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Review

Potential therapeutic targets and the role of technology in developing novel cannabinoid drugs from cyanobacteria

S. Vijayakumar*, P. Manogar, S. Prabhu

Computational Phytochemistry Lab, P.G. and Research Department of Botany and Microbiology, A.V.V.M. Sri Pushpam College (Autonomous), Poondi-613 503, Thanjavur district, Tamil Nadu 613 503, India

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ABSTRACT

Cyanobacteria find several applications in pharmacology as potential candidates for drug design. The need for new compounds that can be used as drugs has always been on the rise in therapeutics. Cyanobacteria have been identified as promising targets of research in the quest for new pharmaceutical compounds as they can produce secondary metabolites with novel chemical structures. Cyanobacteria is now recognized as a vital source of bioactive molecules like Curacin A, Largazole and Apratoxin which have succeeded in reaching Phase II and Phase III into clinical trials. The discovery of several new clinical cannabinoid drugs in the past decade from diverse marine life should translate into a number of new drugs for cannabinoid in the years to come. Conventional cannabinoid drugs have high toxicity and as a result, they affect the efficacy of chemotherapy and patients' life very much. The present review focuses on how potential, safe and affordable drugs used for cannabinoid treatment could be developed from cyanobacteria.

Contents

* Corresponding author.
E-mail address: svijaya_kumar2579@rediff.com (S. Vijayakumar).

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1. Introduction

Cyanobacteria are the oldest prokaryotic organism evolved over two billions years ago. This belongs to monophyletic group and responsible for accumulating atmospheric oxygen and photosynthetic capacity of plants [1,2]. Generally cyanobacteria are being existed in numerous habitats like fresh water, terrestrial and marine environments. Climate extremes can be tolerated by cyanobacteria. These types of cyanobacteria are schematically categorized based on phenotype with the help of classifications I–V, I–II, III–V [1–3]. They are morphologically and genotyphically diverse. It is more geotypical diverse of than morphological [4].

Richard E. Moore popularized cyanobactetria derived natural products during 1970, and in collaboration with William H. Gerwick during the late 1980. Later he changed his focus to terrestrial cyanobacteria [5]. The result from this research proved that cyanobacteria are prolific sources of bioactive and chemically diverse secondary metabolites. Nearly 58% of cyanobacterial metabolites have been produced by Ocillatoriales, and a study on *Lyngbya* genus reports 35% production. Common species in marine are *Lyngbya majuscula*, *Lyngbya semiplena*, and *Lyngbya boullonii*. From these, natural products are being extracted. The isolated natural products are historically ascribed to chemical diversity. However, in current studies polyphyly of the marine *Lyngbya* lineage is indicated as the most prolific source of cyanobacterial metabolites [6].

At present day, sequence data for many *Cannabis sativa* are available in outnumber. These strains connected to genes that is encoding for the biosynthesis of secondary compounds of therapeutic interest are responsible for improving and developing the advanced tools in order to breed and choose the therapeutic Cannabis varieties are alike, that devote themselves produce a specific a single cannabinoid, a specific blend of various cannabonoids, and also zero-cannabinoid varieties. These are very useful in modern pharmaceutical industries. Both the cannabis genomes completion and the alleles extensive characterization in addition to widen the portfolio of phytocannabinoids available (or) existing for the therapeutic. Not only that, but also the present explanation on THCAS' tertiary structure by X-ray crystallography at the 2.75 A° resolution give way to many biotechnological for the cannabinoids explacta's synthesis [7].

2. Cyanobacterial derived lead compounds

Research is on cyanobacterial lead compounds to make it a better therapeutic. The quantity of it is numerous, so it is very difficult to categorize within the context. These compounds rise up from the geographically diversed cyanobacteria. To highlight the structural ingenuity and impressive biologic profiles of the lead compounds, the representative compounds are elaborated.

There are many cyanobacterial lead compounds like Somocystinamide A, Hoiamide A, Coibamide A, Curacin A, Apratoxicins and Largazole. Somocystinamide A is extracted from a Fijan assemblage of *Lyngbya majuscula* and *Schizothrix* sp. Early data on bioactivity had indicated neuro-2A cytotoxcity (IC50 = 1.4 μg/ml) [8].

2.1. Somocystinamide A

This compound is extracted from *Lyngbya majuscula* (Fig. 1a). According to Mollay, and Karla Lynn tested on screening program in a cancer centre showed the potent activity of cytotoxic towards caspase 8 expressing cells. And also extensive studies on mechanistic prove that Somocystinamide A kindled apoptosis via a caspase 8 dependent pathway. It inhibits both endothelial tube formation *in vitro* and angiogenesis in zebra fish. The inhibition of caspase 8-expressing neuroblastoma tumor growth was clearly shown *in vivo*. Total data suggest that Somocystinamide A is a possible lead angiogenic and caspase 8 dependent tumor inhibitor [8,9].

2.2. Hoiamide A

Hoiamide A is extracted from a Papua New Guinea; it is an assemblage of *Lyngbya majuscula* and *Phormidium gracile* (Fig. 1b). It is a modified isoleucine moiety, and a highly oxidized and methylated C15 polyketide extension. It inhibits (^{3}H) batrachotoxin binding to voltage- gated sodium channels (VGSCs). Its potency far surpasses the veratridine's potency (IC 50 = 33.0 μM) in the prototypic site 2 VGSC agonist derived from a higher plant. It also activated sodium influx (EC50 = 2.31 μM) in murine neocortical neurons. Hoiamide A is a candidate lead compound to modulate the neuron growth and plasticity and harbours significant potency as VGSC modifiers capable of influencing NMDA signaling involved in neuronal growth and plasticity [10].

2.3. Coibamide A

This compound is extracted from Panamanian *Leptolyngbya* sp. (Fig. 1c). The structure of coibamide A is completely NRPS derived with a high degree of methylated residues. It displays potent cytotoxicity properties against the H460 lung carcinoma and neuro-2a neuroblastoma cell line (LC50 < 23 nM) but at the same it is active in tubulin. It shows the greatest potency when it was screened in the NCI 60 cell line cancer assays. The research is on Coibamide A compound to know more about its biological activities [11].

2.4. Curacin A

Curacin A is extracted from *Lyngbya majuscula* (Caribbean). It inhibits cross-linking of tubulin. It shows potent cytotoxicity with breast, colon, and renal cell selectivity when it was examined in the NC I60 cell line assay (Fig. 1d). As per SAR (Systemic Acquired Resistance) studies report, the major contributors to tubulin binding are thiazoline, olefin and methyl groups. Besides, action studies show that Curacin A depolymerizes tubulin by binding to the colchicines site. To know more about the availability and potency of Curacin A [12].

2.5. Apratoxin A

This compound is extracted from numerous collections of *Lyngbya sp* (Fig. 1e) from Papua, New Guinea and Palmyra [13,14]. It is the source of biosynthesis [15]. Nanomolar cytotoxicity is harboured by the compounds in many cell lines, such as Apratoxin A and Apratoxin G. Both are similar structurally and the action of apratoxin A is attributed to interact with heat shock protein (HSP) 90 and reverse the inhibition of secretary pathway for cancer associated receptors [8,15,16]. Apratoxin G absorbs an alanine residue in the terminal proline's place, and also it maintains the cytotoxicity (IC50 = 14 nM) in the H460 cell line [14]. In this type of compounds the terminal residue is not central to bio activity.

2.6. Largazole

Largazole compound is extracted from *Symploca* sp. [17]. 4-methylthiazoline and thiazoleheterocyclic system and a unique 3-hydroxyl-7-mercaptohept-4-enoic acid are features of Largazole's structure (Fig. 1f). Early biological screening shows the potent growth inhibition and cytotoxicity of Largazole in numerous cell lines such as human memory cell line, fibroblastic osteosarcoma cell line, colon cancer cell line and neuroblastoma cell line [18]. As