Review

Nutraceutical and Dietary Measures with Potential for Preventing/Controlling Non-Alcoholic Fatty Liver Disease and Its Complications

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Nutraceutical and Dietary Measures with Potential for Preventing/Controlling Non-Alcoholic Fatty Liver Disease and Its Complications

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Abstract: Non-alcoholic fatty liver disease (NAFLD), a frequent complication of metabolic syndrome and visceral obesity, is characterized by marked accumulation of lipids in hepatocytes, accompanied by oxidant stress. In a substantial minority of cases, this progresses to steatohepatitis, which in turn can lead to life-threatening hepatic fibrosis and/or hepatocarcinogenesis. This essay analyzes the molecular biology underlying fat accumulation and oxidant stress in NAFLD, and identifies targets that can be addressed by nutraceutical or dietary measures. Nutraceuticals with potential for prevention or control of NAFLD – as suggested on theoretical grounds, and borne out by experience in rodent studies and/or clinical trials - include ferulic acid, melatonin, methylnicotinamide, tetrahydrocurcumin, nicotinamide riboside, carnosic acid, urolithin A, quercetin, high-dose biotin, citrulline, astaxanthin, long-chain omega-3 fatty acids, berberine, lipoic acid, silibinin, N-acetylcysteine, taurine, capsaicin, spermidine, spirulina, and carnitine. Some of these agents can also address the NLRP3 inflammasome activation and transforming growth factor-β signaling that play a role in driving the transition to steatohepatitis and fibrosis. In addition, soy isoflavones, via estrogen receptor-beta agonism, have anti-fibrotic potential, and supplemental glycine may blunt the contribution of Kupffer cells to the progression of NAFLD. Whole-food plant-based diets of modest protein content, owing to their impact on hormones such as fibroblast growth factor 21 and adiponectin, as well as on the obesity and metabolic syndrome underlying NAFLD, may also be protective in this syndrome. There is considerable potential for complex medical foods or nutraceutical supplementation regimens of rational design to aid prevention and control of NAFLD.

Keywords: non-alcoholic fatty liver disease; nutraceuticals; Sirt1; AMPK; Nrf2; cAMP; cGMP; fibroblast growth factor 21; adiponectin; vegan diet

1. Pathogenesis of Non-Alcoholic Fatty Liver Disease and Its Complication – an Overview

Non-alcoholic fatty liver disease (NAFLD) is a common complication of metabolic syndrome and visceral obesity; hence, its prevalence is rising in conjunction with the increasing prevalence of these disorders. It is characterized by markedly elevated hepatocyte fat content accompanied by increased oxidative stress.[1] Since the efficiency of the mechanisms whereby triglycerides and cholesterol are exported from the liver in very-low-density lipoproteins does not appear to be compromised in NAFLD – hepatic levels of microsomal triglyceride transport protein are elevated in this disorder2 - the accu-mulation of lipids reflects increased free fatty acid (FFA) uptake from plasma (largely attributable to physiologically inappropriate excess release of FFAs from hypertrophied, insulin-resistance visceral adipocytes), increased de novo lipogenesis (DNL), and insuf-ficient

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capacity of hepatocyte mitochondria to oxidize FFAs. High fructose ingestion exacerbates this situation, as most dietary fructose is preferentially oxidized in the liver, where it can provide the backbone for triglycerides (glycerol-3-phosphate) and substrate for DNL.3 Moreover, hepatic fructose metabolites also promote DNL via activation of carbohydrate response element-binding protein (ChREBP), a transcription factor that promotes expression of key enzymes that catalyze DNL.4 Diets and adipocytes high in saturated fats are more prone than those high in unsaturated fats to provoke NAFLD, for reasons not fully clarified; palmitate's role as a precursor of ceramide likely plays a role in this regard.5-8 Much of the hepatic oxidative stress associated with NAFLD is generated by dysfunctional mitochondria oxidizing increased amounts of fatty acids; however, in-creased NADPH oxidase activity also contributes to oxidant overload.9-11

NAFLD is worrisome, not so much because any overt symptoms it causes, but be-cause in a substantial minority of cases it can progress to non-alcoholic steatohepatitis (NASH); this inflammatory liver disorder often over the course of time leads to liver cirrhosis as well as hepatocellular cancer, which are typically fatal unless a successful liver transplant or curative cancer surgery can be performed. NASH entails inflammatory activation of liver-resident Kupffer cells, and phenoconversion of retinol-storing hepatic stellate cells to myofibroblasts that promote cirrhosis by secreting excessive levels of collagen and other components of the extracellular matrix. Activation of NLRP3-dependent inflammasomes and increased transforming-growth factor-β (TGF-β) signaling play prominent roles in this pathology.12-18

Precisely how NAFLD progresses to NASH is still a matter of considerable contro-versy; no doubt, a plethora of interacting mechanisms are involved. However, it is clear that both hepatic lipid overload and oxidative stress are mediators of this process. He-patic triglyceride overload per se does not appear to be pathogenic; rather ancillary lipids such as free fatty acids, diacylglycerol, ceramide, lysophosphatidylcholine, and free cholesterol are suspected as mediators of the transition to NASH.19-23 Absent correction of the underlying metabolic syndrome – a strategy that can be feasible in dedicated patients willing to make lasting lifestyle changes, but that usually is undermined by poor com-pliance – a straightforward strategy for controlling and reversing NAFLD requires measures for up-regulating hepatic capacity for mitochondrial oxidation of FFAs while concurrently suppressing DNL. Concurrent antioxidant measures are also appropriate, and, in particular, it is crucial to rectify impaired mitochondrial structure and function so that measures which promote an increased rate of mitochondrial FFA oxidation to address lipid overload don't concurrently amplify excessive oxidant generation. This latter goal requires up-regulating physiologically appropriate mitophagy – thereby disposing of mitochondria with defective electron transport chains (ETCs) that overproduce superoxide – coupled with increased mitochondrial biogenesis, generating mitochondria with effi-cient ETCs and effective antioxidant mechanisms.

Notable progress in molecular biology, and in the understanding of the physiological impacts of nutraceuticals, now makes it feasible to define nutraceutical measures which have credible potential for controlling and reversing NAFLD, and preventing its pro-gression to NASH and its further complications. Figures 1–3 outline in diagrammatic form some suggestions in this regard.

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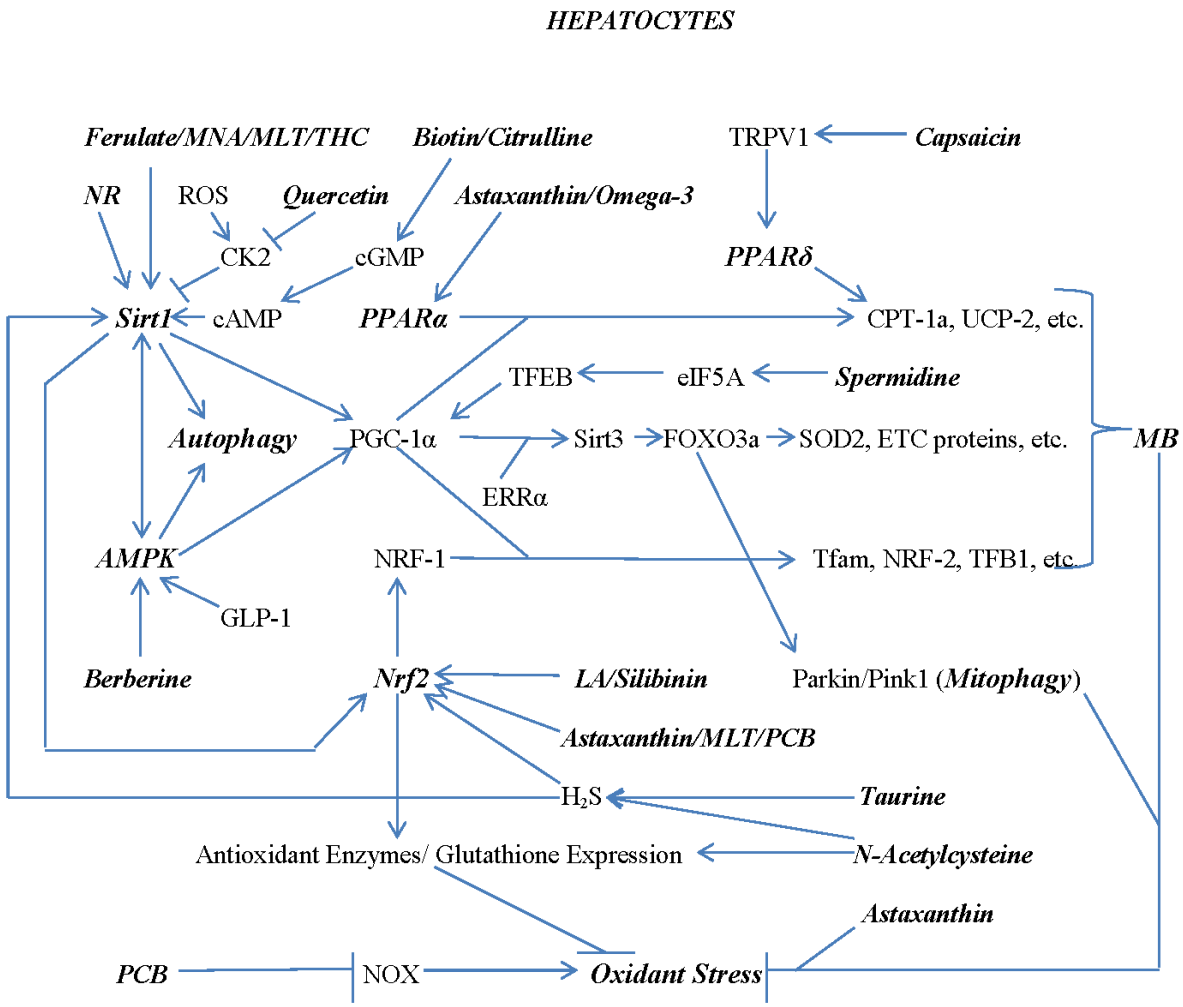

Figure 1. Roles for Sirt1, AMPK, Nrf2, PPARα and TFEB nutraceutical activators in promotion of mitochondrial biogenesis (MB), autophagy/mitophagy, and antioxidant enzyme/glutathione expression in hepatocytes. MNA = N1-methylnicotinamide. LA = Lipoic Acid. MLT = melatonin. PCB = phycocyanobilin. THC = tetrahydrocurcumin. NR = nicotinamide riboside.

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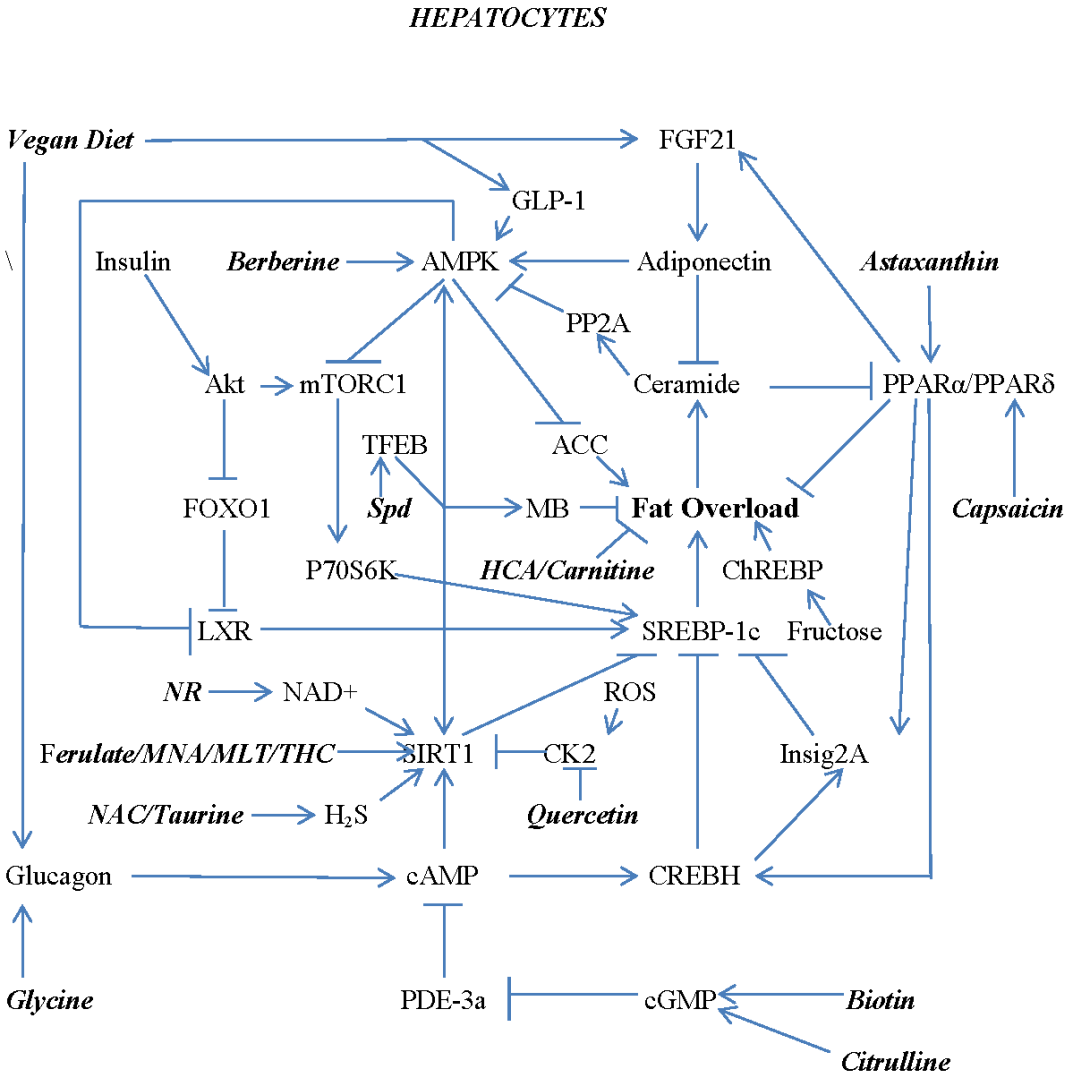

Figure 2. Nutraceutical and dietary strategies for combatting hepatic fat overload. Spd = spermidine.

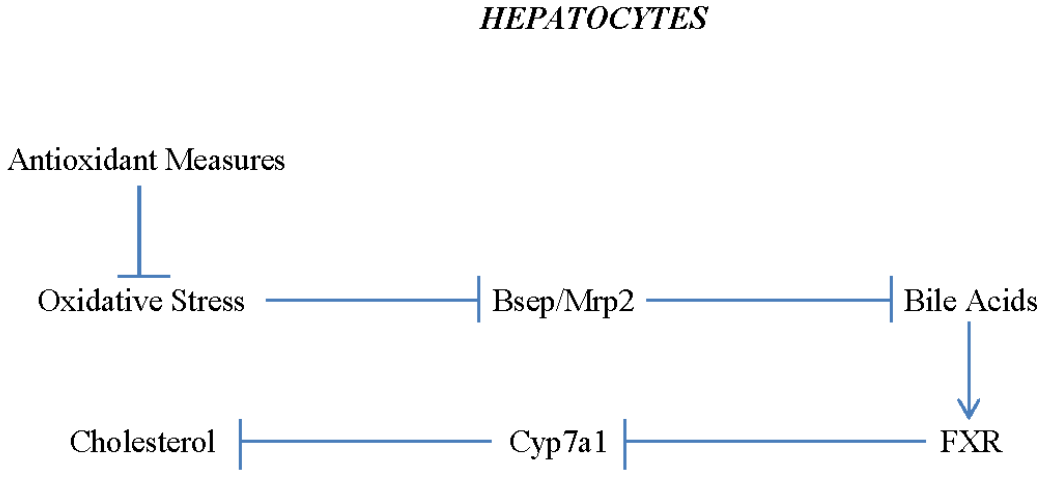

Figure 3. How control of hepatocyte oxidative stress prevents elevation of intracellular free cholesterol, a potential mediator of NASH.

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2. Nutraceutical Promotion of Mitochondrial Biogenesis, Mitophagy, and Antioxidant Expression

Concurrent up-regulation of mitochondrial biogenesis (MB), accompanied by enhanced mitophagic destruction of dysfunctional mitochondria, should take center stage in regimens for remediating NAFLD, as this should aid control of oxidative stress while concurrently optimizing capacity of oxidative disposal of FFAs, thereby decreasing hepatic fat content. Figure 1 depicts a strategy for achieving this.

The deacetylase Sirt1, AMP-activated kinase (AMPK), and transcription factor EB (TFEB) collaborate in boosting MB and mitophagy by up-regulating the expression and activity of PPARγ-coactivator-1α (PGC-1α).[24–27] Via interaction with the transcription factors PPARα, NRF-1, and ERRα, PGC-1α drives the transcription of genes coding for a wide range of proteins required for generation of mitochondria that are efficient both with respect to FFA oxidation and enzymatic disposal of harmful oxidants.[28, 29] Moreover, the ERRα/PGC-1α complex, by boosting transcription and expression of Sirt3, aids the generation of Parkin and Pink1, proteins which detect and mark for autophagic disposal dysfunctional mitochondria, as indicated by diminished inner membrane potential.[30–32] Hence, nutraceuticals which boost Sirt1 expression or activity, or which activate AMPK or TFEB, have important potential in the management of NAFLD.

MB and mitophagy can be further aided by agents which increase the expression of or act as agonists for PPARα or PPARδ, or which enhance NRF-1 expression. The Nrf2 transcription factor, which drives the expression of a number of antioxidant enzymes as well as the rate-limiting enzyme for glutathione synthesis (so-called phase 2 induction), also promotes transcription of the gene coding for NRF-1.[33] The nuclear level of Nrf2, in turn, can be boosted by a number of nutraceuticals which function, directly or indirectly, as phase 2 inducers.[34] PPARα and PPARδ each up-regulate at the transcriptional level the rate-limiting enzyme for mitochondrial fatty acid oxidation, carnitine palmitoyltransferase-1a (CPT-1a), as well as other mitochondrial enzymes required for this purpose.[35] They also enhance expression of uncoupling factor-2 (UCP-2), which, when the mitochondrial respiratory chain is glutted with electrons owing to rapid Krebs cycle activity, enables mild uncoupling so that generation of superoxide is moderated and efficiency of substrate oxidation is optimized.[36, 37]

3. Multiple Strategies for Sirt1 Activation

With respect to Sirt1 activity, ferulic acid, melatonin, and N1-methylnicotinamide (MNA) have been shown to boost its protein expression in rodent and/or cell culture experiments. Ferulic acid and melatonin also enhance its mRNA expression[38–45] – suggesting that they up-regulate it at the transcriptional level or increase the stability of its mRNA– whereas MNA slows its proteasomal degradation.[46, 47] The latter is a non-toxic natural metabolite of nicotinamide that has shown intriguing anti-inflammatory effects in rodents, and has been developed s a nutraceutical in Poland.[48] Ferulic acid is a bacterial metabolite of anthocyanins and certain other dietary phytochemicals, and is suspected to be a primary mediator of the health benefits of anthocyanins demonstrated in rodent research and suggested by epidemiological studies.[49] The neurohormone melatonin is employed as a nutraceutical, and its anti-inflammatory and antioxidant effects are mediated, at least in part, by increased transcription of the genes coding for Sirt1 and Nrf2; melatonin achieves this by enhancing the expression of the clock transcription factor Bmal1.[44, 50]

Urolithin A (the absorbed metabolic thought to mediate the protective effects of the ellagitannin-rich pomegranate juice), carnosic acid (a prominent component of the medicinal herb rosemary), and neochlorogenic acid (from mulberry leaves) have shown potential for boosting Sirt1 expression by suppressing expression of microRNA-34a (miR-34a);[51–59] the latter binds to the 3′-UTR of Sirt1 mRNA, inhibiting its transcription and decreasing its half-life.[60, 61] Moreover, miR-34a also targets the mRNA for nicotinamide phosphoribosyltransferase (NAMPT); this enzyme is rate-limiting for the conversion of nicotinamide, a product of Sirt1 activity that mediates product inhibition of this enzyme, to NAD+, Sirt1's obligate substrate.[62, 63] Hence, phytochemicals which suppress miR-34a also

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boost Sirt1 activity by increasing NAD+ levels. It would be interesting to know whether ferulic acid influences miR-34a expression, as it is structurally similar to neochlorogenic acid.

The mystery of the anti-inflammatory activity of oral curcumin – the plasma concentrations of unconjugated curcumin following oral administration are far too low to be physiologically meaningful – may have been unraveled by recent reports that tetrahydrocurcumin (THC), a much more prominent metabolite, can markedly increase Sirt1 protein expression in the heart and kidney of mice.[64, 65] These findings are likely to be pertinent to the many reports that oral curcumin is beneficial in rodent models of NAFLD and in the clinical disorder.[66, 67] Indeed, THC itself has been found to be protective in rodent NAFLD.[68, 69] The efficacy of curcumin preparations in this regard may vary considerably dependent on their relative bioavailabilities; since THC appears to more absorbable, it may be the superior clinical choice.[70]

Sirt1 activity requires NAD^+ as an obligate substrate; the fact that the NAD+/NADH ratio rises in the context of a deficit of oxidizable substrate (as with underfeeding) explains why Sirt1 activity, like AMPK, can act as a signal for cellular energy deficit. Sirt1 activity is compromised when the total NAD+/NADH pool declines, as it does when PARP becomes activated in the context of oxidant damage to DNA. Indeed, this phenomenon occurs in NAFLD, resulting in a decline in NAD+ and a consequent decrease in Sirt1 activity.[71] Hence, pharmaceutical PARP inhibition has potential in the management of this disorder. [72, 73] An alternative strategy would be to boost NAD^+ synthesis by providing an appropriate substrate. Nicotinamide riboside (NR), now available as a nutraceutical, can serve as an efficient precursor for such synthesis, as after phosphorylation it enters the pathway of de novo NAD^+ synthesis.[74] (Nicotinamide is not a good choice for supporting Sirt1 activity, as it is a product of Sirt1 activity that acts as a feedback inhibitor.) Promising results have been reported with NR in rodent models of NAFLD.[75, 76]

There is recent evidence that hepatic expression of the kinase CK2 is greatly elevated at both the mRNA and protein level in NAFLD, both in rodent models and clinically.[77] While the basis of this effect requires more clarification, oxidant stress has been shown to boost CK2 expression in lungs and alveolar macrophages of mice in a manner dependent on p38 MAP kinase activation; hence, it is reasonable to suspect that oxidant stress drives CK2 expression in NAFLD.[78] Importantly, CK2 can confer a phosphorylation on Sirt1 (S164) that promotes its exclusion from the nucleus while also modestly inhibiting its deacetylase activity.[77] Moreover, mice transfected with a mutant Sirt1 resistant to phosphorylation at this site (S164A) are protected from fatty liver induction when fed a high-fat diet. These considerations suggest a mechanism whereby, via Sirt1 inhibition, oxidative stress in NAFLD becomes self-amplifying and also promotes steatosis. Fortuitously, quercetin and a range of other flavonols can inhibit CK2 in high nanomolar concentrations – possibly of clinical relevance in the context of supplementation with high-absorption sources of quercetin.[79, 80] Notably, these specific flavonols have shown protective utility in rodent models of NAFLD.[81–89]

The enzymatic activity of Sirt1 is boosted by a phosphorylation conferred by protein kinase A (PKA); the latter of course is activated by cyclic AMP (cAMP).[90] Hepatocyte levels of cAMP can be increased indirectly by cGMP, via inhibition of phosphodiesterase-3b (PDE-3b).[91] High-dose biotin, via direct moderate stimulation of soluble guanylate cyclase, can enhance hepatocyte cGMP levels, and hence has the potential to boost PKA activity.[92, 93] Citrulline supplementation, at least when levels of asymmetric dimethylarginine are elevated, can likewise increase hepatic cGMP protein by increasing nitric oxide production from endothelial nitric oxide synthase.[94–96]

Hydrogen sulfide (H_2S) likewise has been found to enhance Sirt1 activity, apparently via covalent interaction with the protein.[97, 98] N-acetylcysteine supplementation, whereas it is well known to increase hepatic levels of the key antioxidant glutathione, also can serve as substrate for endogenous synthesis of H_2S.[99] Moreover, in vascular and brain tissues, taurine has been shown to increase H_2S synthesis by somehow boosting expression of two enzymes that generate H_2S – cystathionine β-synthase and cystathionine-γ-lyase.[100–102] Whether taurine has such an effect in hepatocytes or other liver cells has not yet been established.

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4. Activating AMPK, PPARα, and PPARδ

The nutraceutical chiefly employed for AMPK activation is berberine, a phytochemical derived from Chinese medicinal herbs that is commonly prescribed in China for treatment of type 2 diabetes and hyperlipidemias.[103–105] Its mechanism of action appears to reflect increased cellular levels of AMP, and is quite analogous to that of the drug metformin (which likewise has potential for the management of NAFLD).[106–108] Curiously, activated AMPK can boost Sirt1 activity via induction of NAMPT.[109–111] Conversely, Sirt1 activity promotes AMPK activation by deacetylating and thereby boosting the half-life and regulating the subcellular location of the kinase LKB1, which collaborates with AMP (and ADP) in the activation of Sirt1.[112, 113] So berberine indirectly boosts Sirt1 activity, and Sirt1 activators indirectly boost AMPK activity.

It should be noted that berberine can slightly impede the efficiency of mitochondrial fatty acid oxidation, as, like metformin, it raises cellular AMP levels by partially inhibiting complex I of the mitochondrial electron transport chain.[107, 108, 114] Fortunately, this inhibition occurs at a proximal level so that mitochondrial superoxide production is decreased.[115] And, as we shall see, AMPK activation has an important inhibitory effect on de novo lipogenesis. These consideration explains why, despite its impact on complex I, the net effect of berberine on NAFLD, both in rodent models and clinically, is protective.[116–118] Indeed, despite its small inhibitory effect on mitochondrial respiration, daily administration of berberine has been found to enhance the lifespan of mice.[119]

As noted, agonists for PPARα and PPARδ contribute to effective MB. Curiously, the xanthophyll carotenoid astaxanthin, which can serve as an outstandingly effective scavenging antioxidant for the mitochondrial inner membrane, also can act as a PPARα agonist in doses that are clinically feasible.[120–126] Also useful for this purpose are the long-chain omega-3 fatty acids found in fish oil; this accounts for their clinical hypotriglyceridemic activity, as discussed below.[127–129] A medical food combining eicosapentaenoic acid and astaxanthin has been shown to be clinically useful for reduction of plasma triglycerides.[130]

Capsaicin, the phytochemical responsible for the pungent flavor of hot chilis, has been shown to boost expression and activity of PPARδ in hepatocytes and various other tissues.[131, 132] This effect is mediated via activation of capsaicin's key receptor transient receptor potential vanilloid type 1 (TRPV1), which enables calcium influx when activated. Why TRPV1 has this effect on PPARδ remains mysterious.

5. Boosting Nrf2 Activity

A number of studies report that Sirt1activation leads to increased activity of the Nrf2 transcription factor and increased expression of the range of antioxidant enzymes whose transcription that latter drives.[133–136] The mechanisms responsible appear to be indirect, as early studies found that directly deacetylation of Nrf2 by Sirt1 decreases its transcriptional activity.[137] A likely explanation is that Sirt1-mediated deacetylation of glycogen synthase kinase-3β (GSK3β) increases the efficiency with which phosphorylation by Akt inhibits GSK3β activity.[138] The latter promotes export of Nrf2 from the nucleus by an indirect mechanism.[139, 140]

Certain nutraceuticals can enhance Nrf2 activity by disrupting its interaction with the protein Keap1; this enables Nrf2 to evade proteasomal degradation and be transported to the nucleus.[141–143] These nutraceuticals include lipoic acid as well as flavolignans form milk thistle collectively known as "silymarin", each of which has been widely used for promotion of liver health.[144] Astaxanthin has also been reported to boost Nrf2 expression, for reasons that aren't clear.[145–148]

Nrf2 levels can also be increased at the transcriptional level by the nutraceuticals melatonin and phycocyanobilin (PCB). The effect of melatonin in this regard likely reflects melatonin receptor-mediated induction of the clock protein transcription factor Bmal1, which in turn promotes transcription of the Nrf2 gene.[149–151] PCB is a biliverdin metabolite which acts as a light-absorbing chromophore in cyanobacteria (such as the food spirulina) and certain types of blue-green algae.[152] PCB is of particular interest in that it appears to mimic the ability of unconjugated bilirubin – as generated by the antioxidant enzyme heme oxygenase – to inhibit certain NADPH oxidase complexes.[152–156] NADPH oxidase activation in hepatocytes, Kupffer cells, sinusoids, and

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myofibroblasts has been found to play a mediating role in the inflammation and fibrosis associated with NASH.[11, 157–160] PCB is also reported to mimic bilirubin's ability to evoke T regulatory cell activity.[161–164] These effects may rationalize the hepatoprotective effects of dietary spirulina (or of its chief protein, phycocyanin, which carries PCB as a chromophore) in rodent and clinical studies.[152, 164]

6. Spermidine Promotes TFEB Expression

As noted, TFEB enhances transcription of the gene coding for PGC-1α.[26, 27] The polyamine spermidine plays a curious role in promoting TFEB expression. TFEB mRNA has a rare structure, coding for 2 stretches of three consecutive prolines, that render it dependent on eukaryotic initiation factor 5A (eIF5A) for efficient translation.[165, 166] And effective activity of eIF5A requires a post-translational modification known as hypusination, in which a specific lysine in this protein is converted to the novel amino acid hypusine in an enzymatically catalyzed reaction in which requires the polyamine spermidine as a substrate.[167] Tissue levels of spermidine decline during aging, and, although spermidine can be synthesized endogenously, provision of extra dietary spermidine boosts eIF5A activity and TFEB expression in aging rodents.[168–170] This phenomenon may be of some importance, as spermidine-enriched diets increase the lifespan of rodents, and higher spermidine diets correlate with decreased total mortality in humans.[171, 172] TFEB promotes not only mitochondrial biogenesis, but also boosts the expression of numerous proteins required for autophagy and lysosomal function.[173]

7. Combating Hepatocyte Lipid Overload with Nutraceuticals and Diet

Figure 2 addresses nutraceuticals and dietary measures which may have potential for preventing or reversing hepatocyte lipid overload in NAFLD. The factors depicted as impacting on hepatic fat overload include SREBP-1c, a key driver of DNL;[174] MB, which insures that the "infrastructure" for mitochondrial fat oxidation is in good order;[175, 176] PPARα and PPARδ, key players in MB that drive expression of enzymes required for FFA oxidation;[177] AMPK, which, by suppressing the activity of acetyl-CoA carboxylase (ACC), disinhibits carnitine palmitoyltransferase-1 (CPT-1), essential for transport of longer-chain FFAs into the mitochondrial matrix for oxidation, and also opposes DNL by decreasing availability of its substrate malonyl-CoA;[178] carnitine, which under some circumstances can be rate-limiting for CPT-1 activity.[179] Also depicted is hydroxycitrate (HCA), a phytochemical which, owing to inhibition of citrate lyase, limits the cytoplasmic availability of acetylCoA; this in turn suppresses DNL and supports mitochondrial FFA oxidation by limiting malonyl-CoA synthesis.[180]

Multiple inputs regulate SREBP-1c activity and thereby influence DNL; this transcription factor also impacts FFA oxidation negatively via induction of ACC.[181] Sirt1 inhibits SREBP-1c's transcriptional activity by deacetylating it; as noted above, ferulic acid, melatonin, and MNA can boost Sirt1 expression, whereas NAC and possibly taurine can enhance its activity by promoting H_2S generation.[182] The transcription factor LXR binds to the promoter of the gene encoding SREBP-1 and stimulates its transcription.[183] A key way in which insulin activity drives DNL is by boosting LXR expression; this in turn reflects it ability, via stimulation of Akt, to promote nuclear export of FOXO1, a factor which suppresses LXR expression at the transcriptional level.[184] In addition, via stimulation of mTORC1 and its downstream mediator p70 S6 kinase, insulin promotes the post-translational proteolytic processing in the Golgi apparatus that generates a mature SREBP-1c transcription factor capable of entering the nucleus and regulating transcription.[185] Moreover, direct phosphorylation of mature SREBP-1c by p70 S6 kinase also prolongs its half-life.[186] A protein which functions to oppose the processing of the SREBP-1c precursor, Insig2A, is positively regulated at the transcriptional level by PPARα.[187] AMPK also dampens the ability of insulin to promote SREBP-1c maturation and prolong its half-life by suppressing mTORC1 activity.[188] Moreover, AMPK suppresses transcription of the gene coding for LXR, and hence suppresses SREBP-1c expression at the transcriptional level.[189] A further determinant of SREBP-1c maturation is the transcription factor cAMP response element binding protein H (CREBH), which drives transcription of the gene coding for Insig-2A.[190] Hepatic glucagon activity, via stimulation of cAMP generation and consequent activation of protein kinase A

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(PKA), activates the DNA-binding ability of CREBH, thereby inhibiting DNL.[190] And PPARα boosts CREBH expression at the transcriptional level.[191] In aggregate, these considerations explain how insulin and glucagon activity regulate DNL positively and negatively, respectively.

Hepatic lipid overload can increase synthesis of ceramide; this synthesis is amplified when availability of palmitate, an obligate substrate for ceramide synthesis, is increased. This offers a partial explanation as to why diets and adipocytes with a high proportion of saturated fat are more likely to give rise to DNL. While ceramide has the potential to stimulate the progression of NAFLD to NASH via its pro-inflammatory effects, it can also positively influence hepatic lipid overload. Via activation of protein phosphatase-2A, which removes an activating phosphorylation from AMPK, ceramide functions to inhibit AMPK activity.[192, 193] Furthermore, for reasons less clear, ceramide also opposes PPARα activity.[194] The adipocyte-derived hormone adiponectin opposes these effects of ceramide on hepatic fat overload and inflammation, as its receptor stimulates a ceramidase activity.[195, 196] This not only disposes of ceramide, but also generates sphingosine; the latter, after phosphorylation, boosts AMPK activity via a receptor-mediated mechanism.[197]

As noted, cAMP mediates the suppressive impact of glucagon on DNL, and also boosts Sirt1 activity via PKA. Also as noted, high-dose biotin and citrulline, by stimulation of cGMP generation and consequent inhibition of PDE-3b, can act to amplify this glucagon signal. Berberine, via activation of AMPK, and astaxanthin, via activation of PPARα, also each can promote hepatic FFA oxidation while opposing DNL.

A further factor which may exert these effects is a plant-based diet of modest protein content. The paucity of certain amino acids in such a diet, via activation of the GCN2 kinase – which functions to detect such paucity – results in increased hepatic production and secretion of the "longevity hormone" fibroblast growth factor 21 (FGF21).[198, 199] This in turn acts on adipocytes to boost their secretion of adiponectin, which we have seen functions to suppress ceramide levels and enhance AMPK activity.[200] Furthermore, some studies suggest that, owing to its characteristic amino acid composition, ingestion of plant protein tends to provoke a higher glucagon response, and a lower insulin response, than is seen after ingestion of animal protein richer in essential amino acids.[201] This higher post-prandial glucagon/insulin ratio could be expected to oppose DNL and encourage FFA oxidation. Additionally, plant-based diets not laced with tropical oils will provide only a small fraction of their fat content from saturated fat, and hence may offer protection from NAFLD in this respect.

Furthermore, a plant-based diet comprised mostly of whole foods often provides a significant amount of substrate, in the form of resistant starch and soluble fiber, that intestinal bacteria can convert to health-protective short-chain fatty acids. These can boost intestinal production of incretin hormones, notably glucagon-like peptide-1 (GLP-1), which can drive AMPK activation in hepatocytes.[202, 203] As we have seen, AMPK activation favorably affects steatosis, MB, and oxidant stress; not surprisingly, drug agonists for the GLP-1 receptor have been proposed as therapies for NAFLD.[204]

One lipid factor capable of driving progression of NAFLD to NASH that is not influenced by modulation of FFA synthesis or oxidation is free cholesterol; this can precipitate into crystals which can induce activation of NLRP3 inflammasomes within Kuppfer cells via destabilization of lysosomes.[19, 205–207] However, effective antioxidant measures have the potential to decrease hepatocyte cholesterol levels. This is because oxidative stress can impair export of bile salts into bile caniculi by promoting endosomal incorporation and lysosomal degradation of membrane proteins which mediate this export, bile salt export protein (BSEP) and Mrp3.[208–210] The consequent back up of bile acids in hepatocytes activates the FXR transcription factor, which suppresses transcription of the gene coding for CYP7a1, the initial enzyme in the pathway converting cholesterol to bile acids.[211] Hence, alleviation of oxidative stress may disinhibit CYP7a1 expression, supporting hepatocyte cholesterol catabolism. (See Figure 3).

8. Avoiding Progression of NAFLD to NASH and Fibrosis – Roles for Soy Isoflavones and Glycine

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The mechanisms which collaborate to drive progression of lipid-loaded, oxidatively-stressed hepatocytes to NASH, fibrosis, and hepatocarcinogenesis are doubtless diverse, and at this point are far from fully understood. Nonetheless, considerable evidence from rodent and pathology studies suggests that NLRP3 inflammasome activation and TGF-β signaling play a prominent role in this regard.[12–18] Nutraceuticals with potential for opposing these processes have been discusses in previous publications, and, fortuitously, it is notable that most of these nutraceuticals have been discussed above as agents with potential for opposing hepatocyte lipid overload and oxidative stress.[212, 213] One exception, though, is soy isoflavones. Pre-menopausal women are at decreased risk for hepatic fibrosis than men of comparable age, and this is thought to reflect activation of estrogen receptor-β (ERβ).[214–216] The latter is expressed in hepatic stellate cells, where, in its agonist-activated form, it can impede Smad3-mediated TGF-β signaling.[217, 218] Curiously, this involves direct interaction of ERβ with c-Jun – a component of the Smad3 transcriptional complex - rather than binding to an estrogen response element. Soy isoflavones – namely genistein and the equol produced by gut bacteria from daidzein – when ingested in amounts achievable with a soy-rich diet, can achieve unbound, unconjugated concentrations in plasma sufficient to serve as agonists for ERβ, while promoting only minimal activation of ERα.[216, 219] Since the latter is responsible for the feminizing and pro-carcinogenic effects of estrogen, diets rich in soy products or supplemented with dietarily relevant doses of soy isoflavones can safely evoke anti-fibrotic ERβ activity, without the potential drawbacks of estradiol or other ERα agonists.

M1-polarized Kuppfer cells and the pro-inflammatory cytokines they generate contribute to the inflammation associated with NASH and the phenotypic transition of stellate cells to myofibroblasts.[220, 221] The amino acid glycine – plasma levels of which tend to be decreased in obesity[222] – can exert anti-inflammatory effects on macrophages in high physiological concentrations.[223] The activation of glycine-triggered chloride channels, expressed by macrophages and a range of other tissues, is a mediator of this effect.[224] Supplemental glycine may also protect hepatocytes challenged by steatosis by supporting gluthathione synthesis.[225] Moreover, when fed on an empty stomach (i.e. in the absences of concurrent carbohydrate ingestion), glycine can evoke a marked secretion of glucagon with very little impact on insulin secretion – an effect that could promote the hepatoprotective effects of cAMP.[226] It is feasible to consume ample daily doses of this amino acid via blending with beverages, as it is highly soluble, inexpensive, and has a pleasant mildly sweet flavor.

It should also be noted that agents which boost Sirt1 activity could be expected to suppress hepatic inflammation via down-regulation of NF-kappaB activity; Sirt1 accomplished this via deacetylation of the p65 subunit.[227] Antioxidant measures might also decrease NF-kappaB activity by opposing the up-regulatory effect of oxidants on signaling pathways leading to NF-kappaB activation.

Summation and Practical Implications: In light of the foregoing, it is logically satisfying to note that ferulic acid,[228–230] melatonin,[231–233] MNA,[234, 235] THC,[68, 69] NR,[75, 76] carnosic acid,[55] pomegranate juice,[236–238] mulberry leaf extract,[239, 240] quercetin,[81] high-dose biotin,[93] citrulline,[241–245] astaxanthin,[246–249] long-chain omega-3 fatty acids,[250–255] berberine,[116–118] lipoic acid,[256–260] silibinin,[261–263] NAC,[264–266] taurine,[267–270] spermidine,[271, 272] capsaicin,[131, 273–275] PCB (or spirulina),[276–279] carnitine,[280] soy isoflavones, [281–283] and glycine[284–286] have each been reported to confer protection in rodent models of NAFLD or NASH, and in some cases the clinical disorders. And this does not exhaust the list of natural products found to confer protection from NAFLD in rodent studies.[287] Functional foods and nutraceutical programs featuring a judicious selection of these agents with complementary actions may have significant potential for preventing and controlling NAFLD and its subsequent progression to NASH, fibrosis, and and hepatic cancer. Importantly, the nutraceuticals cited here are likely to exert additional effects supportive of healthspan. And with respect to plant-based diets of moderate protein content, a small amount of anecdotal evidence suggests that they may have utility for management of NAFLD.[288, 289] Moreover, in the long run, adherence to such diets is likely to favorably impact the visceral adiposity and insulin resistance that is the usual underlying cause of NAFLD.[198] And, with respect to the contribution of fructose to NAFLD, diets consisting primarily of whole foods – that is, low in added sugars or fruit juices – are unlikely to supply enough fructose to be of pathological importance.

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