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Bioactive compounds from Cyanobacteria for sustainable pharmaceutical applications

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Abstract

Cyanobacteria, a varied group of photosynthetic prokaryotes, have become a significant source of diverse and biologically active secondary metabolites. They thrive in both salt and freshwater environments as well as on soil and rock surfaces. This review article explores the potential applications of algae in selected biotechnology fields, such as their use as biocatalysts or in the pharmaceutical sector. These natural substances showcase a broad range of pharmacological effects, including anticancer, antimicrobial, antiviral, anti-inflammatory, and neuroprotective properties, positioning Cyanobacteria as a promising area for pharmaceutical exploration. These microorganisms synthesize a wide variety of secondary metabolites. Cyanobacteria generate bioactive substances, displaying their molecular structures and emphasizing their various chemical classifications. Marine microorganisms are recognized for their capacity to produce an extensive range of secondary bioactive metabolites. Cyanobacteria yield bioactive compounds that are diverse in structure and function, with numerous applications in both medicine and industry. The extracts and isolated compounds from these organisms can be investigated for a variety of important biological activities relevant to therapeutic and industrial purposes. The use of Cyanobacteria for nutritional applications has a history spanning thousands of years; in recent decades, the cultivation of microalgae has advanced to become a prominent area within modern biotechnology. At present, worldwide production of Cyanobacteria primarily focuses on applications that offer significant added value since algal biomass includes pigments, proteins, essential fatty acids, polysaccharides, vitamins, and minerals, all of which are highly sought after in the creation of natural products, for both dietary and cosmetic purposes.

Keywords: Cyanobacteria, Bioactive Compounds, photosynthetic prokaryotes

Introduction

Cyanobacteria, commonly referred to as blue-green algae, are primitive prokaryotic microorganisms that have existed for more than 3.5 billion years. As photosynthetic organisms, they represent an important nutritional source for humans, supplying vital vitamins and proteins. These microorganisms generate a variety of bioactive compounds with notable pharmaceutical promise, including antiviral and anti-cancer agents such as nostoflan and cryptophycin derived from the Nostoc genus. Their diverse secondary metabolites present exciting possibilities in biotechnology for cancer treatment and antimicrobial applications (Heike *et al.* 2006). Furthermore, cyanobacteria are crucial to ecological systems, competing for resources and adapting to environmental challenges. Their distinctive metabolic properties continue to draw interest for their potential in drug discovery and bioscience. Health food stores all around the world carry them since they are a great source of proteins and vitamins (Matthew *et al.* 2008). The antibacterial, anti-cancerous, antifungal, anti-HIV, anti-tumor, antiviral, and food additive properties of these substances are well-established. Cyanobacteria are known to create secondary metabolites and perform a number of ecological tasks, including resource competition, predator protection, and stress adaption (Mazard *et al.* 2016). Because of their possible utility in biotechnology, they have attracted a lot of attention lately. Numerous bioactive chemicals with significant medicinal potential are produced by cyanobacteria. Cyanobacteria have been around for more than 3.5 billion years. These ancient photosynthetic bacteria, known as prokaryotes, are the source of bioactive compounds that may find use in medicine. According to Senadheera *et al.* (2023), cyanobacteria possess a wide variety of bioactive metabolite characteristics. Their biological properties and possible use in medication development. Numerous secondary

metabolites are produced by these microbes. They continue to be important primary producers in aquatic ecosystems and were instrumental in forming Earth's atmosphere. Cyanobacteria's distinct metabolic properties have drawn interest due to possible uses in the pharmaceutical sector (Nand *et al.* 2016). Cyanobacteria are especially utilized in antimicrobial treatments and cancer treatment. Bioactive substances, such as the antiviral nostoflan and the anti-tumor agent cryptophycin, are abundant in the cyanobacterial genus Nostoc (Harada, 2004). The cyanobacteria create several physiologically active metabolites due to their morphological, physiological, and genetic characteristics (Kini *et al.* 2020). Algae are incredibly adaptable and can adapt to a variety of cell growth settings, which allows them to create a wide range of useful bioactive substances (Singh *et al.* 2016). The potential uses of blue green algae and microalgae in biotechnology have drawn a lot of attention in recent years. Algal biomass yields a range of possible bioactive chemicals under ideal growth conditions and stressors (Singh *et al.* 2020, Pal *et al.* 2024). Cyanobacteria's ability to produce oxygen holds promise for the management of illnesses linked to hypoxia (Song & Hu 2021).

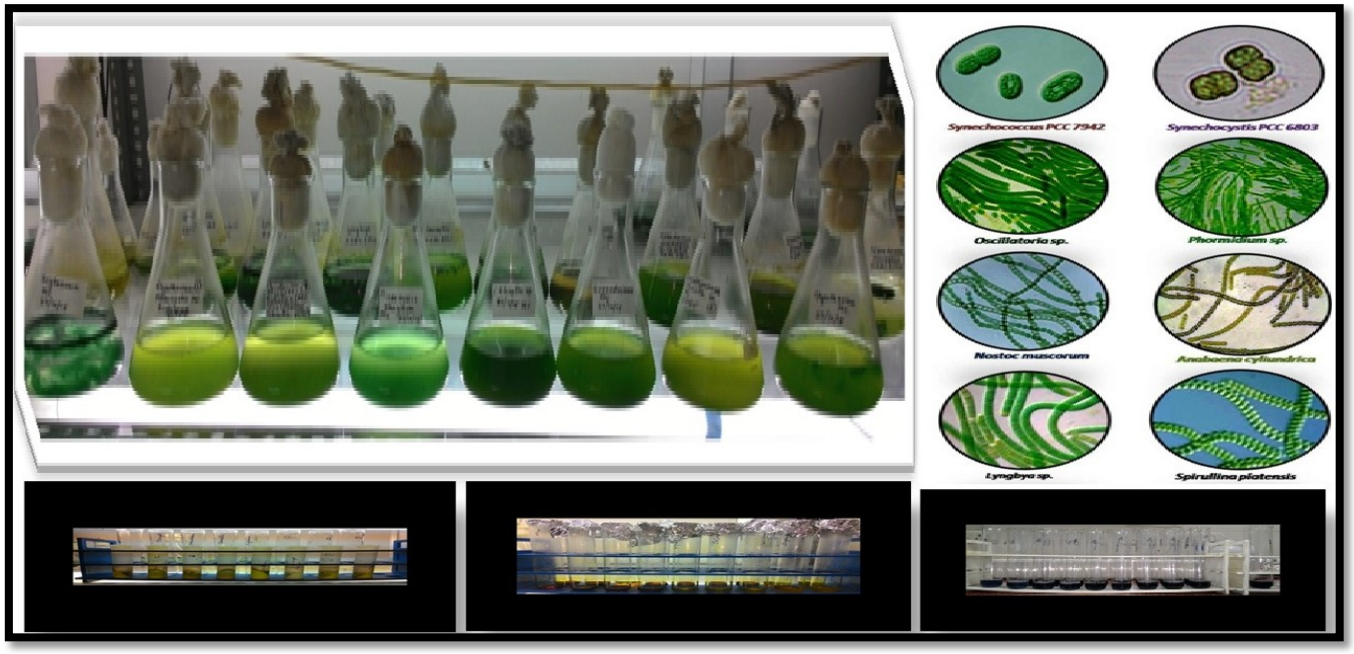

Fig. 1 Hypothetical diagram showing the extraction process of the cyanobacterial bioactive compounds.

Bioactive compound of cyanobacteria:

Cyanobacteria produce various classes of bioactive compounds including-

1. Peptides and Depsipeptides
2. Alkaloids
3. Polyketides
4. Lipopeptides
5. Terpenes

These compounds have shown diverse biological activities, such as antibacterial, antimicrobial, anticancer, antifungal, anti-viral,anti-inflammatory and immune-modulatory properties. Cyanobacteria produce bioactive compounds and showing their molecular structures and highlighting their diverse chemical classes.

Pharmaceutical applications

In addition to being a significant source of new bioactive secondary metabolites, cyanobacteria have recently been found to be a rich source of bioactive molecules such lyngbyabellin, curacin A, and apratoxins. According to Vijayakumar & Menekha (2015), cyanobacterial compounds have a bright and

promising future in scientific study and offer a tremendous chance for the identification of novel drugs. About 450 compounds from marine cyanobacteria were found, mostly from the genera *Lyngba*, *Oscillatoria*, and *Symploca*. Of these natural products, *Lyngbya* accounted for 35% and *Oscillatoria* for 58% of the cyanobacterial metabolites (Zanchett & Oliveira-Filho 2013). Because of their numerous biological functions, cyanobacteria are used in human health and as nutritional supplements. Due to its high nutrient content, it is utilized as a food supplement (Raja *et al.* 2016). Because they have distinct metabolic pathways with special molecules that are effective, defensive, and mechanisms in various habitats, cyanobacteria are very adaptable and can live in difficult environments (Saad *et al.* 2022).

Anticancer agents

Several cyanobacterial compounds have shown promising anticancer activities. Dolastatin 10, is a cyanobacterial compound but originally isolated from the sea hare *Dolabella auricularia*, has led to the development.

Bioactive properties

In addition to being crucial components in the evolutionary and/or phylogenetic classification of organisms, cyanobacteria are used as model systems for comprehending a variety of physiological processes (Jaiswal *et al.* 2008). There are three primary categories of biochemical processes in living cells: basal, synthetic, and secondary.

Basal biochemical's	**Synthetics biochemical's**	**Secondary biochemical's**
supplying the energy and building blocks needed for cell operations	Participating in vegetative growth and reproduction	Engaged in using substarates to produce a range of compounds, many of which are unique to a particular organism.

Antibiotic potential: Cyanobacterial compounds are being explored as alternatives, particularly through non-ribosomal peptide, synthase and polyketide synthase pathway, rising with antibiotic resistance (Hussein *et al.* 2023).

Therapeutic effects: cyanobacteria exhibit anti-bacterial,anti-cancer, anti-diabetic, anti-inflammatory, anti-viral properties which are crucial for developing new therapeutics (Herath *et al.* 2023, Shaaban 2022).

Biotechnological application:

Cultivation ease: Cyanobacteria can be cultured with minimal resources, facilitating their use in drug discovery and development (Shawer *et al.*2022).

Diverse metabolites: Cyanobacteria produce bioactive compounds that can be harnessed for medicinal purpose and in this purpose anti-tumor agents, immunosuppressive are include (Żymańczyk *et al.* 2022)

Anti-cancer properties: Cyanobacteria-derived compound such as apratoxin and symplostatin 1 have properties of anticancer effects against various cell lines.As early as 1500 BC, cyanobacteria were discovered when Nostoc species were utilized to cure fistulas, the gut, and various types of cancer (Nowruzi *et al.* 2018). These include phenolics, phycocyanin, amino acids, triterpenoids, polyunsaturated fatty acids, sulphates, polysaccharides, and carotenoids, among other bioactive substances (Nowruzi *et al.* 2018).

Bioactive are natural product?: Natural products are the new "lead compound" in pharmaceuticals. According to Newman & Cragg (2007) and Prasanna *et al.* (2010), 63% of the 974 compact molecular chemical entities that were introduced as drugs globally between 1981 and 2006 were affected by natural products. These natural goods, which include natural products (6%), natural product derivatives (28%), and synthetic compounds having pharmacophores derived from natural products (5%), are essential. Based on the knowledge gained from using a natural product, other natural items are manufactured. Certain therapeutic areas are more productive than others. Natural products or natural products produced from natural products make up 77.8% of anticancer medications. Figure 1

shows that the vast majority of active chemicals are produced from plants, fungi, and bacteria (Řezanka & Dembitsky 2006). The rediscovery of what were once thought to be natural compounds is known as biologically active molecules.

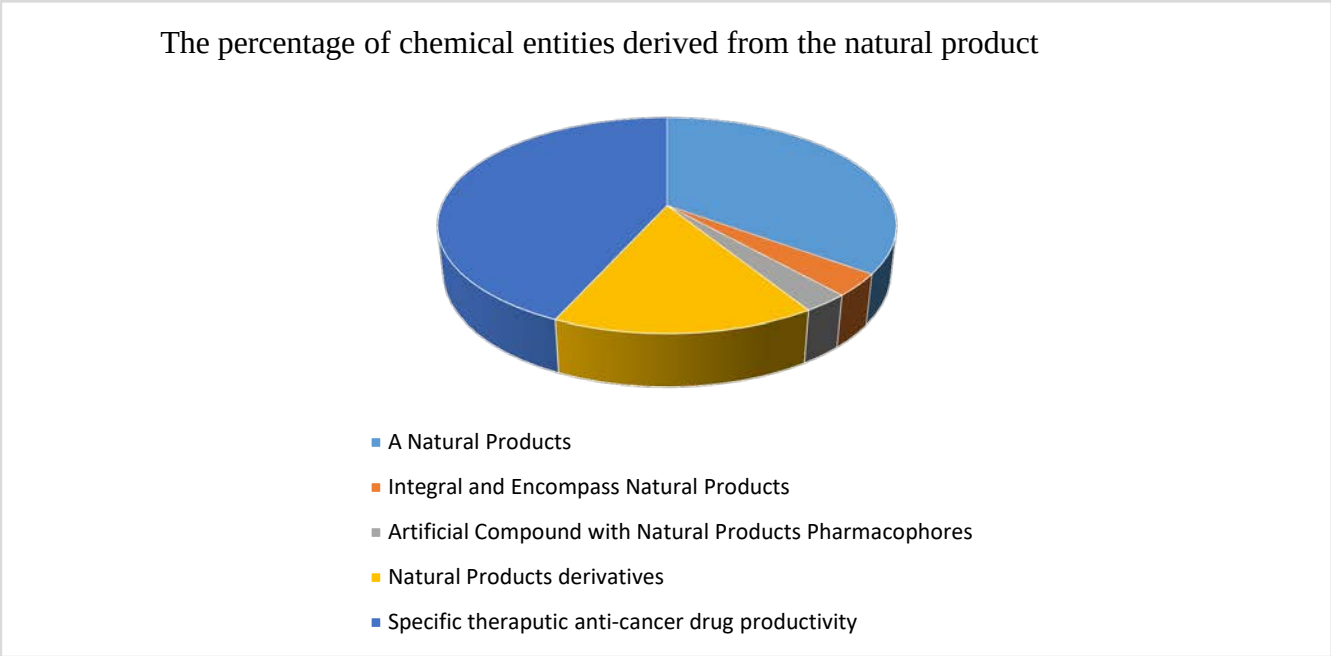

Fig. 2. Cyanobacteria are emerging as a significant of bioactive compounds with pharmaceutical applications.

Toxic metabolites: Bioactive compounds like anatoxin and microcystin show hepatotoxicity and neurotoxicity. In cancer therapy through agents like cryptophycin (Gademann & Portmann 2008).

Iron chelators: Metabolites such as synechobactin and schizokinenplay very important roles in acquisition, which is crucial for various biological processes (Gademann & Portmann, 2008).

Antiviral and anti- cancer properties: Dolastatin and cyanovirin-N are cyanobacterial compounds have demonstrated efficacy against viruses and cancer cells, with some undergoing clinical trial (Khalifa *et al.* 2021).

Biogenetic diversity and drug discovery: According to Wagonar *et al.* (2006) and Sielaff *et al.* (2006), the structural variety of cyanobacterial metabolites has drawn interest for potential pharmacological leads with biosynthetic pathways.

Table 1. Some Cyanobactrial bioactive compounds

Natural compounds	Artificial compounds	UV-Screening	Antifungal compounds	Antibacterial compounds	Biomedical compounds
Phycocyanin	Engineered polyhydroxy alkanoates (PHAs)	Scytonemin	Fishcherellin-A	Microcystin	Dolastatin-10
Cyanovirin-N	Synthetic aromatic compounds	Mycosporine-like- amino acids (MAAs)	Hapalindole	Cyanopeptolin	Cryptophycin-1

Natural compounds	**Artificial compounds**	**UV-Screening**	**Antifungal compounds**	**Antibacterial compounds**	**Biomedical compounds**
Microcystins	Biodegradable plastics	Cyanovirin-N	Scytophycin	Anabaenopeptin	Curacin-A
Spirulina		Phycocyanin	Nostocyclamide	Lyngbyatoxin	Phytoalexin
		Carotenoids	Nostofungicidine	Saxitoxin	Cyanovirin-N
			Amino-6-hydroxy stearic acid	Comnostin	Nostocarboline
			Microviridins	Muscoride A	Certain dioic acid
			Nostopeptolides	Noscomin	
			Nostocyclopeptides	Carbami-docyclophanes	
			Antiprotozoal compound	Dodecahy-drophenanthrene	

In aquatic habitats, cyanobacteria are essential because they are the main sources of nitrogen and oxygen for fixing agents. Numerous new secondary metabolites, including biologically active substances with antibacterial, antiviral, antifungal, and anticancer properties, were produced by cyanobacteria. Enzyme poisons, UV-absorbing pigments, and specific fluorescent dyes are some of the other significant metabolites that have been identified from cyanobacteria (Kumar *et al.* 2019). The ability of cyanobacteria to produce bioactive chemicals with potential pharmaceutical applications, such as cytotoxic agents like dolastatins and cryptophycins, is highlighted by their biosynthetic potential (Baunach *et al.*, 2024). According to de Jesus Raposo *et al.* (2013), cyanobacteria and marine microalgae are extremely rich in a variety of chemical compounds and may have biological uses linked to health advantages.

Table 2. Marine microalgae in bioactive compounds and biological activities (de Jesus Raposo., et al 2013).

Bioactive compounds	**Microalgae**	**Biological activity**
Ecosapentonoic acid	*Pheodactylum*	Neutraceutical; anti-inflammatory
γ-linolenic acid (GLA)	*Arthrospira*	Intigrity of tissues; delay of aging
β-carotene	*Dunaliella*	Healthy vision; cancer prevention; coronary disease prevention
α-tocopherol	*Tetraselmis*	Antioxidant
γ-aminobutyric acid (GABA)	*Porphyridium*	Inhibitory neurotransmitter in the CNS
Okadiac acid	*Gambierdiscus*	Antifungic; Promotion of the NGF secretion
Brassicasterol	*Pavolva*	Hypocholesterolemic
Phycocyanin	*Arthrospira*	Antioxidant; anti-inflammatory
Astaxanthin	*Heamatococcus*	Age-muscular degeneration protection

Herbicides, algicides, nematocides, and insecticides are examples of cyanobacterial chemicals used in non-biomedical applications. According to Singh *et al.* (2016), bioactive substances such as hapalinodles from Fischerella, calothrixin from Calothrix, cyanobacterins LU-1 and LU-2 from Nostoc, and γ-lactone from Scytonema are thought to have an allolopathic impact. While the majority of cyanobacteria live as reliant autotrophs, some species can coexist with fungi, plants, and marine animals including sponges, corals, and

tunicates. Cyanobacteria themselves can be pink, red, yellow, green, and brown (Menaa *et al.* 2021). Because they are dizotrophs, improve the physical and chemical characteristics of soil, support a variety of soil ecologies, and can outcompete native plants and animals, cyanobacteria are increasingly being employed as biofertilizers in agriculture (Singh *et al.* 2016).Antioxidant-active natural bioactive compounds are particularly effective at preventing the production of reactive oxygen species (ROS), which have a number of harmful effects, including DNA damage, cancer, and cellular degenerations (Hamidi *et al.* 2019).

Table 3. Cyanobacterial metabolites with anticancer activity

Compound name	Chemical class	Organism	Anti-cancer Spectrum	References
Apratoxin A	Cyclic depsipeptide	*Lyngbya majuscule*	HT29 colon adenocarcinoma HeLa cervical carcinoma U2OS osteosarcoma.	Ma *et al.* 2006
Apratoxins B	Cyclic depsipeptide	*Lyngbya* sp.	LoVo colon cancer KB oral epidermoid cancer	Luesch *et al.* 2002
Apratoxins C	Cyclic depsipeptide	*Lyngbya* sp.	. LoVo colon cancer KB oral epidermoid cancer	Luesch *et al.* 2002
Benzylthio ether 45	Phenyl ether	*L. majuscule*	HCT-116 colon cancer	White *et al.* 2004
C-Phycocyanin	Pigment-protein complex	*Spirulina platensis*	MDA-MB-231 breast cance	Jiang *et al.* 2018
Cryptophycin-1	Cyclic depsipeptide	*Nostoc* sp.	Several human cancer cell lines, including SKOV3 ovarian carcinoma and Human MDA-MB-435 mammary adenocarcinoma cells	Mooberry *et al.* 1997
Thiol 46 (S)-7-methoxytetradex4(E)-enoic acid	Lipopeptide	*L. majuscula*	MDA-MB-231 breast cancer.	Shaala *et al.* 2013
Scytophycin A-E	depsipeptides	*Scytonema pseudohofmanni*	KB nasopharyngeal carcinoma	Carmeli *et al.* 1990
Somocystinamide A	Lipopeptide	*L. majuscula*	Jurkat CEM leukemia Molt4 T cell leukemia A549 lung cancer U266 myeloma M21 melanoma NB7 Neuroblastoma MCF-7 breast cancer PC3 prostate cancer	Wrasidlo *et al.* 2008

A state-of-the-art method for finding powerful and sustainable bioactive molecules with a variety of uses in environmental management, medicines, nutraceuticals, and agriculture is the biotechnological exploitation of cyanobacteria and microalgae (Abdul *et al.* 2016). Researching an organism's possible bioactivities is still a fantastic way to create new pharmaceutical medicines (Butler 2004). One of the most promising options for producing different biomolecules for use in biotechnological applications is cyanobacteria. Four cyanobacterial isolates' methanolic extracts were evaluated for total phenolics, total flavonoid levels, antioxidant, and antibacterial properties in the current investigation (Shawer *et al.* 2022). For the extraction, separation, detection, and purification of cyanobacterial bioactive compounds, several methods have been developed and standardized (Amado & Monserrat 2010). Marine microorganisms have gained notoriety in recent decades for their capacity to generate a vast array of

secondary bioactive compounds. In order to create new bioactives for the food and pharmaceutical industries, a number of chemicals have been extracted from marine microorganisms (Alsenani *et al.* 2020). Numerous bioactive chemicals of medical significance have been produced by microorganisms, which also stand out as a new and lucrative source of secondary metabolites. Actinomycetes, fungi, and bacteria have created a sizable portion of the antibiotics and other bioactive compounds that have been discovered thus far; yet, these still fall well short of meeting pharmaceutical and human needs (Lopes *et al.* 2020). According to Paz-Montelongo *et al.* (2024), some cyanobacterial pigments have anti-inflammatory and antioxidant qualities, and their potential for treating and preventing chronic illnesses including diabetes and Alzheimer's disease is being researched. Numerous plant, animal, marine, and microbial compounds have been studied for their ability to fend against HIV and HSV (Alam *et al.* 2021). Using the best machine learning (ML) model, the biochemical descriptors were then utilized to identify the most promising protein targets for environmental bioremediation and human medicinal methods (Soares *et al.* 2024). Numerous bioactive metabolites with a variety of structural and functional variations are produced by phytoplanktons and have numerous uses in both business and medicine. By acting as antidiabetic, antioxidant, antibacterial, anti-inflammatory, anticancer, antifungal, antimalarial, antiviral, and preventing other metabolic diseases, phytoplankton metabolites (secondary or non-primary metabolites) like fatty acids, phycobiliproteins, fucoidans, fucoxanthin, laminarin, mannitol, alginic acids, carotenoids, vitamins, and mineral salts have been demonstrated to prevent a variety of human diseases. According to Menon *et al.* (2024), certain metabolites have a longer-term function in Défense (allelopathic, antipredator, and antibacterial chemicals) and/or cell-to-cell communication (polyunsaturated aldehydes, or PUAs). Compounds from Arthrospira species often function as anticancer medicines by preventing tumor cell growth, causing cell cycle arrest, and causing apoptosis through several signaling pathways (Amor *et al.* 2017). Around 80% of the world's population uses plants and their metabolites for therapeutic purposes, making them a promising path for the production of pharmaceutical molecules. Microbes also contribute significantly to global health by creating beneficial secondary metabolites (Srivastava *et al.* 2024).

Expected outcome

List of all the bioactive substances that come from cyanobacteria, together with information about their chemical makeup and characteristics. Information about these bioactive chemicals' potential uses in medicine, including their antiviral, anticancer, and antibacterial properties. Knowing the processes via which these substances influence the body can help create new medications and treatments. Evaluation of the environmental effects and sustainability of using cyanobacteria as a source of bioactive chemicals. Increase the productivity of chemical manufacturing from cyanobacteria and investigate new uses. Provide important information to the scientific community regarding the various applications of cyanobacteria in biotechnology and medicine.

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