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Cyanobacteria Bioactive Compound, their Production and Extraction with Pharmaceutical Applications – A Review

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ABSTRACT

Bio-active compounds are of high aesthetic value in pharmaceutical industries but they are not widely explored. These compounds derived from plant, fungi and bacteria cannot really satisfy even a small fraction of the existing demand of the growing population day by day. In recent years, there is a great deal of attention towards cyanobacteria as they are a vast reserve of bioactive molecules with wide pharmaceutical importance. Extremophiles cyanobacteria have the ability to endure extreme conditions and posses a great capacity for producing biologically active compounds that are capable of meeting the global demand as an alternative source of drugs with economic sustainability. Thus, approaches for making extremophiles cyanobacteria as therapeutic agents specifically focused on antimicrobial activities can hold a scintillating future in scientific research to get invested in the field of pharmaceuticals as well as for industrial applications.

Introduction

In past few years, due to exponential rise in population and changing lifestyles, microorganisms have developed resistant against many drugs which are used in treating many infectious diseases. Multi drug resistance is the resistance of microorganisms against the targeted drugs (Tanwar *et al.*, 2014). The prolonged use of antibiotics, over or under use of antibiotics, use of antibiotics without any information regarding antibiotic sensitivity pattern of the pathogens, non completion of doses etc. have lead to the development of MDR among pathogens for the treatment of diseases. According to WHO report 80% of the world population gamble on plants for traditional medicines and 40% of the industries depend on plants to produce drugs (Jain, 2017). However, many challenges have been lined up regarding the pharmaceutical application of plants which include authentication of plant material, large scale industrial output of bioactive products from plants to meet the never ending demands of brimming population (Bijauliya *et al*., 2017). This necessitates a demand for discovery of antimicrobial compounds from microorganisms.

Among microorganisms, Algae have a significant attraction as natural source of bioactive molecules with broad range of biological activities such as antibiotics, antiviral, antitumoural, antioxidant and anti-inflammatory (Devi and Mehta, 2016; Hassouani *et al*., 2017; Bule *et al*., 2018). Algae are swiftly proving to be an extremely important source of biologically active secondary metabolites (Ramya and Muralitharum, 2019) which could be used for the biological control of pathogens. Secondary or primary metabolites of algae consist of diverse group of chemical compounds. Report on antibiotic activity of algae was first reported by Pratt *et al*., (1944). Cyanobacteria natural products are considered to be one of the accessible origins in the microbial world which are useful to humankind in several ways due to their potential application (Lau *et al*., 2015; Demay *et al*., 2019). The widespread distribution of these organisms reflect the tolerance of cyanobacteria towards environmental stress due to their morphological and broad spectrum of specific properties in physiology (Uzair *et al*., 2012; Nguyen *et al*., 2017; Soa and Samuel, 2018; Godlewska *et al*., 2019). Generally, microorganisms forming microbial mats in extreme environment have been recently identified as a good source of bioactive compounds for different biotechnological applications (Bhatnagar and Kim, 2010). Modern research has focused on a variety of bioactive compounds produced by cyanobacteria from various biotypes and has been tested for antimicrobial activity e.g marine (Kumar *et al*., 2019) and terrestrial (Safavi *et al*., 2019). Considering sub-aerial ecosystem as an extreme environment (due to adverse condition and nutrient depletion, few studies have yet identified the antibacterial potential of cyanobacteria isolates from this habitat (Panigrahi *et al*., 2015; Sahu *et al*., 2017; Pattnaik and Samad, 2018; Bhakat *et al*., 2020) still however no studies till date are adequate. Several researchers have investigated bioactive compounds with a diverse range of biological activities and chemicals structures including novel cyclic and linear lipopetides, fatty acids, alkaloids and other organic chemicals (Singh *et al*., 2016; Bule *et al*., 2018).

Bioactivity of compounds extracted from cyanobacteria

Cyanobacteria earlier known as blue green algae are photosynthetic prokaryotes among the oldest extant organisms on Earth, dating back to fossil records of nearly 3.5 billion years. These organisms have been identified as a new and rich source of bioactive compounds (Abed *et al*., 2009; Shalaby, 2011; Nowruzi *et al*., 2017).

Reports available indicate that bioactive compounds contradict synthetic drugs in their composition and their arrangement of radicals and atoms. They are much more potent in inhibiting protein-protein interactions resulting in effective immune response, signal transduction; mitosis and ultimately apoptosis without causing much harm to living organisms (Koehn and Carter, 2005; Guaadaoui *et al*., 2014). However, few compounds like hassallidin, hapalindole and *Y*- lactone isolated from *Nostoc* sp. CENA 219 KP701037 and *Nostoc calcicula* 6sf Cale KP701034, *Fischerella* sp. and *Scytonema* sp. (Shishido *et al.*, 2015; Singh *et al*., 2016) have attained importance for their antimicrobial activity in the field of biotechnology. Still further research needs to be carried out to isolate bioactive compounds possessing antimicrobial property from cyanobacteria for betterment of the society. Cyanobacteria can be potential source of such compounds which may have haemolytic or anti-haemolytic effect on human erythrocytes. Therefore, many of the cyanobacteria species need to be evaluated for their potential haemolytic activity to be categorized as a safe remedy to cure diseases.

Biosynthesis of bioactive compounds in cyanobacteria

Bioactive compounds can be broadly categorized into terpenes, alkaloids, fatty acids, UV-absorbing compounds, peptides and polyketides etc. Peptide biosynthesis in cyanobacteria occurs through ribosomal and non-ribosomal pathways (Marahiel and Essen, 2009) shown in (Fig. 1). Cyanobacterial polyketide consists of *cis*- and *trans*-acyltransferases. The *cis*- polyketide synthase have repetitive acyltransferases. The *trans*-polyketide have non-repeatative acyltransferases. Only one acyltransferase can be repeated several times. There are three types of polyketide synthase (Type - I, II and III), out of which Type - II and III work in a repetitive manner and synthesize aromatic compounds (Hertweck, 2009; Piel, 2010; Helfrich *et al*., 2014). Non-ribosomal peptides are synthesized through non-ribosomal peptide synthetases (NRPS). One amino acid molecule is added to the growing amino acid chain by each NRPS module (Fischbach and Walsh, 2006; Kehr, *et al*., 2011; Marahiel, 2016). An adenylation (A) domain, a peptidyl carrier protein and a condensation (C) domain are needed for the activation and identification of the amino acid, (PCP) to move the amino acid, to make the peptide bond respectively. In addition, thioesterase (TE) domain plays a key role in releasing the final compound and terminates chain-elongation.

Decision-making factors for production and extraction of bioactive compound from cyanobacteria

Sub-aerial cyanobacteria grow on exposed surface of walls of building facades, monuments and temples (Cutler and Viles 2010; Rossi *et al*., 2012; Keshari and Adhikary, 2014). They are found in abundance in tropical climate rather than temperate climate due to their ability to withstand adverse environmental conditions like high light intensity, high temperature, and drought conditions. They produce bioactive compounds to have a favourable growth when they are subjected to stress conditions. Environmental factors like culture age, temperature, salinity, pH, macro and micronutrients and light play a key role in manufacturing bioactive compounds (Noaman *et al*., 2004). The most important requirement for obtaining bioactive compound from sub-aerial cyanobacteria is selection of standard extraction and purification protocol (Fig. 2). Mass cultivation of axenic culture of sub-aerial cyanobacteria with maximum biomass for small scale production can be carried out in conical flasks or small photo bioreactors with pH of media 7.0-9.0, light intensity 2800-3000lux and temperature 28°C. The environmental conditions may vary depending on the type of species and specific substratum. Among various artificial media, blue green eleven (BG-11) media (Rippka *et al*., 1979) was considered more suitable to obtain maximum yield.

Strategies for large scale biomass production of sub-aerial cyanobacteria and bioactive compound with pharmacological utility

Scientific research is always focused to find its application for human welfare. Therefore, any study relating to its application must aim two things. One is its safety to human beings or the target host and secondly its cost effectiveness. Researchers and academicians over the Globe have always tried to use different novel techniques to produce value added products with low cost. The cost of extracting bioactive compounds from cyanobacteria can be minimised by using a photobioreactor and improving the efficiency of cyanobacteria through genetic engineering. The entire process of bioactive compound extraction can be cost effective by increasing physiological and environmental factors through optimization of extraction protocol with respect to culture media, pH, temperature and cell disruption technique etc. (Fig. 2) favouring bioactive compounds production (Chisti, 2007). There are two types of photobioreactor: open bioreactors and closed photobioreactor. But for bioactive substances having pharmacological utility, mostly closed bioreactors are preferred to avoid contamination (Singh *et al*., 2005). With the advent technologies, emphasis have been given to the molecular level i.e. the genes working behind the bioactive compounds production can be enhanced through recombinant DNA technology as represented in (Fig. 3).

Diversity of sub-aerial cyanobacteria on extreme environments and their importance in Bhubaneswar and Puri, Odisha

Cyanobacteria are mediated as being one of the potential organisms, instituting a versatile group of microorganisms and residing in diverse habitat ranging from alkaline hot spring to permanent snow fields in the poles can be profitable to mankind in multidirectional ways. They constitute a principal group of organisms for biotechnological exploitation, especially for valuable products, processes and services, with important impact in food and pharmaceutical industries as well as in public health. In recent years, a number of significant advancements have occurred in Cyanobacterial biotechnology from natural resources like marine, freshwater**,** and very few terrestrial etc. Odisha one of the mega diversified tropical states where 90% of inhabitants gamble on agriculture for their sustenance and people predominantly trust on customary medication for healing many diseases is beautified with many temples, monuments and building facades bearing historical importance. In Tropical regions of Odisha, especially Bhubaneswar (20°29'61''N, 85°82'45''E) and Puri (19°81'34''N, 85°83'15''E) which are considered as historically important places, the exterior surfaces of temples, monuments as well as building facades are the residence of microorganisms. Twenty six sampling sites were analyzed for biofilms and crusts sample from old/new buildings temples and monuments for the cyanobacterial diversity which is represented in Map (Fig. 4). The study revealed occurrence of 28 species belonging to six genera, five families and 3orders. Dominated Cyanobacteria of these two areas are mainly *Scytonema*, *Tolypothrix* and *Lyngbya* (Fig. 5 & 6). Other associated organisms are found be *Phormidium* sp., *Westiellopsis* sp. and *Nostoc* sp. Such cyanobacteria inhabiting extreme environments can be rightly called as sub-aerial cyanobacteria and due to their ability to endure extreme conditions, these organisms have been known as "Extremophiles". Extremophiles thrive on the edge of temperature, pH, pressure, hyper salinity, dryness and desiccation. Research so far has shown that these organisms' posses a great capacity for producing biologically active compounds because of their special growing conditions, their survival and mechanisms that are not found in marine and freshwater species. Some scientists believe that more harsh and extreme conditions lead to a wider production of a diverse range of more or less, specific substances thus pointing towards these organisms as brilliant candidates for biotechnological application.

In earlier studies, cyanobacteria isolated from marine and freshwater with their biologically active compounds are well endowed (Singh *et al*., 2005; Madhumati *et al*., 2011; Srikong *et al*., 2015).

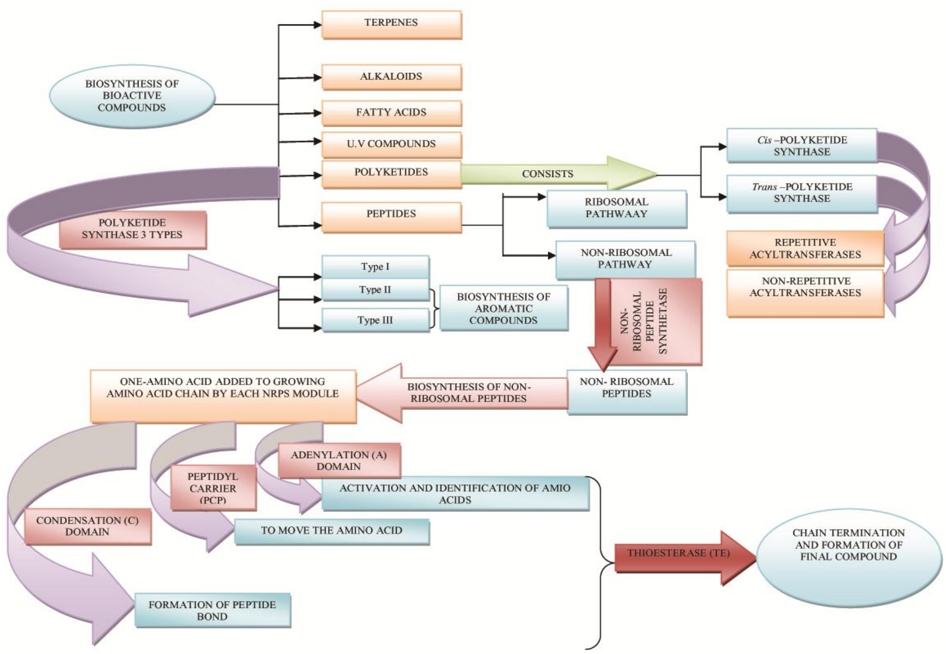

Fig.1 Flow chart showing the biosynthesis pathway of the bioactive compounds in cyanobacteria (Kultschar and Llewellyn, 2018)

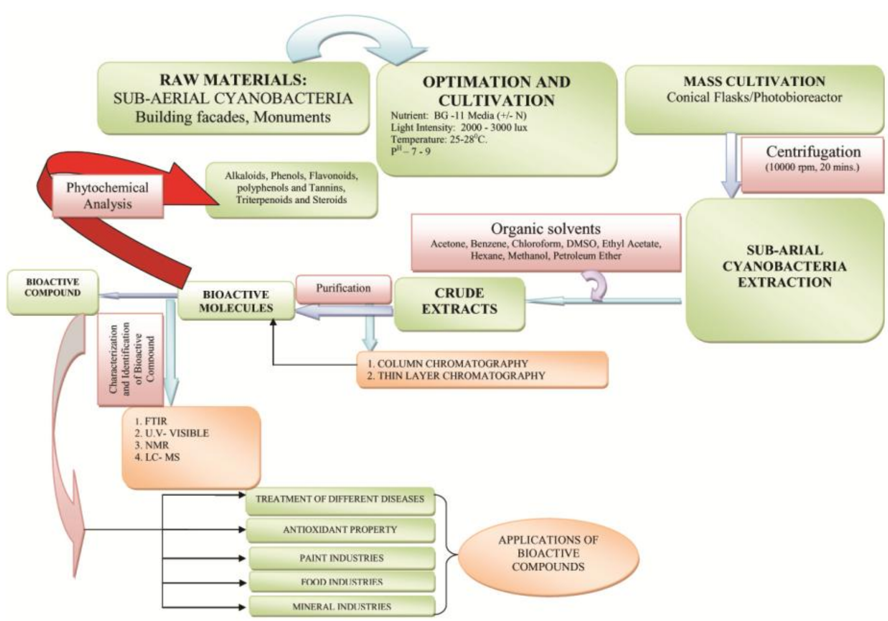

Fig.2 Traditional strategy investigated for production and extraction of bioactive compounds from cyanobacteria (Delattre *et al*., 2016)

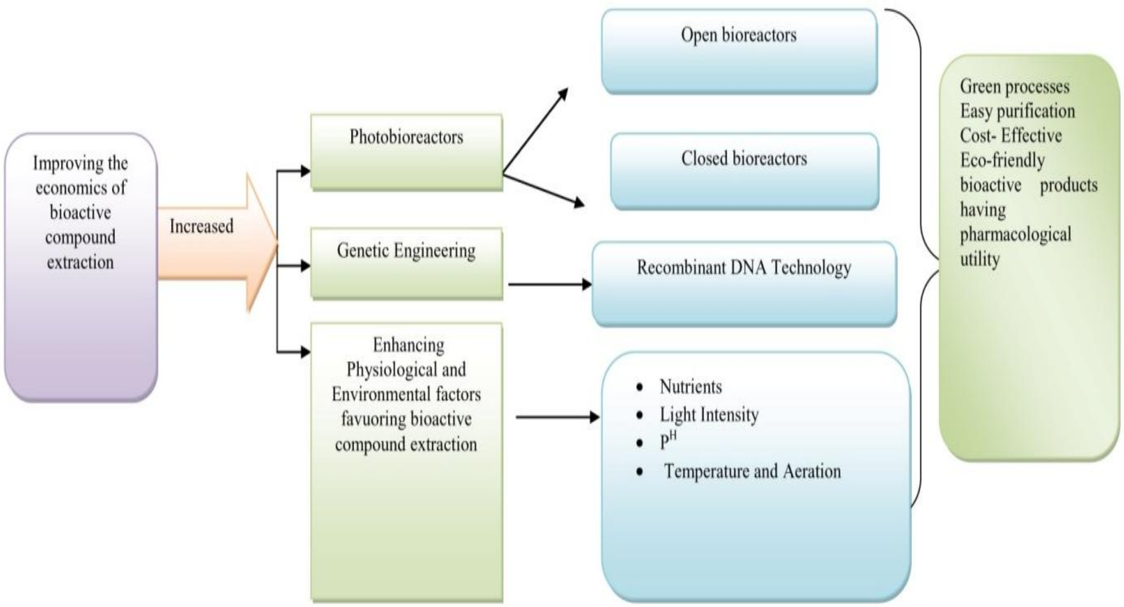

Fig.3 Flow chart for improving economics of cyanobacteria bioactive compound in pharmacological utility (Delattre *et al*., 2016)

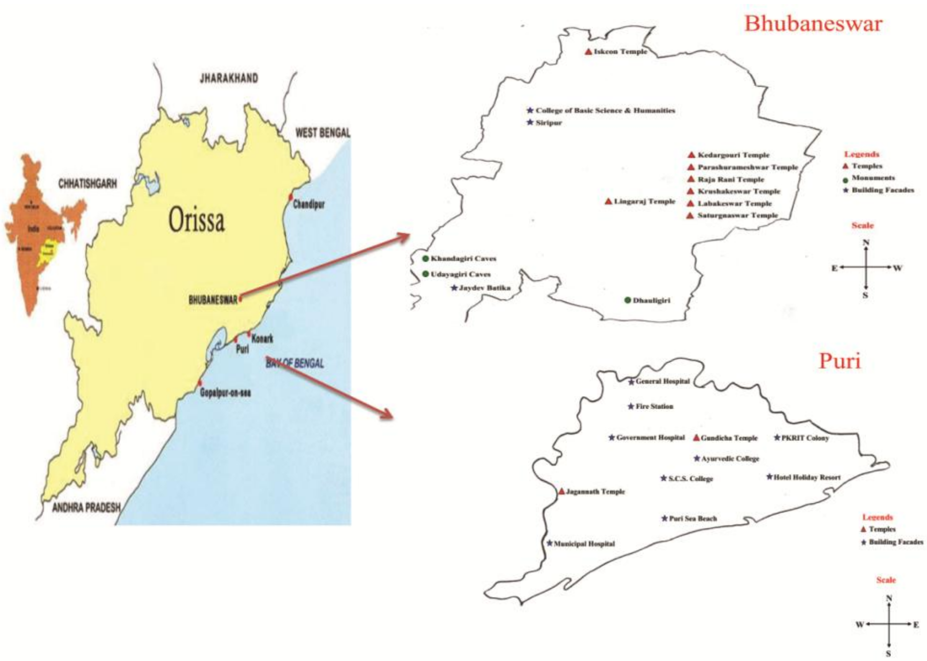

Fig.4 Map showing Bhubaneswar and Puri of Odisha where cyanobacteria samples were collected Bhubaneswar and Puri

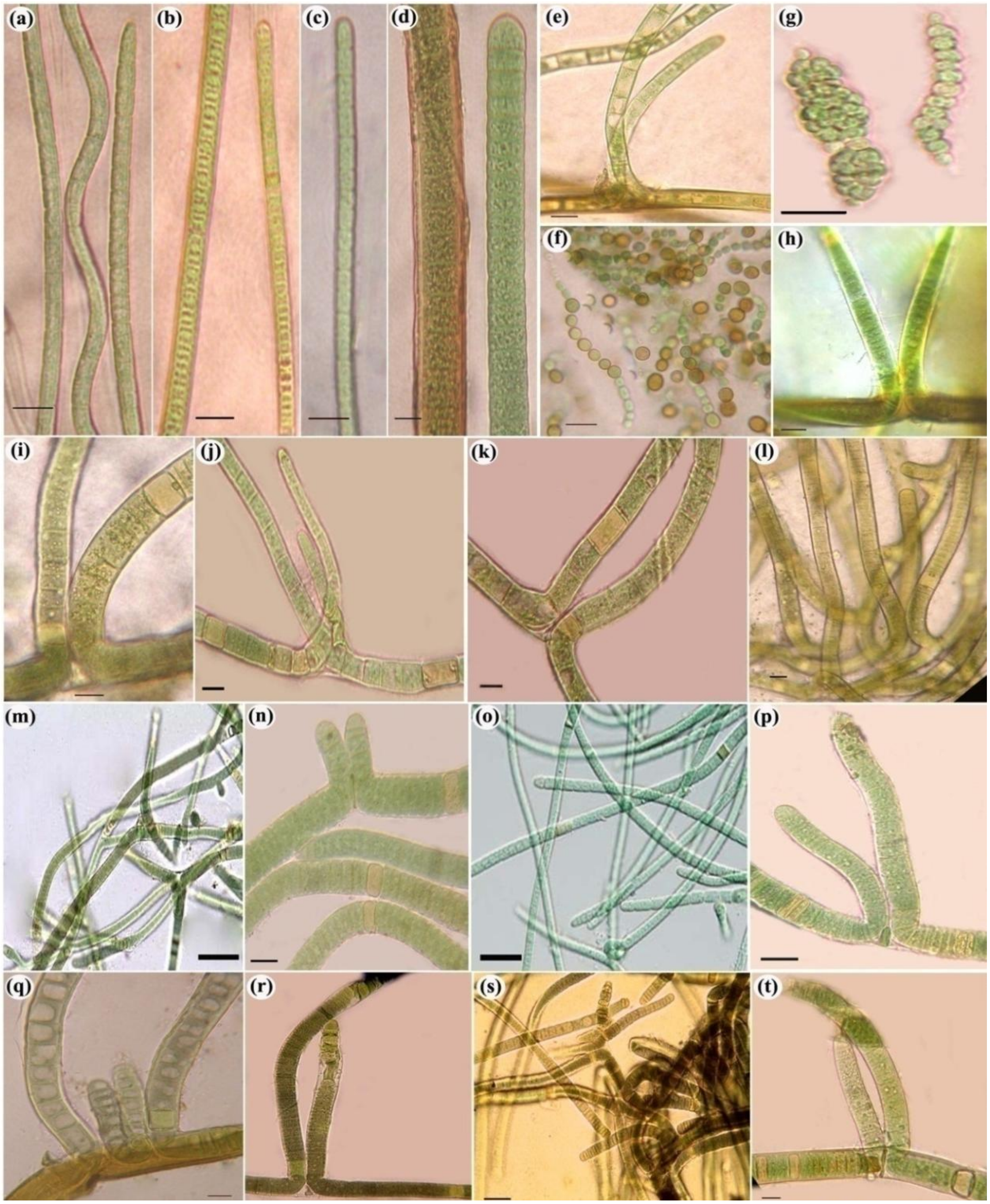

Fig.5 Microphotographs of sub-aerial cyanobacteria isolated from the exterior surface of different sites (Building facades, temples and monuments) of Bhubaneswar and Puri, Odisha. (a) *Phormidium autumnale*, (b) *Phormidium ambigum*, (c) *Phormidium retzii*, (d) *Lyngbya kuetzingiana*, (e) *Leptolyngbya* sp., (f) *Nostoc linkia*, (g) *Nostoc punctiforme*, (h) *Scytonema bohneri*, (i) *Scytonema crispum*, (j) *Scytonema geitleri*, (k) *Scytonema pseudohofmanii*, (l) *Scytonema hofman-bangii*, (m) *Scytonema hyalinum*, (n) *Scytonema stuposum*, (o) *Scytonema multiramosum*, (p) *Scytonema schmidtii*, (q) *Scytonema pseudoguyanensis*, (r) *Scytonema punctatum*, (s) *Scytonema ocellatum* and (t) *Scytonema mirabile*. Scale bar: Fig. A-t = 10µm

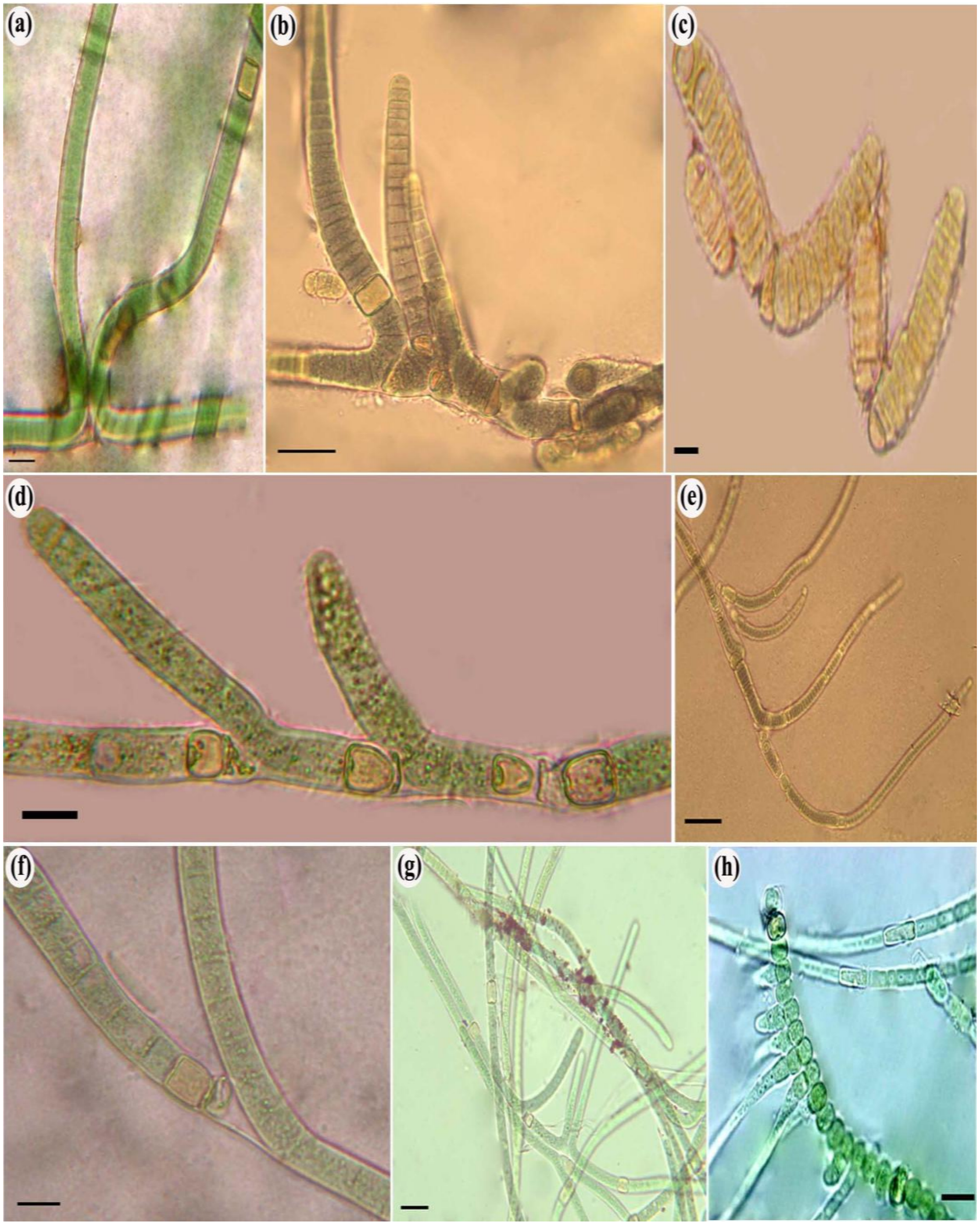

Fig.6 Microphotographs of sub-aerial cyanobacteria isolated from the exterior surface of different sites (Building facades, temples and monuments) of Bhubaneswar and Puri, Odisha. (a) *Scytonema* sp., (b) *Scytonema* sp., (c) *Hassallia byssoida*, (d) *Tolypothrix distorta*, (e) *Tolypothrix rechingeri*, (f) *Tolypothrix tenuis*, (g) *Fischerella* sp., and (h) *Westiellopsis prolifica*. Scale bar: Fig. a-h = 10µm

Sub-aerial cyanobacteria are demonstrated to be one of richest sources of novel biological compounds having biotechnological implications which are yet to be investigated. Keeping in view the beneficial aspects of these microorganisms especially in pharmaceutical field, the cyanobacterial flora from building facades and monuments of Bhubaneswar and Puri in the state of Odisha can be taken into account for exploration as remedial drugs against many human diseases. To the best of our knowledge, very little scientific investigations have been carried out deal specifically with extremophilic cyanobacteria and their biological activities (Drobac *et al*., 2007; Lamprinou *et al*., 2015; Kultschar and Llewellyn, 2018). Moreover, sporadic reports are available on isolation of sub-aerial cyanobacteria from the monuments and building facades in the state of Odisha with their antimicrobial activities (Samad and Adhikary, 2008; Adhikary and Kovacik, 2010; Keshari and Adhikary, 2014; Keshari *et al*., 2015). However, no effective steps on biologically active compounds of extremophiles cyanobacteria have been employed as an antimicrobial agents isolated from sub-aerial surface of building facades and monuments has been reported for which search is on.

In conclusion, exploration of new natural products as antimicrobial agents against resistant pathogens is very important for clinical medicine and public health. The sub-aerial cyanobacteria have the ability to endure extreme conditions and possess a great capacity for producing biologically active secondary metabolites which might be benefit directly or as supplements to curb human diseases. Thus modern research should be intensified having effective, non-toxic, eco-friendly natural bioactive compounds which can be exploited in the field of Pharmaceutical industries. Sub-aerial habitat of Odisha is rich in diverse cyanobacteria. So far little work has been done on the bioactive compound of sub-aerial cyanobacteria. So in this study we have undertaken to assess the diversity of sub-aerial cyanobacteria and their production and extraction of bioactive compounds.

Future prospective

Cyanobacteria are the promising sources of useful natural products. There is indeed a wide range of applications of Cyanobacteria in biotechnology. There is great potential to further exploit the rich Cyanobacterial resources of Odisha for various biotechnological applications. Presently, the isolation of number of natural products is increasing. However few compounds have reached the market. Limited number of identified Cyanobacterial biomolecules and analogues are in clinical trials and some of them have passed phases of clinical trials to prove them as potential drugs. In order to discover the new opportunities available, there is demanding need for extensive research in their new emerging field of drug exploration which should be regarded as a priority area of research in Odisha.

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