

Phycocyanobilin from Spirulina - the Master Antioxidant

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Most antioxidants you are familiar with – vitamins such as E or C, selenium, and phytochemical antioxidants such as those in green tea or wine – act, directly or indirectly, as scavengers of oxidant molecules; in other words, they try to clean up the damage after it has already been done. This is worthwhile, of course – but unfortunately, these scavengers fail to prevent many of the downstream consequences of oxidant stress that contribute to disease and dysfunction. That's one key reason why clinical trials with antioxidant vitamins have often yielded rather paltry results.

Phycocyanobilin (PhyCB) is an antioxidant with a difference. PhyCB is a key component of the blue-green algae spirulina, constituting about 0.6% of its dry weight. Although it also can scavenge oxidants, recent research has established that PhyCB, like its chemical relative bilirubin, can act as a very potent inhibitor of the NADPH oxidase enzyme complex – the chief source of pathological oxidant stress in the body.^{1, 2} **In other words, PhyCB goes right to the source of the oxidant stress, turning it off.**

Here's a simple analogy. Visualize a faucet that is jammed open, with water filling the basin and lapping over onto the floor. Think of the water on the floor as oxidant stress. Most antioxidants act like mops – though typically each antioxidant can work on only part of the floor. In contrast, PhyCB simply shuts off the faucet!

Why does PhyCB have such exciting potential for promoting health? Medical science is establishing that oxidant stress generated by overactive NADPH oxidase plays a key mediating role in a vast range of health disorders, including:

Atherosclerosis / Hypertension / Cardiac Hypertrophy and Congestive Failure / Tissue Damage from Heart Attack or Stroke / Insulin Resistance Syndrome / Complications of Diabetes – Kidney Failure, Blindness, Heart Disease / Osteoporosis / Osteoarthritis / Inflammatory Carcinogenesis / Alzheimer's Disease / Parkinson's Disease / Chronic Inflammatory Disorders / Erectile Dysfunction / Sleep Apnea/ Sun-Induced Skin Damage / Liver Cirrhosis / Pulmonary Fibrosis/ Killer Influenzas...and more!³

Some scientists also suspect that oxidative stress from NADPH oxidase contributes to the loss of cognitive function associated with aging, and can adversely affect exercise performance. And NADPH oxidase is active in many cancers, making them grow more aggressively.⁴

It is becoming clear that, in a high proportion of health disorders, NADPH oxidase becomes activated in afflicted tissues, and the resulting oxidative stress either drives or exacerbates the disorder.

And there is another line of evidence suggesting that PhyCB may be markedly protective in humans. As we've noted, PhyCB is a close chemical relative of the compound bilirubin, which is produced in the human body and likewise can inhibit NADPH oxidase.⁵⁻⁷ Owing to a harmless genetic fluke, some people – said to have “Gilbert’s syndrome” – have chronically elevated blood levels of bilirubin throughout life. Not only does this appear to be completely safe, but studies are now showing that people with Gilbert’s syndrome enjoy substantial protection from heart disease and the complications of diabetes.⁸⁻¹⁰ And a very recent study found that the age-standardized rate of all-cause mortality was about *half* as high in people with Gilbert’s as in people without it!¹¹

Unfortunately, there aren’t any rich naturally occurring sources of bilirubin, or of its immediate precursor biliverdin – and these compounds are extremely expensive to synthesize, so it doesn’t look like they will come into use as supplements any time soon. Which makes it all the more fortunate that spirulina is such a rich source of the bilirubin mimic PhyCB.

The recent discovery that PhyCB can inhibit NADPH oxidase – even when ingested orally – casts an intriguing light on the ample research literature that has evaluated spirulina and its chief protein phycocyanin (which carries the PhyCB molecule) in rodents. In study after study, orally administered spirulina or phycocyanin has provided important protection in rodent models of human health disorders. The diseases shown to benefit from spirulina or phycocyanin in these rodent models include atherosclerosis, diabetes, diabetic kidney damage, Parkinson’s disease, fatty liver disease, allergies, rheumatoid arthritis, colitis, multiple sclerosis, stroke, hypertension, premature senility, and drug-induced birth defects.¹²⁻³⁶ The list will no doubt grow longer as more scientists begin to appreciate the antioxidant power of PhyCB.

But what does this mean for us humans? So far, the very limited clinical evaluations of spirulina supplementation have used doses so low – usually only 2 or 3 grams daily, or 4-6 capsules – that they can’t be expected to replicate the impressive results seen in rodent studies. By using standard techniques to extrapolate to humans the spirulina doses that have been highly protective in rodents, it has been estimated that a daily intake of 15-30 grams might be required – about 1-2 rounded tablespoons daily.³ In capsule form, 15 grams corresponds to 30 capsules daily!

Aye – there’s the rub! Because spirulina does not taste good – and it smells worse. Which explains why, with one exception, published clinical trials with spirulina haven’t tested doses within this range. (The one exception, which tested 19 grams daily, reported that spirulina markedly improved the impaired insulin sensitivity of drug-treated HIV patients – but 40% of patients dropped out because they didn’t like the spirulina!)³⁷

And so far, no nutraceutical company has taken the trouble and expense to develop a PhyCB-enriched spirulina extract for use in supplementation, so you will need to ingest whole spirulina to get the benefit of PhyCB. (One company, Desert Lake Technologies, is now offering a source of phycocyanin that might eventually be distributed in supplement form – but it is 4-5-fold more expensive per unit phycocyanin than the phycocyanin in intact spirulina, so it will be a pricey proposition.)

Fortunately, the flavor of spirulina can be masked to a degree. It can be reasonably palatable when a tablespoon of spirulina is blended with a cup of soy milk and a ripe banana or other fruit, with a little extra sweetener. In a commercial product known as Chocolatl Verde, the flavor of spirulina is masked with cocoa powder; most people find this acceptable – some even like it - when two scoops (providing 15 grams of spirulina) are blended into a cup of vanilla soy milk. (Available online: <http://www.nutriguard.com/vitamin-store/phytochemicals-protective-foods/50-chocolatl-verde.html>. Mea culpa: the author developed and markets this product.)

At this point, no one can guarantee that spirulina will provide humans with the range of health benefits seen in rodents – the clinical trials necessary to assess this simply haven't been done to date, and we can't yet be sure that humans metabolize PhyCB the way that rodents do. But nothing prevents you from using your common sense and adding spirulina to your daily diet. In fact, spirulina was a key component of the diet of the Aztecs, and is still used as food by some tribes in East Africa; these groups simply skimmed wild-growing spirulina from the surface of lakes. Spirulina is rich in protein and low in fat, a good source of essential vitamins and minerals, and is notably high in the eye-protective carotenoid zeaxanthin. It has proved to be safe in both rodent and clinical studies, and the farmed spirulina grown in the U.S. – made by the Earthrise and Cyanotech companies - has been awarded Generally Recognized As Safe status from the U.S. government. In rodents, not only is spirulina not teratogenic – it prevents birth defects when pregnant rodents are fed teratogens!^{35, 36} Adding spirulina to your diet is simply a smart choice.

References

- (1) McCarty MF. Clinical potential of Spirulina as a source of phycocyanobilin. *J Med Food* 2007 December;10(4):566-70.
- (2) Zheng J, Inoguchi T, Sasaki S et al. Phycocyanin and phycocyanobilin from *Spirulina platensis* protect against diabetic nephropathy by inhibiting oxidative stress. *Am J Physiol Regul Integr Comp Physiol* 2013 January 15;304(2):R110-R120.
- (3) McCarty MF. "Iatrogenic Gilbert syndrome"--a strategy for reducing vascular and cancer risk by increasing plasma unconjugated bilirubin. *Med Hypotheses* 2007;69(5):974-94.

- (4) McCarty MF, Barroso-Aranda J, Contreras F. A two-phase strategy for treatment of oxidant-dependent cancers. *Med Hypotheses* 2007;69(3):489-96.
- (5) Lanone S, Bloc S, Foresti R et al. Bilirubin decreases nos2 expression via inhibition of NAD(P)H oxidase: implications for protection against endotoxic shock in rats. *FASEB J* 2005 November;19(13):1890-2.
- (6) Matsumoto H, Ishikawa K, Itabe H, Maruyama Y. Carbon monoxide and bilirubin from heme oxygenase-1 suppresses reactive oxygen species generation and plasminogen activator inhibitor-1 induction. *Mol Cell Biochem* 2006 October;291(1-2):21-8.
- (7) Jiang F, Roberts SJ, Datla S, Dusting GJ. NO modulates NADPH oxidase function via heme oxygenase-1 in human endothelial cells. *Hypertension* 2006 November;48(5):950-7.
- (8) Vitek L, Jirsa M, Brodanova M et al. Gilbert syndrome and ischemic heart disease: a protective effect of elevated bilirubin levels. *Atherosclerosis* 2002 February;160(2):449-56.
- (9) Schwertner HA, Vitek L. Gilbert syndrome, UGT1A1*28 allele, and cardiovascular disease risk: possible protective effects and therapeutic applications of bilirubin. *Atherosclerosis* 2008 May;198(1):1-11.
- (10) Inoguchi T, Sasaki S, Kobayashi K, Takayanagi R, Yamada T. Relationship between Gilbert syndrome and prevalence of vascular complications in patients with diabetes. *JAMA* 2007 September 26;298(12):1398-400.
- (11) Horsfall LJ, Nazareth I, Pereira SP, Petersen I. Gilbert's syndrome and the risk of death: a population-based cohort study. *J Gastroenterol Hepatol* 2013 May 22.
- (12) Romay C, Gonzalez R, Ledon N, Ramirez D, Rimbau V. C-phycoerythrin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. *Curr Protein Pept Sci* 2003 June;4(3):207-16.
- (13) McCarty MF. Clinical potential of Spirulina as a source of phycocyanobilin. *J Med Food* 2007 December;10(4):566-70.
- (14) Chamorro G, Perez-Albiter M, Serrano-Garcia N, Mares-Samano JJ, Rojas P. Spirulina maxima pretreatment partially protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity. *Nutr Neurosci* 2006 October;9(5-6):207-12.
- (15) Riss J, Decorde K, Sutra T et al. Phycobiliprotein C-Phycocyanin from Spirulina platensis Is Powerfully Responsible for Reducing Oxidative Stress and NADPH Oxidase Expression Induced by an Atherogenic Diet in Hamsters. *J Agric Food Chem* 2007 September 19;55(19):7962-7.
- (16) Zheng J, Inoguchi T, Sasaki S et al. Phycocyanin and Phycocyanobilin from Spirulina Platensis Protect against Diabetic Nephropathy by Inhibiting Oxidative Stress. *Am J Physiol Regul Integr Comp Physiol* 2012 October 31.
- (17) Chen LL, Zhang SF, Huang DN, Tan JQ, He SH. [Experimental study of spirulina platensis in treating allergic rhinitis in rats]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2005 February;30(1):96-8.

- (18) Kim HM, Lee EH, Cho HH, Moon YH. Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by spirulina. *Biochem Pharmacol* 1998 April 1;55(7):1071-6.
- (19) Gonzalez de RC, Miranda-Zamora R, Diaz-Zagoya JC, Juarez-Oropeza MA. Preventive effect of *Spirulina maxima* on the fatty liver induced by a fructose-rich diet in the rat, a preliminary report. *Life Sci* 1993;53(1):57-61.
- (20) Rodriguez-Hernandez A, Ble-Castillo JL, Juarez-Oropeza MA, Diaz-Zagoya JC. *Spirulina maxima* prevents fatty liver formation in CD-1 male and female mice with experimental diabetes. *Life Sci* 2001 July 20;69(9):1029-37.
- (21) Fujimoto M, Tsuneyama K, Fujimoto T, Selmi C, Gershwin ME, Shimada Y. *Spirulina* improves non-alcoholic steatohepatitis, visceral fat macrophage aggregation, and serum leptin in a mouse model of metabolic syndrome. *Dig Liver Dis* 2012 September;44(9):767-74.
- (22) Pabon MM, Jernberg JN, Morganti J et al. A spirulina-enhanced diet provides neuroprotection in an alpha-synuclein model of Parkinson's disease. *PLoS ONE* 2012;7(9):e45256.
- (23) Tobon-Velasco JC, Palafox-Sanchez V, Mendieta L et al. Antioxidant effect of *Spirulina* (*Arthrospira*) *maxima* in a neurotoxic model caused by 6-OHDA in the rat striatum. *J Neural Transm* 2013 February 21.
- (24) Ramirez D, Gonzalez R, Merino N, Rodriguez S, Ancheta O. Inhibitory effects of *Spirulina* in zymosan-induced arthritis in mice. *Mediators Inflamm* 2002 April;11(2):75-9.
- (25) Rasool M, Sabina EP, Lavanya B. Anti-inflammatory effect of *Spirulina fusiformis* on adjuvant-induced arthritis in mice. *Biol Pharm Bull* 2006 December;29(12):2483-7.
- (26) Kumar N, Singh S, Patro N, Patro I. Evaluation of protective efficacy of *Spirulina platensis* against collagen-induced arthritis in rats. *Inflammopharmacology* 2009 June;17(3):181-90.
- (27) Ramirez D, Gonzalez R, Merino N, Rodriguez S, Ancheta O. Inhibitory effects of *Spirulina* in zymosan-induced arthritis in mice. *Mediators Inflamm* 2002 April;11(2):75-9.
- (28) Gonzalez R, Rodriguez S, Romay C et al. Anti-inflammatory activity of phycocyanin extract in acetic acid-induced colitis in rats. *Pharmacol Res* 1999 January;39(1):55-9.
- (29) Coskun ZK, Kerem M, Gurbuz N et al. The study of biochemical and histopathological effects of spirulina in rats with TNBS-induced colitis. *Bratisl Lek Listy* 2011;112(5):235-43.
- (30) Penton-Rol G, Martinez-Sanchez G, Cervantes-Llanos M et al. C-Phycocyanin ameliorates experimental autoimmune encephalomyelitis and induces regulatory T cells. *Int Immunopharmacol* 2011 January;11(1):29-38.
- (31) Penton-Rol G, Marin-Prida J, Pardo-Andreu G et al. C-Phycocyanin is neuroprotective against global cerebral ischemia/reperfusion injury in gerbils. *Brain Res Bull* 2011 August 10;86(1-2):42-52.
- (32) Ichimura M, Kato S, Tsuneyama K et al. Phycocyanin prevents hypertension and low serum adiponectin level in a rat model of metabolic syndrome. *Nutr Res* 2013 May;33(5):397-405.

- (33) Wang Y, Chang CF, Chou J et al. Dietary supplementation with blueberries, spinach, or spirulina reduces ischemic brain damage. *Exp Neurol* 2005 May;193(1):75-84.
- (34) Hwang JH, Lee IT, Jeng KC et al. Spirulina prevents memory dysfunction, reduces oxidative stress damage and augments antioxidant activity in senescence-accelerated mice. *J Nutr Sci Vitaminol (Tokyo)* 2011;57(2):186-91.
- (35) Vazquez-Sanchez J, Ramon-Gallegos E, Mojica-Villegas A, Madrigal-Bujaidar E, Perez-Pasten-Borja R, Chamorro-Cevallos G. Spirulina maxima and its protein extract protect against hydroxyurea-teratogenic insult in mice. *Food Chem Toxicol* 2009 November;47(11):2785-9.
- (36) Paniagua-Castro N, Escalona-Cardoso G, Hernandez-Navarro D, Perez-Pasten R, Chamorro-Cevallos G. Spirulina (*Arthrospira*) protects against cadmium-induced teratogenic damage in mice. *J Med Food* 2011 April;14(4):398-404.
- (37) Marcel AK, Ekali LG, Eugene S et al. The effect of *Spirulina platensis* versus soybean on insulin resistance in HIV-infected patients: a randomized pilot study. *Nutrients* 2011 July;3(7):712-24.