People's Democratic Republic of Algeria

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Master's Thesis in Applied Microbiology

Anticancer activity of cyanobacteria

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Academic Year: 2022-2023

Acknowledgments

First and foremost, we thank God for giving us strength, determination, willingness and patience to complete our research on time.

We thank our supervisor Doctor BENREDJEM Lamia for her guidance, advice, constant and continuous support, and for her motivation and trust in us; we thank her for facilitating the difficulties.

We thank the members of the discussion committee, Dr. HANOUN Saida and Dr. BOUTARFA Soumia, for accepting to discuss our graduation note and for expressing their views on it.

Thank you all

Dedication

- To each and every science student who wants to advance his or her knowledge and earn scientific credit.
- To my father, the kindest and dearest person in the universe, the one who did not spare me anything, the one who sought out my comfort and prosperity.
- To my heart, my beloved mum.
- To my cherished, my only sister Rihame.
- To Achraf and Ayhem, my brothers.
- To my close buddies Rouba and Amel.
- To my partners Meriem and Dounia.

Chahinaze

Dedication

I dedicate this modest work as
proof of love to those who are very dear to me with enormous pleasure, an open heart, and immense joy, that I dedicate my work to my mother: GHANIA SABEG who supported me throughout my life in the light of my life my father: SAÏD SABEG to my very dear sisters: AHLEM, RANIA, NESRINE to my dear partner: Chahinaze and Meriem to my friend: ISMAIL. A special dedication to my family and all the people I love. To all my colleagues from the Master Microbiology 2022 promotion.

Dounia

Dedication

Thanks be to God who gave me the strength
and health to complete my graduation thesis on time.

To the one who never refused me a request, but went above and beyond to get what I asked for. To the one who lit the first candle for me, to the scent of my childhood, to the warmth of my life, to the scent of my youth, to my refuge and sanctuary, to the one who endured every moment of pain in my life and the turned into moments of joy, to the one who shielded me from the heat of summer with roses of spring flowers, to my beloved and the soul of my heart to my father.

To the one who gave me love so that I would know its true meaning, to the one who spared no effort on me until she saw me happy, to the one who throughout his life preferred my comfort to his. My mother! You always believed in me and gave me the strength to go back and try harder when everyone was laughing at my dreams, you supported me and made me believe that no dream is not impossible to achieve.

To the good friend who pushes me to succeed for free. She filled my life with joy and happiness. She accompanied me in every detail of my life, my sister.

For my support and motivation to move, forward in the paths of success and knowledge, my brother.

To my beautiful spoiled little boy, the source of my happiness, my cat.

To my partners who shared with me the effort to complete our graduation memory, Chahinaze and Dounia.

To all friends: Souad, Salima ...

Meriem

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Abstract

ABSTRACT

Cyanobacteria are photosynthetic Gram-negative prokaryotic organisms called "blue-green algae". The classification of cyanobacteria is mainly based on morphological, ecological and ultra-structural characteristics as well as molecular characteristics. Modern biology methods, especially genetic procedures, have significantly changed their classification criteria, but the problem with this approach is that the results do not always conform to traditional criteria. Cyanobacteria are widely used in the medical field, and among their uses is anticancer activity. The anticancer activity of cyanobacteria is to produce metabolites that kill cancer cells, with different types of metabolites, different target cells, and different ways of killing a cancer cell. Among the cyanobacteria known to produce anticancer metabolites *Lyngbya bouillonii*, *L. majuscula* and *Symploca* sp. whose belamide a is produced by *Symploca sp.* targets cell cycle arrest, tubulin, and Lyngbyabellin J produced by *L. bouillonii*. Targets actin, mitochondrial dysfunction, and oxidative damage

Key words: Cyanobacteria, anticancer activity, secondary metabolites, *Lyngbya*, *Symploca*

RÉSUMÉ

Les cyanobactéries sont des organismes procaryotes photosynthétiques à Gram négatif appelés « algues bleu-vert ». La classification des cyanobactéries est principalement basée sur des caractéristiques morphologiques, écologiques et ultra structurales ainsi que sur des caractéristiques moléculaires. Les méthodes de la biologie moderne, en particulier les procédures génétiques, ont considérablement modifié leurs critères de classification, mais le problème de cette approche est que les résultats ne sont pas toujours conformes aux critères traditionnels. Les cyanobactéries sont largement utilisées dans le domaine médical, et parmi leurs utilisations figure l'activité anticancéreuse. L'activité anticancéreuse des cyanobactéries consiste à produire des métabolites qui tuent les cellules cancéreuses, avec différents types de métabolites, différentes cellules cibles et différentes manières d'éliminer une cellule cancéreuse. Parmi les cyanobactéries connues pour produire des métabolites anticancéreux *Lyngbya bouillonii*, *L. Majuscula* et *Symploca* sp. dont la belamide a est produite par *Symploca* sp. cible l'arrêt du cycle cellulaire, tubulin et la Lyngbyabellin j produite par *L. bouillonii*. cible l'actine, dysfonction mitochondriale et dommage oxydatif.

Mots clés : Cyanobactéries, activité anticancéreuse, métabolites secondaires, *Lyngbya, Symploca*.

الملخص

البكتيريا الزرقاء هي كائنات بدائية النواة في التمثيل الضوئي تسمى "الطحالب الخضراء المزرقة" ، سالبة الجرام. يعتمد تصنيف البكتيريا الزرقاء بشكل أساسي على الخصائص المورفولوجية والبيئية والبنية التحتية بالإضافة إلى الخصائص الجزيئية. لقد غيرت طرق البيولوجيا الحديثة ، وخاصة الإجراءات الجينية ، معايير تصنيفها بشكل كبير، لكن المشكلة في هذا النهج هي أن النتائج لا تتوافق دائمًا مع المعايير التقليدية. تستخدم البكتيريا الزرقاء على نطاق واسع في المجال الطبي ، ومن بين استخداماتها نشاط مضاد للسرطان. يتمثل النشاط المضاد للسرطان للبكتيريا الزرقاء في إنتاج مستقلبات تقتل الخلايا السرطانية ، مع أنواع مختلفة من المستقلبات ، وخلايا مستهدفة مختلفة ، وطرق مختلفة لقتل الخلايا السرطانية. من بين البكتيريا الزرقاء المعروفة بإنتاج المستقلبات المضادة للسرطان
لينجبيا (بويوني، ماجيسكيلا، لينجبيا أسبي) ، سمبلوكا (سمبلوكا أسبي). مثال: بيلاميد أ ينتج من قبل سامبلوكا ليستهدف توقف دورة الخلية وتيبيلين وكذلك لينجبيابولين ج ينتج من قبل لينجبيا بويوني ليستهدف الأكتين، الاختلال الوظيفي للميتوكوندريا والضرر التأكسدي.

الكلمات المفتاحية: البكتيريا الزرقاء، النشاط المضاد للسرطان، المستقلبات الثانوية، لينجبيا، سيمبلوكا.

Abbreviations

A-549: cells are adenocarcinoma human alveolar basal epithelial cells

Bcl: Lymphoma in cells B

G1: first gap

G2: second gap

HL: human leukemia cell line

Kb: Kilo base

M: mitosis

S: synthesis of DNA

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Introduction

INTRODUCTION

The cyanobacteria are members of the bacterial kingdom in the living organism tree. These organisms are phylogenetically old, Gram-negative procaryotes living in a wide range of ecologies. The morphological diversity of cyanobacteria ranges from small, unicellular forms,such as the pico-plankton, which has a size of less than 2-3 µm, to larger forms, such as colonials, lament uses, or ramies. Some groups have specialized cells, such as heterocyst (which are sites of atmospheric azote, N_2) and akinetes (which are thought of as spores). The unique featureofcyanobacteria is that theyexhibit properties that are shared by bacteria and/or eucaryotic photosynthetic organisms (often referred to as "the microalgae") **(Bernarda, 2014).**

The characteristics of cyanobacteria and bacteria are: (i) the absence of nuclear and plastid membranes, mitochondria, endoplasmic reticulum, and dictyosomes; and (ii) the presence of a cell wall component characteristic of bacteria (Gram-positive), including murine). Like eucaryotic microalgae, cyanobacteria have two photosynthetic systems (photosystems I and II) and chlorophyll a. They use water as an electron source and perform a photosyntheticprocess that produces oxygen. They have unique photosynthetic pigments known as phycobiliproteins that are shared by some lichens (such as Rhodophytes or Cryptophytes).Some types of cyanobacteria also have real ramifications and cell junctions that allow for cell-to-cell exchanges **(Bernarda, 2014).**

Cyanobacteria are an excellent source of biologically active chemicals used for competition, defense against predators, and communication. Even though there is still much to learn, comprehensive research has been done on the origins and functions of these molecules. They incorporate peptide and polyketide synthetases and synthases, as well as cascades of biosynthetic transformations that give rise to novel chemical structures, to produce a wide variety of chemical compounds. Numerous glycolipid, macrolide, peptide, and polyketide compounds produced bycyanobacteria have been identified and studied to date **(Robles-Bañuelos *et al.*, 2022).**

Cyanobacteria are used to make a variety of products, including fuel, polymers, cosmetics, food additives, and pharmaceuticals. Because of their antioxidant, antiviral, anti-inflammatory, antifungal, anticancer, immunosuppressive, antibacterial, anticoagulant, antimalarial, antiprotozoal, anti-tuberculosis, and antitumor activities, cyanobacteria have biochemical pathways that produce distinctive bioactive

molecules with potential for use in both commercial and medical applications. Some are presently being studied in clinical settings. Research into anticancer medications from novel sources, such as marine cyanobacteria, is required because current chemotherapy treatments use chemicals with a wide variety of recognized negative effects **(Tiwari & Tiwari, 2020).**

The present work is devoted to a bibliographic analysis of cyanobacteria's anticancer activity. The content divided into four chapters:

- Cyanobacteria in general is covered in the first chapter;
- The classification of cyanobacteria is covered in the second chapter;
- The third chapter discusses the cancer;
- The final chapter discusses the cyanobacteria's anticancer activities.

The memoir ends with a conclusion that gives an overview of the chapters. A complete list of references is also provided.

Chapter I: Generalities of cyanobacteria

1. Origin of different classes of algae

Algae are a class of primarily aquatic, nucleus bearing creatures that lack true roots, stems, and leaves and can be found in a broad range of environments, including brackish, marine,freshwaters, hot and cold springs, desert soils, and on bare rocks **(Sharif *et al.*, 2017).** Cyanobacteria, eukaryotic microalgae, and seaweed are all examples of algae **(Smith *et al.*, 2021).**

Plant-specific organelles known as plastids have a tiny eubacteria-type genome. Here, we explore how ancient cyanobacteria's endosymbiosis relationship with other primordial eukaryotic cells is thought to be the origin of plastids **(Takahashi & Tanaka, 2002).** In plantsand algae, plastids are double membrane-bound organelles **(Sharif *et al.*, 2017).**

The Latin word for algae originally meant "seaweeds," and the first recorded use of the word inWestern literature was by the poet Virgil, who said, "Nihil vilior alga" (literally, "nothing is asworthless as algae"). Despitethis, records fromChina and Japan at least 2500 years ago show that algae have been consumed by humans from the dawn of time. Seaweeds were occasionally utilized as fodder and as soil additions in Europe. In Africa and Central America, *Spirulina (Arthrospira)* biomass has been ingested for generations, while biomass from macro-algae has been heavily employed as a soil amendment, including in Ireland. Microalgae research began in the 17th century after the advent of the microscope.

The diatom *Tabellaria* was the first microalga to be named, while *Chlorella* was among the first to be cultured in Europe in 1890. Europe has been at the forefront of the exploitation of algae for new meals, feeds, and chemicals for the past 100 years, and its research and commercial applications of microalgae and seaweed have developed significantly **(Smith *et al.*, 2021).**

1.1. Eukaryotic family tree

This tree appears to be made up of five significant assemblages, or "super groups." The photosynthetic organelles of plants and algae, as well as their no photosynthetic descendants, the plastids, are dispersed throughout four of the five super groups. This is due to the complicated evolutionary history of plastids, which included a number of endosymbiosis interactions and resulted in their transmission from one group to another. Here, the evolution ofthe plastid and its numerous hosts is examined, paying close

attention to the quantity and kind of endosymbiosis interactions that resulted in the current distribution of plastids.

With the intriguing potential exception of the little-studied amoeba *Paulinella*, mounting evidence points to a single primary origin of plastids from cyanobacteria. This origin was then followed bythe diversification of glaucophytes, red, and green algae, and the evolution of plants from green algae. Following this, some of these algae took part in subsequent endosymbiosis interactions. According to the best available evidence, Euglenids and Chlorarachniophytes were created by two separates secondary endosymbiosis with green algae, whereas the Chromalveolates, a diverse group that includes crypto monads, haptophytes, heterokonts, and alveolates, were created by a single endosymbiosis with a red alga. Dinoflagellates (alveolates) have since established serial secondary and tertiary endosymbiosis with other algae, raising questions about the origin of their plastids and, consequently, the recently discovered cryptic plastid of the closely related apicomplexan parasites (**Figure 1**) **(Keeling, 2004).**

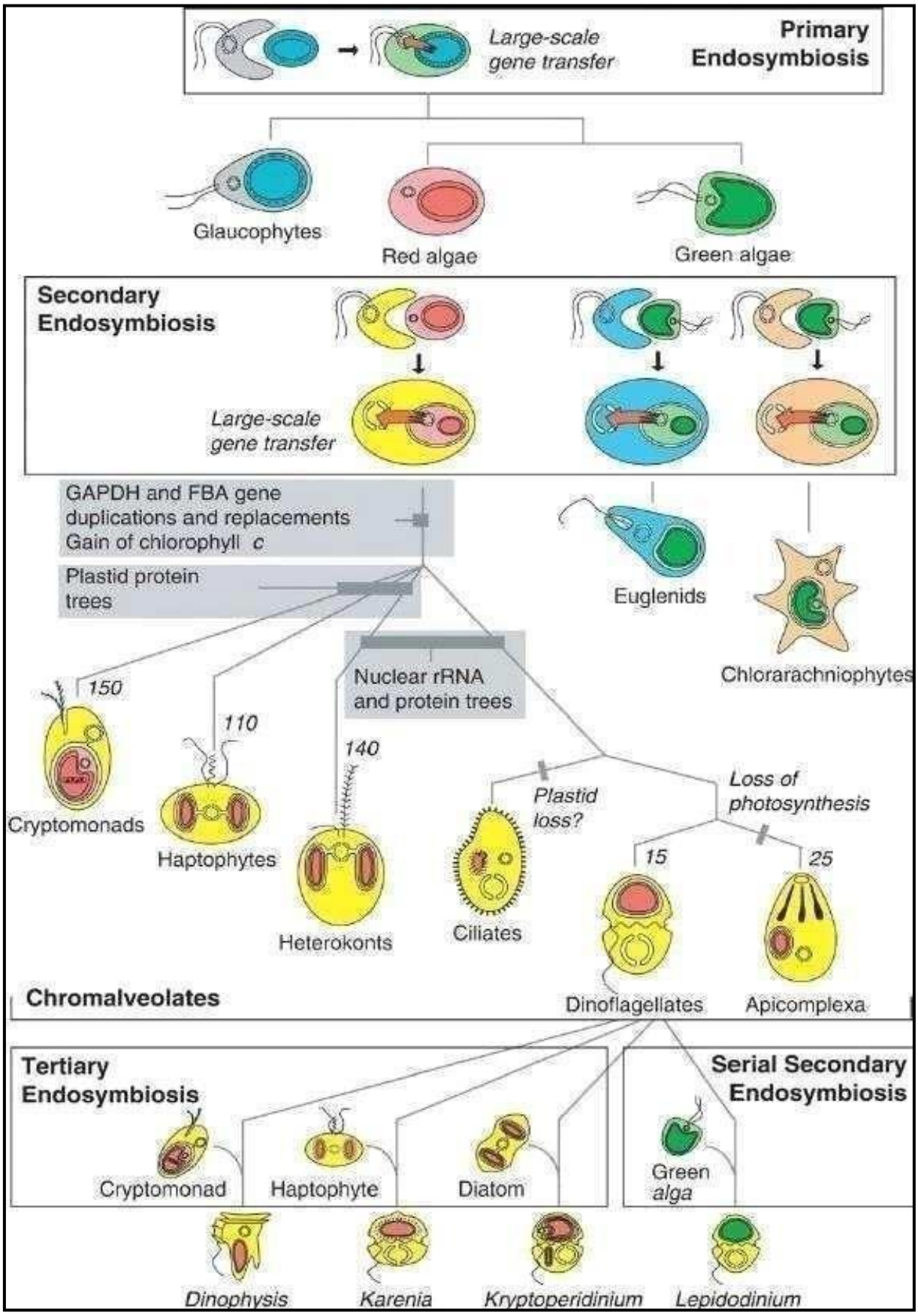


Figure 1. Origin of algae and their plastids **(Keeling, 2004).**

2. Appearance of cyanobacteria

Cyanobacteria were referred to as "blue-green algae," "Schizophyceae," "Cyanophyta," or "Cyanophyceae" and were thought to be plants or organisms that resembled plants. The term "cyanobacteria" (or rarely "cyanoprokaryotes") has been accepted in the scientific literature because its prokaryotic nature has been conclusively demonstrated **(Vidal *et al.*, 2021).**

Due to disagreements over how to interpret Precambrian fossils, it is still unclear when the firstcyanobacterial-like microbes appeared on Earth **(Vincent, 2019).** However, much of their current diversity was attained more than 2 billion years ago, and some claim that it first appeared on Earth about 3,5 billion years ago **(Paerl & Paul, 2012).**

3. Description of cyanobacteria

3.1. Morphology

According to their morphological characteristics, cyanobacteria are divided into five subsections:I (unicellular), II (unicellular with baeocytes), III (unbranched filamentous without heterocyst), and IV (false-branched or unbranched filamentous with heterocyst), and V (branched filamentous with heterocyst) **(Nandagopal *et al.*, 2021).**

Cyanobacteria can be single celled, colonial, or filamentous. In the majority of species, each cell is covered by a gelatinous or mucilaginous sheath that is comprised of layers of peptidoglycan and lipopolysaccharide **(Maria & Xavier, 2011).** Cyanobacteria exhibit a remarkable diversity in morphology from unicellular and filamentous forms of it are present **(Figure 2).**

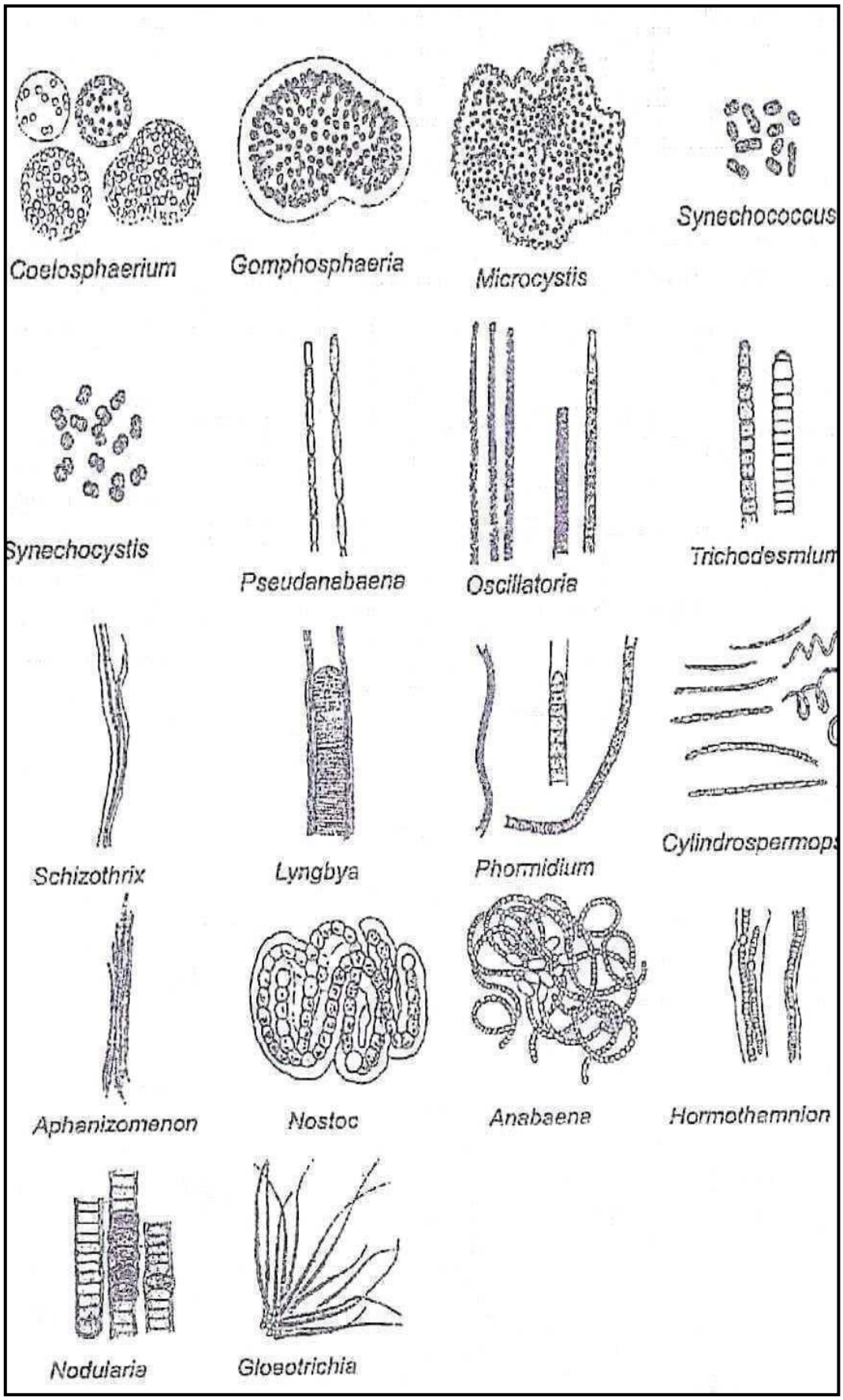


Figure 2. The morphological diversity of cyanobacteria **(Silvano, 2005).**

3.2. Cytology

3.2.1. Size

The cells' widths can range from 0.6 mm to 10 mm. The typical cell diameter is between that of bacteria and algae strictly speaking **(Silvano, 2005).**

3.2.2. Structure

The transmission electron microscope analysis of a cyanobacterium reveals the following cell structure: envelope, cell wall, plasma membrane, lipid droplets, outer membrane, protein granule, nucleoid (genetic material) and ribosomes. There may be cytoplasmic growths called pili (**Figure 3) (Silvano, 2005).**

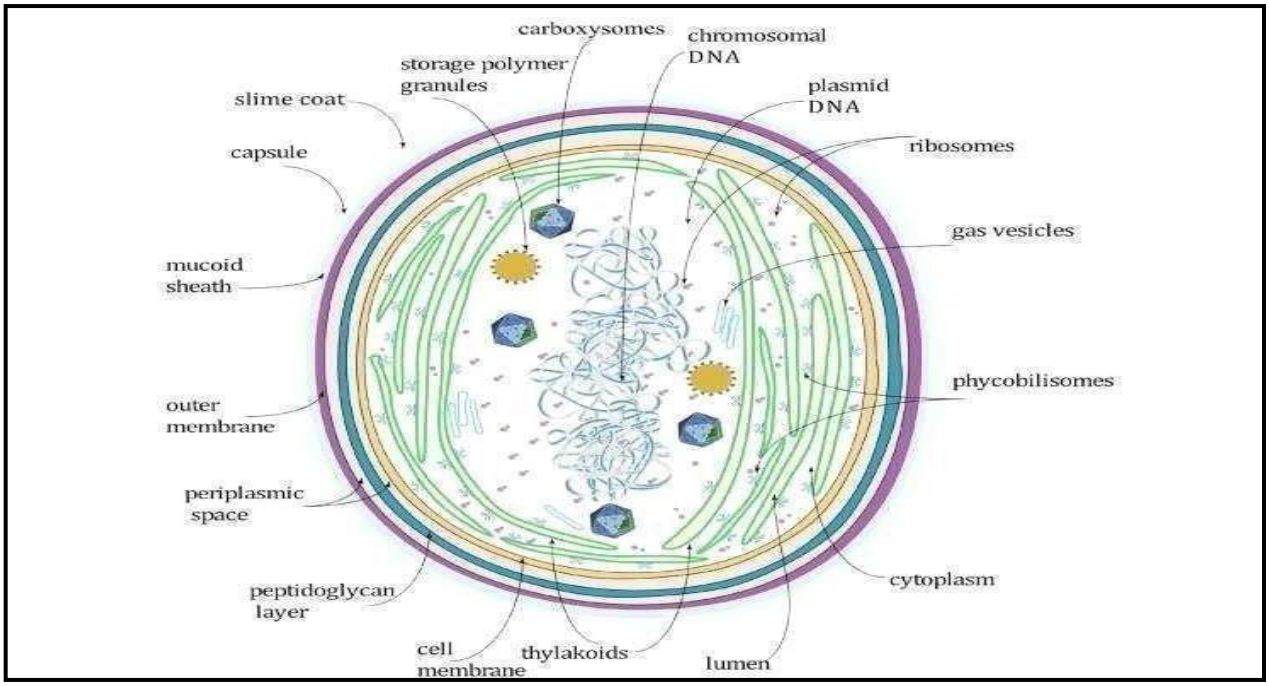


Figure 3. Cyanobacteria structure **(Noreña-Caro & Benton, 2018).**

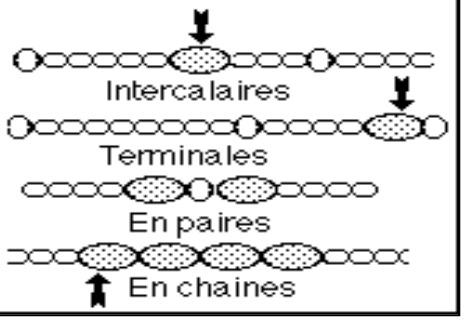
3.2.3. Cell type

Vegetative cells: have very refractile gas vacuoles (aerotopes), which are responsible for the buoyancy of the thalli that contain them. They also have a wide range of colors as a result of the different photosynthetic pigments they contain, such as chlorophyll a (green), phycocyanin (blue), and phycoerythrin (red) **(Levi *et al.*, 2006).**

Heterocytes (H): can usually be distinguished from vegetative cells by their larger, more rounded form, lessened pigmentation, thicker cell envelopes, and frequently noticeable cyanophycin granules at poles next to vegetative cells. The extra envelope layers that wrap heterocysts aid to protect the enzyme nitrogenase from oxygen **(Kumar *et al.*, 2010)**.

Akinetes (A): are perpetual spore like cells designed to withstand cold and desiccation. **(Kumar *et al.*, 2010).**

Table 1. Cell types of cyanobacteria **(Roger, 2006).**

Cellules végétatives	Hétérocystes	Spores ou Akinètes
Activité photosynthétique	Fixation de l'azote	Conservation Dissémination
	 Intercalaire bipolaire  Terminal unipolaire	 Intercalaires Terminales En paires En chaines

3.3. Photosynthetic pigments

Pigments are found in all organisms that use photosynthetic processes to absorb light. Chlorophylls, carotenoids, and phycobilins are the three primary categories of pigments. The chlorophyll molecule consists of a long hydrocarbon side chain or supplementary pigments like phycocyanin, phycoerythrin, and allophycocyanin, as well as a tetrapyrrole porphyrin ring with a magnesium atom in the center **(Encarnação *et al.*, 2015)**.

The ability of cyanobacteria to alter the composition of the pigment-proteins in their photosynthetic complexes (light harvesting complexes), which gives them a changing color depending on the lengths of waves in which they develop, is a significant property of cyanobacteria **(Bouallegue & Araar, 2021).** Different cyanobacterial species' abilityto absorb light can also be influenced bythe shape oftheir cells and the size of their colonies **(Vincent, 1989).** Allcyanobacteria have phycocyanin and chlorophyll.

3.4. Cell division and reproduction

Cyanobacteria reproduction is asexual. The most common kind of cell division is simple binary fission, in which the cell wall extends into the protoplast and the cell splits into two daughter cells that are isomorphic or, less frequently, asymmetrical **(Drews & Weckesser, 1982).** One of two ways is used to carry out this process. In general, succeeding generations of cells can divide in one, two, or three planes that are roughly perpendicular to one another. This procedure is performed frequently and is distinctive to the many genotypes (genera and families). Optional asymmetric binary fission in single genera, which can occur under less-than-ideal circumstances and is seen in some species of the Synechococcaceae and Chamaesiphonaceae families, is one type of this cell division. Another is routinely asymmetrical in the upper part of polarized cells **(Levi *et al.*, 2006).**

Scissiparity: The division occurs because of the appearance of an annular membrane that develops toward the center, causing a constriction and then a break in the chromatic network.

Thalle fragmentation: Among species withtrichomes.

Specialized structures: such as coccospores or hormospores.

3.5. Life cycle

The steps of the cyanobacterial life cycle is related to resistance cells. Both single and multicellular resistance cells are possible. They can occasionally have a similar appearance, but the envelope that surrounds them is usually thicker. The steps of the life cycle are as follows: recruitment (movement of sediments towards the water column), germination (change from a state of resistance to an active state), growth, and reproduction. Sedimentation (cell differentiation or the death of a portion of the filament) or the development of resistant cells (movement towards sediment) **(Figure 4) (Bouchareb, 2016)**.

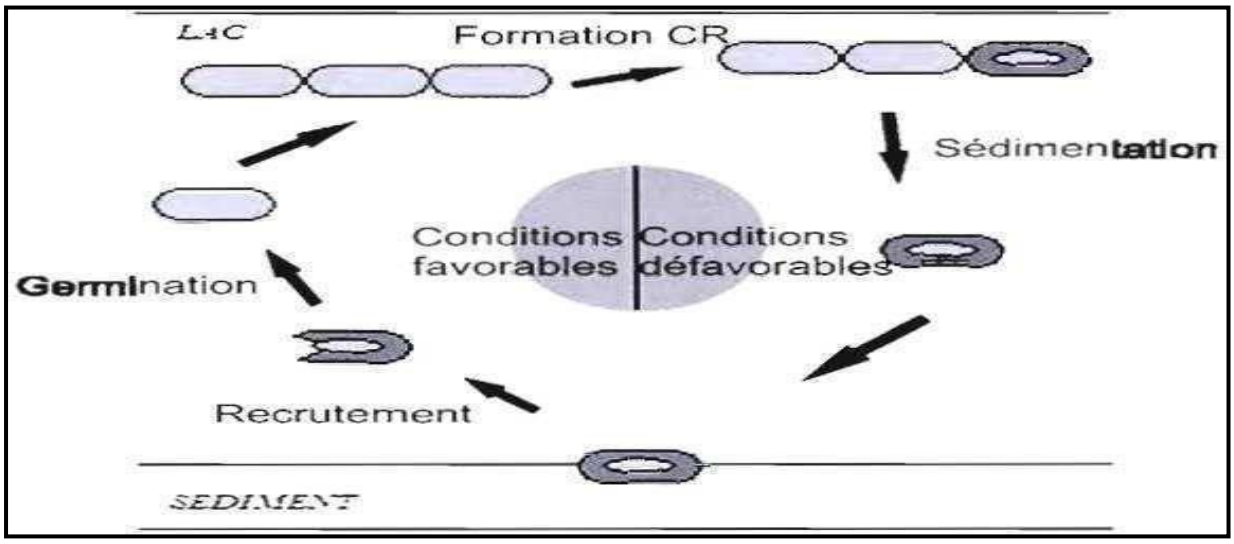


Figure 4. Life cycle of cyanobacteria during the production of akinetes **(Bouchareb, 2016).**

3.6. Ecology

Cyanobacteria are widespread and can be found in lakes, ponds, springs, marshes, streams, andrivers. They are important for the dynamics of nitrogen, carbon, and oxygen in many aquatic environments **(Vincent, 2019).**

3.6.1. Ubiquitous bacteria

Cyanobacteria can be found in a variety of common environments, including fresh water (mostly in lakes), air, beaches, seas, damp ground, and even rocks **(Reviers, 2003).**

3.6.2. Symbiosis

They can also be found in symbiotic relationships with a wide range of hosts. Symbiotic partnerships have benefits and drawbacks for the participating organisms. In fact, symbiosiscan benefit both or just one of the organisms involved (commensalism, parasitism) (mutualism) Symbiotic relationships frequently occur between organisms from different life domains, including both Eukaryote and Procaryote (Archaea and Bacteria) **(Mutalipassi *et al.*, 2021).**

4. Proliferation

The phrase "cyanobacteria proliferation" has been mentioned in the regulations. However, it is not defined internationally. At the current level of scientific understanding, cyanobacteria blooms arise as events of a dynamic naturethat cannot be precisely described bythreshold valuesofcell numbers or doubling times.

Because the phenomena are typically quite quick, populations' dynamics are observed by implementing a sampling and counting program whose frequency allows for the observation of the beginning of growth kinetics.

It is feasible to more accurately define the key times by having the best understanding of the pastand evolution of the resource's quality and behavior **(Levi *et al.*, 2006)**.

4.2. Cyanobacteria proliferation-favoring factors

According to the scientific community, there are three key elements that are most frequentlylinked to the proliferation of cyanobacteria:

- High levels of stability in the water column at the time of the bloom development and, in the time, leading up to this event **(Visser *et al.*, 1996)**;
- High concentrations of nutrients, particularly phosphorus and/or nitrogen, which are frequently the elements limiting nutrients in water bodies **(Chorus & Bartram, 1999)**;
- Favorable meteorological conditions, such as luminosity and temperature **(Levi *et al.*, 2006).**

4.3. Undesirable effects of cyanobacteria proliferations

Whenthese proliferations are extremely large, they have a varietyof implications.

4.3.1. About the environment and the living environment

- A change in the resource's appearance due to a unique hue (blue, red, or green), iridescence on the surface, or masses of foam blowing in the wind.
- An odor that is undesirable during the proliferation's decomposition **(Levi *et al.*, 2006).**

4.3.2. About local organizations

- Disturbance ofthe biodiversity ofthe aquatic ecosystem.
- Disturbance ofthe aquatic food webs because cyanobacteria are rarely or never consumed by zooplankton and their proliferation frequently occurs at the expense of the growth of other photosynthetic microorganisms (competition for nutrients and light).
- Fish mortalities from intoxication or a drop in water oxygen levels.
- Bird mortality through direct poisoning or through their diet (mollusks fish, etc.) **(Levi *et al.*, 2006).**
- Poisoning of domestic or wild animals by watering near toxic scum **(Briand, 2003).**

4.3.3. About affecting the ecological equilibrium

Cyanobacteria blooms have severely harmed animals, natural environments, and aquaculture ponds, resulting in huge financial losses. More than 80 cases of cyanobacteria poisoning have been documented in the literature, and they have occurred across all five continents since 1878.Most of the animals affected by these poisonings are cattle, sheep, dogs, birds, and fish. Animals with neurotoxins and hepatotoxins are more likely to develop tumors **(Carmichael & Falconer,1993).**

Several species of zooplankton and crustaceans are affected negatively by cyanobacteria in terms of growth, development, and reproduction **(Vasconcelos, 1999)**.

Higher aquatic plants' ability to photosynthesize can be inhibited by hepatotoxins, which can accumulate after cell lysis and discharge them into the environment **(Codd *et al.*, 1989)**.

Cyanotoxins induce significant disruptions in the development of fish fry embryos and have even been linked to physiological problems, particularly cardiac issues, in some fish, such trout **(Best *et al.*, 2001)**.

The broad spectrum of activity that cyanobacteria have against different species of bacteria, including *Escherichia coli*, is their final noteworthy trait. On the other hand, some types of pathogenic bacteria are favored byother cyanobacterial species. The growth of *Vibrio cholerae* is stimulated in this instance by *Synechocystis* **(Mezrioui *et al.*, 1994)**.

4.3.4. About human health (public health)

Animal deaths caused by cyanobacteria have occurred globally (eg, dogs, cats, cows and sheep).The cyanobacteria's lipopolysaccharides can irritate the skin and trigger allergic responses **(Sivonen et Jones, 1999)**. These patients received care at a facility where the water used for the hemodialysis equipment was tainted with microcystins **(Carmichael, 2001)**.

Chapter II: Classification of cyanobacteria

CHAPTER II: CLASSIFICATION OF CYANOBACTERIA

1. Morphological classification

Microbiologists can identify an organism specifically and by its taxonomic name because of its classification. The classic botanical technique and the bacteriological approach described in Bergey's Manual of Systematic Bacteriology are the two categorization schemes that are most frequently used **(Anagnostidis & Komarek, 1985; Boone & Castenholz, 2001; Komarek, 2003).**

Based on physical characteristics, they were grouped with eukaryotic algae under the classification of blue green algae (Cyanophyta) according to the worldwide conventional Botanical Code of Nomenclature. Cell size, sheath presence or absence, heterocyst and akinete presence or absence, type of reproductive organ, and physiological parameters such pigment composition, presence of gas vesicles, and the composition of reserve compounds are the criteria **(Anagnostidis & Komarek, 1985; Marion, 2009).**

Chroococcales, Pleurocapsales, Oscillatoriales, Nostocales, and Stigonematales are the five orders that make up the botanical system of classification, and they roughly correspond to the five subsections proposed in Bergey's Manual of Systematic, which are divided into families, subfamilies, genera, and species. This classification system, which proved helpful in the assessments of cyanobacterial diversity, was based on the morphological identification of species in natural samples **(Anagnostidis & Komarek, 1985;Knoll, 2008; Whitton, 2008).**

This taxonomy serves as the foundation for the integration of many morphological traits. The most notable traits are:

- aspects of growth: filamentous, colonial, and unicellular
- For colonial formations, the appearance and shape ofthe colony, cell size, shape
- For filamentous organisms:
    - diversification of cells: heterocysts and akinetes;
    - polarity: the filament's base and apex;
    - sheath: thickness, existence, or lack;
    - true or false branches – nature of false branches: simple or geminate due to the polymorphismof cyanobacteria **(Roger, 2006).**

Inthis classification, it is necessaryto do these comments:

- depending on the surroundings, the morphological characteristics may change;
- Depending on the medium, trichome diameter and sheath presence or absence also change;
- Heterocysts can form or not form depending on the combined nitrogen content as well as the genome. In fact, the blue alga does not produce heterocysts when nitrates are present **(Silvano, 2005).**

The bacteriologist consider that this microorganism is photoautotrophic bacteria, and theyare called cyanobacteria in Bergey's Manual. The bacteriological nomenclature code is based on comparative studies between axenic strains in culture. Cyanobacteria were included in the Bacteriological classification because they have the cellular characteristics of prokaryotes.The Bergey's Manual of Systematic Bacteriology, the acknowledged authoritative treatise on bacteriological classification, accepted and revised this. Cyanobacteria are classified into subgroups and genera according to the bacteriological approach, which is based on genetic morphological , physiological characteristics, biochemical, and phenotypic data about these organisms (**Stanier *et al.*, 1978; Rippka & Herdman, 1992; Garrity *et al.*, 2001).**

Using characteristics like shape and mechanism of inheritance, heterocyst and akinetes, spatialized cells that divide and differentiate, bacterial classification mostly adheres to traditional taxonomy in botany **(Geitler, 1932; Rippka *et al.*, 1979).**

Table 2. Classification of cyanobacteria according to bacteriological **(Lapage *et al.*, 1992)** and botanical **(McNeill *et al.*, 2006)** systems**.**

Bacteriological Classification	Botanical Classification
Subsection 1 Unicellular or colonial, multiplication by binary fission and/or exospore formation	Chroococales Unicellular or colonial
Subsection 2 Unicellular or colonial, multiplication by multiple fissions (baeocytes) or in combination by binary fission	Pleurocapsales Colonial or filamentous
Subsection 3 Filamentous uniseriate, not heterocystate, branchless, cell-dividing perpendicular to the axis ofthe trichome	Oscillatoriales Uniseriate filamentous, no heterocystous
Subsection 4 Filamentaire, différenciation cellulaire (heterocysts and akinetes), with cell division in one plane	Nostocales Filamentous, no true branching, cell differentiation (heterocysts and akinetes
Subsection 5 Filamentous, cell differentiation (heterocysts and akinetes), presenting branching, cell-dividing in several planes	Stigonematales Filamentous, cell differentiation (heterocysts and akinetes), presenting offshoots

2. Phylogenetic classification

Prokaryotic phototrophic microorganisms known as cyanobacteria are a phylogenetically veryold category of creatures. Phylogenetic classification is based on the 16S rRNA gene sequencing. Because 16S rRNA sequences are unaffected by culture or growth conditions, this method of phylogenetic classification of cyanobacteria is currently the most popular **(Nubel *et al.*, 1997).**

The 16S rRNAs of 29 cyanobacterial strains, including important reference strains from each of the five orders, were examined in a more thorough investigation. This research allowed for the identification of the main phylogenetic patterns of the pure-culture cyanobacteria now accessible **(Giovannoni *et al.*, 1988).**

Contradictory findings with the morphological classification of some cyanobacterial taxa havebeen found in phylogenetic analyses. This is the situation with *Oscillatoria* and *Microcoleus*, which are classified as physically distinct genera yet were clustered together in the same taxa by 16S rRNA studies **(Wilmotte *et al.*, 1992).**

The phylogenetic tree contains members of the Chroococcales and Oscillatoriales, demonstrating that these two orders do not now reflect cohesive evolutionary lineages. Pleurocapsales members belong to a single lineage, showing that multiple fission reproduction has monophyletic roots. Because members of the Nostocales and Stigonematales belong to the same coherent lineage, it is possible that the two groups' ordinal separation is unnecessary.

The outcomes of molecular analyses don't always match up with conventional criteria, which has been acknowledged as a disadvantage with this approach. The use of careless and arbitrary names for isolated cyanobacterial strains in studies and collections is the biggest issue. According to two studies, the 23S rRNA gene is longer than the 16S rRNA gene, whichresults in more informative sites and better resolution. However, the main disadvantage of sequencing the 23S rRNA gene is that it has a smaller database than the 16S rRNA gene **(Ludwig *et al.*, 2001;Komárek, 2016).**

Recently Komárek proposed a classification of cyanobacteria Organized into eight orders. This last classification is based on a polyphasic approach. using molecular, biochemical and microscopic information (**Figure 5**) **(Komárek *et al.*, 2014).**

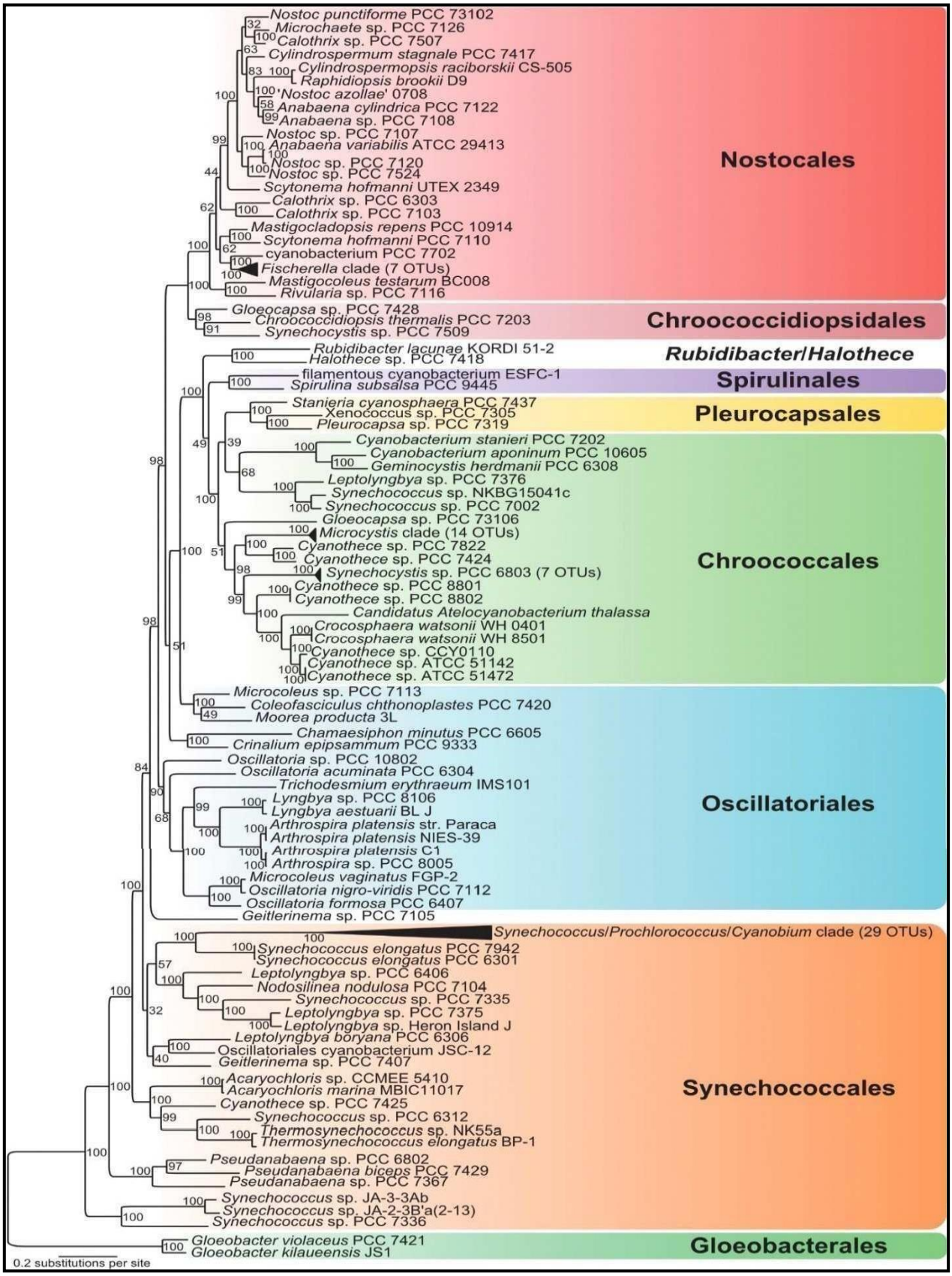


Figure 5. Phylogenetic tree based on 21 conserved proteins including the most recent changes in cyanobacteria classification **(Komárek *et al.*, 2014).**

Chapter III:

Cancer

CHAPTER III: CANCER

1. Definition

Cancer is a condition marked by aberrant cell proliferation within a body tissue. These cells all originate from the same clone, the cancer is initiator cell, which has developed particular properties that enable it to proliferate endlessly while evading the normal mechanisms of differentiation and multiplication control. Some cancer cells may move away fromtheir site of origin and develop metastases as the disease progresses.

Gene alterations in one or more cells are the root cause of cancer. All cells contain DNA (Deoxyribonucleic acid), which is the building block of genes. Some genes educate cells and regulate whenthey should divide and expand. However, if these genes are harmed, the cellmay behave erratically and develop cancer. Once a malignancy has started, malignant cells cangrow unchecked, supplanting healthy cells and impairing their ability to function one **(Eggert, 2017).**

According to the WHO, cancer is the quickly developing of abnormal cells that grow beyond of their normal borders and can subsequently infiltrate nearby body parts and spread to other organs. Metastatic dispersion is the term used to describe this action **(Ferlay, 2023).**

2. Types of cancers

Different cancer types have been listed and classified in accordance with:

- The principal organ, including cancers of the mouth, breast, lungs, prostate, liver, kidney, lung, and brain.
- The tissue that it develops from (anatomopathological categorization) **(Bouksil & Tachour, 2019)**.

Table 3. Anatomopathological classification of cancer **(Bouksil & Tachour, 2019).**

Tissus		Tumor
Epithelium	Glandulated Malpighien Urothelial	Adenocarcinoma Epidermoid carcinoma Epidermoid carcinoma
Conjunctive	Fibroblasty By Adipeux Stripped Muscle muscle smooth	Fibrosarcoma Liposarcoma Rhabdomyosarcome Leomyosarcome
Hematopoetic		Leukemia, Lymphoma
Germinal		Teratocarcinoma
Neuroectodermic		Melanoma

3. Pathophysiology of cancer

Fundamentally, cancer is a disorder of the control of tissue growth. The genes that control cell development and differentiation must be changed in order for a normal cell to convert into a cancer cell. There are two major groups in which the impacted genes fall. Oncogenes are genes that encourage cell division and development. Genes known as tumor suppressors prevent cell proliferation and division.

Malignant transformation can happen as a result of the development of new oncogenes, the inappropriate over expression of normal oncogenes, the under expression or disablement of tumor suppressor genes, or any combination of these. A normal cell must typically undergo alterations in several genes before becoming a cancer cell. Different levels and mechanisms canlead to genetic changes. Errors in mitosis can result in the acquisition or loss of a whole chromosome. Mutations, which are modifications to the genomic DNA's nucleotide sequence,are more frequent.

A significant section of a chromosome may be lost or gained in large-scale changes. Genomic amplification happens when a cell acquires copies (commonly 20 or more) of a tiny chromosomal region, which typically contains one or more oncogenes and nearby genetic material. Point mutations, deletions, and insertions are examples of small-scale mutations. They can occur in a gene's promoter region and impact the expression of the gene, or they can occur in the gene's coding sequence and change the function or

stability of the protein product.The incorporation of genomic material from a DNA virus or retrovirus can potentially cause the disruption of a single gene, resulting in the production of viral oncogenes in the damaged cell and its progeny. Probabilistically, certain errors (mutations) will result from the replication of the information included in the DNA of living cells.

The process includes complex error repair and preventive measures that protect the cell from cancer. A damaged cell may self-destruct through a process known as programmed cell death,or apoptosis, if a severe error happens. If the error correction procedures are unsuccessful, the mutations will endure and be transmitted to daughter cells.

Inhibitory compounds known as carcinogens, recurrent physical harm, heat, ionizing radiation, or hypoxia are examples of such settings. The development of a cancerous cell is comparable to a chain reaction whereby initial mistakes compound into moreserious ones, which progressively free the cell from additional restraints that restrict the growth of normal tissue.

This survival of the fittest-like situation, in which the forces of evolution operate against the body's design and order-enforcing mechanisms, is an unwanted survival of the fittest. This continuing process, known as clonal evolution, propels advancement towards more invasive phases once cancer has started to form. Clonal evolution causes intra-tumor heterogeneity (cancer cells with diverse mutations), which makes it more difficult to develop efficient treatment plans.

Cancers have distinct capacities that fall into three categories: evasion of apoptosis, self-sufficiency in growth signals, and insensitivity to anti-growth signals. Metastasis, prolonged angiogenesis, infinite potential for replication, reprogramming of energy metabolism, and evasion of immunological destruction **(Anubhav *et al.*, 2021).**

4. Different treatments of cancer

There are two primary methods of treatment for cancer. Systemic treatments that do not target the tumor and locoregional treatments that do target the tumor. The various treatments typically coexist together.

4.1. Loco regional treatments

4.1.1. Surgery

The earliest method of treating cancer was surgery, particularly for the treatment of tiny, localized tumors or slowly developing solid tumors, which account for 70% of cancer cases. It entails removing the tumor, it is frequently combined with other treatments including chemotherapy, radiotherapy, or hormone therapy. Only this treatment can address places with weak blood flow that chemotherapy cannot.

4.1.2. Radiotherapy

When the damaged organ needs to be preserved, radiotherapy is an alternative to surgery. The irradiated area is affected locally by radiotherapy. All radiotherapy techniques are based on unionization. Reactive oxygen species (ROS), which are produced when the particles (protons,electrons or X or photons) interact with cell water, kill nearby cells.

There are different types of radiotherapy:

- Transcutaneous radiotherapy: this treatment is based on a generator of radiation outside the body. The beams of radiation emitted by this Generator treat the tumor.
- Interstitial irradiation or brachytherapy: this technique consists of implanting temporarily in the tumor or near radioactive sources.
- Metabolic radiotherapy: this method is based on the use of molecules with ionizing power selectively attaching to the tumor.

A chemical called a photosensitizer and appropriate light irradiation (LASER), which penetrates fabrics well, are both used in conjunction in dynamic phototherapy. The photosensitizing chemical is designed to target the treated tissues as precisely as is humanly possible. Irradiation causes photooxidation of photosensitizing, which leads to oxidative stress (localized generation of ROS), which ultimately leads to cell death **(Chaleix & Gachard- Bouty, 2003).**

The photosensitizing agent may be used topically or intravenously. The majority of molecules used in tumor phototherapy are porphyrin derivatives such texaphyrins, bacteriochlorins, or sporfimer sodium **(Detty *et al.*, 2004).**

4.2. Systemic treatments

4.2.1. Hormonotherapy

These medications suppress or lessen the level or action of hormones that are likely to encourage the growth of tumors. Individuals exhibit vulnerability to cancer breast, prostate,thyroid, endometrial, and, to a lesser extent, testis, ovary, and kidney cancers are all treated with hormones. These medications can stop the growth of these hormone-dependent cancers in two different ways: either by preventing the production of hormones like anastrozole and exemestane, which block the action of aromatase (an enzyme required for the conversion of androgens into estrogen), or by opposing the action of hormones like fulvestrant and tamoxifen, which are anti-estrogen medications. They compete with estrogen and occupycelsurface receptors, reducing their ability to stimulate cancerous cells.

4.2.2. Immunotherapy

These medications are used under the assumption that the body can recognize when healthy cells turn into malignant cells and get rid of them. Immunomodulators, which mostlyconsist of interferons and interleukin 2, are used to boost the immune system in order to accelerate the clearance of malignant cells.

- interferons a naturally occurring protein that the body's cells produce, and which has a variety of impacts on immune system cells. It possesses antiviral, antiproliferative, and antifibrotic effects, and it activates macrophages (phagocytosis).

  Some interferons are now produced industrially and used in medicine, such as in the treatmentof some types of cancer or multiple sclerosis. Interferons inhibit cell proliferation and stimulate immune defenses.

- Interferon is used in oncology to treat specific malignancies, including kidney cancer, leukemia, lymphoma, myeloma (a type of bone marrow cancer), and melanoma. Subcutaneous injections are used to administer it in a variety of doses based on the indications.
- Interleukin-2 (IL-2) is a type of immune system cytokine that stimulates lymphocyte proliferation and aids in the body's defense against microbial

infection. However, its primary function is adversarial. It is a T lymphocyte growth factor that promotes the development and activation of these cells. It is applied to the management of specific kinds of malignant melanoma and advanced kidney cancer **(Jacques & Mortier, 2016; Antoni *et al.*, 2016).**

4.2.3. Chemotherapy

Local treatments like surgery and radiotherapy become ineffective when the cancer spreads and develops secondary tumors. Chemotherapy is used to treat cancer by preventing the growth of cancerous cells, shrinking tumors, and preventing the development of secondary tumors.

Cancers at stages 0 and 1 are not impacted by chemotherapy. Chemotherapy is administered for advanced stage II, III, and IV tumors after surgery and may be utilized in the following circumstances:

- Neoadjuvant therapy: used before surgery to shrink a tumor and make it easier to remove;
- Adjuvant therapy: used after surgery to finish the operation and prevent recurrences; and in conjunction with radiotherapy to make the tumor more sensitive to the latter: concurrent chemotherapy and radiation therapy.
- In cases of disseminated or metastatic malignancies.

Chapter IV: Anticancer activity of cyanobacteria

1. Generality of anticancer

1.1. Definition

Anticancer drugs are those that stop or slow the development and spread of neoplasms. These are used not only for various cancers but also in combination with radiotherapy and immunotherapy for many solid tumors, particularly metastatic ones. Generally, all malignant tumors are referred to as Cancer. These drugs are available as liquids, pills, and other forms **(Mamatha, 2015).**

1.2. Cell cycle

The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division. The goal of the cell cycle is to produce two daughter cells, each containing chromosomes identical to those of the parent cell.

1.2.1. Phases of the Cell Cycle

The cell cycle incorporates two principal phases: the interphase, and the M phase (mitosis).

- **Interphase***:* it represents continuous growth of the cell and is subdivided into three phases, G1 (gap1) phase S (synthesis) phase, and G2 (gap 2) phase.
- **Mitosis** (M): phase mitosis nearly always includes both karyokinesis (division of the nucleus) and cytokinesis(division of the cell) and lasts about 1 hour. Mitosis takes place in several stages described in more detail below. Separation of two identical daughter cells concludes the M phase.

1.2.2. Cell cycle control

The smooth running of the cell cycle depends on the checkpoints:

- **The restriction point:** or starting point, allows the cell to continue the cycle, if cytoplasmicgrowth is complete and the environment is favorable.
- **The G2 point:** controls entry into M phase, and only allows division if all the DNA has replicated, there are no abnormalities, the cellsize is sufficient.

- **The M point:** controls the assembly of the spindle and the alignment of the chromosomesin the equatorial plate **(Figure 6).**

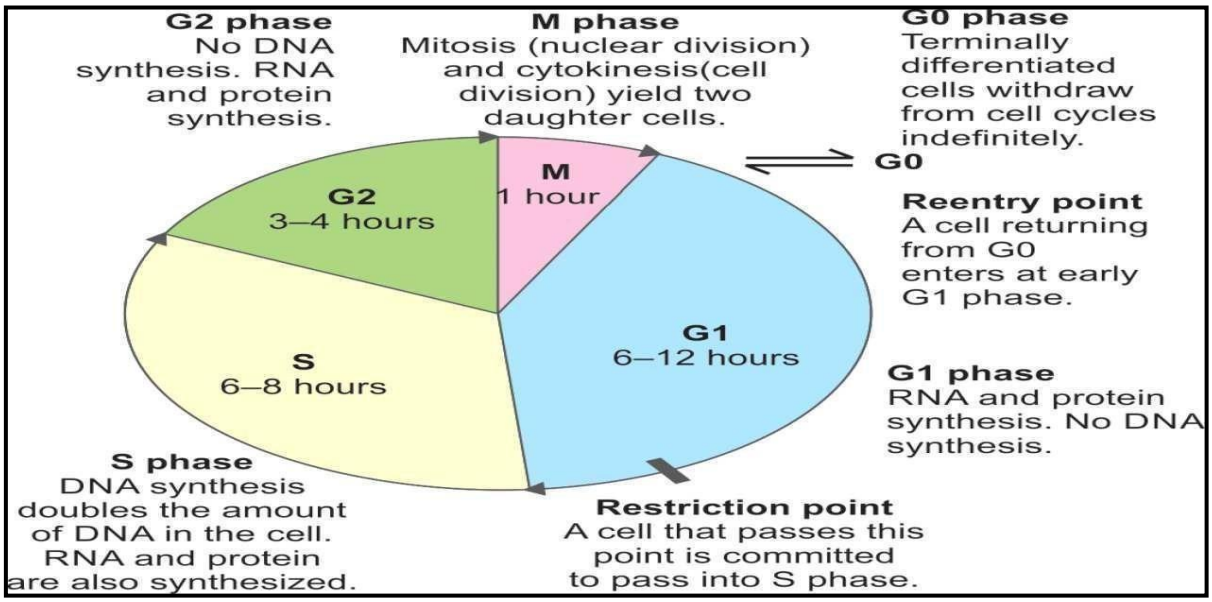


Figure 6. Eukaryotic cell cycle **(Swarup *et al.*, 2019).**

2. Classification of anticancer

The anticancer drug classification is based on:

- The drug's cycle or phase specificity;
- Biochemistry mechanisms ofanticancer effect;
- The drug's chemical structure and source.

2.1. Based on the drug's cycle or phase specificity

The Classification of Anticancer has specificity of the drug:

2.1.1. Cell cycle nonspecific agents (CCNSA)

Can kill both go and cycling cells, while cycling cells are more vulnerable and employed in slowlyexpanding tumors.

2.1.2. Cell cycle specific agents (CCSA)

Which act on proliferating cells, are most successful in solid tumors and hematologic malignancies where a sizable fraction of the tumor's cells is in a proliferative state.

Table 4. Phase specificity of cytotoxic drugs **(Whitehead, 2023)**.

Phase of cell cycle	**Effective agents**
G1	Steroids, asparaginase
S phase	Antimetabolites
G2	Bleomycin, etoposide
Mitosis	Vinea alkaloids, taxanes
Phase nonspecific	Alkalating agents, nitrosoureas, antibiotics, procarbazine, dacarbazine, platinum

2.2. Based on biochemistry mechanisms of anticancer effect

2.2.1. Block nucleic acid (DNA, RNA) biosynthesis

For example antimetabolites:

- ✓ Folic acid antagonist: inhibit dihydrofolate reductase (methotrexate)
- ✓ Pyrimidine antagonist : inhibit thymidylate synthetase (fluorouracil) ; inhibit DNApolymerase (cytarabine)
- ✓ Purine Antagonist: inhibit interconversion of purine nucleotide (mercaptopurine)
- ✓ Ribonucleoside Diphosphate Reductase Antagonist: (hydroxyurea)

2.2.2. Influence the structure and function of DNA

- ✓ Alkylating Agent: mechlorethamine, cyclophosphamide and thiotepa
- ✓ Platinum: cis – platinium
- ✓ Antibiotic: bleomycin and mitomycin C
- ✓ Topoismerase inhibitor: camptothecine and podophyllotoxin

2.2.3. Interfere transcription and block RNA synthesis

- ✓ Bind with DNA to block RNA production, doxorubicin.

2.2.4. Interfere protein synthesis and function

- ✓ Anti-tubulin: vinca alkaloids and taxanes;
- ✓ Interfere the function of ribosome: harringtonines;
- ✓ Influence amino acid supply: L - asparaginase Bind tubulin, destroy spindle to producemitotic arrest.

2.2.5. Influence hormone homeostasis

These drugs bind to hormone receptors to block the actions of the sex hormones, which results in inhibition of tumor growth.

- ✓ Estrogens and the estrogen antagonistic drug
- ✓ Androgens and androgen antagonistic drug
- ✓ Progestogen drug
- ✓ Glucocorticoid drug
- ✓ Gonadotropin - releasing hormone inhibitor: leuprolide, goserelin
- ✓ Aromatase inhibitor: aminoglutethimide, anastrazole

2.3. Based on the drug's chemical structure and source

- Alkylating agents
- Antimetabolite
- Antibioties
- Plants extracts
- Hormones
- Monoclonalantibodies miscellaneous 4 (Whitehead, 2023).

3. Mechanism of action

The anticancer drugs are diverse and have many mechanisms of action (Figure 7).

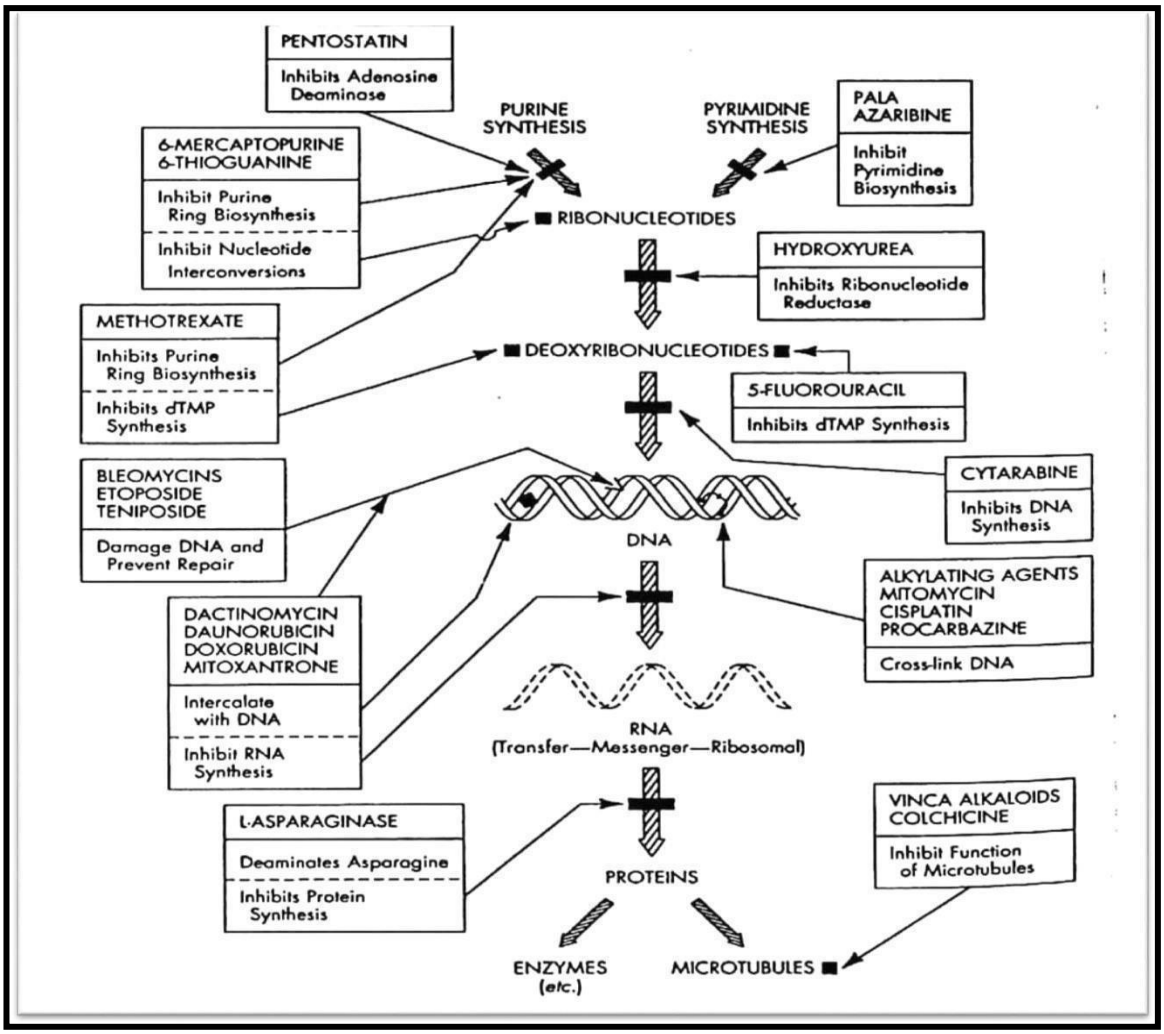


Figure 7. Summary of the mechanisms and site of action of chemotherapeutic agent **(Levi *et al.*, 2006).**

3.1. Alkylating agents

In aqueous solutions under physiological conditions, alkylating agents are a varied set of chemical substances that share the property of generating positively charged (electrophilic - electron deficient) alkyl groups. Alkyl groups with positive charges can react with basic, negatively charged (nucleophilic - electron-rich) groups found in DNA, proteins, and peptides. These events result in the addition of alkyl groups at oxygen,

nitrogen, phosphorous, or sulphur atoms (nucleophilic centers), which changes how DNA and proteins function biologically.

In terms of their anticancer effectiveness alkylating drugs' interactions with DNA nucleobases are the most significant. Guanine is the DNA nucleobase that is most frequently chosen for alkylation, and the alkylation preferentially takes place at the N7 position on guanine. Other nucleobases that have undergone alkylation include guanine, at the N1 and O6 positions, adenine, at the N1, N3, and N7 positions, cytosine, at the N3 position, and thymidine, at the O4 position **(Germanas & Pandya, 2002).**

3.2. Antimetabolites

Antimetabolites that enter RNA or prevent protein synthesis have not been shown to be clinically effective in the treatment of cancer. A few antimetabolites prevent the nucleic acids from being biosynthesized. Cell death occurs when the production of these crucial DNA and RNA building blocks, which each cell needs to operate and reproduce, is disrupted. Antimetabolites with this mode of action are helpful in certain cancer types. The purine bases 6-mercaptopurine and 6-thioguanine inhibit the production of purine rings. To prevent the conversion of folic acid to tetrahydro-folic acid,which transports single carbon fragments for the synthesis of the purine ring and for the methylationof deoxy-uridylic acid to thymidylic acid, a key component of DNA, metho trexate inhibits folic acidreductase. 5-Fluorouracil is metabolized to its deoxynucleotide form to inhibit the enzyme, thymidylate synthetase, which also is involved in the methylation of deoxyuridylic acid to thymidylic acid; arabinosylcytosine blocks the reduction of cytidylic to de oxycytidylic acid, and bypreventing the formation of another essential component of DNA, DNA replication is inhibited **(Karnofsky, 1968).**

3.3. Hormones

The presence of particular hormone receptors in the target tissues affects how specifically a hormonewill function. These receptors are found in the cytoplasm of steroid hormone-containing cells, and it is thought that while the hormone freely crosses all cell membranes, it is only selectively concentrated in the target cells that have these particular cytoplasmic receptors. The hormone enters the nucleus after binding to the cytoplasmic receptor and begins to interact with DNA there. Thus, the hormone has the capacity to modify gene activity and change the regulation of cellular growth. On the other hand,

polypeptide hormones, such as insulin, prolactin, and adrenocorticotrophic hormone (ACTH), do not bind to cytoplasmic receptors; rather, the receptor on the surface of target cells serves as the basis for their selective activity. The second messenger, which is triggered upon the specific binding of the polypeptide to the cell-surface receptors, is thought to mediate the impact of hormones that do not readily permeate the cell membrane. Cyclic AMP adenosine monophosphate, the second messenger, controls different elements of intracellular metabolism **(Kenneth *et al.*, 1980).**

3.4. Others (plants extracts, monoclonal antibodies, miscellaneous)

4. Anticancer activity of cyanobacteria

New anticancer drugs are needed due to the increasing prevalence of cancer and the diversity of the cancers detected. It has been demonstrated that cyanobacteria possess several bioactive derivatives that have the potential to kill cancer cells. Curacin A and cryptophycins isolated from cyanobacteria possess cytotoxic activity through an interaction with microtubule-binding proteins, which arrests cell division and induces apoptosis **(Moore *et al.*, 1996; Jordan & Wilson, 1998;Gerwick *et al.*, 2001; Han *et al.*, 2008).**

Cryptophycin isolated from cyanobacteria, such as *Nostoc sp*. (a *Nostoc* species discovered at the University of Hawaii to be a cryptophycin producer), possess anti-cancer activity against KB human Nasopharyngeal cancer cells and LoVo human colorectal cancer cells.

The Cytotoxicity induced by cryptophycins was due to its interaction with microtubule-bindingproteins disrupting tubulin dynamics and eventually causing death of tumour cells **(Panda *et al.*, 1997)**. Cryptophycin acts as a tubulin-destabilizing agent and Arrests tumour cells into the G- M phase of the cell cycle, resulting in hyper-phosphorylation of Bcl-2 and apoptotic signalling **(Smith *et al.*, 1994; Drew *et al.*, 2002;Dias *et al.*, 2015).**

Curacin and dolastatin have been shown to possess cytotoxic activity **(Moore *et al.*, 1996; Jordan & Wilson, 1998; Gerwick *et al.*, 2001)** and have potential for anti-cancer drug development **(Moore *et al.*, 1996;Chaganty *et al.*, 2004)**. Curacin-A was first isolated from *Lyngbya majuscule* **(Gerwick *et al.*, 1994)** and acts as an inhibitor of

cell growth and mitosis activity by interacting with tubulin **(Verdier-Pinard *et al.*, 1998; Xiong *et al.*, 2006; Yasin *et al.*, 2019).**

Several other cyanobacterial bioactive compounds have been tested in different human tumourcell lines for their cytotoxic activity. Apratoxin D, an analogue of apratoxin (apratoxin family of cytotoxins isolated from a *Lyngbya sp*.) from *L.majascula* is cytotoxic to human lungcancer cells **(Gutierrez *et al.*, 2008; Thornburg *et al.*, 2013; Masuda *et al.*, 2014)** and symplocamide A from *Symploca sp*. possesses cytotoxic activity against lung cancer and neuroblastoma cells **(Tan, 2007;Linington *et al.*, 2008).**

Bioactive compounds isolated from cyanobacteria have the ability to induce apoptosis and autophagy in the cancerous cell **(Han *et al.*, 2008; Kim *et al.*, 2012).** It was shown that HL- 60 (a human leukaemia cell lline) cells incubated with an extract from *Synechocystis* and *Synechococcus sp*. showed cell shrinkage and apoptosis **(Martins *et al.*, 2008).**

There are other cyanobacterial bioactive compounds that have the potential to inhibit cancer by arresting the cell cycle, inducing mitochondrial fragmentation, oxidative damage, alterationof apoptotic signaling pathways, modulation of caspase signaling and via sodium channels **.**

Dragonamide C and dragonamide D isolated from *L. polychroa* displayed anti-cancerous activity similar to that of dragonamides againstleishmaniasis **(Balunas *et al.*, 2009; Jimenez & Scheuer, 2001; McPhail *et al.*, 2007).**

Dolastatins isolated from cyanobacterial strains can arrest cell cycles (**Luesch *et al.*, 2001)**. Hectochlorin and lyngbyabellins, lipopeptides isolated from the genus *Lyngbya*, can induce Arrest in G2/M phase in a human Burkitt lymphoma cell line **(Marquez *et al.*, 2002).**

Aurilides A and B isolated from marine cyanobacteria can induce mitochondrial dysfunction **(Sato *et al.*, 2011)**. Since mitochondria play a key role in the generation of oxidative stress, mitochondrial fragmentation in cancerous cells will affect the oxidative stress level and may cause oxidative damage to the cancerous cells. There are several

cyanobacterial compounds that can alter mitochondrial dynamics and increase oxidative damage to cancerous cells. (Figure 8)

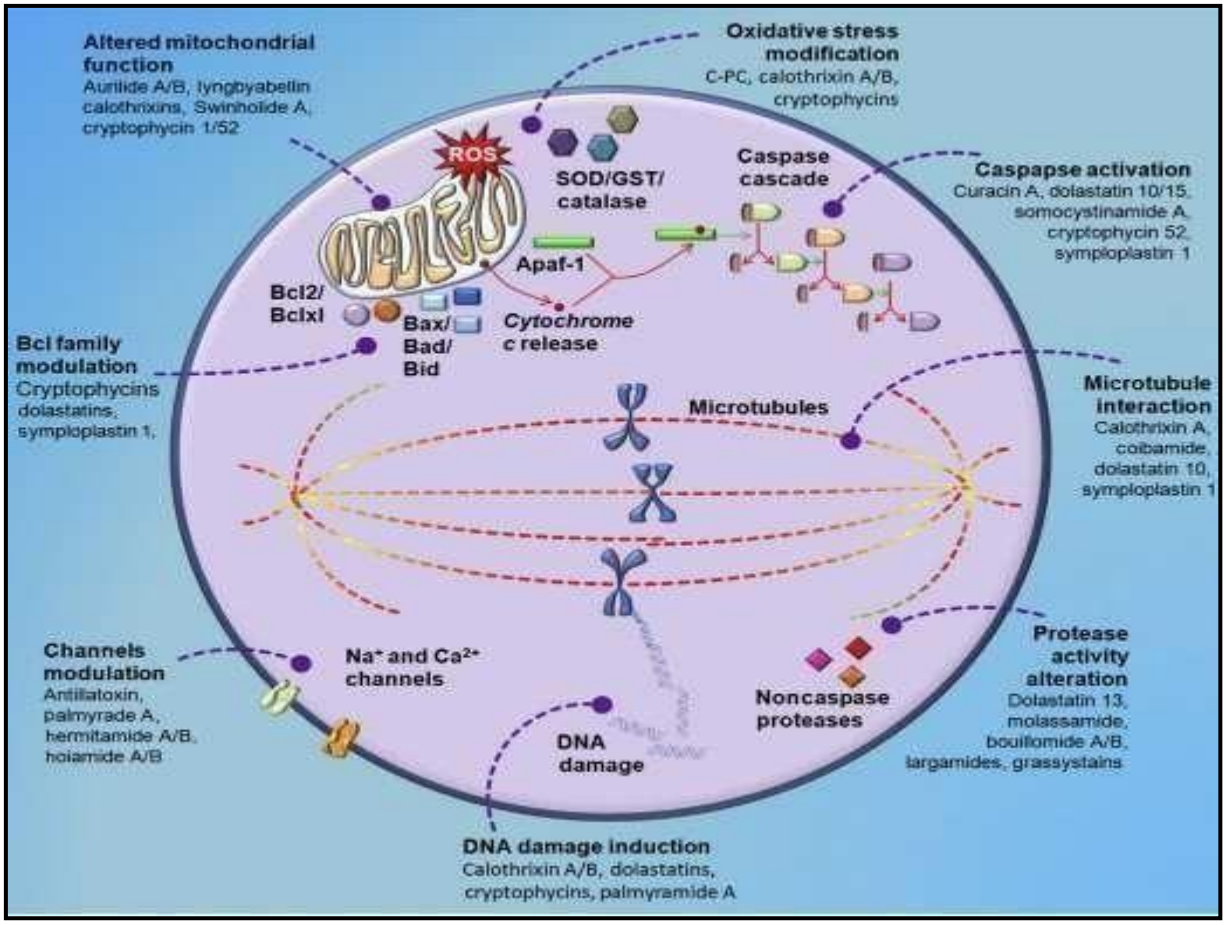


Figure 8. Possible of mechanisms of anticancer activity of cyanobacteria compounds **(Arundhati *et al.*, 2020).**

4.1. Cyanobacteria compound with anti-cancer functions

There are many genera of cyanobacteria that synthesis the compounds with anticancer function.

4.1.1. Lyngbya

L. bouillonii makes the 2-epi-lyngbyaloside, 18 E and 18 Z lyngbyalosides C to traget the HT-29(cell line with epithelial morphology); HeLa cells (Henrietta Lacks was an African American who was given cervical cancer).
L. bouillonii makes alotamide A, the mechanism of this metabolite is Ca^{+2} influx.
L.bouillonii makes apratoxin E, F and G to target the following cells respectively U2OS (cell line with epithelial morphology), HT-29 and HCT-126 (human colon cancer cell line). The mechanism of these metabolites is cell cycle arret and growth signal.
L. bouillonii makes lyngboilloside to target neuroblastoma.
L. bouillonii makes lyngbyabellin J to target HT-29, HeLa. The mechanism of this metabolite is mitochondrial dysfunction, oxidative damage and actin.

L. majuscula makes homodolastatin 16, indanone, isomalyngamide A and A-1, itralamide B, jamaicamides A-C, Kalkitoxin, Lagunamide C, Lagunamide A-B, Lyngbyabellin A , B to target the following cells respectively NHCO-1 : cytotoxicity quantification esophageal cancer cells), ME-180 (morphology epithelial uterus), Hep 3B (cell line exhibiting epithelial morphology), MCF-7 (is the name of breast tumor cell line). HEK 293 (mammalian cells most commonly used both for academic research and in the pharmaceutical and biotechnology industries), HCT 116, he mechanism of these metabolites' inhibition of ca^{+2} influx, actin oxidative damage and mitochondrial dysfunction.

Lyngbya sp. makes bisebromoamide and biselyngbyaside to target HeLa-S3, SNB-78 (cell line panel) and NCL-H522 (cell line exhibiting epithelial morphology lung). The mechanism of these metabolites is cell cycle arrest, kinases and actin.

Lyngbya sp. makes kempopeptin A, B and koshikalide to target a- chymotrypsin and trypsin. The mechanismofthese metabolites is inhibition ofnon-caspase serine proteases.

4.1.2. Symploca

Symploca sp. makes belamide A to target HCT-116. The mechanism of this metabolit is cell cycle arrest.

Symploca sp. makes dolastatine 10 to target A-549 (cells are adenocarcinomic human alveolar basal epithelial cells), NCL-H69 (is an aneuploid human male cell line), -H82 (is an epithelial-like cell line), -H446 (cell cancer of the lung), and –H510 (is an epithelial-like cell that was isolated from an adrenal metastasis). The mechanism of this metabolit is cell cycle arrest, caspase, microtubule, bad protein activation caspases and microtubule.

Symploca sp. makes largazole to target MDA-MB-23I (cell line is epithelial-like), U2OS (is a cell line with epithelial morphology), A-549 (adenocarcinomic human alveolar basal epithelial cells), HCT-116 (cell line of colon cancer). The mechanism of this metabolit is cell cycle arrest and histone deacetylases.

Symploca sp. makes symplocamide A to target H-460 (cell cancer of lung). The mechanism of this metabolite noncaspase serine protease and chymotrypsin.

Analogues of dolastatin 13 make bouillomides A and B to traget serine proteases elastases and chymotrypsin. The mechanism of these metabolites is inhibition of noncaspase serine proteases **(Arundhati *et al.*, 2020).**

5. Increase in yield

After the analysis of the 16S marker and the metabolites of cyanobacteria. A comparison is made between metabolite in terms of percentage of effectiveness in eliminating cancer cells. Next, the species of cyanobacteria that produces the most effective metabolites is chosen. Providing all the conditions necessary for cyanobacteria to grow to produce this metabolite, then extracting it and recycling it as an anticancer drug or mixing it with another chemical compound to make it an effective drug.

Conclusion

CONCLUSION

The work entails a bibliographical analysis of cyanobacteria's anticancer properties. Gram- negative photoautotrophic prokaryotes known as "cyanobacteria" or "blue-green algae" are common and can be found in the environment in unicellular, filamentous, or colonial forms thatare encased in a mucilaginous sheath. Evidence of their existence dates back to 3.3–3.5 billion years. They have several uses in the biomedical area because of their widespread presence andthe enormous variety of their metabolites.

The key criteria used to classify cyanobacteria are their morphological, ecological, and ultrastructural properties, as well as their inherent traits and molecular research. The techniquesof contemporary biology, 16S rRNA, the taxonomic criteria used by genetics have changed significantly, however the outcomes of this technique are not necessarilyconsistent with the traditional standards.

Lots different metabolites, some of which may be low weight peptides, are produced by cyanobacteria. Alkaloids, terpenoids, polysaccharides, and lipopolysaccharides are all types ofmolecules. Extracellular metabolites are often a bioactive material with a wide range of biological effects, including antifungal, antiviral, antibacterial, antialgal, antioxidant, andanticancer properties.

There are a number of bioactive compounds that may be able to eradicate cancer cells’aurilides A and B, symplocamide A, dragonamide C, and dragonamide D, as well as Curacin A and cryptophycins, Aparatoxine D, Calothrixin A, Dolastatins, Hectochlorin and lyngbyabellins, These bioactive compounds can be produced by several cyanobacterial species, including *Nostoc* sp., *Lyngbya majuscula*, *Symploca* sp., *Synechocystis* and *Synechococcus* species, *Calothrix* sp., *L. polychroa*, and marine cyanobacteria.

In perspective, cyanobacteria from Algerian ecosystems should be explored for their anticancer activities.

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