Nutraceutical Prevention of Diabetic Complications—Focus on Dicarbonyl and Oxidative Stress

Mark F. McCarty 1,*, James J. DiNicolantonio 2 and James H. O’Keefe 2

1 Catalytic Longevity Foundation, San Diego, CA 92109, USA
2 Saint Luke’s Mid America Heart Institute, St. Louis, MO 64111, USA
* Correspondence: markfmccarty@gmail.com

Abstract: Oxidative and dicarbonyl stress, driven by excess accumulation of glycolytic intermediates in cells that are highly permeable to glucose in the absence of effective insulin activity, appear to be the chief mediators of the complications of diabetes. The most pathogenically significant dicarbonyl stress reflects spontaneous dephosphorylation of glycolytic triose phosphates, giving rise to highly reactive methylglyoxal. This compound can be converted to harmless lactate by the sequential activity of glyoxalase I and II, employing glutathione as a catalyst. The transcription of glyoxalase I, rate-limiting for this process, is promoted by Nrf2, which can be activated by nutraceutical phase 2 inducers such as lipoic acid and sulforaphane. In cells exposed to hyperglycemia, glycine somehow up-regulates Nrf2 activity. Zinc can likewise promote glyoxalase I transcription, via activation of the metal-responsive transcription factor (MTF) that binds to the glyoxalase promoter. Induction of glyoxalase I and metallothionein may explain the protective impact of zinc in rodent models of diabetic complications. With respect to the contribution of oxidative stress to diabetic complications, promoters of mitophagy and mitochondrial biogenesis, UCP2 inducers, inhibitors of NADPH oxidase, recouplers of eNOS, glutathione precursors, membrane oxidant scavengers, Nrf2 activators, and correction of diabetic thiamine deficiency should help to quell this.

Keywords: diabetes complications; dicarbonyl stress; oxidative stress; glyoxalase I; mitochondrial biogenesis; NADPH oxidase; glutathione; thiamine deficiency; nutraceuticals; functional foods

1. How Hyperglycemia Drives Diabetic Complications

The complications of diabetes reflect dysfunction or death of cell types that are highly permeable to glucose in the absence of effective insulin activity. These cells include podocytes, mesangial and tubular cells of the kidney, vascular endothelial cells, neurons, glia, and immune cells [1]. (Note that the macrovascular complications of diabetes—atherosclerosis and cardiomyopathy—appear to stem from dysfunctional vascular endothelium [2].) Such cells express glucose transporters whose activity is not dependent on insulin signaling. As a result, glycolytic intermediates build up to excess levels, and increased accumulation of pyruvate may impose a substrate load on mitochondria. In a classic model, Brownlee and colleagues have proposed that increased levels of certain glycolytic intermediates can provoke cellular damage by inducing oxidative stress (via mitochondrial and PKC activation of NADPH oxidases), dicarbonyl stress, an accelerated polyl pathway, and excess O-GlcNAcylation of proteins [1,3]. Especially in type 2 diabetics, episodic elevations of free fatty acids at physiologically inappropriate times (reflecting adipocyte insulin resistance) may collaborate with hyperglycemia in the induction of diabetic complications—by boosting diacylglycerol levels [4]. It may be feasible to prevent or at least ameliorate diabetic complications by inhibiting several or all of these mechanisms. This essay examines nutraceutical strategies which may have potential in this regard—with particular emphasis on the induction of glyoxalase 1 as a technique for coping with dicarbonyl stress.
2. A Key Role for Dicarbonyl Stress in Diabetic Complications

Although considerable evidence points to oxidative stress as a major driver of diabetic complications, so-called "dicarbonyl stress" has also emerged as a key driver of these complications, the effects of which are mediated only in part by reactive oxygen species (ROS) \[1,5\]. Hence, any plan to prevent diabetic complications much include components intended to address dicarbonyl stress. In cell types exposed to hyperglycemia that are highly permeable to glucose in the absence of insulin signaling, the glycolytic triose phosphates glyceraldehyde-3-phosphate and dihydroxyacetone phosphate accumulate. These are susceptible to spontaneous loss of phosphate, giving rise to the highly reactive dicarbonyl compound methylglyoxal; the rate of this reaction is directly proportional to the concentration of triose phosphates \[6\]. Methylglyoxal reacts most readily with the head groups of arginine residues in proteins, giving rise to a structure known as hydroimidazolone (M-H1); this, along with the hydroimidazolone derived from 3-deoxyglucosone, is the most common advanced glycation end product (AGE) found in the plasma and tissues of diabetics \[7\].

M-H1, as well as arginine-containing proteins or peptides which feature it, can interact with very high (nanomolar) affinity with the receptor for advanced glycation end products—the RAGE receptor—triggering its activation \[8\]. This affinity is far higher than RAGE's affinity for certain other commonly discussed lysine-linked AGES elevated in diabetics such as Nε-carboxymethyl-lysine, and hence is more likely to be of physiologically significance \[8\]. RAGE activation promotes inflammation via stimulation of NF-kappaB activity, can boost ROS production by activating NADPH oxidase, and can drive proliferation via PI3K-Akt and ERK signaling; its role in the genesis of diabetic complications is well established \[9\]. RAGE activation up-regulates its own expression, as NF-kappaB drives the transcription of its gene; this makes RAGE activators that much more potent as triggers for inflammation \[10\]. Additionally, methylglyoxal's protein-binding activity can trigger endoplasmic reticulum stress—another source of inflammation—by impairing protein folding \[11\]. This may reflect in part the ability of M-H1 to promote protein cross-linking, as it contains a carbonyl group susceptible to attack by nucleophilic cysteine groups \[12\]. Methylglyoxal-mediated damage to the mitochondrial electron transport chain boosts superoxide generation while impairing ATP synthesis \[13,14\]. Additionally, methylglyoxal can react directly with 2′-deoxyguanosine residues in DNA, promoting DNA damage and mutagenesis \[15\]. Administration of methylglyoxal to normoglycemic mice has been reported to produce vascular and renal damage analogous to that seen in diabetics \[16–18\].

These considerations suggest that it is hardly accidental that cells have devised a system for detoxifying methylglyoxal that has been conserved throughout evolution. The enzymes glyoxalase 1 and 2, acting in tandem with a catalytic assist from glutathione, convert methylglyoxal to harmless lactate \[19,20\]. In effect, this reaction converts one of the carbonyls to a carboxyl group, and the other to a hydroxyl group—there is no net oxidation or reduction, and the end product is innocuous. Glyoxalase 1 (Glo1) is rate-limiting for this process, and mice with genetic overexpression of Glo1 are protected from renal, retinal, and endothelial dysfunction and damage when rendered diabetic \[1,21–24\]. Conversely, normoglycemic mice with Glo1 knock-down display renal damage analogous to that seen in diabetics \[25\]. These findings suggest that safe, practical strategies for boosting Glo1 expression and/or activity may have important potential in diabetes management.

Attention has been drawn to mechanisms which regulate transcription of the Glo1 gene. The promoter of this gene has been found to contain response elements that are positively responsive to insulin signaling, the Nrf2 transcription factor, and the metal-responsive transcription factor 1 (MTF-1) \[26,27\]. The fact that insulin activity boosts Glo1 expression makes perfect sense homeostatically: insulin signals elevated glucose, and elevated glucose leads to increased methylglyoxal production in glucose-permeable tissues.
3. Nutraceutical Induction of Glyoxalase 1 Expression

The transcription-promoting activity of MTF-1 is activated by binding to zinc; it also mediates zinc-induced increased expression of the antioxidant protein metallothionein [28,29]. Addition of extra zinc to the culture medium of HepG2 cells transfected with the promoter of the Glo1 gene was associated with doubling of promoter activity [26]. This finding may well be pertinent to the clinical literature correlating lower plasma zinc levels in diabetics with increased risk for diabetic complications, including nephropathy, retinopathy, neuropathy, and cataracts [30–35]. These findings, however, should be viewed circumspectly inasmuch as hyperglycemia impairs renal retention of zinc; diabetics therefore tend to be relatively zinc deficient, and lower zinc status in diabetics may thus be a marker for poorer diabetic control [36,37]. The causative association between zinc status and diabetic complications is better established by studies in diabetic rodents—concurrent zinc deficient has been found to aggravate diabetic complications, whereas zinc supplementation has been found to be protective with respect to such complications [36,38–58]. Two small, short term controlled clinical trials of zinc supplementation observed improvements in peripheral neuropathy, as assessed by motor nerve conduction velocity [59,60].

Good zinc status has the further merit that it modestly improves insulin sensitivity—likely through reversible inhibition of tyrosine phosphatase 1B activity targeting the insulin signaling pathway [37,61,62]. Moreover, zinc-inducible metallothionein is an effective scavenger for peroxynitrite-derived radicals—which, in diabetics, promote uncoupling of endothelial nitric oxide synthase by oxidizing its cofactor tetrahydrobiopterin, thereby boosting superoxide generation and impairing the nitric oxide generation vital for vascular health [63–68]. Additionally, supplemental zinc can function as an antagonist of the toxicity of cadmium, which has been linked a range of adverse health outcomes even at ambient non-industrial exposure levels [69]. Remarkably, supplementation with 80 mg zinc daily (accompanied by 2 mg copper to prevent induction of copper deficiency) was associated with a highly significant 27% reduction in total mortality over 6 years of follow-up (RR, 0.73; 95% CI, 0.61–0.89) in the AREDS1 study examining the impact of nutritional supplements on progression of early age-related macular degeneration in the elderly [70]. In light of these findings, a clinical trial examining the impact of graded doses of supplemental zinc on tissue expression of Glo1 and plasma levels of M-H1 in diabetics is clearly warranted. More ambitiously, a long-term randomized controlled trial evaluating the impact of ample zinc supplementation on the development of complications in diabetics would be appropriate—particularly in light of the provocative mortality findings in the AREDS1 trial, that have been mostly ignored.

Nutraceuticals clinically useful for Nrf2 activation—so-called phase 2 inducers—also have potential as Glo1 inducers [27]. Some of these work by interacting covalently cysteinyl residues of Keap1, preventing it from binding Nrf2 in the cytoplasm, and thereby enabling Nrf2 to be transported to the nucleus where it can promote transcription not only of Glo1, but also an entire panoply of antioxidant enzymes (including the enzyme rate-limiting for glutathione synthesis, γ-glutamylcysteine transferase) that could be expected to protect diabetic tissues from the adverse effects of excess ROS production [71–74]. Isothiocyanates (such as sulforaphane) derived from lightly cooked cruciferous vegetables can act as Keap1-binding Nrf2 activators [71,75]. Lipoic acid, in its oxidized form, likewise binds Keap1 and activates Nrf2 activity; it has been explored as an agent for treating diabetic neuropathy [76–79]. The endogenous gasotransmitter hydrogen sulfide also binds to Keap1 and activates Nrf2—an effect which may contribute notably to the health protection associated with adequate H2S production [80,81]. Supplementation taurine can boost the expression of enzymes catalyzing H2S production in vascular tissues—an effect which may explain taurine’s favorable impact on vascular health—and supplemental N-acetylcysteine can increase the availability of cysteine, the key precursor for H2S generation [82–86].
Other nutraceuticals can boost Nrf2 synthesis; melatonin does so by stimulating the clock transcription factor Bmal1, which binds to the promoter of the Nrf2 gene and drives its transcription [87–90]. Another nutraceutical with the potential to promote transcription of this gene is astaxanthin; this can serve as an agonist for the aryl hydrocarbon receptor, which, like Bmal1, can bind the Nrf2 promoter and drive its transcription [91–96]. Hence, the antioxidant benefits of astaxanthin extend far beyond its ability to serve as a highly efficient scavenging antioxidant for biological membranes—most notably the mitochondrial inner membrane [97–99].

Although the amino acid glycine is not a direct activator of Nrf2, a recent study shows that, in the context of hyperglycemia (but not normoglycemia), exposure to increased levels of glycine promotes migration of Nrf2 to the nucleus, much like Nrf2 activators do [100]. The mechanistic basis of this effect currently remains obscure. It is intriguing that methylglyoxal itself can promote nuclear uptake of Nrf2, by inducing a cross-linking of Keap1 subunits that inhibits their ability to interact with Nrf2; could glycine somehow potentiate this cross-linking [12]? In any case, oral glycine supplementation has been shown to boost expression of Glo1 and down-regulate RAGE signaling in the aorta of diabetic rats [101]. Moreover, supplemental glycine may boost the activity of pre-existing Glo1 by increasing glutathione levels [102]; although cysteine availability (which can be amplified with supplemental N-acetylcysteine) is generally considered rate-limiting for glutathione synthesis, glycine availability also has a regulatory impact in this regard, and joint supplementation with N-acetylcysteine and glycine has shown profound antioxidant effects in both rodent and clinical studies [103–108]. Indeed, such supplementation has been reported to reduce insulin resistance in type 2 diabetics, while decreasing their plasma methylglyoxal levels (this latter effect presumably reflecting enhancement of Glo1 activity by elevated glutathione) [107]. Rodent studies reporting that supplemental glycine can prevent cataracts in diabetic rats may conceivably reflect increased Glo1 induction [109,110]. Glycine supplementation also exerts anti-inflammatory effects by activation of glycine receptors expressed on the plasma membranes of many types of myeloid cells [111,112].

The use of high-dose glycine in diabetes management is rendered practical by the fact that glycine is highly soluble, has a pleasant mildly sweet flavor, and is quite inexpensive—for example, it can be employed as a sweetener in coffee or tea [102].

In aggregate, these considerations suggest that the contribution of dicarbonyl stress to diabetic complications may be addressable with a nutraceutical regimen that incorporates zinc, glycine, and one or more agents that target nrf2 activation—such as lipoic acid, sulforaphane (as from broccoli sprout extracts), melatonin and astaxanthin. Fortuitously, each of these agents also can aid antioxidant defenses. More generally, combining a regimen for Glo1 induction with a comprehensive antioxidant supplementation program, targeting the sources of oxidative stress activated in diabetics, may have substantial practical potential for prevention of diabetic complications, provided that complex nutraceutical supplements and functional foods are developed that make such a program fairly easy for patients to implement.

4. Sources of Diabetic Oxidative Stress

The oxidant stress evoked by hyperglycemia, as amplified by the free fatty acid excess associated with insulin resistance, can adversely alter cellular function via such mechanisms as up-regulation of MAP kinase and NF-kappaB signaling, support of transforming growth factor-β pro-fibrotic activity, uncoupling of endothelial nitric oxide synthase, and induction of DNA damage with PARP activation [113–120]. The key sources of oxidant stress in diabetes appear to be structurally damaged mitochondria processing excess substrate, activated NADPH oxidase complexes (particularly NOX2 and NOX4), and uncoupled endothelial nitric oxide synthase (eNOS) [1,5].
5. Nutraceuticals for Promoting Mitophagy and Mitochondrial Biogenesis

Methylglyoxal-mediated damage to the mitochondrial electron transport chain, in conjunction with increased oxidizable substrate provided by enhanced glycolysis and increased free fatty acids, can boost oxidant production by mitochondria. Measures which promote mitophagy of damaged mitochondria, while boosting compensatory mitochondrial mitogenesis, could be expected to quell excessive mitochondrial ROS generation. A recent essay has addressed nutraceuticals with potential for promoting this complex process [121]—they include agents which boost Sirt1 activity (see below), activate AMPK (berberine—a nutraceutical derived from the rhizomes of *Coptis chinensis*, used in traditional Chinese medicine for diabetes control, and now well documented to aid glycemic control in type 2 diabetics), stimulate Nrf2 (as discussed above), and activate PPARα (astaxanthin), as well as the dietary polyamine spermidine [122–131]. In addition, astaxanthin can act as a highly efficient oxidant scavenger for the mitochondrial inner membrane [98,132,133].

With respect to Sirt1 activation—crucial for efficient mitophagy as well as mitochondrial biogenesis—resveratrol, which can boost Sirt1 activity via allosteric interaction, has been somewhat disappointing clinically owing to its inefficient absorption and rapid metabolism; nonetheless, modest reductions in systolic blood pressure and hemoglobin A1c have been observed when diabetics have been treated with resveratrol [134–138]. Nutraceuticals with greater clinical potential for Sirt1 activation include several that somehow enhance Sirt1 synthesis—such as ferulic acid [139–142], melatonin [143–145], tetrahydrocurcumin [146,147], and urolithin A [148–150]—and N1-methylnicotinamide, a natural nicotinamide metabolite that increases the half-life of the Sirt1 protein [151]. (Ferulic acid, tetrahydrocurcumin, and urolithin A are major circulating metabolites of ingested anthocyanins, curcumin, and pomegranate ellagitannins, respectively, thought likely to mediate the health benefits of these compounds.) Cellular levels of Sirt1’s obligate cofactor NAD+ can be increased with nicotinamide riboside or nicotinamide ribonucleotide, both available as nutraceuticals [152–157]. Additionally, berberine-mediated activation of AMPK stimulates rapid reconversion of nicotinamide to NAD+ by promoting induction of nicotinamide phosphoribosyltransferase [158,159].

The ability of thymoquinone (a key component of *Nigella sativa*—black cumin seed—oil) and of pyrroloquinoline quinone (PQQ)—a vitamin-like compound in the diet that binds with high affinity to lactate dehydrogenase—to boost Sirt1 activity rests in their ability to promote oxidation of NADH to NAD+. The antioxidant enzyme NAD(P)H quinone oxidoreductase 1 (NQO1) can reduce thymoquinone to thymohydroquinone, converting NADH to NAD+ in the process; thymohydroquinone can then act as a scavenging antioxidant [160]. This mechanism can explain thymoquinone’s ability to activated Sirt1 [161–163]. NQO1 has been found to bind to Sirt1, and hence, in the presence of reducible quinones, functions physiologically to furnish Sirt1 with the NAD+ it requires [164,165]. In a reaction catalyzed by lactate dehydrogenase, PQQ is reduced and NADH converted to NAD+ in the process [166]. This makes lactate more available for oxidation—while also generating NAD+ needed for Sirt1 activity [167,168]. Thymoquinone can also function as a Keap1-binding Nrf2 activator, giving it particular utility as an antioxidant [169–171]. Thymoquinone can be provided by capsules of *Nigella sativa* oil (standardized to 2–3% potency), and PQQ is available as a pure chemical.

It should be noted that Sirt1 activation has been found to suppress the range of diabetic complications—nephropathy, retinopathy, neuropathy, cardiomyopathy, cataract—in rodent models of diabetes [172,173]. Sirt1 can deacetylate and thereby modulate a wide range of proteins, and these protective effects may stem from mechanisms that are not fully dependent on improved mitochondrial biogenesis. In particular, Sirt1 opposes the pro-inflammatory activity of NF-kappaB via deacetylation of p65 [174].
6. Boosting Expression of Mitochondrial Uncoupling Proteins

The propensity of hyperglycemia to boost mitochondrial oxidant production in glucose-permeable cells can be decreased by increased expression of UCP family uncoupling proteins; by enabling protons to flow back into the mitochondrial matrix, these proteins moderate the elevated mitochondrial electrochemical potential induced by high Krebs cycle activity that results in increased mitochondrial superoxide generation [175,176]. PPARalpha agonists—such as astaxanthin—can increase expression of these proteins [177]. PPARdelta exerts a similar effect and, in certain cell types, such as vascular endothelium, capsaicin-mediated activation of the transient receptor potential vanilloid 1 (TRPV1) receptor boosts its expression and activity [178–180]. In endothelial cells exposed to hyperglycemia, capsaicin exposure enhances UCP2 expression and markedly reduces ROS production [180,181]. In diabetic mice, capsaicin administration likewise alleviated diabetes-induced endothelial dysfunction—an effect negated by UCP2 knockout [180]. The extent to which these effects can be generalized to other glucose-permeable tissues involved in diabetes complications remains to be assessed. Favorable effects of capsaicin feeding on nephropathy and cardiomyopathy in diabetic rodents have been reported [181,182]. Capsaicin, a potent agonist for TRPV1, is the compound responsible for the “heat” of chili peppers, and there is growing evidence that it has important health-protective potential [183]. Prospective Chinese epidemiology has linked regular chili pepper consumption to decreased risk for weight gain—an effect which might be expected with an uncoupling protein inducer [184]. High chili consumption has also been linked to markedly lower cardiovascular, cancer and global mortality, as established by a recent meta-analysis (RR = 0.75 [95% CI: 0.64–0.88; p = 0.0004 for all-cause mortality). For those who do not enjoy the culinary excitement imparted by hot chili, capsaicin supplements featuring cayenne pepper are available for nutraceutical use.

7. Controlling NADPH Oxidase Activity

Increased levels of the glycolytic intermediate glyceraldehyde-3-phosphate, after reduction to glycerol-3-phosphate, can lead to de novo generation of diacylglycerol, particularly in the context of elevated free fatty acids; diacylglycerol, via activation of protein kinase C, can promote assembly and activation of NOX2-dependent NAPDH oxidase; this mechanism is thought to be largely responsible for elevated NADPH oxidase activity in diabetes [4,185–187]. Diabetes can also promote increased expression of NOX4 [188,189]. The free bilirubin generated by induction of heme oxygenase activity can function physiologically as an inhibitor of certain NADPH oxidase complexes, including NOX2 and NOX4 [190–194]. Diabetics with chronically elevated plasma free bilirubin levels owing to Gilbert syndrome are markedly protected from diabetic complications, independent of serum glucose level [195]. Although strategies for boosting plasma levels of free bilirubin have been proposed for management of diabetes and other NADPH oxidase-linked disorders, a nutraceutical strategy may prove to be more practical [196,197]. Phycocyanobilin (PCB), a biliverdin derivative that functions as a light-absorbing chromophore found in cyanobacteria (such as the food spirulina) and certain blue-green algae, appears to mimic the NADPH oxidase-inhibitory impact of bilirubin—a fact which may explain, in part, the potent antioxidant and anti-inflammatory activities of orally administered spirulina or phycocyanin (the spirulina protein to which PCB is covalently attached) in a wide range of rodent models of disease [197–200]. Oral administration of either phycocyanin or PCB has been shown to protect diabetic db/db mice from diabetic nephropathy [198]. Hence, adequate intakes of spirulina (or of more concentrated sources of phycocyanin or PCB) may have important antioxidant potential in diabetics.
8. Recoupling eNOS and Mimicking Its Benefits

In the context of diabetes, eNOS tends to become uncoupled, both because peroxynitrite-derived radicals can oxidize its essential cofactor tetrahydrobiopterin to dihydrobiopterin, and oxidant-mediated inactivation of dimethylarginine dimethylamino-hydrolase (DDAH) increases cellular levels of asymmetric dimethylarginine (ADMA), a functional competitor of arginine’s association with eNOS [66,119,201–204]. These effects are doubly pernicious, as they turn eNOS into a prolific source of superoxide while impeding its ability to produce vascular-protective low-dose nitric oxide. Supplementation with high-dose folate and with the amino acid citrulline can reverse this uncoupling [205,206]. High-dose folate, via induction of increased expression of dihydrofolate reductase, promotes reduction of dihydrobiopterin back to its active tetrahydrobiopterin form [207,208]. Citrulline—more efficiently absorbed and transported to tissues than arginine—is readily converted to arginine within cells, thereby opposing the adverse effect of elevated ADMA on eNOS activity [206,209,210].

The bioactivity of eNOS-generated NO is impaired not only by eNOS uncoupling, but also by a direct quenching of NO by superoxide, yielding the unstable oxidant peroxynitrite. NO-mediated stimulation of soluble guanylate cyclase (sGC) and consequent production of cyclic GMP (cGMP) plays an important role in the prevention of diabetic nephropathy, neuropathy, cardiomyopathy and the endothelial dysfunction promoting atherosclerosis, as can be judged by the fact that treatment with drugs that directly stimulate sGC or that inhibit phosphodiesterase-5 (PDE-5, which selectively degrades cGMP) is protective with respect to these complications in rodent diabetes models [211–226]. High doses of the B vitamin biotin likewise have potential in this regard, as, in pharmaceutically feasible concentrations about a hundred-fold higher than the physiological plasma level, biotin can serve as an agonist for sGC [227–232]. Hence, despite the absence of any published animal studies assessing the impact of high-dose biotin on diabetic complications, there is reason to suspect that biotin could be clinically worthwhile for this purpose. A small case series suggests that 4–8 weeks of supplemental biotin (5–10 mg daily) can achieve marked improvements of clinical and laboratory findings in diabetic neuropathy [233]. Although high-dose biotin is well tolerated—its stimulatory impact on sGC is modest, and hence unlikely to precipitate hypotension—it has the drawback that it can interfere with certain lab assays that employed biotinylated substrates; hence, it is prudent to discontinue its use for at least several days prior to important lab tests [234,235].

Xanthine oxidase activity is expressed in certain diabetic tissues, notably the kidney, and can contribute to superoxide generation; however, research attention has focused on its product uric acid as a possible mediator of diabetic complications [236]. Allopurinol and certain other pharmaceutical xanthine oxidase inhibitors have a protective impact on diabetic nephropathy in rodents, but allopurinol has failed to benefit diabetic renal function in lengthy clinical trials [237–239]. Conceivably, the benefit seen in rodent studies reflects the fact that xanthine oxidase product uric acid can boost NADPH oxidase activity in some tissues [240–242]. However, this effect is maximized at levels below normal human plasma levels—whereas normal plasma levels in rodents are far lower owing to their expression of uricase. Curiously, an increase of uric acid in humans can actually have a net antioxidant effect owing to its ability to scavenge peroxynitrite-derived radicals [243,244]. Meta-analyses of clinical trials also find that allopurinol fails to improve endothelial function or glycemic control in diabetics [245,246]. Targeting xanthine oxidase does not appear to have much promise for quelling complications of diabetes in humans.
9. Inducing Nrf2 and Correcting Thiamine Deficiency

Nutraceuticals which enhance Nrf2 activity—as discussed above—could be expected to counteract the adverse consequences of superoxide/hydrogen peroxide generation in the tissues of diabetics. As noted, zinc-mediated induction of metallothionein could be protective in this regard as well. Additionally, supplemental glycine and N-acetylcysteine can collaborate in enhancing tissue glutathione levels [102].

One key effect of Nrf2 inducers is to increase expression of glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD)—enzymes in the upper pentose phosphate pathway that generate the NADPH reducing power required for glutathione and thioredoxin to act effectively as antioxidants [247,248]. However, diabetics are prone to sub-optimal thiamine status, as hyperglycemia suppresses the ability of the renal proximal tubules to reabsorb thiamine [249]. Poor thiamine status compromises the activity of the enzyme transketolase, an essential mediator in the lower pentose phosphate pathway; this in turn leads to intracellular build up of certain products of the pentose phosphate pathway that can allosterically inhibit both G6PD and 6PGD, impeding NADPH generation [250,251]. Hence, correcting poor thiamine status in diabetics with high-dose thiamine supplementation, or with high-absorption thiamine precursors such as benfotiamine or dibenzoilthiamine, can exert a worthwhile antioxidant effect in diabetics [252,253].

10. Other Suspected Mechanisms for Diabetic Complications—The Glucosamine and Polyol Pathways

A potential mechanism for promotion of diabetic complications, independent of either oxidative stress or dicarbonyl stress, is increased O-GlcNAcylation, reflecting greater availability of the fructose-6-phosphate that is the first substrate for generation of UDP-N-acetylglucosamine [254]. Although increased O-GlcNAcylation can compromise insulin sensitivity via effects on mediators of insulin signaling, this is clearly not the primary mechanism for insulin resistance in type 2 diabetics or hyperglycemia in type 1 diabetics [255]. While there has been considerable speculation that O-GlcNAcylation is a key mediator of diabetic complications, the evidence on this point is not yet clear, reflecting lack of a drug that can be employed quite specifically to inhibit O-GlcNAc transferase activity. Moreover, recent epidemiology finds that regular glucosamine supplementation—which would be expected to enhance cellular pools of UDP-N-acetylglucosamine, and hence up-regulate O-GlcNAcylation—is associated with a marked reduction in total mortality, including cardiovascular mortality [256–259]. Increased longevity has also been reported in mice supplemented with glucosamine beginning in middle age [260]. Glucosamine supplemented at 3 g daily in humans has been found to enhance flow-mediated vasodilation—a marker for endothelial health [261]. Favorable effects of glucosamine on longevity might reflect the fact that O-GlcNAcylation of Sirt1—an enzyme with important anti-inflammatory, antioxidant, and pro-autophagic effects that promote increased healthspan [262]—enhances its catalytic activity [263]. Hence, suppressing glucosamine generation in diabetics, or down-regulating O-GlcNAc transferase activity—if and when a safe drug or nutraceutical capable of doing this is identified—would likely be a mixed blessing at best, and might not prove to be an effective remedy for diabetic complications.

The enzyme aldose reductase is expressed in some tissue susceptible to damage in diabetes and uses NADPH to reduce glucose to sorbitol. This in turn can be reoxidized to fructose by sorbitol dehydrogenase, in a reaction that reduces NAD+ to NADH [264]. The net impact of this polyol pathway is to diminish the pool of NADPH required for the antioxidant efficacy of glutathione and thioredoxin, while also decreasing the pool of NAD+ required for Sirt1 activity. As noted, Sirt1 plays a key role in promoting mitochondrial biogenesis, while also dampening inflammation by opposing the transcriptional activity of NF-kappaB [174].
Drug inhibitors of aldose reductase such as sorbinil have been tested in rodent models of diabetes, and are also receiving clinical evaluation [264,265]. While phytochemicals are suggested to have potential for inhibiting aldose reductase, it is not clear that any such compounds now available in supplement form are effective for this purpose in clinically feasible concentrations [266–268]. Hence, the most effective current way that nutraceuticals might be employed to counteract the adverse impact of the polyol pathway is to compensate for its adverse impact on the NADPH and NAD+ pools. Nrf2 activators increase the expression of the rate-limiting enzymes in the upper pentose phosphate pathway responsible for regenerating NADPH from NADP+. Additionally, as we have noted, restoring good thiamine status in diabetics, by normalizing transketolase activity, alleviates the allosteric inhibition of these rate-limiting enzymes. With respect to NAD+, both thymoquinone and PQQ can promote oxidation of NADH to NAD+. Hence, they may be expected to counteract the adverse impact of the polyol pathway on Sirt11 activity.

In tissues with high glucose permeability in which sorbitol dehydrogenase activity is low relative to aldose reductase activity, the osmotic stress induced by sorbitol accumulation within cells has the potential to induce cell dysfunction. This phenomenon may play a role in the induction of diabetic cataracts [269]. However, rodent studies with sorbitol dehydrogenase inhibitors suggest that osmotic imbalance is not a major cause of neuronal or vascular dysfunction in diabetes [270]. Curiously, control of oxidative stress limits the ability of osmotic stress to induce cataracts in rodents, suggesting a complementary interaction of these two types of stress in cataract induction [269].

11. Toward a Practical Nutraceutical Strategy for Prevention of Diabetic Complications

Hence, considering our current understanding, measures which counteract oxidative stress and/or dicarbonyl stress appear to have the greatest promise for prevention of diabetic complications—in conjunction with measures that can improve glycemic control, of course. Zinc, glycine, and the range of clinically active nutraceuticals which boost Nrf2 activation (lipoic acid, broccoli sprouts, taurine, N-acetylcysteine) may be useful for alleviating dicarbonyl stress. In addition to these agents, promoters of mitophagy and mitochondrial biogenesis (such as ferulic acid, melatonin, urolithin A, N1-methylnicotinamide, nicotinamide riboside, thymoquinone, PQQ, berberine, astaxanthin, spermidine), UCP2 inducers (astaxanthin, capsaicin), inhibitors of NAPDH oxidase (spirulina), recouplers of eNOS (high-dose folate, citrulline), and correction of diabetic thiamine deficiency should help to quell the oxidative stress associated with diabetes. A survey of the pertinent biomedical literature—as by searching for the agent along with key word “diabetes” on pubmed.gov—will readily reveal that each of these agents, apart from spermidine, has been found to alleviate diabetic complications in rodent studies. (Spermidine is still little researched as a supplement but appears to have remarkable health protective potential [130,271–276]). Table 1 summarizes this proposal.

While this prescription might appear to be impossibly complicated, it should be feasible to devise a supplementation program comprising functional foods and several capsule or tablet supplements which would make it reasonably practical to implement. Table 2 provides a provisional sketch of how this might be achieved. The authors do not mean to imply that the suggested program is clinically proven or ideal in its composition; the possibility of unforeseen countervailing effects should be borne in mind. The doses chosen are within ranges that might be expected to have some physiological impact in light of previous clinical studies. The suggested program is not patented, and may be replicated in whole or in part by any nutraceutical manufacturer who cares to do so. Importantly, the agents involved are inexpensive compared to many prescription drugs and can reasonably be presumed to be safe in the suggested doses. Moreover, they might benefit health in several additional ways.
Table 1. Comprehensive Control of Oxidative and Dicarbonyl Stress with Nutraceuticals as a Strategy for Prevention of Diabetic Complications.

| Inhibit NADPH oxidase activity: |
|----------------------------------|
| Spirulina/phytocyanin |

| Promote autophagy/mitophagy/mitochondrial biogenesis: |
|------------------------------------------------------|
| Sirt1 activators—Ferulic Acid, Melatonin, N1-Methylnicotinamide, Nicotinamide Riboside, Urolithin A, Thymoquinone, PQQ, Berberine, Spermidine, Astaxanthin, Nrf2 activators (see below) |

| Induce mitochondrial uncoupling proteins: |
|------------------------------------------|
| Astaxanthin, Capsaicin |

| Protect the inner mitochondrial membrane with lipid-soluble scavenging antioxidants: |
|----------------------------------------------------------------------------------|
| Astaxanthin |

| Re-couple uncoupled eNOS: |
|--------------------------|
| Citrulline, High-Dose Folate |

| Boost expression of antioxidant enzymes, glyoxalase I and glutathione: |
|-----------------------------------------------------------------------|
| Lipoic Acid; Sulforaphane; Melatonin; Glycine; Zinc; H2S generators: Taurine, N-Acetylcysteine |

| Support glutathione synthesis: |
|--------------------------------|
| N-Acetylcysteine; Glycine |

| Promote NADPH generation via the pentose phosphate pathway: |
|-------------------------------------------------------------|
| High-dose Thiamine/Benfotiamine; Nrf2 activators (see above) |

Table 2. Supplementation Program for Diabetics.

| Powder or Bar |
|---------------|
| Per serving: |
| Spirulina—7.5 g |
| Citrulline—2 g |
| Glycine—5 g |
| Taurine—1 g |
| 2 servings daily |

| Capsules |
|----------|
| 4 caps provide: |
| Ferulic Acid—250 mg |
| Nicotinamide Riboside—250 mg |
| Lipoic Acid—600 mg |
| N-Acetylcysteine—600 mg |
| Berberine—500 mg |
| Astaxanthin—12 mg |
| Capsaicin (as cayenne pepper)—3 mg |
| Spermidine—10 mg |
| PQQ—10 mg |
| Folate—20 mg |
| 4 caps twice daily |

| Tablet—Insurance Formula |
|--------------------------|
| Essential vitamins and minerals—including Zinc—25 mg, Thiamine—50 mg |
| 1 tablet twice daily |

| Melatonin Cap |
|---------------|
| 5 mg at bedtime |
12. Some Agents Reducing Risk for Complications May Also Aid Insulin Function

In particular, there is evidence that some of these agents may improve muscle or adipocyte insulin sensitivity and glycemic control in type 2 diabetics or those with metabolic syndrome. Mitochondrial mass and oxidative capacity in skeletal muscle tends to be low in patients with these disorders, and studies suggest that people at increased genetic risk for diabetes tend to be deficient in this respect [277,278]. In the context of fatty diets and/or metabolic syndrome, impaired muscle capacity to oxidize fatty acids can lead to an accumulation of fatty acid derivatives in skeletal muscle—notably, diacylglycerol or ceramide—that, via activation of novel forms of protein kinase C and subsequent downstream activation of the kinases JNK and IKKβ, results in phosphorylations of insulin-responsive substrate-1 (IRS-1) that impede insulin signaling [279–282]. Concurrently, ceramide acts via atypical PKC-ξ, and protein phosphatase 2A to suppress Akt activity [283–285]. Hence, measures which boost mitochondrial biogenesis in muscle—including nutraceuticals and exercise training—have the potential to alleviate muscle insulin resistance [286,287]. Astaxanthin can promote insulin sensitivity in diabetics and pre-diabetics in an additional way—by boosting adiponectin production [128,288–292]. Acting as an agonist for PPARα, astaxanthin can promote hepatic secretion of fibroblast growth factor 21 (FGF21), which in turn acts on adipocytes to increase their secretion of adiponectin [293–295]. The latter, via its characteristic receptor on skeletal muscle, activates a ceramidase activity that promotes insulin sensitivity by decreasing elevated ceramide levels [296,297].

Insulin resistance of the hypertrophied adipocytes in metabolic syndrome appears to be driven by increased oxidant production stemming from both NADPH oxidase (Nox2, Nox4) and mitochondria [298–301]. Infiltrating macrophages attracted by chemotactic factors also contribute to this oxidant production; moreover, oxidants up-regulate macrophage secretion of tumor necrosis factor-a (TNFα) [302]. This oxidant stress in conjunction with TNFα activity promotes JNK and IKKβ activation in adipocytes, which in turn induces adipocyte insulin resistance via IRS-1 phosphorylation—a pathway homologous to that seen in insulin resistant skeletal muscle [301,303]. Hence, suppression of NADPH oxidase activity with PCB or whole spirulina has the potential to alleviate adipocyte insulin resistance [299]. This rationalizes the insulin sensitizing effects observed when rodent or human type 2 diabetics are fed spirulina [304,305]. It is also reasonable to expect that the downstream impact of oxidants on JNK/IKKβ might be blunted to some degree by Nrf2-inducible enzymes; consistent with this possibility, lipoic acid supplementation has been reported to achieve modest dose-dependent improvements in glycemic control in type 2 diabetics [306].

The ability of berberine—an AMPK activator used commonly as an alternative to metformin in China—and of supplemental zinc to improve glycemic control in diabetics has been noted above [68,125,307]. A limited amount of clinical and preclinical literature suggests that high-dose biotin may also have potential for aiding glycemic control in both type 2 and type 1 diabetics [308,309]. These benefits may reflect a cGMP-mediated correction of the under-expression of glucokinase in the hepatocytes and pancreatic beta cells of diabetics [228,231,310,311]. Glucokinase functions as a “glucose sensor” in these cells to regulate insulin secretion and gluconeogenesis in a physiologically appropriate way [312,313].

13. Possible Limitations of this Strategy

A note of caution is in order, however. Whereas the triggers initiating the processes leading to diabetic complications are likely to have been discussed here—dicarbonyl stress, oxidative stress, an accelerated polyol pathway, and possibly increased O-GlcNAcylation (the classic mechanisms proposed by Brownlee and colleagues)—they may have downstream effects that do not readily reverse when the initiating cause is relieved [314]. Notably, changes in differentiation state may be conserved by self-reinforcing regulatory loops and altered DNA methylation patterns in the absence of
the initiating stimulus [315]. Additionally, tissue fibrosis may not be readily reversed. By way of analogy, blowing out a match may do little good once the forest is ablaze. This consideration argues for diagnosing diabetes promptly and starting protective measures as soon as is feasible.

**Funding:** This research received no external funding.

**Conflicts of Interest:** M.F.M. is co-inventor and co-owner of a US patent covering nutraceutical uses of phycocyanobilin oligopeptides derived from spirulina. J.J.D. is affiliated with companies that market nutraceutical supplements. J.O.K. is owner of a supplements company.

**References**

1. Iacobini, C.; Vitale, M.; Pesce, C.; Pugliese, G.; Menini, S. Diabetic Complications and Oxidative Stress: A 20-Year Voyage Back in Time and Back to the Future. *Antioxidants* **2021**, *10*, 727. [CrossRef]

2. Wang, M.; Li, Y.; Li, S.; Lv. J. Endothelial Dysfunction and Diabetic Cardiomyopathy. *Front. Endocrinol.* **2022**, *13*, 851941. [CrossRef]

3. Nishikawa, T.; Edelstein, D.; Brownlee, M. The missing link: A single unifying mechanism for diabetic complications. *Kidney Int.*** **2000**, *58*, S26–S30. [CrossRef]

4. Inoguchi, T.; Li, P.; Umeda, F.; Yu, H.Y.; Kakimoto, M.; Imamura, M.; Aoki, T.; Etoh, T.; Hashimoto, T.; Naruse, M.; et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C—Dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes* **2000**, *49*, 1939–1945. [CrossRef]

5. Derevenskaya, M.A.; Kolesnikova, L.I.; Kolesnikov, S.I. Oxidative Stress: Pathogenetic Role in Diabetes Mellitus and Its Complications and Therapeutic Approaches to Correction. *Bull. Exp. Biol. Med.* **2021**, *171*, 179–189. [CrossRef]

6. Phillips, S.A.; Thornalley, P.J. The formation of methylglyoxal from triose phosphates. Investigation using a specific assay for methylglyoxal. *JBIC J. Biol. Inorg. Chem.* **1993**, *212*, 101–105. [CrossRef]

7. Thornalley, P.J.; Battah, S.; Ahmad, N.; Karachalias, N.; Agalou, S.; Babaei-Jadidi, R.; Dawnay, A. Quantitative screening of advanced glycation endproducts in cellular and extracellular proteins by tandem mass spectrometry. *Biochem. J.* **2003**, *375*, 581–592. [CrossRef]

8. Shkhtman, A.; Xue, J.; Ray, R.; Singer, D.; Bohme, D.; Burz, D.S.; Rai, V.; Hoffman, R. Receptor for Advanced Glycation End Products (RAGE) Specifically Recognizes Methylglyoxal Derived AGEs. *Biochemistry* **2014**, *53*, 3327–3335. [CrossRef]

9. Hudson, B.I.; Lippman, M.E. Targeting RAGE Signaling in Inflammatory Disease. *Annu. Rev. Med.* **2018**, *69*, 349–364. [CrossRef]

10. Li, J.; Schmidt, A.M. Characterization and Functional Analysis of the Promoter of RAGE, the Receptor for Advanced Glycation End Products. *J. Biol. Chem.* **1997**, *272*, 16498–16506. [CrossRef]

11. Palsamy, P.; Bidasee, K.R.; Ayaki, M.; Augusteyn, R.C.; Chan, J.Y.; Shinohara, T. Methylglyoxal induces endoplasmic reticulum stress and DNA demethylation in the Keap1 promoter of human lens epithelial cells and age-related cataracts. *Free Radic. Biol. Med.* **2014**, *65*, 134–148. [CrossRef]

12. Bollong, M.J.; Lee, G.; Coukos, J.S.; Yun, H.; Zambaldo, C.; Chang, J.W.; Chin, E.N.; Ahmad, I.; Chatterjee, A.K.; Lairson, L.L.; et al. A metabolite-derived protein modification integrates glycolysis with KEAP1–NRF2 signalling. *Nature Med.* **2018**, *72*, 600–604. [CrossRef]

13. Wang, H.; Liu, J.; Wu, L. Methylglyoxal-induced mitochondrial dysfunction in vascular smooth muscle cells. *Biochem. Pharmacol.* **2009**, *77*, 1709–1716. [CrossRef]

14. Prestes, A.D.S.; dos Santos, M.M.; Kamdem, J.P.; Mancini, G.; da Silva, L.C.S.; de Bem, A.F.; Barbosa, N.V. Methylglyoxal disrupts the functionality of rat liver mitochondria. *Chem. Interact.* **2022**, *351*, 109677. [CrossRef]

15. Shuck, S.C.; Wueenschell, G.E.; Termini, J.S. Product Studies and Mechanistic Analysis of the Reaction of Methylglyoxal with Deoxyguanosine. *Chem. Res. Toxicol.* **2018**, *31*, 105–115. [CrossRef]

16. Golej, J.; Hoeger, H.; Radner, W.; Unfried, G.; LubeC. G. Oral administration of methylglyoxal leads to kidney collagen accumulation in the mouse. *Life Sci.* **1998**, *63*, 801–807. [CrossRef]

17. Berlanga, J.; Cibrian, D.; Guillen, I.; Freyre, F.; Alba, J.S.; Lopez-Saura, P.; Merino, N.; Aldama, A.; Quintela, A.M.; Triana, M.E.; et al. Methylglyoxal administration induces diabetes-like microvascular changes and perturbs the healing process of cutaneous wounds. *Clin. Sci.* **2005**, *109*, 83–95. [CrossRef]

18. Sena, C.M.; Matafome, P.; Crisóstomo, J.; Rodrigues, L.; Fernandes, R.; Pereira, P.; Seiça, R.M. Methylglyoxal promotes oxidative stress and endothelial dysfunction. *Pharmacol. Res.* **2012**, *65*, 497–506. [CrossRef]

19. He, Y.; Zhou, C.; Huang, M.; Tang, C.; Liu, X.; Yue, Y.; Diao, Q.; Zheng, Z.; Liu, D. Glyoxalase system: A systematic review of its biological activity, related-diseases, screening methods and small molecule regulators. *Biomed. Pharmacother.* **2020**, *131*, 110663. [CrossRef]

20. Inagi, R.; Miyata, T.; Ueda, Y.; Yoshino, A.; Nangaku, M.; Strihou, C.V.Y.D.; Kurokawa, K. Efficient in vitro lowering of carbonyl stress by the glyoxalase system in conventional glucose peritoneal dialysis fluid. *Kidney Int.* **2002**, *62*, 679–687. [CrossRef]
21. Brouwers, O.; Niessen, P.M.; Haenen, G.; Miyata, T.; Brownlee, M.; Stehouwer, C.D.; De Mey, J.G.; Schalkwijk, C.G. Hyperglycaemia-induced impairment of endothelial-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. *Diabetologia* **2010**, *53*, 989–1000. [CrossRef]

22. Brouwers, O.; Niessen, P.M.; Ferreira, I.; Miyata, T.; Scheffer, P.G.; Teerlink, T.; Schrauw, P.; Brownlee, M.; Stehouwer, C.D.; Schalkwijk, C.G. Overexpression of Glyoxalase-I Reduces Hyperglycemia-induced Levels of Advanced Glycation End Products and Oxidative Stress in Diabetic Rats. *J. Biol. Chem.* **2011**, *286*, 1374–1380. [CrossRef]

23. Berner, A.K.; Brouwers, O.; Pringle, R.; Klaassen, I.; Colhoun, L.; McVicar, C.; Brockbank, S.; Curry, J.W.; Miyata, T.; Brownlee, M.; et al. Protection against methylglyoxal-derived AGEs by regulation of glyoxalase 1 prevents retinal neuroglial and vasodegenerative pathology. *Diabetologia* **2012**, *55*, 845–854. [CrossRef]

24. Brouwers, O.; Niessen, P.M.G.; Miyata, T.; Östergaard, J.A.; Flyvbjerg, A.; Peutz-Kootstra, C.J.; Sieber, J.; Mundel, P.H.; Brownlee, M.; Janssens, B.J.A.; et al. Glyoxalase-1 overexpression reduces endothelial dysfunction and attenuates early renal impairment in a rat model of diabetes. *Diabetologia* **2013**, *57*, 224–235. [CrossRef]

25. Giacco, F.; Du, X.; D’Agati, V.D.; Milne, R.; Sui, G.; Geoffrion, M.; Brownlee, M. Knockdown of Glyoxalase 1 Mimics Diabetic Nephropathy in Nondiabetic Mice. *Diabetes* **2014**, *63*, 291–299. [CrossRef]

26. Ranganathan, S.; Ciaccio, P.J.; Walsh, E.S.; Tew, K.D. Genomic sequence of human glyoxalase-I: Analysis of promoter activity and its regulation. *Gene* **1999**, *240*, 149–155. [CrossRef]

27. Xue, M.; Rabbani, N.; Momiji, H.; Imbasi, P.; Anwar, M.M.; Kitteringham, N.; Park, B.K.; Souma, T.; Moriguchi, T.; Yamamoto, M.; et al. Transcriptional control of glyoxalase 1 by Nrf2 provides a stress-responsive defence against dicarboxyl glycation. *Biochem. J.* **2012**, *443*, 213–222. [CrossRef]

28. Laity, J.H.; Andrews, G.K. Understanding the mechanisms of zinc-sensing by metal-response element binding transcription factor-1 (MTF-1). *Arch. Biochem. Biophys.* **2007**, *463*, 201–210. [CrossRef]

29. Radtke, F.; Heuchel, R.; Georgiev, O.; Hergersberg, M.; Gariglio, M.; Dembic, Z.; Schaffner, W. Cloned transcription factor MTF-1 activates the mouse metallothionein 1 promoter. *EMBO J.* **1993**, *12*, 1355–1362. [CrossRef]

30. Luo, Y.-Y.; Zhao, J.; Han, X.-Y.; Zhou, X.-H.; Wu, J.; Ji, L.-N. Relationship Between Serum Zinc Level and Microvascular Complications in Patients with Type 2 Diabetes. *Chin. Med. J.* **2015**, *128*, 3276–3282. [CrossRef]

31. Feng, J.; Wang, H.; Jing, Z.; Wang, Y.; Wang, W.; Jiang, Y.; Sun, W. Relationships of the Trace Elements Zinc and Magnesium With Diabetic Nephropathy-Associated Renal Functional Damage in Patients With Type 2 Diabetes Mellitus. *Front. Med.* **2021**, *6*, 626909. [CrossRef]

32. Rostamkhani, H.; Mellati, A.A.; Tabaei, B.S.; Alavi, M.; Mousavi, S.N. Association of Serum Zinc and Vitamin A Levels with Severity of Retinopathy in Type 2 Diabetic Patients: A Cross-Sectional Study. *Biol. Trace Element Res.* **2019**, *192*, 123–128. [CrossRef]

33. Dasca, A.M.; Anghelache, A.; Stan, D.; Costea, A.C.; Nicolae, V.A.; Tanasescu, D.; Costea, D.O.; Tribus, L.C.; Zgura, A.; Serban, D.; et al. Serum levels of copper and zinc in diabetic retinopathy: Potential new therapeutic targets (Review). *Exp. Ther. Med.* **2022**, *23*, 324. [CrossRef]

34. Hussein, M.; Fathy, W.; Hassan, A.; Elkareem, R.A.; Marzouk, S.; Kamal, Y.S. Zinc deficiency correlates with severity of diabetic polyneuropathy. *Brain Behav.* **2021**, *11*, e2349. [CrossRef]

35. Rahim, A.; Iqbal, K. To assess the levels of zinc in serum and changes in the lens of diabetic and senile cataract patients. *J. Pak. Med. Assoc.* **2011**, *61*, 853.

36. Barman, S.; Srinivasan, K. Diabetes and zinc dyshomeostasis: Can zinc supplementation mitigate diabetic complications? *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 1046–1061. [CrossRef]

37. de Carvalho, G.B.; Brandão-Lima, P.N.; Maia, C.S.; Barbosa, K.B.; Pires, L.V. Zinc’s role in the glycemic control of patients with type 2 diabetes: A systematic review. *Biometals* **2017**, *30*, 151–162. [CrossRef]

38. Tang, Y.; Yang, Q.; Lu, J.; Zhang, X.; Suen, D.; Tan, Y.; Jin, L.; Xiao, J.; Xie, R.; Rane, M.; et al. Zinc supplementation partially prevents renal pathologic changes in diabetic rats. *J. Nutr. Biochem.* **2010**, *21*, 237–246. [CrossRef]

39. Özelbek, D.; Naziroglu, M.; Tunçdemir, M.; Çelik, Ö.; Öztürk, M.; Flores-Arce, M.F. Zinc supplementation attenuates metallothionein and oxidative stress changes in kidney of streptozotocin-induced diabetic rats. *Biol. Trace Elem. Res.* **2016**, *150*, 342–349. [CrossRef]

40. Li, B.; Tan, Y.; Sun, W.; Fu, Y.; Miao, L.; Cai, L. The role of zinc in the prevention of diabetic cardiomyopathy and nephropathy. *Toxicol. Mech. Methods* **2013**, *23*, 27–33. [CrossRef]

41. Sun, W.; Wang, Y.; Miao, X.; Wang, Y.; Zhang, L.; Xin, Y.; Zheng, S.; Epstein, N.P.; Fu, Y.; Cai, L. Renal improvement by zinc in diabetic mice is associated with glucose metabolism signaling mediated by metallothionein and Akt, but not Akt2. *Free Radic. Biol. Med.* **2014**, *68*, 22–34. [CrossRef]

42. Zhang, X.; Liang, D.; Fan, J.; Lian, X.; Zhao, Y.; Wang, X.; Chi, Z.-H.; Zhang, P. Zinc Attenuates Tubulointerstitial Fibrosis in Diabetic Nephropathy Via Inhibition of HIF Through PI-3K Signaling. *Biol. Trace Element Res.* **2016**, *173*, 372–383. [CrossRef]

43. Zhang, X.; Liang, D.; Lian, X.; Chi, Z.-H.; Wang, X.; Zhao, Y.; Ping, Z. Effect of zinc deficiency on mouse renal interstitial fibrosis in diabetic nephropathy. *Mol. Med. Rep.* **2016**, *14*, 5245–5252. [CrossRef]

44. Yang, F.; Li, B.; Dong, X.; Cui, W.; Luo, P. The beneficial effects of zinc on diabetes-induced kidney damage in murine rodent model of type 1 diabetes mellitus. *J. Trace Elements Med. Biol.* **2017**, *42*, 1–10. [CrossRef]
45. Elsaad, W.M.; Mohamed, H.A. Dietary zinc modifies diabetic-induced renal pathology in rats. Ren. Fail. 2017, 39, 246–257. [CrossRef]

46. Barman, S.; Pradeep, S.R.; Srinivasan, K. Zinc supplementation alleviates the progression of diabetic nephropathy by inhibiting the overexpression of oxidative-stress-mediated molecular markers in streptozotocin-induced experimental rats. J. Nutr. Biochem. 2018, 54, 113–129. [CrossRef]

47. Gembillo, G.; Visconti, L.; Giuffrida, A.E.; Labbozzetta, V.; Peritore, L.; Lipari, A.; Calabrese, V.; Piccoli, G.B.; Torreggiani, M.; Siligato, R.; et al. Role of Zinc in Diabetic Kidney Disease. Nutrients 2022, 14, 1353. [CrossRef]

48. Miao, X.; Sun, W.; Miao, L.; Fu, Y.; Wang, Y.; Su, G.; Liu, Q. Zinc and diabetic retinopathy. J. Diabetes Res. 2013, 2013, 425854. [CrossRef]

49. Liu, F.; Ma, F.; Kong, G.; Wu, K.; Deng, Z.; Wang, H. Zinc Supplementation Alleviates Diabetic Peripheral Neuropathy by Inhibiting Oxidative Stress and Upregulating Metallothionein in Peripheral Nerves of Diabetic Rats. Biol. Trace Element Res. 2014, 158, 211–218. [CrossRef]

50. Song, Y.; Wang, J.; Li, X.K.; Cai, L. Zinc and the diabetic heart. Biometals 2005, 18, 325–332. [CrossRef]

51. Wang, J.; Song, Y.; Elsherif, L.; Song, Z.; Zhou, G.; Prabhu, S.D.; Saari, J.T.; Cai, L. Cardiac Metallothionein Induction Plays the Major Role in the Prevention of Diabetic Cardiomyopathy by Zinc Supplementation. Circulation 2006, 113, 544–554. [CrossRef]

52. Lu, Y.; Liu, Y.; Li, H.; Wang, X.; Wu, W.; Gao, L. Effect and mechanisms of zinc supplementation in protecting against diabetic cardiomyopathy in a rat model of type 2 diabetes. Bosn. J. Basic Med. Sci. 2015, 15, 14–20. [CrossRef]

53. Korkmaz-İçöz, S.; Al Said, S.; Radovits, T.; Li, S.; Brune, M.; Hegedűs, P.; Atmanlı, A.; Ruppert, M.; Brlecic, P.; Lehmann, L.H.; et al. Oral treatment with a zinc complex of acetylsalicylic acid prevents diabetic cardiomyopathy in a rat model of type-2 diabetes: Activation of the Akt pathway. Cardiovasc. Diabetol. 2016, 15, 75. [CrossRef]

54. Wang, S.; Wang, B.; Wang, Y.; Tong, Q.; Liu, Q.; Sun, J.; Zheng, Y.; Cai, L. Zinc Prevents the Development of Diabetic Cardiomyopathy in db/db Mice. Int. J. Mol. Sci. 2017, 18, 580. [CrossRef]

55. Giacconi, R.; Cai, L.; Costarelli, L.; Cardelli, M.; Malavolta, M.; Piacenza, F.; Provinciali, M. Implications of impaired zinc homeostasis in diabetic cardiomyopathy and nephropathy. BioFactors 2017, 43, 770–784. [CrossRef]

56. Wang, J.; Wang, S.; Wang, W.; Chen, J.; Zhang, Z.; Zheng, Q.; Liu, Q.; Cai, L. Protection against diabetic cardiomyopathy is achieved using a combination of sulforaphane and zinc in type 1 diabetic OVE26 mice. J. Cell. Mol. Med. 2019, 23, 6319–6330. [CrossRef]

57. Yu, L.; Liu, Y.; Jin, Y.; Liu, T.; Wang, W.; Lu, X.; Zhang, C. Zinc supplementation prevented type 2 diabetes-induced liver injury mediated by the Nrf2-MT antioxidative pathway. J. Diabetes Res. 2021, 2021, 6662418. [CrossRef]

58. Barman, S.; Srinivasan, K. Zinc Supplementation Ameliorates Diabetic Cataract Through Modulation of Crystallin Proteins and Polyol Pathway in Experimental Rats. Biol. Trace Element Res. 2018, 187, 212–223. [CrossRef]

59. Gupta, R.; Garg, V.K.; Mathur, D.K.; Goyal, R.K. Oral zinc therapy in diabetic neuropathy. J. Diabetes Res. 2016, 75. [CrossRef]

60. Hayee, M.A.; Mohammad, Q.D.; Haque, A. Diabetic neuropathy and zinc therapy. Bangladesh Med. Res. Councl. Bull. 2005, 31, 62–67.

61. Bellomo, E.; Massarotti, A.; Hogstrand, C.; Maret, W. Zinc ions modulate protein tyrosine phosphatase 1B activity. Metallomics 2014, 6, 1229–1239. [CrossRef]

62. Bellomo, E.; Singh, K.B.; Massarotti, A.; Hogstrand, C.; Maret, W. The metal face of protein tyrosine phosphatase 1B. Coord. Chem. Rev. 2016, 327–328, 70–83. [CrossRef]

63. Cai, L.; Klein, J.B.; Kang, Y.J. Metallothionein Inhibits Peroxynitrite-induced DNA and Lipoprotein Damage. Antioxidants Redox Signal. 2005, 3, 251–264. [CrossRef]

64. Sharma, S.K.; Ebadi, M. Metallothionein Attenuates 3-Morpholinosydnonimine (SIN-1)-Induced Oxidative Stress in Dopaminergic Neurons. Antioxidants Redox Signal. 2003, 5, 187–198. [CrossRef]

65. El-Remessy, A.B.; Abu-Mohamed, G.; Caldwell, R.W.; Caldwell, R.B. High glucose-induced tyrosine nitration in endothelial cells: Role of eNOS uncoupling and aldehyde reductase activation. Investag. Ophthalmol. Vis. Sci. 2003, 44, 3135–3143. [CrossRef]

66. McCarty, M.F.; DiNicollantionio, J.J. Non-Occupational Cadmium Exposure is Emerging as a Major Cause of Cancer, Vascular Disorders, and Other Pathologies—A Long-term Controlled Trial of Supplementation with High-Dose Zinc, a Cadmium Antagonist, is Needed. J. Prev. Alzheimers Dis. 2016, 1, 1–10. [CrossRef]

67. Clemons, T.E.; Kurinij, N.; Sperduto, R.D. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. Arch. Ophthalmol. 2004, 122, 716–726.
71. Dinkova-Kostova, A.T.; Holtzclaw, W.D.; Cole, R.N.; Itoh, K.; Wakabayashi, N.; Katoh, Y.; Yamamoto, M.; Talalay, P. Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11908–11913. [CrossRef] [PubMed]

72. Wakabayashi, N.; Dinkova-Kostova, A.T.; Holtzclaw, W.D.; Kang, M.-I.; Kobayashi, A.; Yamamoto, M.; Kessler, T.W.; Talalay, P. Protection against electrophile and oxidant stress by induction of the phase 2 response: Fate of cysteines of the Keap1 sensor modified by inducers. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2040–2045. [CrossRef] [PubMed]

73. Jeyapaul, J.; Jaiswal, A.K. Nrf2 and c-Jun regulation of antioxidant response element (ARE)-mediated expression and induction of gamma-glutamylcysteine synthetase heavy subunit gene. *Biochem. Pharmacol.* **2000**, *59*, 1433–1439. [CrossRef]

74. Kessler, T.W.; Wakabayashi, N.; Biswal, S. Cell Survival Responses to Environmental Stresses Via the Keap1-Nrf2-ARE Pathway. *Annu. Rev. Pharmacol. Toxicol.* **2007**, *47*, 89–116. [CrossRef]

75. Kensler, T.W.; Egner, P.A.; Aygemen, A.S.; Visvanathan, K.; Groopman, J.D.; Chen, J.-G.; Chen, T.-Y.; Fahey, J.W.; Talalay, P. Keap1–Nrf2 Signaling: A Target for Cancer Prevention by Sulforaphane. *Top. Curr. Chem.* **2012**, *329*, 163–177. [CrossRef]

76. Kyung, S.; Lim, J.W.; Kim, H. α-Lipoic Acid Inhibits IL-8 Expression by Activating Nrf2 Signaling in Helicobacter pylori-infected Gastric Epithelial Cells. *Nutrients* **2019**, *11*, 2524. [CrossRef]

77. Lee, J.; Jung, S.Y.; Yang, K.J.; Kim, Y.; Lee, D.; Lee, M.H.; Kim, D.-K. α-Lipoic acid prevents against cisplatin cytotoxicity via activation of the Nrf2/HO-1 antioxidant pathway. *PloS ONE* **2019**, *14*, e0226769. [CrossRef]

78. Han, T.; Bai, J.; Liu, W.; Hu, Y. A systematic review and meta-analysis of Î±-lipoic acid in the treatment of diabetic peripheral neuropathy. *Eur. J. Endocrinol.* **2012**, *167*, 465–471. [CrossRef]

79. Ziegler, D.; Low, P.A.; Freeman, R.; Tritschler, H.; Vinik, A.I. Predictors of improvement and progression of diabetic polyneuropathy following treatment with α-lipoic acid for 4years in the NATHAN 1 trial. *Diabetes Its Complicat.* **2016**, *30*, 350–356. [CrossRef]

80. Hourihan, J.M.; Kenna, J.G.; Hayes, J.D. The Gasotransmitter Hydrogen Sulfide Induces Nrf2-Target Genes by Inactivating the Keap1 Ubiquitin Ligase Substrate Adaptor Through Formation of a Disulfide Bond Between Cys-226 and Cys-613. *Antioxid. Redox Signal.* **2013**, *19*, 465–481. [CrossRef]

81. Yang, G.; Zhao, K.; Ju, Y.; Mani, S.; Cao, Q.; Puukila, S.; Khaper, N.; Wu, L.; Wang, R. Hydrogen Sulfide Protects Against Cellular Senescence via S-Sulphydration of Keap1 and Activation of Nrf2. *Antioxid. Redox Signal.* **2013**, *18*, 1906–1919. [CrossRef] [PubMed]

82. Sun, Q.; Wang, B.; Li, Y.; Sun, F.; Li, P.; Xia, W.; Zhou, X.; Li, Q.; Wang, X.; Chen, J.; et al. Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. *Hypertension* **2016**, *67*, 541–549. [CrossRef] [PubMed]

83. DiNicolantonio, J.J.; Okeefe, J.H.; McCarty, M.F. Boosting endogenous production of vasoprotective hydrogen sulfide via supplementation with taurine and N-acetylcysteine: A novel way to promote cardiovascular health. *Open Heart* **2017**, *4*, e000600. [CrossRef] [PubMed]

84. Zhao, H.; Qu, J.; Li, Q.; Cui, M.; Wang, J.; Zhang, K.; Liu, X.; Feng, H.; Chen, Y. Taurine supplementation reduces neuroinflammation and protects against white matter injury after intracerebral hemorrhage in rats. *Amino Acids* **2017**, *50*, 439–451. [CrossRef] [PubMed]

85. Guizoni, D.M.; Freitas, I.N.; Victorio, J.A.; Possebon, I.R.; Araujo, T.R.; Carneiro, E.M.; Davel, A.P. Taurine treatment reverses protein malnutrition-induced endothelial dysfunction of the pancreatic vasculature: The role of hydrogen sulfide. *Metabolism* **2021**, *116*, 154701. [CrossRef] [PubMed]

86. Dattilo, M.; Fontanarosa, C.; Spinelli, M.; Bini, V.; Amoresano, A. Modulation of Human Hydrogen Sulfide Metabolism by Micronutrients, Preliminary Data. *Nutr. Metab. Insights* **2022**, *15*, 1176838211065372. [CrossRef]

87. Fang, J.; Yan, Y.; Teng, X.; Wen, X.; Li, N.; Feng, S.; Lu, W.; Donadeu, F.X.; Zhao, S.; Hua, J. Melatonin prevents senescence of canine adipose-derived mesenchymal stem cells through activating NRF2 and inhibiting ER stress. *Aging* **2018**, *10*, 2954–2972. [CrossRef]

88. Early, J.O.; Menon, D.; Wyse, C.A.; Cervantes-Silva, M.P.; Zaslona, Z.; Carroll, R.G.; Palmer-McDermott, E.M.; Angiari, S.; Ryan, D.G.; Corcoran, S.E.; et al. Circadian clock protein BMAL1 regulates IL-1β in macrophages via NRF2. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E8460–E8468. [CrossRef]

89. Kryl'skii, E.D.; Popova, T.N.; Safonova, O.A.; Stolyarova, A.O.; Razuuvaev, G.A.; de Carvalho, M.A.P. Transcriptional Regulation of Antioxidant Enzymes Activity and Modulation of Oxidative Stress by Melatonin in Rats Under Cerebral Ischaemia/Reperfusion Conditions. *Neuroscience* **2019**, *406*, 653–666. [CrossRef]

90. Sun, T.C.; Liu, X.C.; Yang, S.H.; Song, L.L.; Zhou, S.J.; Deng, S.L.; Tian, L.; Cheng, L.Y. Melatonin Inhibits Oxidative Stress and Apoptosis in Cryopreserved Ovarian Tissues via NRF2/HO-1 Signaling Pathway. *Front. Mol. Biosci.* **2020**, *7*, 163. [CrossRef]

91. Wu, Q.; Zhang, X.S.; Wang, H.D.; Zhang, X.; Yu, Q.; Li, W.; Zhou, M.-L.; Wang, X.L. Astaxanthin activates nuclear factor erythroid-related factor 2 and the antioxidant responsive element (Nrf2-ARE) pathway in the brain after subarachnoid hemorrhage in rats and attenuates early brain injury. *Mar. Drugs* **2014**, *12*, 6125–6141. [CrossRef]

92. Xue, Y.; Sun, C.; Hao, Q.; Chen, J. Astaxanthin ameliorates cardiomyocyte apoptosis after coronary microembolization by inhibiting oxidative stress via Nrf2/HO-1 pathway in rats. *Naunyn-Schmiedeberg’s Arch. Pharmacol.* **2019**, *392*, 341–348. [CrossRef]
93. Li, Y.; Wang, Q.; Chu, C.; Liu, S. Astaxanthin protects retinal ganglion cells from acute glaucoma via the Nrf2/HR-1 pathway. J. Chem. Neuroanat. 2020, 110, 101876. [CrossRef]

94. Montazeri-Najafabady, N.; Dabbaghmanesh, M.H.; Chatрабnous, N.; Arabnezhad, M.R. The Effects of Astaxanthin on Proliferation and Differentiation of MG-63 Osteosarcoma Cells via Aryl Hydrocarbon Receptor (AhR) Pathway: A Comparison with AhR Endogenous Ligand. Nutr. Cancer 2019, 72, 1400–1410. [CrossRef]

95. Montazeri-Najafabady, N.; Chatрабnous, N.; Arabnezhad, M.; Azarpira, N. Anti-androgenic effect of astaxanthin in LNCaP cells is mediated through the aryl hydrocarbon-androgen receptors cross talk. J. Food Biochem. 2021, 45, e13702. [CrossRef]

96. Miao, W.; Hu, L.; Scrivens, P.J.; Batist, G. Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: Direct cross-talk between phase I and II drug-metabolizing enzymes. J. Biol. Chem. 2005, 280, 20340–20348. [CrossRef]

97. Kidd, P. Astaxanthin, cell membrane nutrient with diverse clinical benefits and anti-aging potential. Altern. Med. Rev. A J. Clin. Ther. 2011, 16, 355–364.

98. Kim, S.H.; Kim, H. Inhibitory Effect of Astaxanthin on Oxidative Stress-Induced Mitochondrial Dysfunction-A Mini-Review. Nutrients 2018, 10, 1137. [CrossRef]

99. Sztretye, M.; Dienes, B.; Gönnczi, M.; Czirják, T.; Csernocho, L.; Dux, L.; Szentesi, P.; Keller-Pintér, A. Astaxanthin: A Potential Mitochondrial-Targeted Antioxidant Treatment in Diseases and with Aging. Oxidative Med. Cell. Longev. 2019, 2019, 3849692. [CrossRef]

100. Wang, Z.; Zhao, D.; Chen, L.; Li, J.; Yuan, G.; Yang, G.; Zhang, H.; Guo, X.; Zhang, J. Glycine increases glyoxalase-1 function by promoting nuclear factor erythroid Â 2-related factor Â 1 translocation into the nucleus of kidney cells of streptozotocin-induced diabetic rats. J. Diabetes Investig. 2019, 10, 1189–1198. [CrossRef]

101. Wang, Z.; Zhang, J.; Chen, L.; Li, J.; Zhang, H.; Guo, X. Glycine Suppresses AGE/RAGE Signaling Pathway and Subsequent Oxidative Stress by Restoring Gloc1 Function in the Aorta of Diabetic Rats and in HUVECs. Oxidative Med. Cell. Longev. 2019, 2019, 4629692. [CrossRef]

102. McCarty, M.F.; O’Keefe, J.H.; DiNicolantonio, J.J. Dietary Glycine Is Rate-Limiting for Glutathione Synthesis and May Have Broad Potential for Health Protection. Ochsner J. 2018, 18, 81–87.

103. Cieslik, K.; Sekhar, R.V.; Granillo, A.; Reddy, A.; Medrano, G.; Heredia, C.P.; Entman, M.L.; Hamilton, D.J.; Li, S.; Reineke, E.; et al. Improved Cardiovascular Function in Old Mice After N-Acetyl Cysteine and Glycine Supplemented Diet: Inflammation and Mitochondrial Factors. J. Gerontol. A Biol. Sci. Med. Sci. 2018, 73, 1167–1177. [CrossRef]

104. Kumar, P.; Liu, C.; Hsu, J.W.; Chacko, S.; Minard, C.; Jahoor, F.; Sekhar, R.V. Glycine and N-acetylcysteine (GlyNAC) supplementation in older adults improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, and cognition: Results of a pilot clinical trial. Clin. Transl. Med. 2021, 11, e372.

105. Sekhar, R.V. GlyNAC Supplementation Improves Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Aging Hallmarks, Metabolic Defects, Muscle Strength, Cognitive Decline, and Body Composition: Implications for Healthy Aging. J. Nutr. 2021, 151, 3606–3616. [CrossRef]

106. Kumar, P.; Osahon, O.W.; Sekhar, R.V. GlyNAC (Glycine and N-Acetylcysteine) Supplementation in Mice Increases Length of Life by Correcting Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Abnormalities in Mitophagy and Nutrient Sensing, and Genomic Damage. Nutrients 2022, 14, 1114. [CrossRef]

107. Sekhar, R.V. GlyNAC (Glycine and N-Acetylcysteine) Supplementation Improves Impaired Mitochondrial Fuel Oxidation and Lowers Insulin Resistance in Patients with Type 2 Diabetes: Results of a Pilot Study. Antioxidants 2022, 11, 154. [CrossRef]

108. Kaneto, H.; Kajimoto, Y.; Miyagawa, J.; Matsuoka, T.; Fujitani, Y.; Umayahara, Y.; Hanafusa, T.; Matsuzawa, Y.; Yamasaki, Y.; Horii, M. Beneficial effects of antioxidants in diabetes: Possible protection of pancreatic beta-cells against glucose toxicity. Diabetes 1999, 48, 2398–2406. [CrossRef]

109. Bahmani, F.; Batheia, S.Z.; Aldavood, S.J.; Ghahghaei, A. Glycine therapy inhibits the progression of cataract in streptozotocin-induced diabetic rats. Mol. Vis. 2012, 18, 439–448.

110. Li, W.; Zhang, Y.; Shao, N. Protective effect of glycine in streptozotocin-induced diabetic cataract through aldose reductase inhibitory activity. Biomed. Pharmacother. 2019, 114, 108794. [CrossRef]

111. Wheeler, M.D.; Ikejima, K.; Enomoto, N.; Stackelevitz, R.F.; Seabra, V.; Zhong, Z.; Yin, M.; Schemmer, P.; Rose, M.L.; Rusyn, I.; et al. Glycine: A new anti-inflammatory immunonutrient. Cell. Mol. Life Sci. 1999, 56, 843–856. [CrossRef]

112. Zhong, Z.; Wheeler, M.D.; Li, X.; Froh, M.; Schemmer, P.; Yin, M.; Bunzenda, H.; Bradford, B.; Lemasters, J.J. L-Glycine: A novel antiinflammatory, immunomodulatory, and cytoprotective agent. Curr. Opin. Clin. Nutr. Metab. Care 2003, 6, 229–240. [CrossRef]

113. Purves, T.; Middlemas, A.; Agthong, S.; Jude, E.B.; Boulton, A.J.M.; Fernyhough, P.; Tomlinson, D.R. A role for mitogen-activated protein kinases in the etiology of diabetic neuropathy. FASEB J. 2001, 15, 2508–2514. [CrossRef]

114. Ha, H.; Lee, H.B. Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. Kidney Int. 2000, 58, S19–S25. [CrossRef]

115. Lal, M.A.; Brismar, H.; Eklöf, A.-C.; Aperia, A. Role of oxidative stress in advanced glycation end product-induced mesangial cell activation. Kidney Int. 2002, 61, 2006–2014. [CrossRef]
116. Yong, R.; Chen, X.-M.; Shen, S.; Vijayaraj, S.; Ma, Q.; Pollock, C.A.; Saad, S. Plumbagin Ameliorates Diabetic Nephropathy via Interruption of Pathways that Include NOX4 Signalling. *PLoS ONE* 2013, 8, e73428. [CrossRef]

117. Das, S.J.; Wishart, T.L.; Jandeleit-Dahm, K.; Lovicu, F.J. NFX4-mediated ROS production is involved, but not essential for TGFβ-induced lens EMT leading to cataract. *Exp. Eye Res.* 2020, 192, 107918. [CrossRef]

118. Bitar, M.S.; Wahid, S.; Mustafa, S.; Al-Saleh, E.; Dhaunsi, G.S.; Al-Mulla, F. Nitric oxide dynamics and endothelial dysfunction in type II model of genetic diabetes. *Eur. J. Pharmacol.* 2005, 511, 53–64. [CrossRef]

119. Cassuto, J.; Dou, H.; Czikora, I.; Szabo, A.; Patel, V.S.; Kamath, V.; de Chantemele, E.B.; Feher, A.; Romero, M.J.; Bagi, Z. Peroxynitrite Disrupts Endothelial Caveolae Leading to eNOS Uncoupling and Diminished Flow-Mediated Dilation in Coronary Arterioles of Diabetic Patients. *Diabetes* 2014, 63, 1381–1393. [CrossRef]

120. Sun, J.; Chen, L.; Chen, R.; Lou, Q.; Wang, H. Poly(ADP-ribose) Polymerase-1: An Update on Its Role in Diabetic Retinopathy. *Discov. Med.* 2021, 32, 13–22.

121. Lewis Luján, L.M.; McCarty, M.F.; Di Nicolantonio, J.J.; Gálvez Ruiz, J.C.; Rosas-Burgos, E.C.; Plascencia-Jatorma, M.; Iloki Assanga, S.B. Nutraceuticals/Drugs Promoting Mitochondrial Biogenesis May Combat the Mitochondrial Dysfunction Driving Progression of Dry Age-Related Macular Degeneration. *Nutrients* 2022, 14, 1985. [CrossRef]

122. Lee, Y.S.; Kim, W.S.; Kim, K.H.; Yoon, M.J.; Cho, H.J.; Shen, Y.; Ye, J.-M.; Lee, C.H.; Oh, W.K.; Kim, C.T.; et al. Berberine, a Natural Plant Product, Activates AMPK-Activated Protein Kinase With Beneficial Metabolic Effects in Diabetic and Insulin-Resistant States. *Diabetes* 2006, 55, 2256–2264. [CrossRef]

123. Turner, N.; Li, J.Y.; Gosby, A.; To, S.W.; Cheng, Z.; Miyoshi, H.; Taketo, M.M.; Cooney, G.J.; Kraegen, E.W.; James, D.E.; et al. Berberine and its more biologically available derivative, dihydroberberine, inhibit mitochondrial respiratory complex I: A mechanism for the action of berberine to activate AMP-activated protein kinase and improve insulin action. *Diabetes* 2008, 57, 1414–1418. [CrossRef]

124. Hawley, S.A.; Ross, F.A.; Chevtzoff, C.; Green, K.A.; Evans, A.; Fogarty, S.; Towler, M.C.; Brown, L.J.; Ogunbayo, O.A.; Evans, A.M.; et al. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. *Cell Metab.* 2010, 11, 554–565. [CrossRef]

125. Liang, Y.; Xu, X.; Yin, M.; Zhang, Y.; Huang, L.; Chen, R.; Ni, J. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: A systematic literature review and a meta-analysis. *Endocr. J.* 2019, 66, 51–63. [CrossRef]

126. Jia, Y.; Kim, J.-Y.; Jun, H.-J.; Kim, S.-J.; Lee, J.-H.; Hoang, M.H.; Hwang, K.-Y.; Um, S.-J.; Chang, H.I.; Lee, S.-J. The natural carotenoid astaxanthin, a PPAR-α agonist and PPAR-γ antagonist, reduces hepatic lipid accumulation by rewiring the transcriptome in lipid-loaded hepatocytes. *Mol. Nutr. Food Res.* 2012, 56, 878–888. [CrossRef]

127. Jia, Y.; Wu, C.; kim, J.; Kim, B.; Lee, S.-J. Astaxanthin reduces hepatic lipid accumulations in high-fat-fed C57BL/6j mice via activation of peroxisome proliferator-activated receptor (PPAR) alpha and inhibition of PPAR gamma and Akt. *J. Nutr. Biochem.* 2016, 22, 9–18. [CrossRef]

128. Mashhadi, N.S.; Zakerkish, M.; Mohammadiasl, J.; Zarei, M.; Mohammadshahi, M.; Haghighizadeh, M.H. Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus. *Asia Pac. J. Clin. Nutr.* 2018, 27, 341–346.

129. Wang, J.; Li, S.; Wang, J.; Wu, F.; Chen, Y.; Zhang, H.; Guo, Y.; Lin, Y.; Li, L.; Yu, X.; et al. Spermidine alleviates cardiac aging by improving mitochondrial biogenesis and function. *Aging (Albany NY)* 2020, 12, 650–671. [CrossRef]

130. Zhang, H.; Alsaleh, G.; Feltham, J.; Sun, Y.; Napolitano, G.; Riffelmacher, T.; Charles, P.; Frau, L.; Hublitz, P.; Yu, Z.; et al. Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. *Mol. Cell 2019, 76, 110–125.e9. [PubMed]

131. Evans, T.D.; Zhang, X.; Jeong, S.-J.; He, A.; Song, E.; Bhattacharya, S.; Holloway, K.B.; Lodhi, I.J.; Razani, B. TFEB drives PGC-1α activation of peroxisome proliferator-activated receptor (PPAR) alpha and inhibition of PPAR gamma and Akt. *Cell Metab.* 2019, 554–565. [CrossRef]

132. Mashadi, N.S.; Zakerkish, M.; Mohammadiasl, J.; Zarei, M.; Mohammadshahi, M.; Haghighizadeh, M.H. Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus. *Asia Pac. J. Clin. Nutr.* 2018, 27, 341–346.

133. Wang, J.; Li, S.; Wang, J.; Wu, F.; Chen, Y.; Zhang, H.; Guo, Y.; Lin, Y.; Li, L.; Yu, X.; et al. Spermidine alleviates cardiac aging by improving mitochondrial biogenesis and function. *Aging (Albany NY)* 2020, 12, 650–671. [CrossRef]

134. Zhang, H.; Alsaleh, G.; Feltham, J.; Sun, Y.; Napolitano, G.; Riffelmacher, T.; Charles, P.; Frau, L.; Hublitz, P.; Yu, Z.; et al. Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. *Mol. Cell 2019, 76, 110–125.e9. [PubMed]

135. Evans, T.D.; Zhang, X.; Jeong, S.-J.; He, A.; Song, E.; Bhattacharya, S.; Holloway, K.B.; Lodhi, I.J.; Razani, B. TFEB drives PGC-1α activation of peroxisome proliferator-activated receptor (PPAR) alpha and inhibition of PPAR gamma and Akt. *Cell Metab.* 2019, 554–565. [CrossRef]

136. Pearson, K.J.; Baur, J.A.; Lewis, K.; Peshkin, L.; Price, N.L.; Labinskyy, N.; Swindell, W.R.; Kamara, D.; Minor, R.K.; Perez, E.; et al. Resveratrol Delays Age-Related Deterioration and Mimics Transcriptional Aspects of Dietary Restriction without Extending Life Span. *Cell Metab.* 2008, 8, 157–168. [CrossRef] [PubMed]

137. Chimento, A.; De, A.F.; Sironni, R.; Sinicropi, M.S.; Puoci, F.; Casaburi, I.; Saturnino, C.; Pezzi, V. Progress to Improve Oral Bioavailability and Beneficial Effects of Resveratrol. *Int. J. Mol. Sci.* 2019, 20, 1381. [CrossRef]

138. Hausenblas, H.A.; Schoulda, J.A.; Smoliga, J.M. Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus-systematic review and meta-analysis. *Mol. Nutr. Food Res.* 2015, 59, 147–159. [CrossRef]
139. El-Mesallamy, H.O.; Gawish, R.; Sallam, A.-A.M.; Fahmy, H.A.; Nada, A.S. Ferulic acid protects against radiation-induced testicular damage in male rats: Impact on SIRT1 and PARP1. *Environ. Sci. Pollut. Res. Int.* 2017, 25, 6218–6227. [CrossRef]

140. Moghadam, F.H.; Mesbah-Ardakani, M.; Nasr-Esfahani, M.-H. Ferulic Acid exerts concentration-dependent anti-apoptotic and neuronal differentiation-inducing effects in PC12 and mouse neural stem cells. *Eur. J. Pharmacol.* 2018, 841, 104–112. [CrossRef]

141. Hou, T.; Zhang, L.; Yang, X. Ferulic acid, a natural polyphenol, protects against osteoporosis by activating SIRT1 and NF-κB in neonatal rats with glucocorticoid-induced osteoporosis. *Biomed. Pharmacother.* 2019, 120, 109205. [CrossRef]

142. Xu, T.; Song, Q.; Zhou, L.; Yang, W.; Wu, X.; Qian, Q.; Chai, H.; Han, Q.; Pan, H.; Dou, X.; et al. Ferulic acid alleviates lipotoxicity-induced hepatocellular death through the SIRT1-regulated autophagy pathway and independently of AMPK and Akt in AML-12 hepatocytes. *Natu. Metab.* 2021, 18, 13. [CrossRef] [PubMed]

143. CristA²fol, R.; Porquet, D.; Corpas, R.; Coto-Montes, A.; Serret, J.; Camins, A.; Pallas, M.; Sandeliu, C. Neurons from senescence-accelerated SAM-P8 mice are protected against frailty by the sirtuin 1 promoting agents melatonin and resveratrol. *J. Pineal Res.* 2012, 52, 271–281. [CrossRef]

144. Yu, L.; Sun, Y.; Cheng, L.; Jin, Z.; Yang, Y.; Zhai, M.; Pei, H.; Wang, X.; Zhang, H.; Meng, Q.; et al. Melatonin receptor-mediated protection against myocardial ischemia/reperfusion injury: Role of SIRT1. *J. Pineal Res.* 2014, 57, 228–238. [CrossRef]

145. Yang, Y.; Jiang, S.; Dong, Y.; Fan, C.; Zhao, L.; Yang, X.; Li, J.; Di, S.; Yue, L.; Liang, G.; et al. Melatonin prevents cell death and mitochondrial dysfunction via a SIRT1-dependent mechanism during ischemic-stroke in mice. *J. Pineal Res.* 2015, 58, 61–70. [CrossRef] [PubMed]

146. Li, K.; Zhai, M.; Jiang, L.; Song, F.; Zhang, B.; Li, J.; Li, B.; Xia, L.; Xu, L.; et al. Tetrahydrocurcumin Ameliorates Diabetic Cardiomyopathy by Attenuating High Glucose-Induced Oxidative Stress and Fibrosis via Activating the SIRT1 Pathway. *Oxidative Med. Cell. Longev.* 2019, 2019, 6746907. [CrossRef]

147. Li, L.; Liu, X.; Li, S.; Wang, Q.; Wang, H.; Xu, M.; An, Y. Tetrahydrocurcumin protects against sepsis-induced acute kidney injury via the SIRT1 pathway. *Ren. Fail.* 2021, 43, 1028–1040. [CrossRef] [PubMed]

148. Ghosh, N.; Das, A.; Biswas, N.; Gnyawali, S.; Singh, K.; Gorain, M.; Polcyn, C.; Khanna, S.; Roy, S.; Sen, C.K. Urolithin A augments angiogenic pathways in skeletal muscle by bolstering NAD+ and SIRT1. *Sci. Rep.* 2020, 10, 20184. [CrossRef]

149. Liu, J.; Jiang, J.; Qiu, J.; Wang, L.; Zhan, J.; Wang, B.; Sun, D.; Yu, S.; Lou, H. Urolithin A protects dopaminergic neurons in experimental models of Parkinson’s disease by promoting mitochondrial biogenesis through the SIRT1/PGC-1α signaling pathway. *Food Funct.* 2022, 13, 375–385. [CrossRef]

150. Shi, P.Z.; Wang, J.W.; Wang, P.C.; Han, B.; Lu, X.H.; Ren, Y.X.; Feng, H.M.; Cheng, X.F.; Zhang, L. Urolithin A alleviates oxidative stress-induced senescence in nucleus pulposus-derived mesenchymal stem cells through SIRT1/PGC-1α pathway. *World J. Stem Cells* 2021, 13, 1928–1946. [CrossRef] [PubMed]

151. Hong, S.; Moreno-Navarrete, J.M.; Wei, X.; Kikukawa, Y.; Tzameli, I.; Prasad, D.; Lee, Y.; Asara, J.M.; Fernández-Real, J.M.; Maratos-Flier, E.; et al. Nicotinamide N-methyltransferase regulates hepatic nutrient metabolism through Sirt1 protein stabilization. *Nat. Med.* 2015, 21, 887–894. [CrossRef]

152. Canto, C.; Houtkooper, R.H.; Pirinen, E.; Youn, D.Y.; Oosterveer, M.H.; Cen, Y.; Fernandez-Marcos, P.J.; Yamamoto, H.; Andreux, P.A.; Cettour-Rose, P.; et al. The NAD+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab.* 2012, 15, 838–847. [CrossRef]

153. Leduc-Gaudet, J.P.; Dulac, M.; Reynaud, O.; Ayoub, M.; Gouspillou, G. Nicotinamide riboside supplementation to improve mitochondrial dysfunction via a SIRT1-dependent mechanism during ischemic-stroke in mice. *Ren. Fail.* 2019, 43, 271–281. [CrossRef] [PubMed]

154. Martens, C.R.; Denman, B.A.; Mazzo, M.R.; Armstrong, M.L.; Reisdorph, N.; McQueen, M.B.; Chonchol, M.; Seals, D.R. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults. *Nat. Commun.* 2018, 9, 1286. [CrossRef]

155. Yoshino, J.; Mills, K.F.; Yoon, M.J.; Imai, S.; Losordo, D.W. Metformin reduces blood glucose and improves insulin sensitivity by activating the SIRT1-PGC-1β axis in skeletal muscle. *Diabetes Metab. J.* 2011, 35, 464–473. [CrossRef]

156. Caton, P.W.; Kieswich, J.; Yaqoob, M.M.; Holness, M.J.; Sugden, M.C. Nicotinamide mononucleotide protects against pro-inflammatory cytokine-mediated impairment of mouse islet function. *Diabetologia* 2011, 54, 3083–3092. [CrossRef]

157. Liu, X.; Li, D.; Liu, Z.; Song, Y.; Zhang, B.; Zang, Y.; Zhang, W.; Niu, Y.; Shen, C. Nicotinamide mononucleotide promotes pancreatic islet function through the SIRT1 pathway in mice after severe burns. *Burns* 2022, online ahead of print. [CrossRef]

158. Fulco, M.; Cen, Y.; Zhao, P.; Hoffman, E.P.; McBurney, M.W.; Sauve, A.A.; Sartorelli, V. Glucose Restriction Inhibits Skeletal Myoblast Differentiation by Activating SIRT1 through AMPK-Mediated Regulation of Namp. *Dev. Cell* 2008, 14, 661–673. [CrossRef]

159. Costford, S.R.; Bajpeyi, S.; Pasarica, M.; Albarado, D.C.; Thomas, S.C.; Xie, H.; Church, T.S.; Jubrias, S.A.; Conley, K.E.; Smith, S.R. Skeletal muscle NAMPT is induced by exercise in humans. *Am. J. Physiol.—Endocrinol. Metab.* 2010, 298, E117–E126. [CrossRef]

160. Al-Hayali, M.; Garces, A.; Stocks, M.; Collins, H.; Bradshaw, T.D. Concurrent Reactive Oxygen Species Generation and Aneuploidy Induction Contribute to Thymoquinone Anticancer Activity. *Molecules* 2021, 26, 5136. [CrossRef]

161. Yang, Y.; Bai, T.; Yao, Y.-L.; Zhang, D.-Q.; Wu, Y.-L.; Lian, L.-H.; Nan, J.-X. Upregulation of SIRT1-AMPK by thymoquinone in hepatic stellate cells ameliorates liver injury. *Toxicol. Lett.* 2016, 262, 80–91. [CrossRef] [PubMed]
162. Velagapudi, R.; El-Bakoush, A.; Leipiarz, I.; Ogunjraine, F.; Olajide, O.A. AMPK and SIRT1 activation contribute to inhibition of neuroinflammation by thymoquinone in BV2 microglia. *Mol. Cell. Biochem.* 2017, 435, 149–162. [CrossRef] [PubMed]

163. Karandrea, S.; Yin, H.; Liang, X.; Slitt, A.L.; Heart, E.A. Thymoquinone ameliorates diabetic phenotype in Diethylnitrosamine-induced Obesity mice via activation of SIRT-1-dependent pathways. *PLoS ONE* 2017, 12, e0185374. [CrossRef]

164. Tsvetkov, P.; Adler, J.; Stroblert, R.; Adamovich, Y.; Asher, G.; Reuveni, N.; Shaul, Y. NQO1 Binds and Supports SIRT1 Function. *Front. Pharmacol.* 2021, 12, 671929. [CrossRef]

165. Qiu, D.; Song, S.; Wang, Y.; Bian, Y.; Wu, M.; Wu, H.; Shi, Y.; Duan, H. NAD(P)H: Quinone oxidoreductase 1 attenuates oxidative stress and apoptosis by regulating Sirt1 in diabetic nephropathy. *J. Transl. Med.* 2022, 20, 44. [CrossRef] [PubMed]

166. Akagawa, M.; Minematsu, K.; Shibata, T.; Kondo, T.; Ishii, T.; Uchida, K. Identification of lactate dehydrogenase as a mammalian pyrroloquinoline quinone (PQQ)-binding protein. *Sci. Rep.* 2016, 6, 26723. [CrossRef] [PubMed]

167. Saihara, K.; Kamikubo, R.; Ikemoto, K.; Uchida, K.; Akagawa, M. Pyrroloquinoline Quinone, a Redox-Active α-Quinone, Stimulates Mitochondrial Biogenesis by Activating the SIRT1/PGC-1α Signaling Pathway. *Biochemistry* 2017, 56, 6615–6625. [CrossRef]

168. Zhang, H.; Li, J.; Cao, C.; Zhang, B.; Yang, W.; Shi, B.; Shan, A. Pyrroloquinoline quinone inhibits the production of inflammatory cytokines via the SIRT1/NF-κB signal pathway in weaned piglet jejunal. *Food Funct.* 2020, 11, 2137–2153. [CrossRef]

169. Talebi, M.; Talebi, M.; Farkhondeh, T.; Samarghandian, S. Biological and therapeutic activities of thymoquinone: Focus on the NFkB signaling pathway. *Phytother. Res.* 2015, 35, 1379–1753. [CrossRef]

170. Velagapudi, R.; Kumar, A.; Bhatia, H.S.; El-Bakhoush, A.; Leipiarz, I.; Fiebich, B.L.; Olajide, O.A. Inhibition of neuroinflammation by thymoquinone requires activation of NFκB/ARE signaling. *Int. Immunopharmacol.* 2017, 48, 17–29. [CrossRef]

171. Kundu, J.; Kim, D.H.; Kundu, J.K.; Chun, K.S. Thymoquinone induces heme oxygenase-1 expression in HaCaT cells via Nrf2/ARE activation: Akt and AMPKx as upstream targets. *Food Chem. Toxicol.* 2014, 65, 18–26. [CrossRef] [PubMed]

172. Mihanfar, A.; Akbarzadeh, M.; Darband, S.G.; Sadighparvar, S.; Majidinia, M. SIRT1: A promising therapeutic target in type 2 diabetes mellitus. *Arch. Physiol. Biochem.* 2021, 1–16, online ahead of print. [CrossRef]

173. Zeng, K.; Xi, W.; Qiao, Y.; Huang, X.; Liu, X. Paenunflorin inhibits epithelial mesenchymal transformation and oxidative damage of lens epithelial cells in diabetic cataract via sirtuin 1 upregulation. *Bioengineered* 2022, 13, 5903–5914. [CrossRef] [PubMed]

174. Yeung, E.; Hoberg, J.E.; Ramsey, C.S.; Keller, M.D.; Jones, D.J.; Frye, R.A.; Mayo, M.W. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J.* 2004, 23, 2369–2380. [CrossRef] [PubMed]

175. Ardalan, A.; Smith, M.D.; Jelokhani-Niaraki, M. Uncoupling Proteins and Regulated Proton Leak in Mitochondria. *Cardiovasc. Diabetol.* 2013, 12, 1303–1316. [CrossRef] [PubMed]

176. Sun, J.; Pu, Y.; Wang, P.; Chen, S.; Zhao, Y.; Liu, C.; Shang, Q.; Zhu, Z.; Liu, D. TRPV1-mediated UCP2 upregulation ameliorates hyperglycemia-induced endothelial dysfunction. *Cardiovasc. Diabetol.* 2013, 12, 69. [CrossRef] [PubMed]

177. Sun, J.; Pu, Y.; Wang, P.; Chen, S.; Zhao, Y.; Liu, C.; Shang, Q.; Zhu, Z.; Liu, D. TRPV1-mediated UCP2 upregulation ameliorates hyperglycemia-induced endothelial dysfunction. *Cardiovasc. Diabetol.* 2013, 12, 69. [CrossRef] [PubMed]

178. Wei, X.; Wei, X.; Lu, Z.; Li, L.; Hu, Y.; Sun, F.; Jiang, Y.; Ma, H.; Zhewng, H.; Yang, G.; et al. Activation of TRPV1 channel antagonizes diabetic phenotype in diabetic vascular smooth muscle cells by inhibiting endoplasmic reticulum-mitochondria contact in podocytes. *Metabolism* 2020, 105, 154182. [CrossRef]

179. Mccarty, M.F.; DiNicolantonio, J.J.; O’Keefe, J.H. Capsaicin may have important potential for promoting vascular and metabolic health. *Open Heart* 2015, 2, e000262. [CrossRef]

180. Shi, Z.; Riley, M.; Taylor, A.W.; Page, A. Chilli consumption and the incidence of overweight and obesity in a Chinese adult population. *Int. J. Obes.* 2017, 41, 1074–1079. [CrossRef]

181. Sonta, T.; Inoguchi, T.; Tsubouchi, H.; Sekiguchi, N.; Kobayashi, K.; Matsumoto, S.; Utsumi, H.; Nawata, H. Evidence for contribution of vascular NAD(P)H oxidase to increased oxidative stress in animal models of diabetes and obesity. *Free Radic. Biol. Med.* 2004, 37, 115–123. [CrossRef]

182. Quagliaro, L.; Piconi, L.; Assaloni, R.; Martinelli, L.; Motz, E.; Cerielo, A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: The role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes* 2003, 52, 2795–2804. [CrossRef]

183. Akagawa, M.; Minematsu, K.; Shibata, T.; Kondo, T.; Ishii, T.; Uchida, K. Identification of lactate dehydrogenase as a mammalian pyrroloquinoline quinone (PQQ)-binding protein. *Sci. Rep.* 2016, 6, 26723. [CrossRef] [PubMed]

184. Inoguchi, T.; Sonta, T.; Tsubouchi, H.; Etoh, T.; Kakimoto, M.; Sonoda, N.; Sato, N.; Sekiguchi, N.; Kobayashi, K.; Sumimoto, H.; et al. Protein Kinase C–Dependent Increase in Reactive Oxygen Species (ROS) Production in Vascular Tissues of Diabetes: Role of Vascular NAD(P)H Oxidase. *J. Am. Soc. Nephrol.* 2003, 14, S227–S232. [CrossRef]
188. Gorin, Y.; Block, K. Nox4 and diabetic nephropathy: With a friend like this, who needs enemies? Free. Radic. Biol. Med. 2013, 61, 130–142. [CrossRef]

189. Gorin, Y.; Block, K. Nox as a target for diabetic complications. Clin. Sci. 2013, 125, 361–382. [CrossRef]

190. Lanone, S.; Bloc, S.; Foresti, R.; Almolkj, A.; Taille, C.; Callebert, J.; Conti, M.; Goven, D.; Aubier, M.; Dureuil, B.; et al. Bilirubin decreases NO2 expression via inhibition of NAD(P)H oxidase: Implications for protection against endotox shock in rats. FASEB J. 2005, 19, 1890–1892. [CrossRef]

191. Matsumoto, H.; Ishikawa, K.; Iiabe, H.; Maruyama, Y. Carbon monoxide and bilirubin from heme oxygenase-1 suppresses reactive oxygen species generation and plasmogen activating factor-inhibitor-1 induction. Mol. Cell. Biochem. 2006, 291, 21–28. [CrossRef]

192. Jiang, F.; Roberts, S.J.; Datla, S.R.; Dusting, G.J. NO Modulates NADPH Oxidase Function Via Heme Oxygenase-1 in Human Endothelial Cells. Hypertension 2006, 48, 950–957. [CrossRef] [PubMed]

193. Datla, S.R.; Dusting, G.J.; Mori, T.A.; Taylor, C.J.; Croft, K.D.; Jiang, F. Induction of heme oxygenase-1 in vivo suppresses NADPH oxidase derived oxidative stress. Hypertension 2007, 50, 636–642. [CrossRef] [PubMed]

194. Basuroy, S.; Bhattacharya, S.; Lefler, C.W.; Farfenova, H. Nox4 NADPH oxidase mediates oxidative stress and apoptosis caused by TNF-α in human brain cells. J. Neurosci. Res. 2009, 87, C422–C432. [CrossRef] [PubMed]

195. Inoguchi, T.; Sasaki, S.; Kobayashi, K.; Takayanagi, R.; Yamada, T. Relationship Between Gilbert Syndrome and Prevalence of Vascular Complications in Patients with Diabetes. JAMA 2007, 298, 1396–1400. [CrossRef] [PubMed]

196. McCarty, M.F. "Iatrogenic Gilbert syndrome"—a strategy for reducing vascular and cancer risk by increasing plasma unconjugated bilirubin. Med. Hypotheses 2007, 69, 974–994. [CrossRef]

197. McCarty, M.F. Clinical potential of Spirulina as a source of phycocyanobilin. J. Med. Food 2007, 2010, 566–570. [CrossRef]

198. Zheng, J.; Inoguchi, T.; Sasaki, S.; Maeda, Y.; McCarty, M.F.; Fujii, M.; Ikeda, N.; Kobayashi, K.; Sonoda, N.; Takayanagi, R. Phycocyanobilin from Spirulina platensis protect against diabetic nephropathy by inhibiting oxidative stress. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2013, 304, R110–R120. [CrossRef]

199. Pentón-Rol, G.; MarÁn-Prida, J.; McCarty, M.F. C-Phycocyanin-derived Phycocyanobilin as a Potential Nutraceutical Approach for Major Neurodegenerative Disorders and COVID-19-induced Damage to the Nervous System. Curr. Neuropharmacol. 2021, 19, 2250–2275. [CrossRef]

200. Marin-Prida, J.; Liberato, J.L.; Llopiz-Arzuaga, A.; Pavon-Fuentes, N.; Leopoldino, A.M.; Cruz, O.G.; Gonzalez, I.H.; Perez, M.L.; Camins, A.; et al. Novel Insights into the Molecular Mechanisms Involved in the Neuroprotective Effects of C-Phycocyanin Against Brain Ischemia in Rats. Curr. Pharm. Des. 2022, 28, 1187–1197. [CrossRef]

201. Forbes, S.P.; Druhan, L.J.; Guzman, J.E.; Parinandi, N.; Zhang, L.; Green-Church, K.B.; Cardouzel, A.J. Mechanism of 4-HNE Mediated Inhibition of hDDAH-1: Implications in No Regulation. Biochemistry 2008, 47, 1819–1826. [CrossRef] [PubMed]

202. Chen, L.; Zhou, J.-P.; Kuang, D.-B.; Tang, J.; Li, Y.-J.; Chen, X.-P. 4-HNE Increases Intracellular ADMA Levels in Cultured HUVECs: Evidence for miR-21-Dependent Mechanisms. PLoS ONE 2013, 8, e64148. [CrossRef] [PubMed]

203. Hoang, H.H.; Padgham, S.; Meininger, C.J. L-arginine, tetrahydrobiopterin, nitric oxide and diabetes. Curr. Opin. Clin. Nutr. Metab. Care 2013, 16, 76–82. [CrossRef] [PubMed]

204. Gao, L.; Yu, A.; Liu, J.; Ma, L.; Li, J. eNOS Uncoupling: A Therapeutic Target For Ischemic Foot of Diabetic Rat. Exp. Clin. Endocrinol. Diabetes 2019, 127, 303–310. [CrossRef] [PubMed]

205. McCarty, M.F. Supplementation with Phycocyanobilin, Citrulline, Taurine, and Supranutritional Doses of Folic Acid and Biotin-Potential for Preventing or Slowing the Progression of Diabetic Complications. J. Am. Coll. Nutr. 2017, 35, 76–82. [CrossRef] [PubMed]

206. McCarty, M.F. Asymmetric Dimethylarginine Is a Well Established Mediating Risk Factor for Cardiovascular Morbidity and Mortality-Should Patients with Elevated Levels Be Supplemented with Citrulline? Healthcare 2019, 7, 1819–1826. [CrossRef] [PubMed]

207. Siu, K.L.; Mao, X.N.; Cai, H. Recoupling of eNOS with Folic Acid Prevents Abdominal Aortic Aneurysm Formation in Angiotensin II-Infused Apolipoprotein E Null Mice. PLoS ONE 2013, 8, e68899. [CrossRef] [PubMed]

208. Chalupsky, K.; Krcu~n, D.; Kanchev, I.; Bertram, K.; Göräch, A. Folic Acid Promotes Recycling of Tetrahydrobiopterin and Protects Against Hypoxia-Induced Pulmonary Hypertension by Recoupling Endothelial Nitric Oxide Synthase. Antioxidants Redox Signal. 2015, 23, 1076–1091. [CrossRef]

209. Shatanawi, A.; Momani, M.S.; Al-Aqbash, R.; Hamdan, M.H.; Gharabeh, M.N. L-Citrulline Supplementation Increases Plasma Nitric Oxide Levels and Reduces Arginase Activity in Patients with Type 2 Diabetes. Front. Pharmacol. 2020, 11, 584669. [CrossRef]

210. Schwedhelm, E.; Maas, R.; Freese, R.; Jung, D.; Lukacs, Z.; Jambrecina, A.; Spickler, W.; Schulze, F.; Böger, R.H. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: Impact on nitric oxide metabolism. Br. J. Clin. Pharmacol. 2008, 65, 51–59. [PubMed]

211. Mátváss, C.; Németh, B.T.; Oláh, A.; Hidi, L.; Birtalan, E.; Kellermayer, D.; Ruppert, M.; Korkmaz-Icoz, S.; Kokeny, G.; Horvath, E.M.; et al. The soluble guanylate cyclase activator cinaciguat prevents cardiac dysfunction in a rat model of type 1 diabetes mellitus. Cardiovasc. Diabetol. 2015, 14, 145. [CrossRef] [PubMed]

212. Boustany-Kari, C.M.; Harrison, P.C.; Chen, X.; Lincoln, A.K.; Qian, H.S.; Clifford, H.; Wang, H.; Zhang, X.; Gueneva-Boucheva, K.; Bosanac, T.; et al. A Soluble Guanylate Cyclase Activator Inhibits the Progression of Diabetic Nephropathy in the ZSF1 Rat. J. Pharmacol. Exp. Ther. 2016, 356, 712–719. [CrossRef] [PubMed]
213. Czirók, S.; Fang, L.; Radovits, T.; Szabo, G.; Szenasi, G.; Rosivall, L.; Merkeley, B.; Kokeny, G. Cinaciguat ameliorates glomerular damage by reducing ERK1/2 activity and TGF-β expression in type-1 diabetic rats. *Sci. Rep.* 2017, 7, 11218. [CrossRef] [PubMed]

214. Harloff, M.; Prueschen, S.; Seifert, R.; Schlossmann, J. Activation of soluble guanylyl cyclase signalling with cinaciguat improves impaired kidney function in diabetic mice. *Br. J. Pharmacol.* 2022, 179, 2460–2475. [CrossRef]

215. Fleischmann, D.; Harloff, M.; Maslanka, F.S.; Schlossmann, J.; Goepferich, A. Targeted Delivery of Soluble Guanylate Cyclase (sGC) Activator Cinaciguat to Renal Mesangial Cells via Virus-Mimetic Nanoparticles Potentiates Anti-Fibrotic Effects by cGMP-Mediated Suppression of the TGF-β Pathway. *Int. J. Mol. Sci.* 2021, 22, 2557. [CrossRef]

216. Bénarèdeau, A.; Kahnert, A.; Schomber, T.; Meyer, J.; Pavkovic, M.; Kretchmer, A.; Lawrenz, B.; Hartmann, E.; Mathar, I.; Hueser, J.; et al. Runcaciguat, a novel soluble guanylate cyclase activator, shows renoprotection in hypertensive, diabetic, and metabolic preclinical models of chronic kidney disease. *Naunyn-Schmiedeberg’s Arch. Pharmacol.* 2021, 394, 2363–2379. [CrossRef]

217. Hu, L.; Chen, Y.; Zhou, X.; Hoek, M.; Cox, J.; Lin, K.; Liu, Y.; Blumschein, W.; Grein, J.; Swaminath, G. Effects of soluble guanylate cyclase stimulator on renal function in ZSF-1 model of diabetic nephropathy. *PLoS ONE* 2022, 17, e0261000. [CrossRef]

218. Scheele, W.; Diamond, S.; Gale, J.; Clerin, V.; Tamimi, N.; Le, V.; Walley, R.; Grover-Páez, F.; Fersos-Huguet, C.; Rolph, T.; et al. Phosphodiesterase Type 5 Inhibition Reduces Albuminuria in Subjects with Overt Diabetic Nephropathy. *J. Am. Soc. Nephrol.* 2016, 27, 3459–3468. [CrossRef]

219. Wang, L.; Chopp, M.; Szalad, A.; Lu, X.; Jia, L.; Lü, M.; Zhang, R.L.; Zhang, Z.G. Tadalafil Promotes the Recovery of Peripheral Nerve Function by Enhancing Autonomic Nerve Regeneration. *PLoS ONE* 2017, 11, e0159665. [CrossRef] [PubMed]

220. Lee, H.J.; Féliers, D.; Mariappan, M.M.; Sataranatarajan, K.; Choudhury, G.G.; Gorin, Y.; Kasinath, B.S. Tadalafil Integrates Nitric Oxide–Hypoxia–Sulfide Signaling to Inhibit High Glucose-induced Matrix Protein Synthesis in Podocytes. *J. Biol. Chem.* 2015, 290, 12014–12026. [CrossRef]

221. Fang, L.; Radovits, T.; Szabo, G.; Mózes, M.M.; Rosivall, L.; Kökény, G. Selective phosphodiesterase-5 (PDE-5) inhibitor vardenafil ameliorates renal damage in type 1 diabetic rats by restoring cyclic 3′,5′ guanosine monophosphate (cGMP) level in podocytes. *Nephrol. Dial. Transplant.* 2013, 28, 1751–1761. [PubMed]

222. Giannetta, E.; Isidori, A.M.; Galea, N.; Carboni, I.; Mandolesi, E.; Vizza, C.D.; Naro, F.; Morano, S.; Fedele, F.; Lenzi, A. Chronic Inhibition of cGMP phosphodiesterase 5A improves diabetic cardiomyopathy: A randomized, controlled clinical trial using magnetic resonance imaging with myocardial tagging. *Circulation* 2012, 125, 2323–2333. [CrossRef] [PubMed]

223. Wang, L.; Chopp, M.; Szalad, A.; Liu, Z.; Bolz, M.; Álvarez, F.; Lu, M.; Zhang, L.; Cui, Y.; Zhang, R.; et al. Phosphodiesterase-5 is a therapeutic target for peripheral nephropathy in diabetic mice. *Neuroscience* 2011, 193, 399–410. [CrossRef] [PubMed]

224. Radovits, T.; Bönicke, T.; Kökény, G.; Arif, R.; Loganathan, S.; Kecsan, K.; Korkmazs, S.; Barnucz, E.; Sandner, P.; Karck, M.; et al. The phosphodiesterase-5 inhibitor vardenafil improves cardiac dysfunction in experimental diabetic mellitus. *Br. J. Pharmacol.* 2009, 156, 909–919. [CrossRef]

225. Aversa, A.; Vitale, C.; Volterrani, M.; Fabbri, A.; Spera, G.; Fini, M.; Rosano, G.M.C. Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes. *Diabet. Med.* 2008, 25, 37–44. [CrossRef]

226. Pofi, R.; Fiore, D.; De Gaetano, R.; Panio, G.; Gianfrilli, D.; Pozza, C.; Barbagallo, F.; Xiang, Y.K.; Giannakakis, K.; Morano, S.; et al. Phosphodiesterase-5 inhibition preserves renal hemodynamics and function in mice with diabetic kidney disease by modulating miR-22 and BMP7. *Sci. Rep.* 2017, 7, 44584. [CrossRef]

227. Vesely, D.L. Biotin Enhances Guanylate Cyclase Activity. *Science* 1982, 216, 1329–1330. [CrossRef]

228. Spence, J.T.; Koudelka, A.P. Effects of biotin upon the intracellular level of cGMP and the activity of glucokinase in cultured rat hepatocytes. *J. Biol. Chem.* 1984, 259, 6393–6396. [CrossRef]

229. Watanabe-Kamiyama, M.; Kamiyama, S.; Horiuchi, K.; Ohinata, K.; Shirakawa, H.; Furukawa, Y.; Komai, M. Antihypertensive effect of biotin in stroke-prone spontaneously hypertensive rats. *Br. J. Nutr.* 1990, 575–587. [CrossRef]

230. Li, D.; Ferguson, A.; Cervinski, A.M.; Lynch, K.L.; Kyle, P.B. AACC Guidance Document on Biotin Interference in Laboratory Tests. *J. Appl. Lab. Med.* 2020, 5, 579–587. [CrossRef]

231. Liu, J.; Wang, C.; Liu, F.; Lu, Y.; Cheng, J. Metabonomics revealed xanthine oxidase-induced oxidative stress and inflammation in the pathogenesis of diabetic nephropathy. *Anal. Bioanal. Chem.* 2015, 407, 2569–2579. [CrossRef]

232. Hovind, P.; Rossing, P.; Johnson, R.J.; Parving, H.-H. Serum Uric Acid as a New Player in the Development of Diabetic Nephropathy. *J. Ren. Nutr.* 2011, 21, 124–127. [CrossRef]
238. Kosugi, T.; Nakayama, T.; Heinig, M.; Zhang, L.; Yuzawa, Y.; Sanchez-Lozada, L.G.; Roncal, C.; Johnson, R.J.; Nakagawa, T. Effect of lowering uric acid on renal disease in the type 2 diabetic db/db mice. *Am. J. Physiol. Renal. Physiol.* 2009, 297, F481–F488. [CrossRef]

239. Wu, B.; Chen, L.; Xu, Y.; Duan, Q.; Zheng, Z.; Zheng, Z.; He, D. The Effect of Allopurinol on Renal Outcomes in Patients with Diabetic Kidney Disease: A Systematic Review and Meta-Analysis. *Kidney Blood Press. Res.* 2022, 47, 291–299. [CrossRef]

240. Sautin, Y.; Nakagawa, T.; Zharikov, S.; Johnson, R.J. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am. J. Physiol. Physiol.* 2007, 293, C584–C596. [CrossRef]

241. Ko, J.; Kang, H.; Kim, D.; Kim, M.; Ryu, E.; Lee, S.; Ryu, J.; Roncal, C.; Johnson, R.J.; Kang, D. Uric acid induced the phenotype transition of vascular endothelial cells via induction of oxidative stress and glycoalcalyx shedding. *FASEB J.* 2019, 33, 13334–13345. [CrossRef] [PubMed]

242. McIlroy, M.F.; O'Keefe, J.H.; DiNicolantonio, J.J. Glucosamine for the Treatment of Osteoarthritis: The Time Has Come for [CrossRef] [PubMed]

243. Rabbani, N.; Thornalley, P.J. Emerging role of thiamine therapy for prevention and treatment of early-stage diabetic nephropathy. *Proc. Natl. Acad. Sci. USA* 1998, 95, 675–680. [CrossRef]

244. Chen, J.; Ge, J.; Zha, M.; Miao, J.-J.; Sun, Z.-L.; Yu, J.-Y. Effects of Uric Acid-Lowering Treatment on Glycemia: A Systematic Review and Meta-Analysis. *Front. Endocrinol.* 2020, 11, 577. [CrossRef]

245. Alem, M.M. Allopurinol and endothelial function: A systematic review with meta-analysis of randomized controlled trials. *Cardiovasc. Ther.* 2018, 36, e12432. [CrossRef] [PubMed]

246. Waring, W.S.; McKnight, J.A.; Webb, D.J.; Maxwell, S.R. Uric Acid Restores Endothelial Function in Patients with Type 1 Diabetes and Regular Smokers. *Diabetes 2006, 55, 3127–3132. [CrossRef]

247. Thimmulappa, R.K.; Mai, K.H.; Srisuma, S.; Kensler, T.W.; Yamamoto, M.; Biswal, S. Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. *Cancer Res.* 2002, 62, 5196–5203. [CrossRef]

248. Tanito, M.; Agbag, M.-P.; Anderson, B.E. Upregulation of thioferredoxin system via Nrf2-antioxidant responsive element pathway in adaptive-retinal neuroprotection in vivo and in vitro. *Free Radic. Biol. Med.* 2007, 42, 1838–1850. [CrossRef]

249. Larkin, J.R.; Zhang, F.; Godfrey, L.; Molostvov, G.; Zehnder, D.; Rabbani, N.; Thornalley, P.J. Glucose-induced down regulation of thiamine transporters in the kidney proximal tubular epithelium produces thiamine insufficiency in diabetes. *PLOS ONE 2012, 7, e53175. [CrossRef]

250. Perl, A.; Hancu, R.; Telarico, T.; Oaks, Z.; Landas, S. Oxidative stress, inflammation and carcinogenesis are controlled through the pentose phosphate pathway by transaldolase. *Trends Mol. Med.* 2017, 23, 205–220. [CrossRef] [PubMed]

251. Xu, I.M.-J.; Lai, R.K.-H.; Lin, S.-H.; Tse, A.P.-W.; Chiu, D.K.-C.; Koh, H.-Y.; Law, C.-T.; Wong, C.-M.; Cai, Z.; Wong, C.C.-L.; et al. Transketolase counteracts oxidative stress to drive cancer development. *Proc. Natl. Acad. Sci. USA* 2016, 113, E725–E734. [CrossRef] [PubMed]

252. Beltram, E.; Berrone, E.; Tarallo, S.; Porta, M. Effects of thiamine and benfotiamine on intracellular glucose metabolism and relevance in the prevention of diabetic complications. *Geol. Rundsch.* 2008, 45, 131–141. [CrossRef] [PubMed]

253. Rabbani, N.; Thornalley, P.J. Emerging role of thiamine therapy for prevention and treatment of early-stage diabetic nephropathy. *Diabetes, Obes. Metab.* 2011, 13, 577–583. [CrossRef] [PubMed]

254. Vaidyanathan, K.; Wells, L. Multiple tissue-specific roles for the O-GlcNAc post-translational modification in the induction of and complications arising from type II diabetes. *J. Biol. Chem.* 2014, 289, 34466–34471. [CrossRef] [PubMed]

255. Gonzalez-Rellán, M.J.; Fondervila, M.F.; Dieguez, C.; Nogueiras, R. O-GlcNAcylation: A Sweet Hub in the Regulation of Glucose Metabolism in Health and Disease. *Front. Endocrinol.* 2022, 13, 873513. [CrossRef]

256. Mccarty, M.F.; O’Keefe, J.H.; DiNicola-tonio, J.J. Glucosamine for the Treatment of Osteoarthritis: The Time Has Come for Higher-Dose Trials. *J. Diet. Suppl.* 2018, 16, 179–192. [CrossRef]

257. Bell, G.A.; Kantor, E.D.; Lampe, J.W.; Shen, D.D.; White, E. Use of glucosamine and chondroitin in relation to mortality. *Eur. J. Epidemiol.* 2012, 27, 593–603. [CrossRef] [PubMed]

258. Li, Z.-H.; Gao, X.; Chung, V.C.; Zhong, W.-F.; Fu, Q.; Lv, Y.-B.; Wang, Z.-H.; Shen, D.; Zhang, X.-R.; Zhang, P.-D.; et al. Associations of regular glucosamine use with all-cause and cause-specific mortality: A large prospective cohort study. *Ann. Rheum. Dis.* 2020, 79, 829–836. [CrossRef]

259. King, D.E.; Xiang, J. Glucosamine/Chondroitin and Mortality in a US NHANES Cohort. *J. Am. Board Fam. Med.* 2020, 33, 842–847. [CrossRef]

260. Weimer, S.; Priebs, J.; Kuhlow, D.; Groth, M.; Priebe, S.; Mansfeld, D.; Merry, T.L.; Dubuis, S.; Laube, B.; Pfeiffer, A.F.; et al. D-Glucosamine supplementation extends life span of nematodes and of ageing mice. *Nat. Commun.* 2014, 5, 3563. [CrossRef] [PubMed]

261. Katoh, A.; Kai, H.; Harada, H.; Niiyama, H.; Ikeda, H. Oral Administration of Glucosamine Improves Vascular Endothelial Function by Modulating Intracellular Redox State. *Int. Heart J.* 2017, 58, 926–932. [CrossRef] [PubMed]

262. Giblin, W.; Skinner, M.E.; Lombard, D.B. Sirtuins: Guardians of mammalian healthspan. *Trends Genet.* 2014, 30, 271–286. [CrossRef] [PubMed]
263. Han, C.; Gu, Y.; Shan, H.; Mi, W.; Sun, J.; Shi, M.; Zhang, X.; Lu, X.; Han, F.; Gong, G.; et al. O-GlcNAcylation of SIRT1 enhances its deacetylase activity and promotes cytoprotection under stress. Nat. Commun. 2017, 8, 1491. [CrossRef] [PubMed]

264. Jannapureddy, S.; Sharma, M.; Yepuri, G.; Schmidt, A.M.; Ramasamy, R. Aldose Reductase: An Emerging Target for Development of Interventions for Diabetic Cardiovascular Complications. Front. Endocrinol. 2021, 12, 636267. [CrossRef] [PubMed]

265. Liu, Q.; Ouyang, D. Sorbinil, an Aldose Reductase Inhibitor, in Fighting Against Diabetic Complications. Med. Chem. 2019, 15, 3–7. [CrossRef]

266. Grewal, A.S.; Thapa, K.; Kanojia, N.; Sharma, N.; Singh, S. Natural Compounds as Source of Aldose Reductase (AR) Inhibitors for the Treatment of Diabetic Complications: A Mini Review. Curr. Drug Metab. 2020, 21, 1091–1116. [CrossRef]

267. Antony, P.; Vijayan, R. Identification of Novel Aldose Reductase Inhibitors from Spices: A Molecular Docking and Simulation Study. PloS ONE 2015, 10, e0138186. [CrossRef]

268. Balestri, F.; Sorce, C.; Moschini, R.; Cappiello, M.; Misuri, L.; Del Corso, A.; Mura, U. Edible vegetables as a source of aldose reductase differential inhibitors. Chem. Interact. 2017, 276, 155–159. [CrossRef]

269. Chan, A.W.; Ho, Y.S.; Chung, S.K.; Chung, S.S. Synergistic effect of osmotic and oxidative stress in slow-developing cataract formation. Exp. Eye Res. 2008, 87, 454–461. [CrossRef]

270. Tilton, R.G.; Chang, K.; Nyengaard, J.R.; Van den Enden, M.; Ido, Y.; Williamson, J.R. Inhibition of sorbitol dehydrogenase. Effects on vascular and neural dysfunction in streptozocin-induced diabetic rats. Diabetes 1995, 44, 234–242. [CrossRef]

271. Eisenberg, T.; Abdellatif, M.; Schroeder, S.; Primessnig, U.; Stekovic, S.; Pendl, T.; Harger, A.; Schipke, J.; Zimmermann, A.; Schmidt, A.; et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat. Med. 2016, 22, 1428–1438. [CrossRef] [PubMed]

272. Kiechl, S.; Pechlaner, R.; Willeit, P.; Notdurfert, M.; Paulweber, P.; Ruckensuhl, C.; Iglseder, B.; Weger, S.; et al. Higher spermidine intake is linked to lower mortality: A prospective population-based study. Am. J. Clin. Nutr. 2018, 108, 371–380. [CrossRef] [PubMed]

273. Schroeder, S.; Hofer, S.J.; Zimmermann, A.; Pechlaner, R.; Dammbrueck, C.; Pendl, T.; Marcello, G.M.; Bogatschnigg, V.; Bergmann, M.; Sigrist, S.J. Dietary spermidine improves cognitive function. Cell Rep. 2021, 35, 108985. [CrossRef] [PubMed]

274. Schwarz, C.; Benson, G.S.; Horn, N.; Wurdack, K.; Grittnert, U.; Schilling, R.; Marschenz, S.; Kobe, T.; Hofer, S.J.; Magnes, C. Effects of Spermidine Supplementation on Cognition and Biomarkers in Older Adults With Subjective Cognitive Decline: A Randomized Clinical Trial. JAMA Netw. Open 2022, 5, e2213793. [CrossRef] [PubMed]

275. Messerer, J.; Wrede, C.; Shipke, J.; Brandenberger, C.; Abdellatif, M.; Eisenberg, T.; Madeo, F.; Sedej, S.; Muhlfield, C. Spermidine supplementation influences mitochondrial number and morphology in the heart of aged mice. J. Anat. 2021. [CrossRef] [PubMed]

276. Alsaleh, G.; Panse, I.; Swadling, L.; Zhang, H.; Richter, F.; Meyer, A.; Lord, J.; Barnes, E.; Klenerman, P.; Green, C.; et al. Autophagy in T cells from aged donors is maintained by spermidine, and correlates with function and vaccine responses. eLife 2020, 9, e57950. [CrossRef] [PubMed]

277. McCarty, M.F. Up-regulation of PPARgamma coactivator-1alpha as a strategy for preventing and reversing insulin resistance and obesity. Med. Hypotheses 2005, 64, 399–407. [CrossRef]

278. Heilbronn, L.K.; Gan, S.K.; Turner, N.; Campbell, L.V.; Chisholm, D.J. Markers of Mitochondrial Biogenesis and Metabolism Are Lower in Overweight and Obese Insulin-Resistant Subjects. J. Clin. Endocrinol. Metab. 2007, 92, 1467–1473. [CrossRef]

279. Ragheb, R.; Shanab, G.M.; Medhat, A.M.; Seoudi, D.M.; Adeli, K.; Fantus, I. Free fatty acid-induced muscle insulin resistance and glucose uptake dysfunction: Evidence for PKC activation and oxidative stress-activated signaling pathways. Biochem. Biophys. Res. Commun. 2009, 389, 211–216. [CrossRef] [PubMed]

280. Eckardt, K.; Taube, A.; Eckel, J. Obesity-associated insulin resistance in skeletal muscle: Role of lipid accumulation and physical inactivity. Rev. Endocr. Metab. Disord. 2011, 12, 163–172. [CrossRef]

281. Jani, S.; Da, E.D.; Hadday, I.; Bikopoulos, G.; Mohasses, A.; de Pinho, R.A.; Ceddia, R.B. Distinct mechanisms involving diacylglycerol, ceramides, and inflammation underlie insulin resistance in oxidative and glycolytic muscles from high fat-fed rats. J. Clin. Endocrinol. Metab. 2007, 92, 12450–12457. [CrossRef] [PubMed]

282. Gilbert, M. Role of skeletal muscle lipids in the pathogenesis of insulin resistance of obesity and type 2 diabetes. J. Diabetes Sci. Pract. 2012, 6, 142–153. [CrossRef]

283. Fox, T.E.; Houck, K.L.; O’Neill, S.M.; Nagarajan, M.; Stover, T.C.; Pomianowski, P.T.; Unal, O.; Yun, J.K.; Naides, S.J.; Kester, M. Role of skeletal muscle lipids in the pathogenesis of insulin resistance of obesity and type 2 diabetes. J. Biol. Chem. 2007, 282, 12450–12457. [CrossRef] [PubMed]

284. Teruel, T.; Hernandez, R.; Lorenzo, M. Ceramide Mediates Insulin Resistance by Tumor Necrosis Factor-a in Brown Adipocytes by Maintaining Akt in an Inactive Dephosphorylated State. Diabetes 2001, 50, 2563–2571. [CrossRef] [PubMed]

285. Chavez, J.A.; Summers, S.A. A Ceramide-Centric View of Insulin Resistance. Cell Metab. 2012, 15, 585–594. [CrossRef]

286. Sergi, D.; Naumovski, N.N.; Heilbronn, L.H.K.; Abeywardena, M.; O’Callaghan, N.; Lionetti, L.; Luscombe-Marsh, N.L.-M. Mitochondrial (Dys)function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. Front. Physiol. 2019, 10, 532. [CrossRef]

287. Russell, A.P. PGC-1α and Exercise: Important Partners in Combating Insulin Resistance. Curr. Diabetes Rev. 2005, 1, 175–181. [CrossRef]
Radice, R.P.; Limongi, A.R.; Viviani, E.; Padula, M.C.; Martelli, G.; Bermano, G. Effects of astaxanthin in animal models of obesity-associated diseases: A systematic review and meta-analysis. Free Radic. Biol. Med. 2021, 171, 156–168. [CrossRef]

Yoshida, H.; Yanai, H.; Ito, K.; Tomono, Y.; Koikeda, T.; Tsukahara, H.; Tada, N. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis 2010, 209, 520–523. [CrossRef]

Hussein, G.; Nakagawa, T.; Goto, H.; Shimada, Y.; Matsumoto, K.; Sankawa, U.; Watanabe, H. Astaxanthin ameliorates features of metabolic syndrome in SHR/Ndmc-rp. Life Sci. 2007, 80, 522–529. [CrossRef]

Urakaze, M.; Kobashi, C.; Satou, Y.; Shigeta, K.; Toshima, M.; Takagi, M.; Takahashi, J.; Nishida, H. The Beneficial Effects of Astaxanthin on Glucose Metabolism and Modified Low-Density Lipoprotein in Healthy Volunteers and Subjects with Prediabetes. Nutrients 2021, 13, 4381. [CrossRef] [PubMed]

Landon, R.; Gueguen, V.; Petite, H.; Letourneur, D.; Pavon-Djavid, G.; Anagnostou, F. Impact of Astaxanthin on Diabetes Pathogenesis and Chronic Complications. Mar. Drugs 2020, 18, 357. [CrossRef] [PubMed]

Mccarty, M.F. Practical pros for boosting hepatic production of the “pro-longevity” hormone FGF21. Horm. Mol. Biol. Clin. Investig. 2015, 30, 14348. [CrossRef] [PubMed]

Wu, L.; Mo, W.; Feng, J.; Li, J.; Yu, Q.; Li, S.; Zhang, J.; Chen, K.; Ji, J.; Dai, W.; et al. Astaxanthin attenuates hepatic damage and mitochondrial dysfunction in non-alcoholic fatty liver disease by up-regulating the FGF21/PGC-1α pathway. Br. J. Pharmacol. 2020, 177, 3760–3777. [CrossRef] [PubMed]

Lin, Z.; Tian, H.; Lam, K.S.; Lin, S.; Hoo, R.C.; Konishi, M.; Itoh, N.; Wang, Y.; Bornstein, S.R.; Xu, A.; et al. Adiponectin Mediates the Metabolic Effects of FGF21 on Glucose Homeostasis and Insulin Sensitivity in Mice. Cell Metab. 2013, 17, 779–789. [CrossRef] [PubMed]

Holland, W.L.; Adams, A.C.; Brozinick, J.T.; Bui, H.H.; Miyachi, Y.; Kusminski, C.M.; Bauer, S.M.; Wadden, E.; Cheng, C.C.; et al. An FGF21-Adiponectin-Ceramide Axis Controls Energy Expenditure and Insulin Action in Mice. Cell Metab. 2013, 17, 790–797. [CrossRef] [PubMed]

Holland, W.L.; Miller, R.A.; Wang, Z.V.; Sun, K.; Barth, B.M.; Bui, H.H.; Davis, K.E.; Bikman, B.T.; Halberg, N.; Rutkowski, J.M.; et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat. Med. 2011, 17, 55–63. [CrossRef] [PubMed]

Han, C.Y. Roles of Reactive Oxygen Species on Insulin Resistance in Adipose Tissue. Diabetes Metab. J. 2016, 40, 272–279. [CrossRef]

Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact on metabolic syndrome. J. Clin. Investig. 2004, 114, 1752–1761. [CrossRef]

Prokudina, E.S.; Maslov, L.N.; Ivanov, V.V.; Belsalova, I.D.; Pismennyi, D.S.; Voronkov, N.S. The Role of Reactive Oxygen Species in the Pathogenesis of Adipocyte Dysfunction in Metabolic Syndrome. Prospect. Pharmacol. Correction. Vestn. Ross. Akad. Meditsinskikh Nauk. 2017, 72, 11–16. [CrossRef]

Lin, L.; Pang, W.; Chen, K.; Wang, F.; Gengler, J.; Sun, Y.; Tong, Q. Adipocyte expression of PU.1 transcription factor causes insulin resistance through upregulation of inflammatory cytokine gene expression and ROS production. Am. J. Physiol. Metab. 2012, 302, E1550–E1559. [CrossRef] [PubMed]

Kanda, H.; Tateya, S.; Tamori, Y.; Kotani, K.; Hiasa, K.-I.; Kitazawa, R.; Kitazawa, S.; Miyachi, H.; Maeda, S.; Egashira, K.; et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J. Clin. Investig. 2006, 116, 1494–1505. [CrossRef] [PubMed]

Gao, Z.; Zhang, X.; Zuberi, A.; Hwang, D.; Quon, M.; Lefevre, M.; Ye, J. Inhibition of Insulin Sensitivity by Free Fatty Acids Requires Activation of Multiple Serine Kinases in 3T3-L1 Adipocytes. Mol. Endocrinol. 2004, 18, 2024–2034. [CrossRef] [PubMed]

Ghanbari, F.; Amerizadeh, A.; Behshood, P.; Moradi, S.; Asgary, S. Effect of Microalgae Arthrospira on Biomarkers of Glycemic Control and Glucose Metabolism: A Systematic Review and Meta-analysis. Curr. Probl. Cardiol. 2021, 47, 100942. [CrossRef] [PubMed]

Hamedifard, Z.; Milajerd, A.; Reiner, Z.; Taghizadeh, M.; Kolahdooz, F.; Asemi, Z. The effects of spirulina on glycemic control and serum lipoproteins in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. Phytotherapy Res. 2019, 33, 2609–2621. [CrossRef] [PubMed]

Porasuphatana, S.; Suddee, S.; Nartnampong, A.; Konsil, J.; Harnwong, B.; Santaweesuk, A. Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alpha-lipoic acid: A randomized double-blind placebo-controlled study. Asia Pac. J. Clin. Nutr. 2012, 21, 12–21. [CrossRef]

Jafarnejad, S.; Mahboobi, S.; McFarland, L.V.; Taghizadeh, M.; Rahimi, F. Meta-Analysis: Effects of Zinc Supplementation Alone or with Multi-Nutrients, on Glucose Control and Lipid Levels in Patients with Type 2 Diabetes. Prev. Nutr. Food Sci. 2019, 24, 8–23. [CrossRef] [PubMed]

McCarty, M.F. cGMP may have trophic effects on beta cell function comparable to those of cAMP, implying a role for high-dose biotin in prevention/treatment of diabetes. Med. Hypotheses 2006, 66, 323–328. [CrossRef] [PubMed]

McCarty, M.F. In type 1 diabetics, high-dose biotin may compensate for low hepatic insulin exposure, promoting a more normal expression of glycolytic and gluconeogenic enzymes and thereby aiding glycemic control. Med Hypotheses 2016, 95, 45–48. [CrossRef]
310. Zhang, H.; Osada, K.; Sone, H.; Furukawa, Y. Biotin administration improves the impaired glucose tolerance of streptozotocin-induced diabetic Wistar rats. *J. Nutr. Sci. Vitaminol.* **1997**, *43*, 271–280. [CrossRef]

311. Sugita, Y.; Shirakawa, H.; Sugimoto, R.; Furukawa, Y.; Komai, M. Effect of Biotin Treatment on Hepatic Gene Expression in Streptozotocin-Induced Diabetic Rats. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 1290–1298. [CrossRef] [PubMed]

312. Matschinsky, F.M. Glucokinase as glucose sensor and metabolic signal generator in pancreatic beta-cells and hepatocytes. *Diabetes* **1990**, *39*, 647–652. [CrossRef] [PubMed]

313. Matschinsky, F.M.; Wilson, D.F. The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years after Demonstrating the Presence of the Enzyme in Islets of Langerhans. *Front. Physiol.* **2019**, *10*, 148. [CrossRef]

314. Zoungas, S.; Chalmers, J.; Neal, B.; Billot, L.; Li, Q.; Hirakawa, Y.; Arima, H.; Monaghan, H.; Joshi, R.; Colagiuri, S.; et al. Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes. *N. Engl. J. Med.* **2014**, *371*, 1392–1406. [CrossRef]

315. Jazayeri, M.; Eftekhari-Yazdi, P.; Gilani, M.A.S.; Sharafi, M.; Shahverdi, A. Epigenetic modifications at DMRs of imprinting genes in sperm of type 2 diabetic men. *Zygote* **2022**, 1–10, online ahead of print. [CrossRef] [PubMed]