



Nanoparticle-Based Cancer Therapeutics: From Synthesis to Clinical Applications

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Abstract

Nanoparticles are increasingly popular for cancer treatment. They can be modified to researchers' needs, whether that's shape, size, or functionalization, to target a specific cell or travel to a certain area in the body. Synthesis methods vary, and include chemical and biological synthesis. Traditional chemical synthesis methods can produce toxic chemicals, so more eco-friendly techniques have been developed. Biological synthesis is more safe and eco-friendly as it uses microorganisms to make the metallic materials needed to synthesize nanoparticles. Two types of biologically synthesized nanoparticles will be discussed: metallic and polymeric. Although metallic and polymeric nanoparticles are not only synthesized through biological synthesis, this paper will touch specifically upon biological synthesis methods. Nanoparticles are being used to detect and identify cancer cells, predict how a cancer will advance, and to treat cancer. In cancer diagnosis, nanoparticles are used as contrasting agents for imaging and as biomarkers. This paper will also discuss how nanoparticles are being used in treatment techniques, specifically chemotherapeutics, immunotherapy, and radiation therapy. In chemotherapeutics, nanoparticles store the chemotherapeutic drug and release it into targeted cancer cells. Nanoparticles are also used in immunotherapy by increasing the stimulation of innate immune cells. In radiation therapy, nanoparticles can better localize treatment so that healthy cells are less affected. Our knowledge of the abilities and limitations of nanoparticles in cancer therapy has expanded significantly and is expected to continue to grow. In the future, cancer treatment technology may evolve to use hydrogel-embedded nanoparticles, potentially enhancing the controlled delivery of cancer treatments.

Key Words

Nanoparticles, biological synthesis, chemotherapy, radiation therapy, immunotherapy

Introduction

Cancer is a leading cause of death throughout the world. Although there are treatments now, cancer cells are very similar to normal cells. Therefore, it is difficult for treatments, such as chemotherapy, radiation therapy, and immunotherapy, to kill the disease without harming healthy tissue. Nanotechnology offers a solution by providing a way to better target cancerous cells.

Nanotechnology refers to research that manipulates matter that is 1 billionth of a meter in size [1]. Nanotechnology's smallest fundamental unit is the nanoparticle, or tiny structures that usually range from 1 nm to 100 nm. Nanoparticles are structures, which can be modified to have desired traits, that vary in physical and chemical properties. Scientists are currently researching and developing nanoparticles as an up-and-coming form of cancer treatment because of their modifiable capabilities, which include shape, size, and chemical composition [2]. They can be designed to travel to and release the drugs they carry at specific targets or areas.

Synthesis methods of nanoparticles vary. Popular techniques include chemical and biological methods. Chemical synthesis creates nanoparticles by using reducing agents on ions, causing metallic structures to form in clusters [3,4]. Although it is a cheaper and faster method, the toxic by-products of this method limit the use of these particles. Furthermore, biological synthesis relies on organic materials to be reducing and capping agents. Capping agents help to stabilize the nanoparticles. To stabilize in this case means to prevent nanoparticle overgrowth as

well as solidification before completely formed [5]. Reducing agents are also used to stabilize nanoparticles. Organic materials include, but are not limited to bacteria, plants, and fungi. Nanoparticles can be split into three categories: organic, inorganic, and carbon based [6].

Nanoparticles are being used to increase the effectiveness of cancer treatment. Chemotherapy, for example, is a type of cancer treatment that uses chemical compounds to kill or slow the growth of cancer cells or by stimulating the pathways promoting programmed cell death, or apoptosis [7]. The chemicals are traditionally introduced into the body through intravenous, intramuscular, or oral routes to reach a generalized distribution. Since these drugs are not equipped with specific anti-tumor recognition abilities, they often cause harm to non-cancerous cells. Damage to non-cancerous areas around the tumor is referred to as off-target toxicity. Off-target toxicity can lead to non-cancerous cell death [8], low biodistribution of drugs (biodistribution refers to analyzing and tracking the movement of a drug in an experimental animal or human subject), and risk of developing drug resistance [9]. In order to protect the chemical in physiological conditions until it can achieve its therapeutic function, drug delivery systems have been studied for cancer treatment. Nanoparticles offer a solution to this issue since they can be engineered to target therapeutic delivery to tumors, thereby decreasing exposure to healthy cells, as well as by protecting the payload from premature degradation or clearance.

The modifiable capabilities that come with nanoparticles make nanomedicine a promising future in cancer therapy. In this paper, the roles of nanoparticles in chemotherapy, radiation therapy, and immunotherapy will be discussed. Nanoparticles can improve these cancer therapies by decreasing the effects of cytotoxicity, increasing a dose, targeting specific areas/cells, and controlling the release of therapeutic drugs.

Methods

This literature review compiled research and review articles mainly on google scholar and science direct. The search was narrowed down to articles written within the 21st century and with keywords that related to each section. These words included nanoparticle, biological synthesis, chemotherapy, radiation therapy, and immunotherapy. Research which demonstrated and supported points in each section were used.

Biological Synthesis of Metallic Nanoparticles

Metallic nanoparticles are typically structured to have a metallic core, a shell, and a set of surface layers. The core metallic molecule can consist of one metal or a mix of metals. A metallic nanoparticle's shell is made of a material different from that of the core [10]. More specifically, the shell is made of a non-magnetic metal oxide, or a compound of a metal and oxygen. This shell interacts with the metallic core and affects how that core behaves. The surface layers then allow for modifications to the particle [11]. In this way, the nanoparticle can be modified to interact with target molecules. Metallic nanoparticles are synthesized through various methods, including chemical, physical, and biological methods. Biological synthesis uses organic materials, such as algae, bacteria, and fungi, to create the constituents needed to build the nanoparticles. The materials have phytochemicals that are used as metabolites, which are further sorted into primary and secondary metabolites. Primary metabolites are necessary for the growth of a plant, whereas secondary metabolites are synthesized in response to environmental stressors. There are four phases in the biological synthesis of metallic

nanoparticles. This includes the initial phase, activation phase, growth phase, and termination phase (Figure 1).

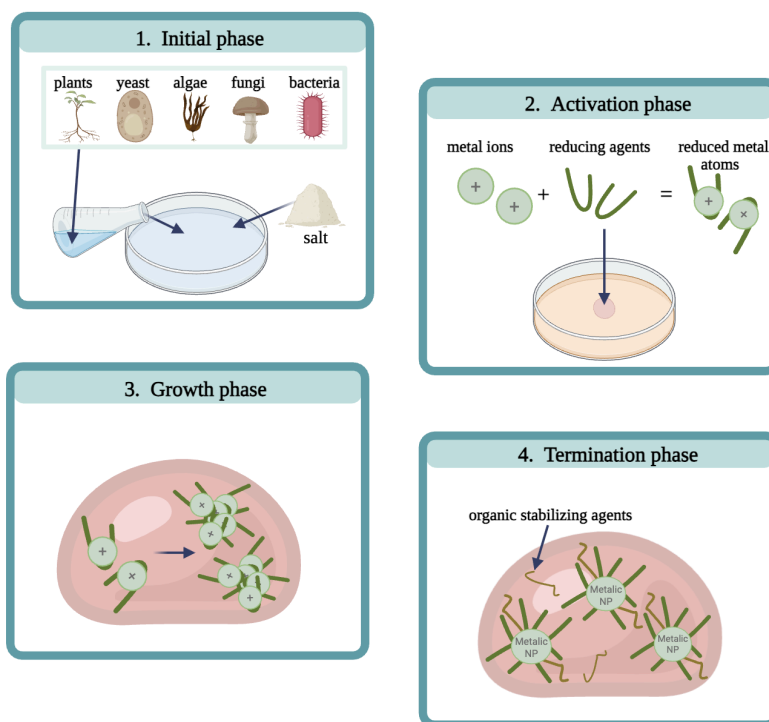


Figure 1: The 4 Stages of Biological Synthesis of Metallic Nanoparticles. The initial phase is when the tissue is selected and dissolved in water. The activation phase begins when a metal is added to the tissues. The combination of biological material as well as the metal ions results in reduced metal atoms. Step three is the growth phase, where more reduced metal atoms cluster and those clusters increase in size. Finally, the metallic particles stop growing in what is called the termination phase. [12]

To begin synthesis, researchers select the species of a living being (ex: bacteria, plant, etc). In one study, *Ginkgo biloba* leaf extract was used to reduce metal ions. *Ginkgo biloba* leaves are particularly known for their medicinal uses, including anti-cancer, anti-inflammatory, antioxidant, anti-allergic treatments [13]. Tissues are turned into a powder and dissolved in distilled water [14]. Researchers add a metal salt, which will eventually change the color of the solution. For example, a colorless solution may change to brown or red. If a change in color is observed, then the metal ions have been reduced by the phytochemicals of the organism (activation phase) and the surface layers of the nanoparticles formed [13,15,16]. Gold is a prominent metal in nanoparticle synthesis due to its ability to be modified to have a specific size and shape while also being stable and biocompatible. Nucleation occurs next and a structure forms. This structure is made of the metal ions which were reduced, and more reduced metal ions will layer on top of the previous layer. A new thermodynamic phase is made and is composed of solid, stable nanoparticles (growth phase). Finally, metallic nanoparticles will reach their final structure (termination phase).

Biological Synthesis of Polymeric Nanoparticles

Polymeric particles are of interest to researchers due to their wide variety of sizes and ability to be shaped. Shapes can grant accessibility to different areas of the body more easily than others. For example, rod shaped nanoparticles cannot pass through blood vessels as smoothly as spherical shaped nanoparticles (Figure 2). The rod shaped particles will become stuck onto the walls of a blood vessel, whereas spherical shaped particles flow in the center of the vessel (Figure 2).

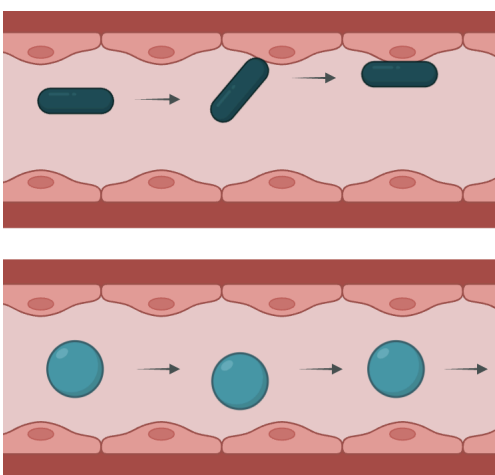


Figure 2: Comparison of Movement Between Differently Shaped Nanoparticles. The rod shaped particles (top) are moving into the walls of the blood vessel whereas the sphere shaped particles (bottom) tend to stay in the center of the blood vessel [17].

Both can have benefits. Notably, spherical shaped nanoparticles can travel longer in the blood stream. Longer circulation time means that nanoparticles can travel the body more efficiently, improving a nanoparticle's ability to target cancerous tissues. Rod shaped nanoparticles, on the other hand, can be beneficial because they are able to penetrate deeper into tissues, meaning that the treatment released will be closer to its target [18].

The size of a nanoparticle determines the size of a nanoparticle's protein corona [18,19]. Polymeric nanoparticles are classified mainly as nanocapsules and nanospheres. Nanocapsules have oily cores, which is where the drug is stored, and a polymeric shell. Nanospheres instead store the drug throughout a solid polymeric matrix (Figure 3).

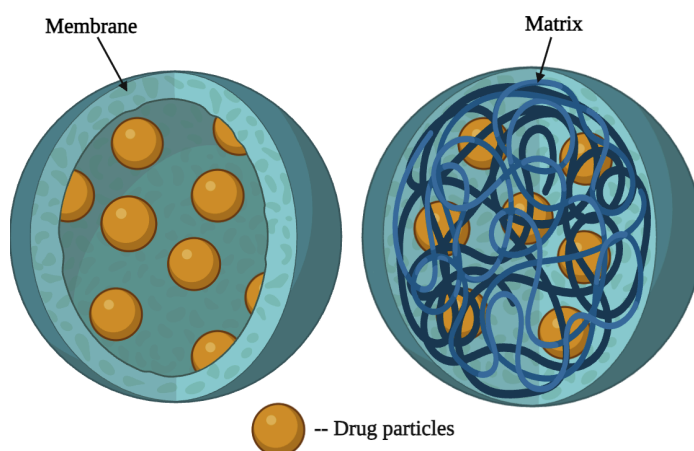


Figure 3: Visual Model of Nanocapsule (left) and Nanosphere (right). The nanocapsule carries drug particles inside a membrane and a nanosphere carries drug particles by trapping them within a matrix [20].

This kind of nanoparticle consists of a natural or synthetic polymeric core and structure. Natural materials refer to biomolecules, such as proteins and carbohydrates. Synthetic materials include polylactic acid (PLA) and polyethylene glycol (PEG). Biological synthesis methods have been used to create polyhydroxyalkanoate (PHA)- based nanoparticles. PHA is a polyester polymer created by microorganisms. Nanosized granules of PHA form inside bacteria cells, and the size of these granules can change based on the bacteria species used, environmental conditions, and allotted time. The ability to control these factors is proven to be an advantage of polymeric nanoparticles; it is easier to determine chemical composition, size, and shape of a polymeric nanoparticle with biological synthesis relative to chemical synthesis [21].

Nanoparticles in Chemotherapy

Although their structure varies depending on the material used, nanoparticles react to external or internal stimuli. They control the release of a drug through methods such as stimuli-controlled release, diffusion, and degradation. Diffusion-based drug release is a method which releases the encapsulated drug through a nanoparticle's matrix or membrane through a concentration gradient. One way to do this is by coating nanoparticles with a polymeric membrane that acts as a barrier to control drug solubility and diffusion [22]. Diffusion-based drug release can occur without a membrane separating the drugs inside and outside of the nanoparticle. In this case, the nanoparticle's matrix controls the release as the molecules of the drug are spread throughout the matrix. Nanoparticle degradation-based release involves storing a drug inside a polymeric matrix within the nanoparticle that can degrade in physiological conditions and release the encapsulated therapeutics [23]. Degradation is specific to polymeric nanoparticles. Nanoparticles made of naturally occurring polymers, such as hyaluronic acid, or synthetic polymers, such as polylactic-co-glycolic acid (PLGA), can biodegrade in physiological conditions which aids in drug release [23]. Bulk degradation ultimately allows nanoparticles to release the treatment at the same time and place, so the treatment will be closer to its target [24]. There is also surface degradation, where the coated surface of the nanoparticles breaks down under certain conditions, releasing the drug stored within the particle [25]. Another method of drug delivery is through endocytosis, where nanoparticles make contact with the cell membrane. Upon contact, the membrane forms intracellular vesicles around the nanoparticles. Absorption into cells, however, appears to be influenced by factors such as cell size and physical properties of nanoparticles [26]. Physical properties of nanoparticles not only include their shape and size, but also their surface coating and protein corona. Protein coronas influence cellular uptake as they influence the surface chemistry of the particles, creating varying sizes as well as surface chemistry [27,28]. For example, a study utilized polymeric nanoparticles to treat colon cancer with combination chemotherapy, where researchers loaded nanoparticles with camptothecin (CPT) and curcumin (CUR). The particles were coated with hyaluronic acid (HA), which would allow the particles to find and bind to surface receptors specifically found on tumor cells. Tumor cells have an excessive amount of HA receptors, so nanoparticles with an HA coating are particularly effective [29,30]. This is seen in an experiment where nanoparticles consisting of PLGA were coated with HA and injected into mice with cancer

metastases. The mice which gained less weight suggest that the HA coated nanoparticles were more cytotoxic to cancer cells compared to those without the coating [31].

Nanoparticles in Radiation Therapy

Radiation therapy is a cancer treatment that uses high-energy waves or streams of particles to destroy or control the growth of cancerous cells by damaging their DNA. Radiation therapy is typically unable to target specific cancer cells and often damages surrounding non-cancerous tissue [32]. Nanoparticles offer a potential solution to this problem. Nanoparticles can recognize and transport molecules throughout the body. To use nanoparticles in radiation therapy, high energy electromagnetic (EM) radiation is directed at the atoms of the nanoparticles. The waves of radiation will hit electrons in a process called the Compton effect. This causes secondary electrons to be released and scattered, forming delta waves. The delta waves in turn are absorbed by surrounding cells, thus inflicting damage to DNA [33]. Furthermore, nanoparticles can selectively scatter the delta wave as they are able to selectively absorb high energy waves, thus controlling the release of delta waves [34,35].

To increase the effectiveness of radiation therapy, radiosensitizers are used to make cancerous cells more susceptible to radiation. Radiosensitizers are drugs that lower radiation resistance by reacting with certain chemicals (such as oxygen) to modify a cell's response to a radiation dose [36]. The impact of nanoparticles in sensitization, however, is dependent on the size of a particle. The greater the diameter of the nanoparticle, the greater the number of tumor cells it will selectively attack. For metallic nanoparticles, gold is the preferred material for radiation therapy. Not only does gold have a lot of electrons that can interact with EM waves, gold is biologically inert [37]. Having more electrons is good for radiation therapy because that increases the amount of electrons an EM wave can hit and cause damage [38]. Gold nanoparticles can also be formed into a wide range of particle size, shape, and surface properties.

Although gold nanoparticles are popular in radiation therapy, there are other materials being tested. For example, one study used a combination of silver and iron oxide to create nanoparticles for radiation therapy. The combination of materials allows researchers to take advantage of different anti-cancer effects presented by the different materials [39]. Another study also uses a combination of silver and iron oxide, where researchers treated Glioblastoma U251 (U-251 MG). Researchers concluded that the cultures with silver/iron nanoparticles had the highest reduction of viable U-251 MG cells, compared to cultures treated with silver particles and without particles [40].

Nanoparticles in Immunotherapy

Immunotherapy is a type of cancer treatment that boosts the immune system's natural ability to recognize and fight cancer [41]. The immune system works in two distinct branches: the "innate" and "adaptive" branches. The "innate" branch is considered the body's first line of defence. It consists of phagocytes and granulocytes that recognize pathogens and travel to infection sites. The "adaptive" branch is the memory of the immune system. T- and B-lymphocytes help to recognize pathogens that were seen before [42]. Immunotherapy aims to attack cancer cells by activating T-cells.

Tumor associated antigens or tumor specific antigens can prime immature T-cells so that they will recognize the antigens of a cancerous cell. Tumor associated antigens show up more in cancer cells and less in non-cancerous cells. If tumor associated antigens are used for

immunotherapy, they can cause an autoimmune response. Tumor specific antigens are different because they show up only in cancerous cells. These are more safe to use in immunotherapy because they do not risk an autoimmune response [43]. However, they easily degrade and have low immunogenicity. Nanoparticles can help these antigens elicit a stronger immune response by transporting the drug to the lymph nodes, where the T-cells are housed. Transporting modulating gene products (mRNA, antigens, cytokines, etc), nanoparticles enter the body through the blood stream. Unfortunately, this also means that the particles are not guaranteed to reach the lymph nodes.

Certain nanoparticle traits will affect the efficiency of immunotherapy. A nanoparticle's size, for example, can cause differences in the absorption of the antigens. The range for smaller nanoparticles is typically less than 5 nm. Larger nanoparticles typically range above 100 nm and are less likely to be taken out of blood vessels compared to small nanoparticles. However, they can get stuck in the extracellular matrix that is created by cancerous cells and so be unable to deliver antigens. Medium sized nanoparticles, which range between 5 nm and 100 nm, are able to navigate most easily throughout the body and better deliver antigens to lymph nodes [43]. Spherical nanoparticles are more easily engulfed by a cell membrane, hence increasing their effectiveness in delivering antigens to lymph nodes [44]. A greater surface area means there are more places for other molecules to bind, which means that a nanoparticle can deliver antigens to more T-cells at once [45,46].

Discussion

Nanoparticles have a promising future in cancer therapy. Nanoparticles can carry and deliver therapeutic drugs to specific targets, be modified to reach different areas of the body, and increase the drug dose on targeted cells while decreasing drug exposure on non-cancerous cells. They can be modified to have a variety of characteristics, including but not limited to different shapes, sizes, and chemical compositions. Different characteristics can lead to unique benefits. Synthesis methods of nanoparticles vary. Chemical synthesis relies on chemical reactions to form nanoparticles, whereas biological synthesis uses organic matter to stabilize and give structure to nanoparticles. In chemotherapy, radiation therapy, and immunotherapy, research has shown that nanoparticles can increase the effectiveness of cancer therapy.

In the synthesis sections, sources which included examples of biological synthesis were used. Research by Xu et. al., for example, demonstrated the use of leaves to act as reducing agents in order to synthesize nanoparticles [13]. Articles by Cardoso et. al. and Deka et. al. explained the steps taken to use biological materials to synthesize nanoparticles [12,15]. For the sections specific to cancer therapy, articles demonstrated which aspect of the therapy was affected by the nanoparticles. In the chemotherapy section, the article by Remya et. al. elaborated on how nanoparticles can biodegrade, which is an important aspect for drug release [23]. Research by Xiao et. al., on the other hand, demonstrated the use of surface coatings to better target cancer cells [29]. For radiation therapy, sources helped explain that nanoparticles could better direct radiation towards cancer cells. Some articles specified how the material of the nanoparticles could enhance the effect of nanoparticles in radiation therapy [34,35]. Finally, an article in the immunotherapy section examined how the shape of the nanoparticle affected its ability to deliver a drug to T-cells [45,46].

Conclusion



Their applications in chemotherapy, immunotherapy, and radiation therapy continue to show the potential to improve treatment outcomes through targeted delivery, immune modulation, and enhanced localization of therapeutic effects. Although challenges such as large-scale manufacturing and long-term safety remain, continued advances in nanoparticle engineering are expected to address many of these limitations. Future strategies, including hydrogel-embedded nanoparticle systems for controlled and localized therapeutic delivery, may further enhance the precision and effectiveness of cancer treatment, bringing nanomedicine closer to widespread clinical implementation.

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