

# openheart Astaxanthin plus berberine: a nutraceutical strategy for replicating the benefits of a metformin/fibrate regimen in metabolic syndrome

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## BERBERINE IS A NUTRACEUTICAL ACTIVATOR OF AMP-ACTIVATED KINASE

The phytochemical berberine, a constituent of certain herbs used in traditional Chinese medicine, has long been in use in China as a well-documented therapy for type 2 diabetes.<sup>1,2</sup> Mechanistic studies demonstrates that, like metformin, it activates AMP-activated kinase (AMPK); this is thought to be the chief basis of its utility in diabetes.<sup>3–5</sup> The typical therapeutic regimen is 500 mg two or three times per day, or 850 mg two times per day. The most common side effect is constipation, which tends to remit during continuing treatment.<sup>6</sup> Unlike metformin, however, berberine upregulates the hepatic expression of LDL receptors, through a mechanism that is complementary to that of statins or red yeast rice (RYR); whereas statins increase transcription of the gene coding for LDL receptors, berberine increases the half-life of LDL receptor mRNA.<sup>7</sup> Hence, the combination of berberine plus RYR—a natural low-potency source of monacolin K (lovastatin) and other monacolins that has moderate hypocholesterolaemic activity in a standardised dose that is well tolerated in most patients who don't tolerate pharmaceutical statins<sup>8–10</sup>—has been recommended as a nutraceutical alternative to pharmaceuticals in the management of hypercholesterolaemia.<sup>11</sup>

## THE CAROTENOID ASTAXANTHIN CAN ACT AS A PPAR $\alpha$ AGONIST

The natural carotenoid astaxanthin is extraordinarily effective—more so than tocopherols—for conferring radical-scavenging antioxidant protection to biological membranes.<sup>12</sup> It may be particularly beneficial for blunting the feedforward loop whereby mitochondria subjected to oxidative stress—as during ischaemia-reperfusion

injury—become greater sources of oxidants owing to damage to their respiratory chains.<sup>13</sup> However, in both clinical and rodent studies, oral astaxanthin has ameliorated the dyslipidaemia and hepatic steatosis associated with metabolic syndrome, suggesting that it has an additional target of action.<sup>14–18</sup> Indeed, there is recent evidence that, in concentrations that can be achieved through oral administration at practical doses, astaxanthin can act as a PPAR $\alpha$  agonist.<sup>19,20</sup> In other words, astaxanthin has the potential to replicate the activity of PPAR $\alpha$  agonist drugs, such as the fibrates, which are known to decrease risk for cardiovascular events in patients with metabolic syndrome.<sup>21,22</sup> In a recent placebo-controlled trial enrolling patients with type 2 diabetes, astaxanthin (8 mg daily for 8 weeks) achieved significant reductions in serum triglycerides (156→128 mg/dL), serum fructosamine (7.4→5.8  $\mu$ mol/L) and systolic blood pressure (143→132 mm Hg), while significantly elevating adiponectin (36→47  $\mu$ g/mL); these parameters all worsened non-significantly in the placebo group.<sup>23</sup>

## AMPK AND PPAR $\alpha$ AGONISTS REINFORCE EACH OTHER'S UTILITY IN METABOLIC SYNDROME

The combination of metformin and fenofibrate has been studied in patients with type 2 diabetes and metabolic syndrome, and has been found more effective for improving lipid profiles and aiding glycaemic control than either agent alone.<sup>24,25</sup> This likely reflects the fact that AMPK and PPAR $\alpha$  interact in mutually complementary ways to promote efficient mitochondrial oxidation of fatty acids, thereby lessening hepatic triglyceride synthesis and decreasing the exposure of tissues to ectopic fat.

The transcription factor PPAR $\alpha$ , after forming a heterodimer with the retinoid

X receptor, stimulates the transcription of genes which promote mitochondrial oxidation of fatty acids and ketogenesis, including carnitine palmitoyl transferases (CPT) 1a and 2, acyl-coenzyme A oxidase and uncoupling protein 2. The favourable impact of PPAR $\alpha$  agonists on human HDL levels reflects the induction of apolipoproteins A-I and A-II—an effect not observed in rodents.<sup>26 27</sup> PPAR $\alpha$  also stimulates hepatic production of fibroblast growth factor 21 (FGF21), a ‘pro-longevity’ hormone which acts on adipocytes to boost their production of adiponectin; the latter, in turn, acts on hepatocytes and other tissues to stimulate AMPK activity.<sup>28–38</sup>

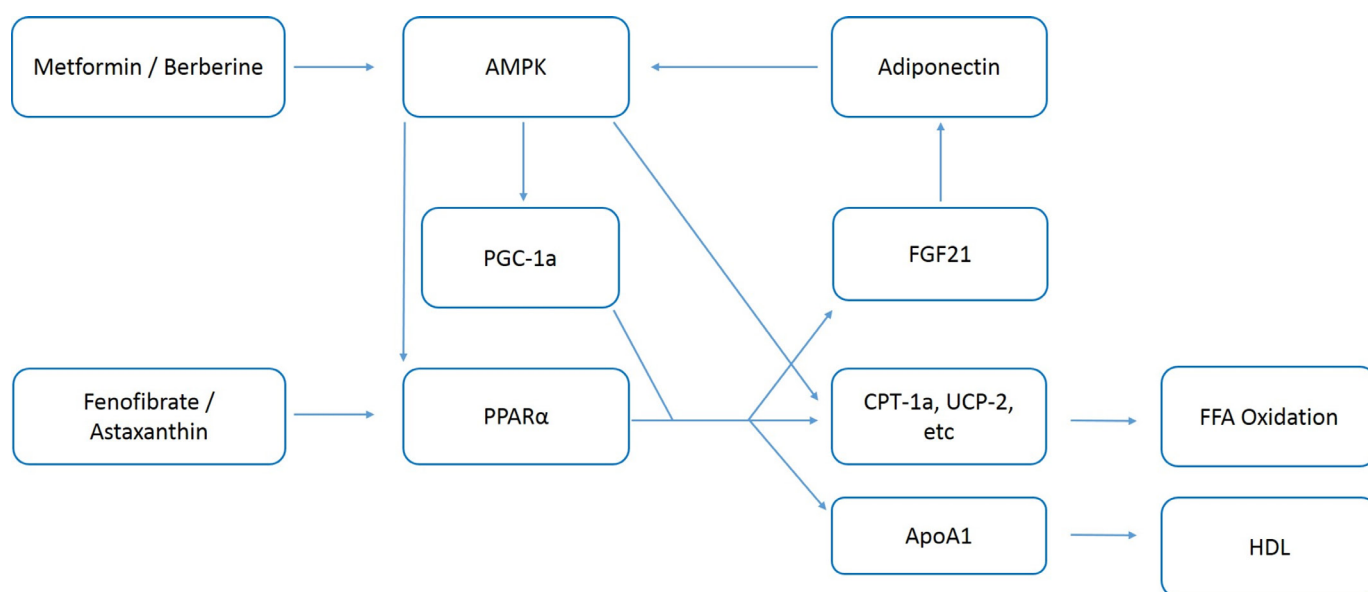
Although there is no evidence that AMPK directly phosphorylates PPAR $\alpha$  to influence its transcriptional activity, AMPK acts to increase both the expression and activity of PPAR $\gamma$  coactivator-1a (PGC-1a), which serves as a coactivator for PPAR $\alpha$  as well as for several other transcription factors that promote mitochondrial biogenesis.<sup>39–43</sup> Also, in some cellular contexts, AMPK boosts the expression of PPAR $\alpha$ , likely by promoting nuclear translocation of transcription factor EB, a master regulator of autophagy and lysosomal activity; this effect might also be partially attributable to enhanced PGC-1 $\alpha$  activity, as PPAR $\alpha$  acts to drive transcription of its own gene.<sup>44–49</sup> Importantly, AMPK complements PPAR $\alpha$  impact on mitochondrial fatty acid oxidation by lowering cytoplasmic levels of malonyl-coenzymeA, an allosteric inhibitor of CPT-1a; it does so by conferring inhibitory phosphorylation on acetyl-coenzymeA carboxylase, and activating phosphorylation on malonyl-coenzymeA decarboxylase,<sup>50 51</sup> and AMPK decreases hepatic triglyceride synthesis both by directing free fatty acids towards mitochondrial oxidation, as well as by suppressing the activity of rate-limiting enzyme for triglyceride synthesis, glycerol-3-phosphate acyltransferase.<sup>52</sup> Concurrently, AMPK inhibits hepatic

gluconeogenesis, an effect in large part responsible for the favourable impact of AMPK agonists on glycaemic control in diabetics; a rate-limiting enzyme for gluconeogenesis, fructose-1,6-bisphosphatase, has recently been identified as AMPK’s target in this regard.<sup>53 54</sup> While, as noted, PPAR $\alpha$  activation in the liver can boost AMPK activity systemically via induced production of FGF21 and adiponectin, it also enhances AMPK activation in hepatocytes and endothelium by promoting cytoplasmic translocation and subsequent activation of LKB1, an upstream activating kinase for AMPK.<sup>55 56</sup> These reinforcing interactions are depicted in figure 1.

Hence, since AMPK and PPAR $\alpha$  complement each other’s activity in multiple ways, the clinical complementarity of metformin and fibrates is predictable.

### PROPOSAL: ASTAXANTHIN PLUS BERBERINE FOR CONTROL OF METABOLIC SYNDROME

We propose that a nutraceutical regimen of berberine plus astaxanthin has the potential of replicating the utility of metformin+fenofibrate for improving the hyperlipidaemia and impaired glycaemic control that characterise metabolic syndrome and type 2 diabetes. Moreover, adding RYR to this regimen would be expected to provide additional control of LDL cholesterol. A regimen of berberine/RYR/astaxanthin might constitute a safe and usually well-tolerated strategy for optimising lipid profiles in patients in whom triglycerides and LDL cholesterol are both elevated, and HDL cholesterol depressed. Krill oil rich in astaxanthin (1 mg or more per gram) could be employed as an astaxanthin source, as this provides an esterified form of this carotenoid that has superior bioavailability, as well as health-protective omega-3 fatty acids, oxidised metabolites of which likewise act as PPAR $\alpha$



**Figure 1** Legend interactions of AMPK and PPAR $\alpha$  in promoting fatty acid oxidation and HDL production. Arrows reflect induction and/or activation. AMPK, AMP-activated kinase; CPT-1a, carnitine palmitoyl transferases-1a; FGF21, fibroblast growth factor 21; PGC-1a, PPAR $\gamma$  coactivator-1a; UCP-2, uncoupling protein-2.

agonists.<sup>57–60</sup> Meta-analysis confirms the utility of krill oil supplementation for improving serum lipid profile.<sup>61</sup> Its efficacy with respect to modulating serum lipids, glucose and C reactive protein appears to be superior to that of fish oil.<sup>62–63</sup> The possibility of incorporating astaxanthin into hypolipidaemic nutraceutical regimens incorporating RYR, berberine and other agents was presciently envisioned by Cicero *et al* over a decade ago.<sup>64</sup>

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