Perspective

Clinical Potential of *Spirulina* as a Source of Phycocyanobilin

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ABSTRACT Recent research reveals that free bilirubin functions physiologically as a potent inhibitor of NADPH oxidase activity. The chromophore phycocyanobilin (PCB), found in blue-green algae and cyanobacteria such as *Spirulina*, also has been found to be a potent inhibitor of this enzyme complex, likely because in mammalian cells it is rapidly reduced to phycocyanorubin, a close homolog of bilirubin. In light of the protean roles of NADPH oxidase activation in pathology, it thus appears likely that PCB supplementation may have versatile potential in prevention and therapy—particularly in light of rodent studies demonstrating that orally administered *Spirulina* or phycocyanin (the *Spirulina* holoprotein that contains PCB) can exert a wide range of anti-inflammatory effects. Until PCB-enriched *Spirulina* extracts or synthetically produced PCB are commercially available, the most feasible and least expensive way to administer PCB is by ingestion of whole *Spirulina*. A heaping tablespoon (about 15 g) of *Spirulina* can be expected to provide about 100 mg of PCB. By extrapolating from rodent studies, it can be concluded that an intake of 2 heaping tablespoons daily would be likely to have important antioxidant activity in humans—assuming that humans and rodents digest and absorb *Spirulina*-bound PCB in a comparable manner. An intake of this magnitude can be clinically feasible if *Spirulina* is incorporated into “smoothies” featuring such ingredients as soy milk, fruit juices, and whole fruits. Such a regimen should be evaluated in clinical syndromes characterized and in part mediated by NADPH oxidase overactivity in affected tissues.

KEY WORDS: • antioxidant • bilirubin • biliverdin • heme oxygenase • inflammation • NADPH oxidase • phycocyanin • phycocyanobilin • *Spirulina* • zeaxanthin

NADPH OXIDASE AS A MEDIATOR OF PATHOLOGY

IN A HIGH PROPORTION of non-infectious pathologies, NADPH oxidase becomes activated in the affected tissues, and the resulting generation of oxidants either mediates or exacerbates the pathology. Thus, as cited earlier,1 overactivity of this enzyme complex appears to play a role in a host of vascular disorders, including atherogenesis, hypertension, left ventricular hypertrophy, aneurysms, and ischemia-reperfusion injury; the insulin resistance associated with obesity; the major complications of diabetes; neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases; various autoimmune conditions, including rheumatoid arthritis and scleroderma; allergy and asthma; hepatic fibrosis; ultraviolet-mediated skin damage; and the cartilage loss associated with osteoarthritis. Oxidant stress generated by NADPH oxidase also sometimes contributes to cancer initiation, boosts growth factor activity in some cancers, and is a mediator of the angiogenic process. Thus, it is reasonable to suspect that tolerable clinical strategies for down-regulating NADPH oxidase activity may have a remarkably versatile potential in both preventive and therapeutic medicine. Indeed, the surprising range of benefits associated with statin and angiotensin converting enzyme inhibitor therapies likely reflects, in part, their ability to suppress NADPH oxidase activation in certain tissues.2,3 Fortunately, Nature has equipped us with feedback mechanisms that help to moderate the generation of oxidant stress. In particular, recent research has established that free bilirubin, in the low nanomolar concentrations that prevail intracellularly, functions physiologically as a potent and highly specific inhibitor of NADPH oxidase.4–6 Intracellular oxidant stress induces expression of heme oxygenase-1, which in turn generates bilirubin from heme via biliverdin7,8; this mechanism provides feedback control of the oxidant stress mediated by NADPH oxidase. Bilirubin’s suppressive impact on NADPH oxidase activity likely explains the growing epidemiological literature that associates increased serum bilirubin, or high-expression polymorphisms of heme...
in the low micromolar range, and near maximal at 20 

molog biliverdin to human cell cultures leads to potent in-

potentiation of NADPH oxidase; this effect is dose-dependent

by the ubiquitously expressed enzyme biliverdin reductase
to phycocyanorubin, a compound nearly identical in struc-

potency to bilirubin.14 Recent studies by T. Inoguchi (personal

ulence of PCB for supplemental use is whole

ments, once available, may have considerable potential for

health protection.30–32 The 3/4 power standard

extrapolating various quantifiable metabolic parameters be-


cyanin.29 It follows that about 0.66% of the dry mass of

ulina cyanin constitutes about 14% of the total dry weight of

Spirulina. The fraction of this that is absorbed in a form ca-

able to inhibit NADPH oxidase is unknown.

SPIRULINA AS PRACTICAL CLINICAL

SOURCE OF PCB

If we make the not unreasonable assumption that ab-

absorption and metabolism of Spirulina-bound PCB are simi-

ilar in rodents and humans, then clinically useful dose regi-

mens of Spirulina can be estimated by extrapolating from

regimens that demonstrate antioxidant efficacy in rodents.

Such dose extrapolation can be done straightforwardly on a

mg/kg basis. However, in clinical practice, dose is often ad-

justed by relative body surface area, which corresponds to

the 2/3 power of the ratio of body weights. This latter stan-

dard evidently yields a much lower correction factor. A com-

monly employed compromise between these two standards is
to adjust dose by the 3/4 power of the ratio of body

weights; this has been found to offer a “best fit” when ex-

trapolating various quantifiable metabolic parameters be-
tween mammalian species.30–32 The 3/4 power standard

yields a correction factor of about 80 if comparing a 200 g

rat with a 70 kg human, or a factor of 450 if comparing a

20 g mouse with a 70 kg human. (In other words, if a rat

receives x mg of an agent, the corresponding human dose

would be 80x mg.)

In an extensive series of investigations, Romay and co-

workers have reported that oral phycocyanin administered

orally to mice and rats exerts a number of dose-dependent

anti-inflammatory effects in a dose range of 50–300

mg/kg/day.13–18 This amounts to a PCB intake of 2.35–14.1

mg/kg. If extrapolated on a mg/kg basis, this corresponds to

a daily intake of 165–990 mg in a 70 kg human. Extrapo-

lation by the 3/4 power standard gives human daily intakes

of 21.2–127 mg (using mice) and 37.6–226 mg (using rats).

Recent studies in which whole Spirulina has been ad-

ministered orally to rodents have also shown anti-inflam-

matory effects, in doses ranging from 150 to 1,000

mg/kg/day.19–24 This amounts to intakes of 1–6.6 mg/kg/day

PCB. Extrapolating on the basis of relative weight, this cor-

responds to an intake of 70–462 mg PCB in a 70 kg human.

Extrapolating on the basis of the 3/4 power standard, it cor-

responds to an intake of 9–59 mg (mouse studies) or 16–106

mg (rat studies). The syndromes in which Spirulina demon-

strated protective efficacy included adjuvant arthritis, MPTP-induced Parkinsonism, doxorubicin-induced cardiomyopathy, and nephropathy mediated by cisplatin and cyclosporine; it is unlikely to be coincidental that activation of NADPH oxidase has been shown to be a key mediator of each of these syndromes.33–44

As noted, a heaping tablespoon of Spirulina contains ap-

proximately 100 mg of PCB. Thus, a regimen of 2 heaping

tablespoons per day—arguably the highest intake that would

be feasible on a long-term basis with well-motivated pa-

patients—would provide about 200 mg of PCB daily. This in-

take is thus within—and in some instances a bit beyond—

the extrapolated dose ranges noted above. It should follow

that—assuming that humans digest and metabolize Spir-

ulina-bound PCB much like rodents do—a daily intake of

2 heaping tablespoons of Spirulina daily should have clini-

cally useful antioxidant activity in humans. Thus, it would

be reasonable to test such a regimen in the prevention or

treatment of the wide range of clinical disorders in which

overactivity of NADPH oxidase plays a pathogenic role. As-

sessing impact on clinical hypertension might be a good

place to start, since an effective dose regimen could be ex-

pected to have a rapid and quantifiable impact.45–51 In this

regard, it is pertinent to note that, in a cohort of 50 middle-

aged Czech subjects with Gilbert’s syndrome (average age

50 years), only one was found to be hypertensive.9 Intrigu-

ingly, Remirez et al.20 stated that “a number of published

reports suggest beneficial effects of this microalgae in hy-

pertension . . .”—without, however, citing these reports.
Ultimately, the availability of PCB supplements—extracted from Spirulina or synthesized—should enable a broader assessment of the dose dependency of PCB’s clinical benefits. Such supplements will improve the convenience of PCB ingestion, and make it possible to achieve PCB intakes greater than those feasible with whole Spirulina. Nonetheless, until PCB can be mass-produced inexpensively via chemical synthesis or bioengineered bacteria, ingestion of whole Spirulina will be the least expensive way to benefit from this phytoneutrient. It should be noted that the relative absorption and bioefficacy of free PCB and Spirulina-bound PCB have not yet been assessed, in either rodents or humans; evidently, this issue requires attention.

Among health food devotees, Spirulina is frequently ingested in “smoothies”; a smoothie made by blending a cup of vanilla soy milk, one banana, and a heaping tablespoon of Spirulina is reasonably palatable (albeit it looks like frothy green slime!), and provides in addition soy isoflavones and an ample amount of potassium (about 1 g). Various fruit juices and whole fruits can also be used to produce Spirulina smoothies; for example, cinnamon-spiced apple juice works very well. The flavor of Spirulina, although unappealing to most people, is relatively mild, and thus susceptible to masking by a variety of flavors.

SAFETY CONSIDERATIONS
AND ANCILLARY BENEFITS

With respect to safety considerations, it should be noted that Spirulina once was a staple of the Aztec diet, and rodents show no ill effects when fed diets in which Spirulina constitutes 30% of total weight.52–54 Fifteen grams of Spirulina provides about 70 mg of total carotenoids—carotenes (54%) and xanthophylls (46%); this may make an ancillary contribution to the physiological antioxidant activity of this food. Of particular note is the xeaxanthin content—12 mg/15 g; if this has reasonable bioavailability, it could have a worthwhile impact on protective macular pigment.55,56 The cell wall polysaccharide content of Spirulina may be a mediator of the immunomodulatory effects reported with Spirulina ingestion; Spirulina polysaccharides can activate antigen-presenting cells and monocytes via Toll-like receptor.

NOTE ADDED IN PROOF

Since the submission of this review, Riss et al.66 have reported that orally administered phycocyanin or whole Spirulina “powerfully prevents the development of atherosclerosis” in cholesterol-fed hamsters. Although this appears to be the first published evidence that Spirulina has vascular-protective potential, it is consistent with the central role that NADPH oxidase plays in atherogenesis.

REFERENCES


