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Metal Nanoparticles: Revolutionizing the Fight against Cancer

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Abstract

Metal nanoparticles have emerged as promising agents in the field of cancer therapy, offering innovative approaches to combat this devastating disease.). This review provides a comprehensive overview of the role of metal nanoparticles in revolutionizing the fight against cancer. Beginning with an introduction to the global health challenge posed by cancer, the unique properties of metal nanoparticles are highlighted, underscoring their potential for therapeutic intervention. Synthesis and characterization techniques are discussed, laying the groundwork for understanding the mechanisms of action by which these nanoparticles exert their anticancer effects. The review delves into the diverse types of metal nanoparticles, with a focus on gold, silver, platinum, and other metals, elucidating their distinctive properties and applications in cancer therapy. Mechanistic insights into how metal nanoparticles interact with cancer cells, induce apoptosis, and modulate the tumor microenvironment are explored, providing a deeper understanding of their therapeutic potential. Preclinical and clinical studies demonstrating the efficacy of metal nanoparticles in various cancer models are critically examined, alongside considerations of biocompatibility and safety. The review also addresses challenges in clinical translation and regulatory considerations. Looking ahead, future directions and emerging trends in nanoparticle design, as well as opportunities for interdisciplinary collaboration, are highlighted. Ultimately, this review underscores the transformative impact of metal nanoparticles in the fight against cancer, paving the way for novel therapeutic strategies and offering hope for improved outcomes in cancer patients worldwide.

Keywords: Bicompatibility; nanoparticles; cancer therapy

1. Introduction to Metal Nanoparticles in Cancer Therapy

1.1. Overview of cancer as a global health challenge.

Cancer is one of the leading causes of death worldwide, accounting for nearly 10 million deaths in 2020. The burden of cancer is rising globally, with new cancer cases projected to increase by over 60% in the next two decades if current trends continue (Kanavos, 2006). Developing countries are disproportionately impacted, accounting for over two-thirds of cancer deaths worldwide despite having only one-third of the global population (Magrath and Litvak, 1993). This reflects not only the rapid population growth and aging in developing regions, but also lower cancer survival rates due to late diagnosis and lack of access to treatment.

Addressing the rising global cancer burden requires a multidimensional response, including primary prevention, early detection, timely and appropriate treatment, and palliative care. Key risk factors driving rising cancer rates in developing countries include tobacco use, unhealthy diets, alcohol use, infections, and environmental pollutant (Kanavos, 2006). Strengthening health systems is critical to enable equitable access to cancer control interventions. Innovative strategies and technologies for prevention, diagnosis and treatment appropriate for resource-limited settings are needed. Partnerships between developing countries and the international community will also play an important role in accelerating progress against cancer on a global scale.

1.2. Overview of Nanoparticles

Metal nanoparticles are emerging as promising therapeutic agents in cancer treatment. They offer unique optical, electrical, and magnetic properties at the nanoscale that can be exploited for biomedical applications (Issa et al., 2013). When light interacts with metal nanoparticles like gold, silver, or iron oxide, it induces a resonant oscillation of conduction band electrons on the nanoparticle surface (Saion and Gharibshahi, 2014).This generates a strong surface plasmon resonance that enhances the scattering and absorption of light in the visible and near-infrared regions. By tuning the size, shape, and material of nanoparticles, their optical properties can be optimized for hyperthermia therapy and imaging applications in cancer (Huang and El-Sayed, 2010).
Additionally, metal nanoparticles have high surface area to volume ratios, allowing them to be coated with diverse functional moieties like antibodies, peptides, nucleic acids, photosensitizers, and drug molecules(Jiang et al., 2021). This facilitates active targeting and controlled delivery of therapeutics to tumor sites. The nanoscale sizes of nanoparticles also promote their passive accumulation in leaky tumor vasculatures via the enhanced permeability and retention effect(Sano et al., 2013).Once internalized by cancer cells, metal nanoparticles can damage cellular components through catalytic generation of reactive oxygen species when exposed to external light or alternating magnetic fields (Wydra et al., 2015).

1.3. Importance of Nanoparticles in Cancer Treatment

Metal nanoparticles hold great promise for improving the diagnosis and treatment of cancer. A key reason is that nanoparticles have similar sizes to large biological molecules and structures, allowing them to effectively interact with cells and organs in the body. For example, the average size of nanoparticles used in biomedicine ranges from 10-100 nm, comparable to the size of most proteins (5-50 nm) (Bamburowicz-Klimkowska et al., 2019). This allows nanoparticles to be taken up directly by cells through endocytosis and other cellular uptake mechanisms. Once inside cells, appropriately designed nanoparticles can deliver cancer drugs, heat cells (hyperthermia), emit cytotoxic species upon irradiation, and provide contrast for cell/tumor imaging (Loomis et al., 2011). Moreover, nanoparticles accumulate preferentially in tumors because of the enhanced permeability and retention (EPR) effect, allowing their passive targeting to cancerous sites. By functionalizing nanoparticle surfaces with antibodies, peptides, or small molecules, active targeting to specific cancer cell receptors can also be achieved(Marques et al., 2020) (Shargh et al., 2016).Compared to traditional small molecule drugs, nanoparticle platforms minimize unintended uptake by healthy cells/tissues, enhancing the therapeutic index. The unique electrical, optical, thermal, and magnetic properties of inorganic nanoparticles at the nanoscale make them invaluable for the detection, targeted treatment, and monitoring of treatment responses in cancer, which remains a major global health challenge (Ferreira et al., 2020) (Melancon et al., 2009).

1.4. Rationale for Using Metal Nanoparticles

Metal nanoparticles are being extensively explored for cancer treatment due to their unique physical, chemical, optical, and magnetic properties that originate from quantum confinement effects at the nanoscale. When the size of metal nanoparticles decreases below 100 nm, a high percentage of atoms can be found on the surface(Sun et al., 2011).This leads to the dominance of surface properties and interactions over bulk properties. As a result, metal nanoparticles exhibit unique size- and shape-dependent optoelectronic properties that differentiate them from bulk metals (Adekoya et al., 2018). For example, noble metal nanoparticles like gold and silver demonstrate strong surface plasmon resonance, an oscillation of surface conduction electrons when excited by light at specific wavelengths(Anderson et al., 2011).This generates enhanced optical scattering and absorption that can be exploited for cancer imaging and photothermal therapy. Additionally, the large surface area to volume ratio facilitates modification of metal nanoparticles with multiple functional moieties like antibodies, drugs, and dyes. This enables targeted multimodal therapy and diagnostic applications (Xie et al., 2011).Other

favorable characteristics like facile surface chemistry, good biocompatibility, and catalytic generation of cytotoxic species make metal nanoparticles versatile platforms for cancer treatment (Vaid et al., 2020). By tuning the properties of metal nanoparticles, they can be designed to actively target tumor sites while minimizing off-target effects, paving the way for the next generation of cancer nanotherapeutics.

2. Synthesis and Characterization of Metal Nanoparticles

2.1. Methods of Synthesis

2.1.1. Chemical Reduction

Chemical reduction is a commonly used method for the preparation of stable metal nanoparticle colloids. In this process, metal salts are reduced by strong reducing agents such as citrate or borohydride in the presence of stabilizing molecules (eg. polymers, ligands or surfactants), resulting in the nucleation and subsequent growth of metal nanoparticles (Lowe et al., 2002). The stabilizing molecules adsorb onto the nanoparticle surfaces, providing electrostatic and/or steric repulsion to prevent aggregation. By controlling the ratio of stabilizers to metal salts, the particle size, morphology, and surface chemistry of nanoparticles can be modified. For example, citrate reduction of gold and silver salts results in spherical nanoparticles that are coated and stabilized via electrostatic repulsion. Varying the citrate to metal ratio influences the size of the nanoparticles. Chemical reduction allows nanoparticle synthesis on a large scale in solution for biomedicine, electronics, and catalysis applications(Liu et al., 2009). One of the major advantages of this method is its simplicity and ease of use with minimal instrumentation. However, the inability to control particle size distribution and difficulty in producing monodisperse spherical particles are some limitations. Usage of strong reducing agents and stabilizers may also warrant post-synthesis cleaning procedures for biological applications (Almería and Gomez, 2014).

2.1.2. Physical Vapor Deposition

Physical vapor deposition (PVD) techniques like thermal evaporation, electron beam evaporation, sputter deposition, and pulsed laser deposition can produce pure metal nanoparticles by condensing atoms vaporized from bulk metal sources (Borra et al., 2015). In PVD processes, bulk metals are vaporized via thermal heating, electron beam bombardment, plasma generation, or high-power pulsed laser irradiation to produce atomic vapors that nucleate homogeneously in the gas phase upon cooling and condensation (Shahidi et al., 2015).The nanoparticle growth process is governed by thermodynamic and kinetic factors like supersaturation ratio, temperature gradients, residence times in the nucleation zone etc (Schmelzer and Schmelzer, 1999). By optimizing these conditions, spherical nanoparticles with well-controlled sizes and uniform morphology can be obtained. Moreover, alloys and multilayered nanoparticles can also be synthesized by using multiple metal sources. Compared to wet chemical methods, PVD techniques do not require chemical precursors, hence the as-synthesized nanoparticles have relatively clean surfaces. However, the deposition rate is usually low (Navinšek et al., 1999). Also, producing large volumes of nanoparticles and preventing particle aggregation during collection remain key challenges. Overall, PVD methods allow precise control over nanoparticle composition, size, and structure, making them useful for fundamental research and specialized applications.

2.1.3. Biological Synthesis

Biological synthesis has emerged as an environmentally benign approach for metal nanoparticle fabrication using microorganisms and plant extracts. This method takes advantage of reducing enzymes and phytochemicals present within biological systems that can convert metal salts into elemental metal nanoparticles (Md Ishak et al., 2019). For instance, bacteria, fungi, and plant extracts containing hydrolytic enzymes and proteins with reducing groups have demonstrated efficient nanoparticle production (Md Ishak et al., 2019).The proteins and secondary metabolites from biological sources act as both reducing and capping agents, controlling nanoparticle nucleation and stabilization (Chugh et al., 2022). Key advantages of this method include elimination of hazardous chemicals, single-step synthesis of uniform nanoparticles under mild conditions, and biocompatible stabilization of

nanoparticles via peptides or plant phytochemicals. However, challenges remain such as demonstration of large scale synthesis capabilities, reproducibility concerns between different microbial/plant batches, and unraveling the complex biochemical mechanisms influencing nanoparticle formation (Gericke and Pinches, 2006).Further optimization of the biological systems and processes can aid the accelerated deployment of biologically inspired nanoparticle manufacturing (Parodi et al., 2017).

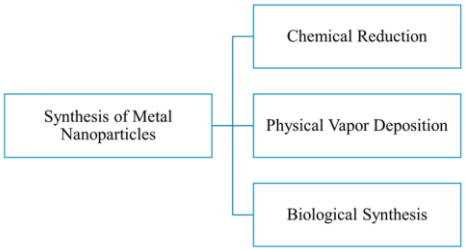

Fig 1: Different methods of nanoparticle synthesis

2.2. Characterization techniques for assessing the properties of metal nanoparticles

2.2.1. Transmission electron microscopy (TEM)

Transmission electron microscopy (TEM) is one of the most vital techniques used to determine the morphology, size, size distribution, and crystal structure of metal nanoparticles (Kikuchi and Yasuhara, 2012). In TEM, a focused high-energy electron beam is transmitted through an ultra-thin sample, interacting with the specimen as it passes through. The interactions result in the scattering of electrons, which are then detected to form an magnified image of the sample. As it uses electrons instead of light, TEM can achieve significantly higher resolution than traditional optical microscopes, making it possible to examine features less than 1 nm in size (Cowley et al., 1997). Importantly for nanoparticles, TEM imaging allows the direct visualization of the metal nanoparticle shape, size uniformity, and surface structure at the atomic scale (Marks and Smith, 1983). Additional analytical capabilities offered by TEM include selected area electron diffraction to identify crystal structures and energy dispersive X-ray spectroscopy for compositional analysis (Ferraris and Auchterlonie, 2013). However, TEM sample preparation can be complex and extensive data analysis is often needed for statistical assessment of particle size distributions. Overall, TEM serves as an indispensable technique to gain fundamental insights into nanoparticle physicochemical properties, which critically impact their biomedical applications (Reifarth et al., 2018).

2.2.2. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is a versatile characterization technique widely utilized to determine the surface morphology and topology of metal nanoparticles. In SEM, a focused beam of high-energy electrons is rastered over the sample, generating a variety of signals from the specimen-electron interactions (Kammlott, 1971).Detection of secondary electrons emitted from the sample provides topographical details, while backscattered electrons can highlight compositional contrasts. Compared to transmission electron microscopy (TEM), sample preparation for SEM is generally simpler because SEM analyzes surface features rather than interior structures. Moreover, SEM enables the examination of nanoparticle morphology and arrangement over larger regions at higher resolutions than achievable under light microscopes (Foss et al., 2010) (Hodoroaba et al., 2016). Additional coupled techniques like energy-dispersive X-ray spectroscopy can elucidate elemental compositions of nanoparticles during SEM analysis. However, conventional SEM does not readily yield nanoparticle size distributions or crystallographic information. Instead, it serves as a complementary approach to TEM for gaining rapid insights into metal nanoparticle surface traits, aggregation patterns, and integration with biological or material substrates – invaluable for quality control during nanomedicine formulation and manufacturing.

2.2.3. X-ray diffraction (XRD)

X-ray diffraction (XRD) is a fundamental technique used to determine the crystal structure, chemical composition, and size distribution of metal nanoparticles. XRD operates on the principle of constructive interference of monochromatic X-rays scattered by crystal lattices (Bunaciu et al., 2015) (Ahmad et al., 2021). As nanoparticles contain only a

few thousand to million atoms, they exhibit broadening of diffraction peaks compared to bulk materials. By applying the Scherrer equation to XRD patterns, the average nanoparticle size can be calculated. Further peak analysis provides insights into chemical makeup and atomic arrangements within the nanoparticle crystal lattice (Solanki et al., 2018). If nanoparticles are coated or contain capping agents, additional peaks associated with stabilizers may also be observed. Compared to electron microscopy, XRD offers a rapid, averaged measurement of nanoparticle size distributions. However, it lacks the direct visualization and atomic-scale resolution provided by microscopy. Therefore, XRD presents a bulk, ensemble measurement that is statistically more significant for large nanoparticle quantities, complementing microscopy characterization. For metal nanoparticles, XRD remains a powerful standard method for determining crystalline phases, compositions, and average particle sizes across entire samples (Borchert et al., 2005).

2.2.4. Dynamic light scattering (DLS)

Dynamic light scattering (DLS) is a technique widely employed to quantify the hydrodynamic size and size distribution of metal nanoparticles dispersed in liquids. It operates by illuminating a nanoparticle solution with a laser and analyzing the intensity fluctuations in the scattered light over time (Naiim et al., 2015).These intensity fluctuations arise from the Brownian motion of nanoparticles, with smaller particles moving more rapidly resulting in faster intensity variations. By mathematically relating the scattering intensity autocorrelation function to particle diffusion properties, the size distribution profile can be derived using the Stokes-Einsteinequation (Keyes and Oppenheim, 1973) (Heintzenberg and Baker, 1976). Compared to microscopy methods, DLS enables significantly faster size distribution quantification and is well-suited for statistically measuring ensemble nanoparticle behavior across bulk solutions. However, DLS measures hydrodynamic diameter so variations due to particle shape or stabilizer coatings may be observed relative to electron microscopy sizes. Furthermore, DLS technical challenges include distinguishing multiple populations, handling polydispersity, and optimization of nanoparticle concentration to avoid multiple scattering effects. Overall, DLS presents a facile and essential technique for routine quality control assessment of nanoparticle size, dispersion stability, and process reproducibility in solution-based preparation and formulation steps (Langevin et al., 2018).

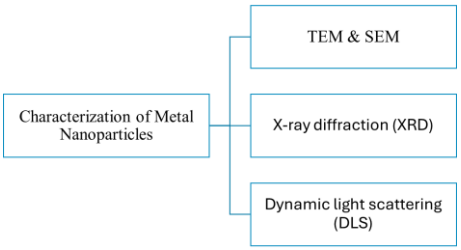

Figure 2: Characterization of different nanoparticles

3. Mechanisms of Action of Metal Nanoparticles in Cancer Therapy

3.1. Cellular uptake mechanisms

The therapeutic efficacy of metal nanoparticles for cancer applications depends significantly on their ability to be internalized by cells (Mohapatra et al., 2021). Major cellular uptake pathways that have been identified include passive diffusion, receptor-mediated endocytosis, caveolae/lipid-raft-mediated endocytosis, macropinocytosis, and phagocytosis. Factors such as nanoparticle size, shape, surface charge, and surface modifications dictate which mechanism(s) are activated to transport nanoparticles across the cell membrane (Behzadi et al., 2017) (S. Zhang et al., 2015). For example, gold nanoparticles less than 50 nm decorated with functional groups that interact with membrane receptors tend to get internalized via receptor-mediated endocytosis while smaller nanoparticles around 10-20 nm can passively diffuse through the cell membrane (Shan et al., 2011). In some cases, metal nanoparticles first bind to the negatively charged cell membrane, triggering cytoskeletal rearrangements that facilitate their active transport into cells through endocytosis (Canton and Battaglia, 2012). Once internalized, nanoparticles typically reside within endo-lysosomal compartments but can also escape these vesicles through endosomal escape mechanisms, allowing their diffusion into the cytoplasm. Understanding how cancer cells take up metal nanoparticles is key to designing more

effective nanomedicines for diagnostics and therapeutic action.

3.2. Interaction with cancer cells

Once internalized by cancer cells, metal nanoparticles can leverage various intracellular targeting strategies to induce toxicity and inhibit tumor growth. A key approach involves functionalization of nanoparticles with biomolecules that specifically recognize overexpressed cancer cell receptors, enabling receptor-mediated endocytosis and delivery to distinct subcellular sites (Avvakumova et al., 2014). For example, nuclear-targeted gold nanoparticles conjugated to nuclear localization signal peptides selectively accumulate in the nucleus where they mediate radiosensitization. Similarly, nanoparticles decorated with mitochondrial-targeting ligands localize to the mitochondria and generate reactive oxygen species that trigger apoptosis (Mallick et al., 2016). Other internal cell structures like lysosomes and endoplasmic reticulum can also be targeted. An alternative technique uses cationic metal nanoparticles that associate with the negative charges on DNA/RNA to disrupt gene regulation and protein translation (Calabrese et al., 2015). Overall, intracellular targeting of metallic nanomaterials can potentiate injury to vital organelles and biomolecules that are critical to cancer cell survival and progression, offering avenues for precision cancer therapy.

3.3. By induction of reactive oxygen species (ROS)

The excessive generation of reactive oxygen species (ROS) through nanoparticle-mediated catalytic reactions is a key cytotoxic mechanism in cancer cells. Several metal nanoparticles like iron oxide, titanium dioxide, zinc oxide, and cerium oxide can produce ROS like superoxide anions, hydroxyl radicals, and hydrogen peroxide (Zou et al., 2017). This typically occurs through Fenton reactions facilitated by transition metal ions on nanoparticle surfaces that catalyze the breakdown of intracellular peroxides. Additionally, metal oxide nanoparticles illuminated with ultraviolet or visible light undergo redox reactions that give rise to singlet oxygen and hydroxyl radicals. At higher concentrations, ROS overproduction overwhelms innate antioxidant defenses in cancer cells, leading to oxidative damage to proteins, lipids, and DNA (Arfin et al., 2021), (Snezhkina et al., 2019). This creates chemical and structural instability in proteins that perform vital cell functions like metabolism, proliferation, and survival signaling pathways. Moreover, ROS can trigger topoisomerase inhibition and chromatin structural changes that affect DNA replication and gene transcription (Cavalli et al., 1996).The collective impact of biomolecule damage and cell signaling disruption leads cells down regulated pathways towards death via apoptosis or necrosis.

3.4. Induction of apoptosis and cell death pathways

Metal nanoparticles can induce cancer cell death by activating various apoptotic signaling cascades. Apoptosis is a form of programmed cell death characterized by distinct biochemical and morphological changes like cell shrinkage, chromatin condensation, and membrane blebbing (Jayakiran, 2015). Many nanoparticles prompt apoptosis by causing DNA damage that upregulates p53 expression. p53 stimulates the transcription of pro-apoptotic proteins like Bax, Bak, Noxa, and Puma and downregulates anti-apoptotic Bcl-2 proteins, triggering the intrinsic mitochondrial apoptosis pathway. This leads to mitochondrial membrane permeabilization, release of cytochrome c into the cytosol and subsequent activation of the caspase cascade (Shi et al., 2010). In addition, elevated intracellular calcium levels brought on by specific nanoparticles can initiate the ER stress-mediated extrinsic apoptosis pathway (Biagioli et al., 2008). Separately, increased production of reactive oxygen species by metal oxide nanoparticles directly activates MAPK signaling proteins including JNK and p38, turning on apoptosis Separately, increased production of reactive oxygen species by metal oxide nanoparticles directly activates MAPK signaling proteins including JNK and p38, turning on apoptosis. Elucidating the specific apoptosis pathways mediated by various metal nanomaterials will facilitate the expansion of targeted cancer treatment strategies (Dai et al., 2018).

3.5. Synergistic effects when combined with traditional cancer therapies like chemotherapy and radiotherapy

Metal nanoparticles demonstrate significant synergistic effects when combined with traditional cancer therapies like chemotherapy and radiotherapy (Villalobos Gutiérrez et al., 2023). For example, gold nanoparticles functionalized with thiol groups can bind and delivery platinum-based drugs like cisplatin directly into cancer cells, enhancing their therapeutic efficacy (Kumar et al., 2014). The large surface area of nanoparticles also enables high drug payload capacity through surface conjugation and entrapment within surface coatings. Moreover, tumor-targeted delivery using antibodies improves drug accumulation specifically in cancerous tissues. Similarly, high-Z metal nanoparticles containing gold, hafnium and bismuth accentuate the localized dose of ionizing radiation. This amplifies DNA damage and cytotoxic radical formation to promote greater cancer cell death (Butterworth et al., 2010). Additionally, the strong X-ray absorption coefficient of certain metal nanoparticles make them excellent contrast agents to precisely guide radiation beams towards tumor tissues using CT imaging. Furthermore, metal nanoparticles can be designed to produce heat when exposed to external light sources, permitting targeted hyperthermia therapy. Overall, metal nanoparticles act as versatile sensitizers and carriers to potentiate conventional anticancer modalities.

4. Types of Metal Nanoparticles in Anticancer Therapy

4.1. Gold nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) have emerged as promising agents in cancer diagnostics and treatment due to their biocompatibility, facile surface chemistry, and unique optical properties. AuNPs can be synthesized in a variety of sizes and shapes such as nanospheres, nanorods, nanoshells, and nanocages using methods like citrate reduction, seed-mediated growth, and galvanic replacement (Kundu, 2013).The strong surface plasmon resonance of AuNPs enables their use as contrast agents for dark-field microscopy, computed tomography and photoacoustic imaging to visualize tumor tissues. Additionally, near-infrared laser excitation of gold nanorods results in strong photothermal heating to induce localized cancer cell death. The high surface area of AuNPs also allows the binding of large numbers of drug molecules, antibodies, and tumor targeting moieties on their surface to achieve active targeting and enhanced intracellular drug delivery in cancers (Z. Zhang et al., 2015). Furthermore, their inert nature coupled with biodegradability and minimal systemic toxicity makes AuNPs attractive for drug delivery, photothermal therapy, and as dose enhancers in radiotherapy treatment to combat tumors.

4.2. Silver nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) have garnered substantial attention for their cytotoxic effects against cancer cells and as transport systems for the delivery of other anticancer drugs and therapeutic molecules. AgNPs have been shown to induce generation of reactive oxygen species, inflict mitochondrial damage, and trigger apoptosis signaling pathways - which hinder proliferation and induce death in a variety of cancer cell lines (Mallick et al., 2016). A major advantage of AgNPs is their higher efficacy in drug resistant cancers, where they act through mechanisms that bypass typical resistance pathways. Moreover, AgNPs release silver ions over prolonged periods, leading to sustained intracellular uptake and long-term cytotoxicity (Singh and Ramarao, 2012). However, optimal biocompatibility and tumor targeting remain key challenges. If delivered precisely, cancer cells show higher sensitivity to AgNP-induced DNA damage and oxidative stress than normal cells. By moderating rate of silver ion release, counteracting bioaccumulation risks, and exploring combination therapies, AgNPs hold promise to tackle multidrug resistant and aggressive tumor types (Kovács et al., 2016).

4.3. Iron oxide nanoparticles (FeNPs)

Iron oxide nanoparticles (FeNPs), including magnetite (Fe_3O_4) and maghemite (Fe_2O_3), are extensively utilized in cancer diagnosis and therapy owing to their biodegradability, biocompatibility, and

inherent magnetic properties (Revia and Zhang, 2016). Their strong superparamagnetic behavior enables FeNPs to act as both contrast agents for improved tumor detection in magnetic resonance imaging (MRI) and as mediators for localized hyperthermia cancer therapy. By applying an alternating magnetic field, FeNPs dissipate heat that raises tumor temperatures between 41-45°C, causing cytotoxicity (Chiriac et al., 2015). Furthermore, surface functionalized FeNPs aid active targeting of tumor tissues for localized therapies and facilitate cellular uptake. FeNP surface coatings can also be tailored to control drug binding and release kinetics for controlled chemotherapeutic delivery. However, mitigating Ostwald ripening effects on particle size and managing rapid renal clearance of FeNPs remain key challenges. Overall, multimodal FeNPs hold significant promise for precise cancer theragnostic by unifying MRI diagnosis, controlled drug delivery, and hyperthermia therapy modalities.

4.4. Platinum nanoparticles (PtNPs)

Platinum-based drugs like cisplatin are commonly used as first-line chemotherapeutics for multiple cancer types (Zhang et al., 2022). However, their clinical efficacy is limited by systemic toxicity and tumor resistance over recurrent dosing regimens. Platinum nanoparticles (PtNPs) have now emerged as attractive alternatives that overcome these limitations owing to their unique cancer cell uptake pathways, ability to evade efflux mechanisms, and inherent catalytic activity. For instance, dendrimer-encapsulated PtNPs exhibit 6- to 7-fold higher accumulation in cancer cells compared to cisplatin leading to superior DNA binding and cytotoxicity (Malik et al., 1999). Additionally, the small size and tunable surface chemistry of PtNPs facilitates cell-specific targeting and enhanced permeation. Once internalized, the oxidizing tumor microenvironment degrades PtNPs to release cytotoxic Pt ions that impact mitochondrial functioning while circumventing drug resistance mechanisms. PtNPs also potentiate radiation therapy by amplifying local energy deposition and radical formation under X-ray beams. Despite these advantages, more rigorous biocompatibility evaluations are warranted for translational success (Daneshvar et al., 2020). Overall, PtNPs display immense potential to improve platinum pharmacology and revive platinum-based combination therapies.

4.5. Other nanoparticles

Besides noble metals and iron oxide, nanoparticles fabricated from transition metals like copper and zinc also demonstrate promising cytotoxicity, drug delivery, and diagnostic imaging capabilities against cancer cells (Rasmussen et al., 2010). Copper nanoparticles induce the generation of damaging reactive oxygen species, cause mitochondrial dysfunction, inhibit key cancer cell signaling kinases, and show preferential toxicity towards tumor cells - while exhibiting biocompatibility at therapeutic concentrations (Vinardell and Mitjans, 2015). Similarly, zinc oxide nanoparticles trigger caspase-dependent apoptosis, reduce growth-promoting enzymes, and sensitize cancer cells to radiation without harming normal cells (Ahamed et al., 2012). Additionally, the strong X-ray attenuation of copper and zinc aid in cancer radiotherapy and computed tomography imaging applications. Copper nanoparticles also enable photoacoustic imaging and photothermal ablation of tumors. However, most copper and zinc nanoparticles remain confined to preclinical stages and face translational challenges in large-scale manufacturing, stability in biological milieu, and predictive toxicological profiling(Heo et al., 2019). Further optimization of their biocompatibility, tumor targeting efficiencies, and therapeutic synergies with existing modalities can accelerate their clinical evaluation and expand nanomedicine-based solutions for cancer.

Figure 3: Types of metal nanoparticles in Anticancer therapy

5. Metal nanoparticles for cancer detection

Metal nanoparticles such as iron oxide and gold nanoparticles have shown great promise as contrast agents for cancer imaging techniques including MRI, CT, and PET scanning. Their unique physical and chemical properties allow them to strongly interact with imaging modalities to produce significant contrast enhancement (Cho et al., 2010). For example, superparamagnetic iron oxide nanoparticles (SPIONs) can substantially increase T2 contrast in MRI, enabling improved visualization of tumors. Gold nanoparticles provide greater X-ray attenuation and higher resolution in CT imaging compared to iodine agents (Bakhtiary et al., 2016).

Radioisotope-conjugated gold nanoparticles can also act as targeted PET imaging agents, allowing quantitative detection of cancer biomarkers. Furthermore, the multifunctionality of nanoparticles has enabled development of multimodal imaging agents that integrate capabilities for both MRI and PET. Targeted metal nanoparticle contrast agents can significantly improve cancer diagnosis by enhancing image contrast and specificity compared to conventional small molecule agents. However, more research is still required to fully assess long-term toxicity before widespread clinical use.

The unique optical and magnetic properties of metal nanoparticles make them highly promising for developing ultrasensitive biosensors for cancer biomarker detection. Gold nanoparticles and magnetic nanoparticles such as iron oxide have been extensively explored for transducing molecular recognition events into measurable signals through techniques including colorimetry, fluorescence, surface plasmon resonance, and magnetic relaxation (Szunerits et al., 2014). For example, gold nanoparticles functionalized with tumor-targeting antibodies can create colorimetric assays for antigens or circulating tumor DNA. Magnetic nanoparticles coated with molecular recognition moieties enable magnetic relaxation switching biosensors for cancer protein biomarkers with detection limits down to femtomolar concentrations. Furthermore, metal nanoparticles amplify signals and reduce interference in electochemical biosensors, enhancing detection of cancer DNA biomarkers (Eskandarinezhad et al., 2022). Their large surface area and ease of functionalization allow multiplexing with different nanoparticles to enable rapid multi-biomarker screening. Metal nanoparticle biosensors can provide real-time, high-sensitivity detection of cancer biomarkers for early diagnosis and point-of-care applications. However, more work is still needed to validate their clinical accuracy and safety.

Metal nanoparticles are enabling combined multimodal imaging strategies for improved cancer detection by integrating the strengths of different techniques. For example, dual-mode MRI-PET or CT-PET imaging can be achieved using a single nanoconstruct functionalized with both a magnetic/X-ray contrast agent like iron oxide or gold along with a radionuclide tracer. This provides the high sensitivity of PET for detecting tumors along with the high resolution anatomical details from MRI or CT (Luo et al., 2011). Similarly, fluorescence imaging can be combined with MRI or CT using nanoparticles tagged with both a fluorophore reporter and magnetic/X-ray contrast payload. Photoacoustic imaging paired with MRI/CT using gold or carbon nanoparticles as contrast generates both functional and structural information. Multimodal nanoparticles amplify signals for each modality, thereby improving overall diagnostic accuracy (Bouchard et al., 2009). They also allow for targeted imaging by attaching cancer-specific antibodies, peptides, or other ligands. The integration of metal nanoparticles with multiple state-of-the-art imaging technologies promises earlier and more reliable cancer diagnosis. However, more clinical translation work is required to validate safety and effectiveness (Fernandez-Fernandez et al., 2011).

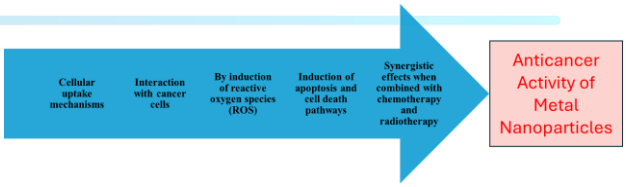

Figure 4: Mechanism of anticancer therapy

6. Future Directions and Challenges

While metal nanoparticles have shown promising capabilities for cancer therapies, their clinical translation faces significant challenges regarding biocompatibility and potential toxicity. Many types of metal nanoparticles like gold, iron oxide, and platinum tend to accumulate in organs such as the liver, spleen, and kidneys. This biodistribution, along

with cellular uptake and circulation in the blood, can potentially trigger inflammatory responses, oxidative stress, and DNA damage. The small size and high surface area of nanoparticles allows them to interact with biological molecules in unintended ways, sometimes causing adverse effects. Comprehensive in vivo toxicity profiling in cell cultures, animal models, and clinical trials is still needed to fully characterize the safety margins and cytotoxicity issues after both short-term and long-term exposure.

Future research on metal nanoparticles for anticancer therapy should focus on developing "green" synthesis methods to inherently make them less toxic. Testing new biodegradable coatings and surface modifications can help minimize systemic side effects and improve biocompatibility. Rigorous pharmacological and pharmacokinetic studies are also essential to assess the accumulation, metabolism and excretion profiles of nanoparticles in the body, which can guide the establishment of safe dosage levels. Furthermore, standardized regulatory guidelines need to be formulated for preclinical toxicology testing of metal nanoparticles to facilitate their clinical translation and approval as nanomedicines for cancer treatment.

The potential of metal nanoparticles for targeted cancer therapy is limited by difficulties in selectively delivering them to tumor sites. Nanoparticles tend to become trapped in organs like the liver and spleen after systemic administration. Strategies are needed to avoid uptake by healthy cells and increase tumor accumulation. Attaching targeting ligands such as antibodies, peptides, or small molecules to nanoparticles can enhance their uptake by cancer cells overexpressing specific receptors. However, specificity and affinity challenges remain when translating these from laboratory models to in vivo scenarios. Most surface receptors are also not exclusively expressed by cancer cells, leading to off-target effects. Developing novel targeting moieties through cancer cell screenings and understanding cell-particle interactions is critical for improving active targeting capabilities. Future efforts should focus on combinatorial targeting and personalized approaches. Using dual or multifunctional ligands may provide synergistic targeting effects to increase nanoparticle delivery to tumors. Tailoring nanoparticles based on the molecular profiles of individual patients' cancer types could also optimize targeting efficacy. Stimuli-responsive strategies using local cues like pH or enzymatic triggers to activate nanoparticles at tumor sites provide another avenue for enhancing site-specificity. Overall, realizing the full potential of metal nanoparticles for targeted anticancer therapy requires moving beyond conventional delivery schemes towards smart, multi-functional nanosystems capable of molecularly-precise targeting in complex in vivo tumoral microenvironments.

The clinical translation and approval of metal nanoparticle-based cancer therapies faces multiple challenges. Very few nanoparticle platforms have progressed beyond preclinical development due to difficulties in scaling up manufacturing and meeting regulatory requirements. The complexity of nanoparticles makes it hard to produce good manufacturing practice (GMP) grade materials consistently at an industrial scale. Extensive physicochemical characterization and quality control testing is required at each stage. Long-term stability data and standards for storage/transport of nanoparticles need to be established as well. Moreover, regulatory guidelines for metal nanoparticle toxicology testing, pharmacokinetics, and pharmacovigilance are still evolving. Demonstrating efficacy through multi-phase human clinical trials poses both logistical and financial hurdles. Advancing metal nanoparticles into mainstream cancer care will require coordinated efforts between researchers, regulators, and industry. Sustainable funding mechanisms are needed to offset the high costs and risks of clinical development. Regulatory science partnerships can help consensus building on appropriate standards for nanotherapeutics evaluation. Future priorities also include developing standardized models for predictive nanotoxicity screening and pharmacokinetics. Clinical trials should focus on combination therapies leveraging the synergistic effects of nanoparticles with chemo/radiation regimens. Comprehensive post-marketing surveillance will be essential for ongoing safety monitoring of approved nanoparticle therapeutics. Overall, a collaborative long-term strategy is key to realizing the clinical potential of metal nanoparticles while ensuring patient safety.

Several promising directions are emerging to overcome current challenges and advance metal nanoparticles towards clinical realization as anticancer therapeutics. Hybrid nanosystems that

integrate multiple functional modalities into a single nanoplatform are gaining traction. For instance, combining drug delivery with hyperthermia and imaging capabilities can enable theranostic nanoparticles for both targeted therapy and non-invasive monitoring. Advances in components, and biological microenvironments to improve biocompatibility. Furthermore, green synthesis techniques using plant extracts or microbial culture are providing more sustainable and potentially safer methods of metal nanoparticle production. Looking ahead, metal nanoparticles are expected to open new possibilities for personalized cancer medicine by integrating molecular profiling data with programmed drug delivery. Stimuli-responsive strategies and on-demand activation at tumor sites will enhance targeted activity. Combinations with immunotherapy can also leverage possible synergies with the immune system against cancer. However, actualizing the full potential of metal nanoparticles will require multidisciplinary collaboration. Integrating expertise across chemistry, materials science, biology, pharmacology, medicine, and regulatory disciplines will accelerate translation from proof-of-concept to viable clinical tools for advanced anticancer therapy. Close partnership between academia and industry will also be critical for commercial development and clinical implementation.

7. Summary

Cancer remains one of the most pressing global health challenges, demanding innovative therapeutic strategies. In recent years, metal nanoparticles (MNPs) have emerged as promising candidates in revolutionizing cancer treatment. This summary elaborates on the transformative potential of MNPs, their mechanisms of action, applications in cancer therapy, challenges, and future prospects. Cancer's complex nature necessitates novel treatment approaches. MNPs offer unique properties such as tunable size, shape, and surface chemistry, enabling precise targeting and therapeutic efficacy. Their ability to interact with biological systems at the nanoscale presents opportunities for innovative cancer therapies.

Various methods, including chemical, physical, and biological routes, are employed for synthesizing MNPs. Characterization techniques such as electron microscopy, spectroscopy, and dynamic light scattering are crucial for understanding their physicochemical properties. Controlling synthesis parameters facilitates tailoring MNPs for specific biomedical applications. MNPs exert anticancer effects through multiple mechanisms. They can selectively accumulate in tumor tissues via enhanced permeability and retention effect or active targeting strategies. Upon cellular uptake, MNPs induce cancer cell death through apoptosis, necrosis, or autophagy pathways. Additionally, MNPs modulate the tumor microenvironment, inhibiting angiogenesis and metastasis. Gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), platinum nanoparticles (PtNPs), and others exhibit distinct properties and applications in cancer therapy. AuNPs are utilized for imaging, drug delivery, and photothermal therapy. AgNPs possess antibacterial and anticancer properties, while PtNPs are effective in chemotherapy and synergistic combinations.

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