and over half are non-adherent by one year, indicating inadequate long-term control of ongoing lipid-based cardiovascular risk.[2] In addition to non-adherence because of either statin intolerance, patient preference or statin ineligibility, some patients do not meet lipid targets despite statin use. Analysis of data from the U.S. National Health and Nutrition Examination Survey indicates that among patients with known atherosclerotic cardiovascular disease, for example, nearly 80% of those taking statins are not meeting lipid targets.[3] Thus, a solid incentive exists to provide lipid-lowering nutraceuticals with a strong evidence base to either complement drug-based therapies or provide an alternative for patients unable or unwilling to adhere to statin therapy.

Clinical doses of well-researched ingredients, such as red yeast rice, phytosterols, garlic, berberine, and delta-tocotrienol, provide support for healthy lipid metabolism and reduction in cardiovascular disease risk. Clinical trial evidence indicates that individually these ingredients reduce LDL cholesterol (LDL-C), total cholesterol, ApoB, oxidized LDL-C (oxLDL), and triglycerides, while increasing HDL cholesterol (HDL-C) and ApoA1. Additionally, they have distinct mechanisms of action, including the inhibition of cholesterol synthesis, upregulation of cholesterol clearance, and prevention of dietary cholesterol absorption, which allow for a more potent effect together than when used in isolation. More than only a reduction in cholesterol, the combination of these natural ingredients has also been shown to reduce inflammation, lower blood pressure, stabilize arterial plaques, and reduce coronary artery calcium scores. They are also very well-tolerated, and in clinical trials, they have generally enhanced the effects of other lipid-lowering agents.

The International Lipid Expert Panel provides class IA recommendations for both red yeast rice extract and berberine, for example, indicating that they are effective and have supportive data from multiple randomized clinical trials. Furthermore, this same expert panel describes the potential synergy of compounds with different lipid-lowering activities and mechanisms of action when used in combination, as well as the additional benefit observed when used in combination with statins, providing additional clinical evidence for garlic, phytosterols, and tocotrienols.[4] This latter benefit may also include the ability to achieve the same lipid-lowering effects while using a lower (and potentially more tolerable) dose of statin medications.

Red Yeast Rice

Red yeast rice extract (RYR) has extensive clinical evidence as well as many randomized and double-blinded trials demonstrating its lipid-lowering properties. Fermentation of yeast *(Monascus purpureus)* on rice produces the complex of natural compounds found in RYR, including monacolins and polyketides, which act in part by inhibiting 3-hydroxy-3-methyl-glutarylCoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. For example, the most abundant monacolin in RYR is monacolin K, shown to significantly reduce LDL-C in clinical trials, even at low doses.[5,6] RYR provides as many as 23 monacolins, as well as many sterols, flavonoids, lignans, polysaccharides, and other bioactive compounds.[7] Given the diverse nature of the bioactive compounds within RYR, it is likely to have complementary actions in addition to HMG-CoA reductase inhibition; it has also been shown to reduce levels of matrix metalloproteinases 2 and 9, hs-CRP, ox-LDL, to improve markers of arterial health, such as flow-mediated dilation, and to stabilize vulnerable atherosclerotic plaque in experimental studies.[8,9,10,11]

Multiple systematic reviews of randomized and controlled trials indicate that RYR significantly lowers LDL cholesterol by 15-34% (weighted mean difference (WMD) of 28.94 mg/dL), total cholesterol by 16-31% (WMD of 33.16 mg/dL), and triglycerides by 0-36% (WMD of 23.36 mg/dL), while increasing HDL cholesterol by up to 20% (WMD of 2.49 mg/dL), with greater effects observed among study participants with dyslipidemia.[7,12,13,14] In a meta-analysis of trials, RYR was also found to significantly reduce ApoB (mean difference of -27.98), an important indicator of cardiovascular disease risk.[15,16]

These favorable effects on lipids have also translated into risk reduction for hard outcomes; a systematic review of RYR preparations given to participants with metabolic syndrome (Met-S) found significant reductions in the risk for mortality (-38%) and major adverse cardiovascular events (MACEs, -46%), as well as secondary outcomes such as blood glucose, hemoglobin A1c, blood lipids, and blood pressure.[17] An RYR extract also reduced the risk of major coronary events in a study population of 5,000 individuals with a previous heart attack, associated with a 45% relative risk reduction and a 4.7% absolute risk reduction (compared to placebo) over 4.5 years.[18] A meta-analysis of randomized trials of RYR supplementation also found reduced risk for several cardiovascular outcomes among people with borderline hypercholesterolemia.[19]

RYR has been found to be remarkably safe. Analysis of pooled data from 53 randomized clinical trials and over 8,500 participants found RYR and monacolin K to be safe and well-tolerated, with no increase in musculoskeletal adverse events and a lower risk for both non-musculoskeletal and serious adverse events compared to controls.[20] RYR has also been found to be well-tolerated among people intolerant to standard lipid therapy, providing a viable alternative option to control dyslipidemia.[21,22,23]

Phytosterols

Phytosterols, including B-sitosterol, campesterol, and stigmasterol, are natural constituents of plants that are structurally similar to cholesterol. Because of this similarity, they compete with dietary cholesterol for absorption into intestinal micelles via a common transporter (NPC1L1).[24] Yet while approximately 35-70% of dietary cholesterol is absorbed, less than one percent of sterols are ultimately retained (unlike cholesterol, sterols are primarily pumped back into the intestinal lumen by ABCG-5 and -8), with the plasma concentration of sterols 1000-fold lower than plasma cholesterol.[25,26] In addition to reducing the absorption of dietary cholesterol, phytosterols also modify the metabolism of cholesterol in both intestinal and hepatic cells, increasing its excretion and inhibiting its synthesis.[27] Phytosterols have anti-inflammatory and antioxidant properties, reducing the production of proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α.[28] In two randomized clinical trials, supplementation was also shown to improve insulin resistance, as well as reduce both inflammation and liver enzymes among participants with non-alcoholic fatty liver disease (NAFLD).[29,30,31]

Phytosterols have been well-established to improve dyslipidemia, with notable dose-dependent reductions in total cholesterol, LDL-C, and triglycerides. At a dose of 2-3 g/day, LDL-C is reduced by approximately 6-12% and triglycerides 6-9%, with no significant effect on HDL-C.[13] A meta-analysis restricted to studies that enrolled postmenopausal women found that at doses of at least 2 g per day, total cholesterol was reduced by 22.22 mg/dl and LDL-C by 10.14 mg/dl, with larger reductions in LDL-C among women with a BMI ≥25 kg/m2.[32] Some individuals absorb higher amounts of dietary cholesterol, and phytosterol supplementation has a greater magnitude on absolute and percent LDL-C reduction in these individuals.[33] A meta-analysis of 31 randomized and controlled trials, with 51 arms, found that phytosterol supplementation was associated with favorable effects on lipid profiles,

including reductions in ApoB, ApoE, and the ApoB/ApoAI ratio, as well as an increase in ApoAI.[34] Phytosterols have also been used alongside standard lipid therapy, further increasing total and LDL-C reductions.[35] Similarly, phytosterols have been shown to enhance the reductions of LDL-C and ApoB when combined with RYR, indicative of complementary mechanisms.[36]

Garlic

Supplementation with garlic, particularly aged garlic extract (AGE), has also been shown to modulate many cardiovascular risk factors, with lipid-lowering, cardioprotective, and anti-atherogenic properties. Often attributed to its sulfur-containing bioactive compounds, including alliin, allicin, S-allyl cysteine, and diallyl trisulfide, these compounds act through a diverse range of biological mechanisms, having hypolipidemic and hypotensive along with antioxidant, and anti-inflammatory effects.[37] Garlic's lipid-lowering properties appear to be mediated by both an inhibition of dietary cholesterol absorption and inhibition of cholesterol synthesis.[13] Experimental models also suggest garlic may upregulate the expression of lipolytic genes while downregulating fat degradation genes, promoting a "browning" of white adipose tissue.[38,39]

Numerous clinical trials have supported the efficacy of garlic in reducing total and LDL-C. A meta-analysis of 39 clinical trials among hyperlipidemic participants found that garlic supplementation reduced total serum cholesterol by 17 mg/dL and LDL-C by 9 mg/dL.[40,41] Garlic's anti-inflammatory effects were also supported by a meta-analysis of 17 randomized trials which found significant reductions in C-reactive protein and TNF-α with garlic supplementation.[42] A meta-analysis of 19 randomized and controlled trials among study participants with Met-S found that garlic supplementation not only significantly reduced total and LDL-C, but also lowered triglycerides, diastolic blood pressure, waist circumference, and BMI.[43] Improvements in lipid profiles and coronary artery calcium scores among people with coronary artery disease have also been documented with garlic supplementation.[44]

Indeed, in a systematic review of controlled trials evaluating the efficacy of any intervention to attenuate cardiovascular calcification, including other lipid-lowering agents and HMG-CoA reductase inhibitors, only AGE consistently showed benefit.[45] In a randomized and placebo-controlled year-long trial, AGE was shown to inhibit coronary artery calcium progression, and lower IL-6, fasting blood glucose and blood pressure among patients at higher risk for cardiovascular events.[46] The AGE at Heart Trial, a double-blind randomized and placebo-controlled trial that enrolled participants with uncontrolled hypertension, found that AGE supplementation reduced mean blood pressure by 5 mmHg, and among responders, it reduced systolic blood pressure (SBP) by 11.5 and diastolic blood pressure (DBP) by 6.3 mmHg. Improvements in central hemodynamics were also observed in this trial, including central blood pressure and pulse wave velocity.[47] A hypotensive effect of garlic is consistent with findings from a previous meta-analysis which found a reduction of 8.7 and 6.1 mmHg in SBP and DBP, respectively, among people with hypertension.[48]

Berberine

Berberine is an isoquinoline-type alkaloid that occurs naturally in the root and bark of several plant species. It has a long history of use in traditional Chinese medicine as well as a growing evidence base for its favorable effects on both lipid and glucose metabolism. It has many positive metabolic actions, including activation of AMPK (AMP-activated protein kinase), modulation of mitochondrial function, inhibition of adipogenesis signaling (PPARγ and C/EBPα), and enhanced

insulin sensitivity, as well as a lipid-lowering effect mediated via increasing the expression of the LDL receptor (LDLR), which enhances LDL-C clearance.[49] Several mechanisms may drive the increase in LDLR expression; perhaps chief among them, berberine either directly or indirectly downregulates proprotein convertase subtilisin/kexin type 9 (PCSK9), which degrades LDLR. Berberine inhibits PCSK9 transcription and activates regulatory proteins that enhance its degradation.[50] Berberine also stabilizes the LDLR by activating the Jun N-terminal kinase (JNK)/c-Jun signaling pathway. Cumulatively, this increase in LDLR expression increases LDL-C clearance and reduces the amount of circulating LDL-C.[51]

In a systematic review of randomized placebo-controlled trials, which included 18 studies and nearly 1800 participants, berberine supplementation was shown to reduce LDL-C by 17.8 mg/dL, total cholesterol by 18.6 mg/dL, ApoB by 25 mg/dL, and triglycerides by 30.1 mg/dL.[52] Similar lipid reductions as well as slight increases in HDL-C have been observed in other meta-analyses.[53] Given that its primary mechanism of action appears to be inhibition of PCSK9, it has also been shown to enhance the hypolipidemic effects of treatments which act through distinct pathways, including agents that reduce cholesterol absorption as well as standard HMG-CoA reductase inhibitors, including RYR.[54,55] Standard HMG-CoA reductase inhibitors upregulate PCSK9 expression, suggesting berberine may be an important complement to their use.[56]

In addition to its hypolipidemic effects, berberine improves other cardiovascular risk factors. A systematic review and meta-analysis of randomized trials found not only favorable changes to serum lipids, but significant reductions in fasting blood glucose, insulin, hemoglobin A1c, insulin resistance (HOMA-IR), systolic blood pressure, and BMI.[57] The improvements in glucose metabolism appear to be at least partly mediated by modulation of the gastrointestinal microbiota.[58]

Delta-Tocotrienol

Naturally occurring vitamin E is comprised of at least 4 tocopherols and 4 tocotrienols, including delta-tocotrienol. Tocotrienols are antioxidants reported to have diverse cardiovascular benefits, such as lipid-lowering, hypotensive, and anti-atherogenic effects.[59] Delta-tocotrienol reduces cholesterol synthesis via post-translational suppression of the HMG-CoA reductase enzyme, as well as upregulation of its degradation.[60,61]

Delta-tocotrienol supplementation (in combination with resveratrol) has been shown to improve multiple cardiometabolic risk factors among participants with Met-S in a randomized and placebo-controlled trial. This included markers of inflammation, such as C-reactive protein, as well as blood pressure and fasting plasma glucose levels.[62] In a clinical trial that enrolled participants with NAFLD, delta-tocotrienol was found to improve multiple endpoints related to hepatic steatosis and insulin resistance compared to baseline, such as the fatty liver index, liver-to-spleen attenuation ratio, and HOMA-IR. Additionally, it was superior to alpha-tocopherol in terms of reducing inflammation (IL-6, TNF-α) and body weight.[63] In a placebo-controlled trial, delta-tocotrienol was also found to significantly improve glycemic control among individuals with prediabetes.[64]

Research Summation:
Lipid-Modulating Mechanisms of Action of Natural Compounds

- Improvements in lipid profile, including clinically meaningful decreases in LDL and total cholesterol along with triglycerides among people with hyperlipidemia/dyslipidemia
- Significant reductions in ApoB, potentially a better indicator of risk than standard lipids
- Complementary mechanisms of action when aforementioned compounds are combined, including inhibition of HMG-CoA reductase and PCSK9, creates a synergistic effect between ingredients
- Multiple well-validated clinical trials demonstrate lipid-lowering efficacy and reduction of inflammation, as well as significant lowering of blood pressure among people with hypertension
- Multiple metabolic benefits, including support for cardiovascular health, glucose control, and insulin sensitivity
- Well-tolerated, without adverse musculoskeletal effects of standard lipid-lowering treatment

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