THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 10

CASE REPORT

A Novel Supplement Regimen for Healthy Aging: A Case Series

Joseph Keenan, M.D.[1]

[1] Professor Emeritus, University of Minnesota, Department of Family Medicine & Community Health; Associate Professor of Food Science & Nutrition; Director of the University Geriatric Fellowship; Founder and first president of The American Academy of Home Care Medicine.

OPEN ACCESS

PUBLISHED
31 October 2024

CITATION
Keenan, J., 2024. A Novel Supplement Regimen for Healthy Aging: A Case Series. Medical Research Archives, [online] 12(10). https://doi.org/10.18103/mra.v12i10.5830

DOI
https://doi.org/10.18103/mra.v12i10.5830

ISSN
2375-1924

ABSTRACT

Objective: This case series aims to evaluate a novel supplement regimen for healthy aging in older adults, assess its potential to reduce reliance on prescription, and inform the design of a larger clinical trial.

Background: The convergence of an aging population and increasing prevalence of age-related chronic diseases continues to strain limited healthcare resources and exert financial pressures on healthcare systems and individuals alike. For this reason, cost-effective, readily available solutions are needed more than ever to help reduce the disease burden among older adults.

Methods: Participants included 10 men and women living in the United States, aged 62-91 years, who were given a supplement regimen providing niacin (extended-release tablets), dihydroberberine (sustained-release tablets), taxifolin (sustained-release tablets), and mixed tocotrienols (immediate-release softgels) along with diet instructions. Participants were required to share the study protocol with their personal doctors, and agree to periodic in-person home visits. Blood tests (lipid profile including Lp(a), comprehensive metabolic profile, uric acid, homocysteine, and HbA1c) were completed at baseline and repeated at 6 weeks, 12 weeks and quarterly thereafter to monitor benefits and possible adverse side effects, unless abnormal results warranted closer monitoring. Participants underwent cognitive and well-being assessments at baseline and study completion.

Results: Supplement intervention lasted 16 months, on average, resulting in clinically relevant reductions in total cholesterol, LDL cholesterol, and triglycerides, and an increase in HDL cholesterol. All participants with elevated Lp(a) levels at baseline (n=3) experienced reductions by study completion. All seven participants on statin drugs at baseline were able to discontinue use while achieving similar or better lipid outcomes after withdrawal. Only one participant resumed statin use, despite lipid improvements, due to digestive issues. Participants completing the self-reported assessment of well-being (n=10) reported generally stable or positive physical and mental function compared to baseline. Drop-outs were prevented with the successful management of transient side effects.

Conclusions: While more research is needed, this case series validates the therapeutic potential of a novel dietary supplement regimen to promote healthy aging in older adults, including treating dyslipidemia, promoting well-being, and reducing prescription drug use, as well as inform the design of a larger clinical trial.

Keywords: niacin, nicotinic acid, niacinamide, dihydroberberine, taxifolin, mixed tocotrienols, cardiovascular disease, cognitive function, healthy aging

Abbreviations

ALT: alanine transaminase
AST: aspartate transferase
CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
CVD: cardiovascular disease
HbA1c: glycated hemoglobin
HDL: high-density lipoprotein
LDL: low-density lipoprotein
Lp(a): lipoprotein (a)
NA: nicotinic acid
NAD+: nicotinamide adenine dinucleotide
NSAID: non-steroidal anti-inflammatory drug
SAGE 2: Self-Administered Gerocognitive Exam 2

Introduction

As the global population continues to age and the prevalence of age-related chronic diseases rises,[1] healthcare systems around the world are facing a unique 21st century challenge. The increasing demand for healthcare services for older individuals with complex health issues is likely to strain limited healthcare resources and exert financial pressures on healthcare systems and individuals alike as they manage the cost-burden of related expenses. For this reason, innovative solutions, preventative measures, and sustainable healthcare policies are needed more than ever. One such potential solution to help reduce the disease burden in older adults is the use of readily available, cost-effective dietary supplements that offer therapeutic benefits.

Based on 40-plus years of my research and extensive research by others, four dietary ingredients have been identified as having therapeutic benefits for healthy aging, particularly for older adults: (1) niacin; (2) dihydroberberine; (3) taxifolin (dihydroquercetin); and, (4) mixed tocotrienols. This case series, conducted from September 2022 to August 2024, explores the use of a novel supplement regimen that combines unique forms of these four dietary ingredients to reduce disease burden and promote healthy aging in older adults. Additionally, the study findings offer insight for managing dosing, assessing side effects, tailoring supplement regimens to individual needs, and reducing prescription drug burden (e.g., metformin and statin drugs). This information helps inform the design of a larger controlled clinical trial aimed at addressing the growing healthcare needs of the aging population.

The supplements for this case series were selected based on their potential to support cardiovascular health, metabolic function, immune defense, and other key health concerns of aging adults (see **Table 1**). Each has unique benefits for improving the health of older persons, and they complement the benefits of each other.

Table 1. Healthy Aging Supplement Regimen: Key Therapeutic Targets

Therapeutic Action	Nicotinic Acid	Niacinamide	Dihydroberberine	Taxifolin	Mixed Tocotrienols
Reduce risk of CVD/stroke	✓		✓	✓	✓
Reduce risk of cancers (i.e., breast, prostate, glioblastoma, gastrointestinal, liver, lung, leukemia/lymphoma, pancreatic, skin)			✓	✓	✓
Improve immune function; reduce serious post-viral infections, including pneumonia			✓	✓	✓
Prevent/improve glaucoma (the main cause of age-related blindness)		✓			
Reduce renal failure	✓				
Treat metabolic syndrome, pre-diabetes, type 2 diabetes			✓		
Improve stem cell production (essential precursor for NAD+ required for stem cell production)	✓	✓			
Reduce alcoholic and non-alcoholic fatty liver disease			✓		
Prevent/improve chronic bronchitis & COPD					✓
Reduce arthritis-related inflammation and joint damage					✓
Reduce metformin-related cancer (by replacing metformin)			✓		
Raise HDL cholesterol (associated with improved longevity)	✓				
Reduce small, dense LDL particles (the most pathogenic form)	✓				
Reduce oxidation of LDL (which makes it pathogenic)	✓		✓	✓	✓
Reduce intimal thickness/improve circulation	✓				
Reduce atherogenic lipoprotein (a)	✓				
Neuroprotective					✓

CVD indicates cardiovascular disease; NAD+, nicotinamide adenine dinucleotide; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Niacin, as nicotinic acid (NA) or niacinamide, was included in the supplement regimen primarily to support cardiovascular health and cellular metabolism. Decades of compelling clinical research support the therapeutic use of NA, including the wax-matrix delivery form, for the treatment of dyslipidemia and cardiovascular disease (CVD).[2] Although, its effectiveness has been unfairly questioned based on two high-profile, flawed clinical trials[3,4] and at least one meta-analysis based on this flawed data.[5] NA may help reverse chronic kidney disease (CKD) by improving dyslipidemia and reducing blood phosphorus levels[6] and shows promise as a potential therapeutic agent for certain neurological disorders and early stroke recovery.[7]

Both types of niacin (NA and niacinamide) serve as precursors for the body's production of nicotinamide adenine dinucleotide (NAD+). NAD+ is the active form of niacin that is essential for cellular metabolism and stem cell production, and supplementing with niacin helps counteract the age-related decline in NAD+ production.[8] Finally, niacinamide may help prevent or delay the progression of glaucoma, the leading cause of age-related blindness, by protecting retinal cells from stress and dysfunction.[9,10]

Dihydroberberine was included in the supplement regimen primarily to support metabolic health. Dihydroberberine is a highly bioavailable form of berberine,[11] a plant compound used in traditional medicines. Dihydroberberine is a more convenient and comfortable alternative to berberine because it requires a lower therapeutic dosage that helps eliminate the digestive upset commonly associated with berberine use. Once absorbed, dihydroberberine rapidly converts to berberine, enters the bloodstream, and is taken up by tissues and cells throughout the body. A robust body of clinical research supports the therapeutic use of berberine for common age-related diseases such as type 2 diabetes, hyperlipidemia, hypertension, stroke, metabolic syndrome, polycystic ovarian syndrome, and nonalcoholic liver disease.[12,13] Pre-clinical studies support its therapeutic potential for other age-related diseases such as certain cancers, especially glioblastoma,[14] alcohol-induced liver disease,[15] and viral infections.[16]

Taxifolin (dihydroquercetin) was included in the supplement regimen primarily to support immune health. Taxifolin is a naturally occurring bioflavonoid found in some plant foods, culinary spices, therapeutic herbs, and in the bark of certain trees (the typical source for dietary supplements). Taxifolin exerts a wide range of pharmacologic activities that are primarily attributed to its antioxidant and anti-inflammatory properties, including cardiovascular protection, liver support, neuroprotection, and antimicrobial, antiviral, and anticancer activity. It is reported to promote faster recovery of acute pneumonia, and is the top antiviral candidate against SARS-CoV-2 based on virtual screening and molecular docking assays using millions of natural compounds.[17]

Mixed tocotrienols were included in the supplement regimen primarily for their neuroprotective properties. While tocotrienols belong to the vitamin E family of antioxidants, their chemical makeup (unsaturated side chains) allows them to distribute more evenly in cell membranes than tocopherols, which results in better antioxidant defense.[18] This protective feature is especially beneficial for neurons that function in an oxygen-rich environment.

Mixed tocotrienols are reported to help reduce neurotoxicity and protect against mitochondrial dysfunction,[19] delay progression of white matter lesions and reduce the incidence and severity of stroke,[20] reduce elevated total and LDL cholesterol,[21] protect LDL cholesterol from oxidation,[22] and reduce arthritis-related inflammation and joint damage.[23] Moreover, mixed tocotrienols are reported to exert potent immune-modulating actions involved in fighting infections, including respiratory infections,[24] protect against pulmonary fibrosis[25] (especially important for smokers and people with chronic asthma or other types of chronic bronchitis), and play a potential role in cancer treatment.[26] For the most part, the therapeutic actions of mixed tocotrienols are attributed to their antioxidant and anti-inflammatory properties.[27]

Wax-matrix tablets (Endurance Products Company, Inc.; Sherwood, Oregon) were chosen for the water-soluble ingredients (niacin, dihydroberberine, and taxifolin) because an appropriate controlled-release nutrient delivery is critical for optimal benefits, including maintaining therapeutic blood levels without higher or more frequent dosing and minimizing side effects of too rapid absorption. These tablets are produced using a proprietary cold-extrusion, vegetable wax-matrix process and direct compression that helps ensure tablet stability and allows for a slow, steady nutrient release over 4 to 8 hours, depending on the supplement. A hydrophobic casing eliminates any unintentional release of active ingredient(s), thereby preventing "dose dumping." An immediate-release softgel was chosen for the mixed tocotrienols to provide a fat-soluble suspension to help ensure optimal absorption even if not taken with fat in a meal.

Methods

Inclusion criteria for this prospective case series included free-living, independent older adults living in the United States, aged 60 years or older, who were either apparently healthy or had managed chronic disease(s). The principal investigator met with each participant initially to review the study protocol, obtain informed consent, assess health history, lifestyle habits, and evaluate each participant's support system. Participants were not asked to change their lifestyle habits other than encouraged to increase "methyl donor" foods in their diet, avoid hot foods or beverages when taking supplements, and exercise regularly to support longevity.

Participants were asked to work with their primary doctor as a co-investigator. They received a book to share with their doctor with general supplement and protocol information as well as a personalized protocol sheet, contact information for questions, and requests for specific lab tests using standard reference ranges from their doctors' preferred labs to monitor benefits and side effects.

Quarterly home visits were scheduled to assess protocol compliance, deliver the next quarter's supplement supply, review diet/lifestyle goals, identify behaviors that might compromise progress, review lab results, and adjust dosing as needed to reduce side effects or target better benefits. The Self-Administered Gerocognitive Exam (SAGE 2), a validated cognitive screening tool, and a self-reported assessment of physical/mental well-being were conducted at baseline and study completion.

Blood chemistries were evaluated to assess changes in key values and monitor for possible adverse side effects. Blood draws were completed at baseline, 6 weeks, 12 weeks, and quarterly thereafter unless abnormal results warranted closer monitoring. Blood parameters analyzed included: lipid profile including lipoprotein (a) (Lp[a]), a comprehensive metabolic profile, uric acid, homocysteine, and hemoglobin A1C. Liver hypersensitivity was monitored by checking liver enzymes (AST, ALT) as part of the comprehensive metabolic profile and when participants reported gastrointestinal symptoms. If liver enzymes were elevated, NA was withheld until levels returned to normal.

Supplement Dosing Schedule

NIACIN SUPPLEMENTS

A participant's medical background and current medications dictated the form of niacin administered. For standard blood lipid management and cardiovascular support, extended-release wax-matrix tablets containing NA were chosen to provide controlled-release of NA over 6-8 hours, similar to prescription niacin,[28] and cardiovascular benefits supported by numerous clinical trials. The protocol involved a gradual dose increase over 6 weeks: Week 1, 250mg twice daily; week 2, 500mg twice daily; week 3, 750mg twice daily for 3 weeks. Participants were informed that taking NA may cause mild flushing initially, which typically improves within a few weeks. They were advised to use aspirin or a non-steroidal anti-inflammatory drug (NSAID) to help prevent skin flushing, if needed, and to increase their intake of methyl donor foods to support liver metabolism of NA.

Participants taking a statin drug at baseline were started on extended-release (5-7 hours) wax-matrix tablets containing NA (500mg) and pantethine (200mg) for more aggressive lipid management. Dosage started at 1 tablet twice daily, increasing to 2 tablets twice daily after 6 weeks. Participants tapered down/off statin use if blood lipids were as good or better than baseline. Also, participants were given sustained-release (5-7 hours) wax-matrix tablets containing niacinamide (750mg) with a dosage of 2 tablets twice daily. Participants on statin therapy who showed lipid improvements with study supplements gradually reduced their statin dosage. Lipid levels were rechecked after 6-8 weeks. If appropriate lipid levels were achieved, statins were discontinued, and lipid levels were monitored for stability.

DIHYDROBERBERINE SUPPLEMENT

Sustained-release (5-7 hours) wax-matrix tablets containing dihydroberberine (150mg) were given with a dosage of 2 tablets twice daily for participants with metabolic syndrome or type 2 diabetes, otherwise the dosage was 1 tablet twice daily.

TAXIFOLIN SUPPLEMENT

Sustained-release (5-7 hours) wax-matrix tablets containing taxifolin (50mg), vitamin C (500mg) and zinc (15mg) were given with a dosage of 1 tablet twice daily. If a participant developed symptoms of infection, they were advised to double the dosage (2 tablets twice daily) until symptoms of infection resolved.

MIXED TOCOTRIENOLS SUPPLEMENT

Immediate-release softgels providing mixed tocotrienols (50mg) in a fat-soluble suspension were given with a dosage of 4 softgels twice daily.

Results

This case series, conducted from September 2022 to August 2024, included a convenience sample of 10 adults (7 men; 3 women) living in the United States, average age 80 years (range 62-91 years). The supplement intervention lasted 16 months, on average. Most participants (7/10) were taking a statin at baseline.

All participants achieved comparable lipid benefits post-statin withdrawal with an average 25% decrease in total cholesterol, 35% decrease in low-density lipoprotein (LDL) cholesterol, 52% increase in high-density lipoprotein (HDL) cholesterol, and 46% decrease in triglycerides compared to baseline (see **Table 2**). Most participants (6/7) either maintained or improved their blood lipid levels without statin therapy. One participant discontinued his supplement regimen and resumed statin therapy, despite achieving an LDL cholesterol level of 2.12 mmol/L (82 mg/dl) and improving other blood lipids. This choice was made due to digestive upset, which his doctor attributed to the supplement regimen.

Table 2. Effect of Supplement Regimen on Blood Lipid Parameters After Statin Drug Discontinuation (n=7)

Lipid Parameter	Baseline	Post Statin Discontinuation	Percent Change
Total cholesterol	4.63 mmol/L (179 mg/dl)	3.47 mmol/L (134 mg/dl)	-25%
LDL cholesterol	2.43 mmol/L (94 mg/dl)	1.58 mmol/L (61 mg/dl)	-35%
HDL cholesterol	1.58 mmol/L (61 mg/dl)	2.40 mmol/L (93 mg/dl)	+52%
Triglycerides	1.14 mmol/L (101 mg/dl)	0.62 mmol/L (55 mg/dl)	-46%

LDL indicates low-density lipoprotein, HDL, high-density lipoprotein.

Three participants had elevated Lp(a) at baseline (213, 313, 640 nmol/L [85, 125, 256 mg/dl]). The two participants with the lower Lp(a) levels were able to achieve normal levels (<75 nmol/L [<30 mg/dl]) after 6 weeks of supplementation with wax-matrix NA/pantetheine and wax-matrix dihydroberberine. The participant with the higher baseline Lp(a) level of 640 nmol/L (256 mg/dl) initially improved to 370 nmol/L (148 mg/dl), but then appeared to develop liver hypersensitivity to NA. Her NA treatment was

temporarily stopped to allow the side effect to resolve, then resumed at a lower dose.

All 10 participants completed the cognitive and well-being assessments, reporting generally stable or positive physical and mental functions compared to baseline (see **Table 3**). One participant reported improved balance; another reported improved energy and alertness. Side effects were successfully managed (see **Table 4**).

Table 3. Effect of Supplement Regimen on Cognitive Function as Assessed by Changes in the SAGE 2 Score (Normal Score=22)

		SAGE 2 Score	
Participant		**Baseline**	**Post Supplementation**
91 yr	male	10	16
77 yr	male	18	22
89 yr	male	22	22
81 yr	male	22	22
73 yr	female	16	21
61 yr	male	21	22
73 yr	female	21	22
80 yr	male	18	22
64 yr	female	22	22
81 yr	male	22	22
Average Score		**19.5**	**21.3**

SAGE 2 indicates Self-Administered Gerocognitive Exam, a validated cognitive assessment tool.

Table 4. Adverse Side Effects: Occurrence and Management

Adverse Effect	**Management**
Skin Flushing (n=4)	Take supplements with meals; avoid hot foods/beverages; avoid chewing tablets; take aspirin/NSAID as needed to reduce flushing.
Elevated Blood Homocysteine (n=3)	Add a vitamin B12/folate supplement until homocysteine level returns to normal.
Upset Stomach (n=4)	Check liver enzymes, if normal, use antacids/acid blocking agents for relief.
Liver Hypersensitivity (n=2)	Withdraw NA temporarily until liver enzymes (AST, ALT) return to normal, encourage more methyl-donor foods in diet, then resume NA gradually to a lower maintenance dose (usually 500mg twice daily)

NSAID indicates a non-steroidal anti-inflammatory drug; NA, nicotinic acid; ALT, alanine transaminase; AST, aspartate transferase.

Discussion

This case series reveals the potential value of a unique supplement regimen for older adults. Overall, the supplement regimen had a positive effect on blood lipid profiles, especially for those taking a statin at baseline. Indeed, the clinically relevant improvements in blood lipid profiles, including total, LDL and HDL cholesterol, triglycerides, and Lp(a), suggest therapeutic promise for dyslipidemia and cardiovascular health.

Impressively, all participants taking statins at baseline were able to discontinue use while maintaining blood lipid levels that were as good as and often better than their baseline levels, suggesting the potential to eliminate statin drug use and its associated adverse side effects. This is important because statins deplete intracellular levels of CoQ10,[29] an important molecule for muscular health and function. Indeed, statin-induced CoQ10 depletion contributes to a high rate of statin intolerance, reaching approximately 18% to 20%.[30] Statins are associated with dementia in older people,[31] further limiting their utility in this population. Statins can raise Lp(a) by up to 20%,[32] a concern given Lp(a) is significantly more atherogenic than LDL cholesterol.[33] Moreover, the affordability of statin drugs in developing countries can be a challenge.

Interestingly, two participants, who were previously on statins and had baseline lab values suggesting borderline metabolic syndrome achieved significant results after supplementation. One maintained excellent blood lipid levels and discontinued two blood pressure medications. With added exercise and weight loss, his elevated HbA1c returned to normal. The second participant saw only a slight rise in blood lipids after stopping statins for 8 months and achieved normal blood glucose and HbA1c levels with supplementation. Notably, he tested positive for COVID-19, doubled his taxifolin dosage, and returned to normal in less than two days.

It is important to note that, even if the LDL level remains the same after discontinuing statins, supplementation helps reduce two pathogenic factors: the number of small, dense LDL particles and the level of LDL oxidation.

The supplement regimen helped improve physical and mental function, including balance, energy, and alertness, all crucial for older individuals to remain independent. That all participants maintained or improved their SAGE 2 scores is encouraging and suggests supplementation may play a direct role in helping maintain cognitive function.

The fact that no deaths, strokes, heart attacks, cancer, or serious infections occurred, despite conducting the study

during two severe winter flu/virus seasons, suggests the supplement regimen has a potential role in disease prevention.

Separately, the successful management of the transient adverse side effects underscores the importance of customizing supplement regimens to meet individual needs. Indeed, findings from this case series support the lessons learned from previous wax-matrix NA studies, including the importance of a "start low and go slow" approach when initiating NA treatment. Even though the average maintenance dosage of wax-matrix NA for most patients is 750-1,000mg twice daily with meals, it will dramatically increase flushing and other adverse side effects if treatment is initiated at that level.

Successful side effect management also helped prevent drop-outs. Two participants who were not taking statins improved their lipid levels, but experienced NA hepatic hypersensitivity. Therapy was temporarily paused, and the participants were encouraged to talk to their doctors about resuming NA at a lower dosage. In my research experience, individuals with NA-related liver hypersensitivity often do better than average on a lower dosage. Also, adding a vitamin B12/folate supplement helps reduce elevated homocysteine. Remarkably, no deaths, strokes, heart attacks, cancer, or serious infections occurred, despite conducting the study during two severe winter flu/virus seasons.

Due to the preliminary nature of this study, more research is needed to determine how well the findings apply to the broader population of older adults. In addition, the extent to the individual dietary ingredients in the supplement regimen contributed to the observed results is unclear. Finally, improvements in diet and lifestyle habits may have contributed to the positive outcomes.

Conclusion

This case series validates the therapeutic potential of a novel dietary supplement regimen to promote healthy aging in older adults, including treating dyslipidemia, promoting physical and mental well-being, and reducing the burden of prescription drugs like statin drugs. While the exploratory nature of this study makes further research necessary, its findings offer insight for the design of a larger controlled clinical trial aimed at addressing the growing healthcare needs of the aging population.

Conflicts of Interest Statement

The author declares no conflict of interest.

Funding Statement

This study was funded by Endurance Products Company (Sherwood, Oregon) and the author.

Acknowledgements

The author would like to acknowledge Endurance Products Company, Inc. for generously providing the dietary supplements used by the participants in this case series. Special thanks to Kathleen Dunn, MPH, RD, for her valuable review and contributions to the manuscript.

References

1. Patwardhan V, Gil GF, Arrieta A, et al. Differences across the lifespan between females and males in the top 20 causes of disease burden globally: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Public Health*. 2024;9(5):e282-e294. doi:10.1016/S2468-2667(24)00053-7

2. Keenan J. The niacin rebirth: revisiting the potential of nicotinic acid therapy for cardiovascular disease and niacin supplementation for healthy aging. *Med Res Arch*. 2024;12(7):1-9. doi:10.18103/mra.v12i7.5521

3. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). *Am Heart J*. 2011;161(3):471-477.e2. doi:10.1016/j.ahj.2010.11.017

4. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34(17):1279-1291. doi:10.1093/eurheartj/eht055

5. D'Andrea E, Hey SP, Ramirez CL, Kesselheim AS. Assessment of the role of niacin in managing cardiovascular disease outcomes: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(4):e192224. doi:10.1001/jamanetworkopen.2019.2224

6. CW. Niacin in patients with chronic kidney disease: is it effective and safe?. *Kidney Res Clin Pract*. 2013;32(1):1-2. doi:10.1016/j.krcp.2013.02.001

7. Wuerch E, Urgoiti GR, Yong VW. The promise of niacin in neurology. *Neurotherapeutics*. 2023;20(4):1037-1054. doi:10.1007/s13311-023-01376-2

8. McReynolds MR, Chellappa K, Baur JA. Age-related NAD+ decline. *Exp Gerontol*. doi:10.1016/j.exger.2020.110888

9. Tribble JR, Otmani A, Sun S, et al. Nicotinamide provides neuroprotection in glaucoma by protecting against mitochondrial and metabolic dysfunction. *Redox Biol*. 2021;43:101988. doi:10.1016/j.redox.2021.101988

10. Hui F, Tang J, Williams PA, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. *Clin Exp Ophthalmol*. 2020;48(7):903-914. doi:10.1111/ceo.13818

11. Feng R, Shou JW, Zhao ZX, et al. Transforming berberine into its intestine-absorbable form by the gut microbiota. *Sci Rep*. 2015;5:12155. doi:10.1038/srep12155

12. Song D, Hao J, Fan D. Biological properties and clinical applications of berberine. *Front Med*. 2020;14(5):564-582. doi:10.1007/s11684-019-0724-6

13. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (*Berberis vulgaris*): a clinical review. *Phytother Res*. 2019;33(3):504-523. doi:10.1002/ptr.6252

14. Bibak B, Shakeri F, Keshavarzi Z, et al. Anticancer mechanisms of berberine: a good choice for glioblastoma multiforme therapy. *Curr Med Chem*. 2022;29(26):4507-4528. doi:10.2174/0929867329666220224112811

15. Ke X, Zhang R, Li P, et al. Hydrochloride Berberine ameliorates alcohol-induced liver injury by regulating inflammation and lipid metabolism [published correction appears in Biochem Biophys Res Commun. 2022 Aug 20;617(Pt 1):68-69. doi: 10.1016/j.bbrc.2022.05.077]. *Biochem Biophys Res Commun*. 2022;610:49-55. doi:10.1016/j.bbrc.2022.04.009

16. Warowicka A, Nawrot R, Goździcka-Józefiak A. Antiviral activity of berberine. *Arch Virol*. 2020;165(9):1935-1945. doi:10.1007/s00705-020-04706-3

17. Das A, Baidya R, Chakraborty T, Samanta AK, Roy S. Pharmacological basis and new insights of taxifolin: a comprehensive review. *Biomed Pharmacother*. 2021;142:112004. doi:10.1016/j.biopha.2021.112004

18. Kanchi MM, Shanmugam MK, Rane G, Sethi G, Kumar AP. Tocotrienols: the unsaturated sidekick shifting new paradigms in vitamin E therapeutics [published correction appears in Drug Discov Today. 2019 Jul;24(7):1421. doi: 10.1016/j.drudis.2018.02.010]. *Drug Discov Today*. 2017;22(12):1765-1781. doi:10.1016/j.drudis.2017.08.001

19. Naomi R, Shafie NH, Kaniappan P, Bahari H. An interactive review on the role of tocotrienols in the neurodegenerative disorders. *Front Nutr*. 2021;8:754086. doi:10.3389/fnut.2021.754086

20. Gopalan Y, Shuaib IL, Magosso E, et al. Clinical investigation of the protective effects of palm vitamin E tocotrienols on brain white matter. *Stroke*. 2014;45(5):1422-1428. doi:10.1161/STROKEAHA.113.004449

21. Zuo S, Wang G, Han Q, et al. The effects of tocotrienol supplementation on lipid profile: a meta-analysis of randomized controlled trials. *Complement Ther Med*. 2020;52:102450. doi:10.1016/j.ctim.2020.102450

22. O'Byrne D, Grundy S, Packer L, et al. Studies of LDL oxidation following alpha-, gamma-, or delta-tocotrienyl acetate supplementation of hypercholesterolemic humans. *Free Radic Biol Med*. 2000;29(9):834-845. doi:10.1016/s0891-5849(00)00371-3

23. Radhakrishnan A, Tudawe D, Chakravarthi S, Chiew GS, Haleagrahara N. Effect of γ-tocotrienol in counteracting oxidative stress and joint damage in collagen-induced arthritis in rats. *Exp Ther Med*. 2014;7(5):1408-1414. doi:10.3892/etm.2014.1592

24. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life*. 2019;71(4):487-494. doi:10.1002/iub.1976

25. Lu Y, Zhang Y, Pan Z, et al. Potential "therapeutic" effects of tocotrienol-rich fraction (TRF) and carotene "against" bleomycin-induced pulmonary fibrosis in rats via TGF-β/Smad, PI3K/Akt/mTOR and NF-κB signaling pathways. *Nutrients*. 2022;14(5):1094. doi:10.3390/nu14051094

26. Sailo BL, Banik K, Padmavathi G, Javadi M, Bordoloi D, Kunnumakkara AB. Tocotrienols: the promising analogues of vitamin E for cancer

therapeutics. *Pharmacol Res*. 2018;130:259-272. doi:10.1016/j.phrs.2018.02.017

27. Zainal Z, Khaza'ai H, Kutty Radhakrishnan A, Chang SK. Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: evidence from preclinical and clinical studies. *Food Res Int*. 2022;156:111175. doi:10.1016/j.foodres.2022.111175

28. Poon IO, Chow DS, Liang D. Dissolution profiles of nonprescription extended-release niacin and inositol niacinate products. *Am J Health Syst Pharm*. 2006;63(21):2128-2134. doi:10.2146/ajhp060089

29. Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(19):e009835. doi:10.1161/JAHA.118.009835

30. Saxon DR, Eckel RH. Statin intolerance: a literature review and management strategies. *Prog Cardiovasc Dis*. 2016;59(2):153-164. doi:10.1016/j.pcad.2016.07.009

31. Prasanna P, Liu S, Silverman D. 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. *J Nucl Med*. 2021;62(supp 1). Abstract 102. doi.org/10.1002/alz.069394

32. Zhu L, Fang Y, Gao B, et al. Effect of an increase in Lp(a) following statin therapy on cardiovascular prognosis in secondary prevention population of coronary artery disease [published correction appears in BMC Cardiovasc Disord. 2022 Dec 30;22(1):577. doi: 10.1186/s12872-022-03027-4]. *BMC Cardiovasc Disord*. 2022;22(1):474. doi:10.1186/s12872-022-02932-y

33. Björnson E, Adiels M, Taskinen MR, et al. Lipoprotein(a) is markedly more atherogenic than LDL: an apolipoprotein b-based genetic analysis. *J Am Coll Cardiol*. 2024;83(3):385-395. doi:10.1016/j.jacc.2023.10.039

