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Gold Nanoparticles in Cancer Treatment and Diagnostics: A Review of Emerging Trends and Therapeutic Potential

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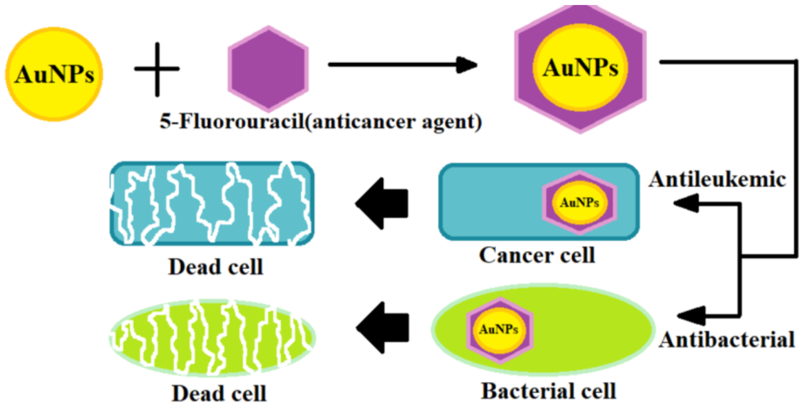
This comprehensive review delves into the burgeoning role of gold nanoparticles in both cancer treatment and diagnostics. The advent of gold nanoparticle (AuNP) vaccines has opened avenues for therapeutic and prophylactic applications, suggesting the potential to prevent or treat infections and various pathologies. The exceptional efficacy of AuNPs in cancer treatment is a focal point of exploration, with ongoing investigations into their utility for targeted delivery and therapy across diverse cancer types. A distinctive attribute of AuNPs lies in their ability to selectively target cancerous cells while safeguarding healthy cells, attributed to their unique size and shape that facilitate selective accumulation in cancer cells. Upon cellular entry and aggregation, they exhibit prompt activation to eradicate cancer cells. Furthermore, AuNPs possess inherent capabilities to enhance and modulate immune responses, functioning as both an adjuvant and a delivery system. Another advantageous feature is their amenability to functionalization with diverse molecules, including antibodies and drugs, augmenting specificity and effectiveness. This customization enables precise targeting of cancer cells and direct delivery of therapeutic agents to tumor sites, mitigating the adverse effects associated with conventional chemotherapy. Despite ongoing research, the promise of AuNPs as a potent tool in the battle against cancer is evident, underscoring their potential significance in future therapeutic strategies.

Graphical abstract



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1. Introduction

Gold nanoparticles, ranging in size from 1 to 100 nanometres, possess unique optical, physical, electrical, and chemical characteristics distinct from bulk gold due to their nanoscopic size, compact structure, and higher surface area

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to volume ratio. They come in various shapes, such as spheres, rods, and triangles, and can be modified with different molecules for specific applications [1,2]. Their applications span diverse fields, including medicine, electronics, and catalysis. In medicine, gold nanoparticles are utilized for drug delivery, cancer diagnosis, therapy, and imaging. In electronics, they find applications in electronic displays, sensors, and memory devices. In catalysis, AuNPs serve as catalysts in various chemical reactions owing to their high catalytic activity. The exceptional properties of gold nanoparticles make them attractive for a wide range of applications, and their usage is expected to grow [3,4].

Recently, gold nanoparticles have been engineered with different shapes, sizes, and materials, coupled with diverse surface groups, each with specific functionalization and properties. Carbon nanotubes, polymer particles, and lysosomes have gained widespread use, being targeted to specific sites due to their unique shape, size, and coating, acting as adjuvants, as illustrated in Figure 1. Nanoparticles in the size range of 1nm to 100nm contribute to lighter, cleaner, stronger, and brighter surfaces and systems. At the nanoscale, nanoparticle properties are unpredictably modified, such as increased mobility in the free state, exhibit of quantum effects, and having an enormous surface area.

Key characteristics of gold nanoparticles include:

a) Size and Shape: AuNPs can be produced in various forms like spheres, diamonds, rods, and triangles, with dimensions precisely controlled during synthesis.

b) Optical Properties: Due to their small size, AuNPs interact with light differently than bulk gold, displaying unique optical properties, such as surface plasmon resonance (SPR), influencing light absorption and scattering based on size, dimension, shape, and the surrounding environment [5].

c) Chemical Stability: AuNPs are highly stable and resistant to degradation or oxidation, making them suitable for diverse applications.

d) Biocompatibility: Generally considered biocompatible, AuNPs do not typically elicit a significant immune response or toxicity in biological systems. However, biocompatibility can vary based on size, shape, dimension, surface charge, and chemistry [6].

e) Surface Functionalization: The surface of AuNPs can be modified with various functional groups, such as thiols, amines, and carboxylates, allowing customization for specific applications.

f) Conductivity: Gold's high conductivity extends to AuNPs, making them suitable for applications in electronics and sensors [6].

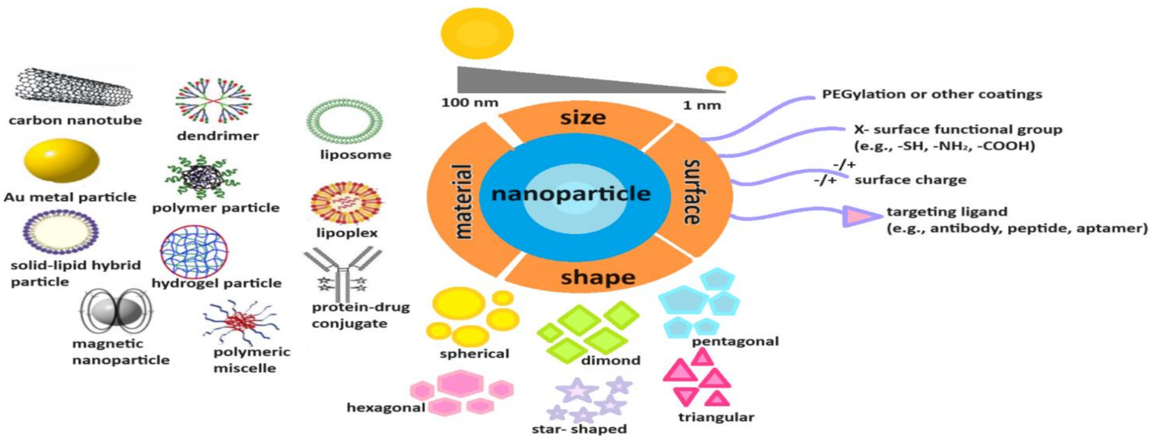

Fig. 1. Schematic representation of shape, size, material, and surface groups of AuNPs.

In recent times, gold nanoparticles have emerged as a promising and innovative tool in the field of vaccinology. Their development has given rise to therapeutic and prophylactic vaccines, presenting a potential approach to prevent or treat infections and diseases such as cancer and autoimmune disorders. Among various nanomaterials, gold nanoparticles (AuNPs) have gained popularity and are now considered a novel technology for vaccine development. This is attributed to their inherent ability to modulate and enhance the immune system's reactions. Vaccination stands out as a highly effective strategy in preventing mortality and morbidity by eliciting pathogen-specific humoral immune responses associated with infectious diseases. In recent years, vaccines have been a crucial medical breakthrough, contributing to improved life expectancy, providing sustainable defensive immunity to communities, treating numerous individuals, and contributing to the eradication of certain bacterial and viral infections [7,8]. Vaccines prepare the immune system to initiate an adaptive response, which can be either cellular (involving "CD4+ or CD8+ T-cells") or antibody-based [9]. Consequently, immunomodulation plays a pivotal role in advancing therapies for various diseases. The immune system's ability to combat infectious diseases and other disorders is harnessed through vaccines, which may consist of purified proteins, and live-attenuated or inactivated pathogens, triggering specific immune responses.

1.1 Synthetic approach for gold nanoparticle

The synthetic approach for gold nanoparticles involves a meticulous and controlled process to engineer these nanoscale structures with specific properties. Typically, a variety of methods are employed to synthesize gold nanoparticles, each with its advantages and applications.

One common method is the chemical reduction of gold ions in a solution, where a reducing agent facilitates the conversion of gold ions into elemental gold, forming nanoparticles [10]. Additionally, the use of stabilizing agents such as surfactants or polymers is crucial to prevent particle aggregation and ensure a stable dispersion. Other techniques include physical methods like laser ablation and green synthesis methods using biological entities. The choice of synthetic approach depends on the desired characteristics of the gold nanoparticles, such as size, shape, and surface properties. The versatility of synthetic approaches for gold nanoparticles underscores their significance in various fields, particularly in medicine, where they play a pivotal role in the development of novel technologies for applications ranging from diagnostics to drug delivery and vaccine design [11].

1.2 Chemical synthesis

The chemical synthesis of gold nanoparticles is a widely employed method, offering precise control over the size, shape, and surface properties of the resulting nanomaterials. One common approach involves the reduction of gold ions (usually Au^{3+}) in a solution, often using a strong reducing agent. Sodium citrate or trisodium citrate is a frequently used reducing agent that facilitates the reduction of gold ions, leading to the formation of gold nanoparticles. The process typically begins with the preparation of a gold salt solution, commonly chloroauric acid ($HAuCl_4$) [12]. The addition of the reducing agent triggers the reduction of gold ions to elemental gold, initiating the nucleation and growth of nanoparticles. The size of the nanoparticles can be controlled by adjusting the concentration of the reducing agent and other reaction parameters. Stabilizing agents such as capping ligands or surfactants are often introduced to prevent particle aggregation and stabilize the nanoparticles in solution. The resulting gold nanoparticles exhibit unique optical, electronic, and catalytic properties, making them valuable in a range of applications, including biomedical research, diagnostics, catalysis, and materials science [13,14]. The chemical synthesis of gold nanoparticles continues to be a versatile and well-established method for tailoring nanomaterials with specific characteristics for diverse applications.

In general, the production of gold nanoparticles (AuNPs) with precisely controlled dimensions necessitates the careful selection and optimization of various parameters to achieve the desired properties. The specific conditions and parameters of the synthesis process may vary depending on the methodology employed and the intended characteristics of the AuNPs.

The generation process of AuNPs involves four distinct steps, as illustrated in Figure 2: nucleation, growth by aggregation, slow further growth, and fast final growth [15]. Here is a concise description of each step:

i. Nucleation: The initial phase of AuNP generation involves the spontaneous formation of tiny clusters of gold atoms, or nuclei, in the solution. Nucleation can also be induced by introducing a reducing agent to a solution containing gold ions.

ii. Growth by aggregation: Following nucleation, the gold nuclei aggregate to form larger clusters [16]. This aggregation can occur through the adsorption of additional gold ions onto the nuclei's surface or by the coalescence of neighboring nuclei.

iii. Slow further growth: Once the clusters reach a specific size, further development proceeds at a slower rate [17]. This deceleration is attributed to the decrease in the concentration of gold ions in the solution, limiting their adsorption onto the clusters' surface.

iv. Fast final growth: The concluding step in the AuNP generation process involves the rapid growth of clusters to their final size. This acceleration is achieved by introducing a significant excess of gold ions to the solution, leading to a burst of growth as the gold ions are swiftly absorbed onto the clusters' surface [18].

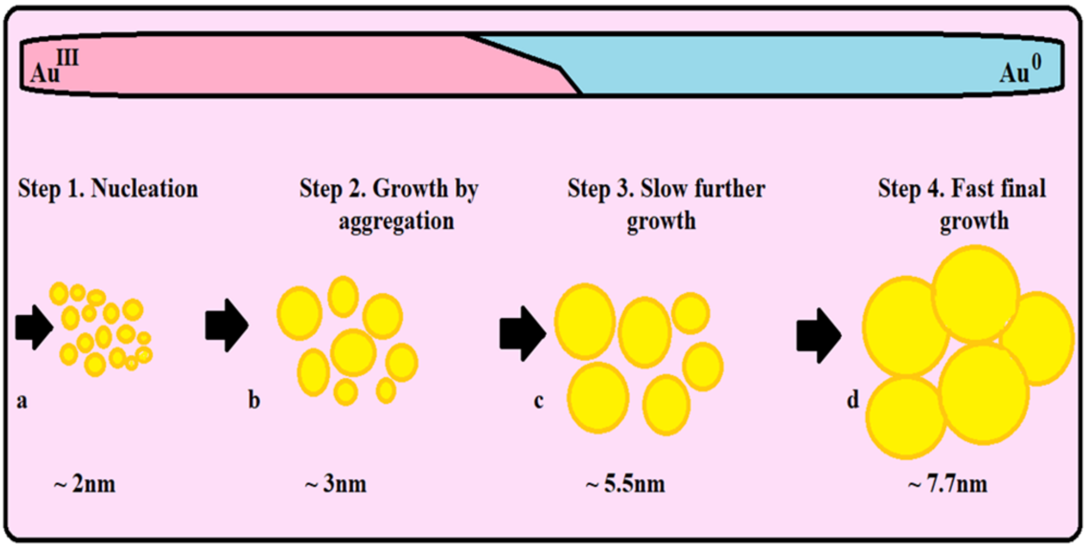

Fig. 2. A schematic description of the deduced gold nanoparticle generation process.

The generation process of gold nanoparticles (AuNPs) can exhibit variations in specific conditions and parameters, influenced by the chosen procedure and the desired characteristics of the AuNPs. Monitoring and control of the generation process are facilitated through diverse analytical techniques, such as ultraviolet-visible spectroscopy. This method enables the measurement of absorbance exhibited by the Au nanoparticles during their formation and growth

[19].

1.3 Green synthesis

Green synthesis of gold nanoparticles involves the utilization of natural or biodegradable substances as reducing agents, stabilizers, or templates in the synthesis of AuNPs [20]. Several standard methods for green synthesis include:

Plant extracts: Extracts from various plants like neem, Tulsi, and Aloe vera serve as both reducing agents and stabilizers for AuNP synthesis [21]. These extracts contain phytochemicals like polyphenols, flavonoids, and terpenoids, which effectively reduce and stabilize gold ions, leading to the formation of AuNPs.

Microorganisms: Certain microorganisms such as bacteria (e.g., cyanobacteria), fungi, and algae can be employed for AuNP synthesis. These microorganisms produce enzymes like nitrate reductase and hydrogenase, facilitating the reduction of gold ions to AuNPs. Moreover, microorganism cell walls can act as templates, resulting in the formation of AuNPs with unique shapes and sizes [22-24].

Biodegradable polymers: Polymers with biodegradable properties, including chitosan, starch, and cellulose, can function as reducing agents and stabilizers in AuNP synthesis. Through electrostatic or hydrogen bonding, these polymers interact with gold ions, contributing to the formation of AuNPs [25-27].

Green solvents: Utilizing green solvents like water and ethanol, as opposed to toxic solvents like chloroform and hexane, represents another environmentally friendly approach to AuNP synthesis [28]. This choice minimizes the environmental impact of the synthesis process and enhances the biocompatibility of AuNPs. The benefits of green synthesis over conventional methods include reduced toxicity, cost-effectiveness, and sustainability, as illustrated in Figure 3.

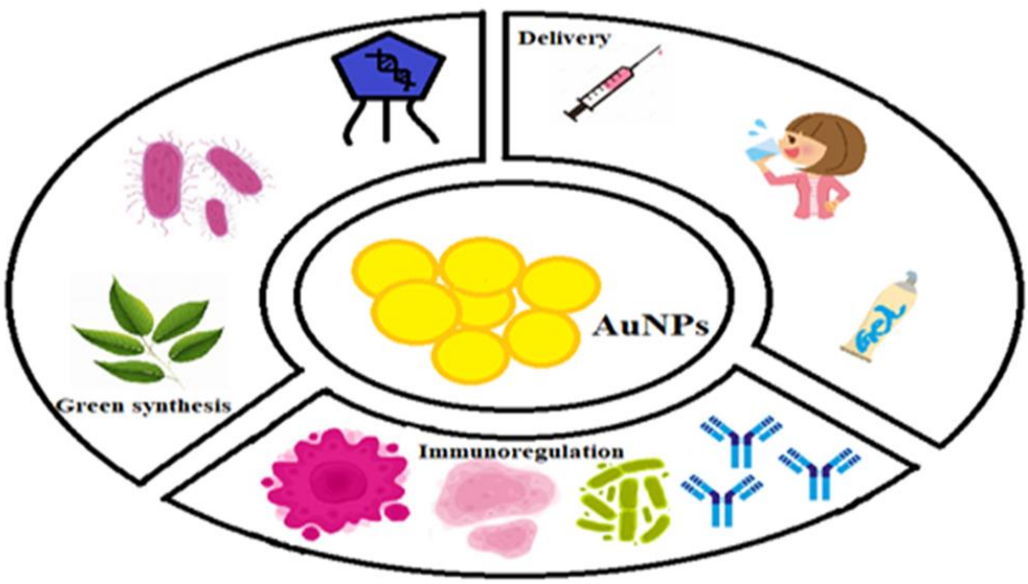

Fig. 3. The green blending of AuNPs can be used for medication administration and immunological control, as seen in the diagram. AuNPs made by bacteria, fungi, plants, and biological extracts have excellent biocompatibility and stability. These can significantly contribute to various medication delivery systems, whether oral or parenteral.

1.3. a) Synthesis from plant extract

Plant extract-based synthesis of gold nanoparticles (AuNPs) represents a compelling and rapidly advancing area, characterized by its environmentally friendly nature and avoidance of harsh chemicals, aligning with sustainable nanoparticle synthesis practices [29,30]. The steps for synthesizing AuNPs from plant extract are as follows:

a) Preparation of the plant extract: Choose a plant species rich in phytochemicals, such as flavonoids, alkaloids, and terpenoids. Collect fresh leaves or stems, thoroughly wash them, and blend them with distilled water to obtain a crude extract.
b) Reduction of gold ions: Introduce the plant extract into a solution of gold ions (e.g., HAuCl4). The phytochemicals in the extract act as reducing agents, converting the gold ions into metallic gold nanoparticles.
c) Characterization of the nanoparticles: After the reduction, employ techniques like UV-Vis spectroscopy, transmission electron microscopy (TEM), and dynamic light scattering (DLS) to characterize the dimension, shape, and stability of the AuNPs.
d) Purification of the nanoparticles: Purify the synthesized AuNPs through centrifugation or filtration to eliminate impurities or unreacted plant extract.
e) Applications of the nanoparticles: Utilize the AuNPs for various applications, including drug delivery, bioimaging, catalysis, and sensing [31].

This process can be illustrated using black pepper extract, known for its manganese content and health benefits. Synthesizing AuNPs from black pepper extract is a straightforward and cost-effective process that leverages the natural compounds in black pepper as both reducing agents and stabilizers (Figure 4) [32,33]. The steps for synthesizing AuNPs from black pepper extract are as follows:

a) Preparation of black pepper extract: Grind black pepper into a fine powder and soak it in water or ethanol for several hours to extract the natural compounds.

b) Addition of gold ions: Combine a solution of gold ions (e.g., HAuCl4) with the black pepper extract, ensuring uniform mixing.

c) Heating and reducing gold ions: Heat the mixture to a temperature between 80-100°C while stirring continuously to reduce the gold ions into metallic gold nanoparticles. The natural compounds in black pepper act as reducing agents and chitosan is added as a surface enhancement agent [34].

d) Purification of the AuNPs: Purify the synthesized AuNPs through centrifugation or filtration to remove impurities or unreacted black pepper extract [34,35].

Applications of the nanoparticles: The AuNPs obtained from black pepper extract find utility in various applications, including biomedical imaging and sensing. Additionally, the natural compounds in black pepper extract serve as both reducing and stabilizing agents, making it a promising source for AuNP synthesis [34-36].

1.3.b) Synthesis of AuNPs from microorganisms

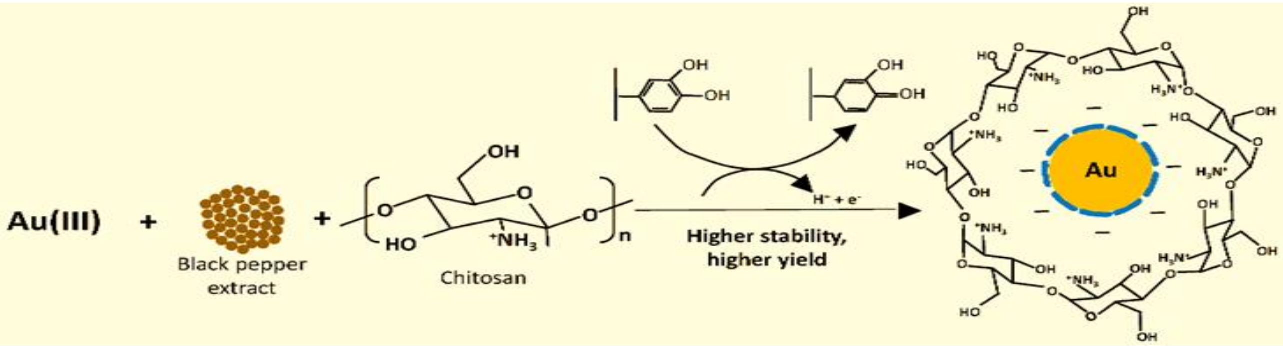

Fig. 4. Preparation of gold nanoparticles from black pepper extract.

The synthesis of AuNPs from microorganisms is a sustainable and cost-effective approach that involves using microbial cells or their extracts as reducing agents [37-39]. Here are the steps for synthesizing gold nanoparticles from microorganisms:

a) Selection of microorganisms: Varied types of microorganisms like bacteria, viruses, fungi, and algae can be used to produce AuNPs. Choose a microorganism that is readily available and has a high reducing potential.

b) Culturing the microorganism: Grow the microorganism in a nutrient-rich medium under optimal conditions to obtain high biomass.

c) Preparation of the cell-free extract: After culturing the microorganism, centrifuge the cells and collect the supernatant containing the cell-free extract. This extract can be utilized as a reducing agent for generating AuNPs.

d) Reduction of gold ions: Take a solution of gold ions (e.g., HAuCl4) and add the cell-free extract. The reducing agents in the extract will reduce the gold ions into metallic gold nanoparticles.

e) Purification of the nanoparticles: The synthesized gold nanoparticles can be purified by centrifugation or filtration to remove any impurities or unreacted microorganism extract [40].

The synthesis of AuNPs from microorganisms is valued for its eco-friendly and sustainable nature, relying on the reducing potential of microorganisms to drive the reduction of gold ions. This approach has found applications in nanotechnology, biomedical research, and environmental science, showcasing the versatility and adaptability of AuNPs synthesized through microbial routes.

1.3.c) Synthesis of AuNPs from biodegradable polymers

The synthesis of gold nanoparticles (AuNPs) from biodegradable polymers is a promising and environmentally friendly approach that involves utilizing biodegradable materials as both reducing agents and stabilizers [41-44]. This method offers a sustainable means of producing AuNPs with potential applications in various fields, including biomedicine and nanotechnology. Here is an overview of the synthesis process:

a) **Selection of Biodegradable Polymer:** The first step involves selecting a biodegradable polymer with high reducing potential and the ability to stabilize the resulting nanoparticles. Common examples of biodegradable polymers used in this process include chitosan, poly (lactic acid), and poly(caprolactone).

b) **Preparation of Polymer Solution:** The chosen biodegradable polymer is dissolved in a suitable solvent, such as water or ethanol, to create a homogeneous polymer solution. This solution serves as the medium for the subsequent steps in the synthesis process [45-48].

c) **Addition of Gold Ions:** A solution containing gold ions (commonly HAuCl4) is added to the polymer solution. This step ensures that the gold ions are evenly distributed within the polymer matrix.

d) **Reduction of Gold Ions:** To initiate the reduction process, reducing agents are introduced into the solution. Sodium borohydride (NaBH4) or ascorbic acid are commonly used reducing agents in this context. The reducing agents react with the gold ions, leading to the reduction of gold ions into metallic gold nanoparticles [49, 50].

e) **Purification of AuNPs:** The synthesized AuNPs may be subjected to purification steps to remove any impurities or unreacted components. Common purification techniques include centrifugation or filtration.

The biodegradable polymer not only acts as a reducing agent but also provides stabilization to the AuNPs, preventing their agglomeration and enhancing their colloidal stability. The resulting AuNPs are characterized by their biocompatibility, making them suitable for applications in drug delivery, imaging, and other biomedical fields.

This synthesis approach aligns with the principles of green chemistry, emphasizing sustainability, reduced environmental impact, and the use of biodegradable materials. The resulting AuNPs, derived from biodegradable polymers, hold promise for advancing environmentally conscious nanomaterial applications.

1.3.d) Synthesis of AuNPs from green solvents

The synthesis of gold nanoparticles (AuNPs) from green solvents is a sustainable approach that involves environmentally friendly solvents, such as water, vegetable oils, or ionic liquids [51-56]. This method aligns with the principles of green chemistry, emphasizing the use of non-toxic, biodegradable, and environmentally benign materials. Here is an explanation of the synthesis process:

Selection of Green Solvent: The first step involves choosing a green solvent suitable for the synthesis of AuNPs. Criteria for selecting a green solvent include biodegradability, non-toxicity, and high solubility for both gold ions and reducing agents. Examples of green solvents include water, vegetable oils like olive or soybean oil, and ionic liquids such as choline chloride-based ionic liquids [57].

Preparation of Solvent: Depending on the chosen green solvent, appropriate preparation is carried out [58,59]. For vegetable oils, the oil may be heated to a temperature above its melting point to obtain a liquid solvent. In the case of ionic liquids, they are dissolved in water to form a liquid solvent.

Addition of Gold Ions: A solution containing gold ions (commonly HAuCl4) is added to the green solvent. The solution is stirred to ensure uniform mixing of gold ions within the solvent.

Addition of Reducing Agents: To initiate the reduction of gold ions into metallic gold nanoparticles, reducing agents are introduced into the solution. Common reducing agents include sodium borohydride (NaBH4) or ascorbic acid. These reducing agents play a crucial role in facilitating the reduction process [60,61].

Purification of AuNPs: After the synthesis, the AuNPs may undergo purification steps to remove impurities or unreacted components. Common purification methods include centrifugation or filtration.

The use of green solvents in the synthesis of AuNPs not only contributes to the sustainability of the process but also enhances the biocompatibility of the resulting nanoparticles. This environmentally conscious approach reduces the reliance on traditional solvents that may be harmful to human health and the environment [62].

The resulting AuNPs synthesized from green solvents find applications in various fields, including biomedicine, catalysis, and environmental science, where the emphasis is on developing technologies that are both effective and environmentally friendly.

1.3.e) Benefits of green or biosynthesis of AuNPs

Green synthesis of gold nanoparticles (AuNPs) refers to the eco-friendly and sustainable production of AuNPs using natural sources, such as plant extracts, microbes, and other biological materials, instead of conventional chemical methods [63-65]. The benefits of green synthesis of AuNPs are numerous and can be summarized as follows:

- **Eco-friendly:** Green synthesis of GNPs is a sustainable process that uses non-toxic and biodegradable materials, thereby reducing the environmental impact of conventional synthesis methods.
- **Cost-effective:** Green synthesis of GNPs is a cost-effective process that uses low-cost and readily available natural sources as starting materials, such as plant extracts and microorganisms, compared to conventional synthesis methods that require expensive reagents and solvents [66].
- **Enhanced biocompatibility:** Green synthesized GNPs are generally more biocompatible than conventionally synthesized GNPs because they are produced using natural sources and do not contain toxic chemicals that can harm living organisms.
- **Improved stability:** GNPs synthesized using green methods exhibit improved stability compared to conventionally synthesized GNPs because of the presence of natural capping agents in the biological extracts that prevent the aggregation and precipitation of the particles [67].
- **Tuneable properties:** The properties of GNPs synthesized using green methods can be easily tuned by changing the concentration of the biological extract or by using different plant extracts or microorganisms, thereby allowing for the production of GNPs with specific properties and applications.
- **Potential for vast-scale production:** green synthesis of GNPs can be easily scaled up for larger-scale production because of the availability of low-cost and readily available starting materials.

To summarize, the green synthesis of GNPs offers a sustainable and cost-effective approach for producing GNPs with improved biocompatibility, stability, and tunable properties, which can be utilized in various applications, like medicine, nanotechnology, and environmental remediation [68, 69].

2. Mechanism of AuNPs

The mechanisms of gold nanoparticles (AuNPs) vary depending on their size, shape, and surface properties [71]. Here are some key mechanisms through which AuNPs exert their effects in various applications:

Surface Plasmon Resonance (SPR): One of the unique features of AuNPs is their ability to exhibit surface plasmon resonance (SPR), which is a collective oscillation of electrons on the nanoparticle's surface when exposed to light. The SPR phenomenon is highly dependent on the size and shape of the AuNPs [72]. This optical property is exploited in various applications, including sensing and imaging, where changes in the SPR wavelength are indicative of alterations in the nanoparticle environment.

Photothermal Effect: AuNPs have exceptional photothermal properties, especially in the near-infrared (NIR) region. When exposed to light within this range, AuNPs absorb and convert the light into heat. This photothermal effect is harnessed in photothermal therapy for cancer treatment, where AuNPs are selectively heated to destroy cancer cells while minimizing damage to surrounding healthy tissues [73-75].

Catalytic Activity: AuNPs exhibit catalytic activity, particularly in reactions involving oxidation and reduction. Their catalytic properties are highly dependent on their size, shape, and surface structure [76,77]. This catalytic activity is utilized in various chemical transformations and green chemistry applications.

Drug Delivery: AuNPs serve as carriers for drug delivery. Drugs or therapeutic agents can be attached to the surface of AuNPs, taking advantage of their ability to penetrate cell membranes. The release of the therapeutic payload can be controlled through stimuli-responsive coatings or triggered by external factors, enhancing the precision and efficiency of drug delivery [78,79].

Enhancement of Imaging Contrast: In biomedical imaging, AuNPs act as contrast agents. Their ability to scatter or absorb light enhances imaging contrast in techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and photoacoustic imaging. AuNPs improve the visibility of tissues and aid in the early detection of diseases.

Antimicrobial Action: AuNPs exhibit antimicrobial properties. Their interaction with microbial cells can lead to structural damage, disruption of cellular membranes, and inhibition of vital cellular processes. This antimicrobial action is explored in various applications, including wound healing and as coatings for medical devices [80].

Electrical Conductivity: AuNPs are excellent conductors of electricity. This property is utilized in electronics and sensing devices, contributing to the fabrication of sensors, memory devices, and conductive films [81].

Immunomodulation: AuNPs can modulate the immune system by interacting with immune cells and influencing cytokine release. This property is explored in immunotherapy applications, where AuNPs are used to enhance the immune response against cancer cells [82].

ROS Generation: AuNPs can induce the generation of reactive oxygen species (ROS) within cells. This property is exploited in cancer therapy, where ROS contributes to cell death mechanisms [83].

Understanding these mechanisms is crucial for tailoring AuNPs for specific applications and optimizing their performance in various fields of science and technology. Researchers continue to explore and refine these mechanisms to unlock new possibilities and applications for gold nanoparticles.

Dectin-1 is a receptor on the surface of phagocytes and macrophages that recognizes beta-glucans, constituents of fungal cell walls. Activation of dectin-1 triggers a series of signaling events that lead to phagocytosis and subsequent killing of the fungal cell [84-85]. Similarly, AuNPs (gold nanoparticles) can be functionalized to target specific cells and activate macrophages, leading to phagocytosis and cell death. In addition, activating macrophages by dectin-1 and AuNPs can also release several immune-regulatory molecules or substances, such as cytokines, leukotrienes, and interleukins, as shown in Figure 5.

These molecules or substances play a vital role in regulating the proliferation and activity of T-cells, which are critical constituents of the immune system [86]. Therefore, the activation of macrophages by dectin-1 and AuNPs can have a significant impact on the immune response and potentially can be used for therapeutic purposes. Overall, the mechanism of action of dectin-1 and AuNPs in activating macrophages and regulating immune response is a potential area of research, and studies are required to fully understand their potential for clinical applications [87,88].

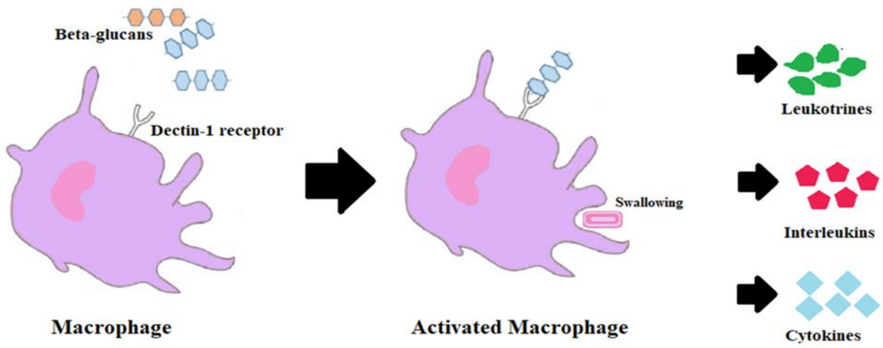

Fig. 5. The activation of macrophages from yeast-procured β-1,3-glucan (B13G) by binding to Dectin-1.

3. Applications of AuNPs

Gold nanoparticles (AuNPs) have a vast range of potential applications owing to their unique properties. Some of the most common applications of AuNPs include [89-91]:

Biomedical imaging: AuNPs are often seen as contrast agents in medical imaging techniques like computed tomography (CT) and photoacoustic imaging. Their excellent S/V ratio and ability to scatter and absorb light make them ideal for enhancing image contrast.

Drug delivery: AuNPs can be functionalized with drugs or therapeutic agents and targeted to specific cells or tissues. The small dimension and surface characteristics of AuNPs allow them to easily penetrate cell membranes, making them a promising option for drug delivery [92].

Cancer Therapy: AuNPs can be used in cancer therapy because they absorb and scatter light, which can selectively heat and kill cancer cells (photothermal treatment). AuNPs can also be functionalized with chemotherapy drugs or other therapeutic agents to target cancer cells

Biosensors: AuNPs can be utilized in biosensors to spot the presence of particular biomolecules, like DNA or proteins. When these biomolecules bind to the AuNPs, it causes a change in their optical properties, which can be easily detected [93].

Environmental remediation: AuNPs can be used to remove contaminants from water or soil in environmental remediation. Their high S/V ratio and ability to bind to organic and inorganic pollutants make them practical for cleaning up pollution [94].

Overall, the unique properties of AuNPs make them promise a vast range of usage in biomedical, environmental, and industrial fields, as shown in Figure 6.

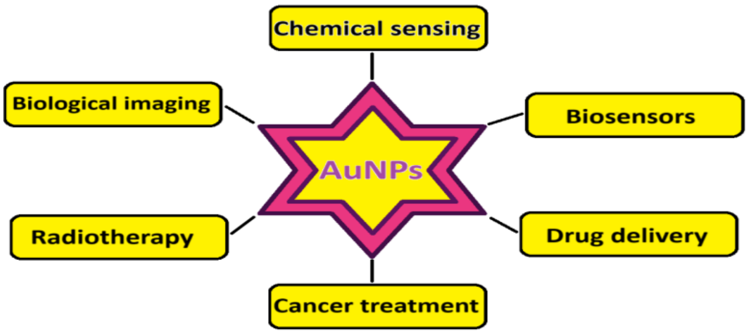

Fig. 6. The schematic representation of uses/functionalization of AuNPs.

3.1 Application of gold nanoparticles in vaccinology

AuNPs have been explored as a promising vaccine development platform known as "nanovaccinology". Here are some ways in which AuNPs can be used in vaccinology:

Antigen delivery: AuNPs can be utilized as carriers to transport antigens to immune cells. Attaching antigens to the surface of AuNPs can be delivered directly and immediately to antigen-presenting cells (APCs), such as dendritic cells, which can activate the immune system [95].

Adjuvant delivery: Adjuvants are substances that can enhance the immune responses to antigens. AuNPs can be used as carriers to transport adjuvants, such as toll-like receptors, i.e., α-adrenergic agonists, to immune cells, which can further enhance the immune response [96].

Immune cell activation: AuNPs can directly interact with immune cells and systems, such as dendritic cells, phagocytes, and macrophages, to activate them and promote the production of cytokines, which are important signaling molecules for immune activation [97].

Immunomodulation: AuNPs can modulate the immune system by inducing tolerance or suppressing the immune response, which can be helpful in specific applications, such as transplantation and autoimmunity.

Tracking and imaging: AuNPs can be used as imaging agents to track the migration of immune cells and the distribution of vaccines in vivo.

Overall, AuNPs have the potential to improve vaccine efficacy and safety, as well as enable the evolution of new types of vaccines [98]. The most feasible way to synthesize AuNPs is the Turkevich and Brust-Schiffrin technique to synthesize thermally and air-stable AuNPs in which chloroauric acid ($HAuCl_4$) reacts reductively by surface modification, functionalization, and application [99] as shown in Figure 6.

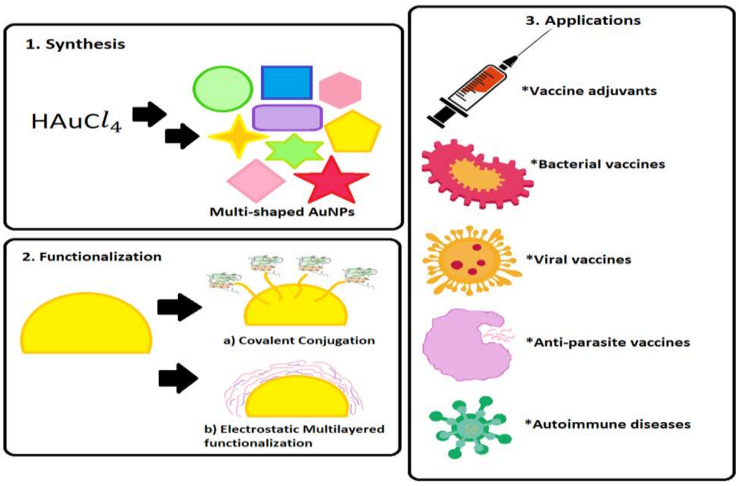

Fig. 6.1. Synthesis: Accurately functionalized gold nanoparticles can be made from Au III salts, and their structure and form can be fine-tuned. **6.2)** Functionalization: Using reliable Au-S chemistry, the gold surface is functionalized with oligo or polysaccharides, ligands, and proteins. A multi-layered method can be used to achieve surface functionalization. **6.3)** Applications: AuNPs can benefit a wide range of sectors, and they will be discussed in this study in terms of their most recent progress.

AuNPs can interact with both the adaptive immune system and humoral immunity, as shown in Figure 7. Adaptive immunity and humoral immunity are two components of the immune system that work together to defend the body against pathogens such as bacteria, viruses, and parasites.

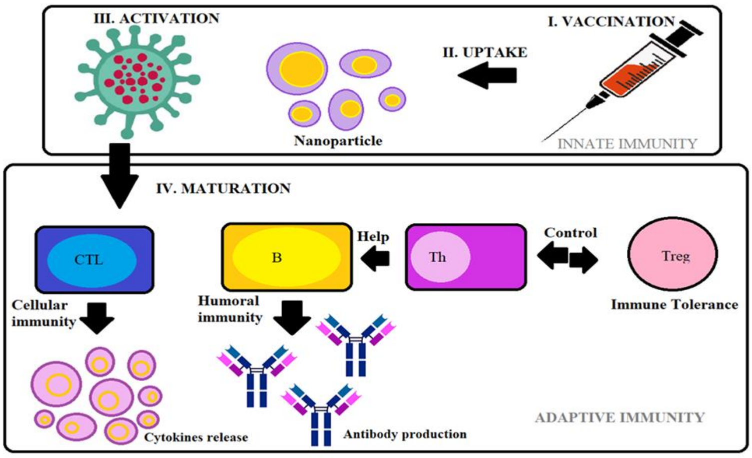

Fig. 7. shows the adaptive and innate immune responses of AuNP vaccines in the schematic diagram. Antigens are processed by APCs (antigen-presenting cells), which facilitate T-cell proliferation in the direction of cellular (cytokines) and humoral (antibodies). CTL stands for cytotoxic thymus-derived lymphocytes; B denotes Bursa-derived lymphocytes; The denotes T lymphocytes helper cells; and Treg is regulatory T cells.

Adaptive Immunity: Adaptive immunity, also known as acquired immunity or specific immunity, is the immune response that is tailored to a particular pathogen [100]. It is characterized by its ability to recognize specific antigens, which are unique molecules present on the surface of pathogens. Adaptive immunity involves the activation of specialized immune cells called lymphocytes, particularly B cells and T cells.

a) T-cells: AuNPs can activate T-cells and release cytokines, which are important cells of the innate immune systems, i.e., lymphocytes. T-cells can recognize and attack cells that are infected with a virus or have become cancerous. In one study, AuNPs were found to activate T-cells in mice, indicating their potential as a therapeutic agent for cancer [101]. **b)** B-cells: AuNPs can also activate B-lymphocytes, which are accountable for producing antibodies. In a study, AuNPs were set forth to stimulate the production of B-lymphocytes and escalate the levels of antibodies in mice [102].

Humoral Immunity: Humoral immunity is a component of adaptive immunity that involves the production of antibodies, also known as immunoglobulins (Ig), by B cells. Antibodies are proteins that circulate in the bloodstream and other body fluids. They can recognize and bind to specific antigens on pathogens, neutralizing them or marking them for destruction by other immune cells [101,103]. This process is referred to as antibody-mediated or humoral immunity because antibodies are the key effectors in this immune response. Humoral immunity is effective against extracellular pathogens, such as bacteria and toxins, that are present in body fluids. Antibodies can prevent pathogens from entering host cells, enhance phagocytosis (the engulfment and destruction of pathogens by immune cells), and activate the complement system, which is a group of proteins that help eliminate pathogens.

a) Antibodies: AuNPs can be coated with proteins or other substances the immune system identifies. When these coated AuNPs are introduced into the body, they can stimulate the production of antibodies. For example, in one study, AuNPs covered with the protein ovalbumin were found to stimulate the production of antibodies in mice [104]. **b)** Complement system: AuNPs can also activate the complement system, a part of the humoral immune system that helps clear pathogens from the body. In a study, AuNPs were illustrated to activate the complementary system in vitro [105].

3.2 Gold nanoparticle as conjugated system

A gold nanoparticle (AuNP) as a conjugated system refers to the attachment or linkage of various molecules, typically organic compounds, to the surface of the gold nanoparticle. This conjugation creates a hybrid structure where the unique properties of gold nanoparticles are combined with the functional characteristics of the attached molecules. The conjugation of different entities to gold nanoparticles can serve various purposes, ranging from enhancing stability and solubility to enabling specific functionalities for applications in areas such as medicine, sensing, and catalysis [106].

Here are key aspects of gold nanoparticles as conjugated systems:

- **Surface Functionalization:**

Gold nanoparticles have a high surface area, providing ample sites for functionalization. The surface of these nanoparticles can be modified by attaching organic molecules, ligands, or biomolecules. The process of attaching these entities is often referred to as surface functionalization or conjugation [107].

- **Enhanced Stability and Solubility:**

Conjugating molecules to the surface of gold nanoparticles can enhance their stability and solubility in different environments [108]. This is particularly important for applications in biological systems where maintaining stability and preventing aggregation are critical.

- **Biological and Medicinal Applications:**

Gold nanoparticles are extensively explored in biomedicine. Conjugation with biomolecules, such as antibodies, peptides, or drugs, allows for targeted delivery, imaging, and therapeutic interventions. The conjugated system can be designed to recognize specific cells or tissues, enabling precision in medical applications [109].

- **Sensing and Detection:**

Gold nanoparticles serve as excellent platforms for sensing and detection applications. Conjugation with molecules that exhibit selective binding to certain analytes enables the development of highly sensitive and specific sensors. These systems find use in detecting various substances, including biomolecules, pollutants, and pathogens.

- **Catalysis:**

Gold nanoparticles, when conjugated with specific ligands or catalysts, can exhibit unique catalytic properties. This has applications in green chemistry and catalysis, where the conjugated system can facilitate specific chemical transformations with high efficiency [110].

- **Optical and Electronic Properties:**

The optical and electronic properties of gold nanoparticles are highly tunable, and conjugation with certain molecules can further modify these properties. This is exploited in various applications, such as enhancing the absorption of light for photothermal therapy or creating materials with tailored electronic characteristics.

- **Customization for Specific Applications:**

The conjugation of molecules to gold nanoparticles allows for the customization of these nanoparticles for specific applications. By choosing the appropriate ligands or functional groups, researchers can design conjugated systems with desired properties suited to their intended purpose [111].

In summary, gold nanoparticles as conjugated systems represent a versatile platform where the properties of gold nanoparticles are combined with the functionalities of attached molecules. This conjugation opens up a wide range of possibilities for tailored applications in fields such as medicine, sensing, catalysis, and beyond, making gold nanoparticles highly sought after in nanotechnology and materials science.

Gold nanoparticles or AuNPs conjugated with varied types of anticancer or antibacterial agents as shown in table 1 and table 2. When incorporated or targeted to the cancer cell or bacterial cell, these recognize the cell type and kill the cell by blocking the pathway or by phagocytosis and ultimately stopping the proliferation of the sick cell, as conveyed in the graphical abstract. Such types of AuNPs are 1) highly potent, 2) with a defined mechanism of action, 3) stable in circulation and lysosome forms 4) amenable to modifications that allow fast and easy linker attachment [112].

3.3. Gold nanoparticle as a cancer vaccine

Gold nanoparticles (AuNPs) have been explored as a potential avenue for cancer vaccination owing to their distinctive physicochemical attributes, particularly their capacity to carry and deliver antigens to immune cells. When coated with antigens, AuNPs exhibit the capability to elicit an immune response against cancer cells [113]. Although the use of gold nanoparticles in cancer vaccines is a relatively nascent area of research, preliminary studies have yielded encouraging outcomes. In a notable study, gold nanoparticles coated with a protein derived from the HER2/neu gene effectively stimulated an immune response in mice with breast cancer. Another study demonstrated that gold nanoparticles, cloaked with a peptide from the melanoma-associated antigen MART-1, induced an immune response in mice with melanoma [114]. Despite these promising findings, several challenges must be addressed before incorporating gold nanoparticle-based cancer vaccines into human use. A critical hurdle involves ensuring that the generated immune response is sufficiently robust to effectively target cancer cells. Additionally, further research is essential to determine the optimal size, shape, and coating of Au nanoparticles for cancer vaccines.

Table 1. Anticancer agents conjugated to gold nanoparticle.

S.No.	Anticancer agent	Nanoparticle
1.	chlormethine	Gold nanoparticle
2.	cyclophosphamide	Gold nanoparticle
3.	chlorambucil	Gold nanoparticle
4.	carmustine	Gold nanoparticle
5.	dacarbazine	Gold nanoparticle
6.	temozolomide	Gold nanoparticle
7.	methotrexate	Gold nanoparticle
8.	6-mercaptopurine	Gold nanoparticle
9.	cisplatin{cis-diamminedichloroplatinum(II)}	Gold nanoparticle
10.	5-fluorouracil (pyrimidine antagonist)	Gold nanoparticle

Table 2. Antibacterial agents conjugated to gold nanoparticle.

S.No.	Antibacterial agent	Nanoparticle
1.	ampicillin	Gold nanoparticle
2.	amoxicillin	Gold nanoparticle
3.	ceftriaxone	Gold nanoparticle
4.	chloramphenicol	Gold nanoparticle
5.	erythromycin	Gold nanoparticle
6.	streptomycin	Gold nanoparticle
7.	ciprofloxacin	Gold nanoparticle
8.	sulfamethazine	Gold nanoparticle
9.	augmentin	Gold nanoparticle

One of the most promising mechanisms for the application of gold nanoparticles in cancer treatment lies in their ability to selectively target and eliminate cancerous cells while safeguarding healthy cells. AuNPs can be tailored with various ligands and molecules designed to specifically target cancer cells, as depicted in Figure 8. For instance, they can be coated with antibodies or peptides that recognize and bind to specific receptors on the surface of cancer cells. Following binding, gold nanoparticles can be internalized into the cancer cells through endocytosis [115]. Once inside the cancer cell, these nanoparticles can induce cell death through diverse mechanisms, including the generation of reactive oxygen species (ROS), disruption of cellular signaling pathways, and initiation of apoptosis (programmed cell death). Furthermore, gold nanoparticles can act as radio sensitizers, augmenting the effectiveness of radiation therapy by increasing the production of ROS in cancer cells [116].

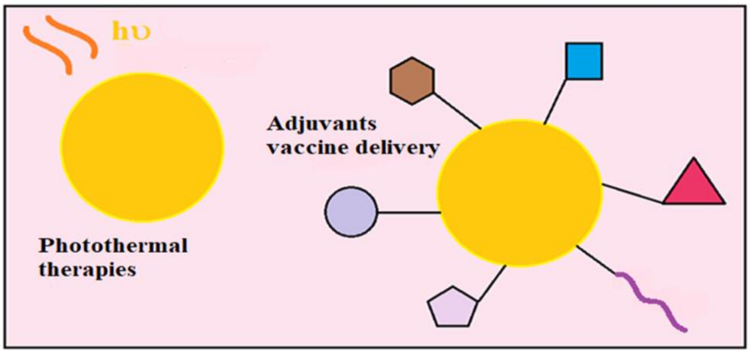

Fig. 8. AuNP vaccine with surface ligands used in cancer treatment.

Beyond their direct cytotoxic effects, gold nanoparticles possess the capability to modulate the immune system, amplifying the body's inherent ability to combat cancer. They can stimulate the release of cytokines and chemokines, activating immune cells such as B cells, T cells, and natural killer cells to recognize and eliminate cancer cells. The multifaceted potential of gold nanoparticles in cancer therapy, encompassing both direct cytotoxicity and immune system modulation, positions them as promising candidates for further exploration and development in the realm of oncology [117].

Gold nanoparticles offer unique properties that make them attractive candidates for developing cancer vaccines.

Here's how gold nanoparticles can function as a cancer vaccine:

- **Antigen Presentation:**

Cancer cells produce specific proteins or antigens that can be targeted by the immune system. Gold nanoparticles can be engineered to carry these cancer-specific antigens. When coated with antigens, AuNPs serve as carriers that present these cancer markers to immune cells, particularly antigen-presenting cells (APCs) like dendritic cells [118].

- **Immune System Activation:**

The immune system needs to be activated to recognize the presented cancer antigens as threats. Gold nanoparticles, acting as carriers, can stimulate the activation and maturation of dendritic cells. These activated dendritic cells then migrate to lymph nodes, where they present the cancer antigens to T cells, initiating a targeted immune response [119].

- **T Cell Activation:**

T cells, a crucial component of the immune system, play a central role in recognizing and destroying cancer cells. Gold nanoparticles assist in priming T cells by presenting cancer antigens. This process activates both cytotoxic T cells, responsible for directly attacking cancer cells, and helper T cells, which coordinate immune responses [120].

- **Immunological Memory:**

An effective cancer vaccine should not only stimulate an immediate immune response but also establish immunological memory. This means that the immune system remembers and recognizes the cancer antigens, allowing for a rapid and efficient response if cancer cells reappear. Gold nanoparticle-based vaccines aim to induce long-lasting immunity against specific cancer markers [121].

- **Promising Results in Preclinical Studies:**

Early studies exploring the use of gold nanoparticles as cancer vaccines have shown promising results. For example, researchers have coated gold nanoparticles with specific proteins or peptides from cancer cells, such as those associated with breast cancer or melanoma. In animal studies, these AuNP-based vaccines induced immune responses that targeted and inhibited the growth of cancer cells [122].

Despite these promising outcomes, challenges remain. It is crucial to optimize the design of gold nanoparticle-based vaccines, including determining the ideal size, shape, and surface properties for effective antigen presentation. Additionally, researchers must ensure that the induced immune response is potent enough to combat cancer cells effectively [123].

In summary, gold nanoparticles hold significant potential as carriers for cancer vaccines, leveraging their unique properties to stimulate and enhance the immune system's ability to recognize and eliminate cancer cells. Ongoing research in this field aims to refine the design and effectiveness of gold nanoparticle-based cancer vaccines for potential clinical applications in the future.

4. Conclusions

Gold nanoparticles hold great promise as a potential boon for cancer treatment and prevention. They offer several advantages over traditional cancer therapies, such as high selectivity, minimal side effects, and the ability to be functionalized with specific targeting ligands. Studies have shown that gold nanoparticles can effectively induce an immune response against cancer cells when used as a vaccine. They can also directly target cancer cells and cause cell death through various mechanisms. Gold nanoparticles can also act as radiosensitizers, enhancing the effectiveness of radiation therapy. Despite the promising results, more research is needed to fully understand the mechanisms of action of gold nanoparticles and optimize their use as cancer therapies. Before using, gold nanoparticle-based therapies in clinical settings, one must approve safety concerns and regulatory approval. In conclusion, gold nanoparticles have the potential to revolutionize cancer treatment and prevention, and ongoing research in this area offers hope for developing safe and effective cancer therapies that can improve the lives of millions of people worldwide.

Future prospective

The future of gold nanoparticles (AuNPs) in cancer treatment and diagnostics holds immense promise, with several emerging trends set to revolutionize oncology. Targeted drug delivery systems using AuNPs functionalized with ligands for precision targeting of cancer cells are expected to enhance treatment specificity and reduce side effects. Combining AuNPs with other therapies, such as immunotherapy or photothermal therapy, could lead to more effective multimodal treatments, while advances in theranostics will enable real-time imaging and monitoring during therapy. However, challenges remain, particularly in improving the biodegradability and reducing the long-term toxicity of AuNPs in the body. Future research will need to focus on optimizing their safety and efficacy for clinical applications, potentially making AuNPs a cornerstone in personalized cancer therapy.

Author Contributions

Anjali Yadav conducted the literature review, synthesized the emerging trends, and contributed to the analysis of the therapeutic potential of gold nanoparticles in cancer treatment and diagnostics. Ruchi Bharti provided critical feedback, guided the structure of the review, and supervised the overall development of the manuscript. Both authors discussed the findings and contributed to writing and finalizing the manuscript.

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