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Potential complementarity of high-flavanol cocoa powder and spirulina for health protection

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SUMMARY

Recent studies show that ingestion of flavanol-rich cocoa powder provokes increased endothelial production of nitric oxide - an effect likely mediated by epicatchin – and thus may have considerable potential for promoting vascular health. The Kuna Indians of Panama, who regularly consume large amounts of flavanol-rich cocoa, are virtually free of hypertension and stroke, even though they salt their food. Of potentially complementary merit is the cyanobacterium spirulina, which has been used as a food in certain cultures. Spirulina is exceptionally rich in phycocyanobilin (PCB), which recently has been shown to act as a potent inhibitor of NADPH oxidase; this effect likely rationalizes the broad range of anti-inflammatory, cytoprotective, and anti-atherosclerotic effects which orally administered spirulina has achieved in rodent studies. In light of the central pathogenic role which NADPH oxidase-derived oxidant stress plays in a vast range of disorders, spirulina or PCB-enriched spirulina extracts may have remarkable potential for preserving and restoring health. Joint administration of flavanol-rich cocoa powder and spirulina may have particular merit, inasmuch as cocoa can mask the somewhat disagreeable flavor and odor of spirulina, whereas the antioxidant impact of spirulina could be expected to amplify the bioactivity of the nitric oxide evoked by cocoa flavanols in inflamed endothelium. Moreover, there is reason to suspect that, by optimizing cerebrovascular perfusion while quelling cerebral oxidant stress, cocoa powder and spirulina could collaborate in prevention of senile dementia. Thus, food products featuring ample amounts of both high-flavanol cocoa powder and spirulina may have considerable potential for health promotion, and merit evaluation in rodent studies and clinical trials.

Vascular-protective benefits of flavanol-rich cocoa powder

A growing number of clinical studies indicate that regular ingestion of flavanol-rich cocoa exerts a range of effects potentially favorable to vascular health – improving endothelial function, reducing elevated blood pressure, increasing insulin sensitivity, and suppressing platelet aggregation [1–14] There is recent evidence that the epicatchin content of cocoa is primarily responsible for its favorable impact on vascular endothelium, which reflects both an acute and chronic up-regulation of nitric oxide production [15,16]. As is well known, physiological levels of nitric oxide support vascular health and efficient tissue perfusion by promoting vasodilation, opposing inflammation and structural remodeling in the vascular wall, and stabilizing platelets [17]. Other research demonstrates that ingestion of flavanol-rich cocoa protects skin from UV damage and has a positive cosmetic impact on the skin of women, increasing its moisture content [18].

The fact that the Kuna Indians of Panama are virtually immune from hypertension and the typical age-related rise of blood pressure, so long as they live a traditional lifestyle, is likely attributable to their regular heavy intake of flavanol-rich raw cocoa [10] Moreover, the Kuna appear to be virtually free of stroke [19] – a finding consistent with evidence that cerebrovascular nitric oxide production is a key determinant of stroke risk [20]. Although a diet that is nearly pesco-vegan undoubtedly has a favorable impact on the Kuna's health status, hypertension and stroke tend to be quite common in many Asian groups whose traditional diets are quasi-vegan – even though these groups enjoy considerable protection from coronary heart disease, diabetes, and certain "Western" cancers [21–23]. It should be emphasized that, unlike all other unacculturated societies that have been found to be free of essential hypertension, the Kunas make ample use of added salt in their diets; thus, cocoa flavanols appear to confer important protection from hypertension and stroke even in the context of a salty diet.

Although the prevalence of senile dementia among the Kuna has not been formally assessed, other Third World cultures in which hypertension and stroke are quite rare are characterized by a near absence of dementia [20,24]. This phenomenon may reflect a key role for intermittent or chronic cerebral hypoxia

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in triggering and sustaining the inflammatory process that mediates Alzheimer's disease. Indeed, many commentators have noted that a number of vascular risk factors are likewise risk factors for Alzheimers, and that many measures which boost endothelial nitric oxide function are linked to decreased risk for this disorder [24–34]. Recent research has established that hypoxia boosts neuronal expression of BACE1 (a.k.a. beta-secretase), a protease whose activity can be rate-limiting for the production of the amyloid-beta peptides thought to drive the inflammatory process in Alzheimers [35,36]. Since amyloid-beta antagonizes endothelium-dependent vasodilation in the cerebral microcirculation by inducing severe endothelial oxidative stress [37–41], a vicious cycle mechanism may act to sustain and exacerbate local hypoxia (and thus increased BACE1 activity) in regions of the brain where Alzheimers inflammation becomes well established; indeed, endothelial nitric oxide is a mediator of the crucial autoregulatory mechanisms whereby cerebral blood flow is matched to metabolic demand and maintained in the face of reduced central blood pressure [42–46]. A recent clinical study has demonstrated an acute increase of brain perfusion following ingestion of flavanol-rich cocoa [47,48]. Moreover, long-term administration of cocoa flavanols to aging rats is associated with preservation of youthful cognitive performance [49] – raising the possibility that cerebral hypoxia (and/or suboptimal cerebrovascular nitric oxide production) might also play a role in the more modest fall-off in cognitive function associated with healthy aging. These considerations suggest that regular consumption of cocoa flavanols might have important potential for promoting retention of cognitive function as humans age.

Spirulina has profound antioxidant potential

Another food with potential for superstar status as a health aid is the cyanobacterium spirulina. While spirulina – once harvested as a food by the Aztecs, and still used by Africans living near Lake Chad – has been popular as a supplement in "health food" circles for several decades, its true health-protective merit has only recently been discovered: phycocyanobilin (PCB), the chromophore bound to spirulina's chief protein, phycocyanin, can function as a potent inhibitor of NADPH oxidase, the enzyme complex that is the chief source of pathological oxidant stress in a wide range of health disorders [50,51]. In this regard, it appears to mimic the physiological activity of free bilirubin [52–55]; PCB can be converted within cells to phycocyanorubin, which is nearly identical in structure to bilirubin [56]. Although the clinical utility of ample intakes of spirulina has so far received little research attention, in numerous rodent studies orally administered spirulina or phycocyanin has shown potent anti-inflammatory, cytoprotective, and anti-atherogenic activities; these effects are most likely attributable to down-regulation of NADPH oxidase activity [50,51,57,58]. A consideration of the central role of NADPH oxidase over-activity in a range of disorders suggests that ample intakes of spirulina may have preventive and therapeutic potential with respect to many vascular diseases (including atherogenesis, hypertension, and congestive heart failure), cancers, complications of diabetes, and a range of neurodegenerative, fibrotic, or inflammatory disorders [50,51] It should be emphasized that measures which inhibit NADPH oxidase activity could be expected to have a much more profound health impact than antioxidant vitamins or phytochemicals that act merely as oxidant scavengers – the latter, while helping to preserve the structural integrity of membrane lipids or proteins, have little influence on the signal-modulatory activity of hydrogen peroxide, or on the nitric oxide-quenching activity of superoxide. The versatile heath protection associated with statin therapy or angiotensin II antagonism – seemingly greater than would be predicted from their hypolipidemic or anti-hypertensive activities – may be largely attributable to their down-regulatory impacts on the NADPH oxidase activity of certain tissues [59].

Spirulina also is a source of polysaccharide that has immunostimulant activity (reflecting the activation of TLR2 receptors on macrophages) [60–62], and is very rich in zeaxanthin, a dietary carotenoid that has been linked to decreased risk for macular degeneration [63]. A recent open clinical trial reports worthwhile reductions in blood pressure and improvements in blood lipid profile in healthy volunteers receiving 4.5 g spirulina daily; this suggests that spirulina-bound PCB may have good oral bioavailability in humans [64]. The reduction in LDL cholesterol observed in this study might reflect phycocyanin-mediated inhibition of cholesterol and bile acid (re)absorption, as demonstrated in rats [65].

Cocoa can mask spirulina's flavor, while complementing its health benefits

Spirulina's chief drawback as a food is that it has a foul odor, and a flavor that most find unappealing. However, these authors have observed that, when pre-blended with spirulina, cocoa powder can do an excellent job of masking spirulina's odor and flavor. When blended with soy milk, cow's milk, or rice milk, along with an added sweetener, a cocoa–spirulina powder can yield a drink with a rich and creamy chocolate flavor – though some may initially find its dark green color somewhat disconcerting!

Moreover, the antioxidant activity of PCB in the inflamed vasculature – where NADPH oxidase is the chief source of oxidant stress [66–68] – could be expected to nicely complement the impact of cocoa-derived epicatechin on nitric oxide bioactivity. As is well known, superoxide antagonizes the bioactivity of nitric oxide by spontaneously reacting with it to generate the dangerous oxidant peroxynitrite. Furthermore, by oxidizing the cofactor tetrahydrobiopterin, oxidant stress (i.e. peroxynitrite) transforms the endothelial nitric oxide synthase into an enzyme that not only is less competent at generating nitric oxide, but that also produces superoxide [69,70]. Hence, the protective impact of epicatechin on an inflamed vasculature would be expected to be greater if concurrently administered PCB is employed to quell vascular oxidant stress. And the antioxidant impact of PCB on vascular endothelium would be expected to act in other ways, complementary to but independent of nitric oxide, to minimize endothelial inflammation and thus promote vascular health [59,67,71,72].

Oral administration of phycocyanin or of whole spirulina has exerted central neuroprotective effects in rodent studies – an observation which strongly suggests that PCB can transit the blood–brain barrier [73–75]. This is of considerable interest in light of evidence that oxidant stress generated by NADPH oxidase in activated microglia and possibly neurons as well plays an important pathogenic role in many common neurodegenerative disorders – including Alzheimers disease [75–81]. Indeed, oxidative stress up-regulates transcription of BACE1, an effect mediated by the stress-activated MAP kinases [82–87]; the resulting increase in amyloid-beta production then triggers further oxidative stress via activation of NAPDH oxidase, completing a feed-forward loop [80,79,88,41,89,90]. Oxidative stress also promotes transcription of presenilin-1, the catalytic component of the gamma-secretase also required for amyloid-beta production [86]. Evidently, PCB has the potential to suppress this vicious cycle, and also would likely antagonize the adverse impact of amyloid-beta on cerebrovascular endothelial function, which appears to be mediated by NADPH oxidase activation [41]. These considerations suggest that cocoa flavanols and PCB could work in tandem to counteract the cerebral hypoxia and oxidative stress that sustain excessive

amyloid-beta production and that mediate, at least in part, the neuronal dysfunction and death that characterize Alzheimers [76,77,80,79,88,25,91–93]. Thus, it is conceivable that spirulina could complement the utility of flavanol-rich cocoa in dementia prevention – only by aiding efficient cerebrovascular perfusion, but also by blunting the key contribution of oxidative stress to Alzheimers pathology.

In regard to the UV-protective effect documented for cocoa flavanols, there is suggestive evidence that UV-induced skin damage is mediated by activation of NADPH oxidase in keratinocytes, an effect contingent on concurrent activation of EGF receptors [94–97]. If this is the case, PCB may be able to complement the utility of cocoa flavanols in serving as an "internal sun screen".

It is therefore proposed that commercial products combining ample amounts of flavanol-rich cocoa powder and phycocyanin-rich spirulina should be developed, and their effects assessed both in rodent studies and in clinical trials. Consumed regularly, such products may have considerable potential for preventing and treating the wide range of disorders in which excessive oxidative stress plays a pathogenic role – and possibly for preserving youthful cognitive function into ripe old age.

If this proposal proves to have merit, it may ultimately prove feasible to provide the key active components of cocoa powder and spirulina in capsule form. Flavanol-rich cocoa powder extracts are already commercially available, and it seems likely that PCB-enriched spirulina extracts could be developed for use in nutraceuticals.

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