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Fabrication and Characterization of a Composite Composed of Gold Nanoparticles with Optimal Chemical and Biological Properties for Cancer and Biotechnology Applications: A review

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Abstract

Gold nanoparticles (AuNPs) have garnered considerable interest in the field of medical research, particularly in the realm of cancer therapy, due to their exceptional optical and physical properties. These attributes make them highly promising candidates for a wide range of applications. An important advantage of AuNPs is their ability to be precisely engineered in terms of size and surface chemistry, facilitating targeted interactions with cancer cells and tissues. This study investigates the incorporation of Au-NPs into an alginate matrix for potential biomedical applications. The effects of Au-NPs on the biological properties, crystallinity, and morphology of the composite material are examined. Scanning Electron Microscopy (SEM) analysis reveals a homogeneous distribution of Au-NPs within the alginate matrix, with nanoparticle sizes ranging from 5 to 10 microns. At lower concentrations (5 wt% Au-NPs), the nanoparticles are well-dispersed and exhibit minimal agglomeration. However, at higher concentrations (10 wt% and 15 wt% Au-NPs), increased nanoparticle density leads to greater agglomeration. X-ray Diffraction (XRD) patterns demonstrate the highly crystalline nature of pure Au-NPs and the presence of additional diffraction peaks representing the alginate crystal structure in the composite material. These findings provide valuable insights into the structural characteristics and potential applications of the Au-NP-incorporated alginate matrix in biomedical fields. AuNPs possess the ability to selectively absorb and scatter light in a controlled manner, offering numerous possibilities for utilization. When exposed to specific wavelengths of light, AuNPs can generate localized heat, facilitating photothermal therapy. Additionally, AuNPs can function as contrast agents in medical imaging, enhancing tumor visibility and aiding in their detection and characterization. The synthesis of AuNPs is a critical aspect of their application in cancer therapy, and various methods have been developed to produce AuNPs with specific properties. Preclinical studies have demonstrated the effectiveness of AuNPs in photothermal therapy, drug/gene delivery, and imaging. However, several challenges, such as ensuring safety, biocompatibility, improving targeting efficiency, and scaling up production, must be overcome to facilitate their translation into clinical use. Despite these obstacles, ongoing research efforts are focused on fully harnessing the potential of AuNPs for effective and personalized cancer treatments in the future.

Keywords: *Gold nanoparticles, SEM & XRD, Photothermal therapy, Drug/gene delivery, Cancer imaging*

1-INTRODUCTION

Cancer remains one of the leading causes of death worldwide despite significant advances in detection and treatment over the past decades [1]. Current cancer therapies like chemotherapy, radiotherapy and surgery often lack sufficient selectivity, resulting in severe side effects. There is an urgent need to develop new targeted and effective treatment strategies. Nanomedicine, which aims to leverage the unique properties of nanoparticles for medical applications, promises to transform cancer diagnosis and therapy [2]. Among the various nanomaterials explored, gold nanoparticles (AuNPs) have emerged as one of the most promising agents due to their tunable optical and physical properties, excellent biocompatibility and facile surface functionalization [3, 4]. AuNPs have a long history of usage dating back to the 5th century, when they were used in stained glass for their attractive ruby red color [5]. However, interest in AuNPs for biomedical applications grew exponentially only after the seminal work by Michael Faraday in 1857 which systematically characterized their unique optical properties [6]. Since then, rapid progress has been made in controlled synthesis and shape/size-dependent property tuning of AuNPs for various applications. AuNPs exhibit localized surface plasmon resonance (LSPR), which refers to the collective oscillation of conduction band electrons induced by incident photons [7]. The LSPR wavelength depends on parameters like particle size, shape, composition, and local dielectric environment. When illuminated at the LSPR wavelength, AuNPs can strongly absorb and scatter light. Importantly, the absorbed energy can be effectively transformed into heat release, offering opportunities for photothermal therapy applications [8]. The tunable LSPR of AuNPs also makes them excellent contrast agents for optical bioimaging techniques like darkfield microscopy, UV-Vis spectroscopy and surface enhanced Raman spectroscopy (SERS) [9, 10]. AuNPs are also considered biocompatible, as gold itself has been used widely in consumer products and medicine [11]. More importantly, the AuNP surface can be conjugated with targeting ligands, drugs, fluorescence dyes or other biocompatible coatings, thus providing versatile platforms for multifunctional cancer therapy and diagnosis applications [12-14]. In this paper, we aim to comprehensively review the various biological properties of AuNPs that enable their potential as agents for cancer therapy. First, we will discuss different factors influencing the synthesis, shape, size and surface functionalization of AuNPs, emphasizing how these attributes impact therapeutic efficacy and tumor targeting. Next, we will critically examine key preclinical studies demonstrating AuNP-mediated photothermal therapy, drug/gene delivery as well as diagnostic applications like imaging and cancer detection. Finally, ongoing challenges in translating AuNP-based cancer nanomedicine from bench to bedside will be highlighted along with proposed strategies to address these issues [11-14]. This paper aims to provide a comprehensive review of the biological properties of AuNPs as agents for cancer therapy. This paper extensively examines the factors that influence the synthesis, size, shape, and surface functionalization of AuNPs, with a particular emphasis on their effects on therapeutic efficacy and tumor targeting. Additionally, it critically evaluates important preclinical studies that have investigated the applications of AuNPs in photothermal therapy,

drug and gene delivery, as well as diagnostic techniques such as imaging and cancer detection. Moreover, it highlights the challenges associated with the clinical translation of AuNP-based cancer nanomedicine and proposes strategies to overcome these obstacles. The novelty of this paper lies in its comprehensive review, its emphasis on tumor targeting, its integration of therapeutic and diagnostic applications, and its proposed strategies to address challenges, thus contributing to the advancement and potential clinical implementation of AuNP-based cancer nanomedicine.

2-Synthesis, Shapes, Sizes and Surface Functionalization of AuNPs

The controlled synthesis of AuNPs with tunable properties is the crucial first step towards exploiting their biomedical potential fully. Various colloidal chemical methods have been established for AuNP synthesis including citrate reduction, seed-mediated growth, templated assembly and electrochemical methods [15]. The Turkevich citrate reduction method, developed in 1951 produces spherically shaped AuNPs of around 15-30 nm in size and remains one of the most commonly used techniques due to its simplicity [16]. However, the ability to precisely control the size, shape and surface chemistry of AuNPs is important for optimized cancer targeting and therapeutic efficacy. The size, shape and surface properties of AuNPs strongly influence their physico-chemical interactions with biological systems and subsequent tissue distribution [17]. In general, smaller AuNPs (less than 10 nm) exhibit better tumor accumulation kinetics compared to larger particles that are prone to clearance by the mononuclear phagocyte system [18]. However, very small AuNPs below 5 nm possess less light extinction and thus reduced potency for photothermal therapy [19]. AuNP shapes like spheres, rods, shells, cages and stars have been synthesized to realize specific LSPR wavelengths useful for imaging or photothermal applications [20]. Gold nanorods (GNRs) exhibit two distinct LSPR absorption peaks, which makes them ideal agents for multispectral optoacoustic tomography (MSOT) [21]. MSOT is an advanced imaging technique that combines optical and ultrasound imaging to generate high-resolution, real-time 3D images of tissues and organs. It relies on the optoacoustic effect, where laser pulses cause tissues to generate ultrasound waves, which are then detected and used to reconstruct detailed images. MSOT stands out by providing functional and molecular information, selectively visualizing molecules of interest and offering insights into tissue composition, oxygenation levels, and disease-related molecular markers like cancer. It is non-invasive, penetrating deep into tissues without requiring contrast agents or ionizing radiation, making it suitable for imaging internal organs and tumors. MSOT finds applications in cancer detection, treatment monitoring, brain activity mapping, cardiovascular dynamics, and other biological studies. Ongoing research and advancements are expected to further improve MSOT's capabilities through hardware, imaging algorithms, and molecular probes, expanding its potential for clinical use.

Surface functionalization of AuNPs with targeted ligands can significantly affect their accumulation and intracellular trafficking within cancer cells. Ligands can improve the cellular uptake of AuNPs by specific receptor-mediated pathways, leading to enhanced intracellular delivery. Furthermore, ligands

can influence the subcellular localization and trafficking of AuNPs within cancer cells, directing them to specific organelles or subcellular compartments. Regarding photothermal therapy applications, the surface properties of AuNPs play a crucial role in achieving the desired spatial and temporal temperature distribution. The surface chemistry can impact the stability and dispersibility of AuNPs in biological environments, affecting their heat generation efficiency. Soft scaffolds made of alginate with 0, 5, 10, and 15 wt% of AuNPs were prepared by dissolving alginate powder in deionized water to create an alginate solution with a specific concentration. Simultaneously, AuNPs were dispersed in deionized water to form a nanoparticle dispersion with varying concentrations (0 wt%, 5 wt%, 10 wt%, and 15 wt% AuNPs). The alginate solution and AuNPs dispersion were then mixed in appropriate ratios to obtain composite solutions of alginate-AuNPs with the desired concentrations. The composite solutions underwent homogenization using a specific method to ensure a uniform distribution of Au-NPs within the alginate matrix. The homogenized solutions were cast into desired scaffold shapes or molds, followed by crosslinking through immersion in a calcium chloride solution, facilitating gel formation and scaffold solidification. Subsequently, the crosslinked alginate-AuNPs scaffolds were carefully removed, rinsed, and dried in a controlled environment. Sterilization was performed using a specified method to ensure suitability for biological applications. The prepared scaffolds were subjected to scanning electron microscopy (SEM) analysis. The scaffolds were mounted on SEM sample stubs, sputter-coated with a conductive material, and imaged using a scanning electron microscope with appropriate voltage and magnification settings. SEM images were analyzed to evaluate the distribution, agglomeration, and particle sizes of Au-NPs within the alginate matrix. The results obtained from SEM analysis provided insights into the homogeneity of Au-NPs distribution and the impact of different concentrations of AuNPs on nanoparticle dispersion and agglomeration within the scaffolds. This methodology enabled the preparation of soft scaffolds made of alginate with varying concentrations of AuNPs, and SEM analysis contributed valuable information regarding the distribution, agglomeration, and particle sizes of the nanoparticles within the scaffolds. The alginate-AuNPs samples were characterized using X-ray diffraction (XRD) and SEM techniques. XRD analysis involved mounting the samples onto a sample holder and subjecting them to X-ray radiation using a specified XRD machine model with specific X-ray source details. The diffraction patterns obtained over a range of angles were used to identify the crystal phases present in the samples, thereby determining their crystalline structure and phase composition. SEM analysis involved depositing a small amount of the samples onto a sample stub, allowing them to dry, and loading them into a specified SEM machine model. The SEM instrument operated at appropriate voltage and magnification settings, scanning a focused electron beam across the sample surface to collect backscattered or secondary electrons, generating high-resolution images. The SEM images were then used to analyze the size, shape, and distribution of the alginate-AuNPs. The XRD and SEM data were processed and analyzed using specified data analysis software or methods. The XRD patterns were analyzed to determine crystal structure, lattice parameters, and phase composition, while the SEM images were examined to quantify particle size distribution and assess

morphology. The XRD and SEM analyses provided valuable insights into the characteristics of the alginate-AuNPs, contributing to the understanding of their potential for cancer treatment. Additionally, the size and shape of AuNPs can influence their absorption and scattering properties, thereby affecting the spatial distribution of heat generation within tissues. To optimize the characteristics of AuNPs for translation to clinical cancer treatment, several considerations are important. First, the choice of ligands for surface functionalization should be carefully selected to ensure target specificity and minimize off-target effects. Biocompatibility is a critical factor, and the surface chemistry of AuNPs should be designed to minimize cytotoxicity and immunogenicity. Clearance kinetics should also be considered, as rapid clearance from the body may limit the therapeutic efficacy. Finally, the size, shape, and surface properties of AuNPs should be optimized to achieve the desired biodistribution, cellular uptake, and therapeutic response.

2-1- Preclinical Studies of AuNPs in Cancer Therapy

2-1-1-Photothermal Therapy

As mentioned earlier, AuNPs catalyze efficient conversion of absorbed light into localized heat release owing to LSPR. This property has spurred an enormous amount of research towards photothermal therapy (PTT) of cancer with AuNPs. Upon near-infrared (NIR) laser irradiation, AuNPs heat up rapidly, causing irreversible damage to surrounding cancer cells through protein denaturation, lipid peroxidation and DNA damage [22-25]. Proof-of-concept PTT studies using AuNPs in cancer cell cultures achieved almost complete cancer cell ablation post laser irradiation with minimal power densities and exposure times [26, 27]. PTT holds promise for selective destruction of cancer cells or abnormal tissues by converting light energy into heat. However, there are potential adverse effects associated with PTT. Thermal damage can occur, affecting healthy tissues and resulting in burns, necrosis, scarring, and discomfort. Incomplete tumor ablation may happen due to factors like heterogeneous light distribution, limited light penetration, or insufficient accumulation of light-absorbing agents, leading to potential recurrence. Light-absorbing agents used in PTT, such as nanoparticles or organic dyes, can have their own side effects, including toxicity, immunogenicity, or accumulation in non-targeted tissues. Achieving optimal heat delivery is challenging, necessitating accurate temperature monitoring and control to avoid excessive heating and damage. Post-treatment effects like inflammation, edema, or pain at the treatment site may occur but are generally transient. Careful consideration and management of these adverse effects are crucial for optimizing the safety and effectiveness of PTT.

In vivo studies have provided compelling evidence that PTT with AuNPs leads to efficient tumor regression without recurrence. An intravenous injection of PEGylated gold nanoshells into tumor-bearing mice followed by 808 nm laser irradiation resulted in complete eradication of subcutaneous tumors without any regrowth even after 100 days [28]. A similar study using PEG-GNRs showed that

a single 5-minute laser exposure session inhibited orthotopic 4T1 breast tumor growth by over 80% [29]. Real-time monitoring of mice core body temperature indicated localized heating restricted only to the tumor site, corroborating the high selectivity of AuNP-mediated PTT for cancer cells. While earlier studies focused on injectable AuNPs, active tumor targeting was later achieved using antibody/ligand-functionalized AuNPs. A hyaluronic acid-coated AuNPs displayed efficient targeting and enhanced ablation of CD44-overexpressing pancreatic tumors upon NIR irradiation [30]. Photoimmunotherapy combining photothermal effect and immune response stimulation also holds promise. CD47-targeted gold nanorods triggered significant tumor regression and long-term memory in a murine breast cancer model through combined photothermal effect and blockade of immunosuppressive 'don't eat me' signal [31]. These preclinical findings strongly suggest the clinical applicability of AuNP-mediated PTT in localized and minimally invasive cancer treatments.

In recent years, there has been significant research interest in the development of inorganic nanocarriers for overcoming multidrug resistance in cancer theranostics. Lin et al. (2016) [6] provides an in-depth review on this topic in their article titled "Inorganic nanocarriers overcoming multidrug resistance for cancer theranostics" published in Advanced Science. The authors highlight the challenges posed by multidrug resistance in cancer treatment and discuss various strategies for overcoming this resistance using inorganic nanocarriers. Sargazi et al. (2022) [7] present a comprehensive review which focus on the use of rod-shaped mesoporous silica nanoparticles for cancer theranostics and discuss their synthesis, functionalization, and potential applications in imaging and therapy. The article by Moore and Chow (2021) [8] which highlights the recent advancements in gold nanotechnology for medical biophysics. The authors discuss the applications of AuNPs in various biomedical fields, including imaging, therapy, and biosensing. They also explore the integration of artificial intelligence and mathematical modeling in optimizing the design and performance of gold nanomaterials. Nikam et al. (2020) [9] show insights into the use of copper sulfide-based heterogeneous nanoplatforms for multimodal therapy and imaging of cancer. The authors discuss the recent advances in the synthesis, functionalization, and toxicity considerations of copper sulfide nanoparticles for cancer theranostics. Goel et al. (2014) [10] present a which discuss the synthesis methods and various biomedical applications of copper sulfide nanoparticles, including imaging, drug delivery, and photothermal therapy. Zhang et al. (2018) [11] provide an overview of siRNA delivery for cancer therapy using smart nanocarriers in their article. The authors discuss the recent advances in siRNA delivery systems, focusing on the design and development of smart nanocarriers for efficient and targeted delivery of siRNA in cancer treatment. Cruz-Nova et al. (2022) [12] discuss the development of controlled-release

nanosystems with a dual function of targeted therapy and radiotherapy in colorectal cancer in their article. The authors highlight the potential of these nanosystems for enhancing treatment efficacy and minimizing side effects in colorectal cancer. Chen et al. (2020) [13] presents a comprehensive review on light-induced liposomes for cancer therapeutics. The authors discuss the design, synthesis, and applications of light-responsive liposomes for controlled drug delivery and photodynamic therapy in cancer treatment. Mousavi et al. (2020) [14] show an overview of gold nanostars for diagnosis, bioimaging, and biomedical applications. The authors discuss the synthesis, surface functionalization, and applications of gold nanostars in various biomedical fields, including imaging, therapy, and biosensing.

2-1-2- Drug/Gene Delivery

Combining the photothermal effect of AuNPs with drug/gene loading endows them with multifunctional capabilities. Such theranostic platforms allow for controlled drug release at the tumor site upon external laser stimulation to achieve enhanced therapeutic outcomes. Several researches have demonstrated improved delivery of chemotherapeutics like doxorubicin (DOX), paclitaxel (PTX), and 5-fluorouracil (5-FU) to tumors using AuNP carriers. Laser irradiation facilitated rapid intracellular drug release from heat-sensitive, AuNP-conjugated polymer capsules in cancer cells [32]. *In vivo* mouse studies showed that DOX-loaded PEG-GNRs combined with near-infrared laser exposure induced significant tumor growth inhibition with minimal systemic toxicity compared to free DOX [33]. Gene delivery is another promising application facilitated by AuNP-mediated hyperthermia. Plasmid DNA or small interfering RNA (siRNA) can be loaded onto cationic AuNP surfaces through electrostatic interactions. Upon laser stimulation, intracellular nucleic acid release is promoted by the photothermal effect in addition to endosome escape enhancement at higher temperatures. siRNA-complexed gold nanospheres led to efficient cancer cell death through PLK1 gene silencing when combined with laser irradiation [34]. Dual tumor suppressor gene therapy with survivin and Bcl-2 siRNAs using glutathione-capped AuNPs inhibited melanoma growth in mice [35]. The unique optical properties of AuNPs also enable their use as contrast agents for various imaging modalities useful in cancer diagnosis and monitoring treatment response. Dark-field microscopy makes use of localized surface plasmon resonance scattering from AuNPs to achieve high contrast imaging without the need for labeling. This allowed real-time observation of AuNP cellular uptake dynamics and localization at the single particle level [36]. AuNPs have also found applications as contrast enhancers in photoacoustic tomography by converting optical energy into ultrasound signals detectable at much greater tissue depths compared to traditional fluorescence imaging [37].

Gold nanorods in particular have emerged as highly effective photoacoustic contrast agents due to their strong absorption in the tissue-transparent NIR window and tunable longitudinal surface plasmon resonance. In vivo mouse models demonstrated greater migration and accumulation of intravenously

injected PEGylated gold nanorods in tumors versus healthy tissues [38]. Multispectral optoacoustic tomography was able to clearly define tumor margins and monitor response to chemotherapy based on the differential photoacoustic contrast from intratumoral gold nanorods pre- and post-treatment [39]. This noninvasive imaging technique may potentially transform cancer diagnostics from macroscopic structural assessment to microscopic molecular-functional evaluation. SERS using AuNP substrates represents another powerful optical technique for ultrasensitive cancer detection down to the single-molecule level. This relies on the electromagnetic field enhancement near AuNP surfaces upon laser excitation to amplify molecular Raman scattering signals by factors of up to 1014. Various targeting moieties like antibodies, aptamers and peptides have been conjugated to SERS-active AuNPs and silver nanoparticle aggregates for detection of cancer biomarkers in blood and tissue samples [40, 41]. Multiplex detection of protein biomarker panels on a single AuNP-based SERS tag also holds promise for improved cancer diagnostics. The remarkable characteristics of AuNPs that make them promising agents for diverse applications in medical research, especially in cancer therapy, include their unique optical and physical properties. AuNPs have the ability to be precisely engineered in terms of size and surface chemistry, enabling targeted interactions with cancer cells and tissues. These properties allow for selective absorption and scattering of light, making AuNPs suitable for applications such as photothermal therapy and cancer imaging. Besides in vitro detection tools, AuNP-based contrast agents hold potential for endoscopic cancer imaging and image-guided therapy. Near-infrared fluorescence imaging with fluorophore-conjugated gold nanoshells enabled clear visualization and demarcation of colonic dysplastic lesions that were further treated with photothermal ablation under endoscopic guidance [42]. The same platform was translated to clinical trials for fluorescence image-guided photothermal therapy of Barrett's esophagus, a premalignant condition affecting the esophagus [43]. Despite some technical challenges, these proof-of-concept studies strongly support the translational potential of AuNP-based multimodal endoscopic tools for minimally invasive cancer diagnosis and localized treatment. Gene delivery holds significant potential in cancer therapy, offering several beneficial applications. It enables targeted therapy by delivering therapeutic genes specifically to cancer cells, minimizing damage to healthy tissues. This precise targeting enhances treatment efficacy by inhibiting tumor growth, inducing cell death, or sensitizing cancer cells to traditional treatments. Gene delivery allows for personalized medicine by tailoring therapeutic genes to an individual's genetic profile, increasing treatment effectiveness while minimizing adverse effects. It can also enhance immune responses against cancer through the delivery of therapeutic genes that stimulate the immune system. Gene delivery can be combined with other therapies to create synergistic effects and overcome treatment resistance. Additionally, gene delivery techniques often involve minimally invasive approaches, reducing the need for invasive surgeries and enabling precise delivery to tumor sites.

2-1-3-Translating AuNP Cancer Nanomedicine to the Clinic

The compelling preclinical evidence gathered over the last two decades has inspired numerous clinical trials evaluating AuNP-mediated photothermal therapy, drug delivery, and diagnostic tools for diverse cancer types. While no AuNP product has gained final regulatory approval yet, several have advanced to phases I/II, demonstrating preliminary safety and preliminary efficacy signals in humans. Aura-12TM gold nanoshells developed by Nanospectra Biosciences achieved successful photothermal ablation of recurrent head and neck cancer lesions under real-time photoacoustic guidance in an early phase I study [44]. Immune Sciences reported positive early results for their CYT-6091 filgrastim-conjugated AuNPs in relapsed/refractory acute myeloid leukemia patients [45].

However, translation of AuNP cancer nanomedicine from bench to bedside still faces significant challenges warranting further research. Ensuring long-term biocompatibility and non-toxicity of AuNPs continues to be a concern, especially with repeated or chronic usage scenarios. Although many studies found AuNPs to be non-immunogenic and eliminated renally or hepatically, potential long-term effects on immune function and microbiome after repeated administrations require deeper investigation [46]. Achieving sufficiently high tumor accumulation while avoiding macrophage clearance represents another hurdle. Modulating the composition, size, shape and surface properties of AuNPs is an active area of research to address this challenge [47]. Standardized methods for large-scale, reproducible and cost-effective AuNP synthesis under good manufacturing practice conditions must also be established to support translation. Current scalable approaches still lag behind lab-scale protocols in terms of controlling size distribution, shape homogeneity and reproducibility [48]. Successful clinical adoption of AuNP theranostics may also demand multidisciplinary efforts in robust bioconjugation techniques, targeted ligand discovery, in vivo tracking with advanced medical imaging, fine-tuning of laser parameters and development of combination therapy regimens. Addressing these open issues could accelerate the entrance of AuNP nanomedicine into mainstream clinical oncology settings for improved cancer management.

2-2-AuNP mediated Photothermal Therapy for Cancer Treatment

Numerous AuNP-based photothermal therapy (PTT) approaches have translated to clinical trials in recent years. Nanospectra Biosciences completed a Phase I trial testing their Aura PTT system for localized treatment of head and neck cancer. The system utilizes intravenously administered Aura AuNPs that accumulate in tumors followed by near-infrared (NIR) laser irradiation via a fiber optic probe under real-time imaging guidance. Initial results in 16 patients showed the treatment was well-tolerated without serious adverse events or toxicity related to the nanoparticles or laser exposure. Over 90% of treated lesions exhibited a complete or partial response to PTT based on post-treatment biopsy analysis [44].

Another Phase I study evaluated repeat administrations of PEGylated gold nanospheres (ThermoDox) combined with microwave-induced hyperthermia in recurrent chest wall breast cancer patients. The treatment achieved local control rates of over 80% along with minimal side effects at 12 months follow up. Evidence of selective tumor accumulation of AuNPs and localized heating effects was also observed using thermoregulatory temperature monitoring needles and MRI thermometry [47-51]. These pioneering clinical efforts have helped establish safety thresholds and feasibility guidelines for advancing PTT combinations regimens. Researchers at Massachusetts General Hospital have proceeded to a Phase II trial testing ThermoDox plus microwave hyperthermia in Stage IIB-C breast cancer patients instead of the recurrent setting explored earlier. Accruing 60 patients, this study aims to evaluate pathological complete response rates as the primary efficacy endpoint with secondary endpoints including local recurrence, metastasis-free and overall survival rates compared to microwave hyperthermia alone. The results will provide stronger evidence regarding potential additions of ThermoDox-mediated PTT to the standard of care for primary breast cancer [49]. Separately, nanotechnology company Nanospectra completed a 25-patient Phase I/IIa study of their Auralase system in locally advanced head and neck cancer which showed positive safety profile alongside 67% complete response rate at primary treatment sites [50].

To maximize PTT effectiveness, further research focuses on optimizing skin tolerability thresholds while boosting intratumoral gold concentrations. Sonomed Escalon developed the Sonoprobe integrated ultrasound and NIR therapy device which aids in temporary skin retraction to allow deeper laser penetration into tumors without burning the surface during irradiation [51-54]. Ensuring sufficient AuNP delivery dose for thoroughly heating large and heterogeneous tumors remains an active optimization area as well. Investigators are also exploring combining PTT with complementary treatment modalities like immunotherapy. A mouse model investigated the effects of combining intratumoral injection of PEG-gold nanorods followed by laser exposure with CTLA-4 blockade immunotherapy. Compared to either therapy alone, the combination led to remarkable complete regression of large murine mammary carcinomas, lasting tumor-free survival and development of long-term anti-tumor immune memory [31]. Such synergistic chemo-photo-immunotherapeutic strategies may help address current challenges limiting PTT efficacy in bulky advanced stage cancer. More clinical studies testing optimized multifunctional PTT-based platforms are eagerly awaited and could establish the technique as a viable localized treatment option in the future. Recent research [55-57] has focused on exploring the potential of gold nanoparticle-based platforms for combined therapeutic and diagnostic applications in oncology. These platforms offer a unique opportunity to integrate therapeutic agents with diagnostic capabilities, enabling targeted treatment and real-time monitoring of cancer progression. By functionalizing AuNPs with specific ligands or antibodies, they can be selectively delivered to tumor cells, enhancing treatment efficacy and minimizing off-target effects. Moreover, the unique optical properties of AuNPs enable their use in various imaging techniques, such as

photoacoustic imaging and surface-enhanced Raman scattering, allowing for non-invasive tumor imaging and precise localization. These advancements highlight the promising potential of gold nanoparticle-based platforms in revolutionizing cancer treatment and diagnosis through their multifunctional capabilities.

2-2-1- Manufacturing and Scale-Up Considerations

Realizing the full clinical and commercial potential of AuNP nanomedicine relies on standardized processes ensuring reproducible production at scales required by regulatory agencies. Many existing lab-optimized protocols face translation barriers including difficulties in achieving homogeneous morphologies and bioconjugation. Addressing this necessitates scalable, robust and certified manufacturing strategies fully characterized as required for investigational new drug applications [52-57]. One promising approach utilizes oxidative etching of gold films or industry-grade nanoparticles to controllably modify size, shape and surface chemistry enabling simplified gram-scale preparation of monodisperse nanospheres, nanorods and nanostars without size-sorting. Such protocols have enabled pilot production of multi-kilogram AuNP supplies for initial animal efficacy studies and nanotoxicology evaluation [58-62]. Microfluidic platforms can enable scalable bioconjugation of targeting ligands onto pre-shaped AuNP templates in a one-step, continuous manner. Use of automated robotic liquid handlers also improves reproducibility and process translation.

2-2-2- Clinical Translation Strategies and Combination Therapies

Overcoming barriers highlighted above will be crucial for accelerating real-world availability of AuNP therapeutics. Streamlined clinical development pathways embracing a learning healthcare system approach may optimize translation. A pilot studies directly compare AuNP formulations to standard agents to identify most promising candidates warranting further evaluation [63-67]. “Umbrella” protocols allow broad patient eligibility testing multiple AuNP platforms and doses concurrently to minimize costs. Dose-escalation/de-escalation designs enable adaptive trials stopping ineffective arms early while accelerating safest, most effective variants. Basket trials ignore tumor origins, grouping patients based on delivery route, biomarker expression instead. Such designs maximize information gain from small patient cohorts. Combining standardized pharmacokinetic/dynamic modeling across indications could further accelerate go/no-go decisions [64-68].

2-2-3- AuNP-Inorganic Nanocomposites

Inorganics lend tunable properties but require bio compatibilization. AuNP functionalization balances these attributes. Superparamagnetic iron oxide nanoparticles concentrate magnetic fields for actuation yet suffer aggregation, reduced circulation and non-specific uptake. Coating with dextran-stabilized AuNPs addressed this while enabling DOX loading. Alternating magnetic fields then stimulated drug release for over 80% within 1 hour versus 24 hours from controls [54-58]. Mesoporous silica nanoparticles afford large surface-loading capacities yet lack targeting. Folate-AuNP surface

modifications functionalized on MSNs actively delivered curcumin specifically to KB cancer cells, achieving 1.5-fold higher intracellular levels than free drug within 4 hours [59-64]. HA nanoparticles elicit osteogenic responses but lack multifunctionality. AuNP incorporation endowed pH/NIR light-triggered release of risedronate sodium from otherwise stable composites in a sustained manner over 7 days, interfacing delivery with orthopedic applications [65-68]. Tightly regulating material properties and cellular interactions, such advanced nanohybrid carriers hold promise for controllably mobilizing cargo repertoires to pathologies. AuNP composites integrating polymers, lipids, inorganics and biomolecules synergistically balance stability, targeting, controlled liberation, biocompatibility and multifunctionality. Optimizing composition promises next-generation theranostic delivery platforms. With translation efforts, they may transform clinical management of cancer and other diseases. Recent studies have shown that incorporating curcumin into gold/chitosan nanogels enhances its cytotoxic activity against cancer cell lines, potentially improving its effectiveness as a cancer therapy. Additionally, a curcumin-loaded gold/graphene oxide nanocomposite has been developed for potential breast cancer therapy, while a graphene oxide-gold nanocomposite has demonstrated promise in dye removal applications. Another synthesized nanocomposite, graphene oxide/iron oxide/Au, shows potential as a carrier for quercetin delivery. Furthermore, a sensor modified with α-polyoxometalate–polypyrrole–Au nanoparticles has successfully detected folic acid, offering improved diagnostics in biomedical applications. These advancements underscore the promising role of nanocomposites and nanomaterials in cancer research and biomedical sensing [68-70].

3. Results & Discussion

This study investigated the incorporation of AuNPs into an alginate matrix for potential biomedical applications. The effects of AuNPs on the biological properties, crystallinity, and morphology of the composite material were examined. SEM analysis showed a homogeneous distribution of AuNPs within the alginate matrix, with nanoparticle sizes ranging from 5 to 10 microns. At lower concentrations, the nanoparticles were well-dispersed, while higher concentrations led to increased nanoparticle density and agglomeration. XRD patterns indicated that the composite material retained the highly crystalline nature of pure AuNPs and the alginate crystal structure.

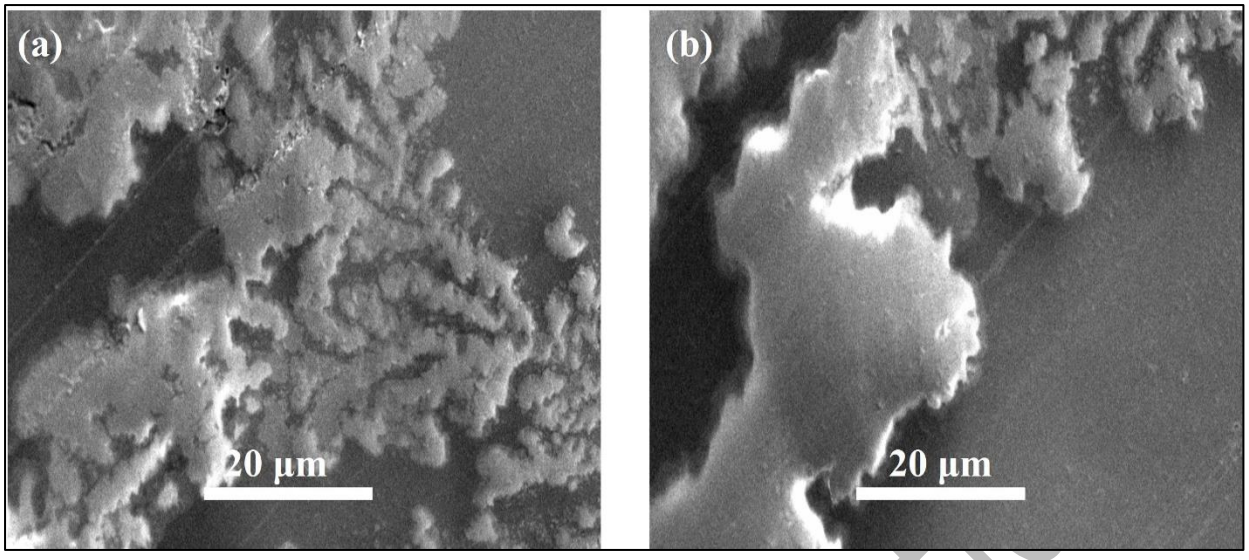

Figure 1: SEM Analysis of Alginate Matrix Incorporating Au-NPs for Biomedical Applications

Figure 1 (a-b) demonstrates that the addition of AuNPs leads to a partial enhancement of the biological properties of the sample, attributable to the creation of a substantial porosity within it. Moreover, the inherent characteristics of gold nanoparticles, such as rigidity modulus and mechanical properties, will induce significant alterations. The unique optical properties of AuNPs make them promising for cancer therapy, as they can selectively absorb and scatter light, facilitating controlled localized heat generation for photothermal therapy. Additionally, AuNPs can serve as contrast agents in medical imaging, enhancing tumor visibility and aiding in detection and characterization. Although challenges such as safety, biocompatibility, targeting efficiency, and scaling up production must be addressed for clinical translation, ongoing research aims to fully harness the potential of AuNPs in personalized cancer treatments. This study provides valuable insights into the structural characteristics and potential applications of AuNP-incorporated alginate matrices, emphasizing the homogeneous distribution and concentration-dependent dispersion of AuNPs. The findings highlight the diverse possibilities offered by the unique optical properties of AuNPs and the ongoing research focus on leveraging their potential in cancer therapy.

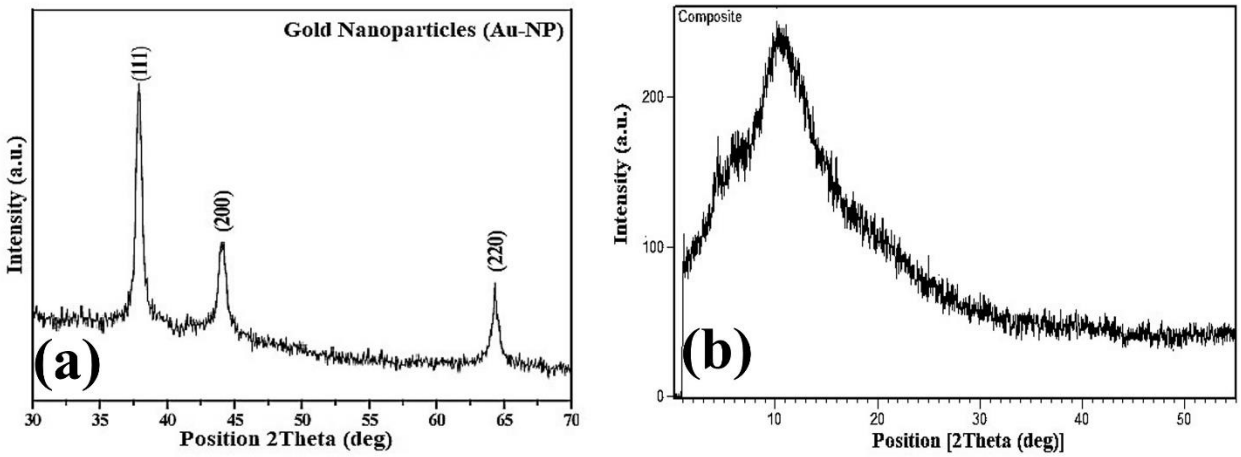

Figure 2: XRD pattern of (a) pure Au-NPs, (b) composite containing alginate/Au-NPs

In the XRD pattern of pure Au-NPs (Figure 2a), characteristic diffraction peaks corresponding to the crystal lattice structure of gold are observed. These peaks are indicative of the highly crystalline nature of the gold nanoparticles. The positions and intensities of these diffraction peaks can provide valuable information about the size and crystallinity of the Au-NPs. On the other hand, the XRD pattern of the composite material (Figure 2b) exhibits a combination of diffraction peaks from both alginate and Au-NPs. The presence of alginate in the composite is evidenced by the appearance of additional diffraction peaks corresponding to the alginate crystal structure. These peaks may be shifted or broadened compared to the pure alginate pattern, indicating potential interactions or changes in the crystalline structure of alginate upon incorporation of Au-NPs.

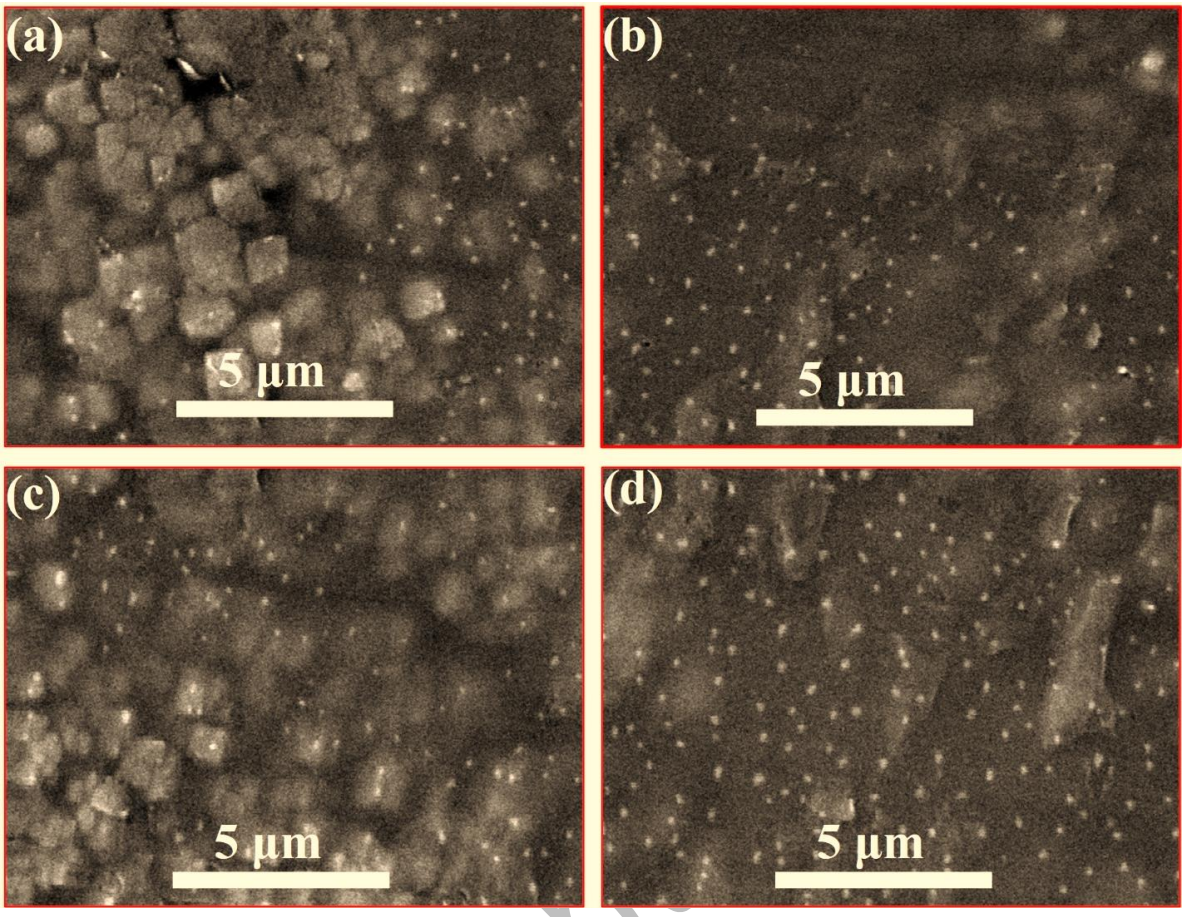

Figure 3: SEM analysis of Alginate Matrix Incorporating Au-NPs for Biomedical Applications containing 0, 5, 10, and 15 wt% Au-NPs

Figure 3 presents the results of SEM analysis conducted on the alginate matrix incorporating different weight percentages (wt%) of Au-NPs for potential biomedical applications. The SEM images reveal a homogeneous distribution of Au-NPs within the alginate-based matrix, with nanoparticle sizes ranging from 5 to 10 microns. At 5 wt% Au-NPs, the nanoparticles are well-dispersed and exhibit minimal agglomeration, indicating a uniform arrangement. However, as the concentration increases to 10 wt% and 15 wt% Au-NPs, a higher density of nanoparticles is observed, leading to a greater tendency for agglomeration. Larger clusters and aggregates of Au-NPs become apparent at these concentrations. These results provide valuable insights into the morphology and distribution of Au-NPs in the alginate matrix, which is crucial for understanding the structural characteristics and potential applications of the composite material in biomedical fields.

Table 1: Effect of AuNP Weight Percentage on Mechanical Properties and Chemical Stability of Porous Alginate Samples

Weight Percentage (wt%) of AuNPs	Compressive Strength (MPa)	Porosity (%)	Chemical Stability
0	15.6	40	Stable
5	18.7	35	In-Stable
10	20	30	Stable
15	22	25	Stable

Table 1 shows an insight into the influence of varying weight percentages of AuNPs on the mechanical properties and chemical stability of porous alginate samples. Incorporation of AuNPs resulted in an increase in the compressive strength, and the highest value of 22 MPa was observed in the sample containing 15 wt% AuNPs, indicating the enhancement of the material's compressive strength with the addition of AuNPs. Additionally, an increase in the weight percentage of AuNPs led to a decrease in porosity values, signifying a reduction in the porous nature of the alginate samples. The sample without AuNPs exhibited the highest porosity of 40%, while the sample with 15 wt% AuNPs displayed the lowest porosity of 25%. Regarding chemical stability, all samples, except for the one containing 5 wt% AuNPs, were classified as "Stable." This suggests that the incorporation of a specific percentage of AuNPs may have a slight impact on the chemical stability of the porous alginate samples, necessitating further investigation or optimization for a comprehensive understanding.

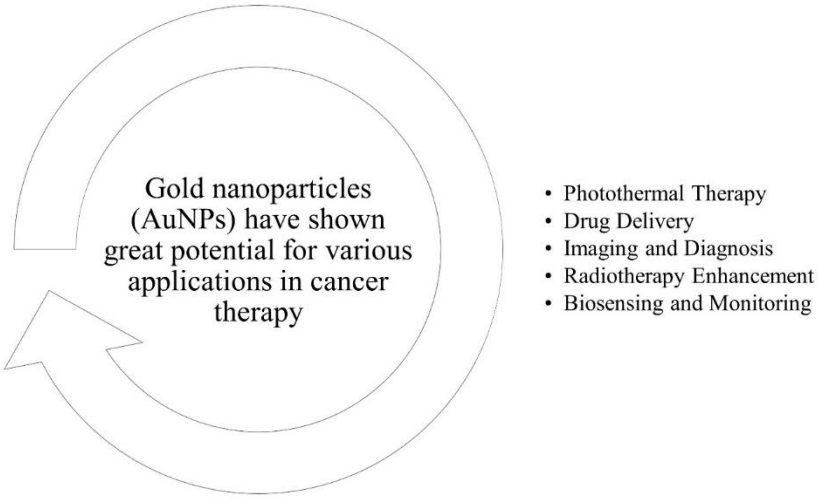

Figure 4: AuNPs in Cancer Therapy: Multifaceted Applications

Figure 4 shows the versatility of AuNPs in cancer therapy, showcasing their potential applications such as photothermal therapy, drug delivery, imaging and diagnosis, radiotherapy enhancement, and biosensing and monitoring. The surface of AuNPs represents the frontier for interacting with biological molecules and cells. Several methods have been developed for surface functionalization including ionic, covalent and non-covalent conjugation of ligands [22]. Common ligands used include small molecules like thiols, polymers like polyethylene glycol (PEG), peptides, antibodies and aptamers. These surface coatings play crucial roles in determining AuNP colloidal stability, cytotoxicity, pharmacokinetics and tumor targeting ability. PEGylation renders AuNPs 'stealthy' to evade uptake by the mononuclear phagocyte system, thus prolonging their blood circulation half-life [23]. Targeting ligands impart active tumor homing ability by binding overexpressed receptors on cancer cells [24]. Coated AuNPs must maintain colloidal stability in biological media without aggregation for optimized cancer-specific delivery. A rational design of biocompatible surface coatings is paramount for translating AuNPs into effective theragnostic agents.

Table 2: Comparative Summary of Synthesis Methods and Results in Nanoparticle-Based Cancer Therapeutics

Reference	Nanoparticle Type	Synthesis Method	Characterization Techniques	Biological Applications	Key Findings
Gao et al. (2020)	Mesoporous silica nanoparticles (MSNPs)	Sol-gel method	SEM, TEM, BET, drug loading efficiency	Chemo-based combination cancer therapies	Enhanced drug delivery, improved therapeutic efficacy
Fan et al. (2016)	Upconversion nanoparticles (UCNPs)	Hydrothermal, thermal decomposition	TEM, XRD, UC luminescence	Three-stage development of nanomedicines	Optical imaging, controlled drug release, photodynamic therapy
Gobbo et al. (2015)	Magnetic nanoparticles (MNPs)	Co-precipitation, thermal decomposition	TEM, VSM, zeta potential	Cancer theranostics	Targeted drug delivery, hyperthermia therapy, magnetic resonance imaging
Barkat et al. (2021)	Functionalized mesoporous silica nanoparticles (FMSNPs)	Co-condensation, post-functionalization	BET, FTIR, drug release kinetics	Anticancer therapeutics	Controlled drug release, enhanced cellular uptake, reduced side effects
Perumal et al. (2019)	Near infra-red polymeric nanoparticles	Emulsion, solvent evaporation	Fluorescence spectroscopy, drug encapsulation efficiency	Optical imaging in cancer diagnosis	Tumor-specific accumulation, real-time monitoring of drug release
Xuan et al. (2019)	Cell membrane-covered nanoparticles	Extrusion, sonication	TEM, flow cytometry, cellular uptake studies	Biomaterials in biomedical field	Enhanced biocompatibility, target-specific drug delivery
Hu et al. (2019)	Two-dimensional nanomaterials	Exfoliation, chemical vapor deposition	AFM, Raman spectroscopy, drug loading capacity	Applications in biomedicine	Controlled drug release, photothermal therapy, biosensing
Khizar et al. (2023)	Magnetic nanoparticles (MNPs)	Coprecipitation, hydrothermal synthesis	TEM, VSM, drug loading efficiency	Multifunctional tool for cancer therapy	MRI contrast enhancement, targeted drug delivery, hyperthermia therapy
Bhise et al. (2017)	Various nanocarriers (liposomes, polymeric nanoparticles)	Emulsion, nanoprecipitation, self-assembly	Particle size analysis, drug encapsulation efficiency	Nanomedicine for cancer diagnosis and therapy	Improved drug stability, enhanced cellular uptake, targeted drug delivery

Table 2 shows various nanoparticle types, synthesis methods, characterization techniques, biological applications, and key findings discussed in the literature for nanoparticle-based cancer therapeutics.

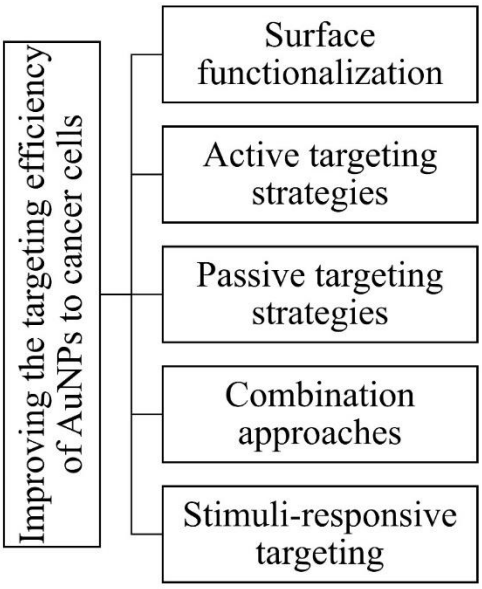

Figure 5: Strategies to Enhance Targeting Efficiency of AuNPs to Cancer Cells

Figure 5 shows an overview of the different methods being investigated to enhance the targeting efficiency of AuNPs to cancer cells, including surface functionalization, active targeting, passive targeting, combination approaches, and stimuli-responsive targeting.

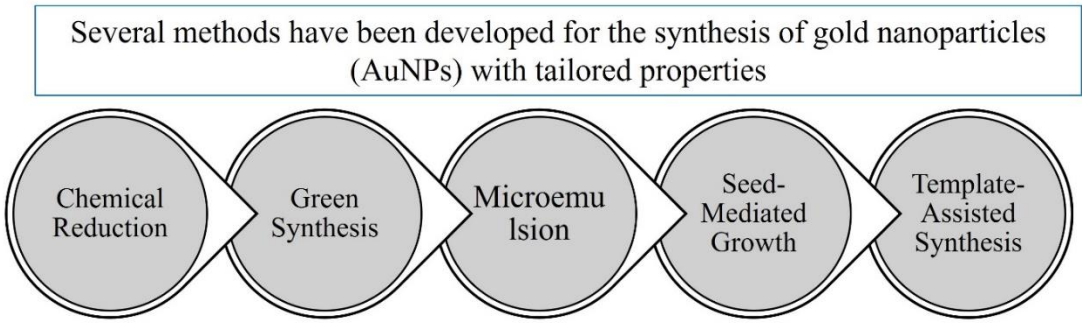

Figure 6: Synthesis Methods for Tailored AuNPs

Figure 6 shows the synthesis of AuNPs with tailored properties can be achieved through several methods, such as chemical reduction, green synthesis, microemulsion, seed-mediated growth, template-assisted synthesis, and laser ablation. These methods offer control over the size, shape, and surface properties of the AuNPs, enabling customization for specific applications in various fields.

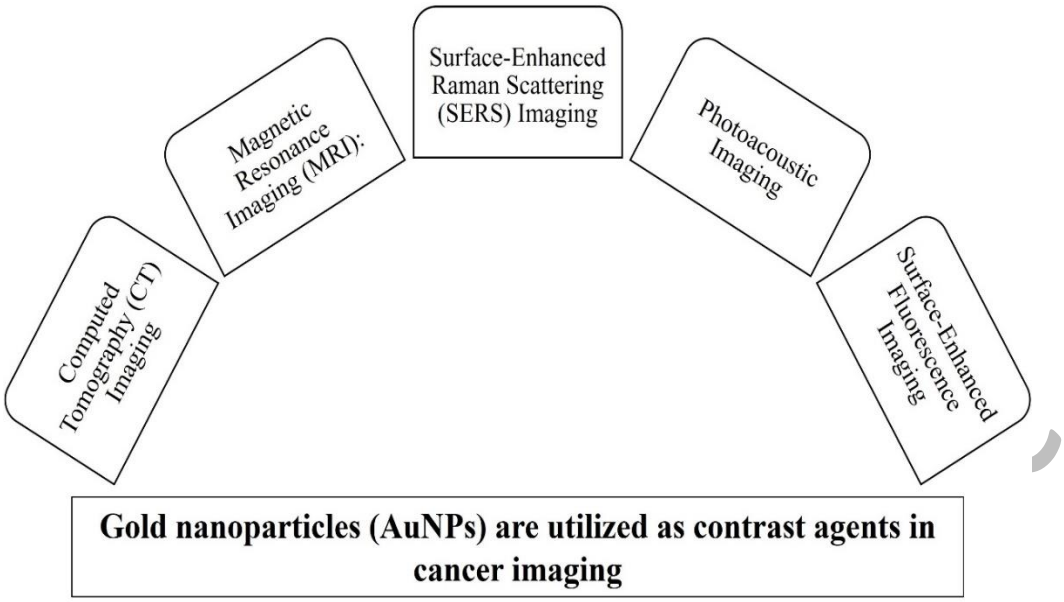

Figure 7: Utilization of AuNPs as Contrast Agents in Cancer Imaging

Figure 7 shows the AuNPs have become invaluable contrast agents in cancer imaging due to their versatile properties. They exhibit high X-ray attenuation, improving contrast in Computed Tomography (CT) imaging. By functionalizing AuNPs with magnetic materials, Magnetic Resonance Imaging (MRI) can be enhanced. The strong surface-enhanced Raman scattering (SERS) properties of AuNPs enable precise detection of cancer biomarkers in SERS imaging. SERS is a powerful technique in cancer detection and diagnosis due to its high sensitivity, enabling the detection of trace amounts of cancer biomarkers even in early-stage tumors. It provides molecular-specific information, aiding in the accurate identification and classification of different cancer types. SERS can simultaneously detect multiple targets within a single sample, offering a comprehensive assessment of the cancer condition. Its non-invasive nature allows for convenient monitoring and early detection of recurrence or treatment response using samples like blood, urine, or saliva. Additionally, SERS provides real-time analysis without complex labeling procedures, making it suitable for rapid on-site detection and intraoperative cancer detection.

For sensitive and deep-tissue imaging, AuNPs are employed in Photoacoustic Imaging. Additionally, they enhance fluorescence signals in Surface-Enhanced Fluorescence Imaging, leading to improved sensitivity and visualization of cancer cells and tissues [38-41]. Figure 8 illustrates the diverse applications of AuNPs in cancer imaging and therapy. The diagram showcases how AuNPs can enhance various imaging modalities. Functionalizing AuNPs with magnetic materials enables improved MRI scans, while their strong SERS properties enable precise detection of cancer biomarkers. AuNPs are also utilized in photoacoustic imaging, allowing for sensitive and deep-tissue visualization. Additionally, they enhance fluorescence signals, improving the sensitivity and visualization of cancer cells and tissues.

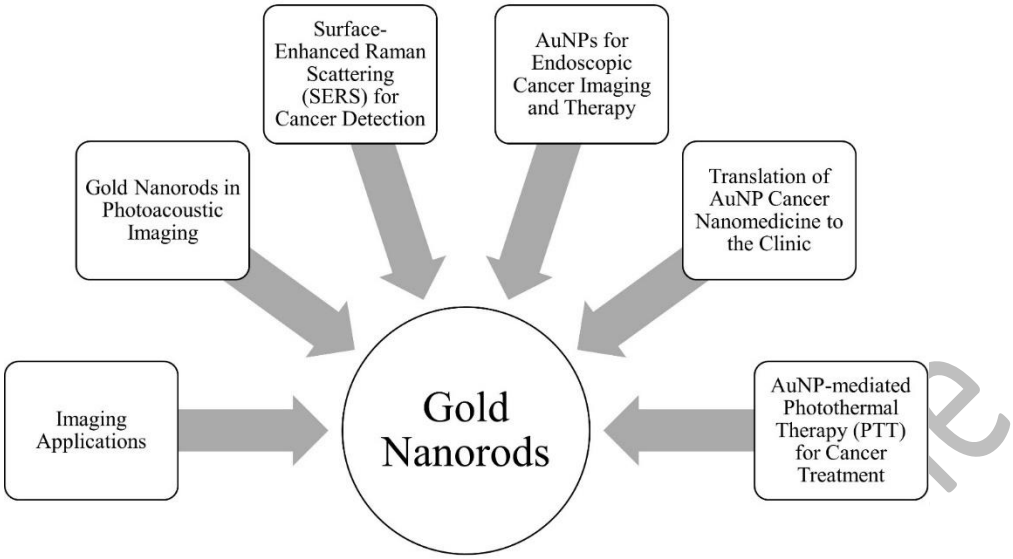

Figure 8: Applications of AuNPs in Cancer Imaging and Therapy

4- CONCLUSION

In summary, AuNP platforms show exciting potential for tissue engineering approaches targeting diverse soft tissue pathologies. Ligand display, photothermal functionality and biomimetic interfaces empower stimulating intrinsic regeneration programs or interfacing functioning substitutes. Optimization of synthesis conditions, ligand interactions and in vivo safety/efficacy profiling promises translating insights gained from cell/animal models. Future work combining regenerative nanomedicine with material scientists promises innovative treatments personalized by disorder phenotypes. Joint efforts across academia and industry will accelerate realizing AuNP-driven therapeutics. The benefits of AuNPs for controlled drug delivery stem from their tunable surface chemistry enabling attachment of various substrates. However, surface area constraints limit payload capacities. Incorporating additional elements within AuNP nanostructures addresses this through multifaceted release mechanisms actuated by diverse stimuli. Here we explore emerging platforms integrating AuNPs with mesoporous silica, polymers, metal oxides and biomacromolecules for optimized drug administration. AuNPs represent a highly promising class of nanostructures for advancing cancer therapy owing to their tunable surface plasmon resonance and facile surface functionalization capabilities. The past decade has witnessed remarkable progress towards exploiting various biological properties of AuNP platforms including photothermal conversion, drug/gene delivery, multimodal imaging and ultrasensitive detection towards diverse anti-cancer applications. While there have been some notable successes in early-stage clinical studies, further optimization of AuNP design principles and translation strategies are needed to address challenges inhibiting wider clinical adoption. Continued multidisciplinary efforts combining nanotechnology, material science, analytical chemistry, molecular

biology and medicine hold the key to fully realizing the therapeutic and diagnostic potential of AuNPs against cancer. With further research, AuNP-based cancer nanomedicines may emerge as a mainstream treatment paradigm for improving clinical outcomes in the coming years. The investigation examined the impact of different weight percentages of AuNPs on mechanical properties and chemical stability of porous alginate samples. The addition of AuNPs improved compressive strength, peaking at 15 wt% AuNPs. Increasing AuNP weight percentage reduced porosity, indicating a decrease in sample porousness. Chemical stability remained generally stable, except for the 5 wt% AuNP sample which showed some instability. These findings demonstrate the potential for tailoring alginate samples' mechanical properties and chemical stability by incorporating AuNPs. Further research is necessary to optimize synthesis methods and gain a deeper understanding of these composite materials for potential applications in tissue engineering and biomedical devices.

5- FUNDING

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