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REVIEW
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Therapeutical and Nutraceutical Roles of Cyanobacterial Tetrapyrrole Chromophore: Recent Advances and Future Implications

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Cyanobacteria have attracted the attention of researchers because of their promising role as primary and secondary metabolites in functional food and drug design. Due to an ever-increasing awareness of health and the use of natural products to avoid the onset of many chronic and lifestyle metabolic diseases, the global demand for the use of natural drugs and food additives has increased in the last few decades. There are several reports about the highly valuable cyanobacterial products such as carotenoids, vitamins, minerals, polysaccharides, and phycobiliproteins showing antioxidant, anti-cancerous, anti-inflammatory, hypoglycemic, and antimicrobial properties. Recently, it has been shown that allophycocyanin increases longevity and reduces the paralysis effect at least in *Caenorhabditis elegans*. Additionally, other pigments such as phycoerythrin and phycocyanin show antioxidative properties. Because of their high solubility in water and zero side effects, some of the cyanobacterial tetrapyrrole derivatives, i.e., pigments, facilitate an innovative and alternative way for the beverage and food industries in place of synthetic coloring agents at the commercial level. Thus, not only are the tetrapyrrole derivatives essential constituents for the synthesis of most of the basic physiological biomolecules, such as hemoglobin, chlorophyll, and cobalamin, but also have the potential to be used for the synthesis of synthetic compounds used in the pharmaceutical and nutraceutical industries. In the present review, we focused on the different aspects of tetrapyrrole rings in the drug design and food industries and addressed its remaining limitations to be used as natural nutrient supplements and therapeutic agents.

Keywords: tetrapyrrole, antioxidants, phycobiliprotein, phycocyanin, therapeutic agent

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INTRODUCTION

Cyanobacteria are the earliest inhabitants of the earth and flourish in almost every habitat such as soil, rock, fresh water, and marine water, including some of the toughest environments such as hot springs. The secret behind their universal distribution in each and every corner of the globe lies in their ability to produce a wide range of bioactive compounds that evolved to protect them from various exogenous and endogenous environmental insults. Recently, with the advanced biotechnological route, humans have started to use the same cyanobacterial compounds in agriculture, pharmacology, and formulation of functional foods because of their ability to be used as an alternative source of cytoprotective, nutritive, and therapeutic compounds that may be present at suboptimal levels in human body under certain pathological conditions (Fernández-Rojas et al., 2014a; Pagels et al., 2019). This is the reason why researchers have started to pay attention to extracting the novel bioactive components from cyanobacteria at a low cost and in an efficient way. It has been established already that most cyanobacterial compounds have tetrapyrrole rings in the heart of their supermolecular structure. Tetrapyrrole pigments are closely related to bilirubin molecules showing potent antioxidative and anti-proliferative properties when used as food supplements (Dillon et al., 1995; Konícková et al., 2014). There are several reports that most of the cyanobacterial species are laden with a higher quantity of essential amino acids, proteins, vitamins, flavonoids, unsaturated fatty acids, vitamins, and minerals as compared to traditional food such as milk, vegetables, fruits, soybean, egg, fish, and meat (Pervushkin et al., 2001; Khan et al., 2005; Jin et al., 2021). Therefore, due to their enriched nutritional value, the extraction of bioactive components from cyanobacteria has been proven as a boon for health. They serve as a sustainable source of raw material for drug development for the cure of various diseases and nutrient-related deficiencies (Ferris and Hirsch, 1991; Pyne et al., 2001; Soares et al., 2015). In recent years, researchers are focused on the biocompatibility of these compounds, especially with proteins in the nanosystem of host cells, to maintain human's cellular health along with the correction of lifestyle and dietary-related diseases.

One of the most important natural antioxidant compounds present in cyanobacteria is its pigment, a tetrapyrrole linear derivative, along with a rich source of vitamins and minerals; however, their primary biological role is to do photosynthesis, thus contributing to the production of a major amount of biomass in the ecosystem (Romay et al., 1998, 2003; Romay and Gonzalez, 2000; Remirez et al., 2002; Eriksen, 2008; Thangam et al., 2013; Zhang et al., 2022). Among the functional components identified in cyanobacteria, natural pigments such as chlorophylls, carotenoids, and phycobilins have received attention due to their linear tetrapyrrolic structure. The tetrapyrrolic derivatives have many potential applications in the cosmetics, pharmaceutical food, and textile industries. In fact, the derivatives of tetrapyrrole form a battery of novel bioactive compounds that may be used to improve the human health as they show the antibacterial, antiviral, antiarthritic, cytotoxic, and immunoregulative properties (Ou et al., 2010; Zheng et al., 2013; Young et al., 2016). The aim of the present review was to discuss the use of tetrapyrrole pigment of cyanobacterial origin for nutraceutical and therapeutical purposes.

TETRAPYRROLE PIGMENT IN THE NUTRACEUTICAL INDUSTRY

Due to the ever-increasing population throughout the entire globe, it has become a challenging task to help the population maintain a balanced nutritional state. Since agricultural production cannot be increased with the pace of the increasing population, researchers now have started to look toward alternative food sources to fulfill the global demand for healthier food products. They have started to focus on the cyanobacteria being a rich source of proteins, the most important food component for a balanced diet. One of the cyanobacterial species, i.e., *Spirulina*, has made its way to the dining table because of its high nutritional values. The other bioactive compounds present in *Spirulina* show antioxidative, antimicrobial, anti-cancer, antiviral, and anti-inflammatory activities (Hayashi et al., 1994; Bath and Madyastha, 2000; Carmichael et al., 2000; Hirata et al., 2000). There is scientific evidence that *Spirulina*'s is a novel food supplement and is well-recognized for preventing and managing certain diseases such as hypercholesterolemia and cancer. A number of cyanobacterial species host a wide range of secondary metabolites and natural pigments such as β carotene, scytonemin, phycoerythrin, phycocyanin, and phycobilisomes. These pigments have been proved as healthy bioactive constituents of cyanobacterial species and are being utilized by researchers' disease diagnostics, supplementary food, and herbal medicines (Sielaff et al., 2006; Tan, 2007; Gademann and Portmann, 2008; Ghosh et al., 2016). Phycocyanin extracted from *S. platensis* widely used as a cosmetic colorant and food additive. Recently, researchers have moved their focus to the use of cyanobacterial pigments such as phycobiliprotein as food supplements in the nutraceutical industry. The dried contents of *Arthrospira platensis* may play an important role in functional foods because of the bioactive compounds showing immunoregulative and antioxidative properties. *A. platensis* also suppresses the inflammation, viral infection, cancer progression, and maturity of cholesterol-related diseases (Jensen et al., 2001; Matsui et al., 2012).

ANTITUMOR EFFECT OF TETRAPYRROLE PIGMENT

Cancer is the worst result of harmful mutations in the nuclear and mitochondrial genes along with the foul games of free radicals in the cellular ecosystem, causing several unwelcomed molecular changes. Many of the cyanobacterial compounds are reported to check cancer and tumor progression. Natural compounds obtained from *Spirulina platensis* exhibit antiproliferative properties (Mysliwa-Kurdziel and Solymosi, 2017). The possible paths of this mechanism lie in the activity of tetrapyrrole compounds, such as phycobiliproteins and phycocyanin, being nucleophilic in nature and thus being able to prevent the cellular damage by neutralizing the excess reactive oxygen species. Thangam et al. (2013) investigated in detail the effectiveness of phycobiliprotein in the inhibition of colon cancer (HT-29) and lung cancer (A549). Gupta and Gupta (2012) suggested that phycobiliprotein may have suppressive effects on TPA-induced tumors on mice skin. Jiang et al. (2017) reported that phycocyanin is effective in checking the entry of HeLa cancerous cells into the G2 phase of the cell cycle. Recently, Liu et al. (2012) noted that phycocyanin promotes the release of cytochrome c (Cyt c), which in turn repair the damaged DNA and promote apoptosis in Hepal-6 cells. A cyanobacterial tetrapyrrole pigment also ameliorates the cellular damage in normal cells done by chemotherapy and radiotherapy by reducing the oxidative stress and enhancing the antioxidative defense system.

NEPHROPROTECTIVE EFFECT OF TETRAPYRROLE PIGMENT

Kidney disease and failure occur under several pathophysiological conditions such as severe diabetes, pesticides, and heavy metal contamination (nephrotoxins) and due to sepsis syndrome, cardiorenal syndrome, and obstruction of the urinary tract. Renal diseases are diagnosed by the Renal Function Test in which abnormal serum creatinine level and urine output are the most important parameters. It is reported that oxidative load in such critical conditions acts synergistically enhancing nephrotoxicity. The nephroprotective effects of phycoerythrins and phycobiliproteins, which contain tetrapyrrole, play a key role in lowering oxidative stress and minimizing damage to renal cells. *Spirulina* and its extracted components have the potential to improve the glomerular functions in renal cells by maintaining the normal redox environment under oxidative stress conditions. Natural pigments from cyanobacteria are involved in the regulation of mitochondrial activity especially in renal cells *via* energy production and control the apoptosis progression. Experimental pieces of evidence suggest that oxidative load is one of the major causes of nephrotoxicity and renal dysfunction which can be determined by measurement of biomarkers by the level of malondialdehyde, glutathione, and activity of superoxide dismutase, and catalase. It is quite evident that *Spirulina* extract can diminish the level of malondialdehyde and glutathione while enhancing the biosynthesis and activity of superoxide dismutase and catalase in mesangial renal cells restoring the normal functions of the kidney. Phycocyanins from *Spirulina* are reported to modify the physicochemical forces such as oncotic and hydrostatic pressures which are suspected to influence the pressure along with the glomerular filter (Europa et al., 2010; Lim et al., 2012; Fernández-Rojas et al., 2014b; Liu et al., 2017; Mysliwa-Kurdziel and Solymosi, 2017). Phycocyanins from *Spirulina* also prevent the formation of oxalic acid which may form the calcium oxalate in renal calculi. Additionally, phycocyanins down-regulate the ROS production and lipid peroxidation in kidney cells (Riss et al., 2007; Zheng et al., 2013; Farooq et al., 2014).

HEPATOPROTECTIVE EFFECT OF TETRAPYRROLE PIGMENT

Liver diseases are caused by different etiological conditions such as viral infections, metabolic syndrome, alcohol and drug abuse, autoimmune diseases, and toxins, including pesticides, heavy metal contamination, and microplastics. The cyanobacterial extract is reported to have excellent hepatoprotective bioactive compounds that inhibit the kinases activity, a key protein of the cell cycle that cures the hyperproliferative disease without any chemical toxicity. Vadiraja et al. (1998) noted the pharmacological activities of phycocyanin and reported that it could neutralize the effect of ROS in liver cells. Cyanobacterial phycocyanin is also branded to control the synthesis and activity of many hepatic enzymes such as microsomal cytochrome P450, aminopyrine-N-demethylase, and glucose-6-phosphatase. Phycocyanin can suppress inflammation by blocking the hepatocyte growth factor (Vadiraja et al., 1998; Riss et al., 2007). Further, along with phycocyanin, phycocyanobilin also exhibits free radical scavenging activity (Bath and Madyastha, 2000; Ou et al., 2010).

CARDIO-PROTECTIVE EFFECT OF TETRAPYRROLE PIGMENT

Arterial thrombotic stress such as myocardial infarction and heart stroke is the foremost cause of cardiovascular diseases, ranking at the first position in the list of causes of human mortality worldwide. The platelet activity, particularly the aggregation and activation of platelets, significantly controls the debut of atherothrombotic disease. In traditional and modern medical practices, cyanobacterial extracts, particularly from *Spirulina*, are known to lower the serum cholesterol level as phycocyanin is involved in regulating the cholesterol absorption and the bile acid reabsorption process (Iwata et al., 1990; Shibata et al., 2001; Nagaoka et al., 2005; Radibratovic et al., 2016). Also, phycocyanin's constituent compounds, a class of covalently bonded open-chain tetrapyrrole derivatives, work as a pro-drug after its break down due to gastrointestinal enzymes and extend its therapeutic effects (Radibratovic et al., 2016). Tetrapyrrole pigments are well-established in preventing redox environmental disturbances, thus increasing the myocardial enzymatic activity. On the one hand, phycocyanin downregulates the signaling pathways, leading to inflammation by inhibiting the phospho-NFκB p65 enzyme while decreasing the synthesis of mRNAs of proinflammatory cytokines (Hao et al., 2018). On the other hand, the same pigment is also known to promote the heme oxygenase-1 molecular pathway enhancing the anti-inflammatory processes. It also diminishes the activity of caspase, thus minimizing the cell death but endorsing the synthesis of antioxidant enzymes (Gao et al., 2016; Kim et al., 2018).

ANTIDIABETIC EFFECT OF TETRAPYRROLE PIGMENT

Diabetes mellitus is a metabolic disorder in which lifelong hyperglycemia is manifested due to a decline in glycogen synthesis, leading to abnormal glucose levels in the blood. Prolonged hyperglycemia leads to other chronic diseases such as heart disease, kidney failure, and blindness. In 2010, Ou et al. showed that cyanobacterial pigments, especially phycocyanin, significantly enhance the muscular and hepatic glycogen synthesis, restoring the glucose homeostasis. Insulin secretion is directly related to the bio efficiency of α cells whose hormonal synthesis and secretion decrease significantly under stress, hypertension, inflammation, obesity, and aging. deKoning et al. (2008) reported that phycocyanin can control the size of the endocrine portion of the pancreas, influencing insulin secretion significantly (Yu et al., 2013). Ghosh et al. (2016) found that glucose metabolism is influenced by oxidative stress, which in turn is dropped off by the free radical scavenging activity of cyanobacterial pigments. Further, extracted pigments from *Synechocystis*, *Lyngbya*, and *Microcoleus* species inhibit the α-glycosidase and α-amylase activities, leading to hypoglycemic conditions. Additionally, the α-amylase and α-glucosidase inhibitions also decline the occurrence of diarrhea and flatulence, both of which are linked to indigestion of food in the gastrointestine tract. Cyanobacterial pigments enhance the digestion *via* fermentation done by lactic acid bacteria. The crude as well as purified phycoerythrin and phycocyanin play a dual role as hypoglycemic and antioxidative activities and could be used as food additives in food industries.

CONCLUSION

The successful use of cyanobacteria in nutraceutical and pharmaceutical applications will depend on its novel tetrapyrrole-derived bioactive compounds which encompass antiallergic, anticarcinogenic, antibacterial, anticoagulant, antifungal, antihypertensive, anti-inflammatory, antinociceptive, antioxidant, antipyretic, cholesterol-lowering, hepatoprotective, and immune enhancement properties. Positive health effects have been related to the fact that the structure of phycocyanorubin and bilirubin resembles each other. In addition to their valuable role in medicinal and functional food, this group of natural pigments from cyanobacteria represents an attractive source of bioactive sustainable compounds. Tetrapyrrole-derived compounds in cyanobacteria have been used as a food additive in chewing gum, candies, food supplements, beverages such as soft drinks, and cosmetics products such as lipsticks and eyeliners. They also show therapeutic properties such as antitumor, nephroprotective, hepatoprotective, anti-diabetes, and antioxidant activities. These scientific studies announce that the consumption of edible cyanobacteria may be a safe alternative approach in the therapeutic and nutraceutical industries without any side effect.

AUTHOR CONTRIBUTIONS

JR wrote this article. Ka collected the research article. KS edited and corrected this article. All authors contributed to the article and approved the submitted version.

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