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Stress Enhances the Synthesis of the Therapeutically Important Secondary Metabolites in Cyanobacteria

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Abstract: This review is an extension of my original study "Characterization of Nitrogen Stress Induced Alterations in Cyanobacterial Photosynthesis." It was clear from the literature that other secondary metabolites were produced during stress. Secondary metabolites are generally defined as compounds that are no longer needed for a primary metabolism of an organism. While most of the metabolites can be categorized as primary or secondary, there is a certain overlap. Some are essential for primary metabolism, however, are only synthesized by species and thus secondary metabolites. Under nitrogen stress conditions, the number of phycobiliproteins increased considerably, accompanied by an increase of their antioxidant activities. Moisturizers are synthesized from the secondary metabolites of extremophilic cyanobacteria. Cyanobacteria protective methods for counteracting harmful ultraviolet radiation from the sun are now widely discussed. Several clinical studies have found a high efficacy secondary metabolite in cancer treatment. Low external pH triggers heat shock proteins which have medicinal principles including antimicrobial and antioxidative action. In HIV patients, insulin sensitivity increases more when Spirulina is used as a nutritional supplement instead of soya. Cyanobacteria provide a rich wealth of chemicals for the discovery of lead compounds and new medicines that are safe yet promising. Pharmaceutical companies should conduct clinical trials on several bioactive molecules obtained from cyanobacteria exhibiting a broad spectrum of activities, such as antitumor, antibacterial and antiviral effects and protease inhibition. Recently, also a growing interest has been shown in the development of bioactive compounds for trade or medical applications.

Key words: Chromosomal Damage · Anti-Carcinogenic · Anti-Microbial · Conventional Moisturizers · Phenylketonuria · And Hyperlipidemia

INTRODUCTION

Cyanobacteria are considered a rich source of secondary metabolites that could be used in the pharmacological field as biotechnology. Recently also a growing interest has been shown in the development of bioactive compounds for trade or medical applications. Intracellular and extracellular metabolites are known to produce by cyanobacteria which have potential biological activities such as antibacterial, anti-fungal, antiviral, anti-inflammatory, anti-pathological, herbicide and immunosuppressive effects [1-3]. The therapeutic benefit of Spirulina has been recorded in several studies. It also offers improved immune responses and decreases serum glucose and lipid levels to heavy and medicinal drugs, including its use for hyperlipidemias, obesity, HIV, diabetes, obesity and hypertension [4-7].

Spirulina platensis is the nature's richest source of vitamin B12 with high levels of amino acid (62%), antiviral, anti-cancer, anti-diabetic, antioxidant, anti-inflammatory and anti-metastasistic function. Such features make *S. platensis* extract a potential biomedical pharmaceutical. Spirulina has been well established in industry. It has a wide range of protein sources, polyunsaturated fatty acids (γ-linoleic acid [GLA]), antioxidants (phycocyanin and carotenoids) and vitamins as health food [8].

Thousands of medical, pharmaceutical and nutritional articles on the importance of different cyanobacteria are available, particularly S. *platensis*.

This paper is an extension of my original study "Characterization of Nitrogen Stress Induced Alterations in Cyanobacterial Photosynthesis." The analysis of work in *S. platensis* was noteworthy for alterations in photosynthesis under nitrogen pressure (40ug) [9]. It was clear from the results

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Table 1: List of secondary metabolites accumulated during stress conditions in Spirulina

SN	Stress condition	Chemical group	Name of secondary metabolites	Protecting mechanism	Reference
1.	UV stress	UV-absorbing compounds	Mycosporine-like amino acids and Scytonemin (Scy)	Photoprotection	[17]
2.	Carbon stress	Polyketides,	Indolactam ring composed L-valine, L-tryptophan and methionine.	Restoring the carbohydrate levels in organisms.	[18]
3.	Oxidative stress causing gene mutations.	Peptides	Aeruginosamide Patellamide	Self-protecting of genetic materials.	[19]
4.	Heavy metals & free radicles & Reactive oxygen spices	Isoprenoids & Terpenoids	Diphosphate and Dimethylallyl triphosphate (DMADP) precursors & phycocyanin.	For protecting the self-genetic materials & lipids	[20]
5.	Ammonia stress	Nitrogen-containing compounds	Phenylalanine ammonia-lyase	To protect self-cytoskeleton assembly, immune stress, oxidative stress and signal transduction of apoptosis	[21]
6.	Iron stress	Phytohormones, iron-chelators Hepatotoxin, neurotoxins	Cytokinin and gibberellin-like compounds, schizokinen, anachelin and synechobactins, etc. Saxitoxin, anatoxines, microcystins and nodularins.	To improve their growth. and heavy metal poisonings Which are poisonous compounds and exerts a toxic effect on another animal.	[22]
7.	Temperature stress	Carotenoids, Unsaturated fatty acids	Antifreeze proteins, astaxanthin	To protect membranous Rigidity.	[23]
8.	Salt & PH stress	Secondary carotenoids, Heat shock Proteins.		To preserve homeostatic changes.	[24]

that other secondary metabolites were produced during stress. What are they? What is the meaning of secondary stress metabolites? Could we treat different cancers using their special medicinal properties?

Secondary metabolites are generally defined as compounds that are no longer needed for a primary metabolism of an organism. Those are also listed as natural products. These secondary metabolites are usually specific to some organisms and do not occur in each environment.

While most of the metabolites can be categorized as primary or secondary, there is a certain overlap. Some are essential for primary metabolism; however, secondary metabolites are only synthesized by specific species.

Depending on the stress environment, different suites of secondary metabolites can be generated with a high level of structural variations across the different compound groups. A range of secondary metabolites for the development of healthier food products are available from some algal species, namely Chlorella, Hematococcal, Dunaliella and Spirulina [10, 11]. However, algae produce secondary alkaloids, flavonoids, glycosides, terpenoids or phenazines [12]. Algae are a product of algae. These thus have a wide range of roles, such as cell defense, chemosensory, photoprotection and antioxidant, defense against predators and grazers. Such products can be used as nutraceuticals, cosmeceuticals and medicines in industrial biotechnology.

Current review focused on different secondary metabolites produced by cyanobacteria when exposed to stress environment.

Secondary metabolites are produced by cyanobacteria often by providing protection and helping to survive as a reaction to the biotic or abiotic pressure of the surrounding environment [13, 14]. Cyanobacteria are a rich source of secondary metabolites because they survive in a variety of environments. Non-ribosomal peptide (NRPs) are widely used as secondary metabolites for cyanobacteria, which are generated using non-ribosomal peptide synthetases. Polyketides which are biosynthesized with polyketide synthase (PKS) from acetyl-CoA are another big group of secondary metabolites. Alkaloids are natural compounds containing nitrogen, commonly poisonous, such as the paralytic poison of shellfish, saxitoxins contained in several cyanobacteria [15, 16]. This class also contains ribosomal peptides and isoprenoids (carotenoids). Table 1 summarizes the list of accumulated secondary metabolites under various stress conditions.

UV radiation exposure can contribute to cyanobacteria's oxidative stress [25]. Cyanobacteria produce secondary UV-absorptive screening biomolecules, such as Mycosporin-like amino acids (MAAs) and scytonemine (Scy) during oxidative stress [17]. which may be capable of free radicles detoxifying. Cyanobacteria protective methods for counteracting

harmful UV radiation from the sun are now widely discussed. Several clinical studies have found a high efficacy secondary metabolite in cancer treatment [26].

Under carbon famine or stress conditions, by synthesizing the secondary metabolites, such as indolactam ring composed of L-valine, L-tryptophan and methionine, the cyanobacteria can be adapted to a new environment. Recent clinical studies have shown that many species of staphylococcus, streptococcus and clostridium microorganisms are effectively killed by these secondary metabolites [27].

Aerobic metabolism byproducts and potent agents causing oxidative damage are reactive oxygen species (ROS). Cyanobacteria are often subjected to external changes in their natural habitat, such as dramatic variations in light intensity, the ability to perceive ROS and rapidly cause antioxidant survival [28].

The generation of ROS, including superoxide, hydrogen peroxide and radical hydroxyl radicals, also causes oxidative stress by causing nuclear acid, protein and lipid damage. Cyanobacteria generate enzyme catalyzed and non-enzyme catalyzed antioxidants to neutralize the toxic effect of ROS [28].

The reduction in the concentration of nitrogen from 200 ug to 40 ug in our experiment led to alterations in the photosynthesis; in electron transport chain [9] and a changed energy transfer between photosynthesis pigments [29]. The rise in nitrogen pressure cannot affect carotenoids-chlorophyll absorption ratio, but the ratio has dropped, suggesting that pigment protein phycobilisome are major targets [29]. In additional experiments to cultivate cyanobacterial (Spirulina platensis and Nostoc muscorum) under nitrogen stress conditions, the number of phycobiliproteins increased considerably, accompanied by an increase of their antioxidant activities.

The organism has the synthesis of Phenylalanine Ammonia Lyase (PAL) secondary metabolite, which can be removed by using phenolic composites and can be used for the treatment of phenylketonuria [30].

Different secondary metabolites including flavodoxin, saxitoxins, anatoxins, Microcystis, nodularin & phytohormones, iron-chelators to regulate the variety of metabolisms and growth rates, oxidative stress and others trigger deficiency of iron. The researchers have found that these secondary metabolites can have anti-microbial action and heavy metal poisoning antidote by generating their toxic effect on microorganisms and neutralizing heavy metals. According to previously published research studies [31].

Conventional moisturizing products, such as urea, glycerin and propylene glycol, have high absorptiveness of moisture, but their capacity for preservation of humidity is insufficient [32]. Extremophilic cyanobacteria species have defensive mechanisms that allow them to survive inhospitable environments like the hyper-arid desert and salt. One such mechanism is the production, in form of protective sheaths, slims, or capsules, of copious external polysaccharide layers. Through synthesizing both internal and external polysaccharides, cyanobacteria such as Chroococcidiopsis and Nostoc species may live with minimal water. Such metabolites can produce hydrating agents [33]. Additional studies have shown in Nostoc community, extra polymeric substances (EPS) have high moisture absorption and retention compared to chitosan (hygroscopic agent) and urea (humectant). They noticed that the moisture absorption level of EPS (10.1%) was much higher than the moisture content chitosan (6.3%) and urea (5.8%), despite exposure to 43% of relative moisture for 24hours [34].

Various cyanobacteria may tolerate extremely low temperatures. Ambient temperature transitions can cause a change in diaphragm stiffness and metabolic reaction rates or lower at suboptimal temperatures. Temperature-induced stress reactions can be used to produce useful metabolites, including unsaturated fatty acids, anti-freeze proteins, astaxanthanes or antioxidants, such as antioxidants, anticancer, anti-microbial impact, etc [35].

At different pH, cyanobacteria live for the maintenance of optimal metabolic rates and development. Under low pH than neutral pH, photosynthesis rates can be significantly higher to compensate for higher breathing rates. Increased membranes fatty acid concentration and acid-tolerant wall cell proteins are pathways often associated with low pH adaptation. Low external pH is shown to trigger heat shock protein, as is the case with some other types of stress. Studies have shown that their medicinal principles including antimicrobial and antioxidative action have been demonstrated in the previously published study [36].

The moisture retention capacities of cyanobacteria shall be related to EPS. The genes associated with EPS production are affected by several environmental factors. In many species of cyanobacteria, EPS production rates increase due to excess photo assimilated carbon nutrient deficiency (nitrogen and phosphor) and excretion is a flood mechanism to prevent harm to the photosynthesis devices [37].

Table 2: List of various biomedically interesting secondary metabolites.

S. no	Name of Secondary metabolite	Clinical use	Reference
1	Mycosporine-like amino acids	Sunscreen agent	[39]
2	Spirulan	Antiviral	[40]
3	γ-linolenic acid	Precursor to prostaglandins	[41]
4	Phycocyanin	Cosmetic colorants	[42]
5	Apratoxins	Anticancer	[43]
6	Nostodione	Antifungal	[44]
7	Carotenoids	Antioxidant	[45]
8	Anatoxin-a	Anti-Inflammatory	[46]
9	Fischerellin	Antifungal	[46]
10	Scytonemin	Anti-inflammatory, Anti-proliferation	[47]

Table 3: Various Bioactive Metabolites of Cyanobacteria used in Cancer Treatment

Cancer	Active Metabolite	Cyanobacteria	Ref
Lung Cancer	Grassystatin A-B	Lyngbya confervoides	49
	Hectochlorin	L. majuscula	50
	Hermitamides A-B	L. majuscula	51
	Lyngbyastatin 1	L. majuscula	52
	Lyngbyastatin 4	L. confervoides	53
	Lyngbyastatin 5-7	Lyngbya spp.	54
	Lyngbyastatin 8-10	Lyngbya semiplena	55
	Malyngamide 2	L. sordida	56
	Malyngamide C, J and K	L. majuscula	57
	Malyngolide dimmer	L. majuscula	57
	Palmyramide A	L. majuscula	58
	Veraguamides A-G	S. cf. hydnoides	59
	Wewakazole	L. sordida	60
	Wewakpeptins	L. semiplena	59
Colon Cancer	Lagunamide C	L. majuscula	61
	Largazole	Symploca sp.	62
	Belamide A	Symploca sp.	63
	Apratoxins F and G	L. bouilloni	62
	Apratoxins B-C	Lyngbya sp.	62
	Borophycin	N. linckia and N. spongiaeforme	62
	Apratoxin A	Lyngbya majuscula	62
	Ankaraholide A	Geitlerinema	64
	Nostocyclopeptides A1 and A2	Nostoc sp.	65
	Obyanamide	L. confervoides	65
	Tasiamide	Symploca sp.	66
Cervical Cancer	Apratoxin A	Lyngbya majuscula	62
	Caylobolide B	Phormidium spp.	67
	Cryptophycin-1	N. linckia	68
Breast Cancer	Ankaraholide A	Geitlerinema	69
	TZT-1027 analog of dolastatin 10	Symploca sp.	70
	Dolastatin 15	Lyngbya sp.	66
	Cematodin	Lyngbya sp.	66
	synthadotin	Lyngbya sp.	66
	Isomalyngamide A and A-1	L. majuscula	71
	Pitipeptolide C	L. majuscula	72
	Symplostatin 1	S. hydnoides	73
Epidermoid Cancer	Symplostatin 3	Symploca sp.	70
	Tasiamide	Symploca sp.	66
	Tasiamide B	Symploca sp.	74
	Tasipeptins A&B	Symploca sp.	66
	Tiglicamides A&C	L. confervoides	75
	Ulongapeptin	Lyngbya sp.	74
Leukemia	Calothrixin B	Calothrix	76
	Coibamide A	Leptolyngbya sp.	77
	Cryptophycin-1	N. linckia	68

Secondary Metabolites in Cancer Treatment: As per GLOBECAN 2018 estimates, cancer is the second leading cause of death worldwide and estimated to be responsible for 9.6 million deaths, about 1 in 6 cancer deaths worldwide [38]. Many cancer therapies are available but are limited due to some serious side effects and the development of drug-resistant cancer cells. Their goal is to encourage the use in conjunction with established Golden Standard Medicines of the use of natural anticancer products. Cyanobacteria make a variety of biomedically important, therapeutically useful bioactive compounds.

One of the most important cancer and other disease treatments available nowadays is chemotherapy with limited effectiveness due to some serious side effects and the development of medical-resistant cancer cells. Cyanobacteria provide a rich wealth of chemicals for the discovery of lead compounds and new medicines that are safe yet promising. Natural products are up to 80 % of the most recent antibacterial and cancer medicines approved between 1983 and 1994 [48]. Table 3 summarizes various anti-carcinogenic biologically active metabolites produced by cyanobacteria.

S. subsalsa extract was tested by the MTT viability test to T47D human cell line. The highest power in decreasing the viability of T47D cells has been found at 1, fractions 40, 60, 80 and 90. [78]. Considering that Spirulina strain from the Baltic compounds is produced, *S. subsalsa* not only have high activity with T47D cells, but they seem also to operate selectively because they have no strong inhibitory effect against the enzymes tested. This shows the potential of cyanobacteria as an origin of significant cytotoxic agents [78].

HIV Infection: Patients with HIV may experience sugar irregularities due to infections and antiretroviral medications. A randomized trial to determine the effect of Spirulina platensis versus soybean was conducted in 33 insulin-resistant HIV-infected patients as food supplements on HIV / HAART-associated resistance to insulin (IR). This pilot study reveals that in HIV patients, insulin sensitivity increases more when spirulina is used as a nutritional supplement instead of soya [79].

Chromosomal Damage: Spirulina has shown that the chromosome aberrations caused by CCl4 in bone marrow cells are ameliorating, which confirms its defense from chromosome damage [80].

CONCLUSIONS

Cyanobacteria are a rich source of secondary metabolites due to their ability to thrive under a variety of environments. Depending on the stress environment different sequences of secondary metabolites can be produced with a high structural variation across the various compound groups. The properties of cyanobacterial extracts are antiviral, anticancer, hypocholesterolemic, anti- diabetic, antioxidant, non-inflammatory and anti-metastasistic, potential for biomedical applications. The review demonstrates that the cyanobacteria have the potential for expanded utilization in drug discovery. Hence, pharmaceutical companies should conduct clinical trials on several bioactive molecules obtained from cyanobacteria exhibiting a broad spectrum of activities.

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