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Marine Cyanobacteria-Assisted Metallic Nanoparticles: A Review on Anticancer Activity and Mechanism of Action

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Marine cyanobacteria, known as blue-green algae, are ancient microorganisms with oxygenic photosynthetic capability. They have diverse biochemical capabilities, including production of bioactive secondary metabolites. We studied the anti-cancer properties of cyanobacterial nanoparticles through various literatures. We focused on mechanistic studies of the anticancer properties of metal and metal oxide nanoparticles. Our research gathered information from patent

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databases, conference abstracts, publications, and news releases, as well as PubMed searches for peer-reviewed articles and Google searches for gray literature. We used strict criteria for selecting sources, and our search ended on 30 October, 2022. Metal nanoparticles, such as gold and silver, have unique physicochemical properties, making them suitable for therapeutic applications in nanomedicine. Cyanobacteria-assisted synthesis is environmentally sustainable and results in mild reaction conditions and minimal toxic byproducts. These nanoparticles have potential applications in cancer therapy, including drug delivery systems and targeted therapies. This study further explored the mechanistic aspects of cancer development, emphasising the role of genetic mutations, uncontrolled cell growth, and metastasis. Cyanobacterial biogenic nanoparticles demonstrate cytotoxicity, apoptosis induction, ROS generation, and immunomodulation, contributing to their anticancer efficacy. Additionally, these nanoparticles serve as carriers for drug delivery, enabling the targeted and controlled release of therapeutic agents. The review ends by emphasising how crucial it is to comprehend how cyanobacteria extract assists metallic nanoparticles. Cyanobacterial biogenic synthesis using microemulsion synthesis methods, UV-initiated photoreduction, microwave assistance, and polymer/polysaccharide-mediated approaches was investigated. The field of marine cyanobacteria, biogenic metal nanoparticles, and their anticancer potential is dynamic and has important implications for future therapeutic approaches.

Keywords: Marine cyanobacteria; nanomaterials; anticancer; drug delivery systems; secondary metabolites.

1. INTRODUCTION

Marine cyanobacteria, often referred to as blue-green algae, are fascinating microorganisms that play a crucial role in the Earth's ocean (Dai et al., 2013). These microscopic photosynthetic organisms belong to the phylum Cyanobacteria and are among the oldest known life forms on our planet. Their existence dates back billions of years, showcasing their resilience and adaptability. One of the distinctive features of marine cyanobacteria is their ability to perform oxygenic photosynthesis, a process that utilises sunlight to convert carbon dioxide into organic compounds while releasing oxygen as a byproduct (Mutalipassi et al., 2021). Production of secondary metabolites by marine cyanobacteria is a fascinating aspect of their biochemistry, offering unique compounds with potential applications in various fields. Marine cyanobacteria have been found to produce a wide array of secondary metabolites, demonstrating their biochemical diversity. These compounds can be classified into various groups including alkaloids, peptides, polyketides, and terpenes. Each group had a distinct chemical structure and biological activity (Salvador-Reyes and Luesch, 2015). Secondary metabolites produced by marine cyanobacteria have shown promise for their potential benefits. Some cyanobacteria produce bioactive compounds that have pharmaceutical applications. For example, compounds with anti-inflammatory, antiviral, and anticancer properties have been identified. These compounds are of great interest to researchers for the development of new drugs and treatments (Tan, 2007).

Secondary metabolites from marine cyanobacteria have unique chemical structures that make them valuable for biotechnological applications. For example, some cyanobacterial compounds have been explored for their potential use in the development of new materials or as leads for the synthesis of novel chemicals. The production of secondary metabolites by marine cyanobacteria is influenced by various environmental factors including nutrient availability, light conditions, and interactions with other organisms. Understanding the regulation of secondary metabolite production is crucial for optimising conditions for large-scale cultivation of cyanobacteria and harnessing their bioactive compounds for practical applications (Tan, 2007).

Metallic nanoparticles have emerged as promising candidates for therapeutic applications because of their unique physicochemical properties, which differ significantly from those of their bulk counterparts. These nanoparticles, typically in the range of 1–100 nm, exhibit enhanced surface area, reactivity, and novel optical, magnetic, and catalytic properties (Sharma et al., 2016). The application of metallic nanoparticles in medicine, known as nanomedicine, has opened new avenues for diagnosis, imaging, and treatment. Metallic nanoparticles are employed as carriers for drug delivery, facilitating the targeted and controlled release of therapeutic agents. Their size and surface properties can be tailored to enhance the bioavailability of drugs, improve their solubility, enable sustained release, minimise side effects,

and increase their therapeutic efficacy. Gold and silver nanoparticles have been extensively studied for use in cancer therapy. These nanoparticles can be functionalized with targeting ligands to specifically accumulate in tumour tissues. Once localised, they can be used for photothermal therapy, where they absorb light and convert it into heat, selectively destroying cancer cells (AlNadhari et al., 2021). Additionally, metallic nanoparticles can be loaded with anticancer drugs for combination therapies.

Microbial-assisted synthesis of metal nanoparticles harnesses the unique capabilities of microorganisms for environmentally sustainable and controlled nanoparticle production (Vinardell et al., 2015). Bacteria, fungi, and algae serve as natural bio-factories, reducing metal ions to nanoparticles and providing an eco-friendly alternative to conventional chemical methods (Rana et al., 2020). This approach offers advantages, such as mild reaction conditions, minimal toxic byproducts, and scalability. The resulting microbial-assisted metal nanoparticles have applications in diverse fields, including catalysis, sensing, medicine, and environmental remediation, highlighting the significance of this green synthesis method in advancing sustainable nanotechnology (Tan, 2007).

We conducted a systematic examination of cyanobacterial biogenic synthesis of metallic nanoparticles and their anti-cancer significance. This review focuses on mechanistic studies that explain the anti-cancer properties of various metal and metal oxide nanoparticles, such as silver, gold, zinc oxide, titanium dioxide, and selenium. The report also provides a clear overview of key attributes, including stability and specific targeting, that contribute to the effectiveness of metallic anticancer nanoparticles. Our research encompassed patent databases, conference abstracts, publications, and news releases to gather information on eco-friendly synthesis and anticancer potential. To supplement these sources, we also conducted PubMed searches for peer-reviewed journal articles and Google searches for grey literature. The green approach to silver nanoparticle synthesis is environmentally friendly, non-toxic, and cost-effective, and it makes use of a variety of biological entities. Cyanobacteria, in particular, have garnered the most attention because of the abundance of bioactive substances that they contain, which serve both as reducing agents and as stabilizing agents during the process of biosynthesis (Maheswari et al., 2024).

2. CANCER

Cancer is a cluster of diseases involving unrestrained and abnormal cell growth. This process becomes disordered in cancer, with abnormal cells continuing to divide and form a mass of tissue called a tumour. Uncontrollable growth and spread of these abnormal cells can hinder the body's regular functions and can be fatal if left untreated (Reyes-Gibby et al., 2013).

2.1 Cancer Cause Mechanism

Cancer development involves complex cellular and molecular mechanisms. Changes in the DNA sequence of genes can lead to cancer development. Mutations may be inherited or acquired due to exposure to carcinogens such as tobacco smoke, UV radiation, or certain chemicals. Genetic mutations are changes in the DNA sequence of an organism's gene. These mutations can occur for various reasons and can have different effects. Mutations play a significant role in cancer initiation and progression (Li et al., 2014). There are some key points regarding genetic mutations in the context of cancer: mutations occur in the DNA of somatic cells, which are non-reproductive cells. Somatic mutations are not passed on to offspring and are responsible for the development of cancer within an individual. Mutations occur in the DNA of germ cells and can be inherited from parents. In some cases, individuals with inherited germline mutations may have a higher risk of developing certain types of cancers. Mutations that activate oncogenes can promote cell growth and division. Normally, these genes regulate cell growth, but when mutated, they can contribute to the uncontrolled growth observed in cancer. Mutations that inactivate tumour suppressor genes eliminate normal constraints on cell growth. Tumour suppressor genes play a crucial role in preventing cancer development by inhibiting cell division or promoting cell death. Mutations in genes involved in DNA repair can lead to accumulation of additional mutations. This can contribute to genomic instability, which is a hallmark of many cancer types. Exposure to certain environmental factors such as tobacco smoke, UV radiation, and certain chemicals can increase the likelihood of DNA mutations. These environmental factors are known to be carcinogens. Driver mutations directly contribute to the development of cancer by conferring a growth advantage to affected cells. Passenger

mutations, on the other hand, are incidental and do not drive cancer development, but may accumulate alongside driver mutations. Uncontrolled cell growth lies in the heart of cancer, disrupting the finely tuned orchestration of cellular processes. In this aberrant scenario, normal regulatory mechanisms govern cell division, propelling cells into a relentless cycle of unbridled proliferation. Oncogenes, when activated, fuel this growth, while the loss of function of tumour suppressor genes relinquishes the natural checks on cellular expansion (Weber et al., 2013). The cell cycle, intricately choreographed in healthy cells, succumbs to dysregulation, and signals that would typically inhibit growth are ignored. Furthermore, cancer cells become adept at resisting programmed cell death, acquiring stubborn resilience that contributes to their survival and perpetual division. This intricate dance of genetic and molecular irregularities underscores the formidable challenge of reinforcing the uncontrolled growth that characterizes cancer. Cancer cells can stimulate the formation of new blood vessels (angiogenesis) to supply nutrients and oxygen to the growing tumour. This helps cancer cells survive and proliferate. Cancer cells can break away from the primary tumour, enter the bloodstream or the lymphatic system, and travel to other parts of the body. This process is known as metastasis, and is a major factor in the spread of cancer. Cancer cells may develop mechanisms to evade detection and destruction by the immune system. This allows them to thrive and avoid being eliminated by their body's natural defences. Cancer cells often exhibit high levels of genomic instability, which leads to genetic mutations. This instability contributes to the adaptability of cancer cells and their ability to resist treatments (Lim et al., 2014). Understanding these mechanisms is crucial for the development of targeted therapies and interventions to treat and prevent cancer. Researchers have continually explored these processes to uncover new insights and to improve cancer treatment strategies.

2.2 Chemical Methods for Synthesis of Biogenic Cyanobacterial Metallic Nanoparticles

Biogenic synthesis of cyanobacterial metal nanoparticles by microemulsion: Cyanobacterial biogenic nanoparticles synthesised using the microemulsion method represent a convergence of green synthesis and nanotechnology (Walczak et al., 2013). This method harnesses the principles of microemulsion, a stable dispersion of oil and water stabilised by surfactants, to facilitate the eco-friendly synthesis of nanoparticles using biological entities such as cyanobacterial microorganisms. The importance of this approach lies in its potential to provide sustainable and biocompatible nanoparticles with applications ranging from medicine to environmental remediation. In the microemulsion method for cyanobacterial biogenic nanoparticle synthesis, water, oil, and biologically active molecules are combined with surfactants. The microemulsion provided a controlled environment for the reduction and stabilisation of metal ions, resulting in the formation of nanoparticles. This process offers advantages such as precise control over the particle size, improved reaction kinetics, and the ability to tailor the properties of nanoparticles for specific applications. One of the advantages of cyanobacterial biogenic nanoparticles synthesised using the microemulsion method is the green and sustainable nature of the process (Jahangirian et al., 2019). Unlike traditional chemical methods, which often involve harsh chemicals and energy-intensive processes, the microemulsion method utilises natural extracts or microorganisms, aligned with the principles of green chemistry. This eco-friendly approach reduces the environmental impact of nanoparticle synthesis, making it an attractive alternative for industries striving for sustainability.

Cyanobacterial biogenic synthesis of metal nanoparticles by UV-imitation photoreduction: The synthesis of biogenic cyanobacterial metal nanoparticles through UV-initiated photoreduction represents a cutting-edge approach at the intersection of green synthesis and nanotechnology. In this method, the reducing potential of biological entities such as cyanobacterial microorganisms is harnessed under the influence of ultraviolet (UV) light. UV initiation accelerates the reduction process, allowing for rapid and efficient synthesis of metal nanoparticles with controlled sizes and shapes. This method not only provides versatility in the selection of metal precursors but also ensures the sustainability and biocompatibility of the resulting nanoparticles (Elbialy et al., 2014). The synthesised nanoparticles hold promise for applications ranging from photocatalysis and photothermal therapy to antimicrobial coatings and environmental remediation, highlighting the multifaceted significance of this innovative synthesis approach (Li, R., Chen et al. 2013).

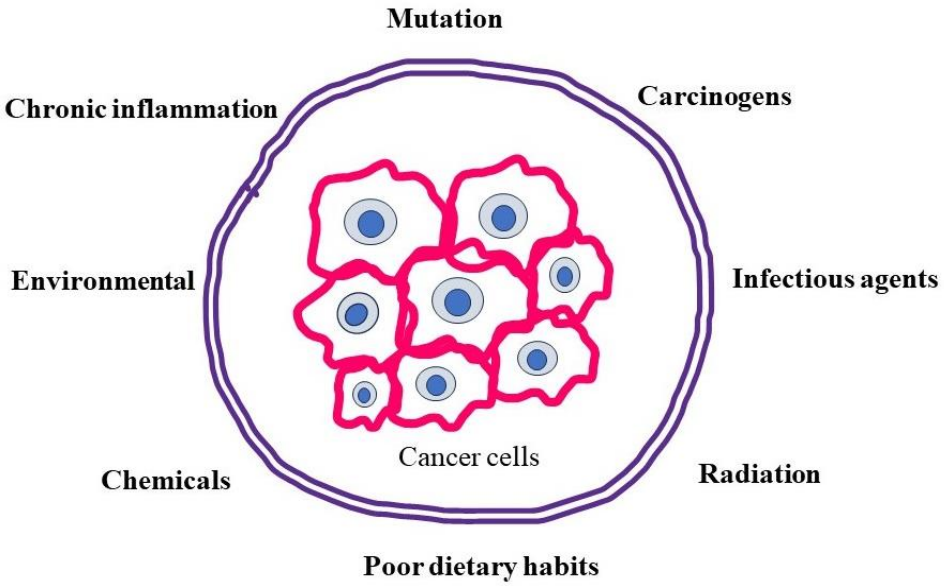

Fig. 1. Cancer casing

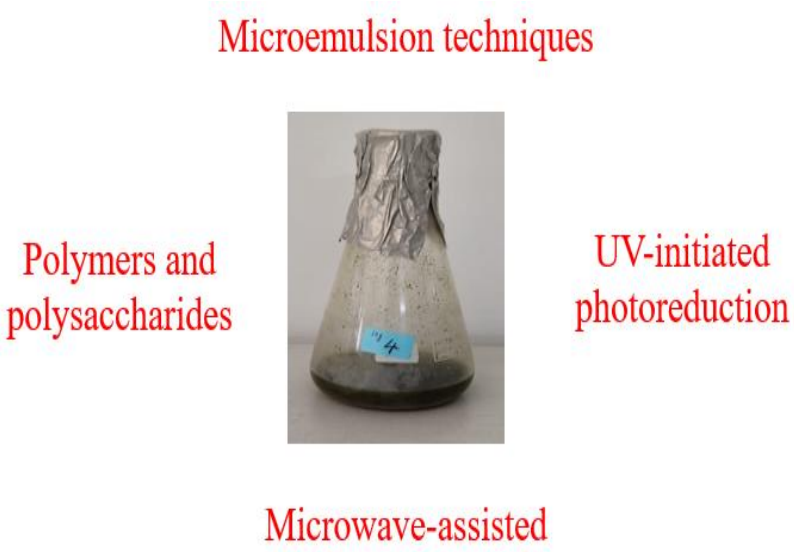

Fig. 2. Chemical methods used for the synthesis of cyanobacterial biogenic nanoparticles

Cyanobacterial biogenic synthesis of cyanobacterial metal nanoparticles by microwave-assisted: The microwave-assisted synthesis of cyanobacterial biogenic metal nanoparticles combines the principles of green synthesis with the rapid and controlled heating capabilities of microwaves. This innovative approach accelerates the reduction of metal ions by biological entities such as plant extracts or microorganisms, resulting in the rapid and efficient production of nanoparticles (Zhang et al., 2014). Controlled heating allows for tunability of particle size and morphology, which is a critical factor in tailoring nanoparticles for specific applications. This method not only offers energy efficiency but also ensures biocompatibility, making the synthesised nanoparticles suitable for diverse applications in medicine, catalysis, and environmental technologies. Microwave-assisted synthesis is a promising and sustainable method for green nanotechnology (Lakshmanan et al., 2017).

Biogenic synthesis of cyanobacterial metal nanoparticles by polysaccharide of polymer method: The synthesis of cyanobacterial biogenic metal nanoparticles through the polymer or polysaccharide method represents a

noteworthy intersection of green synthesis and nanotechnology. By harnessing the reducing potential of natural polymers or polysaccharides such as chitosan or starch, this method provides a sustainable and environmentally friendly route for nanoparticle synthesis (Lakshmanan et al., 2017). These biogenic cyanobacterial nanoparticles exhibit biocompatibility, making them particularly suitable for applications in medicine, including drug delivery systems and imaging. The versatility of this approach allows for the controlled manipulation of nanoparticle characteristics such as size and morphology, offering tailored properties for specific applications. Additionally, the environmentally benign nature of the process aligns with green synthesis principles, contributing to the development of eco-friendly nanotechnologies with potential applications in biotechnology, catalysis, and other fields (Das and Brar, 2013).

Biogenic synthesised cyanobacterial nanoparticles and its anticancer activity mechanism: Biogenically synthesised nanoparticles, particularly those derived from natural sources, have gathered attention for their potential anticancer properties. These nanoparticles are often synthesised using extracts from plants, fungi, and bacterial biological materials. The anticancer activity of these nanoparticles is attributed to their unique physicochemical properties and interactions with cancer cells (Bethu et al., 2018).

Cytotoxicity and Apoptosis Induction: Biogenic nanoparticles can induce cytotoxic effects on cancer cells, leading to their death. They may trigger apoptosis, a programmed cell death mechanism crucial for maintaining cellular homeostasis. Nanoparticles can modulate signalling pathways involved in apoptosis, promoting the selective elimination of cancer cells (Thangam et al., 2013).

ROS Generation: Reactive oxygen species (ROS) play a role in cell signalling and induce apoptosis. Biogenic nanoparticles can enhance ROS production within cancer cells, causing oxidative stress and ultimately leading to cell death (Bleier and Dröse, 2013).

Cellular Uptake and Targeting: The unique surface characteristics of biogenic nanoparticles enable their efficient cellular uptake. Once inside cancer cells, these nanoparticles may interfere with vital cellular processes, disrupt cellular structures, or release cytotoxic agents, selectively targeting cancer cells while sparing healthy cells (Nagano et al., 2013).

Inhibition of Angiogenesis: Biogenic nanoparticles can interfere with angiogenesis, which is the formation of new blood vessels that the tumour relies on for nutrient supply. By inhibiting angiogenesis, these nanoparticles limit the ability of the tumour to grow and metastasise. Apoptosis or programmed cell death is a fundamental process that regulates tissue homeostasis by eliminating damaged or unwanted cells. Nanoparticles can modulate apoptotic pathways and influence cell survival and death. Nanoparticles induce apoptosis by affecting the mitochondrial pathway. They may disrupt mitochondrial function, leading to the release of pro-apoptotic factors and the activation of caspases, which are key enzymes in the apoptotic cascade. Nanoparticles may engage death receptors on the cell surface, initiating the extrinsic pathway of apoptosis. This pathway involves the activation of caspases through receptor-ligand interactions (Weeraratne et al., 2013).

Immunomodulation: Cyanobacterial biogenic nanoparticles have immunomodulatory effects that enhance the body's immune response against cancer cells. This includes the activation of immune cells such as T lymphocytes and natural killer (NK) cells, which contribute to the destruction of cancer cells (Yazdi et al., 2015).

Drug Delivery-Metal Nanoparticles: Cyanobacterial biogenic nanoparticles can serve as carriers for anticancer drugs, improving drug solubility, stability, and targeted delivery to cancer cells. Targeted drug delivery minimises the damage to healthy tissues and enhances the therapeutic efficacy of drugs. Nanoparticles play a crucial role in drug delivery owing to their unique properties and capabilities (Georgantzopoulou et al., 2013).

Targeted Drug Delivery: Nanoparticles can be engineered to carry drugs to specific target sites in the body, such as tumour tissues. This targeted delivery minimises damage to healthy cells and tissues, enhancing the therapeutic effect of the drug while reducing its side effects. Targeted drug delivery using nanoparticles is a sophisticated approach that aims to deliver therapeutic agents specifically to the site of action within the body. This strategy offers several advantages over conventional drug delivery methods (Swiech et al., 2013).

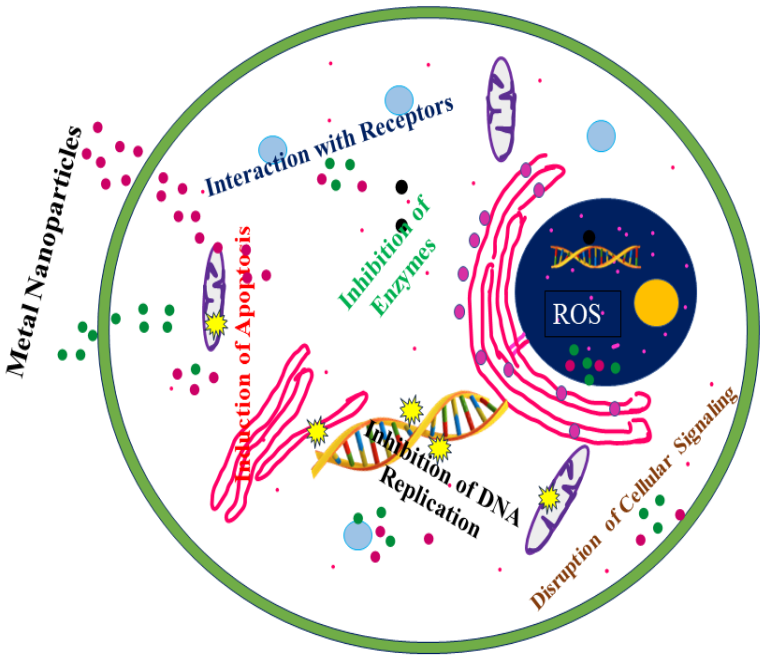

Fig. 3. Nanoparticle anticancer activity mechanism

Site-Specific Targeting: Nanoparticles can be engineered to specifically target certain cells or tissues. Ligands, such as antibodies or peptides, can attach to the surface of nanoparticles. These ligands recognise and bind to specific receptors on target cells, ensuring precise delivery of the drug to the intended site. Nanoparticles can take advantage of the enhanced permeability and retention effect, which is prominent in certain pathological conditions such as tumours. Owing to leaky blood vessels and impaired lymphatic drainage in these areas, nanoparticles tend to accumulate selectively in the target tissues, enhancing drug delivery to the site of the disease. By delivering drugs directly to the target site, nanoparticles minimise exposure to healthy tissues and organs. This targeted approach reduces the side effects associated with systemic drug administration, making treatment more tolerable for patients.

Nanoparticles can facilitate the intracellular delivery of drugs, allowing them to reach targets inside cells. This is particularly important for drugs that act on specific intracellular organelles or signalling pathways. Nanoparticles can be designed to release drugs in a controlled manner. Factors such as pH, temperature, and enzymatic activity in the target environment can trigger the release of the drug from nanoparticles, providing a tailored and sustained therapeutic effect (Mei et al., 2016).

Multiple drug carriers: Nanoparticles can simultaneously carry multiple drugs or therapeutic agents. This enables combination therapy, in which different drugs with complementary mechanisms of action are delivered together to enhance efficacy and overcome resistance. Nanoparticles can incorporate imaging agents, allowing simultaneous diagnostic imaging and therapeutic interventions. This integration enables real-time monitoring of drug delivery and treatment responses. The design of targeted nanoparticles can be customised based on the specific characteristics of a patient's disease. This personalised approach has potential for more effective and individualised treatment strategies (Demir and Forgan, 2021).

Control released: Many drugs have limited water solubility, which can affect their bioavailability. Nanoparticles can encapsulate poorly soluble drugs, improve their solubility, and enhance their absorption in the body. Nanoparticles can be designed to release drugs in a controlled and sustained manner. This prolonged release profile can reduce the frequency of drug administration, improve patient compliance, and maintain therapeutic drug levels over extended periods. Drug nanoparticles can protect drugs from degradation, metabolism, and premature release in the body. This protection helps to maintain the stability and effectiveness

of the drug until it reaches the target site. The small size of the nanoparticles allows for efficient cellular uptake. This is particularly important for drugs that need to reach their intracellular targets. Nanoparticles can facilitate drug delivery into cells, thereby improving the overall efficacy of treatment (Rushworth and Megson, 2014).

Permeability Enhancement: Nanoparticles can exploit the enhanced permeability and penetration effect, which is the tendency of nanoparticles to accumulate in tumour tissues owing to their leaky blood vessels. This phenomenon enhances the selective delivery of drugs to tumour sites. Nanoparticles can be designed to carry multiple therapeutic agents, allowing for combination therapy. This is especially valuable in cancer treatment, where a combination of drugs may target different aspects of tumour growth and overcome drug resistance. Nanoparticles can serve as contrast agents for imaging techniques, aiding in the diagnosis and monitoring of various diseases. In addition, they can be engineered to respond to specific stimuli, enabling the detection of physiological changes in the body. The versatility and tunability of nanoparticles make them a promising tool in drug delivery, offering solutions to the challenges associated with conventional drug administration. Ongoing research in nanotechnology continues to advance the design and application of nanoparticles in drug delivery systems, with the potential to revolutionise therapeutic approaches across various medical fields (Fei et al., 2013).

3. CONCLUSION

Marine cyanobacteria are photosynthetic microorganisms that produce a wide array of secondary metabolites. These compounds have unique chemical structures and biological activities, and have shown promise for their potential benefits. Some cyanobacterial compounds have anti-inflammatory, antiviral, and anticancer properties, which make them of great interest to researchers for the development of new drugs and treatments. Biogenic and cyanobacterial metallic nanoparticles have unique physicochemical properties and are used in medicine for therapeutic applications. Gold and silver nanoparticles have been extensively studied for use in cancer therapy. This review focuses on mechanistic studies that explain the anti-cancer properties of various metal and metal oxide nanoparticles and provides a clear overview of the key attributes that contribute to the effectiveness of metallic anticancer nanoparticles. This article encompassed patent databases, conference abstracts, publications, and news releases to gather information on eco-friendly synthesis and anticancer potential. The metal nanoparticles, cyanobacteria and its anticancer activity has important role in future therapeutic purposes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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