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REVIEW ARTICLE

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The role of biofactors in the prevention and treatment of age-related diseases

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Abstract

The present demographic changes toward an aging society caused a rise in the number of senior citizens and the incidence and burden of age-related diseases (such as cardiovascular diseases [CVD], cancer, nonalcoholic fatty liver disease [NAFLD], diabetes mellitus, and dementia), of which nearly half is attributable to the population ≥60 years of age. Deficiencies in individual nutrients have been associated with increased risks for age-related diseases and high intakes and/or blood concentrations with risk reduction. Nutrition in general and the

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AD, Alzheimer's disease; AHA, American Heart Association; ALA, α-linolenic acid; ALT, alanine amino transferase; AST, aspartate aminotransferase; CHD, coronary heart disease; CVD, cardiovascular diseases; DGE, German Nutrition Society; DHA, docosahexaenoic acid; EC, epicatechin; ECG, epicatechin gallate; EFSA, European Food Safety Authority; EGC, epigallocatechin; EGCG, epigallocatechin gallate; ElOVL6, fatty acid elongase 6; EPA, eicosapentanoic acid; FDA, U.S. Food and Drug Administration; FFA4, free fatty acid receptor 4; $GABA_A$, γ-aminobutyric acid type A; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MMSE, mini-mental state examination; NAFLD, nonalcoholic fatty liver disease; NAS, NASH Clinical Research Network scoring system; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, *N*-methyl-D-aspartate; omega-3 PUFA, omega-3 polyunsaturated fatty acids; PCSK 9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; SOD1, superoxide dismutase 1; SREBP-1, sterol regulatory element-binding protein-1; UL, upper intake level; VLDL, very low-density lipoprotein; αT, α-tocopherol.

dietary intake of essential and nonessential biofactors is a major determinant of human health, the risk to develop age-related diseases, and ultimately of mortality in the older population. These biofactors can be a cost-effective strategy to prevent or, in some cases, even treat age-related diseases. Examples reviewed herein include omega-3 fatty acids and dietary fiber for the prevention of CVD, α-tocopherol (vitamin E) for the treatment of biopsy-proven nonalcoholic steatohepatitis, vitamin D for the prevention of neurodegenerative diseases, thiamine and α-lipoic acid for the treatment of diabetic neuropathy, and the role of folate in cancer epigenetics. This list of potentially helpful biofactors in the prevention and treatment of age-related diseases, however, is not exhaustive and many more examples exist. Furthermore, since there is currently no generally accepted definition of the term *biofactors*, we here propose a definition that, when adopted by scientists, will enable a harmonization and consistent use of the term in the scientific literature.

KEYWORDS

biofactor definition, cancer epigenetics, cardiovascular diseases, diabetes mellitus, micronutrients, neurodegenerative diseases, nonalcoholic fatty liver disease

1 | INTRODUCTION

On a global scale, life expectancy at birth has been increasing throughout the history of humankind, in particular during the last centuries. This has largely been explained by reduced infant and child mortality as a result of fewer deaths caused by infectious diseases. The still continuing increase in longevity, and the accompanying global increase in the number of senior citizens, is primarily a result of reduced mortality at old age (≥60 years).[1] The World Health Organization estimated that the mean life expectancy of 60-year-old women and men in 2012 was 21.5 and 18.5 years, respectively,[1] and that the number of persons aged 60 years or older will exceed that of children under the age of 5 years by the year 2020.[2] According to data from the United Nations, this estimation was correct and as of April 2020, the global population of people aged >60 years of 1.05 billion exceeded that of children under 5 years (678 million) by a factor of 1.55.[3] In Europe and Northern America, the number of persons older than 60 years was even five, respectively, four times higher than that of children under 5 years, and about two times higher than that of children under 10 years (Figure 1[3]).

In high income, but not in low- and middle-income countries, the gain in life expectancy at old age is mainly driven by reductions in the mortality due to noncommunicable diseases, primarily cardiovascular diseases

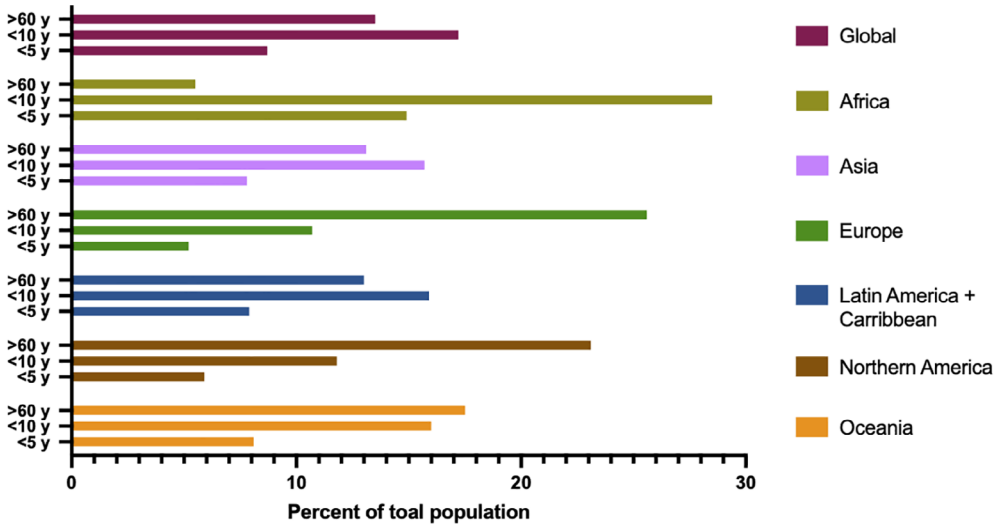

FIGURE 1 Percentage of the total population in 2020 comprised by the age groups <5, <10, and >60 years in different geographic regions and globally. In all regions except Africa, there are presently more people older than 60 years than children under 5 years. In Europe, Northern America and Oceania, the number of seniors (>60 years) even exceeds the number of children under 10 years[3]

(CVD).[1,4] Noncommunicable diseases, led by CVD (30%) and cancer (15%), are also the main contributors to disease burden in older persons and, in high-income countries, nearly half (49%) of the total disease burden is attributable to the population ≥60 years of age.[5] Noncommunicable diseases, including CVD, cancer, nonalcoholic fatty liver disease (NAFLD), diabetes mellitus, and dementia, are therefore not only major determinants of mortality but also of morbidity and consequently the healthy lifespan of humans.[4]

In the 21st century, human aging will be among the most challenging problems for societies around the world, because, first, it differs from most other health-alterations in that it affects all members of a species and, second, because it is one of the main risk factors for the development of many noncommunicable diseases.[5,6] The underlying causes for these so-called age-related diseases are manifold, but they do share a number of risk factors, including obesity, low physical activity, and an unbalanced diet. Insufficient intake and deficiencies in individual micronutrients (vitamins and essential minerals) have been associated with increased risks for these age-related diseases and high intakes and blood concentrations with risk reduction.[6,7] Not only the provision with essential micronutrients but also the intake and tissue concentrations of nonessential food factors, such as long-chain omega-3-fatty acids, flavonoids, and other phytochemicals, have been associated with the risk of age-related diseases and mortality, with low intake, respectively, status of these biofactors increasing, and high intake/status decreasing risk.[7–10]

About a decade ago, Bruce Ames proposed the "triage theory," which postulates that the organism uses essential micronutrients first for biological functions that are required for short-term survival (i.e., functions for which deficiency symptoms are known) and only after these needs are satisfied, directs micronutrients toward functions (e.g., by targeted tissue distribution) that are required for the prevention of age-related diseases.[6]

In summary, nutrition in general and the dietary intake of essential and nonessential biofactors is a major determinant of human health, the risk to develop age-related diseases, and ultimately of mortality in the older population.

2 | WHAT ARE BIOFACTORS?

Despite the existence of a journal devoted to and named *BioFactors*, there is currently no generally agreed definition of the term. As stated in the scope of this journal: "The word 'biofactors' refers to the many compounds that regulate biological functions. Biological factors comprise many molecules produced or modified by living organisms and present in many essential systems like the blood, the nervous or immunological systems. A non-exhaustive list of biological factors includes neurotransmitters, cytokines, chemokines, hormones, coagulation factors, transcription factors, signaling molecules, receptor ligands and many more. In the group of biofactors we can accommodate several classical molecules not synthetized in the body such as vitamins, micronutrients or essential trace elements." This text already gives examples for substances that could be classified as biofactors, but it does not clearly define the term. Generally, one may suggest that biofactors could be used synonymously for terms such as *bioactives* or *biofunctionals*, which are frequently used to describe compounds that exert a biological function. But then again, neither are these terms clearly characterized, nor is their use in the literature standardized.[11]

Here, we propose the following definition for the term *biofactors*: Biofactors are substances required by the body for its normal physiological functioning and/or with health-beneficial and/or disease-preventive biological activities.

It is noteworthy, however, that the scientific evidence required from human trials to support health-beneficial or disease-preventive effects of biofactors is high and difficult to obtain.

Based on this definition, biofactors can be subdivided into further and partly overlapping categories, such as endogenous (produced in the organism) versus exogenous (taken in from external sources), essential (with known deficiency symptoms) versus nonessential (health beneficial), organic (e.g., macronutrients and vitamins) versus inorganic (minerals), and more (Figure 2). Even these subcategories can be further subdivided.

Essential biofactors are those that the organism cannot produce or not produce in sufficient quantity and which therefore need to be supplied from external sources. An important class of exogenous biofactors are dietary biofactors, which include vitamins and pro-vitamins, minerals, enzymes, peptides, amino acids, fatty acids, phytochemicals and more, which are the focus of the present review.

3 | OBJECTIVES

This review aims to synthesize the role of selected dietary biofactors in the prevention of the most important age-related diseases, to identify new trends, and to point toward promising future research topics. The review does not intend to provide an exhaustive overview over all available literature on the health benefits of all dietary biofactors.

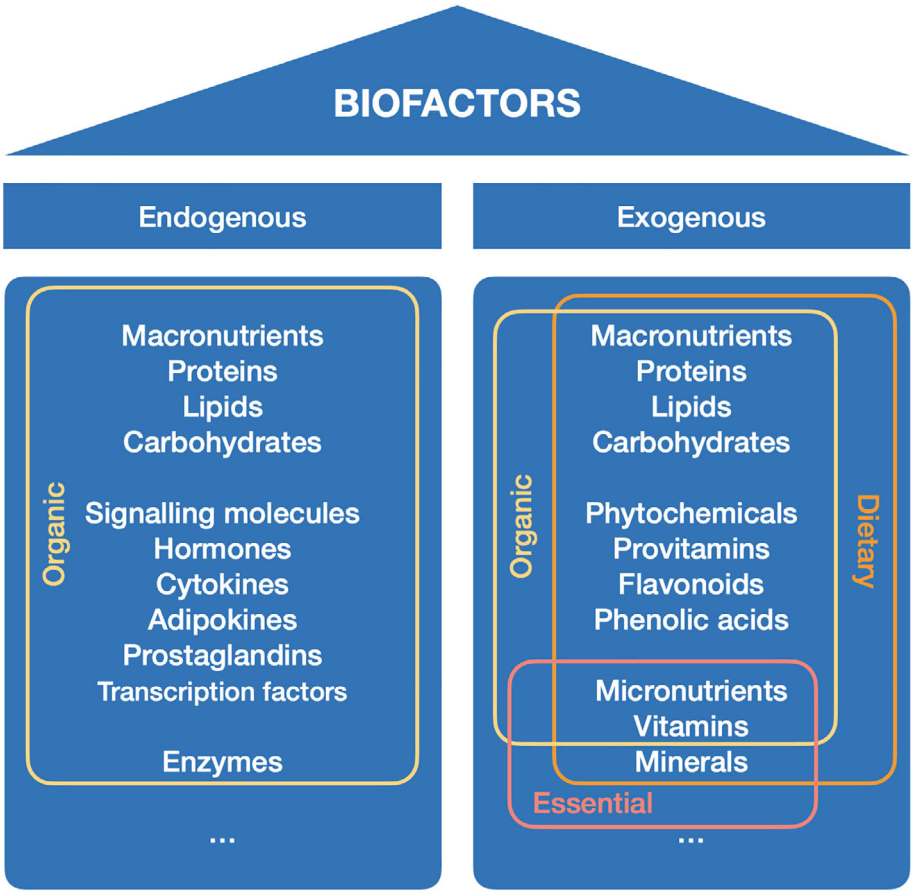

FIGURE 2 Biofactors are substances required by the human body for its normal physiological functioning and/or with health-beneficial and/or disease-preventive biological activities and can be subclassified into endogenous (produced in the organism) or exogenous (taken in from external sources) biofactors; further subdivisions are possible and some examples are shown

4 | ROLE OF BIOFACTORS IN CANCER AND EPIGENETICS

4.1 | Pathophysiology and burden of cancer

According to the International Agency for Research on Cancer, the number of new cancer cases and cancer deaths will globally rise.[12] Cancer shows a remarkable diversity and primary tumorigenesis, tumor progression and metastasis have a multifactorial and complex pathophysiology.[13] In particular, epigenetic changes seem to impact the initiation, development, and progression of different cancer types. Moreover, it is likely that these epigentic alterations are not limited to cancer cells but are also present in the altered cells of the tumor-associated stroma and influence the tumor microenvironment.[13,14] Different epigenetic mechanisms can be distinguished and include changes in DNA methylation, modifications of histone proteins, alterations of microRNA regulation, and interactions thereof.[14,15] Because epigenetic changes are highly dynamic and reversible, they have attracted considerable research interest, especially as possible novel targets for cancer treatment.

The methylation and demethylation of the DNA are one of the best-characterized epigenetic mechanisms.[14,15] DNA methyltransferases can modulate the chromatin structure and thereby impact transcriptional activation or repression by the addition of a methyl group to the fifth carbon of a cytosine residue. Methylation of DNA occurs mainly at cytosine- and guanine-rich areas of promotor regions, the so-called CpG islands.[16] In general, methylated promotor regions are less accessible and transcription is repressed, whereas gene expression can take place in unmethylated promotor regions. Interestingly, unlike normal cells, cancer cells show highly variable CpG methylation and progressive changes during tumorigenesis and cancer onset but also throughout tumor progression and metastasis.[15,17] Especially genes for cell cycle regulation and tumor suppressors display hypermethylated promotor regions and subsequently a diminished level of transcription in tumor cells. Therefore, biofactors that modulate DNA cytosine methylation affect epigenetic transcription–regulation and may thereby also influence susceptibility, genesis, and treatment of cancer. In this context, a number of dietary biofactors that regulate DNA methylation in tumor cells have been characterized and are currently under investigation for possible therapeutic applications.[18–20]

4.2 | Folate

The term folate (also known as vitamin B_9) describes a group of heterocyclic compounds based on pteroic acid linked by a methylene bridge to a *p*-aminobenzoyl group and conjugated with one or more L-glutamate units.[21] Whereas natural folate forms are usually polyglutamylated and a mixture of reduced folates, folic acid is the synthetic monoglutamate form with a fully oxidized pteridine ring.[22,23] While folic acid occurs in the human diet mostly in supplements and fortified foods, natural folates can be found, among others, in leafy vegetables, beans, liver, and yeast.[24] Noteworthy, the synthetic folic acid shows a superior stability and much greater bioavailability than natural food folates. Folate and other B vitamins, namely vitamins B_2 (riboflavin), B_6 (pyridoxine respectively its active form pyridoxal-5′-phosphate), and B_{12} (cobalamin), have essential functions in the human C1 metabolism. Folate is a cofactor in the biosynthesis of DNA and RNA and required for methylation processes, such as the remethylation of homocysteine to methionine, which is an important step for the methylation of DNA. Deficiency of folate causes a hyperhomocysteinemia that affects various biomolecules and cellular processes, including epigenetic mechanisms, such as methylation of the DNA and histone proteins and modifications of noncoding RNA.[25] Collectively, B vitamins, including folate, are critical factors for nucleotide synthesis, cell proliferation, and epigenetic regulation.[26]

Insufficient intakes and deficiencies in folate and vitamins B_6 and B_{12} are common in the elderly polulation.[27] Inadequate intake and deficiency of folate are associated with increased risks for cancer, including, but not limited to, pancreatic, bladder, and cervix cancer.[28–30] A meta-analysis on the effects of folic acid supplementation (0.5–40 mg/day) on overall and site-specific cancer incidence evaluated data for 50,000 individuals and found no substantial increase or decrease in cancer incidence during the first 5 years of treatment.[31] On the other hand, a meta-analysis of six RCT found an increased risk for prostate cancer after folic acid supplementation, indicating that further prospective studies are needed.[28,32]

On the cellular level, folate can modulate overall and/or gene-specific DNA methylation. But again, animal and human trials showed conflicting results. Despite the role of folate as a methyl donor, a folate-deficient diet does not necessarily correlate with DNA hypomethylation and conversely folate supplementation does not always induce hypermethylation.[33,34] These inconsistent findings demonstrate the complexity of the interplay between folate, diet, epigenetic regulation of DNA methylation, and the resulting effects on cancer. In order to better understand these apparently contradictory findings, several aspects and confounding factors need to be considered. Studies that analyzed folate supplementation used diverse dosages and varied in observation periods. The dose, in particular, is an important factor. A dose–response meta-analysis of prospective studies discovered a potential J-shaped correlation between folate intake and breast cancer risk. While a daily intake of 200–320 μg folate was associated with a lower breast cancer risk, a daily intake of >400 μg significantly increased the risk.[35] Studies that focused on gene-specific methylation, instead of global methylation, observed more consistent and reproducible findings.[36]

It should also be taken into account that other factors influence the role of folate in the human C1 metabolism and as a methyl donor, respectively.[33] The generation of S-adenosylmethionine, a key molecule for DNA methylation, requires not only folate but also the vitamins B_2 (riboflavinbe), B_6 (pyridoxal 5′-phosphate), and B_{12} (cobalamin). Vitamin B_6 is required for the reaction of tetrahydrofolate to 5,10-methylene-tetrahydrofolate, vitamin B_2 for the generation of 5-methyl-tetrahydrofolate, and B_{12} for the remethylation of homocysteine to methionine (Figure 3). Deficiency of one or more of these B vitamins consequently affects DNA methylation irrespective of folate status.[24] Due to these close metabolic interactions of the B vitamins, folate-mediated health effects cannot be viewed independently from an adequate supply of these cofactors.

Moreover, animal studies suggest that the consequences of folate supplementation on DNA methylation may also be strongly affected by the different stages of the life cycle.[34] In addition, folate-mediated effects may be influenced by the folate diet of the parent generation and in particular the maternal nutritional status. Thus, the accurate timing of folate supplementation might also be an important but also highly complex factor in the human diet.

Nutrition is an important contributor to epigenetic changes and thereby modulates the susceptibility to diseases, including cancer. Undoubtedly, folate has an impact on the epigenetic regulation via DNA methylation. Alterations in the cellular methylation status play an evident role in cancer onset, progression, and the tumor microenvironment. Currently, further nutritional and clinical studies are needed to clarify the optimum folate intake, possible further cofactors, and timing of administration in order to maximize folate-mediated health effects, including therapeutical epigenetic modulation of DNA methylation. Although folate is biochemically well characterized, it is so far difficult to evaluate its potential as epigenetic modifier for cancer prevention and therapy.

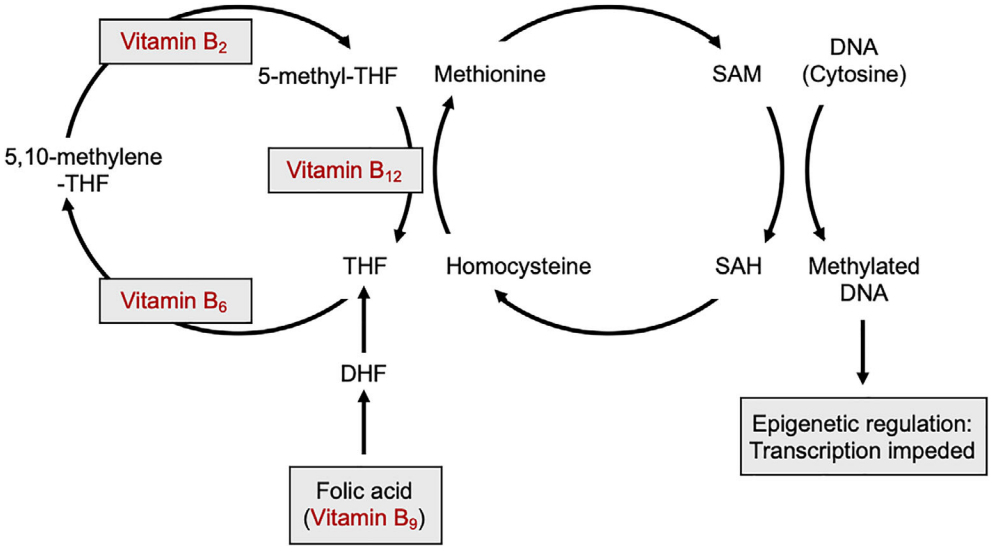

FIGURE 3 Overview of the role of folic acid and interactions with other B vitamins in DNA methylation. B vitamins involved in C1 metabolism are colored in red. DHF, dihydrofolate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; THF, tetrahydrofolate

5 | THE ROLE OF BIOFACTORS IN CVD

5.1 | Pathophysiology and burden of CVD

CVD are disorders of the heart and arterial vessels and are categorized as coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease, respectively.[37] The extensive morphological changes of the vascular wall during atherosclerosis are a major cause of CVD. The initial event in atherosclerosis is endothelial dysfunction, which is caused by different types of pathological stimuli that trigger inflammatory processes in the arterial wall and eventually lead to thickening, adaptive enlarging, and stiffening of the arterial wall.

In brief, key events contributing to the progression of atherosclerosis include macrophage proliferation, monocyte infiltration and differentiation, immigration and proliferation of smooth muscle cells, and lipid accumulation (mostly in macrophages [foam cell formation]). Following further propagation, excessive lipid accumulation and proliferation of lipid-loaded macrophages, and deposition of cholesterol and fibrotic material result in fatty streak formation, elasticity loss and vascular lumen reduction with parallel widening of the arterial diameter (wall thickening).[38] Consequently, plaque rupture and thrombus formation can cause vascular occlusion, causing acute events such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke, or an occlusion of the artery itself.

In 2016, 85% of CVD-related deaths were due to the acute complications myocardial infarction and stroke.[37] Overall, CVD are still the leading cause of all global deaths (31%), thus causing a significant global burden. An unbalanced diet is one of the leading causes for CVD,[39] causing an estimated 50%–70% of cardiovascular and cardiometabolic disease-related deaths.[40] Hence, most of the cardiovascular complications could be prevented by a healthy lifestyle that avoids or contributes significantly to minimizing risk factors, such as tobacco use, unbalanced diet, obesity, physical inactivity, and excessive alcohol consumption.[37]

5.2 | Biofactors and CVD

While conventional medication, such as low-density lipoprotein (LDL) cholesterol-lowering drugs (e.g., cholesterol synthesis inhibitors, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) and antihypertensive drugs (e.g., calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and beta blockers) remain the first choice in the treatment of CVD, supplementing phytochemicals and micronutrients are an attractive and potentially cost-effective approach for their prevention and adjuvant therapy. In this context, micronutrient deficiencies, as reported for vitamin D, have been considered as cardiovascular risk factors.[41] For this reason, dietary supplements have been propagated globally to prevent or even cure CVD and remain popular in the United States and Europe, despite the fact that numerous studies failed to show benefits from dietary supplements.[42]

From 2012 to 2017, more than 1400 published studies investigated the effects of vitamins and minerals on CVD. A recent meta-analysis analyzed 179 randomized controlled trials (RCTs) with respect to the effects of selected individual supplements as well as multinutrient

supplements on fatal and nonfatal events from CVD and coronary heart disease and their complications myocardial infarction and stroke and found no effect on the event rate of CVD for multivitamins, vitamin D, calcium, and vitamin C, whereas folic acid significantly decreased the event rate of stroke and total CVD, and other vitamin B-complexes decreased stroke with numbers needed to treat of 167, 111, and 250, respectively.[42] It is noteworthy that calcium and magnesium are the most popular supplemented minerals in Germany,[43] Europe,[44] and the United States.[45]

5.3 | Calcium

In addition to a lack of benefit from calcium supplementation, the question has arisen whether (high dose) supplementation of calcium may even increase CVD risk.[46] The German Nutrition Society (DGE) and the U.S. Food and Drug Administration (FDA) recommend a daily intake of 1000 mg calcium for adults to maintain optimum bone mineralization[47,48] and the European Food Safety Authority (EFSA) and the FDA set a tolerable upper intake level (UL) for adults, which is not associated with any harm, at 2500 mg/day.[49] The source of calcium (diet vs. supplements) may be of relevance, as supplementation of more than 1000 mg/day calcium was reported to increase cardiovascular mortality due to incident calcification of coronary arteries, whereas no adverse effects were observed for calcium-rich diets (dairy products, green vegetables, calcium-rich mineral water).[50]

The above-mentioned meta-analysis found no significant effect of calcium supplementation on coronary and cardiovascular events or mortality but observed trends toward an 1.69-fold increase in risk for myocardial infarction ($p = 0.08$) and 1.29-fold increase in risk for stroke ($p = 0.09$).[42] As dietary supplementation with calcium did not prevent CVD and due to potential adverse effects, individual calcium status and requirements should be assessed prior to supplementing calcium.[46] However, as long as calcium intake from the diet or supplements does not exceed the UL of 2500 mg, there is no evidence that the mineral may positively or negatively alter the cardiovascular risk in healthy adults.[51]

5.4 | Magnesium

Magnesium is the fourth most abundant mineral in humans and the second most abundant intracellular cation. A daily intake of 400 mg magnesium (e.g., from avocado, banana, dairy products, and nuts) is recommended.[47,48] Magnesium ions interact with several hundred enzymes, especially those involved in energy metabolism, such as phosphate transfer reactions with ATP,[52] and are therefore essential for many cellular functions.[53] Magnesium also affects processes involved in blood pressure regulation; it dose-dependently blocks calcium channels,[54] antagonizes *N*-methyl-D-aspartate (NMDA)-receptor signaling, stimulates γ-aminobutyric acid type A ($GABA_A$)-receptors, and inhibits glutamate release from presynaptic neurons by antagonizing Ca^{2+}.[55]

Meta-analyses of clinical trials on the effects of magnesium therapy and blood pressure reported varying results, depending on the inclusion and exclusion criteria. A meta-analysis of 34 trials involving 2028 participants found that magnesium supplementation at a median dose of 368 mg daily for a median duration of 3 months significantly reduced systolic blood pressure by 2.0 mm Hg and diastolic blood pressure by 1.8 mm Hg. These effects were accompanied by an increase in serum magnesium of 0.05 mmol/L.[56] In 20 studies on 1220 participants, dose-dependent reductions of 4.3 mm Hg systolic and 2.3 mm Hg diastolic blood pressure for each 240 mg/day increase in magnesium intake (range 240–960 mg/day) were observed.[57] Overall, these meta-analyses suggest that oral magnesium may be helpful in lowering high blood pressure.[58]

In a monocentric, controlled, double-blinded study, 79 patients with severe congestive heart failure received either magnesium-orotate (6 g for 1 month, 3 g for 11 months, $n = 40$) or placebo ($n = 39$) and survival rate was 75.7% in the verum versus 51.6% in the placebo group ($p < 0.05$) after 1 year.[59] These data were confirmed in a study with similar design[60] and are in accordance with the role of orotic acid as magnesium-fixing agent.[61]

In agreement, one meta-analysis reported that high serum magnesium concentrations were associated with lower risk of CVD; each 0.2 mmol mg/L increment lowered the risk by 30%.[62] Another meta-analysis of 450,000 individuals revealed a decreased risk for cardiovascular mortality with high magnesium intake (women: relative risk [RR] 0.84 [95% CI: 0.77; 0.92]; men: RR: 0.92 [95% CI: 0.86; 0.98]).[63] The risk of CVD mortality was reduced by 24%–25% per 100 mg/day increment of dietary magnesium intake in women. However, an overall dose–response relationship was not found.[63] In contrast, another recent meta-analysis found no correlation between magnesium intake and prevention of CVD.[42] Despite the positive effects of dietary and supplemental magnesium on blood pressure, its impact on CVD risk is less clear and requires further research.

5.5 | Vitamin D

Vitamin D insufficiency is common and estimated to affect over 1 billion people worldwide.[64] Food is a poor source of vitamin D and even though the vitamin is generated in the skin by UV-B-induced conversion of its precursor 7-dehydrocholesterol, there is insufficient sunlight intensity for several months of the year in nonequatorial regions to produce adequate amounts of vitamin D. Not only does the ability to synthesize vitamin D in the skin diminish with aging, but vitamin D deficiency has also been proposed to accelerate aging and increase the risk of age-related diseases.[7,65] Supplementation with vitamin D may therefore be an important strategy to maintain sufficient status and potentially mitigate the risks for age-related diseases.

Vitamin D is a precursor of the steroid hormone calcitriol and important for bone and mineral physiology.[64,66] As mentioned above, vitamin D is unique in that it is mainly obtained from sunlight-induced biosynthesis in the skin, while dietary intake contributes only little to vitamin D status.[64,67] Serum 25-hydroxyvitamin D (25(OH)D) concentrations are used to assess vitamin D status, with the recommended target blood concentrations ranging from 50 to 75 nmol/L (20–30 ng/ml).[64,66,67] The recommended upper limit (UL) for vitamin D is 100 μg/day (4000 IU/day) for all adults.[68]

Both the high prevalence of vitamin D deficiency in the general population and the identification of the vitamin D receptor throughout the cardiovascular system raised interest in the potential cardiovascular effects of vitamin D.[69,70] Evidence from experimental studies showed beneficial effects of vitamin D on heart and vessels, while in animal models (e.g., mice, rats, pigs), vitamin D intoxication (doses beyond 100,000 IU/kg bodyweight and day, by far exceeding the UL in humans) led to hypercalcemia and vascular calcification.[71] It is suggested that both hypervitaminosis and hypovitaminosis D can contribute to the development of vascular calcification via multiple complex mechanisms, indicating a biphasic impact of vitamin D on the vasculature.[71]

Epidemiological studies show that 25(OH)D concentrations are inversely associated with an increased CVD risk itself but also with established cardiovascular risk factors, such as arterial hypertension, and underlying pathological processes, such as endothelial dysfunction and atherosclerosis.[70] In contrast, RCT conducted so far have not convincingly demonstrated a positive effect of vitamin D supplementation on CVD risk or events or markers of vascular function.[70,72] For example, two recent meta-analyses reported that vitamin D supplementation had no significant effect on arterial blood pressure,[73,74] even in those participants with low baseline 25(OH)D concentrations or with elevated baseline blood pressure.[74] Similarly, meta-analyses of cardiovascular outcomes show no effect of vitamin D supplementation on myocardial infarction or stroke[75] and no beneficial effects on left ventricular function and exercise tolerance in the treatment of chronic heart failure.[76]

Potential explanations for the differences between evidence from epidemiological studies and intervention trials may lie in differences in reference ranges or the possibility that low vitamin D concentrations in CVD are only an epiphenomenon. While we wait for new data from a large number of ongoing intervention studies, the current conclusion is that vitamin D is a strong marker for CVD risk factors or for CVD itself.[70] More data from individuals with 25(OH)D deficiency (<25 nmol/L) or sensitive high-risk individuals are needed. The effects of vitamin D supplementation on CVD at doses that achieve 25(OH)D concentrations exceeding 100 nmol/L over the long term are currently not fully known and therefore caution is advised in this regard.[66,77]

5.6 | Omega-3 fatty acids

The three most relevant omega-3 polyunsaturated fatty acids (PUFA) are α-linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexaenoic acid (DHA). While ALA is predominantly found in plant oils such as flaxseed oil, DHA and EPA are found in fish and other seafood. ALA is an essential fatty acid, while EPA and DHA can be synthesized, even though at a low conversion capacity, from ALA.[78]

Despite the disappointing results of several intervention trials, the beneficial effects of omega-3 PUFA are still of interest. The use of DHA and EPA supplements increased more than nine-fold from 1999 to 2012,[45] most likely due to a statement of the advisory board of the American Heart Association (AHA) in 2002 referring to two RCTs, which revealed that fatal cardiac events were reduced upon DHA and EPA supplementation. At that time, supplementation of 1 g/day DHA plus EPA has been recommended for patients with documented CHD or increased blood triacylglycerols.[79] In the following years, several RCT failed to show consistent beneficial effects of omega-3 PUFA on primary and secondary cardiovascular events. Therefore, the AHA advisory board reconsidered its recommendation in 2017.[80] In summary, no recommendation can be made for the primary prevention of CHD, since data from RCT without prior CHD are still on demand. For primary prevention of CVD with omega-3 PUFA, the studies show inconsistent results. Furthermore, supplementation of DHA/EPA for patients

at high cardiovascular risk is no longer recommended by the majority of the members of the advisory board of the AHA.[80] In contrast, treatment with omega-3 PUFA supplements may be more reasonable for the secondary prevention of fatal CHD, although no reduction in the incidence of recurrent nonfatal myocardial infarction can be expected. In addition, no benefits of omega-3 PUFA supplementation were found for the primary or secondary prevention of stroke or heart failure.

Promising results from two large RCT, the *Vitamin D and Omega-3 Trial* (VITAL) study and the *Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial* (REDUCE-IT) study, have rekindled the interest in omega-3 PUFA in the prevention of CVD. The VITAL study, with 25,871 healthy middle-aged men and women enrolled, is one of the largest trials on this issue. In this study, supplementation with omega-3 PUFA at a dose of 1 g/day was not effective in the primary prevention of CVD with respect to the expanded composite end-point of cardiovascular events (0.93 [95% CI: 0.82–1.04]), total stroke (1.04 [95% CI: 0.83–1.31]), and death from cardiovascular causes (0.96 [95% CI: 0.76–1.21]), but was effective for total myocardial infarction (0.72 [95% CI: 0.59–0.90]) compared to placebo over 5.3 years.[81] These results are in line with the conclusions from previously published studies.[80,82]

In the REDUCE-IT trial, the efficacy of a total daily dose of 4 g/day icosapent ethyl, a highly purified EPA ethyl ester known to reduce plasma triacylglycerol concentrations, was investigated to reduce cardiovascular events in 8179 patients with established CVD or with diabetes mellitus and other risk factors, who had been receiving statin therapy and who had elevated fasting triacylglycerol concentrations.[83] The primary composite endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) occurred in 17.2% and 22.0% of icosapent ethyl-treated patients versus placebo, respectively (RR 0.75; [95% CI: 0.68–0.83]; $p < 0.001$). Therefore, this study presents the potential of omega-3 PUFA for therapy of CVD. However, serious issues of the REDUCE-IT trial are currently discussed: (i) as placebo, mineral oil was used which affects statin absorption and may in turn influence the rate of cardiovascular events in the placebo group over time; (ii) hospitalization for atrial fibrillation or flutter and serious bleeding events significantly increased under icosapent ethyl supplementation; and (iii) the different baseline concentrations of plasma C-reactive protein between the treatment groups at baseline.

In summary, omega-3 PUFA supplementation may reduce secondary but not primary cardiovascular events. However, the effects of DHA/EPA supplementation on CVD seem to be more pronounced in older studies, which may be explained, at least in part, by the higher fish consumption nowadays, due to an increasing knowledge about health-promoting effects of omega-3 PUFA. Some RCT may have been underpowered, thus explaining the lack of effect of omega-3 PUFA on the primary endpoints.[80] Further clarification on the potential of omega-3 PUFA to prevent CVD was expected from the Statin Residual Risk Reduction with EpaNova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH) trial which investigated the effect of the marine omega-3 PUFA on cardiovascular events in statin-treated patients with hypertriglyceridemia, low HDL cholesterol and high risk for CVD (ClinicalTrials.gov identifier: NCT02104817). However, the STRENGTH trial was recently terminated because cardiovascular events were similar between the omega-3 PUFA treatment group and the placebo group. Further, compared with placebo, omega-3 PUFA treatment was associated with more atrial fibrillation and gastrointestinal adverse events.[84] The reason for the neutral finding of the STRENGTH trial and the positive effects observed in the REDUCE-IT trial is likely due to the different composition of the omega-3 PUFA intervention used. Like the positive Japan EPA Lipid Intervention Study (JELIS),[85] the REDUCE-IT trial studied a purified formulation of high-dose EPA, whereas the STRENGTH trial used a combination of EPA and DHA. It is thus possible that DHA may counteract the benefits of EPA.

5.7 | Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the predominant flavonoids, ubiquitously found in (edible) plants and one of the most potent in vitro antioxidants of plant origin.[86] The richest food sources for quercetin are onions, asparagus, broccoli, kale, unpeeled apples, and blueberries. Red wine and tea (*Camellia sinensis*) can also contain quercetin in substantial amounts.[87] In some countries, quercetin is available as a dietary supplement with recommended daily doses of supplemental quercetin of 200–1200 mg.[88] The mean dietary intake in Western populations is estimated to be approximately 10–30 mg/day.[89–91] In epidemiological studies, regular consumption of flavonoids in general and quercetin in particular has been associated with a decreased risk of CVD.[92] This beneficial effect is supported by data from animal models and some clinical trials that have demonstrated effects of quercetin supplementation on a number of CVD risk factors, risk markers, and physiological pathways.[93–98]

For example, it was shown that supra-nutritional doses of quercetin significantly reduced systolic blood pressure[96–98] and plasma concentrations of oxidized low-density lipoprotein[98] in overweight to obese patients with metabolic syndrome traits. In addition, two recent meta-analyses of placebo-controlled trials (the majority of which involved normotensive or prehypertensive individuals) showed significant reductions in both systolic and diastolic blood pressure after quercetin supplementation.[99,100] Overall, the quercetin-induced reductions in blood pressure (range 3–5 mmHg) are similar to those experienced following current recommended lifestyle modifications to reduce elevated blood pressure (e.g., reducing sodium intake and body weight, increasing physical activity).[101] The mechanisms by which quercetin exerts these effects are not completely understood, although they most likely arise from modulation of cell signaling and gene expression in different cell types. Hypotheses tested in different experimental and clinical trials include lowering of oxidative stress, interference with the renin-angiotensin system, and improvement of endothelial function.[102]

In addition, anti-inflammatory effects of quercetin have been described in cell culture and animal studies.[94,95,103,104] Human intervention trials that investigated the effects of quercetin on biomarkers of systemic inflammation and endothelial activation (e.g., soluble adhesion molecules) showed inconsistent results.[105–107] Potential protective effects of quercetin may depend on the health status of the study population (e.g., effects in healthy young subjects are unlikely or small and are therefore difficult to observe), the quercetin dosage, the supplementation period, and concentrations of inflammatory markers at baseline.

The effects of quercetin on lipid profiles have been summarized in four meta-analyses of RCTs with inconclusive results.[100,108–110] For example, Sahebkar[109] found a significant decrease in triacylglycerols at pharmacologic doses (>500 mg/day), but no significant effects on LDL-cholesterol and HDL-cholesterol. The proposed lipid-lowering mechanisms of quercetin include an increase in fecal cholesterol and bile-acid excretion and inhibition of de novo triacylglycerol synthesis leading to reduced VLDL-triacylglycerol concentrations.[109] In the meta-analysis of Menezes et al.,[110] supplementation with flavonols (primarily quercetin) was associated with a decrease in triacylglycerols as well as total and LDL-cholesterol. However, subgroup analyses revealed no significant effects in healthy individuals or in those with normal baseline concentrations for any of the blood lipids.

As summarized above, there is striking evidence that quercetin mediates cardioprotective effects in humans, especially in subjects with CVD risk factors.

5.8 | Dietary fiber

Different types of dietary fiber, β-glucan in particular, have been studied thoroughly for their total and LDL-cholesterol-lowering effects.[111–113] A meta-analysis of 14 observational studies involving 400,492 participants and 14,427 patients with CHD indicates a protection against CHD by higher whole-grain intake (highest vs. lowest intake RR: 0.787 [95% CI: 0.743, 0.833]).[114] Subgroup analyses revealed inverse associations of whole-grain intake with CVD risk (RR: 0.762 [95% CI: 0.693; 0.838]) but not with myocardial infarction.[114] Similar findings have been reported in meta-analyses of 185 observational studies and 58 RCT.[115] The meta-analysis of the observational studies confirmed the beneficial effects of a daily intake of 25–29 g dietary fiber compared to a diet low in fiber, as higher fiber intake was associated with decreased all-cause mortality (RR: 0.85 [0.79–0.91]), cardiovascular mortality (RR: 0.69 [95% CI 0.60; 0.81]), incidence of CHD (RR: 0.76 [95% CI: 0.69; 0.83]), stroke (RR: 0.78 [95% CI: 0.69; 0.88]), and stroke mortality (RR: 0.80 [95% CI: 0.56; 1.14]). The meta-analysis of RCT revealed significantly lower concentrations of total cholesterol for high-fiber consumers (MD −0.15 [95% CI: −0.22; −0.07]).[115] A daily intake of 25–29 g fiber was found to be the minimum for significant beneficial effects on CVD and might be even greater with a fiber intake of >30 g/day. Intervention studies showing effects of fiber in general and β-glucan in particular for primary or secondary prevention of cardiovascular events are still on demand. Although the cholesterol-lowering effects of β-glucan are widely accepted (health claim ID 1236 and 1299),[116] large-scale intervention trials and meta-analyses[117] are still on demand to obtain sufficient evidence for recommending β-glucan intake for the prevention of CVD events.

6 | ROLE OF BIOFACTORS IN NONALCOHOLIC FATTY LIVER DISEASES

6.1 | Pathophysiology and burden of nonalcoholic fatty liver disease

The hallmark of nonalcoholic liver disease (NAFLD) is steatosis, the accumulation of lipids in hepatocytes, for reasons other than the consumption of alcohol or steatogenic medication. NAFLD is not a single disease but rather a spectrum of liver diseases ranging from steatosis to nonalcoholic steatohepatitis (NASH) to fibrosis. In 2017, almost a quarter of the global population were estimated to have NAFLD[118] and it is predicted that

this number will increase to a third of the global population by 2030.[119] Of NAFLD patients who undergo a liver biopsy, 7%–30% show signs of the more severe form NASH.[120] NASH can progress to cirrhosis and hepatocellular carcinoma[121,122] and is becoming the leading cause of liver transplantation in the United States[123] and Europe.[124] NAFLD is associated with an increase in mortality with the major cause of death being CVD.[125]

Clinically, NAFLD is most commonly diagnosed due to abnormally elevated liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) that have no viral, hereditary or drug-induced origin and are not related to alcohol consumption. NAFLD can be diagnosed by imaging studies, but for a definite diagnosis of NASH as well as for disease staging, a liver biopsy is required. Biopsies are graded with the NASH Clinical Research Network scoring system (NAS), a histopathological system containing scores for steatosis, lobular inflammation and hepatocyte ballooning (abnormal enlargement of hepatocytes).[126] NAFLD is linked to the metabolic syndrome and disease development is strongly associated with obesity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia,[127] although up to 15% of patients with NAFLD have normal bodyweight.[128]

Multiple factors contribute to NAFLD pathogenesis including environmental, gut microbiota, insulin resistance, and genetics.[129] NAFLD pathogenesis is incompletely understood and while steatosis is generally viewed as benign, NASH involves hepatocyte injury, inflammation, fibrogenesis and increased production of reactive species.[129–131] Lifestyle interventions (e.g., reducing energy intake and increasing physical activity) remain the best course of action for the treatment of NAFLD, but prolonged dietary and behavioral changes are difficult to sustain. For the treatment of NASH, there are currently no approved drugs available and safe and efficient treatments are urgently needed and offer an exciting opportunity for the study of biofactors.

6.2 | Vitamin E

Vitamin E is a family of eight different lipid-soluble substances, namely α-, β-, γ-, and δ-tocopherol, and -tocotrienol.[132] Vitamin E acts as chain breaking antioxidant, terminating lipid peroxidation. α-Tocopherol (αT), the main vitamin E congener found in the human body,[133] has been extensively investigated in preclinical and clinical studies for the treatment of NAFLD.

In rats fed a high-fat diet, αT supplementation (250 mg/kg bodyweight/day, oral gavage, 4 weeks) decreased high-fat diet induced hepatic steatosis and circulating ALT. αT further reduced the oxidative stress marker malondialdehyde, S-nitrosylation of proteins as well as TNFα, a proinflammatory cytokine.[134] In line with the assumption that vitamin E is a potent hepatic antioxidant, rats presupplemented with αT showed lower markers of liver damage (ALT, AST) compared to their non-supplemented controls after carbon tetrachloride exposure, a potent inducer of hepatic oxidative stress.[135] Steatosis was also reduced by αT (250 mg/kg/diet, 6 weeks) in guinea pigs fed a high-fat diet and hepatic triacylglycerols were similar to animals fed a normal control diet.[136]

Besides targeting steatosis, αT has also been investigated in models of more advanced forms of NAFLD. In a dietary NASH model in guinea pigs, αT (1125 mg/kg diet for 8 weeks) supplementation was able to reduce hepatocyte ballooning while not affecting inflammation or fibrosis.[137] Integrity of the gut barrier and translocation of bacterial products are believed to be associated with the progression of steatosis to NASH.[138] An animal model recapitulating this are ob/ob mice, which already develop hepatic steatosis under standard feeding conditions,[139] and, upon a single injection of lipopolysaccharide (LPS), present hepatic oxidative stress and increased serum TNFα and ALT.[140] Mice that received αT and γT supplementation (500 mg/kg diet, 5 weeks) prior to LPS injection were protected against the LPS-induced increase in oxidative stress, TNFα and ALT.[140] By quenching LPS-induced oxidative stress, vitamin E may be able to reduce the proinflammatory action of LPS.

Overall, the majority of animal models indicate an improvement of NAFLD through a reduction of oxidative stress, however nonantioxidant functions, cannot be excluded.

In adult NASH patients without diabetes mellitus (PIVENS trial), treatment with 800 IU/day of αT for 2 years ($n = 84$) was associated with improvement in histological features in 43% of patients ($p = 0.001$ vs. placebo) and resolution of NASH in 36% ($p = 0.05$).[141] The PIVENS trial also showed a significant reduction of steatosis through a yet unidentified mechanism. A resolution of NASH (33% of patients, $p = 0.04$ vs. placebo) and reduction of steatosis ($p = 0.02$) was also observed in adult, biopsy-confirmed NASH patients with type 2 diabetes mellitus who received 400 IU αT b.i.d. for 18 months.[142] In children and adolescents with biopsy-proven NAFLD, 800 IU/day αT ($n = 58$, TONIC trial) compared to placebo ($n = 58$) for 96 weeks, had no effect on ALT at the end of the study but significantly reduced it at earlier timepoints (weeks 24 and 48), indicating that early benefits were overtaken by general improvement in both groups, likely induced by lifestyle modification. In the subgroup of patients who had NASH or borderline NASH at baseline, αT was associated with significant histological improvement compared to placebo.[143]

Recent work has begun to unravel some of the mechanisms underlying the improvements in NAFLD, especially hepatic steatosis, under vitamin E supplementation. NAFLD does not appear to be a disease of vitamin E deficiency, but rather of aberrant subcellular distribution in which αT is trapped within lipid droplets and unavailable at other sites within the cell.[144] How this may affect vitamin E metabolism and in particular the activities of long-chain metabolites, which have unique biological functions,[145] especially in regard to inflammation,[146] remains to be elucidated. It was further shown that αT supplementation decreases hepatic lipid peroxidation in patients with NAFLD, indicating, in agreement with the animal models, that the decrease of oxidative stress plays a major role in the improvement of NAFLD by αT.[147] Lipid peroxidation might be a direct driver of hepatic steatosis through upregulation of steatogenic pathways. A decrease of one of the pathways, de novo lipogenesis, after 4 weeks of supplementation with αT (200–800 IU/day αT) was associated with improvements of hepatic steatosis after 24 weeks of treatment. Inhibition of de novo lipogenesis by αT was also observed in vitro, where it was dependent on the antioxidant function of αT, highlighting once again the interplay between oxidative stress and steatosis.[148] A meta-analysis of eight clinical trials (including 465 NAFLD patients) showed an overall benefit of vitamin E-supplementation on histological parameters of NAFLD that appear to be especially pronounced in patients with NASH.[149] None of the clinical trials reported any adverse events attributed to treatment.[141–143]

In summary, there is good preclinical and clinical evidence for a benefit of αT supplementation in NAFLD and the 2018 practice guidelines of the American Association of Liver Disease recommends 800 IU/day αT for the treatment of biopsy-proven, nondiabetic NASH patients.[150] Furthermore, up to now, αT is the only therapeutic intervention that has been shown to improve transplant-free survival and reduce mortality in NASH patients.[151]

6.3 | Green tea

Green tea (*Camellia sinensis*) is rich in flavonoids from the subclass flavan-3-ols (catechins), including epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG).[152] Green tea catechins are believed to be hepatoprotective through antioxidant, anti-inflammatory, and hypolipidemic properties.[153] Feeding ob/ob mice a diet containing green tea extract (1 or 2% wt:wt) dose dependently reduced hepatic triacylglycerols, serum ALT and AST, and bodyweight.[154] In mice fed a high-fat diet either alone or with 3.2 g/kg diet EGCG for 16 weeks, the EGCG group showed a significant reduction in bodyweight, ALT and liver steatosis. Animals treated with EGCG excreted more triacylglycerols with their feces, which may be a partial explanation for the observed benefit.[155] In mice with high-fat diet-induced fatty liver, injections of EGCG (10, 20, 40 mg/kg bodyweight/day, control saline) for 4 weeks while sustaining the high-fat diet showed a dose dependent reduction in hepatic triacylglycerols, liver enzymes, reduced hepatocyte ballooning and improved insulin sensitivity.[156] EGCG has beneficial effects both as a preventive and treatment strategy in mouse models of NAFLD.

Clinically, only one study has investigated green tea extracts in patients with biopsy-proven NASH. Patients ($n = 38$) receiving 600 mg green tea catechins for 6 months showed reduced BMI and improved insulin resistance, but no changes in ALT and AST compared to controls.[157] This trial is limited by the small sample size, lack of placebo or randomization and significant differences of studied parameters (ALT and AST) between treatment group and controls at baseline. Large-scale clinical trials on green tea extracts or isolated catechins are currently not pursued due to toxicological concerns. Although, in healthy men, high doses of green tea polyphenols (714 mg/day, including 50 mg EGCG for 3 weeks) did not affect safety parameters, including ALT and ALT.[158] Preclinical models, on the other hand, demonstrated hepatotoxicity[159,160] and a retrospective analysis of high-dose green tea supplementation (>800 mg EGCG 12 months) showed increases of ALT and AST compared to placebo.[161] The EFSA has currently not set a safe intake level for EGCG, but cautions that ≥800 mg EGCG/day may be associated with significant increases in ALT.[162] Although the preclinical models suggest a benefit, toxicological concerns need to be addressed first before continuing research on the benefit of green tea or components in the treatment of NAFLD.

6.4 | Silymarin

Milk thistle (*Silybum marianum*) has been used as a medicinal plant for centuries with the first recorded description by the Greek physician and botanist Dioscsorides (40–90 BC).[163] In a survey of patients with chronic liver disease, milk thistle was the most commonly consumed dietary supplement.[164] Silymarin is a standardized extract of milk thistle seeds that consists of a mixture of flavonolignans, including silychristin and silydianin, and two groups of diastereoisomeric flavonolignans, silybin (A and B) and isosilybin (A and B).[165]

In mice fed a high-fat diet for 27 weeks, daily administration of silymarin by oral gavage (30 mg/kg bodyweight) for 4 weeks, while maintaining the high-fat diet, significantly reduced steatosis and histological severity compared to vehicle control. Changes were accompanied by a reduction of gene expression of acetyl-carboxylase-1 and fatty acid synthase involved in de novo lipogenesis, as well as superoxide dismutase 1 (SOD1) and catalase, which are upregulated under conditions of oxidative stress.[166]

One model of NASH comprises feeding of a methionine-choline deficient diet, leading to hepatic steatosis and inflammation through a reduction of β-oxidation and very low-density lipoprotein (VLDL) synthesis.[167] Rats fed a control diet or a high-fat methionine-choline deficient diet with and without 400 mg/kg silybin-phospholipid complex for 7 or 14 weeks showed significant improvement of NASH-related parameters. Compared to the control diet, the methionine-choline deficient diet significantly increased ALT and induced hepatic lobular inflammation (14 weeks), which were both reversed by the inclusion of silybin in the diet. Animals receiving silybin further had increased hepatic glutathione concentrations, reduced 4-hydroxynonenal and malondialdehyde protein adducts, and improved mitochondrial function, indicating reduced hepatic oxidative stress.[168] Taken together, silymarin may act as a hepatic antioxidant, decrease hepatic lipid accumulation, and reduce hepatic inflammation in animal models of NAFLD.

Clinically, 12 months supplementation with 600 mg/day silymarin ($n = 30$) reduced fasting glucose and glycated hemoglobin (HbA1c) as well as circulating malondialdehyde in diabetic patients with liver cirrhosis compared to patients who did not receive silymarin ($n = 30$).[169] In multiple clinical trials, silymarin was administered in combination with other compounds, for example, vitamin E,[170] which hampers the ability to asses potential benefits by silymarin. A meta-analysis of five clinical trials with silymarin monotherapy (210–1120 mg/day; 8–24 weeks) found a significant reduction of ALT.[171] In contrast, high-dose silymarin supplementation (700 mg three times per day, $n = 49$) for 48 weeks was well tolerated and significantly improved fibrosis but did not reduce NAS score, ALT, or AST in patients with biopsy-proven NASH compared to placebo ($n = 50$).[172]

One of the challenges for silymarin as a treatment is the low bioavailability and extensive first-pass metabolism of its constituents, resulting in rapid excretion in bile and urine.[173] Strategies that successfully improved bioavailability are complexation with phospholipids or β-cyclodextrins.[173] The preclinical data for silymarin are promising and benefits seem to be mainly mediated through a reduction of oxidative stress and inflammation.

6.5 | Omega-3 fatty acids

Omega-3 fatty acid supplementation in NAFLD is believed to be beneficial through three mechanisms: (i) activation of peroxisome proliferator-activated receptors and hepatic β-oxidation of fatty acids; (ii) inhibition of sterol regulatory element-binding protein-1 (SREBP-1) and carbohydrate-responsive element-binding protein transcriptional activity and thereby de novo lipogenesis; and (iii) reduction of inflammation by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and reduction of arachidonic acid-derived eicosanoids.[78]

In mice, feeding of DHA or EPA in a high-fat, high-cholesterol diet improved hepatic triacylglycerol and ALT concentrations, with EPA having a stronger effect on triacylglycerols than DHA. EPA and DHA both suppressed high-fat diet-induced SREBP-1 mRNA expression and reduced the expression of downstream genes fatty acid synthase, stearoyl-coenzyme A desaturase and fatty acid elongase 6 (ElOVL6). EPA and DHA further reduced the expression of inflammatory markers TNFα, CD68 and monocyte chemoattractant protein-1 (MCP-1) induced by the high-fat diet. In summary, DHA and EPA seem to be able to suppress the synthesis of lipids and inflammation in the liver.

Children with NAFLD ($n = 20$), treated for 18 months with DHA (250 mg/day), showed a significant reduction of ALT and AST, steatosis, histological severity, a reduction in NF-κB nuclear translocation, and a corresponding reduction of proinflammatory cytokines TNFα, IL-6 and IL-1β, as well as an increased protein expression of free fatty acid receptor 4 (FFA4), though the study is limited by lack of controls.[174] In a randomized, placebo-controlled and blinded trial in NAFLD patients ($n = 103$), 15–18 months of EPA + DHA (4 g/day) supplementation did not improve liver fat or fibrosis.[175] Similarly, consuming a combination of ALA + EPA + DHA (0.315 g/day) for 6 months did not improve liver histology in NASH patients ($n = 100$) compared to placebo.[176]

A meta-analysis of seven omega-3 fatty acid supplementation trials in NAFLD patients, with supplementation ranging from 0.83 to 6.4 g/day and treatment duration from 6 to 18 months, showed a significant reduction of ALT, decrease of circulating triacylglycerols and increase of HDL compared to placebo.[177] Although preclinical models and initial studies showed promising results, two large well-controlled studies did not report any benefit of omega-3 fatty acids in the treatment of NAFLD, whereas NAFLD-associated markers were improved according to one meta-analysis.

7 | ROLE OF BIOFACTORS IN NEURODEGENERATIVE DISEASES

7.1 | Pathophysiology and burden of neurodegenerative diseases

Population aging is a worldwide trend with dramatic consequences on public health and the incidence of neurodegenerative diseases, including Alzheimer's disease (AD). AD contributes greatly to the burden of disability experienced at old age. To date, more than 47 million people worldwide suffer from dementia and this number is estimated to triple by 2050, with dramatic personal, social, and economic consequences.[178] Decline of cognition and loss of synapses are well-documented concomitants of normal aging.[179] It has been postulated that AD results from multiple age-associated processes that gradually erode brain structure and function, making it vulnerable to degeneration. The vulnerable aged brain, with normal age-associated changes, may be affected by an additional precipitating event that transforms it from normal aging to AD, resulting in accelerated neuronal and synaptic loss and cognitive decline.[179]

Interventions with approved drugs, if started early enough, may at best slow down the fatal pathophysiological alterations leading to the manifestation of clinical AD. Currently, there is no disease-curing treatment available.[180] New therapeutics that were in the focus of drug discovery programs failed in clinical trials so far.[181–187] Thus, there is increasing interest in strategies based on physical activity and nutrition to support healthy brain aging and to prevent AD.[188–191]

While being no cure, sufficient intakes of certain micronutrients (such as B vitamins and vitamin D) and secondary plant metabolites may prevent or delay disease onset. B vitamins have also been implicated in vascular disease, which frequently co-occurs with or even precedes AD.[192]

7.2 | (Poly)phenols

Phenolics and polyphenols are secondary plant metabolites characterized by the presence of one, respectively, two or more phenolic rings in their chemical structure and are summarized under the term (poly)phenol.[11] In the human diet, several hundreds of different (poly)phenolic compounds have been identified,[193] with flavonoids being the most abundant group among dietary (poly)phenols.[90]

Experimental and epidemiological evidence indicates that a higher intake of (poly)phenols may reduce the risk for AD.[194,195] In rodent models of aging and in human trials, (poly)phenol-rich berry and grape products reduced age-related cognitive impairment and oxidative stress.[196–198] Today, the most-accepted theory of how (poly)phenols and especially their metabolites[199] may exert their neuroprotective effects, is the induction of mild stress enabling neuronal cells to better deal with the stress they are exposed to. Thus, (poly)phenols are proposed to induce survival mechanisms similar to calorie restriction and physical activity, including the stimulation of longevity signaling, which involves sirtuins and mitochondrial biogenesis.[200,201]

The Mediterranean diet, a (poly)phenol-rich dietary pattern, significantly reduces the risk of AD.[202–206] An important component of the Mediterranean diet is the high consumption of extra virgin olive oil,[207] that seems to improve cognitive function.[208–210] Extra virgin olive oil contains a variety of (poly)phenols, including secoiridoids, phenolic alcohols, and lignans, as well as flavonoids that appear to have neuroprotective properties during aging.[211–213] Hydroxytyrosol and oleuropein are two of the most important antioxidants in olives[214] that are neuroprotective.[215–219] Olive (poly)phenols have therefore been proposed as promising agents to combat age-related neurodegeneration.[220] Accordingly, the secoiridoid ligstroside was recently identified as a novel protective agent in models of early AD and brain aging.[221]

Numerous preclinical studies have investigated the effects of plant extracts or isolated (poly)phenols in cellular and animal models of AD. For a comprehensive summary, the reader is referred to recently published reviews.[194,222–224] Beside the well-documented large-scale clinical studies on the *Ginkgo biloba* extract Egb761,[225] only a few randomized, placebo controlled trials have been published.[226–233] The majority of (poly)phenol-rich plant extracts were tested in open-label trials.[234–237] Moreover, most studies tested effects of (poly)phenol-rich extracts over a relative short time on only a small number of participants and the studied plant material was often not well characterized, with some exceptions such as human studies on Egb761R or *Cistanche tubulosa* glycosides (Memoregain^{R}).[225,235] Only a few studies reported effects of single (poly)phenolic compounds, such as resveratrol[238,239] or curcumin.[230,240] Treatment with resveratrol in combination with piperine increased cerebral blood flow, but not cognitive function in one RCT.[232]

In summary, (poly)phenols are abundant in the human diet and experimental and epidemiological evidence suggests that their high intake may be beneficial in the prevention of AD. The leading theory of how (poly)phenols may exert their neuroprotective effect is the induction of mild stress enabling neuronal cells to better deal with the stress they are exposed to.

7.3 | B vitamins

In observational studies, hyperhomocysteinemia (plasma homocysteine concentrations >12 μmol/L) and low concentrations of B vitamins (folate, vitamins B_6 and B_{12}) are associated with dementia.[241–245] Nevertheless, homocysteine-lowering did not show any benefits in trials with dementia patients.[246]

The VITAmins TO Prevent Stroke (VITATOPS) trial is a double-blind, placebo-controlled trial with over 8000 patients with stroke or transient ischemic attack.[247] Patients received either a placebo or B-vitamins (folic acid, 2 mg; vitamin B_6, 25 mg; vitamin B_{12}, 0.5 mg per day) for 3.4 years. The primary outcome was diagnosis of cognitive impairment after the first stroke event. Cognitive decline, mean homocysteine concentrations, and mini-mental state examination (MMSE) scores at final follow-up were recorded as secondary outcomes. Patients who received B-vitamins showed a reduction in mean homocysteine compared with the placebo group (10.2 μmol/L vs. 14.2 μmol/L; $p < 0.001$). No change was detected from baseline in the mean MMSE scores and no differences between vitamins and placebo in the incidence of cognitive impairment (5.51% vs. 5.47%; RR: 1.01 [95% CI: 0.69–1.48]) or cognitive decline (9.1% vs. 10.3%; RR: 0.89 [95% CI: 0.67–1.18]).

In the Newcastle 85+ study, red blood cell folate and homocysteine, but not plasma vitamin B_{12}, were associated with better global cognition in the very old at baseline, but were not predictive of the rate of decline over 5 years.[248] High-dose B-vitamins (5 mg folate, and 50 mg vitamin B_6, and 1 mg vitamin B_{12} vs. placebo) were associated with modest cognitive benefit in a study including kidney transplant recipients with hyperhomocysteinemia at baseline.[249] Pooled mean homocysteine was higher among patients with AD compared with controls (difference 1.04 μmol/L [95% CI: 0.44–1.63]). However, confounding and reverse causality (dementia → deficiency) are possible in all studies including patients with diagnosed dementia. RCT of supplemental folate and vitamins B_6 and B_{12} and cognitive decline reported conflicting results. Two trials that found an improvement of cognitive function by lowering homocysteine have included subjects with elevated homocysteine.[250,251] A meta-analysis suggests that vitamins B_6 (pyridoxal 5′-phosphate), B_{12} (cobalamin), and folate may not be modifiable risk factors for slowing cognitive decline among community-dwelling older individuals[252] , which is supported by a RCT study concluding that vitamin B12 and folic acid supplementation did not reduce cognitive decline in older people with MCI and elevated serum homocysteine.[253] However, the authors of a 6-year observational, retrospective study, concluded that the assessment of B vitamin status among elderly adults can contribute to an economic and practical approach to the prevention and management of cognitive decline.[254] The heterogeneity of the results thus might be due to factors related to the study design, such as selection of the participants and comorbidities.

7.4 | Vitamin D

There are a number of key processes that support a role of vitamin D in brain functioning: (i) The enzyme 25-hydroxyvitamin D_3 1-α-hydroxylase (cytochrome P_{450} 27B1), which catalyzes the conversion of vitamin D from its immediate precursor 25(OH)D to its active form 1,25-dihydroxyvitamin D (1,25(OH)D or calcitriol), is present in neurons and glial cells in the brain in areas important for cognition, including the hippocampus and frontal cortex. (ii) Vitamin D receptors mediating the effects of calcitriol are co-localized with 1-α-hydroxylase, suggesting that vitamin D may have important effects on these cerebral functions.[255] (iii) Vitamin D also increases the concentrations of acetylcholine[256] and hippocampal neuron densities,[257] decreases proinflammatory cytokines,[258] enhances neuroprotection[259] and augments clearance of amyloid-beta,[260] all of which are processes importantly implicated in age-related cognitive decline and dementia.

Vitamin D supplementation studies have demonstrated an improvement in cognition and markers of pathology in rodent models of AD[261,262] and aging.[263] For example, using a mouse model of AD, in which mice spontaneously develop amyloid plaques and associated memory impairment within the first 3–4 months of life, Yu and colleagues[262] randomized mice to one of three different diets for 5 months, starting immediately after weaning: control group, vitamin D-deficient, or vitamin D enriched. Mice fed the vitamin D-enriched diet had significantly fewer amyloid plaques and amyloid-beta peptides, lower levels of inflammation, and significantly increased expression of nerve growth factor. The vitamin D-supplemented mice outperformed the others on the Morris Water Maze task (which assesses spatial working and memory and is a test of hippocampal function) on all measures. In a second study, amyloid-treated rats were fed a normal diet, a vitamin D-deficient diet, or a vitamin D-supplemented diet and were compared to control rats.[261] Long-term potentiation, which is a generally accepted cellular model of learning and memory, was then assessed in the CA3-CA1 pathway of the hippocampus and the findings suggested that vitamin D may help enhance or restore synaptic plasticity. In a third study, middle-aged rats were fed a low, medium or high vitamin

D diet and 5 months later underwent testing of learning and memory in the Morris Water Maze.[263] The high-dose group outperformed the other groups on maze reversal, a particularly challenging task that detects more subtle changes in memory and executive functioning. Long-term potentiation was also enhanced in this group and hippocampal gene expression microarrays identified upregulation of pathways pertaining to synaptic transmission, cell communication and G protein function. The findings provide support for a causal relationship between vitamin D and cognitive function and that vitamin D may improve the likelihood of successful brain aging.

Evidence from human observational studies has been mostly positive, but somewhat more mixed.[264] Several cross-sectional studies have shown significantly lower vitamin D status in AD versus age-matched controls. A meta-analysis demonstrated that on average, individuals with AD had vitamin D concentrations that were 6–15 nmol/L lower[265] and that lower vitamin D status was associated with worse global cognition.[265,266] The cognitive domains most closely associated with vitamin D concentrations in cross-sectional analyses are executive function[267–269] and visual (nonverbal) memory.[270,271] For verbal memory, on the other hand, studies reported a mild positive association,[268] no association,[265] or even a negative association[272] with vitamin D concentrations. A meta-analysis[273] combining five longitudinal studies ($N = 19{,}000$) demonstrated a significantly increased risk 1.54 (1.19–1.99) of developing dementia with baseline vitamin D concentrations <25 nmol/L. The odds of developing age-related cognitive decline was also increased, OR = 1.26(1.09–1.23) with lower concentrations of vitamin D at baseline in another meta-analysis.[266] There have been few RCT, with most being limited by methodological issues (see references[264,274] for further discussion). In an attempt to address many of these limitations, Pettersen randomized healthy adults ($N = 82$) to high dose (4000 IU) or low dose (400 IU) daily vitamin D3. After 18 weeks, visual (nonverbal) memory improved in the high-dose group, particularly among the subgroup of individuals with low vitamin D (<75 nmol/L) at baseline.[274]

Mendelian randomization studies have provided further support for a causal relationship between vitamin D status and cognition as well as risk for AD. For example, in a large genome-wide association study, the SUNLIGHT Consortium found four single nucleotide polymorphisms (SNPs) to be strongly associated with vitamin D concentrations (i.e., their presence is associated with lower vitamin D) in a cohort of 33,996 persons and a significantly increased risk of developing AD.[275] Similarly, in another large cohort, The International Genomics of Alzheimer's Project ($n = 17{,}008$ AD cases and 37,154 controls), all seven 25(OH)D-increasing alleles were inversely associated with AD.[276] A combined score of all seven SNP showed that each standard deviation-increment in 25(OH)D concentrations (about 20–30 nmol/L) is associated with a 14% reduction in the risk of AD ($p = 0.002$). Using data from the Baltimore Study of Aging ($n = 1207$), Mendelian randomization analyses suggested a causal relationship between lower serum 25(OH)D and poorer executive functioning and psychomotor speed among aging adults.[277] These studies, combined with the limited RCT and observational studies to date, suggest that lower or insufficient vitamin D status may be a contributor or even a causal factor to age-related cognitive decline and dementia, while adequate status may be neuroprotective.

In summary, there is accumulating evidence that vitamin D status is related to successful aging and prevention of neurodegenerative conditions, such as age-related cognitive decline and dementia. Low serum 25(OH)D concentrations (i.e., <75 nmol/L) should be corrected; however, the optimal concentration to best mitigate risk of cognitive decline and dementia is not currently known. Well-designed long-term randomized trials investigating this question are required.

8 | ROLE OF BIOFACTORS IN DIABETES MELLITUS AND ITS COMPLICATIONS

8.1 | Pathophysiology and burden of diabetes mellitus and its complications

Diabetes mellitus is a chronic disease characterized by an absolute or relative insulin deficiency and among the major health challenges of the modern world that is growing rapidly. It is estimated that worldwide 463 million people were living with diabetes mellitus in 2019.[278] Diabetes is accompanied by high mortality and morbidity due to macrovascular complications, such as stroke or myocardial infarction, and microvascular complications, such as neuropathy, nephropathy, and retinopathy.[279]

Diabetic neuropathy is one of the most frequent chronic complications of diabetes and presents with a high heterogeneity of symptoms, patterns of neurological involvement, progression, risk factors and underlying pathomechanisms. The typical and clinically most relevant form of diabetic neuropathy is a length-dependent distal-symmetrical sensorimotor polyneuropathy, which accounts for about 75% of all diabetic neuropathies.[280,281] It is estimated that around 50% of patients with diabetes mellitus and a long duration of disease are affected by

sensorimotor polyneuropathy.[280] The treatment of sensorimotor polyneuropathy relies on three pillars: (i) improvement of glucose control and reduction of further risk factors, (ii) drug therapy aimed at alleviating symptoms, and (iii) treatment with the biofactors benfotiamine or α-lipoic acid to target the underlying pathological mechanisms. This chapter will focus on the latter pathogenic oriented treatment with biofactors that is supposed to not only to treat neural damages that occur with diabetic neuropathy but also to alleviate neuropathic symptoms.

8.2 | Benfotiamine (vitamin B_1-prodrug)

Thiamine, vitamin B_1, is essential for the integrity of cellular processes and high concentrations are found in skeletal muscle, heart, liver, kidney, and brain.[282] The active form of thiamine, thiamine diphosphate, is a cofactor for enzymes involved in the synthesis of neurotransmitters, antioxidants, and nucleic acids as well as for enzymes regulating glucose metabolism, such as pyruvate and oxoglutarate dehydrogenases and transketolase.[283] Patients with type 1 and type 2 diabetes mellitus have significantly decreased plasma and serum thiamine concentrations in comparison to healthy controls.[284,285] Such thiamine deficiency can reinforce hyperglycemic damage and its compensation is able to prevent the activation of pathomechanisms underlying the development of diabetic complications.[286–288]

Benfotiamine is an S-acyl thiamine derivative with a significantly higher bioavailability than thiamine and is therefore often preferred in clinical settings.[289] Benfotiamine has been used for decades in the treatment of diabetic polyneuropathy. Clinical studies are available investigating the effects of benfotiamine alone at different dosages, or in combination with pyridoxine hydrochloride and cyancobalamin on measures of sensorimotor polyneuropathy.[290–293]

In a randomized, placebo-controlled, double-blind, two-center pilot study, the efficacy of 400 mg/day benfotiamine orally administered for 3 weeks was studied in 40 patients with type 1 or type 2 diabetes mellitus and diabetic polyneuropathy.[291] In the benfotiamine group, a significant improvement in the Katzenwadel neuropathy score occurred compared to placebo, while no significant change was observed for the tuning fork test. The most pronounced effect was a significant decrease in pain. No side effects attributable to benfotiamine were observed.[291]

In line with these results, a phase III double-blind, placebo-controlled trial randomized 165 type 1 or type 2 diabetes mellitus patients with sensorimotor polyneuropathy to one of three treatments: benfotiamine 200 mg three times per day, benfotiamine 100 mg three times per day or placebo three times per day for 6 weeks.[292] The analysis was then performed in the intention-to-treat and per-protocol groups (133/124 patients, respectively). The primary outcome parameter Neuropathy Symptom Score improved significantly in the high benfotiamine-dose group compared to placebo ($p = 0.033$) in the per-protocol group. In the intention-to-treat group, the improvement of Neuropathy Symptom Score was not significantly different ($p = 0.055$). Even though the Total Symptom Score improvement was more pronounced at the higher benfotiamine dose and increased with treatment duration, this difference was not significant after 6 weeks of treatment. Within the Total Symptom Score, best results were obtained for the symptom pain, whereas paresthesia remained nearly unchanged.[292]

As benfotiamine is a vitamin B_1-derivative, its effects have also been studied as part of combination therapies with vitamins B_6 and B_{12}. Similar to the monotherapy, combinations of benfotiamine with B vitamins improved neuropathic symptoms and deficits as well as nerve conduction velocity in patients with diabetic neuropathy compared to placebo.[290,292,294]

8.3 | α-Lipoic acid

α-Lipoic acid, discovered in 1951, is a molecule of animal and human origin that, due to a chiral center at carbon 6, exists in two enantiomeric forms: *R*(+)- and *S*(−)-α-lipoic acid. The *R*(+)-enantiomer is the naturally occurring and biologically active form and acts as a cofactor for mitochondrial enzymes and thus assists in acyl-group transfer and as a coenzyme in the Krebs cycle. The commercially available α-lipoic acid used in dietary supplements is a racemic mixture and also contains the biologically inactive *S*(−)-form.[295] α-Lipoic acid is instable at low pH and sensitive to heat and light.[296]

α-Lipoic acid is a powerful antioxidant, active on both the lipid and aqueous regions of cells.[295] α-Lipoic acid exerts its strong antioxidant effects via direct mechanisms, that is, neutralizing reactive oxygen species and restoring diminished levels of endogenous antioxidants, as well as via indirect mechanisms by forming stable complexes with prooxidative divalent metal ions.[297] Its bioavailability and good safety profile have been described in detail elsewhere.[298] Hyperglycemia-induced overproduction of reactive oxygen species constitutes a major pathogenetic mechanism underlying the development of diabetic complications[299,300] and increased concentrations of reactive oxygen species in diabetic patients

prior to the development of nerve damage and to an even higher degree in patients with manifest polyneuropathy have been reported.[301]

Clinical studies suggest that α-lipoic acid has an insulin-sensitizing effect in patients with type 2 diabetes mellitus.[302] Nevertheless, the main clinical indication for α-lipoic acid is the treatment of diabetic polyneuropathy. There are several RCT and meta-analyses of RCT showing positive effects of α-lipoic acid both given intravenously or orally.[303–308]

A meta-analysis of four RCT with overall more than 1200 subjects provided evidence that intravenous treatment with α-lipoic acid (600 mg/day) over 3 weeks is safe and significantly improves both neuropathic symptoms and deficits.[303] Oral treatment with α-lipoic acid was investigated in the SYDNEY 2 trial, where doses of 600, 1200, and 1800 mg α-lipoic acid once daily over 5 weeks of treatment (with 1-week placebo run-in) significantly improved neuropathic symptoms compared to placebo. In the group treated with 1200 mg/d, a significant improvement in neuropathic deficits occurred. The dose of 600 mg/day provided, in the opinion of authors, the optimum risk-to-benefit ratio.[309] These findings were strengthened by a critical review of the evidence[310] and an expert opinion concluding that oral α-lipoic acid may improve neuropathic symptoms at a daily dose of 600 mg (number needed to treat, 2.7) over a 5-week treatment period. Higher doses of α-lipoic acid did not prove more effective (number needed to harm, 4.5 and 3 for 1200 and 1800 mg/day, respectively).[311]

The longest study performed in subjects with diabetic neuropathy was the NATHAN 1 trial. In this multicenter, randomized, double-blind parallel-group trial, 460 diabetic patients with mild-to-moderate diabetic polyneuropathy were randomly assigned to oral treatment with 600 mg α-lipoic acid once daily ($n = 233$) or placebo ($n = 227$) for 4 years. The treatment with α-lipoic acid did not alter the primary composite end point (Neuropathy Impairment Score-Lower Limbs and seven neurophysiologic tests) but resulted in a clinically meaningful improvement and prevention of progression of neuropathic impairments and was well tolerated.[312]

A meta-analysis strengthened the conclusion that neuropathic symptoms can be significantly reduced by α-lipoic acid given either intravenously or orally. The analysis revealed that 600 mg α-lipoic acid given orally once daily had effects on symptoms of diabetic polyneuropathy identical to those of 600 mg/day given intravenously.[304] The effectiveness of α-lipoic acid in the treatment of diabetic polyneuropathy was confirmed in four other meta-analyses of randomized controlled trials.[305–308]

8.4 | Benfotiamine plus α-lipoic acid

The combined application of benfotiamine and α-lipoic acid was investigated in a small pilot trial in nine male type 1 diabetes mellitus patients, in which complication-causing processes, such as the production of advanced glycation endproducts and hexosamine, were normalized.[313] In another trial, 120 patients with painful diabetic polyneuropathy were treated with either 300 mg/day benfotiamine, 600 mg/day α-lipoic acid or the combination thereof for 8 weeks. All three therapies were effective with a significant improvement, compared to baseline, of neuropathic deficits and neuropathic pain. The best results were obtained with the combined therapy. Discontinuation of the treatment during a 12-week follow-up period led to the loss of all improvements.[314] However, this trial was neither placebo-controlled nor blinded; therefore these results await and require confirmation by RCT.

In summary, α-lipoic acid is a strong antioxidant and the vitamin B_1 prodrug benfotiamine acts via the activation of the transketolase enzyme. Hence, both biofactors interfere with the pathogenesis of diabetic complications and can reduce neuropathic symptoms and deficits in patients with diabetic polyneuropathy.

9 | CONCLUSIONS

Since there is currently no generally accepted definition of the term biofactors, we here propose a definition whose adoption will enable a harmonization and consistent use of the term in the scientific literature.

The present demographic changes, resulting in a rise in the number of senior citizens, will simultaneously result in a large increase in the incidence and burden of age-related disorders. The intake of dietary biofactors can be a cost-effective strategy to prevent or, in some cases, even treat age-related diseases. Examples reviewed herein include the role of folate in cancer epigenetics, omega-3 fatty acids and dietary fiber for the prevention of CVD, α-tocopherol (vitamin E) for the treatment of biopsy-proven non-alcoholic steatohepatitis, vitamin D for the prevention of neurodegenerative diseases, and thiamine and α-lipoic acid for the treatment of diabetic neuropathy. This list of potentially helpful biofactors in the prevention and treatment of age-related disorders, however, is not exhaustive and many more examples exist.

While ingesting biofactors from food sources is generally safe and unlikely to reach doses triggering potentially adverse effects, the additional use of food supplements may in certain cases bear the risk of exceeding the tolerable upper intake level. It is therefore recommended that

an adequate supply of biofactors should be primarily achieved through intake from a balanced diet. However, in certain cases, such as NAFLD or diabetes mellitus, dietary intake may not suffice to achieve the health-beneficial effects and therefore the consumption in the form of dietary supplements may be warranted.

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CONFLICT OF INTEREST

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REFERENCES

1. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. Lancet (London, England). 2015;385:540–8.
2. Ageing and health. www.who.int/news-room/fact-sheets/detail/ageing-and-health.
3. United Nations Population Division | Department of Economic and Social Affairs. https://population.un.org.
4. Scully T. Demography: to the limit. Nature. 2012;492:S2–3.
5. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet (London, England). 2015;385:549–62.
6. Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. Proc Natl Acad Sci U S A. 2006;103:17589–94.
7. Ames BN. Prolonging healthy aging: longevity vitamins and proteins. Proc Natl Acad Sci U S A. 2018;115:10836–44.
8. Knekt P, Kumpulainen J, Järvinen R, Rissanen H, Heliövaara M, Reunanen A, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr. 2002;76:560–8.
9. Chen G-C, Yang J, Eggersdorfer M, Zhang W, Qin L-Q. N-3 long-chain polyunsaturated fatty acids and risk of all-cause mortality among general populations: a meta-analysis. Sci Rep. 2016;6:28165.
10. Harris WS, Luo J, Pottala JV, Espeland MA, Margolis KL, Manson JE, et al. Red blood cell polyunsaturated fatty acids and mortality in the Women's Health Initiative memory study. J Clin Lipidol. 2017;11:250–259.e5.
11. Frank J, Fukagawa NK, Bilia AR, Johnson EJ, Kwon O, Prakash V, et al. Terms and nomenclature used for plant-derived components in nutrition and related research: efforts toward harmonization. Nutr Rev. 2020;78:451–8.
12. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
13. Hanahan D, Weinberg RA. Hallmarks of Cancer: the next generation. Cell. 2011;144:646–74.
14. Fardi M, Solali S, Farshdousti Hagh M. Epigenetic mechanisms as a new approach in cancer treatment: an updated review. Genes Diseases. 2018;5:304–11.
15. Berdasco M, Esteller M. Aberrant epigenetic landscape in Cancer: how cellular identity Goes awry. Dev Cell. 2010;19:698–711.
16. Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, Tonti-Filippini J, et al. Human DNA methylomes at base resolution show widespread epigenomic differences. Nature. 2009;462:315–22.
17. Vidal E, Sayols S, Moran S, Guillaumet-Adkins A, Schroeder MP, Royo R, et al. A DNA methylation map of human cancer at single base-pair resolution. Oncogene. 2017;36:5648–57.
18. Venturelli S, Sinnberg TW, Berger A, Noor S, Levesque MP, Bäcker A, et al. Epigenetic impacts of ascorbate on human metastatic melanoma cells. Front Oncol. 2014;4:227.
19. Negri A, Naponelli V, Rizzi F, Bettuzzi S. Molecular targets of Epigallocatechin—Gallate (EGCG): a special focus on signal transduction and Cancer. Nutrients. 2018;10:1936.
20. Liu Y, Zhou J, Hu Y, Wang J, Yuan C. Curcumin inhibits growth of human breast cancer cells through demethylation of DLC1 promoter. Mol Cell Biochem. 2017;425:47–58.
21. Blakley RL. IUPAC-IUB joint commission on biochemical nomenclature (JCBN). Nomenclature and symbols for folic acid and related compounds. Recommendations 1986. Eur J Biochem. 1987;168:251–3.
22. Zheng Y, Cantley LC. Toward a better understanding of folate metabolism in health and disease. J Exp Med. 2019;216:253–66.
23. McNulty H, Pentieva K, Hoey L, Strain JJ, Ward M. Nutrition throughout life: folate. Int J Vitam Nutr Res. 2012;82:348–54.
24. McNulty H, Ward M, Hoey L, Hughes CF, Pentieva K. Addressing optimal folate and related B-vitamin status through the lifecycle: health impacts and challenges. Proc Nutr Soc. 2019;78:449–62.
25. Perła-Kaján J, Jakubowski H. Dysregulation of epigenetic mechanisms of gene expression in the pathologies of hyperhomocysteinemia. IJMS. 2019;20:3140.
26. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for Folate's role. Adv Nutr. 2012;3:21–38.
27. Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternat Med Rev. 2003;8:7–19.
28. Pieroth R, Paver S, Day S, Lammersfeld C. Folate and its impact on Cancer risk. Curr Nutr Rep. 2018;7:70–84.
29. Lin HL, An QZ, Wang QZ, Liu CX. Folate intake and pancreatic cancer risk: an overall and dose–response meta-analysis. Public Health. 2013;127:607–13.
30. He H, Shui B. Folate intake and risk of bladder cancer: a meta-analysis of epidemiological studies. Int J Food Sci Nutr. 2014;65:286–92.
31. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al. Effects of folic acid supplementation on overall

and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet (London, England). 2013;381:1029–36.
32. Wien TN, Pike E, Wisløff T, Staff A, Smeland S, Klemp M. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ Open. 2012;2:e000653.
33. Mahmoud A, Ali M. Methyl donor micronutrients that modify DNA methylation and Cancer outcome. Nutrients. 2019; 11:608.
34. Kotsopoulos J, Sohn K-J, Kim Y. Postweaning dietary folate deficiency provided through childhood to puberty permanently increases genomic DNA methylation in adult rat liver. J Nutr. 2008;138:703–9.
35. Zhang Y-F, Shi W-W, Gao H-F, Zhou L, Hou A-J, Zhou YH. Folate intake and the risk of breast Cancer: a dose-response meta-analysis of prospective studies. PLoS One. 2014;9: e100044.
36. Duman EA, Kriaucionis S, Dunn JJ, Hatchwell E. A simple modification to the luminometric methylation assay to control for the effects of DNA fragmentation. Biotechniques. 2015;58: 262–4.
37. Cardiovascular diseases (CVDs). www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
38. Wallert M, Schmölz L, Galli F, Birringer M, Lorkowski S. Regulatory metabolites of vitamin E and their putative relevance for atherogenesis. Redox Biol. 2014;2:495–503.
39. Meier T, Gräfe K, Senn F, Sur P, Stangl GI, Dawczynski C, et al. Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European region from 1990 to 2016: a systematic analysis of the global burden of disease study. Eur J Epidemiol. 2019;34:37–55.
40. Afshin A, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, et al. The impact of dietary habits and metabolic risk factors on cardiovascular and diabetes mortality in countries of the Middle East and North Africa in 2010: a comparative risk assessment analysis. BMJ Open. 2015;5:e006385.
41. Nadir MA, Szwejkowski BR, Witham MD. Vitamin D and cardiovascular prevention. Cardiovasc Ther. 2010;28:e5–e12.
42. Jenkins DJ, Spence JD, Giovannucci EL, Kim Y, Josse R, Vieth R, et al. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol. 2018;71: 2570–84.
43. NVSII: Max Rubner-Institut. https://www.mri.bund.de/de/institute/ernaehrungsverhalten/forschungsprojekte/nvsii/.
44. Skeie G, Braaten T, Hjartåker A, Lentjes M, Amiano P, Jakszyn P, et al. Use of dietary supplements in the European prospective investigation into Cancer and nutrition calibration study. Eur J Clin Nutr. 2009;63:S226–38.
45. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999-2012. JAMA. 2016;316:1464–74.
46. Li K, Wang X-F, Li D-Y, Chen Y-C, Zhao L-J, Liu XG, et al. The good, the bad, and the ugly of calcium supplementation: a review of calcium intake on human health. Clin Interv Aging. 2018;13:2443–52.
47. Referenzwerte. www.dge.de/wissenschaft/referenzwerte.
48. Nutrition Education Resources & Materials. https://www.fda.gov/food/food-labeling-nutrition/nutrition-education-resources-materials.
49. Scientific Opinion on the Tolerable Upper Intake Level of calcium. https://www.efsa.europa.eu/de/efsajournal/pub/2814.
50. Anderson JJ, Kruszka B, Delaney JA, He K, Burke GL, Alonso A, et al. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the multi-ethnic study of atherosclerosis (MESA). J Am Heart Assoc. 2016;5:e003815.
51. Kopecky SL, Bauer DC, Gulati M, Nieves JW, Singer AJ, Toth PP, et al. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. Ann Intern Med. 2016;165:867–8.
52. de Baaij JHF, Hoenderop JGJ, Bindels RJM. Magnesium in man: implications for health and disease. Physiol Rev. 2015;95:1–46.
53. Al Alawi AM, Majoni SW, Falhammar H. Magnesium and human health: perspectives and research directions. Int J Endocrinol. 2018;2018:1–17.
54. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984;108:188–93.
55. Murck H. Ketamine, magnesium and major depression--from pharmacology to pathophysiology and back. J Psychiatr Res. 2013;47:955–65.
56. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, et al. Effects of magnesium supplementation on blood pressure: a meta-analysis of randomized double-blind placebo-controlled trials. Hypertension (Dallas, Tex: 1979). 2016;68: 324–33.
57. Jee SH, Miller ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. Am J Hypertens. 2002;15:691–6.
58. Costello RB, Elin RJ, Rosanoff A, Wallace TC, Guerrero-Romero F, Hruby A, et al. Perspective: the case for an evidence-based reference interval for serum magnesium: the time has come. Adv Nutr (Bethesda, Md.). 2016;7:977–93.
59. Stepura OB, Martynow AI. Magnesium orotate in severe congestive heart failure (MACH). Int J Cardiol. 2009;134:145–7.
60. Kisters KK, Gremmler B, Grober U. Natriuretic peptides, hypertension, heart insufficiency and magnesium. Adv Tech Biol Med. 2015;3:134.
61. Rosenfeldt FL, Richards SM, Lin Z, Pepe S, Conyers RA. Mechanism of cardioprotective effect of orotic acid. Cardiovasc Drugs Ther. 1998;12 Suppl 2:159–70.
62. Del Gobbo LC, Imamura F, Wu JHY, Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2013;98:160–73.
63. Fang X, Liang C, Li M, Montgomery S, Fall K, Aaseth J, et al. Dose-response relationship between dietary magnesium intake and cardiovascular mortality: a systematic review and dose-based meta-regression analysis of prospective studies. J Trace Elem Med Biol. 2016;38:64–73.
64. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357: 266–81.
65. Berridge MJ. Vitamin D deficiency accelerates ageing and age-related diseases: a novel hypothesis. J Physiol. 2017;595: 6825–36.

66. Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect. 2019;8:R27–43.
67. Pilz S, März W, Cashman KD, Kiely ME, Whiting SJ, Holick MF, et al. Rationale and plan for vitamin D food fortification: a review and guidance paper. Front Endocrinol. 2018;9:373.
68. Tolerable upper intake levels for vitamins and minerals. http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf.
69. Pilz S, Verheyen N, Grübler MR, Tomaschitz A, März W. Vitamin D and cardiovascular disease prevention. Nat Rev Cardiol. 2016;13:404–17.
70. Grübler MR, März W, Pilz S, Grammer TB, Trummer C, Müllner C, et al. Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence. Rev Endocr Metab Disord. 2017;18:259–72.
71. Wang J, Zhou JJ, Robertson GR, Lee VW. Vitamin D in vascular calcification: a double-edged sword? Nutrients. 2018;10:652.
72. Beveridge LA, Khan F, Struthers AD, Armitage J, Barchetta I, Bressendorff I, et al. Effect of vitamin D supplementation on markers of vascular function: a systematic review and individual participant meta-analysis. J Am Heart Assoc. 2018;7:e008273.
73. Swart KM, Lips P, Brouwer IA, Jorde R, Heymans MW, Grimnes G, et al. Effects of vitamin D supplementation on markers for cardiovascular disease and type 2 diabetes: an individual participant data meta-analysis of randomized controlled trials. Am J Clin Nutr. 2018;107:1043–53.
74. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, et al. Effect of vitamin D supplementation on blood pressure: a systematic review and meta-analysis incorporating individual patient data. JAMA Intern Med. 2015;175:745–54.
75. Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M, et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr. 2014;100:746–55.
76. Jiang W-L, Gu H-B, Zhang Y-F, Xia Q-Q, Qi J, Chen JC. Vitamin D supplementation in the treatment of chronic heart failure: a meta-analysis of randomized controlled trials. Clin Cardiol. 2016;39:56–61.
77. Zittermann A. Vitamin D status, supplementation and cardiovascular disease. Anticancer Res. 2018;38:1179–86.
78. Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. Annu Rev Nutr. 2013;33:231–48.
79. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106:2747–57.
80. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease. Circulation. 2017;135:e867–84.
81. Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and Cancer. N Engl J Med. 2019;380:23–32.
82. Goel A, Pothineni N, Singhal M, Paydak H, Saldeen T, Mehta J. Fish, fish oils and Cardioprotection: promise or fish tale? Int J Mol Sci. 2018;19:3703.
83. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with Icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11–22.
84. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose Omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA. 2020;324:2268–80.
85. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA lipid intervention study (JELIS). Atherosclerosis. 2008;200:135–40.
86. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. Nat Prod Rep. 2009;26:1001–43.
87. USDA Database for the Flavonoid Content of Selected Foods: Release 3.2. (2015): https://data.nal.usda.gov/dataset/usda-database-flavonoid-content-selected-foods-release-32-november-2015.
88. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol. 2007;45:2179–205.
89. Erdman JW, Balentine D, Arab L, Beecher G, Dwyer JT, Folts J, et al. Flavonoids and heart health: proceedings of the ILSI North America flavonoids workshop, may 31-June 1, 2005, Washington, DC. J Nutr. 2007;137:718S–37S.
90. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130:2073S–85S.
91. Zamora-Ros R, Forouhi NG, Sharp SJ, González CA, Buijsse B, Guevara M, et al. Dietary intakes of individual flavanols and flavonols are inversely associated with incident type 2 diabetes in European populations. J Nutr. 2014;144:335–43.
92. Wang X, Ouyang YY, Liu J, Zhao G. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Br J Nutr. 2014;111:1–11.
93. Boesch-Saadatmandi C, Egert S, Schrader C, Coumoul X, Coumol X, Muller MJ, et al. Effect of quercetin on paraoxonase 1 activity--studies in cultured cells, mice and humans. J Physiology Pharmacol. 2010;61:99–105.
94. Boesch-Saadatmandi C, Loboda A, Wagner AE, Stachurska A, Jozkowicz A, Dulak J, et al. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: role of miR-155. J Nutr Biochem. 2011;22:293–9.
95. Boesch-Saadatmandi C, Wagner AE, Wolffram S, Rimbach G. Effect of quercetin on inflammatory gene expression in mice liver in vivo - role of redox factor 1, miRNA-122 and miRNA-125b. Pharmacol Res. 2012;65:523–30.
96. Brüll V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Müller C, et al. Effects of a quercetin-rich onion skin extract

on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. Br J Nutr. 2015;114:1263–77.
97. Egert S, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. J Nutr. 2010;140:278–84.
98. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr. 2009;102:1065–74.
99. Serban M-C, Sahebkar A, Zanchetti A, Mikhailidis DP, Howard G, Antal D, et al. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2016;5:e002713.
100. Huang H, Liao D, Dong Y, Pu R. Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: a systematic review and meta-analysis. Nutr Rev. 2020;78:615–26.
101. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and Management of High Blood Pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–324.
102. Larson AJ, Symons JD, Jalili T. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Adv Nutr (Bethesda, MD). 2012;3:39–46.
103. Boots AW, Wilms LC, Swennen ELR, Kleinjans JCS, Bast A, Haenen GRMM. In vitro and ex vivo anti-inflammatory activity of quercetin in healthy volunteers. Nutrition (Burbank, Los Angeles County, Calif). 2008;24:703–10.
104. Sato S, Mukai Y. Modulation of chronic inflammation by quercetin: the beneficial effects on obesity. J Inflamm Res. 2020;13:421–31.
105. Tabrizi R, Tamtaji OR, Mirhosseini N, Lankarani KB, Akbari M, Heydari ST, et al. The effects of quercetin supplementation on lipid profiles and inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2020;60:1855–68.
106. Brüll V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Müller C, et al. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-) hypertension: a randomized double-blinded, placebo-controlled crossover trial. Eur J Nutr. 2017;56:2265–75.
107. Mohammadi-Sartang M, Mazloom Z, Sherafatmanesh S, Ghorbani M, Firoozi D. Effects of supplementation with quercetin on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2017;71:1033–9.
108. Guo W, Gong X, Li M. Quercetin actions on lipid profiles in overweight and obese individuals: a systematic review and meta-analysis. Curr Pharm Des. 2019;25:3087–95.
109. Sahebkar A. Effects of quercetin supplementation on lipid profile: a systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2017;57:666–76.
110. Menezes R, Rodriguez-Mateos A, Kaltsatou A, González-Sarrías A, Greyling A, Giannaki C, et al. Impact of flavonols on cardiometabolic biomarkers: a meta-analysis of randomized controlled human trials to explore the role of inter-individual variability. Nutrients. 2017;9:117.
111. Behall KM, Scholfield DJ, Hallfrisch J. Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. Am J Clin Nutr. 2004;80:1185–93.
112. AbuMweis SS, Jew S, Ames NP. β-Glucan from barley and its lipid-lowering capacity: a meta-analysis of randomized, controlled trials. Eur J Clin Nutr. 2010;64:1472–80.
113. Ho HVT, Sievenpiper JL, Zurbau A, Blanco Mejia S, Jovanovski E, Au-Yeung F, et al. The effect of oat β -glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials. Br J Nutr. 2016;116:1369–82.
114. Tang G, Wang D, Long J, Yang F, Si L. Meta-analysis of the association between whole grain intake and coronary heart disease risk. Am J Cardiol. 2015;115:625–9.
115. Reynolds A, Mann J, Cummings J, Winter N, Mete E, te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 2019;393:434–45.
116. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the substantiation of health claims related to beta-glucans from oats and barley and maintenance of normal blood LDL-cholesterol concentrations (ID 1236, 1299), increase in satiety leading to a reduction in energy intake (ID 851, 852), reduction of post-prandial glycaemic responses (ID 821, 824), and "digestive function" (ID 850) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. ESFA J. 2015;9: 2207.
117. Pastor-Villaescusa B, Rangel-Huerta OD, Aguilera CM, Gil A. A systematic review of the efficacy of bioactive compounds in cardiovascular disease: carbohydrates, active lipids and nitrogen compounds. Ann Nutr Metab. 2015;66:168–81.
118. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15:11–20.
119. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology (Baltimore, Md.). 2018;67:123–33.
120. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore, MD). 2016;64:73–84.
121. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with Long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149:389–97.e10.
122. Satapathy SK, Sanyal AJ. Epidemiology and natural history of nonalcoholic fatty liver disease. Semin Liver Dis. 2015;35:221–35.

123. Noureddin M, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. Am J Gastroenterol. 2018; 113:1649–59.
124. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol. 2018;69: 810–7.
125. Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology (Baltimore, MD). 2010;51:595–602.
126. Kleiner DE, Brunt EM, van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology (Baltimore, MD). 2005;41:1313–21.
127. Sanyal AJ. Mechanisms of disease: pathogenesis of nonalcoholic fatty liver disease. Nat Clin Pract Gastroenterol Hepatol. 2005;2:46–53.
128. van Wagner LB, Armstrong MJ. Lean NAFLD: a not so benign condition? Hepatol Commun. 2017;2:5–8.
129. Arab JP, Arrese M, Trauner M. Recent insights into the pathogenesis of nonalcoholic fatty liver disease. Annu Rev Pathol. 2018;13:321–50.
130. Seki S, Kitada T, Yamada T, Sakaguchi H, Nakatani K, Wakasa K. In situ detection of lipid peroxidation and oxidative DNA damage in non-alcoholic fatty liver diseases. J Hepatol. 2002;37:56–62.
131. Feldstein AE, Lopez R, Tamimi TA-R, Yerian L, Chung Y-M, Berk M, et al. Mass spectrometric profiling of oxidized lipid products in human nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Lipid Res. 2010;51:3046–54.
132. Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science (New York, NY). 1922;56:650–1.
133. Traber MG, Burton GW, Ingold KU, Kayden HJ. RRR- and SRR-alpha-tocopherols are secreted without discrimination in human chylomicrons, but RRR-alpha-tocopherol is preferentially secreted in very low density lipoproteins. J Lipid Res. 1990;31:675–85.
134. Raso GM, Esposito E, Iacono A, Pacilio M, Cuzzocrea S, Canani RB, et al. Comparative therapeutic effects of metformin and vitamin E in a model of non-alcoholic steatohepatitis in the young rat. Eur J Pharmacol. 2009;604:125–31.
135. Iida C, Fujii K, Koga E, Washino Y, Kitamura Y, Ichi I, et al. Effect of α-tocopherol on carbon tetrachloride intoxication in the rat liver. Arch Toxicol. 2009;83:477–83.
136. Podszun MC, Grebenstein N, Spruss A, Schlueter T, Kremoser C, Bergheim I, et al. Dietary α-tocopherol and atorvastatin reduce high-fat-induced lipid accumulation and down-regulate CD36 protein in the liver of Guinea pigs. J Nutr Biochem. 2014;25:573–9.
137. Klaebel JH, Rakipovski G, Andersen B, Lykkesfeldt J, Tveden-Nyborg P. Dietary intervention accelerates NASH resolution depending on inflammatory status with minor additive effects on hepatic injury by vitamin E supplementation. Antioxidants. 2020;9:808.
138. Llorente C, Schnabl B. The gut microbiota and liver disease. Cell Mol Gastroenterol Hepatol. 2015;1:275–84.
139. Trak-Smayra V, Paradis V, Massart J, Nasser S, Jebara V, Fromenty B. Pathology of the liver in obese and diabetic Ob/-Ob and db/db mice fed a standard or high-calorie diet. Int J Exp Pathol. 2011;92:413–21.
140. Chung M-Y, Yeung SF, Park HJ, Volek JS, Bruno RS. Dietary α- and γ-tocopherol supplementation attenuates lipopolysaccharide-induced oxidative stress and inflammatory-related responses in an obese mouse model of nonalcoholic steatohepatitis. J Nutr Biochem. 2010;21:1200–6.
141. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362: 1675–85.
142. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. Dia Care. 2019;42:1481–8.
143. Lavine JE, Schwimmer JB, van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011;305:1659–68.
144. Violet P-C, Ebenuwa IC, Wang Y, Niyyati M, Padayatty SJ, Head B, et al. Vitamin E sequestration by liver fat in humans. JCI insight. 2020;5:e133309.
145. Podszun MC, Jakobi M, Birringer M, Weiss J, Frank J. The long chain α-tocopherol metabolite α-13′-COOH and γ-tocotrienol induce P-glycoprotein expression and activity by activation of the pregnane X receptor in the intestinal cell line LS 180. Mol Nutr Food Res. 2017;61:1600605.
146. Pein H, Ville A, Pace S, Temml V, Garscha U, Raasch M, et al. Endogenous metabolites of vitamin E limit inflammation by targeting 5-lipoxygenase. Nat Commun. 2018;9:3834.
147. Podszun MC, Chung J-Y, Ylaya K, Kleiner DE, Hewitt SM, Rotman Y. 4-HNE immunohistochemistry and image analysis for detection of lipid peroxidation in human liver samples using vitamin E treatment in NAFLD as a proof of concept. J Histochem Cytochem. 2020;68:635–43.
148. Podszun MC, Alawad AS, Lingala S, Morris N, Huang W-CA, Yang S, et al. Vitamin E treatment in NAFLD patients demonstrates that oxidative stress drives steatosis through upregulation of de-novo lipogenesis. Redox Biol. 2020;37:101710.
149. Vadarlis A, Antza C, Bakaloudi DR, Doundoulakis I, Kalopitas G, Samara M, et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2021;36: 311–19.
150. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology (Baltimore, MD). 2018;67:328–57.
151. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology (Baltimore, MD). 2020;71:495–509.

152. Wang Y, Ho C-T. Polyphenolic chemistry of tea and coffee: a century of progress. J Agric Food Chem. 2009;57:8109–14.
153. Masterjohn C, Bruno RS. Therapeutic potential of green tea in nonalcoholic fatty liver disease. Nutr Rev. 2012;70:41–56.
154. Bruno RS, Dugan CE, Smyth JA, DiNatale DA, Koo SI. Green tea extract protects leptin-deficient, spontaneously obese mice from hepatic steatosis and injury. J Nutr. 2008;138:323–31.
155. Bose M, Lambert JD, Ju J, Reuhl KR, Shapses SA, Yang CS. The major green tea polyphenol, (−)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. J Nutr. 2008;138:1677–83.
156. Gan L, Meng Z, Xiong R, Guo J, Lu X, Zheng ZW, et al. Green tea polyphenol epigallocatechin-3-gallate ameliorates insulin resistance in non-alcoholic fatty liver disease mice. Acta Pharmacol Sin. 2015;36:597–605.
157. Fukuzawa Y, Kapoor MP, Yamasaki K, Okubo T, Hotta Y, Juneja LR. Effects of green tea catechins on nonalcoholic steatohepatitis (NASH) patients. J Funct Foods. 2014;9:48–59.
158. Frank J, George TW, Lodge JK, Rodriguez-Mateos AM, Spencer JPE, Minihane AM, et al. Daily consumption of an aqueous green tea extract supplement does not impair liver function or alter cardiovascular disease risk biomarkers in healthy men. J Nutr. 2009;139:58–62.
159. Lambert JD, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (−)-epigallocatechin-3-gallate in mice. Food Chem Toxicol. 2010;48:409–16.
160. Wang D, Wang Y, Wan X, Yang CS, Zhang J. Green tea polyphenol (−)-epigallocatechin-3-gallate triggered hepatotoxicity in mice: responses of major antioxidant enzymes and the Nrf2 rescue pathway. Toxicol Appl Pharmacol. 2015;283:65–74.
161. Yu Z, Samavat H, Dostal AM, Wang R, Torkelson CJ, Yang CS, et al. Effect of green tea supplements on liver enzyme elevation: results from a randomized intervention study in the United States. Cancer Prev Res (Phila). 2017;10:571–9.
162. Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, Filipič M, et al. Scientific opinion on the safety of green tea catechins. EFS2. 2018;16:e05239.
163. Siegel AB, Stebbing J. Milk thistle: early seeds of potential. Lancet Oncol. 2013;14:929–30.
164. Strader DB, Bacon BR, Lindsay KL, La Brecque DR, Morgan T, Wright EC, et al. Use of complementary and alternative medicine in patients with liver disease. Am J Gastroenterol. 2002;97:2391–7.
165. Lee JI, Narayan M, Barrett JS. Analysis and comparison of active constituents in commercial standardized silymarin extracts by liquid chromatography-electrospray ionization mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;845:95–103.
166. Ni X, Wang H. Silymarin attenuated hepatic steatosis through regulation of lipid metabolism and oxidative stress in a mouse model of nonalcoholic fatty liver disease (NAFLD). Am J Translat Res. 2016;8:1073–81.
167. Hebbard L, George J. Animal models of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2011;8:35–44.
168. Serviddio G, Bellanti F, Giudetti AM, Gnoni GV, Petrella A, Tamborra R, et al. A silybin-phospholipid complex prevents mitochondrial dysfunction in a rodent model of nonalcoholic steatohepatitis. J Pharmacol Exp Ther. 2010;332:922–32.
169. Velussi M, Cernigoi AM, Ariella DM, Dapas F, Caffau C, Zilli M. Long-term (23 months) treatment with an antioxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol. 1997;26:871–9.
170. Aller R, Izaola O, Gómez S, Tafur C, González G, Berroa E, et al. Effect of silymarin plus vitamin E in patients with non-alcoholic fatty liver disease. A randomized clinical pilot study. Eur Rev Med Pharmacol Sci. 2015;19:3118–24.
171. Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease. Medicine. 2017;96:e9061.
172. Wah Kheong C, Nik Mustapha NR, Mahadeva S. A randomized trial of Silymarin for the treatment of nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol. 2017;15:1940–1949.e8.
173. Javed S, Kohli K, Ali M. Reassessing bioavailability of silymarin. Alternat Med Rev. 2011;16:239–49.
174. Nobili V, Carpino G, Alisi A, de Vito R, Franchitto A, Alpini G, et al. Role of docosahexaenoic acid treatment in improving liver histology in pediatric nonalcoholic fatty liver disease. PLoS One. 2014;9:e88005.
175. Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the welcome* study. Hepatology (Baltimore, MD). 2014;60:1211–21.
176. Nogueira MA, Oliveira CP, Ferreira Alves VA, Stefano JT, Rodrigues LSDR, Torrinhas RS, et al. Omega-3 polyunsaturated fatty acids in treating non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled trial. Clin Nutri (Edinburgh, Scotland). 2016;35:578–86.
177. He X-X, Wu X-L, Chen R-P, Chen C, Liu X-G, Wu BJ, et al. Effectiveness of Omega-3 polyunsaturated fatty acids in non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. PLoS One. 2016;11:e0162368.
178. WHO. World report on ageing and health. Geneva: WHO; 2015.
179. Drachman DA. The amyloid hypothesis, time to move on: amyloid is the downstream result, not cause, of Alzheimer's disease. Alzheimers Dement. 2014;10:372–80.
180. Citron M. Alzheimer's disease: strategies for disease modification. Nat Rev Drug Discov. 2010;9:387–98.
181. Lansdall CJ. An effective treatment for Alzheimer's disease must consider both amyloid and tau. Bioscience Horizons. 2014;7:hzu002.
182. Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alz Res Therapy. 2017;9:795.
183. Amanatkar HR, Papagiannopoulos B, Grossberg GT. Analysis of recent failures of disease modifying therapies in Alzheimer's disease suggesting a new methodology for future studies. Expert Rev Neurother. 2016;17:7–16.
184. van Dyck CH, Nygaard HB, Chen K, Donohue MC, Raman R, Rissman RA, et al. Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: a randomized clinical trial. JAMA Neurol. 2019;76:1219–229.
185. Atri A, Frölich L, Ballard C, Tariot PN, Molinuevo JL, Boneva N, et al. Effect of Idalopirdine as adjunct to

cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. JAMA. 2018;319:130–42.
186. Coric V, Salloway S, van Dyck CH, Dubois B, Andreasen N, Brody M, et al. Targeting prodromal Alzheimer disease with Avagacestat. JAMA Neurol. 2015;72:1324–33.
187. Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, et al. Randomized trial of Verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019;380:1408–20.
188. Brini S, Sohrabi HR, Peiffer JJ, Karrasch M, Hämäläinen H, Martins RN, et al. Physical activity in preventing Alzheimer's disease and cognitive decline: a narrative review. Sports Med (Auckland, NZ). 2018;48:29–44.
189. Shlisky J, Bloom DE, Beaudreault AR, Tucker KL, Keller HH, Freund-Levi Y, et al. Nutritional considerations for healthy aging and reduction in age-related chronic disease. Adv Nutr. 2017;8:17.2–26.
190. Rege SD, Geetha T, Broderick TL, Babu JR. Can diet and physical activity limit Alzheimer's disease risk? Curr Alzheimer Res. 2017;14:76–93.
191. Hill E, Goodwill AM, Gorelik A, Szoeke C. Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging. 2019;76:45–52.
192. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun. 2016;7:11934.
193. Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr. 2005;45:287–306.
194. Schaffer S, Asseburg H, Kuntz S, Muller WE, Eckert GP. Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria. Mol Neurobiol. 2012;46:161–78.
195. Gaudreault R, Mousseau N. Mitigating Alzheimer's disease with natural polyphenols: a review. Curr Alzheimer Res. 2019;16:529–43.
196. Shukitt-Hale B, Carey AN, Jenkins D, Rabin BM, Joseph JA. Beneficial effects of fruit extracts on neuronal function and behavior in a rodent model of accelerated aging. Neurobiol Aging. 2007;28:1187–94.
197. Krikorian R, Boespflug EL, Fleck DE, Stein AL, Wightman JD, Shidler MD, et al. Concord grape juice supplementation and neurocognitive function in human aging. J Agric Food Chem. 2012;60:5736–42.
198. Allam F, Dao AT, Chugh G, Bohat R, Jafri F, Patki G, et al. Grape powder supplementation prevents oxidative stress-induced anxiety-like behavior, memory impairment, and high blood pressure in rats. J Nutr. 2013;143:835–42.
199. Dilberger B, Passon M, Asseburg H, Silaidos CV, Schmitt F, Schmiedl T, et al. Polyphenols and metabolites enhance survival in rodents and nematodes-impact of mitochondria. Nutrients. 2019;11:1886.
200. Murugaiyah V, Mattson MP. Neurohormetic phytochemicals: an evolutionary-bioenergetic perspective. Neurochem Int. 2015;89:271–80.
201. Asseburg H, Schäfer C, Müller M, Hagl S, Pohland M, Berressem D, et al. Effects of grape skin extract on age-related mitochondrial dysfunction, memory and life span in C57BL/6J mice. Neuromolecular Med. 2016;18:378–95.
202. Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA. 2009;302:638–48.
203. Scarmeas N, Stern Y, Tang M-X, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006;59:912–21.
204. Yusufov M, Weyandt LL, Piryatinsky I. Alzheimer's disease and diet: a systematic review. Int J Neurosci. 2017;127:161–75.
205. Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv Nutr (Bethesda, MD). 2016;7:889–904.
206. Feart C, Samieri C, Barberger-Gateau P. Mediterranean diet and cognitive health: an update of available knowledge. Curr Opin Clin Nutr Metab Care. 2015;18:51–62.
207. Trichopoulou A, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med. 2014;12:112.
208. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013;84:1318–25.
209. Martínez-Lapiscina EH, Clavero P, Toledo E, San Julián B, Sanchez-Tainta A, Corella D, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. J Nutr Health Aging. 2013;17:544–52.
210. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de La Torre R, Martínez-González MÁ, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med. 2015;175:1094–103.
211. Bayram B, Ozcelik B, Grimm S, Roeder T, Schrader C, Ernst IMA, et al. A diet rich in olive oil phenolics reduces oxidative stress in the heart of SAMP8 mice by induction of Nrf2-dependent gene expression. Rejuvenation Res. 2012;15:71–81.
212. Fernández del Río L, Gutiérrez-Casado E, Varela-López A, Villalba JM. Olive oil and the hallmarks of aging. Molecules (Basel, Switzerland). 2016;21:163.
213. Angeloni C, Malaguti M, Barbalace M, Hrelia S. Bioactivity of olive oil phenols in neuroprotection. Int J Mol Sci. 2017;18:2230.
214. Gorzynik-Debicka M, Przychodzen P, Cappello F, Kuban-Jankowska A, Marino Gammazza A, Knap N, et al. Potential health benefits of olive oil and plant polyphenols. Int J Mol Sci. 2018;19:686.
215. Reutzel M, Grewal R, Silaidos C, Zotzel J, Marx S, Tretzel J, et al. Effects of Long-term treatment with a blend of highly purified olive Secoiridoids on cognition and brain ATP levels in aged NMRI mice. Oxid Med Cell Longev. 2018;2018:4070935.
216. Schaffer S, Podstawa M, Visioli F, Bogani P, Müller WE, Eckert GP. Hydroxytyrosol-rich olive mill wastewater extract protects brain cells in vitro and ex vivo. J Agric Food Chem. 2007;55:5043–9.
217. Schaffer S, Müller WE, Eckert GP. Cytoprotective effects of olive mill wastewater extract and its main constituent hydroxytyrosol in PC12 cells. Pharmacol Res. 2010;62:322–7.
218. Pantano D, Luccarini I, Nardiello P, Servili M, Stefani M, Casamenti F. Oleuropein aglycone and polyphenols from

olive mill waste water ameliorate cognitive deficits and neuropathology. Br J Clin Pharmacol. 2017;83:54–62.
219. Casamenti F, Grossi C, Rigacci S, Pantano D, Luccarini I, Stefani M. Oleuropein alycone: a possible drug against degenerative conditions. In vivo evidence of its effectiveness against Alzheimer's disease. J Alzheimers Dis. 2015;45:679–88.
220. Casamenti F, Stefani M. Olive polyphenols: new promising agents to combat aging-associated neurodegeneration. Expert Rev Neurother. 2017;17:345–58.
221. Grewal R, Reutzel M, Dilberger B, Hein H, Zotzel J, Marx S, et al. Purified oleocanthal and ligstroside protect against mitochondrial dysfunction in models of early Alzheimer's disease and brain ageing. Exp Neurol. 2020;328:113248.
222. Colizzi C. The protective effects of polyphenols on Alzheimer's disease: a systematic review. Alzheimer's Dementia. 2019;5:184–96.
223. Malar D, Devi K. Dietary polyphenols for treatment of Alzheimer's disease– future research and development. Curr Pharm Biotechnol. 2014;15:330–42.
224. Jayasena T, Poljak A, Smythe G, Braidy N, Münch G, Sachdev P. The role of polyphenols in the modulation of sirtuins and other pathways involved in Alzheimer's disease. Ageing Res Rev. 2013;12:867–83.
225. Müller WE, Eckert A, Eckert GP, Fink H, Friedland K, Gauthier S, et al. Therapeutic efficacy of the Ginkgo special extract EGb761® within the framework of the mitochondrial cascade hypothesis of Alzheimer's disease. World J Biol Psychiat. 2019;20:173–89.
226. Tajadini H, Saifadini R, Choopani R, Mehrabani M, Kamalinejad M, Haghdoost AA. Herbal medicine Davaie Loban in mild to moderate Alzheimer's disease: a 12-week randomized double-blind placebo-controlled clinical trial. Complement Ther Med. 2015;23:767–72.
227. Farokhnia M, Shafiee Sabet M, Iranpour N, Gougol A, Yekehtaz H, Alimardani R, et al. Comparing the efficacy and safety of *Crocus sativus* L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. Hum Psychopharmacol. 2014;29:351–9.
228. Burns A, Perry E, Holmes C, Francis P, Morris J, Howes MJR, et al. A double-blind placebo-controlled randomized trial of *Melissa officinalis* oil and donepezil for the treatment of agitation in Alzheimer's disease. Dement Geriatr Cogn Disord. 2011;31:158–64.
229. Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther. 2010;35:581–8.
230. Baum L, Lam CWK, Cheung SK-K, Kwok T, Lui V, Tsoh J, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharmacol. 2008;28:110–3.
231. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry. 2003;74:863–6.
232. Wightman EL, Reay JL, Haskell CF, Williamson G, Dew TP, Kennedy DO. Effects of resveratrol alone or in combination with piperine on cerebral blood flow parameters and cognitive performance in human subjects: a randomised, double-blind, placebo-controlled, cross-over investigation. Br J Nutr. 2014; 112:203–13.
233. Mollace V, Scicchitano M, Paone S, Casale F, Calandruccio C, Gliozzi M, et al. Hypoglycemic and hypolipemic effects of a new lecithin formulation of bergamot polyphenolic fraction: a double blind, randomized, placebo- controlled study. Endocr Metab Immune Disord Drug Targets. 2019;19:136–43.
234. Wang G, Wang L, Wang C, Qin L. Spore powder of Ganoderma lucidum for the treatment of Alzheimer disease. Medicine. 2018;97:e0636.
235. Guo Q, Zhou Y, Wang C-J, Huang Y-M, Lee Y-T, Su MH, et al. An open-label, nonplacebo-controlled study on Cistanche tubulosa glycoside capsules (Memoregain[®]) for treating moderate Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2013;28:363–70.
236. Remington R, Chan A, Lepore A, Kotlya E, Shea TB. Apple juice improved behavioral but not cognitive symptoms in moderate-to-late stage Alzheimer's disease in an open-label pilot study. Am J Alzheimers Dis Other Demen. 2010;25: 367–71.
237. Heo J-H, Lee S-T, Chu K, Oh MJ, Park H-J, Shim JY, et al. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimers disease. Eur J Neurol. 2008;15:865–8.
238. Turner RS, Thomas RG, Craft S, van Dyck CH, Mintzer J, Reynolds BA, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85:1383–91.
239. Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, et al. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J Neuroinflammation. 2017;14:1202.
240. DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J. 2012;11:511.
241. Hooshmand B, Mangialasche F, Kalpouzos G, Solomon A, Kåreholt I, Smith AD, et al. Association of vitamin B12, Folate, and sulfur amino acids with brain magnetic resonance imaging measures in older adults: a longitudinal population-based study. JAMA Psychiat. 2016;73:606–13.
242. Madsen SK, Rajagopalan P, Joshi SH, Toga AW, Thompson PM. Higher homocysteine associated with thinner cortical gray matter in 803 participants from the Alzheimer's disease neuroimaging initiative. Neurobiol Aging. 2015;36: S203–10.
243. Hooshmand B, Solomon A, Kåreholt I, Rusanen M, Hänninen T, Leiviskä J, et al. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med. 2012;271:204–12.
244. Gopinath B, Flood VM, Rochtchina E, Thiagalingam A, Mitchell P. Serum homocysteine and folate but not vitamin B 12 are predictors of CHD mortality in older adults. Eur J Prev Cardiolog. 2011;19:1420–9.
245. Bailey RL, Jun S, Murphy L, Green R, Gahche JJ, Dwyer JT, et al. High folic acid or folate combined with low vitamin B-12 status: potential but inconsistent association with cognitive function in a nationally representative cross-sectional sample

of US older adults participating in the NHANES. Am J Clin Nutr. 2020;112:1547–57.

246. Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen SJPM, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. Am J Clin Nutr. 2014; 100:657–66.
247. Hankey GJ, Ford AH, Yi Q, Eikelboom JW, Lees KR, Chen C, et al. Effect of B vitamins and lowering homocysteine on cognitive impairment in patients with previous stroke or transient ischemic attack: a prespecified secondary analysis of a randomized, placebo-controlled trial and meta-analysis. Stroke. 2013;44:2232–9.
248. Mendonça N, Granic A, Mathers JC, Martin-Ruiz C, Wesnes KA, Seal CJ, et al. One-carbon metabolism biomarkers and cognitive decline in the very old: the Newcastle 85+ study. J Am Med Dir Assoc. 2017;18:806.e19–27.
249. Scott TM, Rogers G, Weiner DE, Livingston K, Selhub J, Jacques PF, et al. B-vitamin therapy for kidney transplant recipients lowers Homocysteine and improves selective cognitive outcomes in the randomized FAVORIT ancillary cognitive trial. J Prev Alzheimers Dis. 2017;4:174–82.
250. Durga J, van Boxtel MPJ, Schouten EG, Kok FJ, Jolles J, Katan MB, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet (London, England). 2007;369:208–16.
251. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 2012;27:592–600.
252. Zhang C, Luo J, Yuan C, Ding D. Vitamin B12, B6, or folate and cognitive function in community-dwelling older adults: a systematic review and meta-analysis. J Alzheimers Dis. 2020; 77:781–94.
253. Kwok T, Wu Y, Lee J, Lee R, Yung CY, Choi G, et al. A randomized placebo-controlled trial of using B vitamins to prevent cognitive decline in older mild cognitive impairment patients. Clin Nutr (Edinburgh, Scotland). 2020;39:2399–405.
254. Baroni L, Bonetto C, Rizzo G, Bertola C, Caberlotto L, Bazzerla G. Association between cognitive impairment and vitamin B12, Folate, and Homocysteine status in elderly adults: a retrospective study. J Alzheimers Dis. 2019;70: 443–53.
255. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005;29:21–30.
256. Sonnenberg J, Luine VN, Krey LC, Christakos S. 1,25-Dihydroxyvitamin D3 treatment results in increased choline acetyltransferase activity in specific brain nuclei. Endocrinology. 1986;118:1433–9.
257. Landfield PW, Cadwallader-Neal L. Long-term treatment with calcitriol (1,25(OH)2 vit D3) retards a biomarker of hippocampal aging in rats. Neurobiol Aging. 1998;19:469–77.
258. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83:754–9.
259. Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, Porter NM. Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. J Neurosci. 2001;21:98–108.
260. Masoumi A, Goldenson B, Ghirmai S, Avagyan H, Zaghi J, Abel K, et al. 1alpha,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer's disease patients. J Alzheimers Dis. 2009;17:703–17.
261. Taghizadeh M, Talaei SA, Djazayeri A, Salami M. Vitamin D supplementation restores suppressed synaptic plasticity in Alzheimer's disease. Nutr Neurosci. 2014;17:172–7.
262. Yu J, Gattoni-Celli M, Zhu H, Bhat NR, Sambamurti K, Gattoni-Celli S, et al. Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AβPP transgenic mice. J Alzheimers Dis. 2011;25:295–307.
263. Latimer CS, Brewer LD, Searcy JL, Chen K-C, Popović J, Kraner SD, et al. Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats. Proc Natl Acad Sci U S A. 2014;111:E4359–66.
264. Maretzke F, Bechthold A, Egert S, Ernst JB, van Melo Lent D, Pilz S, et al. Role of vitamin D in preventing and treating selected Extraskeletal diseases-An umbrella review. Nutrients. 2020;12:969.
265. Balion C, Griffith LE, Strifler L, Henderson M, Patterson C, Heckman G, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology. 2012;79: 1397–405.
266. Goodwill AM, Szoeke C. A systematic review and Meta-analysis of the effect of Low vitamin D on cognition. J Am Geriatr Soc. 2017;65:2161–8.
267. Pettersen JA, Fontes S, Duke CL. The effects of vitamin D insufficiency and seasonal decrease on cognition. Can J Neurol Sci. 2014;41:459–65.
268. Annweiler C, Montero-Odasso M, Llewellyn DJ, Richard-Devantoy S, Duque G, Beauchet O. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis. 2013;37:147–71.
269. Pettersen JA. Vitamin D and executive functioning: are higher levels better? J Clin Exp Neuropsychol. 2016;38:467–77.
270. Darwish H, Zeinoun P, Ghusn H, Khoury B, Tamim H, Khoury SJ. Serum 25-hydroxyvitamin D predicts cognitive performance in adults. Neuropsychiatr Dis Treat. 2015;11: 2217–23.
271. Nagel G, Herbolsheimer F, Riepe M, Nikolaus T, Denkinger MD, Peter R, et al. Serum vitamin D concentrations and cognitive function in a population-based study among older adults in South Germany. J Alzheimer's Dis. 2015;45:1119–26.
272. Lam V, Albrecht MA, Takechi R, Prasopsang P, Lee YP, Foster JK, et al. Serum 25-hydroxyvitamin D is associated with reduced verbal episodic memory in healthy, middle-aged and older adults. Eur J Nutr. 2016;55:1503–13.
273. Sommer I, Griebler U, Kien C, Auer S, Klerings I, Hammer R, et al. Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. BMC Geriatr. 2017;17:16.
274. Pettersen JA. Does high dose vitamin D supplementation enhance cognition?: a randomized trial in healthy adults. Exp Gerontol. 2017;90:90–7.

275. Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB. Genetically decreased vitamin D and risk of Alzheimer disease. Neurology. 2016;87:2567–74.
276. Larsson SC, Traylor M, Markus HS, Michaëlsson K. Serum parathyroid hormone, 25-Hydroxyvitamin D, and risk of Alzheimer's disease: a Mendelian randomization study. Nutrients. 2018;10:1243.
277. Kueider AM, Tanaka T, An Y, Kitner-Triolo MH, Palchamy E, Ferrucci L, et al. State- and trait-dependent associations of vitamin-D with brain function during aging. Neurobiol Aging. 2016;39:38–45.
278. International Diabetes Federation IDF Diabetes Atlas Ninth edition 2019.
279. American Diabetes Association. Introduction: standards of medical Care in Diabetes-2018. Dia Care. 2018;41:S1–2.
280. Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33:2285–93.
281. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Dia Care. 2017;40:136–54.
282. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. Curr Mol Med. 2001;1:197–207.
283. Volvert M-L, Seyen S, Piette M, Evrard B, Gangolf M, Plumier JC, et al. Benfotiamine, a synthetic S-acyl thiamine derivative, has different mechanisms of action and a different pharmacological profile than lipid-soluble thiamine disulfide derivatives. BMC Pharmacol. 2008;8:10.
284. Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, et al. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. Diabetologia. 2007;50:2164–70.
285. Anwar A, Ahmed Azmi M, Siddiqui JA, Panhwar G, Shaikh F, Ariff M. Thiamine level in type I and type II diabetes mellitus patients: a comparative study focusing on hematological and biochemical evaluations. Cureus. 2020;12:e8027.
286. Page GLJ, Laight D, Cummings MH. Thiamine deficiency in diabetes mellitus and the impact of thiamine replacement on glucose metabolism and vascular disease. Int J Clin Pract. 2011;65:684–90.
287. Hammes H-P, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003;9:294–9.
288. Berrone E, Beltramo E, Solimine C, Ape AU, Porta M. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. J Biol Chem. 2006;281:9307–13.
289. Schreeb KH, Freudenthaler S, Vormfelde SV, Gundert-Remy U, Gleiter CH. Comparative bioavailability of two vitamin B1 preparations: benfotiamine and thiamine mononitrate. Eur J Clin Pharmacol. 1997;52:319–20.
290. Ledermann H, Wiedey KD. Behandlung der manifesten diabetischen Polyneuropathie. Therapiewoche. 1989;39:1445–9.
291. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study). Int J Clin Pharmacol Ther. 2005;43:71–7.
292. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. Exp Clin Endocrinol Diabetes. 2008;116:600–5.
293. Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. Exp Clin Endocrinol. 1996;104:311–6.
294. Winkler G, Pál B, Nagybéganyi E, Ory I, Porochnavec M, Kempler P. Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. Arzneimittelforschung. 1999;49:220–4.
295. Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. Free Radic Biol Med. 1995;19:227–50.
296. Matsugo S, Han D, Tritschler HJ, Packer L. Decomposition of alpha-lipoic acid derivatives by photoirradiation-formation of dihydrolipoic acid from alpha-lipoic acid. Biochem Mol Biol Int. 1996;38:51–9.
297. Rochette L, Ghibu S, Muresan A, Vergely C. Alpha-lipoic acid: molecular mechanisms and therapeutic potential in diabetes. Can J Physiol Pharmacol. 2015;93:1021–7.
298. Stirban A. Drugs for the treatment of diabetes complications. Zycose: a new player in the field? Drugs Today (Barc). 2008; 44:783–96.
299. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–20.
300. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54:1615–25.
301. Ziegler D, Sohr CGH, Nourooz-Zadeh J. Oxidative stress and antioxidant defense in relation to the severity of diabetic polyneuropathy and cardiovascular autonomic neuropathy. Dia Care. 2004;27:2178–83.
302. Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, et al. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneimittelforschung. 1995;45:872–4.
303. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabetic Med. 2004;21:114–21.
304. Çakici N, Fakkel TM, van Neck JW, Verhagen AP, Coert JH. Systematic review of treatments for diabetic peripheral neuropathy. Diabetic Med. 2016;33:1466–76.
305. Amato Nesbit S, Sharma R, Waldfogel JM, Zhang A, Bennett WL, Yeh HC, et al. Non-pharmacologic treatments for symptoms of diabetic peripheral neuropathy: a systematic review. Curr Med Res Opin. 2019;35:15–25.
306. Dy SM, Bennett WL, Sharma R, Zhang A, Waldfogel JM, Nesbit SA, et al. Preventing complications and treating symptoms of diabetic peripheral neuropathy. Rockville (MD); Agency for Healthcare Research and Quality (US); 2017.
307. Rutkove S, McIlduff. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. Therapeutics and Clinical Risk Management. 2011;7:377–85.
308. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract. 2014;14:167–84.
309. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, et al. Oral treatment with alpha-lipoic acid improves

symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Dia Care. 2006;29:2365–70.
310. Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy. Treat Endocrinol. 2004;3:173–89.
311. Tang J, Wingerchuk DM, Crum BA, Rubin DI, Demaerschalk BM. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. Neurologist. 2007;13:164–7.
312. Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, et al. Efficacy and safety of antioxidant treatment with α-Lipoic acid over 4 years in diabetic polyneuropathy. Dia Care. 2011;34:2054–60.
313. Du X, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. Diabetologia. 2008;51:1930–2.
314. Popa AR, Bungau S, Vesa CM, Bondar AC, Pantis C, Maghiar O, et al. Evaluating the efficacy of the treatment with benfotiamine and alpha-lipoic acid in distal symmetric painful diabetic polyneuropathy. Rev Chim. 2019;70:3108–14.

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