

Marine Sponge Assisted Metallic Nanoparticles and its Biological Activity and its Mechanism

Shilpa Valiyaparambil*, Amal Jaseem Kuvapra, Naheema Farhath Kundil, Hanna Vadakkan, Huda Karumannil, Sirajudheen Mukriyan Kallungal

Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, Kerala, INDIA.

ABSTRACT

Background: This study presents a systematic analysis of the biogenic synthesis of metallic nanoparticles and their significant biological activities, including anti-inflammatory, antioxidant and anticancer properties. **Aim:** Green synthesis methods, utilizing various biological materials, such as plant extracts and marine sponges, offer environmentally friendly approaches for the production of metallic nanoparticles with specific biological functions. **Methodology:** Synthesized nanoparticles, including silver, gold, zinc oxide and titanium dioxide, exhibit promising therapeutic potential against skin cancer, inflammation and oxidative stress. **Results:** Skin cancer, particularly melanoma and non-melanoma types, is discussed alongside the anatomy of normal skin, diagnostic techniques such as skin biopsy and pathophysiology of skin cancer. Furthermore, this study delves into the mechanisms of inflammation and the roles of metallic nanoparticles in modulating inflammatory responses, emphasizing their potential in targeted therapy. Additionally, the anti-cancer action of metallic nanoparticles, especially in enhancing drug delivery and therapeutic efficacy, has been elucidated. Moreover, the antioxidant properties of metallic nanoparticles and their implications for mitigating oxidative stress-related diseases are discussed. **Conclusion:** Study underscores the importance of metallic nanoparticles in biomedical applications, offering insights into their synthesis, characterization and therapeutic potential across various pathological conditions.

Keywords: Metallic nanoparticles, Green synthesis, Skin cancer, Inflammation, Antioxidant.

Correspondence:

Mrs. Shilpa Valiyaparambil

Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram-673637, Kerala, INDIA.
Email: shilpavp24@gmail.com

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INTRODUCTION

Over the past 20 years, there has been a significant increase in the use of nanotechnology. According to the National Nanotechnology Initiative, structures that fall roughly around the 1-100 nm scale in no less than one direction are considered nanotechnology. Materials are designed and produced using nanotechnology at the atomic and molecular levels.¹ Nanoparticles have emerged as highly promising instruments, with an assortment of applications in medical delivery, diagnosis, skincare products and numerous other biotic and non-biological sectors. Nanoparticles exhibit a range of characteristics based on their dimensions and exterior functions. Nanoparticles are widely used in multiple fields, including electronics, skin care products and both therapeutic and diagnostic medical applications. This is because of the large area they cover and their small stature.² Plants are considered bioreactors for the creation of metal nanoparticles. A range of chemical and physical approaches have been used to produce

metal nanoparticles with the required properties. Conifers possess particular qualities for the creation of metal nanoparticles. A biological synthesis method that is effective, trouble-free, affordable and environmentally benign is called "Green synthesis" for metallic nanoparticles. Metal oxides and pure metals are both included in metallic nanoparticles, which have a variety of benefits.³ In the field of medical science and illness therapy, the creation of biologically inspired green production of AgNPs has garnered significant attention globally. The environmentally friendly production of AgNPs is used to treat cancer and germs resistant to antibiotics.⁴ Among the several metallic nanoparticles employed for biomedical applications, one of the most significant and fascinating nanomaterials is AgNPs. AgNPs are crucial in nanoscience and nanotechnology, especially in nanomedicine. Although several valuable metals have been used for diverse purposes, silver nanoparticles are drawing attention because of their potential use in the detection and therapy of cancer. AgNPs have become increasingly prevalent in a range of industries, including the food, pharmaceutical, medical, consumer and industrial sectors, owing to their distinctive chemical and physical characteristics. Multiple biological and therapeutic applications of AgNPs include anti-bacterial, anti-viral, anti-fungal, anti-inflammatory, anti-cancer and anti-angiogenic properties.⁵



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Marine sponges are porous protozoans of the phylum Porifera that are multicellular and filter-feeders. The sessile creatures were sponges. Marine sponges yield more than 5,000 naturally occurring chemicals.⁶ Currently, marine sponges are the richest source of potent anticancer substance is marine sponges.⁷ Marine sponges are among the best sources of naturally occurring bioactive substances with potential applications in medicine.⁸ Certain medications made from marine sponges have been shown to affect Hodgkin's disease, malignant lymphoma and metastatic breast cancer.⁹ There are numerous applications for metabolites from bacteria, fungi and algae that live on sponges in cosmetics, medicine and environmental preservation. Microorganisms found in sponges produce substances with anti-viral, anti-oxidant, anti-inflammatory, anti-cancer and anti-bacterial properties. Moreover, alkaloids with pharmacological properties have been obtained from marine sponges.¹⁰

METHODOLOGY

In this study, we first performed a systematic analysis of the biogenic synthesis of metallic nanoparticles.¹¹ In addition, they exhibit anti-inflammatory, anti-oxidant and anticancer activities. Green synthesized nanoparticles are now employed to inhibit the expression of proinflammatory cytokines and ROS scavenging methods by suppressing the NF- κ B and COX-2 pathways.¹² Various metal and metal oxide nanoparticles, such as platinum,¹³ silver,¹⁴ titanium dioxide,¹⁵ gold,¹⁶ and zinc oxides,¹⁷ have certain biological activities. Silver-fortified Sponge (AFS) spheres were successfully synthesized after method optimization using various extracts of marine sponges. Gram-positive and gram-negative bacteria are effectively inhibited by growth by AFS, which are precisely spherical, micro-sized and effective. 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl Tetrazolium bromide (MTT) and morphological alterations were used to evaluate the cytotoxic response of AFS. The patent database, conference abstracts, publications, news releases and current pipeline

reviews were analyzed to provide a wealth of knowledge on the environmentally friendly synthesis of metallic

Skin Cancer

Skin cancer is the most prevalent type of cancer worldwide. Most skin cancers are not melanomatous. Melanoma arises when the pigment-producing cells of the skin exhibit malignant tendencies. Prolonged exposure to Ultraviolet (UV) radiation is the primary risk factor. When an older, fair-skinned person develops scaly, indurated lesions on sun-exposed areas, especially the head and neck, diagnosis is typically assumed. With a dermatoscope, proper lighting and magnification, clinical diagnosis accuracy can be improved. For a conclusive diagnosis, biopsy along with histopathological confirmation is required. Because the depth of the lesions determines how the cancer will be treated and how long it will last, a full-thickness biopsy is necessary for melanoma evaluation. Globally, there has been an increase in the number of instances of skin cancer among all types.¹⁹

Anatomy of normal skin

Clinicians need to have a fundamental understanding of the skin to properly comprehend skin cancer. The layers of the epidermis, reticular and papillary dermis and subcutaneous fat comprise normal skin. Four major cell types and four sublayers constitute the epidermis. Over the course of 30 days, actively dividing cells or keratinocytes undergo several stages of maturation, which are represented by these sublayers.²⁰

Skin biopsy

Skin biopsy is an important diagnostic technique for cutaneous malignancies. It can also be helpful for the detection of infectious and inflammatory diseases when used in conjunction with clinicopathological correlations. Biopsy is performed to indicate suspected neoplastic lesions, bullous disorders (a rare skin condition that causes large, fluid-filled blisters) and if the

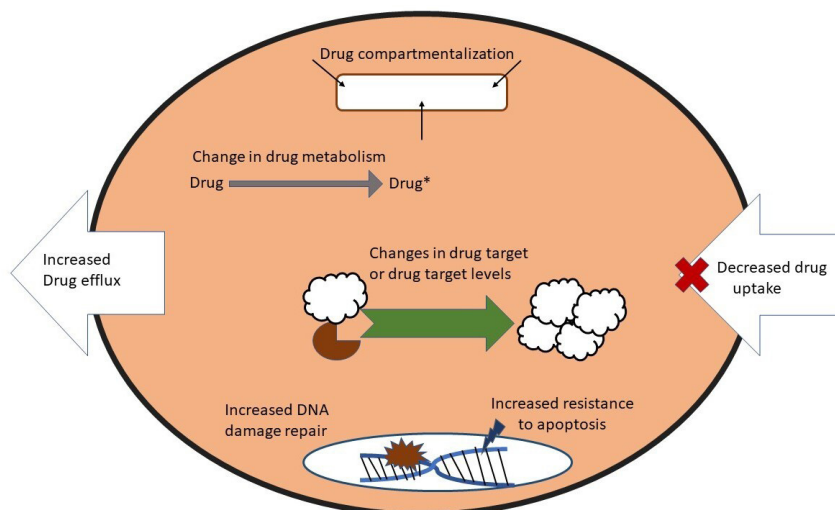


Figure 1: Drug resistance possible mechanisms in cancer cells.

diagnosis is not cleared and/or for therapeutic treatment. The site selected for biopsy has the following properties: thickest, most pigmented area, area with the most inflammatory changes and newly formed vesicles should be chosen for blistering lesions. There are three types of skin biopsy is present, they are punch biopsy, shave biopsy and excision biopsy.

Skin cancer pathophysiology

Skin cancer has a multifactorial etiology. The primary causative factor for the formation of NMSC and malignant melanoma is UVR from sunshine. UVA and UVB are the two primary subtypes of Ultraviolet (UV) radiation. Compared with UVB rays, UVA rays can cause deeper skin damage (Figure 1), such as elastosis, because they can penetrate the skin more deeply. Sunburn and erythema are the main effects of UVB irradiation. Inflammatory reactions, oxidative stress, immuno suppression, DNA damage and gene alterations are all induced by UVR.²⁰

Types of cancers

Malignant melanoma and Non-Malignant Squamous Cell carcinoma (NMSC), of which Basal Cell carcinoma (BCC) and Squamous Cell Carcinoma (SCC) are the two most common types of skin cancers. Because BCC and SCC cases are exempt from reporting requirements to national registries, it is challenging to estimate the true number of NMSC.¹⁹

Basal cell carcinoma

BCC cancer initiates growth in the epidermal basal layers and auxiliary cells. This cancer growth will be present in almost all the places in the human body and exclusively, frequently visible open skin areas such as the nose, ears and cheeks, where most of the sun's UV light will fall. This type of cancer is inactive and rarely spreads slowly throughout the body.

Squamous cell carcinoma

Cutaneous SCC is the second most common type of skin cancer worldwide. Epidermal keratinocytes proliferate in a malignant and controllable manner, leading to cutaneous SCC. Similar to BCC, UV exposure is the primary cause of SCC. An estimated 20% of the occurrences of nonmelanoma skin cancer in the US are thought to be SCC instances.

Melanoma

Melanoma is an aggressive malignant tumor that originates in melanocytes. Epidermal melanocytes are present in the basal layer. A buildup of genetic alterations that activate oncogenes inactivates tumor suppressor genes and impedes DNA repair when exposed to ultraviolet radiation. Melanoma may result from these pathways, as melanocytes proliferate uncontrollably.¹⁹

Enzyme involved in cancer treatment

A few specific enzymes play a role in identifying cancer cells and in eliminating and killing these cells. Enzymes degrade the environment surrounding cancer cells.²¹ The enzymes glutaminase, phenylalanine ammonia lyase, lysin oxidase and methionase are utilized in cancer treatment.²² Dihydropyrimidine Dehydrogenase (DPD) is one of the enzymes used in chemotherapy to break down the medications fluorouracil and capecitabine. 5,6-dihydrothymine are produced when uracil and thymine are reduced by the DPD enzyme.²³ Drug-metabolizing enzymes play a role in cancer and cancer therapy by metabolizing medications that can boost their effectiveness. Consequently, drugs are processed in tumors and metabolic organs with the aid of drug-metabolizing enzymes.²⁴

Skin cancer is prevented by avoiding sun exposure, use of full-length clothing that covers exposed skin, use of hats and sunglasses and use of broad-spectrum (UVA/UVB) sunscreens and unblocks with frequent reapplications.¹⁹

Inflammation

Infection or other types of damage can cause inflammation in any part of the body, leading to redness, pain, swelling and other symptoms. It is thought to be a pathological cornerstone. Because of the favorable host reaction, cellular homeostasis, tissue form and function are restored. Infections, wounds and tissue damage cannot heal without an inflammatory response (Figure 2). Innate and adaptive immune responses are the two main mechanisms of host defence that control this reaction. Granulocytes, phagocytes and other cells are involved in the adaptive immune response, whereas the innate immune response is the initial reaction of the host to any foreign substance. The hallmark of adaptive immunity, which aids in the early stages of infection, is specific. There are situations in which the inflammatory response can persist longer than necessary and cause more harm. As more blood must be delivered to the injured area, the small artery branches that supply it swell. Redness and heat are produced by increased blood flow through dilated arteries, which are transported by an increase in the erythrocyte count. Increased phagocytic cell infiltration in this region causes swelling and discomfort. When a host with a functioning innate immune system interacts with external stimuli, inflammation usually begins within minutes.²⁵ As innate immunity is the primary cause of inflammation, both immune and non-immune cells, including fibroblasts and endothelial cells, contribute to the inflammatory process. Immune cells include neutrophils, mast cells, macrophages, dendritic cells and Endothelial Cells (ECs). Depending on the type of stimulation, inflammatory pathways and target tissues are activated. Inflammation has a set duration that varies according to the extent of damage caused by inflammation. Extended inflammation also has a systemic effect: elevated levels of cytokines and coagulation factors cause hepatocytes to produce

prostaglandins and acute-phase proteins such as C-reactive protein, which affect the central nervous system and cause pain, exhaustion and fever. Acute inflammation is more localized and less severe than chronic inflammation, which arises when pathogens causing acute inflammation are not eliminated.²⁶

Methods for synthesis of metallic nanoparticles

Metallic nanoparticles have unique properties that make them useful for a variety of applications.²⁷ Metallic nanoparticles can be synthesized using a variety of physical and chemical approaches. Principal methodologies include green synthesis, top-down and bottom-up techniques.

Green synthesis

Green synthesis is one of the most effective methods for creating metallic nanoparticles is green synthesis. Plant extracts, fungi, bacteria and other biological materials can be processed using green synthesis. The availability of phytoconstituents in specified species, such as ascorbic acid, carboxylic acid, phenols, aldehydes, ketones, flavones, amides and terpenoids, must be considered in order to synthesize metallic nanoparticles.²⁸ Metal salts can be reduced to metal nanoparticles. This technique is safer for the environment, uses safe solvents, lowers pollution and prevents the formation of harmful byproducts.

Mechanism for metals and their oxides

Through various processes, distinct microorganisms can be used to form different nanoparticles. Through the influence of electrostatic interactions between silver ions and negatively charged enzymes on the cell wall, silver ions are introduced onto the surface of fungal cells. Silver ions are subsequently

reduced to the corresponding nuclei and grow as separate silver nanoparticles.²⁹

Top-down technique

Metallic nanoparticles are produced from the bulk of materials, which involves the use of physical methods and employs mechanical energy, which is used in grinding, milling and crushing, as well as electrical energy used in the electrical arc discharge and thermal energy. The nanoparticles obtained using this technique have sizes in the range of 10-100 nm.³⁰ The nanoparticles were of high purity and had a uniform size distribution.

Bottom-up technique

This involves the formation of complex clusters and the nucleation and growth processes. They commonly use chemical and biological syntheses.³¹

Characterization

Numerous nanoparticles created using environmentally friendly methods have been characterized using a range of techniques such as Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), X-ray Diffraction (XRD) and spectroscopic techniques such as UV-vis and FT-IR.³²

Silver nanoparticles

They have a wide variety of applications in various fields, such as industry, food and biomedicine. AgNPs have multiple biological and therapeutic applications, including antifungal, antibacterial and anti-inflammatory activities.³³

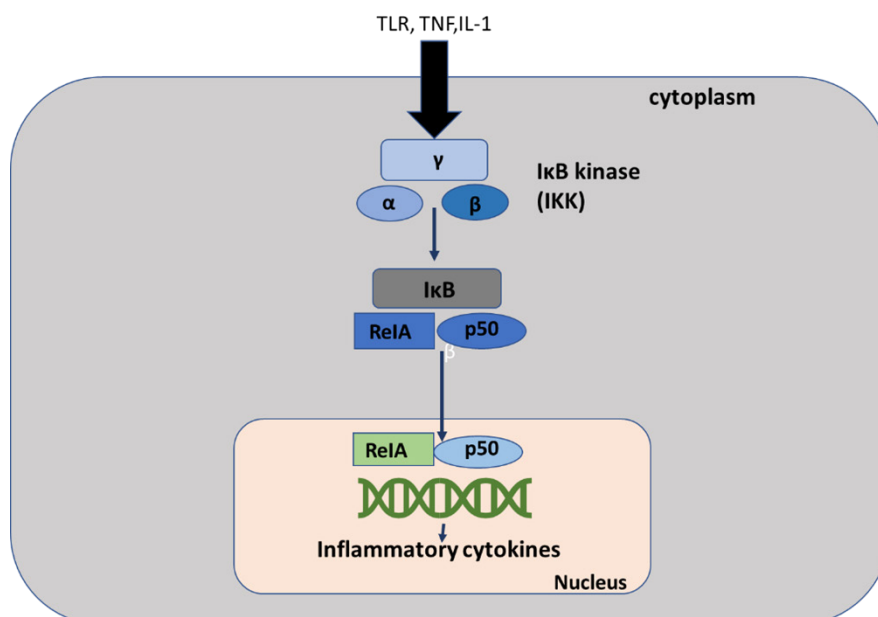


Figure 2: Mechanism of Inflammation.

Zinc oxide nanoparticles

They are widely used in medical applications and possess good biocompatibility, making them suitable for anti-fungal, anti-bacterial, anti-viral and anti-cancer activities. They show selective toxicity towards tumor cells.³⁴

Gold nanoparticles

They have a wide variety of applications owing to their highly efficient drug-delivery ability. They exhibit excellent properties such as stability, biocompatibility and physical and chemical properties. Nanogold particles can easily bind to enzymes, antibodies and cytokines. They also exhibit anti-oxidant and anti-inflammatory properties. Cytotoxic drugs can also be directly targeted to cancerous cells.^{35,36}

Titanium nanoparticles

They exhibit excellent antimicrobial properties and can be used in various biomedical applications. They also exhibit immunomodulatory and immune-toxic effects.^{37,38}

Selenium nanoparticles

They have a wide range of applications in the medical field. They can target drugs in cytotoxic and normal cells. The main principle is the generation of Reactive Oxygen Species (ROS). They play an important role in protection against oxidative stress and inflammatory reactions.^{39,40}

The anti-inflammatory action of metallic nanoparticles

A localized physical condition known as inflammation occurs when an infection or injury causes a portion of the body to

become swollen, red, or painful. This is recognized as the fundamental basis of pathology. When pathogenic germs injure or infect tissues, the body produces an inflammatory response. This response attracts macrophages, killer cells and stem cells, all of which help regulate the reaction. Large, heterogeneous, mononucleated, phagocytic cells called macrophages are produced in the bone marrow and flow in the bloodstream as monocytes or mobile White Blood Cells (WBCs). These leukocytes travel from macrophages to infection sites in different tissues. There are two types of macrophages: M1 and M2. M2 macrophages, which are activated in response to anti-inflammatory reactions, cause the remodeling of struck tissues and organs and are pro-inflammatory. M1 macrophages, whose production induces inflammation, During an inflammatory response, macrophages produce activation signals to further trigger inflammation, in addition to phagocytosing cellular and tissue debris and causing macrophage activation. Activation signals involved in this process include extracellular matrix proteins, Lipopolysaccharide (LPS) and cytokines such as tumor necrosis growth factor, chemokines, lymphokines, interleukins and interferons.

The improved ability of nanoparticles to penetrate inflammatory and epithelial cells results in improved therapeutic efficacy and stability. Additionally, their ability to target specific areas, such as inflammatory cells or tissues, is enhanced. Anti-inflammatory activities have been shown for a number of metals and metal oxide nanoparticles, such as nickel, zinc oxide, zinc peroxide, magnesium oxide, titanium dioxide,⁴¹ silver,⁴² gold,⁴³ selenium,⁴⁴ copper,⁴⁵ iron oxide,⁴⁶ and cerium oxide.⁴⁷

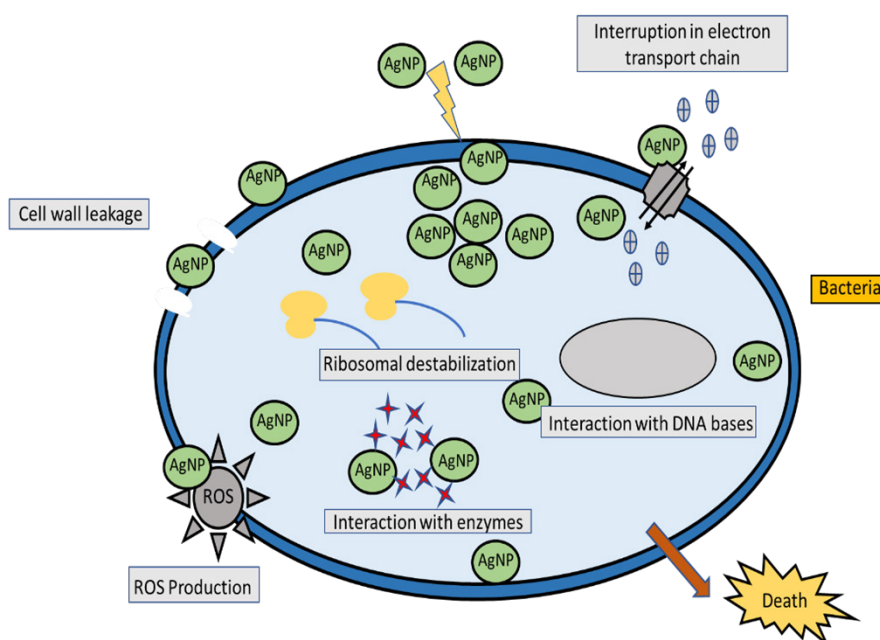


Figure 3: Anti-Cancer action of metallic nanoparticles.

The anti-cancer action of metallic nanoparticles

A malignant tumor mass is more likely to occur in the body when cells continue to proliferate uncontrollably owing to genome instability, deficiencies in the DNA repair mechanism and harmful mutations in tumor suppressor genes. By targeting the pathophysiology of tumor cells, metallic nanoparticles enable efficient transport of anticancer medications into tumors, thereby improving therapeutic outcomes (Figure 3). Applications of metallic nanoparticles in cancer detection and treatment include Magnetic Resonance Imaging (MRI) and colloidal mediators for the magnetic hyperthermia effect with Photothermal Ablation (PTA) therapy using magnetic nanoparticles. When the gold nanoparticles were coupled with other medications, such as TMZ and Cisplatin, something newly developed. In particular, they have the ability to attach to a wide range of chemical and biological molecules, a strong absorption range and minimal toxicity. Silver nanoparticles have generated much interest because of their potential use as antitumor agents in cancer therapy. It serves as a delivery system for medications containing antisense oligonucleotides and other small molecular structures. Drug transporters, better stability of surface-bound nucleic acids, a variety of surface ligand attachments, transmembrane delivery, protection of the attached therapies from degradation and the possibility for improved regulated intracellular drug delivery are just a few of the advantages that AgNPs provide. Nanoparticles have been used in many advanced tests to treat a range of illnesses.⁴⁸ The anti-cancer potential of the ZnO Nanoparticles was assessed after they were conjugated with unique hydrophobic peptides. Better cytotoxicity was observed for the nanoparticle-peptide complex than for the peptide or nanoparticle alone. Therefore, the ZnO nanoparticles tested in our study demonstrated anti-cancer activity against colon cancer cells. Moreover, it can be conjugated with peptides to more effectively target cancer cells.⁴⁹

Anti-oxidant Action of Metallic Nanoparticles

Oxidative stress is a condition that occurs when an excess of oxidants, such as Reactive Oxygen Species (ROS), Nitrogen Species (RNS) and organic molecules, upsets the balance between the cell's antioxidative defense and oxidants. Contains sulfur and produces alkyl sulfinyl radicals.⁵⁰ One class of factors linked to a number of illnesses and aging is oxidants. Electrical stimulation or natural oxidative processes, which are produced by reduction-oxidation activities, are the usual sources of Reactive Oxygen Species (ROS). Research has revealed a possible relationship between aging and ROS damage. Recently, there has been an increase in interest in the free radical theory of aging, which focuses on mitochondria as both a source and target of ROS. The majority of current research has focused on identifying ways to reduce the effects of these oxidants. Although some metallic and metallic oxide nanoparticles have been shown to behave well as antioxidants, others are considered to have the potential to cause oxidative stress and result in unfavorable health outcomes.

The unique properties of AuNPs have led to their application in many different industries.⁵¹ The Antioxidant properties of AgNPs may be used to treat degenerative Alzheimer's disease and cancer. For instance, human lung cancer cells were treated with well-characterized PVP-coated AgNPs to examine the reactive oxygen species that lead to programmed cell death.⁵⁰ To discover novel compounds derived from organic compounds, anti-oxidant capabilities are currently being thoroughly investigated for a wide range of materials, especially organic compounds.⁵²

CONCLUSION

In conclusion, silver nanoparticles were consistently produced using a marine sponge to decrease the silver precursor concentration. Silver nanoparticles are one of the most important nanoparticles that exhibit cytotoxic activity towards cancer cells. Silver nanoparticles produce an autophagy effect on cancerous cells and lead to the death of cancer cells. AgNPs are effective against inflammation without any toxic effects. *In vitro* and *in vivo* experiments showed that AgNPs have better anti-inflammatory activity. Nanoparticles up to 100 nm in size are useful for anti-cancer, anti-inflammatory and anti-oxidant activities because of their nanoscale size, which is highly permeable and has the strongest structure and provides better pharmacological actions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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