



# ADVANCEMENTS OF METAL-BASED NANOPARTICLES; A FAMILY OF NANOMATERIALS AND THEIR APPLICATIONS IN THE FIELD OF ONCOLOGY

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## Abstract:

Current cancer treatments, particularly chemotherapy, necessitate new approaches due to their adverse side effects. A significant area of recent interest is the use of nanoparticles. Functionalizing metal-based nanoparticles has shown great promise in drug delivery, as several studies have demonstrated that these nanoparticles can enhance target specificity. This improvement allows for lower drug dosages while maintaining treatment efficacy, thereby reducing side effects. This review focuses on metal-based nanoparticles and their advancements in treating various types of cancer.

*IndexTerms* - Metal-based nanoparticles, Breast cancer, Lung cancer, Silver nanoparticles.

## 1.INTRODUCTION

Cancer is defined by the uncontrolled growth of cells, marked by their metastasis property. The progression of cancer in a patient is typically categorized into three distinct stages: avascular, vascular, and metastatic. In clinical practice, a cancer diagnosis is usually confirmed when the disease reaches the metastatic stage. Treating cancer at the metastatic stage presents significant therapeutic challenges, as malignant cells can circulate throughout the body and form new tumors. Cancer is a broad category that includes various diseases capable of affecting any part of the body. Key property is the speedy production of abnormal cells, they grow without any limits, go to nearby regions, and gradually spread to all over the areas. Despite advancements in science and technology, cancer continues to be a major cause of death worldwide. While mono therapeutic strategies are commonly used in medical treatments for various types of cancer, they are often seen as less effective compared to combination therapy approaches. Traditional monotherapies, such as standalone chemotherapy, typically target all actively dividing cells non-selectively, leading to the destruction of both healthy and cancerous cells. Additionally, chemotherapy is well-known for its toxicities, a range of adverse effects, potentially life-threatening complications, myelosuppression, and an increased susceptibility to infections. As a result, there is an increasing demand for cancer treatments that can specifically target tumors while reducing overall toxicity, especially in the context of precision and personalized medicine. Combination therapies offer significant benefits by enhancing the effectiveness of anticancer agents, inducing apoptosis, inhibiting tumor growth, and decreasing the number of cancer stem cells. Conventional cancer treatments often damage normal cells as well, they can cause serious adverse effects to the consumer(1). Thus, there is a need for new methods to treat gastric cancer. Recent advancements involving nanoparticles (NPs) aim to reduce the unwanted problems associated with chemotherapy of tumor. Enhance targeted delivery of drugs, specifically for adenocarcinoma(2). Recently, numerous nanoparticles are employed to impede the progression of tumor cells by minimizing the harmful effects these medications can have on the entire body. Today, advancements in nanoparticle technology have significantly progressed the development of numerous drugs. The production of nanoparticles holds promise for detection and therapy of various diseases, including cancer. Metal based nanoparticles are regarded as potential candidates for therapy of tumors(3).

Metallic nanoparticles have emerged as a major innovation in cancer chemotherapy. Ranging from 1 to 100 nm in size, these nanoparticles exhibit enhanced permeability and retention effects, allowing them to accumulate more effectively in tumour tissues compared to normal tissues. By functionalizing nanoparticles with specific binding molecules, they can recognize and bind to tumours more precisely, thereby minimizing off-target effects. Additionally, precise control of the magnetic field enables targeted heat production within the tumour region, offering a minimally invasive and focused treatment method. The approach can be used in conjunction with other therapies to enhance overall effectiveness. This targeted delivery capability helps reduce the typical adverse reactions linked with traditional tumour treatment. Metallic nanoparticles are engineered to deliver chemotherapeutic medicines to the malignant cells, thereby improving the therapeutic outcome. Their surfaces can be adapted to enhance biocompatibility and lower toxicity, and they can be coupled with ligands, antibodies, or peptides for precise targeting of cancer cells. Additionally, some metallic nanoparticles possess inherent anticancer properties and can generate reactive oxygen species under specific conditions, which induces apoptosis in cancer cells. Therefore, integrating metallic nanoparticles into cancer chemotherapy offers significant potential for creating more effective and less harmful cancer treatments.

### **Metal- based nanoparticles**

Metal- based nanoparticles usually feature a -shell configuration. Core, made of metal, defines the nanoparticles' characteristics. The shell is made of metals or organic polymers that protect the metallic core from chemical reactions with the surroundings and allow the nanoparticles to be attached to different biological molecules. These biological molecules encompass low molecular weight ligands, peptides, proteins, polysaccharides, both polyunsaturated and saturated fatty acids, DNA, plasmids, small interfering RNA (siRNA), antibodies, tumor markers, and small molecules. Often by functionalization metallic nanoparticles are frequently utilized as tumor treatment. Nanoparticle-based delivery systems for recombinant RNA and DNA are employed in gene therapy due to their prominent efficiency in gene transfer, minimal immune response, and compatibility with biological systems, and, most importantly, their ability to protect genetic material from enzymatic degradation. For nanoparticles to exert their effects, their entry into the cellular cytoplasm is crucial, endocytosis, pinocytosis, are essential for this function.

## **2. Advancement of metal-based nanoparticles in oncology**

Even though the conventional tumor treatments are well advanced, they still possess notable drawbacks such as destruction of healthy cells, unwanted outcomes, etc. Recently, cancer therapies mediated by nanotechnology have advanced significantly and garnered substantial attention.

### **2.1. Magnetic hyperthermia cancer therapy**

Magnetic hyperthermia tumor treatment offers a potential method for selectively targeting malignancy by using magnetic nanoparticles and targeted heat production. After administration these agents accumulate on the sites of tumor(4). Metal- based nanoparticles are usually made from materials such as iron oxide, which exhibit low coercivity magnetism and are have a tight hysteresis loop(5). Additionally, they are customized with particular molecules to improve their specificity towards tumor(6). Once accumulated in the tumor, exposure to an Oscillating magnetic field causes oscillations and rise in temperature by mechanisms such as Néel relaxation, Brownian relaxation, and hysteresis loss(7). Hysteresis loss occurs when magnetic materials delay their reaction to changes in the applied magnetic field, causing energy to be dissipated as heat, this heat generated increases the temperature in the tumor area, leading to localized hyperthermia(7). The rise in temperature targets between 42°C and 45°C to induce programmed cell death. Iron oxide-based magnetic nanoparticles are commonly utilized in hyperthermia applications(8).

### **2.2 Breast cancer**

One of the greatest prevalence and second most death rate causing tumour among women(9). WHO projected over 2 million recent cases and more than 0.6 million fatalities from breast cancer in 2022(10). It is the primary invasive disease among females worldwide, particularly in developing countries(11). Cerium oxide nanoparticles (CeO-NPs) produced using alginate possess antioxidant characteristics and exhibit toxicity to breast cancer cells as well as human skin connective tissue cells. As chemotherapeutic agents, CeO-NPs have the potential to specifically target cancer cells while exhibiting minimal harm to healthy cells (12).

The effects of algae-synthesized silver nanoparticles validated on MDA-MB-231 human breast cancer cells and HaCat human keratinocyte normal cells. The cell survival analysis showed a decreased time and dose-dependent survival rate of tissues of breast tumour, with a lesser impact on healthy tissues. Decrease in cell survival is not due to a cytotoxic or antigrowth property of Algae-AgNPs, as indicated by the release of LDH and incorporation of BrdU. Algae-AgNPs demonstrated a remarkable potential to precisely elicit cell death in cancer cells without affecting healthy tissues(13).

ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles (ZnFe<sub>2</sub>O<sub>4</sub>NPs) exhibit stepwise cellular impact on tumour cells. MTT and NRU assays used to measure cell viability, and the results indicated that at low doses, ZnFe<sub>2</sub>O<sub>4</sub>NPs had no noticeable effect on cell growth. Analysis of reactive oxygen species (ROS) generation confirmed that ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles (ZnFe<sub>2</sub>O<sub>4</sub>NPs) are active against breast cancer tissues. Additionally, the transcriptome analysis of P53, caspase-3, Bax, Bcl2 demonstrated that ZnFe<sub>2</sub>O<sub>4</sub> nanoparticles (ZnFe<sub>2</sub>O<sub>4</sub>NPs) induce apoptosis in breast cancer cells(14).



### 2.3 Carcinoma of lungs

Carcinoma of lungs fatal for both men and women and is often cited as the principal cause of death in many countries(15). Histological classifications of lung cancer include small-cell and non-small-cell types(16). Advanced non-small-cell lung cancer, in particular, has been linked to a pessimistic outlook, highlighting the urgent need for effective new treatments. Finding cures for rapidly growing cancers remains an extremely challenging task(17). Biosynthesized NiO nanoparticles feature nanoholes of different sizes, and their cytotoxicity has been validated for different purposes. Metallic-nanoparticles hold significant potential in preliminary research applications in lung cancer treatment(18).

### 2.4 Functionalized nano particles bowel carcinoma

Bowel carcinoma is one of the frequently confirmed tumors globally and one of the leading causes of death for every gender (19). In 2020, approximately 1.9 million occurrences of CRC were noted with 900,000 resulting in death(20). Metastasis is a major factor contributing to the high mortality rate in CRC patients, having metastases frequently found in the liver and peritoneum(21). The cytotoxic effect observed in human colorectal adenocarcinoma cell line following single-dose MOLP-AgNPs therapy and Combined therapies revealed a substantial drop in cell viability and a decrease in cell growth. MOLP-AgNPs exhibited significant cytotoxic activity against human colorectal adenocarcinoma cell line in a manner of dose-dependency. Thus, MOLP-AgNPs hold promise as a promising drug candidate for bowel carcinoma, particularly in suppressing growth and gene expression related to metastasis(22).

Treating chemotherapy-resistant and metastatic colon cancers presents significant challenges. Iron oxide nanoparticles have garnered interest for delivering anticancer agents due to their high biocompatibility and magnetic properties. Papaverine, an alkaloid derived from opium, has demonstrated anticancer effects on various cancer cells. Iron oxide nanoparticles were conjugated with Papaverine using glucose (Glu) functionalization.

$\text{Fe}_3\text{O}_4$ @Glu-Papaverine nanoparticles exhibited anticancer potential in colon cancer cells by inducing apoptotic pathways. They caused cell cycle arrest, increased the expression of the CASP8 gene, and reduced the levels of lncRNA GAS6-AS1.

Pyroptosis, a newly identified type of immunogenic cell death, is crucial in chemotherapy. Zirconium-based metal-organic frameworks (Zr-MOFs) utilized in a range of anticancer therapies. A Zr-MOF-based nano system (DOX@Zr-MOF) developed by loading Zr-MOF nanoparticles and doxorubicin (DOX) to induce cancer cell pyroptosis in a synergistic manner. A Zr-MOF-based nanosystem (DOX@Zr-MOF) was developed by loading Zr-MOF nanoparticles with the chemotherapeutic drug doxorubicin (DOX) to induce tumour tissues inflammatory cell death in a synergistic manner. Moreover, combining DOX@Zr-MOF using PD-1 modulatory therapy significantly enhanced the anticancer effectiveness against CT26 colon tumours(23).

### 2.5 Gastric cancer

Gastric adenocarcinoma is notorious for its high mortality rate and aggressive nature(24). Despite notable advancements in early diagnosis, it remains a difficult challenge owing to resistance to therapeutic agents and High rate of fatality(25).

Zinc oxide nanoparticles (ZnO NPs) have showed significant antitumor potential, but their clinical effectiveness is often affected by the synthesis methods and their specific physicochemical properties. ZnO NPs produced by an economical flame-enhanced spray pyrolysis, and their preferential anticancer activity, the essential intrinsic apoptosis signaling route were studied in cell line of human gastric adenocarcinoma. Zinc oxide (ZnO) nanoparticles (NPs) have garnered significant attention for cancer treatment. Biosynthesized ZnO NPs offer promising utilizations in combined cancer diagnostics and treatment.

### 2.6 Ovarian cancer

Ovarian cancer is a prevalent malignant tumour of the female reproductive organs and the most common gynaecological cancer, characterized by high incidence and mortality rates(26). Currently, chemotherapy is a primary treatment for ovarian cancer; however, conventional chemotherapy drugs often have limited effectiveness and significant side effects, causing considerable suffering and reduced quality of life for patients. Molybdenum selenide ( $\text{MoSe}_2$ ) is extensively researched as a nano-scale absorber of near-infrared radiation for cancer photothermal therapy. However, its use in treating ovarian cancer has been less explored. A novel carbon-coated  $\text{MoSe}_2$  (MEC) NP was synthesized using a single step hydrothermal process. The exploration of MEC nanoparticles revealed; they have enhanced absorbance and can emit more heat during laser treatment, augmenting their therapeutic impact on ovarian cancer. As photothermal agents, MEC NP's exhibit strong anticancer capabilities(27).

### 2.7 Kidney cancer

The kidney is a vital organ responsible for purifying the blood and maintaining fluid, solute balance in the body. Kidney also maintains BP, and produces various hormones(28). Several distinct types of cancers that originate in the kidney, each driven by different genes and characterized by specialized histological features, progression of the condition, and health-promoting responses. Cancerous solid tumors can often be effectively removed by surgical means, particularly when detected early. Combined therapy, which includes surgery, chemotherapy, and radiotherapy,

is commonly used. Nanoparticles are now frequently used as contrast agents and for drug/gene delivery in imaging, reflecting their recent widespread application. In this context, a variety of substances, including organic, inorganic, polymeric, lipid, and glycan materials, are utilized successfully(29). Various oxide nanomaterials (NMs) with strong cell-destructive features are harnessed for drug delivery systems in tumor treatment. (30). Among various NMs, zinc oxide is toxic to bacteria, algae, and yeasts, and possesses strong cell-destructive characteristics(31). ROS are primarily possessing the cell-destructive property of ZnO nanoparticles (NPs)(32).

### 3. Future Perspectives

Nanoparticles (NPs) are emerging as novel, targeted therapy options for certain tumors. Research has demonstrated their cytotoxic effects on tumors via mechanisms such as cell cycle arrest, oxidative stress, ROS production, DNA damage, and cell death. Functionalizing NPs with different biomolecules could enhance their ability to provide targeted, effective, and non-invasive cancer therapy while minimizing damage to healthy tissues. While a number of studies are still in the preclinical stage, the advancement made indicates that these NPs have promising benefits and are expected to be valuable tools in cancer therapy. More studies regarding the functionalized metallic nanoparticles in cancer chemotherapy under progress, hope it will provide more effective and less toxicity to the cancer patients in future.

### 4. Conclusions

This review offers an outline of the use of functionalized nanoparticles and their benefits over current treatments. According to the studies reviewed, nanoparticle-based cancer therapy represents a novel approach. However, several investigations focusing on different tumors have demonstrated the effectiveness of nanoparticles, including those functionalized with different biomolecules, in tumor treatment. Metallic nanoparticles offer a broad range of therapeutic potentials, including light-activated thermal therapy, drug delivery, ROS production, apoptosis triggering, defective mitochondrial function, blockage of the cell cycle, splitting of DNA, inhibition of cellular movement, oxidative degradation of lipids, and immune system alteration through cytokines, among others. Studies consistently demonstrate their in vitro and in vivo encouraging results from antitumor effects even against tumors not susceptible to conventional oncological agents.

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