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Review Article

Spirulina Rising: The Application of Microalgae in Protecting Human Health and Treating Disease

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Abstract

Microalgae constitute two-thirds of the earth's biomass. Microalgae have long been cultivated and consumed by humans and they have been recognized as a vital and highly beneficial food source. Also, microalgae may help prevent certain diseases and be applied to promote health and longevity. The oral administration of PhyCB, phycocyanin, or whole Spirulina have shown potential for preventing or treating many human disorders. Spirulina lowered LDL cholesterol in several clinical trails, and was found to exert exert a positive effect on triglycerides, HDL, total cholesterol, blood pressure, and oxidative stress markers. Microalgae are abundant sources of the essential fatty acid, gamma-linolenic acid (GLA). A marine alga, *Crypthecodinium cohnii*, produces the long-chain omega-3 docosahexaenoic acid (DHA). DHA, taken daily, favorably influences memory function in healthy older adults experiencing age-related cognitive decline. The microalgae of the genus Dunaliella are abundant in the more bioactive 9-cis form (compared to the all-transform) of beta-carotene. Spirulina can lessen exercise-induced blood oxidative stress markers and augment fat burning during submaximal exercise. Diets abundant in these microalgae-derived nutrients protect against macular degeneration. Spirulina may enhance immunity and act as an anticancer and carcinopreventive agent. A commercial preparation, Immulina, has been found to boost natural killer (NK) cell activity stimulating dendritic cells, which are required for NK cell activation. Calcium spirulan, extracted from Spirulina, inhibits the infectivity of specific viruses, including the human immunodeficiency virus (HIV), in cell culture studies. The oral administration of Spirulina can ameliorate for allergic rhinitis. Additional antioxidant options are available to complement PhyCB and AST antioxidant actions. By combining doses of PhyCB and AST with specific adjunctive antioxidants, "full-spectrum antioxidant therapies" may be achieved. Specific research studies have indicated possible contraindications for high doses of Spirulina or PhyCB. However, any side effects should be cleared from the body within 24–48 hours of discontinuing Spirulina administration. Spirulina is the most readily-available and promising microalgae currently under commercial production in various parts of the world. Spirulina, along with other microalgae should be further investigated as supplements for human health promotion and maintenance, and the treatment or amelioration of disease, and as a sustainable, cost-effective, nutrition-rich, conscientious, and sustainable human food source.

Keywords: Anti-Inflammatory; Astaxanthin; HIV; Microalgae; Omega-3 Fatty Acid DHA; Phase 2 Response; Phycocyanobilin; Phyconutrients; Treg Cells; Zeaxanthin

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; AST: Astaxanthin; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; GLA: Gamma-Linolenic Acid; HIV: Human Immunodeficiency Virus; NOX: NADPH Oxidase; O_2: Oxygen; PhyCB: Phycocyanobilin; PPAR: Alpha: Peroxisome Proliferator-Activated Receptor

Introduction

Microalgae are a natural and feasible source of phycochemical antioxidants. They have anti-inflammatory characteristics and may lessen the impact of autoimmune disorders. Specific microalgae can provide omega-3 fatty acid DHA. Microalgae may help prevent specific diseases and could be used to promote health and longevity. Microalgae constitute two-thirds of the earth's biomass; thus, they should be considered for applications in medicine and preventive medicine as well as human nutrition, particularly in countries where people have insufficient food sources and suffer from malnutrition. Microalgae have an extensive history of cultivation and consumption and, historically, have been known for its health benefits and as a food source. However, to achieve their promise, several diverse but interconnected factors must converge. Microalgae, particularly Spirulina, must be successfully cultivated in diverse regions and climates around the world at an affordable end-user price, its taste must become ubiquitously palatable, and governments and people must be made aware of the life-sustaining properties of this elemental and promising phyconutrient and food source.

The implications of this research for human health are significant, with the assumption that humans metabolize oral phycocyanobilin (PhyCB) similar to the metabolic pathways of rodents. The oral administration of PhyCB, phycocyanin, or whole Spirulina shows the potential to prevent and or treat the entire range of human disorders—in which over activation of NOX (or at least those forms of NOX production inhibitable by bilirubin) plays a key pathogenic role. This pathological over-activation of NOX may contribute to a high proportion of the degenerative disorders which afflict humankind; to which PhyCB, phycocyanin, or whole Spirulina could be beneficially applied.

Discussion

Spirulina and PhyCB applications

Can oral PhyCB inhibit NOX activity in humans as it does in rodents? What intake of Spirulina would be required to achieve an optimal antioxidant effect? By extrapolating from rodent studies, it has been estimated that humans might need to take 15–30 grams of Spirulina daily to achieve the high level of antioxidant benefit demonstrated in rodent studies [1]. A few clinical studies have attempted to assess the effects of Spirulina in humans. However, most of those studies used smaller doses, not more than 2–3 grams daily in capsule form. Thus, higher-dose studies are needed: 15–30 grams of Spirulina corresponds to 30–60 Spirulina capsules or tablets.

Most people find Spirulina's flavor and odor unpleasant—which are drawbacks to its consumption, and why pills are the preferred route of administration. Nevertheless, this consumption issue can be addressed partially by creating functional foods or "smoothies", a drink in which Spirulina's flavor and odor are masked to some extent by more desirable flavors, such as cocoa or fruit. Italian scientists have discovered that—by growing Spirulina under specific conditions in wholly-enclosed photobioreactors (as opposed to open ponds currently used by most contemporary Spirulina growers)—Spirulina's undesirable flavor and odor are abated. An adjunctive strategy to overcome the palatability issue is to develop a practical way of producing PhyCB-enriched Spirulina extracts that can be administered in adequate doses in capsule or tablet form.

Although a methanol-based technique for freeing PhyCB from its bond to phycocyanin is known, this technique has a low yield and may not be commercially feasible [2]. An alternative approach may be to hydrolyze Spirulina protein thoroughly, then extract the PhyCB (presumably still attached to short peptide chains) selectively, using appropriate solvents. Experienced extraction chemists, given sufficient time and support, could devise a practical, commercially-viable method for producing PhyCB-enriched Spirulina extracts. In the future, highly-purified PhyCB or PhyCB peptide conjugates could be developed and administered intravenously in the treatment of emergency medical conditions, such as heart attack or stroke. Topical application of PhyCB extracts might prove to have clinical value in specific dermatological conditions characterized by oxidative stress.

Spirulina's effects on triglycerides, HDL, total cholesterol, and blood pressure

In a study comprising healthy young- to middle-aged adults, the daily ingestion of 4.5 grams of Spirulina for 6 weeks was associated with a 29% reduction in triglycerides, a significant increase in HDL cholesterol, an 18-point drop in total cholesterol, and a reduction in

blood pressure, averaging 10 points (systolic) and 7 points (diastolic) [3]. These results can be interpreted as Spirulina having a favorable impact on metabolic syndrome (insulin resistance syndrome), which is mediated in part by oxidative stress in fat cells. However, the reduction in LDL cholesterol cannot be interpreted in this way and might be mechanistically related to increased excretion of cholesterol and bile acids, as demonstrated in a rat study using oral phycocyanin [4]. Analogous findings were observed in a controlled Korean study which tested 8 grams of Spirulina daily in people with diabetes: triglycerides and oxidative stress markers fell significantly, blood pressure was moderated, and a significant rise in adiponectin (a protective hormone produced by fat tissue and inhibited by oxidative stress) was noted [5].

Spirulina lowered LDL cholesterol in several clinical trials. A rat study demonstrated that oral phycocyanin boosted bile acid and cholesterol excretions—an effect that could be expected to lower LDL cholesterol levels. Several drugs used to lower LDL cholesterol block cholesterol or bile acid reabsorption. However, it was unclear why phycocyanin had this effect. The effect may have been mediated by the antioxidant activity of the derived PhyCB, or intact phycocyanin may be required for the effect. Functional foods that are abundant sources of Spirulina can be expected to aid LDL cholesterol control. The proinflammatory effect of LDL particles on the linings of arteries is mediated mostly by NOX.

Spirulina and essential fatty acids

Spirulina advocates often refer to this microalga as a source of the essential fatty acid—the omega-6 type—known as gamma-linolenic acid (GLA). Like the linoleic acid found in many vegetable oils and grains, GLA is a precursor for a class of hormonal compounds, known as prostanoids. However, GLA works much more efficiently in this regard, as linoleic acid must be converted to GLA. The human capacity to perform this conversion is limited as human cells are low in the required enzyme, delta-6-desaturase. Hence, GLA supplementation has been recommended in certain circumstances in which the increased production of specific prostanoids might be desired. Spirulina is of questionable value for this application in that, although GLA constitutes up to a quarter of the fat (fatty acids) in Spirulina; the total Spirulina fat content is about 5% of its dry weight. Subsequently, little more than 100 milligrams of GLA can be obtained from a 10-gram serving of Spirulina—a dose that is unlikely to have significant beneficial impact. Theoretically, Spirulina oil can be extracted for use as a GLA supplement, but terrestrial sources of GLA, such as evening primrose or borage oil, are far more cost-effective to produce.

The long-chain omega-3 fats found in fish are well known to have a range of beneficial effects on human health. In sufficient amounts, they exert anti-inflammatory effects, stabilize blood clotting cells (platelets), boost the production of protective nitric oxide by the endothelial cells that line the arteries, decrease elevated blood levels of triglycerides, aid in blood pressure control, reduce the risk for disorders of heart rhythm that can cause sudden death, possibly reduce the risk for specific cancers, and may protect the retina from macular degeneration [6–8]. However, fish do not synthesize omega-3 fats, instead they obtain them, directly or indirectly, from marine algae, which are adept at omega-3 production. The possibility of obtaining long-chain omega-3s directly from algae is attractive to vegetarians, who avoid consuming fish or products derived from fish. Humans have a limited capacity to convert shorter-chain omega-3s produced by terrestrial plants into longer-chain omega-3s—for example, converting alpha-linolenic acid, found in flax oil and walnuts, into the longer-chain omega-3s, which have the highest health-protective potential [8–10].

Algae as a source of DHA

A marine alga, known as *Crypthecodinium cohnii*, is adroit in the production of the long-chain omega-3 docosahexaenoic acid (DHA) [11–13]. Fat constitutes over 40% of this organism's dry mass and up to half of this fat is DHA. Martek Biosciences Corporation has commercialized the production of DHA from *Crypthecodinium cohnii* and supplies DHA as a triglyceride or ethyl ester. In a recent controlled clinical study, 900 milligrams of this algal DHA daily was found to have a favorable impact on memory function in older adults experiencing age-related cognitive decline [14].

The DHA content of retinal photoreceptors is remarkably high. This DHA appears to play an crucial functional role, as people whose diets are comparatively copious in long-chain omega-3s are less susceptible to macular degeneration [15–18]. Also, DHA is one of the chief fatty acids in the brain. The favorable impact of supplemental DHA on memory in the elderly may reflect a key role for DHA in healthy brain function. People whose diets are plenteous in long-chain omega-3s are at a reduced risk for depressive disorders. The administration of eicosapentaenoic acid (EPA) or fish oil tends to be beneficial for depression. However, the administration of DHA alone has more equivocal benefit [17]. In the endothelial cells, which line the arteries, DHA boosts the production of protective nitric oxide [18–20]. Like other omega-3 fats, the DHA in heart membranes may reduce the risk for sudden death rhythm disorders [21,22]. Algal DHA appears to be as effective as fish oil or pure EPA for stabilizing platelets, decreasing blood pressure, and lowering triglycerides [23].

Some of the anti-inflammatory benefits of long-chain omega-3s are mediated by EPA, not found in algal oil. However, humans are capable of "retroconverting" DHA to EPA to some extent, such that supplementation with algal DHA can modestly increase tissue EPA levels [24]. The current clinical literature suggests that algal DHA may be at least as beneficial as fish oil regarding the range of health benefits attributable to dietary omega-3. The main drawback of algal DHA, at this point is that—milligram per milligram—DHA is decidedly more expensive than fish oil. Thus, vegetarians will likely continue to constitute the leading market for this product, until algal DHA production becomes more cost-efficient compared to current processes or the fish population reaches the brink of extinction, resulting in fish resources becoming scarce and cost-prohibitive.

Algal beta-carotene from Dunaliella; the 9-cis form, RXR, and PPAR-alpha

Most commercial supplements provide synthetic beta-carotene, that has an "all-trans" structure. The vast majority of the beta-carotene in carrots is in this all-trans form. However, an alternate form of beta-carotene, known as 9-cis, is found in varying degrees in fruits and vegetables—and specific algae are rich in this compound. The microalgae of the genus Dunaliella are abundant in beta-carotene; about half of its beta-carotene is in the 9-cis form. Dunaliella is produced commercially as a source of natural beta-carotene for the nutraceutical market [25]. The 9-cis form may have physiological properties not demonstrated by the more widely available all-trans form.

In the intestinal tract, 9-cis beta-carotene can be converted to 9-cis retinoic acid, a compound capable of activating an intracellular receptor, known as retinoid X receptor (RXR). In people whose dietary beta-carotene is entirely in the all-trans form, the liver can convert some of this all-trans form to 9-cis retinoic acid. However, supplementation with 9-cis beta-carotene, as opposed to supplementation with all-trans beta-carotene, may be more helpful for raising tissue 9-cis retinoic acid levels—although this pathway has not yet been established. The RXR receptor interacts with and boosts the activity of a range of other intracellular receptors that respond to specific hormones and drugs. One of these receptors, peroxisome proliferator-activated receptor (PPAR-alpha), is activated by a class of drugs known as fibrates, that are used to improve blood fat profiles by lowering blood triglyceride levels while raising protective HDL cholesterol levels. Israeli scientists have reported that, in fibrate-treated patients, concurrent supplementation with Dunaliella-derived beta-carotene—rich in the 9-cis form—nearly doubled its impact of the drug on HDL levels [26]. The scientists suggested that this augmentation effect reflected a superior activation of the RXR receptor, owing to 9-cis beta-carotene ingestion. More recently, working with genetically-altered mice prone to atherosclerosis (as they lacked LDL receptors), researchers found that the sequelae of a high-fat diet in raising LDL cholesterol levels and the resultant atherosclerosis were attenuated when the mice were also fed Dunaliella beta-carotene. These researchers determined that the magnitude of this protective effect was proportional to the amount of 9-cis beta-carotene that was fed to the mice [27]. It is reasonable to suspect that increased liver levels of 9-cis retinoic acid and RXR activity played a role in this outcome. The authors concluded "9-cis beta-carotene may have the potential to inhibit atherogenesis in humans" [27]. However, there are no reports that algal beta-carotene can influence fat blood levels in people not taking fibrates.

Further research is needed to clarify whether the administration of 9-cis beta-carotene enhances the activation of RXR receptors in the liver and, if so, what implications will this have on liver function and overall health. Potentially, the increased activation of RXR could boost the bioactivity of vitamin D, an effect which might reduce the risk for specific cancers [28].

Spirulina and exercise

A controlled Greek study investigated the impact of Spirulina supplementation (6 grams daily) on exercise [29]. In this study, the subjects were asked to exercise at submaximal intensity on a treadmill for 2 hours; immediately after, they were required to sprint at maximal intensity on the treadmill until exhausted. The time until exhaustion was over 30% longer when the subjects had been taking Spirulina. Moreover, Spirulina prevented exercise-induced increases in blood-based, oxidative-stress markers and increased the net contribution of fat-burning to the submaximal exercise (possibly reflecting the protection of muscle mitochondria from oxidative stress).

Can Spirulina make exercise a more effective adjunct for promoting leanness? The higher relative usage of stored fat during exercise implies enhanced preservation of glycogen stores—that can be rate-limiting for endurance during prolonged moderate-intensity exertion. (Cuban and Chinese Olympic teams have been known to use Spirulina in their dietary regimes while training.)

Spirulina, carotenoids, and macular degeneration

Spirulina, like most microalgae, is replete with carotenoids, including zeaxanthin; however, it fails to make astaxanthin (AST) as it lacks the enzyme beta-carotene ketolase (a flaw that could be corrected by bioengineering). Zeaxanthin, like its chemical cousin lutein, appears to have the potential for preventing and perhaps controlling macular degeneration—the most common cause of blindness in the elderly [30]. A tablespoon dose of Spirulina (about 15 grams) contains approximately 12 milligrams of zeaxanthin—an ample dose compared to usual dietary intakes. Zeaxanthin and lutein may provide crucial protection from oxidative light damage to the macular photoreceptors of the retina. Diets diets rich in these nutrients offer protection from macular degeneration. People consuming such diets are at a lower risk for macular degeneration, whereas people who do develop this disorder tend to have lesser amounts of these antioxidants in their retinas. Supplemental intakes of lutein and zeaxanthin are effective for boosting retinal levels of these nutrients.

Spirulina in enhanced immunity and as an anticancer and carcinopreventive agent

Spirulina contains cell wall polysaccharides (complex chains of sugar molecules) that have notable immunostimulant activity and thus might help protect against infectious diseases and cancer [31–33]. A commercial preparation of these polysaccharides, known as Immulina, has been tested in mice and humans, and has been found to increase the activity of natural killer (NK) cells by exerting a stimulatory effect on dendritic cells, that are required for NK cell activation. NK cells are capable of destroying certain types of cancer cells or precancerous tissues and are considered to be essential mediators of the immune surveillance mechanism—helping the body's immune system ward off cancer. The oral administration of Spirulina polysaccharide in mice was shown to suppress the growth of a transplanted mouse melanoma, known to be a target for the cytotoxic activity of NK cells [33].

The cell walls of several commercially-produced microalgae, such as *Chlorella pyrenoidosa* and *Aphanizomenon flos-aquae*, contain complex polysaccharides which have immunostimulant activity, reflecting their ability to activate specific receptors (known as toll receptors) on dendritic cells [34,35]. This phenomenon presumably reflects that the human immune system evolved to recognize cell wall polysaccharides in the membranes of pathogenic microbes. Although these food algae are not pathogenic, their cell wall polysaccharides are partially absorbable when ingested and effectively trick the immune systems into behaving as if it were under pathogenic attack. This property is not unique to microalgae; specific mushrooms and aloe vera extract are also known to contain immunostimulant polysaccharides. Also, it is worth noting that aphanizomenon (but not chlorella), is a source of phycocyanin and PhyCB [36–39]; however, its commercial production is dwarfed by that of Spirulina.

Spirulina application in HIV and other viral infections

Calcium spirulan is a sulfur-containing polysaccharide extracted from Spirulina. In cell culture studies, it inhibited the infectivity of a range of viruses, including the human immunodeficiency virus (HIV) that causes acquired immune deficiency syndrome (AIDS). Other viruses' replications that are suppressed by this substance include measles, mumps, herpes, influenza type A, and cytomegalovirus—col-

lectively known as "enveloped" viruses in that they are enclosed in a membrane analogous to cellular membranes. For these viruses to invade a cell, their membrane must first fuse with those of the target cell; calcium spirulan appears to work by preventing this membrane fusion. It is unclear if the oral administration of calcium spirulan would be useful for preventing or treating viral infections. Presumably, a sufficient quantity of calcium spirulan would have to be absorbed intact to accomplish this prevention or treatment. Future studies may reveal if calcium spirulan has potential as an antiviral nutraceutical.

Spirulina's ameliorating effects on specific allergies

Oral Spirulina administration can be beneficial for allergies—more specifically, allergic rhinitis, the sniffling and sneezing reaction to allergens in both rats and humans [40–44]. However, the basis of this effect remains undetermined. Allergic reactions typically involve the release of histamine and other proinflammatory mediators by a select type of immune cell, the mast cell. The activation of NOX in mast cells appears to trigger this release; thus, the NOX-inhibitory activity of PhyCB might play a role in Spirulina's favorable influence on allergy [45]. The immune-modulatory effects of Spirulina polysaccharide or PhyCB (independent of NOX inhibition) merit study. There is evidence that Spirulina ingestion boosts intestinal production of a type of antibody (IgA) that tends to decrease the likelihood of allergic reactions. The Spirulina doses used in the clinical studies were quite low (about 2 grams daily), so it is questionable whether NOX inhibition could have been wholly responsible for the observed benefits.

Towards a full-spectrum antioxidant therapy

Under specific conditions, it may prove useful to complement the antioxidant activity of PhyCB and AST with additional antioxidant measures. PhyCB may not be capable of inhibiting all forms of NOX that play a role in health disorders. Moreover, only partial NOX inhibition is appropriate since at least a modest level of NOX activity is needed for destroying bacteria and cellular regulation. Also, AST may not be able to limit increased mitochondrial superoxide production triggered by specific proinflammatory hormones.

Additional antioxidant options are available to complement the antioxidant activity of PhyCB and AST. The expression of a range of cellular antioxidant enzymes, as well as the synthesis of the critical intracellular oxidant scavenger glutathione, can be enhanced by several phytochemicals that trigger a "phase 2 response" [46,47]. Some of these phytochemicals are found in foods thought to have cancer-preventive activity, such as cruciferous vegetables, garlic, and green tea. Thus, relevant extracts of these foods may be clinically useful as antioxidant nutraceuticals. The compound lipoic acid, a bioenergy catalyst found in foods and produced in the human body, can trigger a phase 2 response. This reaction might account for the documented utility of lipoic acid administration in the treatment of diabetic nerve damage [48–51]. The endogenous hormone melatonin exerts an effect on numerous tissues and provokes an increased expression of antioxidant enzymes and synthesis of glutathione [52,53]. Exogenous melatonin can be safely administered orally, but should only be taken before bedtime (as a nocturnal burst of melatonin production plays a vital role in synchronizing the body's biorhythms). Cellular glutathione synthesis can be bolstered by the administration of nutraceuticals—such as N-acetylcysteine or cystine—that increase cellular levels of the amino acid cysteine (required for glutathione synthesis) [54–56]. In very high doses, the vitamin folic acid can demonstrates exceptional oxidant scavenging activity in some tissues. A high-dose of folate has been reported to be protective in a rat model of ischemia-reperfusion damage of the heart. In clinical studies, it has been found to improve the protective function of the endothelial lining of arteries [57–62].

By employing effective doses of PhyCB and AST as a core strategy, and complementing this core strategy with specific adjunctive antioxidant options (noted above), a complex regimen—dubbed "full-spectrum antioxidant therapy"—could be devised [63,64]. Such therapies could ameliorate or eliminate oxidative stress—that induces specific health disorders and contributes to the losses in physiological capacity that is characteristic of aging.

Possible PhyCB and Spirulina side effects

Are there possible side effects to using PhyCB and Spirulina? The excessive production of PhyCB inhibits NOX. The excessive production of NOX is unhealthy; however, some NOX production is beneficial to the human physiology. Thus, strong inhibition of NOX could be counterproductive. Nevertheless, PhyCB is well-tolerated, at least in a modest dose range that corresponds to feasible Spirulina intakes. People with Gilbert syndrome do not appear to have unusual health problems; in some respects, they appear to be quite healthy. Since PhyCB is expected to mimic the bioactivity of bilirubin, people who ingest appropriate amounts of PhyCB are unlikely to be more compromised than those who habor Gilbert syndrome.

Specific Mexican studies have found that prolonged Spirulina intake by rodents or dogs in high amounts appears safe [65,66]. Spirulina exerts no teratogenic effects when fed to pregnant rodents [67,68]. Moreover, recent studies found that Spirulina given to pregnant rodents protected the fetuses from potent teratogens. (NOX-induced oxidative stress is often a mediator of birth defects [69,70].) Spirulina may have the potential for preventing or controlling preeclampsia, a common disorder of pregnancy characterized by high oxidative stress [71–74].

Clinical research may eventually establish specific contraindications for high doses of PhyCB or Spirulina. However, if side effects occur, PhyCB will likely be cleared from the body within a couple of days of discontinuing Spirulina administration. It remains to be established if high-dose of Spirulina has relevant antioxidant activity in humans.

Conclusion

PhyCB, AST, and other protective xanthophyll carotenoids, immunostimulant polysaccharides, DHA, and 9-cis beta-carotene, are phyconutrients with tremendous aggregate potential for health enhancement—all of which can be derived in commercially useful quantities from cultivated microalgae. Given the vast number of species of microalgae that populate the planet, it appears likely that scientists will identify additional algal phyconutrients with potential as health-protective nutraceuticals. The development of microalgae as aids to human health and optimal performance is just beginning. Spirulina is the most readily available and promising microalgae currently under commercial production in various parts of the world. Partnerships among biotechnologists, medical researchers, and nutraceutical entrepreneurs can be expected and should be encouraged in the research and development of microalgae as supplements for human health promotion and maintenance, the treatment or amelioration of disease, and as a sustainable, cost-effective, nutrition-rich, conscientious, and sustainable human food source.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest, at the time of its research and writing. Subsequently, Dr. Mark F. McCarty has become co-inventor and co-owner of U.S. and E.U. patents on the use of PhyCB oligopeptides as nutraceuticals and holds an E.U. patent on the use of PhyCB for the prevention and control of diabetic glomerulosclerosis.

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Supplementary Note

Parts of this paper were previously made available in a copyrighted booklet entitled, *A Guide to Health-Protective Microalgal Phyconutrients*, posted on the Capitalife, Inc. (USA) website, and used with permission.

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