

Bilirubin and Phycocyanobilin vs. the Fifteen Leading Causes of Death

Mark F. McCarty, NutriGuard Research, Inc., 1051 Hermes Ave., Encinitas, CA 92024

Free bilirubin functions physiologically as a potent inhibitor of NADPH oxidase, and this activity can be mimicked by phycocyanobilin (PhyCB), a closely related compound which constitutes about 0.6% of the dry weight of the microalga spirulina.¹⁻⁵ Moreover, rodent studies as well as limited clinical experience suggest that orally administered PhyCB (whether given as whole spirulina, phycocyanin, or free PhyCB) can achieve this inhibition in vivo.⁵⁻¹¹

In a huge recent prospective epidemiological analysis, examining the records of over half a million British primary care patients following for an average of over 8 years, Horsfall and colleagues found that, comparing those in the tenth decile of baseline serum total bilirubin level with those in the first decile, total mortality was about 36% (men) and 25% (women) lower in the former group.¹² Importantly, this study excluded individuals whose baseline bilirubin may have been elevated owing to liver disorders or hemolytic disease.

There is suggestive evidence, derived from bilirubin epidemiology, rodent studies entailing administration of biliverdin/bilirubin or phycocyanin/spirulina, and studies documenting a pathogenic role for activated NADPH oxidase, that optimal free bilirubin levels, as well as administration of optimal amounts of PhyCB, may help to prevent or control 12 of the 15 leading causes of death in the U.S., as enumerated in National Vital Statistics Reports¹³ :

1. Diseases of the heart (heart disease)¹⁴⁻²⁹
2. Malignant neoplasms (cancer)^{12, 30-35}
3. Cerebrovascular diseases (stroke)³⁶⁻³⁹
4. Chronic lower respiratory diseases¹²
5. Accidents (unintentional injuries) ---
6. Alzheimer's disease⁴⁰⁻⁴⁴
7. Diabetes mellitus (diabetes)⁴⁵⁻⁵²
8. Influenza and pneumonia^{53, 54}
9. Nephritis, nephritic syndrome and nephrosis⁵⁵⁻⁶⁷
10. Septicemia⁶⁸⁻⁷³
11. Intentional self-harm (suicide) ---
12. Chronic liver disease and cirrhosis⁷⁴⁻⁸³
13. Essential hypertension and hypertensive renal disease (hypertension)^{29, 84-101}
14. Parkinson's disease^{40, 102-109}
15. Assault (homicide) ---

It is not inconceivable that bilirubin/PhyCB could also influence risk for suicide. Endogenous depression and major anxiety disorders, which greatly increase risk for suicide, may be associated with increased cerebral oxidative stress. Whether this oxidative stress is mediated by NADPH oxidase, and whether it plays a truly mediating role in these disorders, remains to be determined.¹¹⁰⁻¹¹⁴

It is intriguing to note that ingestion of optimal amounts of PhyCB might enable a greater degree of antioxidant protection than is achieved by many subjects in the upper decile of serum bilirubin. Moreover, it should be feasible to complement the antioxidant activity of PhyCB with additional agents that have great potential as clinical antioxidants, such as astaxanthin, phase II inducers (e.g. lipoic acid, green tea, isothiocyanates, garlic extracts, etc.), melatonin, N-acetylcysteine, and high-dose folate; comprehensive antioxidant strategies of this type have been dubbed “full-spectrum antioxidant therapy”.¹¹⁵⁻¹¹⁹ The desirability of complementary measures stems from the facts that bilirubin/PhyCB seem unlikely to inhibit all isoforms of NADPH oxidase, and that alternative sources of oxidative stress, such as mitochondria, uncoupled NO synthase, and xanthine oxidase, contribute significantly to the pathogenesis of many disorders.

Hence, scope for preventing or postponing many leading causes of death and dysfunction with rational complementary antioxidant measures may be extraordinary. In addition, these measures have the potential for preventing or controlling a number of additional disorders which, while not usually lethal, can notably impair the quality of life.

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