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Review Article

Spirulina Consumption: Concerns Regarding Contaminants and Uncommon but Possible Adverse Reactions and Interactions

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Abstract

Humans primarily consume microalgal products due to their nutritional and immunostimulatory properties. However, these products may not benefit all persons since specific microalgae may not be compatible with all humans. While consuming microalgal products in autoimmune diseases and their coadministration with drugs (anticoagulants, hypoglycemics, and certain herbal products), a medical specialist should closely monitor their use in patients. Hence, individuals should consult with medical experts regarding their intake of Spirulina instead of relying wholly from cyberspace. Also, in some circumstances, specific algae can be a significant source of toxins.

Although Spirulina is not intrinsically toxic, it can accumulate toxins or contaminants from the environment that enter the human system when it is consumed. Mass cultivation in open ponds and open photobioreactors is prone to contamination. Also, other toxic cyanobacteria may contaminate the culture medium. The various photobioreactors designs—utilized to increase yield and reduce manufacturing cost—inadvertently provide pathways that adulterate the culture. These dangers must be addressed during the manufacturing and processing of microalgae. With the increasing demand for natural supplements and the growing scientific evidence supporting Spirulina, efforts must be made to boost their production and availability. Moreover, comprehensive research on the safety of these products and possible adverse interactions with medicines, and should be undertaken and supported by the medical and research communities.

This review highlights conditions that require careful monitoring before Spirulina consumption, discusses Spirulina's interactions with specific medicines, and outlines the various sources of contaminants that may enter the algal system at any stage during the organism's life cycle.

Keywords: *Contamination; Cyanobacteria; Microalgae; Photobioreactors; Pollutants*

Abbreviations

FAO: Food and Agriculture Organization; GMP: Good Manufacturing Practice; NCCIH: National Complementary and Integrative Health Center; PBR: photobioreactor; QoL: quality of life; ROS: reactive oxygen species; WHO: World Health Organization

Introduction

The World Health Organisation (WHO) and Food and Agriculture Organization (FAO) consider food and hunger management a core principle. Eradicating hunger and malnutrition are among the prerequisites regarding improving humans' quality of life (QoL).

Dietary supplements, supplementary food products, botanicals, nutraceuticals, and functional foods comprise a new generation of food products. These consumable products can alleviate hunger and provide balanced nutrition to humans across the globe. In this respect, marine life and, especially, algae are receiving significant interest. However, specific regulatory bodies highlight that there should be no compromise in the quality of these supplements.

Therefore, there is an increase in research to generate scientific evidence to support these alternative food sources and determine if they are reliable and harmless comestibles. Formerly, food supplements were considered as providing nutrition and supplying other necessary nutrients absent from a typical daily diet. Such supplements are rich in vitamins, minerals, proteins, and carbohydrates.

Discussion

Terms like dietary supplements, functional foods, and nutraceuticals—used in the commercial world and among food scientists—have specific definitions, but their roles overlap. In short, they provide vital nutrients, aid in disease prevention, and can be ingested as pills or modified food [1]. Furthermore, with technological advancements and the increasing understanding of bodily needs, these supplements were further enriched and fortified with extracts of plants and aquatic organisms. The “natural food” fad helped the popularity and increased the reach of these products among the public—introducing various and novel forms of food [2,3].

The primary difference among these enhanced foods lies in their organic compositions. The initial food supplements contained substances of primary metabolism (carbohydrates, vitamins, and proteins), while the newer forms include secondary products (flavonoids, polyphenols, and organic acids) obtained from plant sources.

The algae advantage as a food supplement is that algae are a source of both forms. Algae-based foods are a growing market. These organisms have long been proven to be a rich source of nutrition [2].

Microalgae constitute the primary biomass of seaweed (a colloquial term). These unicellular organisms naturally inhabit the sea and tropical and subtropical alkaline hot lakes. Among algal species, microalgae form 75% of the species and contribute 40% of the oxygen supply in the atmosphere [4]. Moreover, they can be readily cultivated and have various potential uses. Initially, microalgae were used to feed livestock or as fertilizer.

Historical perspective

The ancient Aztecs harvested algae for food. Spanish soldiers also included it in their diet, consuming it as cakes [5]. Since the benefits of algal extracts have been revealed, food scientists have endeavored to develop and alter specific algae for human consumption. However,

the research has been closely related to the availability of technology, without which the raw materials cannot be converted into usable derivatives.

Nomenclature and taxonomy

Spirulina (belonging to the Arthrospira species) is a cyanobacterium. It is characteristically blue-green, has a left-hand helical morphology, and is known as "spirulina" (*spira* is Latin for spiral). They are free-floating filaments, having cylindrical multicellular trichomes—belonging to the class *Cyanophyceae* and order *Oscillatoriales* [6]. Commercially, the dried biomass of *A. platensis* is known as Spirulina [7].

General assumptions

Microalgae are widely considered to be nontoxic and, hence, popularly used as food supplements. Spirulina as a functional food has many beneficial properties, such as antioxidant, immunostimulatory, anticancer, anti-inflammatory, hypolipemic, and antimicrobial. It is a rich source of vitamins, essential amino acids, and omega 3 fatty acids (alpha-linolenic acid, linoleic acid, stearidonic acid, eicosapentaenoic acid docosahexaenoic acid, and arachidonic acid) [2,8]. The biomass or its phycocyanin-rich fraction can be added to soy milk and fruit juices [9]. A cocoa and Spirulina powder mixture acts as an antioxidant and promotes vascular health, increasing endothelial production of nitric oxide and inhibiting NADPH oxidase [6,10].

Researched and purported benefits

In addition to satisfying human food needs, Spirulina has other valuable properties. Studies by Mathur (2018), Tarantino (2003), Bhowmik., *et al*. (2009), and El-Sheekh., *et al*. (2014) found that Spirulina can inhibit the growth of Gram-negative and Gram-positive bacteria: *E. coli, P. aeruginosa, P. Vulgaris, S. aureus, B. subtilis,* and *B. pumulis*—and the algal extract has antifungal properties against *C. Albicans* [11–14]. The antibacterial property of Spirulina has been applied to create biofunctionalized gold nanoparticles that have antibacterial activity against Gram-positive organisms [15].

Hazards in development, production, and promotion

The nutritional value of microalgae is well-documented. With many consumers moving towards natural supplements, there has been a significant increase in the demand for these products. However, these supplements are not always safe to ingest. Their indiscriminate consumption may lead to an undesirable accumulation of harmful elements or cause drug interactions, adversely affecting human health. Thus, specific diseases and conditions require careful use, close observation, and may be contraindicated. Also, substandard manufacturing practices and storage of these microalgal products may contribute to their toxicity.

With recent research, scores of Spirulina-based products and supplements have found their way to the commercial food market. They are produced and sold in the form of tablets, capsules, and powders. Being easily digestible with high nutrient content, Spirulina has also been validated by the scientific community. As a result, the FDA and the UN consider it safe for human consumption and hail it as food for the future [11,12].

The mass cultivation of Spirulina started in Mexico and China about three decades ago, and later spread to other parts of the world. The cultivation is dependent mainly on environmental conditions, albeit not stringent. Microalgae are relatively straightforward to cultivate. Most commonly, the cultivation of Spirulina is done in open-channel ponds, with paddlewheels used to agitate the water [2].

Adverse effects in physiological conditions, diseases, and drug interactions

Spirulina-based products are generally considered safe, but the literature shows some evidence of mild adverse effects, such as allergy, insomnia, gastric, and autoimmune-mediated skin reactions [16]. A severe case of rhabdomyolysis [17] and one of hepatoxicity [18] have also been reported. The following are possible contraindications, requiring careful consideration before consuming Spirulina as a supplement.

- **Allergy to Spirulina:** The initial ingestion of Spirulina can lead to anaphylaxis, as published in a case report describing a 17-year-old man who had consumed Spirulina tablets, developing an anaphylactic reaction [19]. Also, phycocyanin may be an allergen in some people [20].

- **Pregnancy:** It is generally considered potentially unsafe to consume Spirulina during pregnancy, and Spirulina is not recommended for children. Harmful toxins can reach the infant through breast milk, so lactating women should avoid Spirulina if contamination is suspected. Children are said to be more sensitive to contaminated algal products than adults [21]. Also, neonatal hypercalcemia—due to maternal exposure to a food supplement with Spirulina—has been reported in the literature [22].

- **Phenylketonuria**: Phenylketonuria is an autosomal recessive genetic disorder in which there is an accumulation of phenylalanine. Thus, it is recommended that protein intake be less than 25% of the diet. Spirulina is contraindicated in this condition as it releases phenylalanine [23]. Expectant mothers having phenylketonuria already pose a risk for their unborn child because it is teratogenic (associated with intrauterine growth retardation, low birth weight, microcephaly, and developmental delay, among others).

- **Autoimmune disorders:** There have been sporadic reports cautioning against the use of Spirulina and other herbal products by those afflicted with autoimmune disorders. *A. platensis* was implicated in the exacerbation of Pemphigus Vulgaris and dermatomyositis [24]. The immunostimulatory activity of Spirulina was proven in a human study, which found enhanced natural killer cell function after administration of oral spirulina extract [25].

- **Surgery:** Cyanobacteria have a hypoglycemic effect on the human body. Surgery is a stressful procedure that affects glucose metabolism. Hence, it is recommended to stop the intake of such products at least two weeks before surgery [21].

- **Immunosuppressants:** Spirulina is an immune-stimulator (boosts natural killer cells). In people with autoimmune disorders, medications are prescribed to diminish the immune mechanism of the body. However, coadministration of these drugs with Spirulina-based products results in antagonizing the former by the latter. Commonly prescribed medications for immune disorders are azathioprine, cyclosporine, mycophenolate, tacrolimus, sirolimus, prednisone, and corticosteroids [21].

- **Anticoagulants (in bleeding disorders):** Phycocyanin exhibits COX-2 inhibition and therefore interferes with the blood clotting process. Individuals with bleeding disorders should be vigilant regarding phycocyanin intake [26].

- **Hypoglycemia:** Spirulina is antihyperglycemic as it down-regulates NADPH and NADH, inhibiting fat synthesis. It also enhances hexokinase activity, helping to uptake glucose from the blood by liver cells. Overall, there is higher carbohydrate metabolism and increased glucose utilization at the peripheral body sites. Possibly, Spirulina also inhibits the endogenous synthesis of lipids. Thus, taking Spirulina with antidiabetic medications might pose a hypoglycemic risk [27].

- **Herbals:** Cyanobacteria alter the clotting process. There are herbal products with actions similar to those of Spirulina, such as garlic, ginger, red clover, turmeric, and ginkgo. Combining such products predisposes an individual to bleeding, delays clot formation, and increases the chances of bruising [21].

- Spirulina contaminated with microcystin blue-green algae produce microcystin as part of their defense mechanism and as secondary metabolites that are toxic to higher organisms. When consumed in large quantities, these compounds are hepatotoxic to humans (beyond tolerable daily intake of 0.04 $\mu g \cdot kg^{-1}$ body weight for an adult) [28,29]. As a footnote, Brazil's medical history is blemished by the deaths of 60 people and the suffering of 126 people with various hepatotoxic manifestations (hepatitis and fulminant liver failure), which occurred due to microcystin poisoning as a result of contamination of a hemodialysis system [30].

- **Regarding adverse drug nteractions:** An animal-based study resulted in the down-regulation of the enzymatic activities of CYP1A2 and CYP2E1. There was a significant increase in the levels of mRNA of both CYP2B1 and CYP3A1. These properties indicate that coadministration with cytochrome P substrates may cause drug interactions [31].

- **In microalgal ooverload:** Although Spirulina is packed with nutritional elements, rampant and unwarranted consumption has side effects. High protein and chlorophyll content can cause diarrhoea, nausea, and abdominal cramps. Also, microalgae are rich in phosphorus, which can harm the kidneys when taken beyond the allowed limits. Iron overload can upset the gastrointestinal system and generate reactive oxygen species (ROS), while excessive manganese concentrations have neurotoxic effects [32].

Quality control and good manufacturing practice (GMP)

The quality of microalgal supplements is affected by the presence of cyanotoxins or toxic metals (aluminum, nickel, or lead) that may be due to improper culture, the coexistence of other potentially toxic microalgae linked to a polluted location of cultivation ponds, or from chemical use, such as flocculants and pesticides (Table 1) [32].

How do contamination and toxicity occur?
Through the air; open cultivation systems are more prone to biological pollutants
Coexistence of other potentially toxic microalgae within the culture medium
The geographic location of cultivation ponds (rural, industrial, and agricultural areas) can expose the entire system to polluted water, soil, and air
Large open ponds cannot be sterilized
Sterilization of culture media in mass production uses pesticides that inadvertently contaminate the culture
The design of certain photobioreactors prevents adequate cleaning
Contamination and toxicity controlling factors
Close monitoring during culture to look for physical signs and microscopic evidence
Monitoring of the pH and oxygen concentration of the culture medium
Physical filtration, pulsed electric field application, and ultraviolet radiation eliminate, reduce, or eradicate contaminants
Chemical intervention: triton-N, copper salts, and ammonia
Biological intervention: plant-based pesticides
Using closed-system photobioreactors

Table 1: *Potential sources of toxicity; controlling contamination.*

Large-scale cultivation is prone to biological contaminants, even if the process utilizes open ponds or closed photobioreactors (PBRs). As a result, the quantity and quality of biomass may be adversely affected, with the highest degree of associated risk when the production is for human consumption due to the accumulation of toxins [33]. The biological contaminants that hinder cell growth are zooplankton,

prokaryote bacteria, eukaryotic fungi, eukaryotic protozoa, other algae, and viruses [34]. In general, various harmful elements can reach culture systems and contaminate the biomass.

Contamination can occur due to polluted water. Since mass cultivation of microalgae uses large water bodies, these water bodies cannot be sterilized. However, the culture medium can be disinfected by bleaching or filtering the contaminants before mass cultivation. However, the process is not infallible, and disinfection efficacy lasts only for the growth lag phase. Thus, this water can easily be polluted by filtration [35]. Heavy metals, such as lead, mercury, cadmium, and arsenic (found in fertilizers and pesticides), can also percolate through soil or water, mainly when a cultivation plant is located in agricultural areas [36].

Contamination can occur due to poor air quality. In open ponds, natural air provides the required atmospheric carbon dioxide while removing excess dissolved oxygen. However, an open culture is a prevalent route for biological contaminants. In the case of closed PBRs, the cultures need to be physically agitated to allow a continuous supply of air. Thus, PBRs are susceptible to air pollutants [34].

PBR design

When open cultivation is not feasible—due to space constraints or environmental conditions—PBRs are suitable. An efficient PBR has adequate light penetration, allows quality mixing and mass transfer, and maintains optimal temperature and pH [37]. With increasing scientific and commercial interest in microalgae, newer PBR designs have emerged that enhance yield and reduce production costs. PBRs can be situated outdoors or indoors and provide a more controlled atmosphere—wherein a single species is inoculated and grown.

Closed systems offer a better ceiling regarding yield and are less susceptible to contamination. However, the manufacturing costs are comparatively higher than those of open systems. Advanced PBR designs include tubular PBR, plastic bag PBR, column airlift, and flat-panel airlift. Each design has pros and cons; however, concerning contamination and toxicity, the plastic bag and column airlift designs are challenging to clean and carry higher contamination rates [38,39].

The varied PBR designs result in the formation of "blind angles" within the system: the gas distributor (in membrane photobioreactors), the pipe connection (in tubular photobioreactors), and the sampling systems. Nutrients or microalgae accumulate in these blind angles, contaminating subsequent cultures and corroding the bioreactors [34].

Methods to alleviate contamination

During cultivation and growth, the morphology of the algal species must be evaluated regularly. Contaminant algae are revealed under microscopic evaluation; organisms with varied morphology will be apparent [2]. Thus, the role of an algologist is helpful in this regard. FlowCAM is an automated flow cytometry and microscopy detection system that can monitor microalgae culture by identifying organisms within the culture [40]. Another visual sign of contamination is when the culture gradually becomes yellow or clear [34], or when it begins to stick to the ponds [41]. Monitoring contamination includes checking pH and oxygen concentration; in an ideal condition, these show a diurnal change but may stray in the presence of pollutants.

Pesticides can be applied in microalgal and cyanobacterial cultures [42]. Triton-N is used because it acts as a surfactant, inhibiting the growth of Scenedesmus (a green algae belonging to the class Chlorophyceae) [43]. Copper salts act as a fungicide. Chemical usage is a viable option, but it can reduce the phycocyanin concentration in microalgae—in addition to being an environmental pollutant and toxic to human health [42]. Biological control is the superior alternative.

Plant-based pesticides are used in mass cultivation processes [34]. Contaminants can be sieved through physical filtration and undergo ultraviolet sterilization. Ultrasound treatment is an effective countermeasure; however, its efficacy depends on the contaminant zooplank-

ton's cell size [44]. In large-scale production facilities, pulsed electric fields are applied to control the concentration of rotifer (aquatic multicellular invertebrates belonging to the phylum Rotifera) [45].

Nevertheless, undesirable algal growth may occur in the culture media, resulting in corruption, especially in the open-pond system of Spirulina cultivation. The most frequent invader is Chlorella, which can be constrained if a high bicarbonate concentration is maintained while keeping a low dissolved organic load in the culture medium. Moreover, amoebae growth can be prohibited by adding ammonia [7,46].

Advanced manufacturing techniques use closed photobioreactors that are artificially lit with fluorescent or ultraviolet light [48]. This artificial lighting helps in high-yield biomass production and reduces the contamination chances—but is expensive.

Pre-dehydration treatment and drying are essential for the preservation of Spirulina and its byproducts. Before dehydration, the substance is treated with inactive enzymes, adding antioxidants á-tocopherol and tertiary butyl hydroquinone (TBHQ), and applying blanching methods (such as microwave and water bath) [6]. Low-cost sun and spray drying is practiced to dehydrate the product. However, these drying techniques can disintegrate phycocyanin and carotenoid, affecting biomass [49].

Exposure to prolonged intense illumination causes photolysis of Spirulina filaments, resulting in toxic hydrogen peroxide and triple chlorophyll. These toxic products can be controlled by regular agitation of the culture medium [48].

Summary

In 2013, the WHO published its Traditional Medicine Strategy to support traditional, complementary, and alternative medicine, including medicinal and herbal products for phytotherapy. The primary objective is to increase these traditional and alternative therapies' safety, efficacy, and quality while guiding regulatory bodies to ensure quality production, manufacturing, and storage. The National Complementary and Integrative Health Center (NCCIH) is a United States government agency established to explore complementary and alternative medicine. It funds research works aimed at the safety and usefulness of these therapies and their role in public health [50].

These organizations have acknowledged the burgeoning interest in traditional, complementary, and alternative therapies—and the consumption of natural products as supplemental therapies. With increased public consumption of herbal products and nutraceuticals, regulatory agencies and governments strive to set guidelines and directives that improve knowledge, ensure safety, and strengthen scientific evidence to support their use.

Conclusion

Microalgae have been a source of nutrition for humans for millennia—in addition to having numerous and proven biological benefits. These aquatic organisms are also a source of bioenergy. Nevertheless, consulting with and close monitoring by a medical expert is strongly advised. The dangers of intake of random algae byproducts and contaminants expose an individual to harmful toxic components (many of which occur during algae cultivation or the manufacturing process of algae-based products.

Environmental contaminants, unsuitable manufacturing processes, and adverse interactions with specific traditional herbs and pharmacologic medicines can endanger human health. Continuous and close monitoring during the manufacturing process is critical to ensuring consumer protection. Further research is needed to find methods to keep contaminants nominal to nonexistent, particularly in large-scale production units.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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