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The therapeutical potency of cyanobacterial secondary metabolites compared with chemotherapy against leukemia: Mini-review

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Abstract

Cyanobacteria are a significant group of gram-negative photosynthetic bacteria which have the ability to grow in a broad range of habitat such as lakes, oceans, soil, hot springs, deserts and so on. These photosynthetic organisms are known a potential source of bioactive compounds that can be generated as byproducts during photosynthetic process with antibacterial, anti-tumour, neuroprotective, and anti-cancer activities. So far, several cyanobacterial bioactive compounds with anti-leukemia activities have been evaluated for treatment of leukemia which is one of the most common leading cause of cancer death. However, no review study has been conducted about the anti-leukemia cyanometabolites and their therapeutic mechanisms. Therefore, this review discusses five major striking anti-leukemia cyanometabolites and their therapeutic mechanisms in summarize. Ultimately, the traditional therapeutic procedure, chemotherapy, and its common challenges and issues have been investigated to declare the superiority of natural medicines over chemotherapy.

Key words: Cyanobactria; Algae; Cancer; Leukemia; Chemotherapy



1. Introduction

Cyanobacteria are among the oldest photosynthetic organisms on the earth which can be found in almost all types of water. In an aquatic environment, the water will play the role of electron donor for the respiration of cyanobacteria in photosynthesis by which oxygen will be produced ultimately. Due to the unique ability of these organisms to generate oxygen, they are assumed to be the first oxygen producer on our planet that had an important role in making the current life possible for human beings [1, 2]. Moreover, these microscopic organisms are able to consume CO₂, one of the main greenhouse gases which its high presence in the atmosphere is considered as an environmental pollutant and caused global warming. A sharp increase in global temperature, contamination of water sources, industrial air pollution and energy demands are mainly caused by rapid human population growth. The negative effects of carbon dioxide emission can be diminished during cyanobacteria photosynthetic process[3]. Also, regarding the potential of cyanobacteria to uptake nutrients such as nitrate and phosphorous, it will be more beneficial to the environment if these micro-organisms are cultivated in wastewater. In this way, aiming two various environmental issues will be feasible: air and water pollution.

Nowadays, natural medicine sources have drawn great attention owing their synthetic chemicals distribution via water, soil and air lead to spread and proliferation of various drug resistant micro-organisms. In addition, using synthetic drugs is associated with various related complications. Despite CO₂ utilization and O₂ production, cyanobacteria can produce bioactive secondary metabolites with a variety range of function such as anticancer, antibacterial and anti-fungal properties, during their respiration process. For instance, therapeutic properties such as antibacterial have been detected in some unnatural fatty acids. As a result, if these biosynthetic molecules are used in pharmaceutical industries along with restricting the usage of synthetic chemicals, the consumption of medicine will be optimized along with minimizing related complications [4-7].

On the other hand, discovering and developing a new medicine just by experimental methods at lab is too expensive and takes a lot of time. The reason is that without the in-silico process, a new compound with affinity to a specific target should be selected randomly or by previous research. However, using the in-silico method and virtual screening by which biological experiments conducted on a computer, has led to predict novel bioactive molecules and lessen the spending time on drug discovery and development and makes it more cost effective [5, 8]. A potent in-silico and theoretical tool for identifying unknown compounds in natural products mixtures is Global Natural Product Social Molecular Networking (GNPS). There are also NCBI, UniProt and other data bases which can be used. Moreover, NMR spectroscopy is one of the devices by which detection of molecules is possible. Using these tools along with genomic or biological assays will help us to discover novel bioactive cyanobacterial [8-10]. Leukemia is a type of cancer which is thought to occur in body due to leukocytes pathological mutations [11]. Although, several research have been conducted to identify therapeutic potencies of cyanobacterial secondary metabolites in treatment of different diseases, no review on the usage of cyanobacteria for leukemia was presented.



In this research, the effectiveness of cyanobacterial compounds was discussed in the treatment of leukemia, due to the following reasons: (i) leukemia, it is the fifth most frequent cancer which can lead to the death of patients, (ii) it is noticeable that its incidence has been increasing in Iran, (iii) the conventional treatments of this disease have shown severe side effects and efficiency of drugs has been limited by emerging drug resistance [12, 13]. Therefore, in this mini review, after discussing about the current challenges in cancer treatment and chemotherapy, five main cyanobacterial bioactive secondary metabolite were analysis separately. Finally, the latest studies regard the five metabolites and their applications have been presented.

2. Chemotherapy and challenges in cancer treatment

There are different methods for cancer treatment such as surgery, bone marrow transplantation, radiotherapy, hormone therapy or chemotherapy [14]. The frontline treatment of various types of cancer are chemotherapy and radiation which can damage DNA and lead to the cancer cell destruction or cell growth limitation. Eventually, it will either cure the patient or increase the patient's survival time. Cancer patients undergoing chemotherapy experience intensive side effects comprised harmful effects on immune system, baldness, appetite loss, fatigue, esophagus irritation, vomiting, neutropenia, anemia and so on [15-17]. These side effects show up due to negative effects of chemotherapy on healthy cells which not only weaken the patient, but may reduce the efficiency of chemotherapy [16].

In addition, nowadays, we are exposed to lots of environmental contaminants by which various diseases have been developed. It has been reported that exposure to these substances with toxic properties may cause cancer, cancer progression, and even chemo-resistance and reduction of chemotherapeutic drugs effectiveness [18]. Due to the cyanobacteria advantages and mentioned limitations of using traditional radiotherapy and chemotherapy, it seems cyanobacterial secondary component are striking and attractive enough to be used in drug design and development industry.

3. Cyanobacterial bioactive secondary metabolite

Secondary metabolites are usually known as compounds that are not required for the primary metabolite and are synthesized by certain species. Generally, several classes of secondary metabolite which can be produced by cyanobacteria are peptides, polyketides, alkaloids, terpenoids and UV-absorbing [19]. In this research, the significant metabolites of various cyanobacteria strains including Phycocyanin, Cryptophycins, Dolastatins, Cyclic depsipeptides and Calothrixins are described succinctly in terms of their features and action mechanisms.



3-1- Phycocyanin

Phycocyanin is a light-harvesting pigment-protein in cyanobacteria which is applicable in different industries such as food, feed, beverage, cosmetic and pharmaceutical [20]. So far, several therapeutic activities have been indicated for phycocyanin such as anticancer [21-23], antitumor [24-26], antibacterial [27, 28], antioxidant [29, 30], anti-inflammatory properties [22, 29], anti-arthritic [31] and hepatoprotective effects [32]. In addition, the ability of inducing apoptosis in leukemia cancer cells has been reported for Phycocyanin which *Spirulina platensis*, a planktonic filamentous cyanobacterium is a striking source of this bioactive compound. Cellular tumor antigen p53 [*Homo sapiens* (human)] (uniprot accession number: P04637) can suppress the leukemia cancer cells and it is responsible for controlling the damaged DNA cells' multiplication. Phycocyanin affects the p53 expression and activate apoptotic pathway and lead to cell apoptosis. In spite of cell apoptosis, it has shown that phycocyanin has inhibitory effects on leukemia cell growth (in cell lines HL-60, K-562 and U-937) [33-35].

3-2- Cryptophycins

Cryptophycins are a peptides group which can cause depolymerization of microtubules, inhibit cell duplication, and eventually lead to cell-cycle arrest and apoptosis. Microtubules are one of the main components of cell cytoskeleton and are involved in regulation of cell growth and movement. Due to their role in cell division, they are considered as targets for anticancer drugs. As a result, Cryptophycins have exhibited a promising anticancer activity [36, 37]. Cryptophycins were originally isolated from the cyanobacteria *Nostoc* species. Although Cryptophycins' complex structure led to high Synthetic production cost, it has been found that using cyanobacteria will be a cost-effective way to produce cryptophycins naturally [5, 38, 39]. Smith et al. [40] reported that these bioactive compounds can prevent proliferation of L1210 leukemia cells. Also, Kessel and Luo [41] have claimed that 18 h of murine leukemia L1210 cells treatment with cryptophycin 52 (a member of the cryptophycin family) led to cell-cycle arrest, but apoptosis was observed after 36 h.

3-3- Dolastatins

Dolastatins are cytotoxic peptides which were isolated from a sea hare for the first time. Subsequently, scientists found them in some of cyanobacterial strains. So far, anticancer activities of Dolastatins have been evaluated in several studies. In terms of cytotoxic and microtubule cytoskeleton-disrupting activity, dol-10 and dol-15 are the most striking ones [42]. Hu et al. [43] have demonstrated that dolastatin 10 and dolastatin 15 of this group are significant leukemic B-cell growth inhibitors and apoptosis is the possible mechanism of cell death [44]. Moreover, it has been indicated by In vitro experiments that dolastatin 10 and its derivatives are fatal to L1210 leukemia cells. Binding of dolastatin 10 which has been found in marine cyanobacterium *Symploca* species, to tubulin will lead to inhibition of microtubule assembly and apoptotic cell death [45, 46].



3-4- Cyclic depsipeptides

Cyclic depsipeptides are polypeptides that contains one or more ester linkage in their structure. These bioactive components can be found in fungi, plants, and marine organisms such as cyanobacteria. Up to now, various therapeutic activities have been indicated for these cyclic peptides such as antifungal, anticancer, antitumor and antibacterial activities [47]. Three new cyclic depsipeptides of kulolide superfamily from the filamentous cyanobacteria *Symploca hydnoidea* were previously identified as Tricoveramide A,B and C by Phyto et al.[48]. Among these components, tricoveramide B showed the highest cytotoxic activity against MOLT-4 human leukemia cells. Cytotoxic activity has inhibitory effects on cell growth and division. Furthermore, it has been reported [49] that Lagunamides A and B are two more cyanobacteria cyclic depsipeptides which were isolated from *Lyngbya majuscula* and exhibited significant cytotoxic activity against P388 murine leukemia cell lines.

3-4- Calothrixins

In 1999, Rickards et al [50] isolated two novel cyanobacterial secondary metabolites from *Calothrix* called Calothrixins A and B which are pentacyclic alkaloids[51]. Calothrixins A was found to exhibit potent antiproliferative activity by inducing G2/M cell cycle arrest in a leukemia cell line[52]. Also, cytotoxicity effect of calothrixin A was evaluated against CEM leukemia cell line and its IC50 (50% cell growth inhibitory concentration) value was observed to be 0.2 μ M[53]. Long et al. [54] investigated the anti-leukemic activity of L20, a new chemical analog of Calothrixin B. It was unveiled that a series of molecular events happened after exposing HEL cell to L20. Experiments revealed that L20 showed the ability to inhibit the MAP/ERK pathway which may play a significant role in cell multiplication, migration, differentiation, senescence, and apoptosis [55]. Also, it caused G2/M cell cycle arrest and mitochondrial damage followed by DNA damage, and apoptosis.

3. Current studies about bioactive compounds from cyanobacteria

Table 1 presents current studies about bioactive compounds has been reported in literature. As can be seen from Table 1, Phycocyanin metabolite of different types of cyanobacteria, particularly *Spirulina platensis*, showed promising performance on antitumor and anti-breast, liver and lung cancer activities [56 - 65]. According to Menon et al, 2002 [72] and Trimurtulu et al., 1994 [73], Cryptophycins metabolite of *Nostoc* sp. cyanobacteria found promising applications in antitumor activity [70 -73].

**Table 1: List of bioactive compounds from cyanobacteria which have been reported in literature**

Metabolites	Source	Activities	References
Phycocyanin	<i>Arthronema africanum</i>	Antitumor activity	[24]
	<i>Anabaena sp. ISC55</i>	Antitumor activity	[56]
	<i>Anabaena cylindrica</i>	Antitumor activity	[57]
	<i>Spirulina platensis</i>	Antitumor activity	[58]
	<i>Spirulina maxima</i>	Antitumor activity	[58]
	<i>Spirulina platensis</i>	Anti-breast cancer activity	[59]
	<i>Spirulina platensis</i>	Anti-breast cancer activity	[60]
	<i>Spirulina platensis</i>	Anti-liver cancer activity	[61]
	<i>Spirulina platensis</i>	Anti-lung cancer activity	[62]
	<i>Spirulina platensis</i>	Anti-colon cancer activity	[63]
	<i>Spirulina maxima</i>	Anti-inflammatory activity	[29],[64],[65]
	<i>Spirulina maxima</i>	Hepatoprotective activity	[66]
	<i>Spirulina maxima</i>	Antioxidative activity	[66]
	<i>Spirulina</i>	Hepatoprotective activity	[67]
	<i>Spirulina</i>	antioxidative activity	[67]
Cryptophycins	<i>Nostoc sp. ATCC 53789</i>	Anticancer activity	[70],[71]
	<i>Nostoc sp.</i>	Antitumor activity	[72]
	<i>Nostoc sp. GSV 224</i>	Antitumor activity	[73]
Dolastatin 15	<i>A marine cyanobacteria</i>	Anticancer activity	[42]
Dolastatin 10	<i>Symploca hydnoides</i>	Antitumor activity	[74]
Homodolastatin 16	<i>Lyngbya majuscula</i>	Anticancer activity	[75]
Lagunamides	<i>Lyngbya majuscula</i>	Anticancer activity	[76], [77]
lagunamides A–C	<i>Lyngbya majuscula</i>	antiplasmodial activity	[78]
3-fluorocalothrixin B	<i>Calothrix cyanobacteria</i>	Anticancer activity	[79]

4. Conclusion

Cyanobacteria can be found in a wide range of habitats, such as freshwater, salt water, frigid waters, soil and so on. Although some toxic cyanobacteria bloom have been identified in rivers and streams, some of cyanobacteria strains consist of therapeutically efficient components that make them attractive for further investigation. On the other hand, the life-threatening disadvantages of chemotherapy as a common procedure for leukemia treatment have been proven so far. This mini-review studied the major striking anti-leukemia cyanometabolites and their therapeutic mechanisms. Since after diagnosis, most patients must start treatment quickly, finding natural potent anti-leukemia compounds seems very significant to lessen therapeutic side effects and increase the life quality of patients.



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