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GOLD NANOPARTICLE FOR WOUND HEALING AND ANTIMICROBIAL APPLICATIONS

Aisha Kasim Baraza, Ali Muhammad, Rashmi Pandey*, Sandip Prasad Tiwari

Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)

*Corresponding Author's E mail: rashmi.pandey@kalingauniversity.ac.in
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ABSTRACT

Gold nanoparticles (AuNPs) have gained significant attention in the field of wound healing and antimicrobial applications due to their unique physicochemical properties. Studied have highlighted the recent advances in utilizing AuNPs for wound healing and antimicrobial applications. AuNPs have shown potent antimicrobial activity against a wide range of bacteria. The mechanism of action involves the disruption of bacterial membranes and the generation of reactive oxygen species, leading to bacterial cell death. The use of AuNPs as antibacterial agents has shown promising results in preventing and treating wound infections. Their high surface area and unique physical properties promote cell proliferation, migration, and collagen synthesis. AuNPs also exhibit anti-inflammatory activity, reducing the production of pro-inflammatory cytokines and promoting the resolution of inflammation. As a result, wounds treated with AuNPs show accelerated healing, reduced scar formation, and improved tissue regeneration. The controlled release of bioactive molecules from AuNPs is another area of interest in wound healing applications. Loading therapeutic agents onto the surface of AuNPs enables site-specific delivery and sustained release, improving the therapeutic efficacy. Various bioactive molecules, including growth factors, antimicrobial agents, and anti-inflammatory drugs, have been successfully loaded onto AuNPs for targeted delivery to wounds. Overall, AuNPs hold great potential in wound healing and antimicrobial applications. Their unique physicochemical properties, antibacterial activity, promotion of wound healing, and ability for controlled drug release make them valuable tools in the development of advanced wound care strategies

Keywords: Gold nanoparticles, Antimicrobials, Wound healing, Physicochemical

INTRODUCTION

The largest organ in the human body, the skin acts as an ecosystem that regulates temperature, fights infection, and generates vitamin D in addition to being the body's first line of defence. It can, however, pierce, resulting in burns, falls, or other accidents. Injuries cause tissue disruption in the body and open the interior to infection, necessitating prompt medical attention. A wound is any disturbance or harm to

the tissues of your body, particularly the skin,mucous membranes, or internal organs. Injuries can cause wounds that occur quickly, or an underlying health issue may result in them to grow gradually.

Wound healing process

The process of healing a wound is dynamic and complex, involving several steps, aimed at restoring the structural and functional integrity of damaged tissue. The process can be broadly separated into several phases that overlap Hemostasis phases, Inflammatory phases, Proliferative phases and Remodeling phases. As shown in (Fig:1).The initial response to injury involves vasoconstriction to reduce blood flow and the developing of a temporary blood clot (hemostasis).Platelets play a vital part in forming a plug to stop bleeding. Inflammation is a natural and necessary response to injury. White blood cells (neutrophils and macrophages) migrate to the wound site to remove debris, bacteria, and damaged tissue. Inflammatory mediators, such as cytokines and growth factors, are released to coordinate the healing process. Fibroblasts migrate to the wound site and produce collagen, a protein that provides strength to the healing tissue. Angiogenesis (formation of new blood vessels) occurs to supply nutrients and oxygen to the healing tissue. Epithelial cells proliferate to cover the wound surface (Proliferation phases). Collagen fibers undergo remodeling to increase tensile strength and flexibility. Excess cells undergo apoptosis (programmed cell death). The scar tissue formed during the proliferative phase matures and becomes more organized [1].

Several factors influence the wound healing process:

Nutrition: Adequate nutrients, especially proteins, vitamins, and minerals, are necessary for the operation of cells and tissue repair. Oxygenation: Adequate blood supply is crucial for delivering nutrients and oxygen to the healing tissue. Infection Control: Infections can significantly impede the healing process, so preventing and treating infections is important.

Age: The healing process may be slower in older individuals as a result of a reduction in cell growth and other age-related factors. Various growth factors, cytokines, and cell signaling pathways regulate and coordinate the different phases of wound healing. Disruption or imbalance in any of these phases can lead to impaired healing, chronic wounds, or excessive scar formation. It's important to note that the body's ability to heal can vary based on the type and wound location, additionally the overall health of the individual. Chronic conditions such as diabetes or compromised immune function can impact the normal wound healing process [2].

Gold Nanoparticles in Medicine

A minimum of many millennia have passed since the discovery of gold, making it one of the first metals to be studied and utilised. The first records of colloidal gold is located in the treatises of Arabian, Chinese, and Indian scholars who attempted to obtain it as early as the fifth or fourth century BC. They used it for therapeutic purposes (called "liquid gold" in Indian and "golden solution" in Chinese) as well as other purposes. During the Middle Ages, alchemist laboratories in Europe explored and employed colloidal gold.

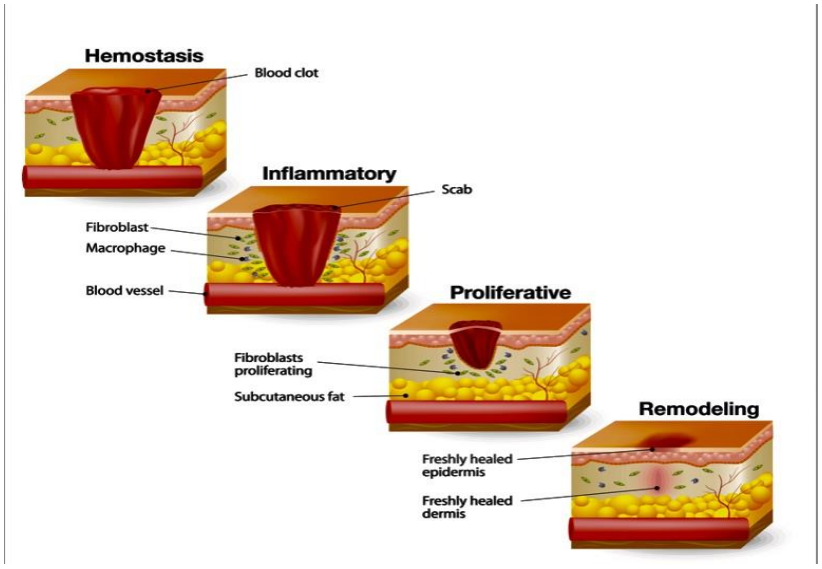

Fig 1: Different stages involved in wound healing mechanism

Paracelsus wrote about gold's quintessence medicinal qualities[11]. Gold nanoparticles (AuNPs) have drawn a lot of interest in the medical community because of its distinctive properties and diverse applications. These nanoparticles, typically ranging in size from 1 to 100 nanometers, can be precisely controlled to synthesize their shape, size, and surface qualities, which make them perfect for biomedical applications[3]. One of the most notable characteristics of AuNPs is their excellent biocompatibility, meaning they are well-tolerated by the human body and do not cause any significant toxicity. This is vital to take into account their potential use in medical treatments.

Gold Nanoparticles as Drug Delivery Vehicles

Despite the lack of a clear understanding of the mechanism(s) involved, nanoparticles can readily infiltrate cells. Endocytosis is the process by which the nanoparticles enter and diffuse across the lipid bilayer of the cell membrane, causing the influx. Additionally, it was shown that these nanoparticles may penetrate cells even after attaching to proteins like antibodies. Furthermore, functionalized nanoparticles have been utilised for targeted cell entrance. A combination of nanoparticles and anti-bodies against

specific receptors on the surface of cancer cells have been used to specifically connect with malignant cells. It's been proven that phthalocyanine-stable gold nanoparticles are a type of viable delivery [4]. These nanoparticles are prized for their special qualities such as focused delivery, safety, and increased uptake, making them efficient transporters for diverse bioactive compounds, thereby enhancing drug efficiency[5]. Due to their antioxidant and anti-inflammatory properties, gold nanoparticles are utilized in the handling of different disorders, including tissue repair. They exhibit substantial antioxidant properties by quenching free radicals and have a high proclivity interacting with oxygen species that are reactive, making them potent antioxidant agents crucial for wound healing [6]. Gold nanoparticles are acknowledged as well for their catalytic activity in free radical scavenging processes and their ability to increase levels of NRF2, a factor that activates antioxidant gene expression, further contributing to wound healing [7]. The size of gold nanoparticles is a critical parameter influencing their behavior in biological systems. Nanoparticle size can affect circulation time, cellular uptake, and biodistribution. The size can be precisely controlled during synthesis. Surface

Chemistry and Zeta Potential: The surface of gold nanoparticles is applicable to different functional groups to enhance stability, biocompatibility, and drug-loading capacity. Zeta potential, which reflects the surface charge of nanoparticles, is crucial for understanding their stability and interaction with biological environments. Controlled surface charge can influence cellular uptake and protein adsorption.

Drug Loading and Release: Gold nanoparticles can carry therapeutic agents, including drugs, peptides or nucleic acids, on their surfaces or within their matrices[8]. Gold nanoparticles have become a promising candidate for delivering various payloads to target sites, spanning from small drug molecules to larger biomolecules like DNA, RNA, and proteins. Their high specific surface area enables nanoscale particles to bind functional ligands or serve as carriers for active substances, enhancing interactions with target bacteria [9].

Mechanisms of Gold Nanoparticles in Wound Healing

Gold nanoparticles act as antioxidants by inhibiting free radicals such as hydroxyl, nitric oxide, and hydrogen peroxide. Gold nanoparticle application on cutaneous wounds increased the angiopoietin, VEGF, and collagen expressions and reduced MMP and TGF-β1 levels. The use of gold nanoparticles has in cancer therapy, biosensing, gene, drug delivery, imaging, and biocompatibility. Besides, antibiotic-coated gold nanoparticles doped PCL/gelatin nanofiber mat was examined on infected full-thickness wounds. It exhibited reduced bacterial load and promoted healing [10]. The mechanisms through which gold nanoparticles contribute to wound healing are multifaceted, involving various biological

processes atom, molecular and cellular level. Gold nanoparticles exhibit anti-inflammatory properties by modulating the immune response. They can attenuate pro-inflammatory cytokine release, such as interleukin-I beta (IL-1) and tumor necrosis factor-alpha (TNF-a), which helps in reducing inflammation at the wound site. Gold nanoparticles possess antioxidant capabilities that can counteract oxidative stress, a common factor in impaired wound healing. By scavenging free radicals and reducing oxidative damage, they contribute to a more favorable wound microenvironment. Promotion of Angiogenesis. Gold nanoparticles promote the development of new blood vessels (angiogenesis) in the area of wound. This is crucial for supplying nutrients and oxygen to the healing tissue, enhancing the overall healing process. Stimulation of Fibroblast Activity. Fibroblasts are in charge of generating collagen, a key component of the extracellular matrix. Gold nanoparticles stimulate fibroblast proliferation and collagen synthesis, contributing to improved tissue structure and strength. Gold nanoparticles facilitate the migration and proliferation of various cell types involved in wound healing, including keratinocytes and endothelial cells. This accelerates the closure of the wound and the re-establishment of tissue integrity. Gold nanoparticles can influence the activity of matrix metalloproteinases (MMPs), enzymes involved in tissue remodeling. Proper regulation of MMPs is essential for balanced tissue repair and scar formation [11].

The necessity for Advanced Wound Healing Approaches

The necessity for advanced wound healing approaches arises from a variety of causes, such as the desire to improve the efficiency, speed, and effectiveness of the natural wound healing process. Advanced wound healing approaches aim to treat issues related to persistent wounds (chronic wounds), slow healing, and complications that can arise in certain medical conditions [12]. Chronic wounds, such as diabetic ulcers, venous ulcers, and pressure ulcers, often present challenges in healing. Chronic wounds are the primary cause of death worldwide owing to sepsis. Wound sepsis is a disease that causes systemic infection at the wound site, increasing the risk of patient death [13]. The growth of biofilm, microbial pathogens, and bioburden at the wound site might impede wound healing. Therefore, there is an immediate need for effective formulations to treat chronic wound infections quickly[14]. Advanced approaches aim in order to hasten the recovery of these wounds and prevent complications. Infections can significantly impede the normal wound healing process. Advanced wound healing strategies may include the development of antimicrobial dressings and therapies to prevent and treat infections. Certain wounds, especially large or deep ones, can lead to excessive scarring. Advanced approaches focus on promoting tissue regeneration and minimizing scar formation, which is particularly important in cosmetically sensitive areas [15]. The use of bioactive materials, such as growth factors, cytokines, and

stem cells, can enhance the healing process by promoting cell proliferation, angiogenesis, and collagen synthesis[16].

Gold Nanoparticle Synthesis

Strategies and Methods

When synthesising gold nanoparticles, (AuNPs), two fundamental strategies are employed: the "Top-Down" approach, involving the reduction of bulk material into nanoparticles, and the "Bottom-Up" approach, which initiates synthesis from the atomic level.

1: Chemical Synthesis:

i. Turkevich Method

AuNPs produced through the Turkevich method typically range in size from 1 to 2 nm. This technique involves reducing gold ions (Au3+) to gold atoms (AuO) using various agents like amino acids, ascorbic acid, UV light, or citrate. The stabilization of AuNPs is achieved through the use of different capping or stabilizing agents

ii. The Brust Method

First reported in 1994, the Brust method utilizes a two-phase reaction to synthesize AuNPs ranging in size from 1.5 to 5.2 nm. The process involves a phase transfer using tetraoctyl ammonium bromide to move gold salt from an aqueous solution to an organic solvent (e.g., toluene). After that, an alkanethiol is added for stability and a reducing agent, like sodium borohydride, is used to decrease the gold. Orange becomes brown as a result of the reaction.

iii. Seed-Mediated Growth

While the Turkevich and Brust methods mainly produce spherical AuNPs, seed-mediated growth allows for the synthesis of different-shaped particles, such rods. Using reducing agents such as NaBH4, this method first creates synthetic seed particles by reducing gold salts. The synthesis of rod-shaped AuNPs is then accelerated by transferring these seeds to a metal salt solution with a mild reducing agent such as ascorbic acid, which stops further nucleation.

iv. **Digestive Ripening**: a practical technique for producing monodispersed gold nanoparticles with excessive ligands is digestive ripening. Alkanethiol is used as a digestive ripening agent in the procedure, which entails heating a colloidal solution at high temperatures (~138°C) for two minutes and then heating it at 1°C for five hours. The temperature has a significant impact on how the gold colloids' size

distribution is determined. These techniques provide flexible ways to control the stability, size, and form of gold nanoparticles for a range of uses in materials science, nanotechnology, and medicine.

2:Biological Gold Nanoparticles Synthesis (AuNPs):

The biological synthesis of AuNPs has garnered increasing attention recently as an environmentally benign substitute for chemical synthesis techniques involving harsh chemicals. Biological synthesis uses resources ranging from small bacterial cells to sophisticated eukaryotes and is regarded as clean, dependable, and environmentally benign.

Characteristics

TEM Provides high-resolution images of size and shape of particles. Gold nanoparticles are dispersed on a grid, and a beam of electrons passes through, revealing nanoparticle details. UV-Visible Spectroscopy; Determines the size and gold nanoparticles concentration.Gold nanoparticles exhibit surface plasmon resonance, resulting in characteristic absorption peaks in the UV-Visible spectrum.Measures hydrodynamic size distribution in solution. Laser light scattering by nanoparticles in Brownian motion is analyzed to determine size distribution and particle size. determines the gold nanoparticles' crystal structure. X-rays are diffracted by the crystal lattice of the nanoparticles, producing a diffraction pattern used to determine the crystal structure. It analyses surface functional groups and stabilizing agents. Measures the absorption of infrared light by functional groups on the nanoparticle surface[31]. Zeta Potential Measurement, determines nanoparticle surface charge, it measures the electric potential of aqueous gold nanoparticles, providing information on stability and potential interactions. Thermogravimetric Analysis (TGA); Quantifies the amount of stabilizing agent on the nanoparticle surface, measures weight changes as A measure of temperature, demonstrating the nanoparticles' thermal stability [17].

Antibacterial Properties of Gold Nanoparticles

The size and dispersibility of gold nanoparticles play an important part in their antibacterial effectiveness. Generally, smaller nanoparticles with diameters of 2-15 nm find applications in tissue immunology, biochemistry, and high-powered microscopy. Medium-sized nanoparticles (20-60 nm) are commonly used in environmental testing, DNA testing, and drug delivery. Larger nanoparticles (80-250 nm) find applications in medical, electrical, and X-ray optics. The transition in gold nanoparticle morphology from dispersed small particles to large aggregates alters the suspension color from red to blue. Gold nanoparticles exhibit antibacterial activity by releasing gold ions. The release of gold ions contributes to the antibacterial effect, with smaller nanoparticles releasing Au+ faster

due to their larger specific surface area. Upon exposure to bacteria, the released Au+ is evenly distributed around the bacteria, penetrating cell walls and entering cells. Within the cells, Au+ reacts with thiol groups to form Au-thiol groups. Thiol groups on cysteine can induce protein coagulation, and Protein folding involves disulfide bridging between cysteine residues. The exchange of gold ions with cysteine also disrupts microbes' respiration and electron transport systems. Because the chemicals (gold ions, surface coating agents, and synthesis chemicals) coexisting in gold nanoparticles are not entirely eliminated, gold nanoparticles may have bactericidal effects [18].

Biocompatibility

The toxicity of AuNPs may also depend on how much of them are given to a model organism. distinct cell types may have distinct absorption processes for the same NP, and the same tested cell line may experience multiple internalisation mechanisms. In general, the absorption and intracellular trafficking of NPs are significantly influenced by their physicochemical features. The biocompatibility was very unique to the organ or tissue. Size, shape, surface charge, and aggregation state are among the physicochemical properties of nanoparticles that have a high correlation with their cytotoxicity. When combined, these show how closely a number of factors, including the inherent characteristics of the particles, the formulation, the biological target, the dose, and even the methodology used to assess their toxicity, affect nanoparticle biocompatibility. Therefore, AuNP size determination significantly influences both their cytotoxicity and absorption by cells. Generally speaking, as particle size decreases, so does the cytotoxic effect of nanoparticles. Size-dependent cytotoxicity of gold nanoparticles (AuNPs) coated in polyethylene glycol (PEG) was shown in a mouse research. Particles in the 10–60 nm size range showed negative effects such DNA mutations, cell shape changes, or proliferative inhibition. Particles between 5 and 30 nm, on the other hand, did not exhibit any toxicity.

Safety consideration

Because nanomaterials are so complex, contradictory research findings have led to divergent perspectives on their safety. As previously discussed regarding the beneficial applications of gold nanoparticles (AuNPs), the fundamental prerequisites include biocompatibility and biological safety. In comparing in vitro and in vivo studies, it is crucial to acknowledge the limitations, as highlighted in numerous articles. In vitro experiments often involve high nanoparticle doses, and direct extrapolation of these findings to in vivo scenarios is impractical due to the gradual clearance of nanoparticles through renal and faecal excretion. For an accurate assessment of nanotoxicity, low doses should be employed in in vitro studies. Additionally, defining nanoparticle dosage as a concentration may not be suitable for establishing a dose-

response relationship, unlike conventional chemicals or drugs. Metrics such as the surface area or number of nanoparticles are probably greater appropriate indicators [19].

CONCLUSION AND FUTURE PROSPECTIVE

The available research supports the application of AuNPs with a range of unique characteristics, including magnetic properties (MRI), surface plasmon resonance, and fluorescence behaviour that is reflected upon conjugation with biological and biocompatible ligands. These attributes enable AuNPs to potentially play a major role in the medical diagnostic industry. Gold nanoparticles (AuNPs) have shown promising potential for wound healing and antimicrobial applications. Studies have highlighted the use of AuNPs in wound healing due to their antimicrobial effects and ability to enhance the healing process. Various methods have been employed to synthesize AuNPs, including hydrogel-based sunlight-assisted synthesis, chitosan-modified AuNPs, and AuNPs stabilized with chitosan and aqueous extract of tiger milk mushroom. These AuNPs have demonstrated efficient antimicrobial activity against a range of pathogens, including bacteria and fungi. Additionally, AuNPs have been found to accelerate wound closure, promote cell proliferation, and enhance the expression of proteins involved in wound healing processes. The unique properties of AuNPs make them a promising candidate for the development of advanced wound dressings and antimicrobial agents.

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