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Review Article

Pharmaceutical applications of cyanobacteria—A review

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Abstract

Cyanobacteria are emerging as an important source of novel bioactive secondary metabolites. Recently, it has also been reported as a rich source of bioactive molecules such as apratoxins, lynbyabellin, and curacin A. Some compounds have exhibited very interesting results and successfully reached Phase II and Phase III clinical trials. Furthermore, cyanobacterial compounds hold a bright and promising future in scientific research and provide a great opportunity for new drug discovery. In 2005, a number of new technologies have led to the development of new miniaturized screens based on cell cultures, enzyme activities, and ligand receptor binding. The use of a computational method based on targeted metabolite data has provided additional insight into the ligand-based approach that employs conformational analysis of known ligands. This approach has implications for developing novel compounds for structure-based drug design. Hence, this review article mainly focuses on baseline information for promoting the use of cyanobacterial bioactive compounds as drugs for various dreadful human diseases, using the computational approach.

Keywords: bioactive compounds; computational approach; cyanobacteria; dolastatin 15; drug discovery; drug for cancer

1. Introduction

Natural products are an important source of new structures leading to drugs in all major disease areas. This issue illustrates current activities and trends in the research of natural products and drug discovery. Medicinal chemistry is the cornerstone for successful hit-to-lead exploration and further lead optimization. An increase in productivity in the drug discovery process has been achieved with the implementation of library chemistry and high throughput screening. Despite these efforts, the number of new chemical entities reaching the market has not increased. Only one drug originated from a *de novo* combinatorial chemistry approach. However, natural products remain an important source of structures contributing mostly to semisynthetic or synthetic drugs in all disease areas. Therefore, therapeutic effects of natural product-derived drugs are predominantly achieved in antibiotic therapies, oncology, and immunoregulation.[1] It is less likely to identify potent natural products against molecular targets of human diseases. Natural products are important sources of new structures, leading to drugs in all major disease areas. Recently, researchers are mainly focusing on developing new drugs from marine cyanobacteria.[2]

2. Cyanobacteria

Studies of biomedical natural products have been concentrated only on Cyanophyta (blue-green algae) and Pyrrophyta (dinoflagellates); most of the metabolites have been isolated from cyanobacteria.[3,4] Cyanobacteria have been considered a rich source of secondary metabolites with potential biotechnological applications in the pharmacological field. Lately, production of bioactive compounds with commercial and medical applications has also increased interest in studying these organisms.[5] In fact, together with the production of

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potent toxins, cyanobacteria produce many substances that are interesting in terms of their antifungal, antibiotic, and anticancerigenous activities.[6,7]

Further, cyanobacterial metabolites show interesting and exciting biological activities, including antimicrobial, immunosuppressant, anticancer, anti-HIV (human immunodeficiency virus), antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, antiviral, and antitumor activities.[8–10]

The main emphasis is given on the search of drugs for dreadful human diseases such as cancer and AIDS. In recent years, scientists from different parts of the world have discovered various drugs for the treatment of such diseases. The chemical and biological diversity of the marine environment is immeasurable, making it an extraordinary resource for the discovery of new anticancer drugs from cyanobacteria (Table 1).[15,22,24,25,47–101] This review highlights several marine natural products and their synthetic derivatives that are currently undergoing clinical evaluation as anticancer drugs.[11] The past decades have seen a dramatic increase in the number of preclinical anticancer lead compounds obtained from diverse marine species that have entered into human clinical trials.[12] Productivity in the past decades in terms of discovery of new clinical anticancer leads from diverse marine life should translate into a number of new treatments for cancer in the years to come.

3. Cyanobacterial drugs for cancer

One of the most important treatments currently available for cancer and other diseases is chemotherapy, which has limited effectiveness due to some serious life-threatening side effects and development of drug-resistant cancer cells. The therapeutic efficacy and possible side effects vary among different agents. Some drugs may have excellent efficacy but can have very serious side effects. In addition, they may have very limited supply and thus can be very expensive. However, new drug discovery is a long and expensive process. It may take as long as 15–20 years and as much as billions of dollars. It is thus worthwhile to pursue a less expensive way for the production of drugs that have been found to be effective, and to develop a new way of administration or new delivery devices to increase their efficacy and eliminate/decrease their side effects. Side effects of anticancer drugs not only reduce the efficacy of chemotherapy, but also compromise the quality of Patient's life.[13] The use of natural anticancer products, for example, cyanobacterial anticancer metabolites, may improve anticancer therapy.

Thus, cyanobacteria are promising but still unexplored natural resources offering a wealth of chemicals for the discovery of lead compounds and new drugs. Of the new antibacterial and anticancer drugs approved between 1983 and 1994, up to 80% were derived from natural products. Traditional microbial drug producers such as actinomycetes and hyphomycetes have been the focus of pharmaceutical research for decades. Due to a decrease in the rate of discovery of interesting compounds in classical source organisms, it is time to turn to cyanobacteria and exploit their potential. The biosynthetic information on the chemical structures unique to these organisms will be very valuable for finding out new anticancer agents.

4. Bioactive compounds from cyanobacteria

Cyanobacteria produce a wide variety of biomedically interesting bioactive compounds, which are described below.

4.1. Borophycin

It is obtained from *Nostoc spongiaeforme* var. *tenue*. It is a boron-containing metabolite and has been found to have effective cytotoxicity for human carcinoma.[14–16]

4.2. Borophycin-8

It is obtained from *Nostoc linckia*.[17] It is made up of two identical halves with an overall structure reminiscent of other boron-containing antibiotics. The C3 starter unit for the biosynthesis of borophycin 8 is derived from acetate and methionine, but not from propionate. Borophycin and four new cyclic hexapeptides containing no boron, tenuecyclamides A–D, were also isolated from the methanol extract of *N. spongiaeforme* var. *tenue* collected from the Volcani Center, Israel.[15]

4.3. Apratoxin A

It is a cyanobacterial secondary metabolite, known as a potent cytotoxic marine natural product. It is a derivative of the apratoxin family of cytotoxins. The mixed peptide–polyketide natural product comes from a polyketide synthase/nonribosomal peptide synthase pathway. This cytotoxin is known for inducing G1-phase cell cycle arrest and apoptosis. This natural product's activity has made it a popular target for the development of anticancer derivatives. Cyanobacterial metabolites are commonly found to be useful in cancer treatment. In particular, apratoxin A has been found to be a potent cancer cell cytotoxin. It has been found to be remarkably cytotoxic in both *in vitro* and *in vivo* studies. Although much work has been done to understand the mechanism of action of this cytotoxin, there is no definite understanding of how apratoxin A mediates antitumor activity in the cell. In addition, apratoxin A lacks necessary selectivity to become a potential antitumor agent, although numerous reports have shown differential cytotoxicity in 60 tumor cell lines.[18]

4.4. Cryptophycin

It works by attacking the tubulin microfilaments found in eukaryotic cells, thereby preventing cell division and reproduction. The main hypothesis as to why blue-green algae produce this energetically expensive compound is that it is used as a strong antifungal agent in order to prevent fungi or other types of algae from competing with the cyanophyceae for nutrients and sunlight. It has been found that the amount of