Nutraceutical activation of Sirt1: a review

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ABSTRACT
The deacetylase sirtuin 1 (Sirt1), activated by calorie restriction and fasting, exerts several complementary effects on cellular function that are favourable to healthspan; it is often thought of as an ‘anti-aging’ enzyme. Practical measures which might boost Sirt1 activity are therefore of considerable interest. A number of nutraceuticals have potential in this regard. Nutraceuticals reported to enhance Sirt1 synthesis or protein expression include ferulic acid, tetrahydrocurcumin, urolithin A, melatonin, astaxanthin, carnosic acid and neochlorogenic acid. The half-life of Sirt1 protein can be enhanced with the natural nicotinamide catabolite N1-methylnicotinamide. The availability of Sirt1’s obligate substrate NAD+ can be increased in several ways: nicotinamide riboside and nicotinamide mononucleotide can function as substrates for NAD+ synthesis; activators of AMP-activated kinase—such as berberine—can increase expression of nicotinamide phosphoribosyltransferase, which is rate limiting for NAD+ synthesis; and nutraceutical quinones such as thymoquinone and pyrroloquinoline quinone can boost NAD+ by promoting oxidation of NADH. Induced ketosis—as via ingestion of medium-chain triglycerides—can increase NAD+ in the brain by lessening the reduction of NAD+ mediated by glycolysis. Post-translational modifications of Sirt1 by O-GlcNAcylation or sulfonation can increase its activity, suggesting that administration of glucosamine or of agents promoting hydrogen sulfide synthesis may aid Sirt1 activity. Although resveratrol has poor pharmacokinetics, it is therefore of importance to devise clinical strategies—preferably involving safe nutraceuticals appropriate for use in primary prevention—for enhancing Sirt1 activity. A growing literature suggests that several phytochemicals, natural metabolites and approved drugs have potential in this regard. The following brief review cites the pertinent literature on these agents and attempts to define their likely mechanisms of action. An understanding of these mechanisms may aid the development of complex nutraceutical regimens that can support Sirt1 activity in complementary ways.

HEALTH PROMOTION VIA SIRTUIN 1 ACTIVATION
The type III deacetylase sirtuin 1 (Sirt1) has aroused considerable interest, as its activity has been linked to enhanced healthspan. 1–3 Sirt1 is particularly intriguing for its wide-ranging modulatory activities—enhancing autophagy, mitophagy, mitochondrial biogenesis (MB), DNA repair, antioxidant enzyme expression, osteoblast generation and endothelial nitric oxide synthase expression and activity, while inhibiting apoptosis, senescence, de novo lipogenesis, atherogenesis and—via suppression of canonical NF-κB activity—inflammation. 4–9 In aggregate, these effects may account for the favourable impact of Sirt1 on healthspan.

With respect to cardiovascular health, Sirt1 opposes atherogenesis both by favourable effects on endothelial function—downregulating inflammation via NF-κB suppression and promotion of endothelial nitric oxide synthase activity—and by opposing foam cell formation under decreasing low-density lipoprotein (LDL) uptake while boosting reverse cholesterol transport. 6,7,9–12 Moreover, measures which increase Sirt1 activity have shown benefit in rodent models of ventricular hypertrophy and heart failure. 13–20

It is therefore of importance to devise clinical strategies—preferably involving safe nutraceuticals appropriate for use in primary prevention—for enhancing Sirt1 activity. A growing literature suggests that several phytochemicals, natural metabolites and approved drugs have potential in this regard. The following brief review cites the pertinent literature on these agents and attempts to define their likely mechanisms of action. An understanding of these mechanisms may aid the development of complex nutraceutical regimens that can support Sirt1 activity in complementary ways.

NUTRACEUTICALS FOR INCREASING SIRT1 SYNTHESIS OR HALF-LIFE
Certain nutraceuticals have the potential to increase protein expression of Sirt1 by promoting its synthesis. These include ferulic acid, tetrahydrocurcumin, urolithin A, melatonin, carnosic acid, neochlorogenic acid and astaxanthin. Ferulic acid, tetrahydrocurcumin and urolithin A may be the...
absorbed metabolites mainly responsible for the health benefits of orally administered anthocyanins, curcumin and pomegranate ellagitannins, respectively. Sodium ferulate has long been used in Chinese cardiovascular medicine. Carnosic acid is a prominent constituent of rosemary extract, and neochlorogenic acid is found in mulberry leaves. Ferulic acid and tetrahydrocurcumin can boost Sirt1 expression at both the mRNA and protein level; how they accomplish this remains obscure. Melatonin likewise can enhance mRNA and protein expression of Sirt1; its activity in this regard has been traced to activation of the clock transcription factor Bmal1, which binds to the promoter of the Sirt1 gene and drives its transcription. Bmal1 activation, in turn, may reflect melatonin’s interaction with its M1 membrane receptor. Urolithin A, carnosic acid and neochlorogenic acid appear to exert their upregulatory impacts on Sirt1 synthesis by suppressing expression of miR-34a, which binds to the 3’UTR of Sirt1 mRNA and promotes its degradation. Agents of this type may be of particular interest in cardiovascular medicine, inasmuch as upregulation of miR-34a, in addition to its suppressive effect on Sirt1 expression, works in additional ways to compromise vascular health. Astaxanthin is reported to increase protein expression of Sirt1 in a range of rodent tissues; the mechanism responsible remains unclear.

Of ancillary interest is evidence that treadmill exercise training in rodents induces Sirt1 expression at the mRNA and protein level in brain and various other tissues. In the brain, the effect is mediated at least in part by lactate; the molecular biology underlying this remains obscure. It is reasonable to suspect that Sirt1 induction is a key mediator of the broad-ranging neuroprotective effects of aerobic exercise training—effects documented both in rodents and via epidemiology. Among other benefits, Sirt1 promotes expression of brain-derived neurotrophic factor.

Sirt1 protein expression may also be increased by prolonging its half-life. The stress-inducible MAP kinase c-Jun N-terminal kinase 1 (JNK1) can confer a phosphorylation on Sirt1 (Ser-46) that promotes its ubiquitination and subsequent proteasomal degradation. N1-methyl-nicotinamide (MNA) is a natural catabolite of nicotinamide known to have anti-inflammatory properties. MNA has been shown to boost Sirt1 protein expression by slowing proteasomal degradation of Sirt1, and this may be traceable to its ability to inhibit phosphorylation of Ser-46. 

**NUTRACEUTICAL ENHANCEMENT OF SIRT1’S SUBSTRATE NAD+**

Sirt1 has an obligate requirement for NAD+ as a substrate. Hence, measures which either increase NAD+ synthesis or increase the NAD+/NADH ratio, can boost Sirt1 activity. With respect to the latter possibility, fasting or calorie restriction can activate Sirt1 by reducing the availability of oxidizable substrate that drives metabolic reduction of NAD+. Quinones susceptible to reversible reduction, notably thymoquinone (from the oil of black cumin seed—*Nigella sativa*) and pyrroloquinoline quinone (PQQ—a vitamin-like compound found in many foods) can boost Sirt1 activity by oxidising NADH. The reduction of thymoquinone is catalysed by the Nrf2-inducible enzyme (NQO1), and PQQ’s high-affinity binding to lactate dehydrogenase promotes PQQ’s reduction by NADH.

The brain readily employs ketones—chiefly β-hydroxybutyrate (BHB)—as an alternative substrate to glucose during fasting. Oxidation of BHB in the brain is associated with a compensatory reduction in glucose uptake. When a molecule of glucose passes down the glycolytic pathway to generate two molecules of acetyl-CoA, two molecules of NAD+ are reduced to NADH in the cytoplasm; when a molecule of BHB is converted to two acetyl-CoAs, no reduction of cytoplasmic NAD+ is induced. For this reason, the brain NAD+/NADH ratio is higher during ketosis than during normal glucose-based metabolism. This effect has been directly demonstrated in the brain of healthy volunteers following administration of medium-chain triglycerides (MCTs). This effect can be expected to be associated with increased brain Sirt1 activity, and it has been suggested that this phenomenon—and perhaps other consequences of an elevated NAD+/NADH ratio—may help to explain the neuroprotective properties of ketogenic diets. Moreover, there is recent evidence that exposure of neurons to BHB in vitro increases their expression of Sirt1 at both the mRNA and protein level.

Evidently, fasting for the purpose of inducing ketogenesis is only a temporary expedient. Diets very high in fats and low in both carbohydrates and protein can be used to achieve ketosis while maintaining an adequate calorie intake, but such diets are too monotonous for most people to practise indefinitely. The most practical approach to boosting plasma BHB levels is through administration of MCTs; the short-chain fatty acids which these supply are not stored in triglycerides, but rather are either oxidised quickly or converted to ketone bodies in the liver. Hence, ingestion of MCTs can be employed to enhance brain Sirt1 activity.

De novo synthesis of NAD+ can be enhanced by precursors such as nicotinamide riboside or nicotinamide mononucleoside, each of which are Sirt1 activators. AMP-activated protein kinase (AMPK) boosts NAD+ synthesis via induction of the enzyme nicotinamide ribosylphosphotransferase (NAMPT), rate limiting for conversion of nicotinamide to NAD+. Since nicotinamide is a product of Sirt1 activity that inhibits Sirt1, NAMPT also promotes Sirt1 activity by alleviating this inhibition. While the therapeutic utility of the drug metformin in diabetes reflects its ability to activate AMPK, this activity is shared by the phytochemical berberine, a component of many Chinese medicinal herbs, that has long been used for management of type II diabetes in China. Both metformin and berberine boost Sirt1 activity.

CD38 functions to degrade NAD+ to generate two molecules which can regulate intracellular calcium, ADP-ribose and cyclic ADP-ribose; its expression is most

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NAD+. Although intraperitoneal administration of a ample dose (100 mg/kg) of apigenin has been reported to alleviate metabolic syndrome in obese mice, presumably via CD38 inhibition, it seems unlikely that this effect could be replicated with oral administration of apigenin or quercetin, for which absorption is inefficient and conjugation rapid.

NUTRACEUTICALS CAN ACTIVATE SIRT1 ALLOSTERICALLY OR VIA POST-TRANSLATIONAL MODIFICATIONS

Certain post-translational modifications of Sirt1 can enhance its activity. O-GlcNAcylation of Sirt1 at Ser-549 boosts its enzymatic activity—an effect which possibly contributes to the anti-inflammatory activity of supplemental glucosamine. It is possible that the favourable effects of glucosamine supplementation on human mortality and lifespan of mice reflect, to some extent, Sirt1 activation. Sirt1 activity is also enhanced by covalent interaction with hydrogen sulfide—suggesting a Sirt1 activating role for nutraceuticals or drugs which promote hydrogen sulfide generation. N-acetylcysteine can serve as a substrate for H₂S generation, whereas turmeric has been shown to induce two key enzymes for H₂S synthesis, cystathionine β-synthase and cystathionine γ-lyase, in vascular tissues.

Sirt1 can also be allosterically activated by certain agents. The lignin phytochemical resveratrol has this potential, and studies with resveratrol in cell cultures and rodents drew early attention to the health-protective potential of Sirt1 activation. Unfortunately, the clinical utility of resveratrol is impaired by poor pharmacokinetics—inefficient absorption and rapid conjugation in the intestinal mucosa and liver. Presumably for this reason, clinical evaluations with supplemental resveratrol have produced inconsistent results. Nonetheless, a meta-analysis of clinical studies with resveratrol in type 2 diabetics has concluded that it has useful effects on systolic blood pressure, haemoglobin A1c and creatinine. Drugs with better pharmacokinetics which can allosterically activate Sirt1—known as sirtuin-activating compounds—may have greater potential if and when they are approved.

COUNTERING OXIDATIVE STRESS MAY SUPPORT SIRT1 ACTIVITY

On the other hand, oxidant stress can oppose Sirt1 activity via multiple mechanisms. Reactive oxidant species (ROS) can increase miR-34a expression via upregulation of NF-κB and p53 activities. In that regard, a report that treatment with the drug salaze can elevate Sirt1 levels in endothelial cells and monocytes may reflect the ability of salicylic acid to suppress activation of NF-κB via 1kB kinase-β. (Salaze is a dimer of the anti-inflammatory phytochemical salicylic acid; esterase activity in the intestinal tract cleaves it to release free salicylic acid. In multigram daily doses, it exerts anti-inflammatory activity useful in rheumatoid arthritis. Unlike its derivative acetylsalicylic acid, it only mildly and reversibly inhibits cyclo-oxygenase activity, and hence is comparatively safe; however, its clinical utility is compromised by the fact that it induces fully reversible ototoxicity in a fairly high proportion of patients.)

ROS can decrease NAD+ levels via DNA damage and consequent PARP activation. And ROS can also promote Sirt1 proteolysis by boosting JNK1 activity, as noted, the latter can confer a phosphorylation on Sirt1 that enables its ubiquitination and subsequent proteasomal degradation (an effect opposed by MNA). Hence, effective antioxidant measures may help support Sirt1 activity in the context of oxidative stress. Moreover, antioxidant supplementation could be expected to complement the anti-inflammatory activity of Sirt1, as reversible oxidation of sulfhydryl groups by hydrogen peroxide works in various ways to upregulate activation of NF-κB and MAP kinases, mediators of the synthesis and activity of many pro-inflammatory cytokines.

SUMMING UP AND FUTURE RESEARCH PROSPECTS

Figure 1 depicts the various mechanisms whereby the nutraceuticals discussed above are believed to promote Sirt1 activity. It is almost surely the case that future research will identify further phytochemicals or metabolites with potential for Sirt1 activation. It is reasonable to expect that additional nutrient and drug intervention will be identified that can enhance the activity of Sirt1 and thereby support a health-protective effect.

**Figure 1** Mechanisms that regulate Sirt1 activity, as modulated by nutraceuticals. Also depicted: exercise-induced lactic acid boosts Sirt1 expression in the brain. AMPK, AMP-activated protein kinase; ASX, astaxanthin; BHB, β-hydroxybutyrate; CA, carnosic acid; DAPA, dapaflogazin; GCA, glucosamine; MCTs, medium-chain triglycerides; MLT, melatonin; NAC, N-acetylcysteine; NAMPT, nicotinamide ribosylphosphotransferase; NCA, neochlorogenic acid; NMA, N1-methylnicotinamide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; PQQ, pyroloquinoline quinone; ROS, reactive oxidant species; RSV, resveratrol; THC, tetrahydrocurcumin; THQ, thymoquinone; URO, urolithin A.
expect that nutraceutical combinations which promote Sirt1 activity by multiple complementary mechanisms may have considerable potential for health promotion. Various combinations of nutraceuticals, thought to boost Sirt1 activity in ways that are potentially complementary or synergistic, could be evaluated in preclinical research to determine which might be most appropriate for clinical study. Although support of Sirt1 activity is likely to benefit cardiovascular health in a great many ways, studying Sirt1-activating regimens in the context of heart failure—the leading overall cause of death—may be of particular interest; Sirt1 supports mitophagy and MB—known to be protective but defective in heart failure—while suppressing inflammation. Curiously, the SGLT2 inhibitors used to treat diabetes—by diminishing renal retention of glucose and hence moderating glycaemia—have been found to be therapeutically useful in heart and renal failure, even in patients who are normoglycaemic. This effect has been traced to their ability to boost Sirt1 and AMPK activity, thereby promoting autophagy, mitophagy and MB. While blunting postprandial rises in glucose may boost Sirt1 and AMPK activity via a reduction in oxidisable substrate—rather like caloric restriction—there is evidence that these drugs can exert this effect on cells in vitro, including in heart tissue, which does not express SGLT2. The molecular biology underlying this latter effect remains unclear. It is reasonable to suspect that the nutraceutical strategies outlined above could complement the benefits of SGLT2 inhibitors for non-diabetic health disorders. These drugs tend to be well tolerated aside from a moderate increase in risk of bladder and genital infections reflecting the increased glucose content of urine.

As noted, promotion of autophagy and of mitophagy/MB is a key mechanism whereby effective Sirt1 activity can maintain or restore health. It is therefore appropriate to comment on ancillary nutraceuticals which may complement Sirt1 in aiding these processes. Two recent essays have addressed this issue. Stimulation of AMPK, in addition to its role in boosting Sirt1 activity, can promote these processes in independent ways—pointing to the potential value of berberine in this regard. The dietary polyamine spermidine—recently available as a nutraceutical—can aid autophagy, mitophagy and MB by promoting efficient translation of the mRNA coding for transcription factor EB. In at least some tissues, nitric oxide aids MB by boosting PGC-1α expression and half-life via cGMP-PKCp38 MAP kinase signalling; recoupling endothelial nitric oxide synthase with citrulline, or directly stimulating soluble guanylate cyclase with high-dose biotin, represents nutraceutical strategies for achieving these effects. The xanthophyll carotenoid astaxanthin can aid MB by acting as an agonist for the PPAR-α transcription factor, and phase 2 activating nutraceuticals, such as lipoic acid or sulforaphane, can analogously aid MB by boosting expression of the transcription factor NRF-1, another key mediator of MB. Hence, administration of berberine, spermidine, citrulline, biotin, astaxanthin, lipoic acid and/or sulforaphane may complement the utility of Sirt1 activators for aiding autophagy, mitophagy and MB.

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