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Review Article

Spirulina (Arthrospira): An Important Source of Nutritional and Medicinal Compounds

Abdulmumin A. Nuhu

Department of Chemistry, Ahmadu Bello University, P.M.B. 1069, Zaria, Kaduna, Nigeria

Correspondence should be addressed to Abdulmumin A. Nuhu; aanuhu@yahoo.com

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Cyanobacteria are aquatic and photosynthetic organisms known for their rich pigments. They are extensively employed as food supplements due to their rich contents of proteins. While many species, such as *Anabaena* sp., produce hepatotoxins (e.g., microcystins and nodularins) and neurotoxins (such as anatoxin a), *Spirulina (Arthrospira)* displays anticancer and antimicrobial (antibacterial, antifungal, and antiviral) activities via the production of phycocyanin, phycocyanobilin, allophycocyanin, and other valuable products. This paper is an effort to collect these nutritional and medicinal applications of *Arthrospira* in an easily accessible essay from the vast literature on cyanobacteria.

1. Introduction

Cyanobacteria are ancient photosynthetic organisms that are found in various aquatic environments [1–3]. Their photosynthetic pigments confer different colors on them, but they are generally regarded as blue-green. Calling them algae is, however, a misnomer since they are truly prokaryotes that share most of the characteristics of eubacteria. Some of these organisms have nitrogen-fixing potential which makes them important in rice paddy waters [4].

Cyanobacteria form colonies [5] or live as individual cells [6]. They also form coccoid [7] or filamentous structures [8]. The filamentous colonies show the ability to differentiate into three different cell types [9]. Vegetative cells, the normal photosynthetic cells formed under favorable growth conditions; climate-resistant spores in harsh environmental conditions and a thick-walled heterocyst containing the enzyme nitrogenase for nitrogen fixation.

In the last 3.5 billion years, cyanobacterial morphology has been largely maintained as they are very resistant to contamination. Sigler et al. [10] have shown that cyanobacteria form monophyletic taxon. Culture-based morphological characteristics of endolithic cyanobacteria have been extensively described by Al-Thukair and Golubic [11]. Since characterization of microorganisms based on morphology is highly subjective and sometimes very speculative, the shift by genome-based characterization is now gaining momentum. Koksharova and Wolk [12] have presented a good review on the available genetic tools for cyanobacteria studies.

Cyanobacteria are very resistant as they produce protective compounds which shield them against harsh environmental conditions [13]. Some of these compounds also have strong insecticidal activities [14]. Toxic species, including *Anabaena* species, produce toxins such as microcystins and nodularins which are hepatotoxic, and neurotoxins such as anatoxin *a* [15, 16].

The Darling River cyanobacterial bloom of 1991 is a clear representation of the environmental hazard that such species pose [17]. However, some species of cyanobacteria possess the ability to produce substances with therapeutic activities such as anticancer and antimicrobial applications [18–22].

Among the myriads of cyanobacteria, *Arthrospira platensis* is a blue-green cyanobacterium that thrives in elevated alkaline pH [23]. *A. platensis* is recognized by its peculiar shape of cylindrical trichomes that are arranged in a left-handed helix throughout the filament [24]. The correct taxonomic definitions of *Arthrospira* have been revealed through the study of the ultrastructural details of its trichomes and 16S rRNA gene sequences [25]. An important ligation detection reaction, in combination with universal array, capable of identifying various cyanobacteria, including *Arthrospira*, in environmental samples, has been developed [26]. Good

understanding of the ecology of this alkaliphilic organism is a catalyst to its mass production and commercial viability as food supplement. By the end of year 2009, its total annual production in Ordos Plateau of Mongolia was in excess of 700 t [27]. With retrospect, the Mexicans [28] and Kanenbu tribe of Chad [29] have been exploiting the protein potentials of *S. platensis* in their diets for long time now, and about 3000 metric tons of *S. platensis* is currently produced for commercial purposes [30]. A fed-batch process has been employed in the cultivation of *Arthrospira* [31], and different solid-liquid separation techniques give various degrees of recovery. Which technique is ultimately selected will depend on the cyanobacterial species, intended concentration of the finished product, and product quality [32]. Cultivation of *A. platensis* under different trophic modes was shown to affect the product yield [33]. High-value compounds from this organism have been put to assorted uses as cosmaceuticals, nutraceuticals, and as functional foods [34]. Phycocyanin and allophycocyanin, two of such important compounds, have been determined in *Spirulina* supplements and raw materials by a 2-wavelength spectrophotometric method [35]. Bioactivity and health functions of *Arthrospira* food supplements have been reviewed [36–38]. Specific functions that have been tested for compounds extracted from this organism are grouped under the following subheadings.

2. Nutritional Functions

Arthrospira (*Spirulina*) is among the richest sources of proteins. Its protein content is about 60–70% [39]. In a study that attempted using *Spirulina* as a protein supplement, it was observed that it can replace up to 40% of protein content in tilapia diets [40]. Rabelo et al. [41] have explained the development of cassava doughnuts enriched with *S. platensis* biomass.

Unlike many other cyanobacteria that have proven toxicity, no such property has been attributed to *Spirulina*. While testing for mutagenicity, acute, subchronic, and chronic toxicities and teratogenicity in animal experimentations, Chamorro et al. [42] have shown that *Spirulina* did not exhibit any potential for organ or system toxicity even though the doses given were elevated above those for expected human consumption. Rather, *Spirulina* was shown to protect fish from sublethal levels of some chemicals [43]. Likewise, dietary supplementation of *Spirulina* has helped in alleviating the incidence of anemia experienced during pregnancy and lactation. In the study conducted by Kapoor and Mehta [44], dietary supplementation of *S. platensis* was found to increase the iron storage of rats, better than achieved from the combination of casein and wheat gluten diets, during the first half of pregnancy and lactation. A review that treats the influence of different compounds from *Spirulina* on the immune system has been written [45].

3. Antioxidant Functions

Apart from its importance as a food additive for supplementary dietary proteins, there are also a lot of potentials for medical and therapeutic applications [46]. For example, *A. platensis* plays a hepatoprotective role [47]. This role, which has to do with the antioxidant activity of *Spirulina*, has been previously asserted by various researchers. The antioxidant activity of *Spirulina* is ascribed to the presence of two phycobiliproteins: phycocyanin and allophycocyanin, as determined by its action against OH radical generated from ascorbate/iron/H_2O_2 system. The activity was found to be proportional to the concentration of the phycobiliproteins and was mainly due to the phycocyanin content [48]. As an antioxidant effect, oxygen stress was inhibited by phycocyanin and phycocyanobilin from *Spirulina* leading to protection against diabetic nephropathy [49]. In an earlier experiment to determine the radical scavenging activity of C-phycocyanin isolate of *S. platensis*, an intraperitoneally administered C-phycocyanin was found to reduce the peroxide values of CCl_4-induced lipid peroxidation in rat liver microsomes [50]. Following a study conducted on 60 patients presenting with chronic diffuse disorders in the liver and on 70 experimental animals, Gorban' et al. [51] have found that *Spirulina* administration prevented the transformation of chronic hepatitis into hepatic cirrhosis. Recently, Paniagua-Castro et al. [52] have demonstrated the protective efficacy of *Arthrospira* against cadmium-induced teratogenicity in mice.

There are indications that these therapeutic potentials are not the exclusive rights of *S. platensis*. *Spirulina fusiformis* also has shown some free radical scavenging activities. In rats, Kuhad et al. [53] have found that radical scavenging activity of *S. fusiformis* did protect against nephrotoxicity resulting from oxidative and nitrosative stress of the aminoglycoside, gentamicin, an antibiotic commonly used for the treatment of Gram-negative bacterial infections. Pretreatment of mice with *Arthrospira maxima* effectively led to the reduction in liver total lipids, liver triacylglycerols, and serum triacylglycerols, thus protecting against Simvastatin-induced hyperlipidemia [54]. The hexane extract of *Spirulina* achieved an impressive 89.7% removal of arsenic from rat liver tissue, which is a better result than obtained with either alcohol or dichloromethane extract [55]. In a more recent finding, aqueous extract of *S. platensis* showed suppressive potency, through free radical scavenging activity, against cyclophosphamide-induced lipid peroxidation in goat liver homogenates [56].

As a nephroprotective activity, *S. platensis* extract counteracted the hyperoxaluria experimentally induced by the administration of sodium-oxalate to rats, through stabilization of antioxidant enzymes and glutathione metabolizing enzymes [57]. Protections against mercuric chloride-($HgCl_2$-) induced renal damage and oxidative stress were attributed to the administration of *A. maxima* to experimental mice [58]. Administration of *A. platensis* to rats also rendered protection against $HgCl_2$-induced testis injury and sperm quality deteriorations [59].

S. platensis biomass preparations have shown some corrective influences on atherosclerotic processes in 68 patients with ischemic heart disease (IHD) and atherogenic dyslipidemia. The patients' immunological states were altered, in addition to changes in lipid spectra [60]. Pretreatment of

experimental animals with *Spirulina* has proved its cardioprotective function, this time against doxorubicin-induced toxicity, as evident from lower mortality, lower degree of lipid peroxidation, decreased ascites, and normalization of antioxidant enzymes, without compromising the antitumor activity of the drug, doxorubicin [61]. The contribution of reactive oxygen species (ROS) to brain injury in neurodegenerative conditions, such as Parkinson's disease, is hampered with proper administration of *A. maxima* supplement. Following a 40-day pretreatment with 700 mg/kg/day of this supplement, various indicators of toxicity in rat injected with a single dose of 6-hydroxydopamine, 6-OHDA (16 μg/2 μL), were decreased [62]. This is an indication of the neuroprotective effect of this supplement against the harmful effect of free radicals. *Arthrospira* supplement has also a radioprotective effect. This is demonstrated by its free radical scavenging function against gamma-irradiation-induced oxidative stress and tissue damage in rats [63]. Cell death through apoptosis is prevented or delayed by using a cold water extract of *S. platensis* [64]. Hence, it is suggested that the inclusion of cyanobacterial supplement in beverages and food products should be strongly considered.

4. Antitumor Functions

Strong evidences have shown that *S. platensis* is also imbued with antitumor and anticancer functions. In this regard, it was discovered that significant to full tumor regression was obtained with intravenous injection of Radachlorin, a new chlorine photosensitizer that was derived from *S. platensis* [65]. It was shown that hot-water extract of *S. platensis* facilitated enhanced antitumor activity of natural killer (NK) cells in rats [66]. Recently, complex polysaccharides from *Spirulina* have brought about suppression of glioma cell growth by downregulating angiogenesis via partial regulation of interleukin-17 production [67]. High production of tumor necrosis factor-α (TNF-α), in macrophages, was recorded in the presence of acidic polysaccharides from *A. platensis* [68]. Li et al. [69] have shown that with increased phycocyanin concentration, expression of CD59 proteins in HeLa cells was promoted while Fas protein that induces apoptosis was increased with an attendant decline in the multiplication of HeLa cells. These findings are an evidence for the multidimensional applications of phycocyanin content of *S. platensis.*

5. Antiviral Functions

Many compounds with antimicrobial activities have been isolated from different marine organisms, and a number of evidences are put forward for the antiviral activity of *Spirulina* [70, 71]. This antiviral activity, in a large part, is attributable to the richness of *S. platensis* in vital proteins, fatty acids, minerals, and other important constituents [72].

Previously, calcium spirulan (Ca-SP), a novel sulfated polysaccharide that was isolated from hot water extract of *S. platensis*, has shown antiviral activities against different enveloped viruses such as *Herpes simplex* virus type-I, measles virus, HIV-I and influenza virus. This high sought for antiviral activity has been suggested to be due to the effect that chelation of calcium ions to sulfate groups has on molecular conformation [73]. Both extracellular and intracellular spirulan-like molecules from the polysaccharide fractions of *A. platensis* displayed significant antiviral activities against wide range of viruses, including human cytomegalovirus and HIV-I [74]. About 50% and 23% reductions in viral load were recorded for methanolic and aqueous extracts of *S. platensis*, respectively [75]. Reduction in viral load was attributed to inhibition of HIV-I replication in human T cells, langerhans cells, and peripheral blood mononuclear cells (PBMCs), with up to 50% reduction accorded to PBMCs [76]. Antiviral and immunostimulatory properties of *S. platensis* preparations were elicited through increased mobilization of macrophages, cytokine production, antibodies generation, accumulation of NK cells, and mobilization of B and T cells [77]. A recent study on the antiviral activity of *Spirulina* has resulted in the isolation of Cyanovirin-N (CV-N), a novel cyanobacterial carbohydrate-binding protein that inhibits HIV-I and other enveloped viral particles [78]. The Kanenbu tribe of Chad and most people in Korea and Japan, who consume *Spirulina* diet daily, have been shown to display lower cases of HIV/AIDS than their surrounding neighbors who do not take such diet. Therefore, it is expected that consistent intake of diets containing *Spirulina* can help in reducing the prevalence of HIV/AIDS [79]. Antiherpetic activities were noted for the crude extracts of *S. fusiformis* [80]. While Hernández-Corona et al. [81] have reported antiviral activity of *S. maxima* against HSV-2, Shalaby et al. reported similar activity for *S. platensis* against HSV-I [82].

6. Antibacterial Functions

Spirulina is not without antibacterial activity. In 3-week-old chicks injected with either *Escherichia coli* or *Staphylococcus aureus* suspensions, 0.1% *Spirulina* was found to enhance their bacterial clearance abilities, as shown by the improvement in the activities of different phagocytotic cells, including heterophils, thrombocytes, macrophages, and monocytes in the chickens [83]. Microalgal cultures of *A. platensis* have displayed significant antibacterial activity against six *Vibrio* strains: *Vibrio parahaemolyticus, Vibrio anguillarum, Vibrio splendidus, Vibrio scophthalmi, Vibrio alginolyticus*, and *Vibrio lentus* [84]. Antibacterial activity against *Streptococcus pyogenes* and/or *S. aureus* was proven for the phycobiliproteins isolated from *A. fusiformis* [85]. Purified C-phycocyanin from *S. platensis* markedly inhibited the growth of some drug resistant bacteria: *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and S. aureus* [86]. This shows the potentials of compounds isolated from these cyanobacterial species in the fight against drug resistance.

7. Antifungal Functions

Recently, *Spirulina* has also exhibited antifungal activities [87]. Activity of 13 mm was recorded against *Candida glabrata*

in the butanol extract of *Spirulina* sp. [88]. The immunostimulatory effect of *S. platensis* extract was tested in Balb/C mice infected with candidiasis [89]. In this experiment, pretreatment of the mice with 800 mg/kg of the extract for 4 days before intravenous inoculation with *C. albicans* resulted in increased production of cytokines TNF-α and interferon-gamma (IFN-γ), leading to increased survival time and better fungal clearance than in control groups. Glucosamine production was reduced by about 56% when the antifungal activity of the methanolic extract of *S. platensis* was tested against *Aspergillus flavus* [90]. Contrary to these findings, *S. platensis* grown in Zarrouk media, DB_1 media and papaya skin extract media did not show any antifungal activity [91]. In some instances, extracts from *S. platensis* may display a stimulatory effect toward cultured microorganisms. It was found by Gorobets et al. [92] that different doses of *S. platensis,* when added to culture fluid, displayed important stimulatory and inhibitory effects on the cultured microorganisms due to the presence of complex metabolites that were active in the prepared nutrient agar. Similarly, *S. platensis* biomass was used to maintain the counts of starter organisms in acidophilus-bifidus-thermophilus (ABT) milks at satisfactory levels during whole duration of storage. This is a novel opportunity for the production and maintenance of functional dairy foods [93].

8. Miscellaneous Functions

Many compounds produced from marine organisms, including cyanobacteria, have important protective functions against various allergic responses such as asthma, atopic dermatitis, and allergic rhinitis [94].

Powders of *S. platensis* have inhibited anaphylactic reaction resulting from antidinitrophenol IgE-induced histamine release or from TNF-α of rats [95]. *Spirulina* was also found effective against allergic rhinitis [96]. In an earlier human feeding study conducted in this regard, *Spirulina*-based dietary supplement was found effective in suppressing the level of interleukin- (IL-) 4 [23]. Zymosan-induced upsurge in the level of beta-glucuronidase of experimental mice was significantly reduced following the administration of phycocyanin [97]. This antiarthritic action may be due to the combination of various mechanisms such as free radical scavenging, inhibition of arachidonic acid metabolism as well as inhibition of TNF-α within the mice.

S. platensis has also neuroprotective ability. Its neuroprotective effect was demonstrated in adult Sprague-Dawley rats through a significant reduction in the volume of cerebral cortex infarction and increased poststroke locomotor activity. Hence, it is suggested that chronic treatment with *Spirulina* can reduce ischemic brain damage [98]. A report has shown that lead-induced increase in mast cells in rat ovary, during estrous cycle, is curtailed by using *Spirulina* at 300 mg/kg [99].

Another important compound synthesized by *Spirulina*, which equally has a lot of vital applications, is polyhydroxyalkanoates. These are polyesters produced by bacterial fermentation of sugars or lipids. According to Campbell et al. [100], *S. platensis* stores about 6% of its total dry weight and this value decreases during stationary phase of its growth profile. However, Jau et al. [101] have posited that this value can be increased to 10% when the organisms are grown under nitrogen-deficient, mixotrophic culture medium. The use of recombinant *E. coli*, due to its fast rate of growth and minimal nutrient requirements, to overproduce polyhydroxyalkanoates, has the potential of increasing the number of polyhydroxyalkanoates inclusions per cell [102]. Polyhydroxyalkanoates hold an assuring promise in therapeutic applications as drug carriers that display a release pattern similar to those of monolithic devices; an early rapid release followed by a prolonged, but slower release pattern. This type of drug-release behavior is normally required for depositing adequate concentration of drug of interest at the site of infection [103]. Among the polyhydroxyalkanoates, 4-hydroxybutyrate has long been advocated for the treatment of alcohol withdrawal syndrome in alcohol-dependent subjects [104].

9. Conclusions

In the foregoing essay, various nutritional and medicinal potencies have been attributed to metabolites from the cyanobacteria, *Spirulina (Arthrospira)* sp. In the present clamor for alternative medicine, these organisms serve as very viable potential sources of bioactive products with commercial imports. Therefore, more should be done in the study, culture, isolation, and purification of these organisms to enable beneficial harvest of their important inclusions.

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