STUDY OF NANOSTRUCTURED METAL OXIDES IN CANCER THERAPY AND THEIR PERSPECTIVE ROLE IN DIAGNOSIS

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Abstract: One of the worst and the most dangerous diseases in the world now is cancer. Cancer remains prevalent even with the number of medical professionals increasing. There are certain clinical limitations to the cancer treatment methods used today. There are numerous causes for this, such as inadequate treatment, delayed diagnosis, and serious adverse effects from anticancer medications. The majority of tumors have developed resistance to the anti-cancer drugs presently available in the market, which lowers the overall survival rate of cancer patients. Therefore, there is an urgent need for more effective anticancer medication therapy. Nanotechnology has recently provided a ray of hope for more effective cancer treatment. The synthesis and use of nanomaterials and nanoparticles, comes under the area of nanotechnology, becoming more and more interesting in the treatment of cancer because of their vital roles as drug carriers and photo-sono-sensitizers. As a result, two new therapies have been developed: sonodynamic therapy (STD) and photodynamic therapy (PDT). This review mainly focuses on the overall status of cancer, its many stages, existing pharmacological treatments, and the use of nanomaterials in the treatment and diagnostics of different cancer subtypes.

Keywords: Anticancer Drugs; Nanostructured metal oxides; Cancer Therapy and Diagnostics

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I.Introduction

Cancer is a group of diseases characterized by uncontrolled growth and the spread of abnormal cells. Worldwide, cancer has produced severe public health issues and has become the second major cause of high mortality and morbidity after cardiovascular diseases [Globocon, 2020]. The diagnosis and treatment of this dangerous disease are very challenging as there are many clinical limitations to conventional therapies like surgery, radiotherapy, immunotherapy, hormone therapy, and chemotherapy. The main disadvantage of conventional treatments is their minimal specificity, where the current method is unable to deliver the drug only to the affected tissue, resulting in damage to healthy tissues. For many years, chemotherapy has been considered the most effective cancer treatment; however, due to various side effects and multidrug resistance (MDR), this antineoplastic therapy`s use is limited. The primary cancer cells can travel and re-establish in other organs (metastasis) [1-3].

The manufacturing and characterization of customized metal oxide nanoparticles (NPs) for the treatment of tumors have advanced significantly in the search for new anticancer medications. Thus, metallic NPs were created using synthetic or organic processes and various metals (such as titanium, silver, and zinc) to increase their potential for usage in medicine and pharmaceuticals. These metal oxide nanoparticles can induce cell apoptosis through ROS production and subsequent antitumor effects in vitro [4].

Major challenges in the treatment of cancer may be resolved by the use of nanoparticles made of organic and inorganic components. Distinctive characteristics of optical, magnetic, and electrical activity can be found in metal oxide nanoparticles. Some very important effects of metal oxide nanoparticles are the induction of oxidative stress, DNA damage, genotoxic effects, and anti-inflammatory responses, which make them useful for cancer treatment. Figure 1 shows the possible uptake of nanoparticles by the cell [5].

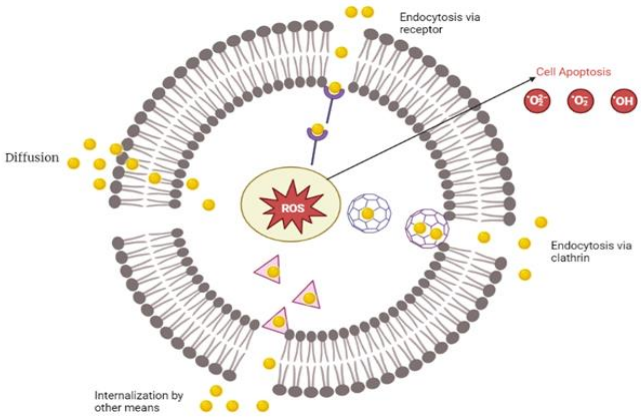

Figure 1: Various modes of internalization of MO-NPs

In this review, we shall focus on the use of mixed metal oxide nanoparticles, their mechanism, and their application to different types of cancer.

II.Statistics of cancer

The global burden of cancer seems to enforce the problems, due to the increasing population and, in addition, the adoption of cancer-causing behaviors as shown in Figure 2 Female breast cancer, lung cancer, and colorectal cancer have higher frequencies in many developing countries in comparison with other types of cancer [6].

Figure 2: Major causes of cancer

The cancer surveillance branch at the IARC maintains a record of cancer burden every year. GLOBOCAN updates the previously published estimates of cancer incidences; it has a data set for 185 countries. It was found that in 2020, most of the commonly diagnosed cancers were female breast cancer (2.26 million cases), lung cancer (2.21 million cases), and prostate cancer (1.41 million cases) as shown in Figure 3 and 4 [7].

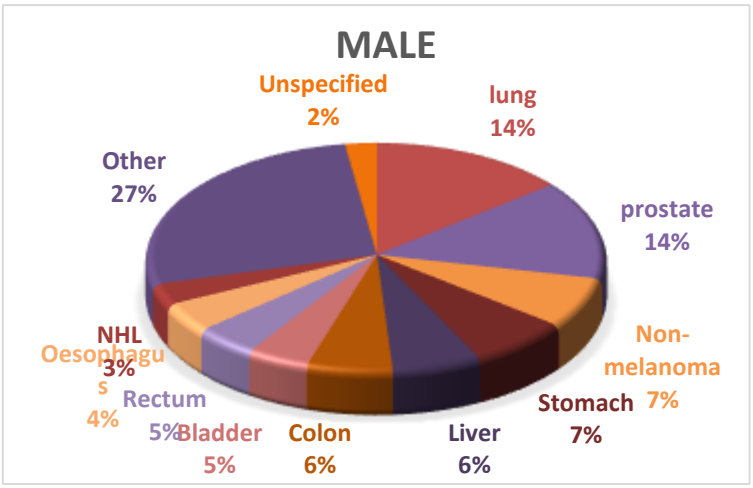

Figure 3: Percentage of new cases in each tumor type in 2020 for males globally

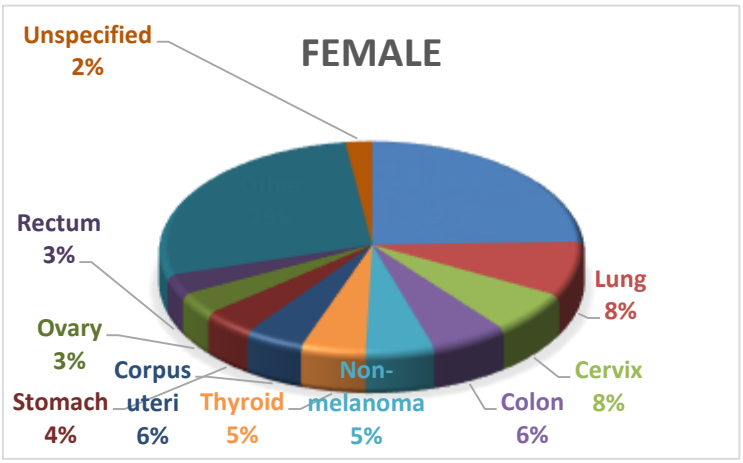

Figure 4: Percentage of new cases in each tumor type in 2020 for females globally

III.Classifications of cancer

Zhang.et.al gathered huge data of cancer genome to classify various cancer types. They used RPPA (reverse phase protein array) data to carry out the classification. The major types of cancer they came through are listed in Table 1 [8].

Table 1: Major types of cancer

Sr. No	Abbreviation	Cancer Name
1	BLCA	Bladder Urothelial Carcinoma
2	BRCA	Breast Invasive Carcinoma
3	COAD/READ	Colon Adenocarcinoma and Rectum Adenocarcinoma
4	GBM	Glioblastoma Multiforme
5	HNSC	Head And Neck Squamous Cell Carcinoma
6	KIRC	Kidney Renal Clear Cell Carcinoma
7	LUAD	Lung Adenocarcinoma
8	LUSC	Lung Squamous Cell Carcinoma
9	OV	Ovarian Serous Cystadenocarcinoma
10	UCEC	Uterine Corpus Endometrioid Carcinoma

a) Breast cancer

Breast cancer is the most common cancer in women in India and accounts for 14% of all cancers in women. [9]. In 2016, the estimated number of incident breast cancer cases in India was 118000, with 98% being female breast cancer. New cases registered according to GLOBOCAN in 2020 are 178361, and the death number is 90408 [10]. Cancer immunoediting is a complex process by which the host immune system tends to destroy the tumour cells in three different stages, which include elimination, equilibrium, and escape. In the elimination stage, the host immune system recognizes and responds to the tumour cells, destroying them. In the equilibrium stage, the surviving tumour cells remain dormant. At last, in the immune evasion stage, the tumour cells attain the ability to escape the identification and response by the host immune system, thus surviving and growing enormously [11]. Breast cancer involves the TNM staging system, where T stands for tumour size, N stands for lymph node involvement, and M stands for metastasis of cancer, i.e., TNM, tumour node metastasis as shown in Figure 5.

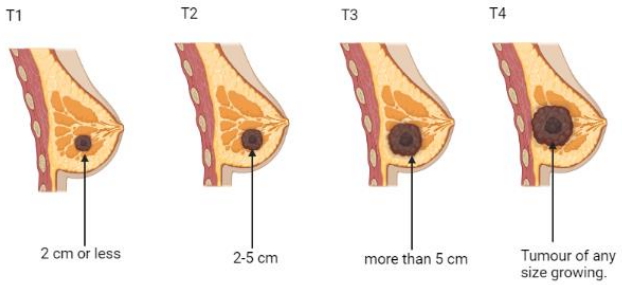

Figure 5: Different stages of breast cancer depending on the tumor size

b) Oral cancer

Cancer developing in the oral cavity is called oral cancer. It is a heterogeneous group of cancers that develop from different parts of the oral cavity, with different genetic factors, prevalence, and treatment outcomes. India has one-third of the oral cancer cases in the world. According to GLOBOCAN, India had 119992 new cases and 72616 deaths in 2018 [12]. The studies indicate 57% of all men and 11% of women between 15-49 years of age use some form of tobacco [13].

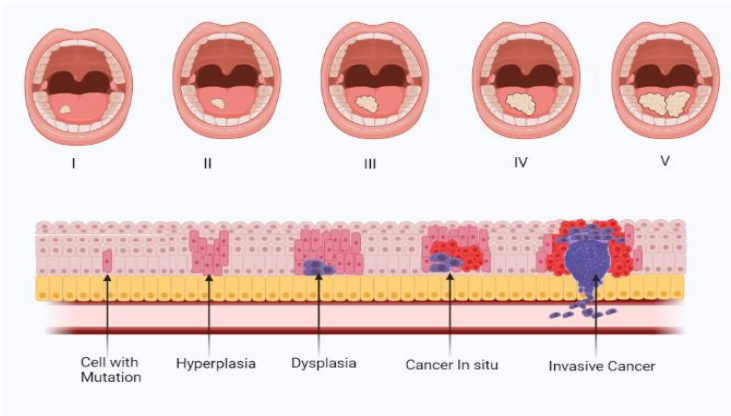

Figure 6: Various stages of oral cancer

Polycyclic aromatic hydrocarbons (PAH) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) are two other tobacco carcinogens [14]. All these carcinogens cause genetic mutations in the epithelial cells of the oral mucosa, which leads to genomic instability and the development of premalignant lesions that result in invasive carcinoma (Figure 6) [15].

c) Lung cancer

Lung cancer is the leading cause of cancer death in men and the second most common reason for cancer death in women all over the world. According to GLOBOCAN's 2012 cancer data, 19% of all cancer deaths were due to lung cancer [16]. Cigarette smoking is one of the most important causes of lung cancer [17].

Lung cancer is broadly classified as small-cell lung carcinoma and non-small-cell carcinoma. Lung cancer is highly heterogeneous and can occur at various sites in the bronchial tree, as shown in Figure 7, therefore having variable symptoms and signs [18].

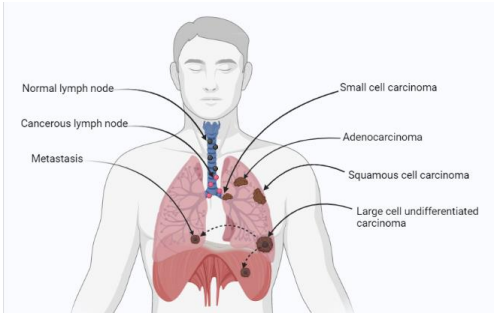

Figure 7: Classification of lung cancer

We have fighters in our body for the foreign material, Figure 8 shows those fighters, which include cytochrome P-450, glutathione S-transferases, UDP-glucuronoxylan transferase, and sulfotransferase. These enzymes convert the carcinogenic material into a more water-soluble product that can be easily eliminated from our bodies.

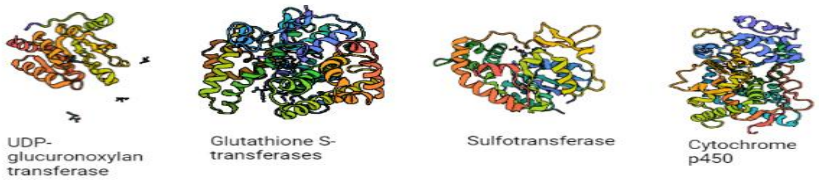

Figure 8: Various enzymes in the body that degrade carcinogenic material

Figure 9 represents the metabolic activity of carcinogens which are inhaled due to cigarette smoking, which forms DNA adducts leading to mutations in oncogenes and tumor suppressor genes which causes loss of normal growth control mechanism which ultimately leads to cancer

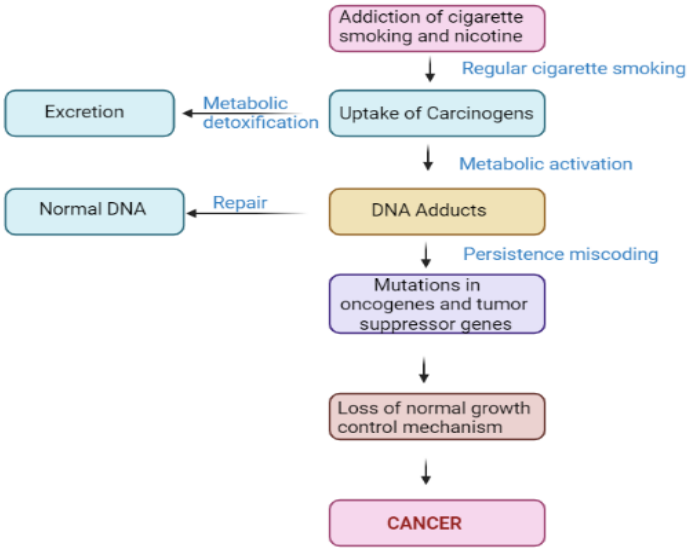

Figure 9: The path followed by the carcinogens in tobacco smoke that cause cancer

Figure 10 shows the various methods for cancer treatment which include the conventional as well as new cancer treatments. The various mixed metal oxides focus on targeted therapy for cancer, which include iron oxide, titanium oxide, nickel oxide and zinc oxide.

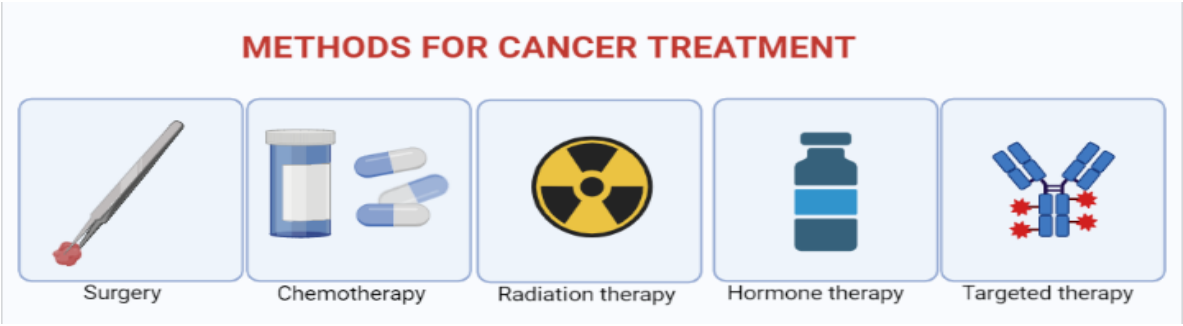

Figure 10: Various methods for cancer treatment which include conventional as well as new treatments for cancer

IV.Metal oxide nanoparticles used for cancer treatment

a) Iron oxide

Iron oxide nanoparticles have gained interest in the past decades in the field of biomedical applications due to their exclusive properties [19]. The IONP are used for magnetic drug targeting (MDT), which includes injecting the anticancer agent onto the IONP, injecting them in the bloodstream, and guiding them to the cancerous cells aided by an external magnetic feild. In this way, an increase in antineoplastic agent dose is achieved in the tumour region with a decrease in overall dose [20].

The use of IONP has helped in overcoming one more side effect of cancer treatment which is multidrug resistance. The IONP induces local hyperthermia, or MFH, due to its capacity to convert magnetic field energy into heat when an outside magnetic field is present. This increases the drug cytotoxicity and improves the intracellular uptake of the anticancer agents as a result of enhanced cell membrane permeability and a suppression of DNA repairs [21]. In a mouse mammary cancer model, Petryk et al. revealed that cisplatin with MFH had more harmful effects than the therapies alone. [22].

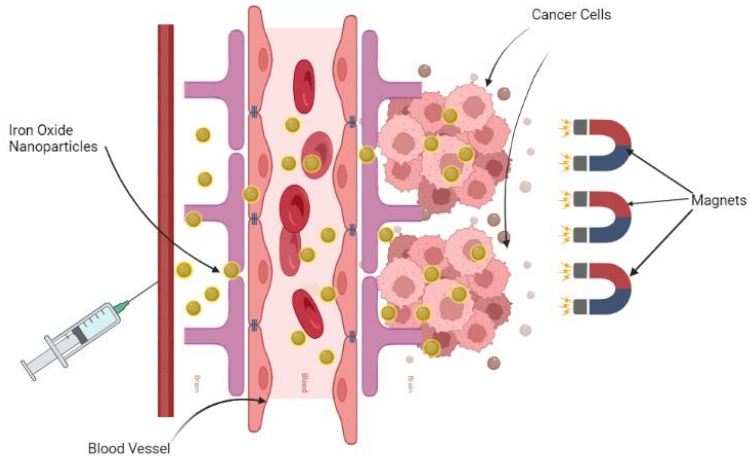

Figure 11: Mechanism of magnetic drug targeting using iron oxide nanoparticles

The IONPs are modified by using them with molecules that target the antigens on metastatic cancer cells as shown in Figure 11. A study was carried out where the patients had T1, T2, or T3 prostate cancer. They were all under observation before and after the intravenous injection of 2.6 mg of iron per kg of body weight of the e-lymphotropic superparamagnetic particle. With the help of high-resolution MRI and these magnetic nanoparticles, node-by-node analysis was done, and found that patients with prostate cancer had modest lymph node metastases. [23].

The capable system's heating magnetic core and multi-stimuli-sensitive shell work together to deliver drugs. Upon reaching the target site, the drug is placed into the shell; as the temperature of the magnetic site rises, covalent and non-covalent connections break, releasing the drug onto the malignant site. Another drug delivery method that includes covalently attaching genistein to Fe_3O_4 MNP coated with cross-linked carboxymethylated chitosan (CMCH) has been originated. Together, these methods indicate that the Fe_3O_4-CMCH-genistein nano system significantly improved cancer cell apoptosis (Figure 12) [24]. Future chemotherapeutic usage of this drug delivery method appears favorable.

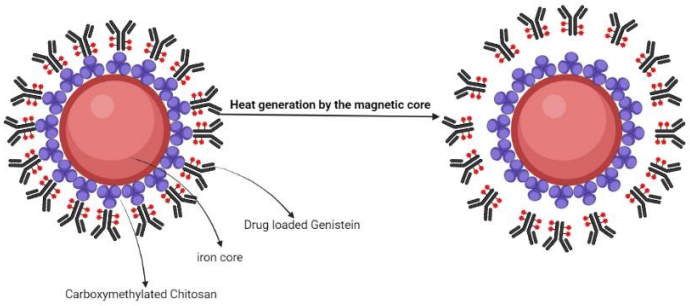

Figure 12: Release of the drug on the cancerous site after the bond dissociation due to the high temperature created by the magnetic core

The combined effect of drugs and magneto-sensitive NP, that is, IONP, increases the antitumor effect as compared to the conventional method. The drugs doxorubicin and IONP together make a strong therapy for cancer treatment, as the external magnetic field induces electron transitions in the nano-complexes. This magneto-complex has a free radical, and in addition, the doxorubicin acquires magnetic properties. [25].
By combining hyperthermia therapy, magnetic nanoparticles like IONP are intended to provide additional medicinal benefits. These nanoparticle formulations frequently have the ability to operate as a fluorescent probe and an MRI contrast agent for monitoring distribution in vivo. Nanoparticles are typically utilized in dendritic cell vaccines to transport antigens to antigen-presenting dendritic cells, which then need to move to lymph nodes to activate antigen-specific cytotoxic T lymphocytes to limit tumor growth. A Fe_3O_4-ZnO core-shell nanoparticle formulation created by Cho et al. demonstrated effective dendritic cell uptake without the requirement of extra transcription agents. [26].

b) Titanium dioxide

In the pharmaceutical and cosmetics sectors, titanium dioxide nanoparticles (TNPs) are frequently utilized. [27]. According to a new study, malignant cells exposed to titanium dioxide nanoparticles produce more reactive oxygen species. TiO_2 NP has cytotoxic action against human breast cancer MCF-7 cells. K. Murungan et al. synthesized TiO_2 using the sol-gel method. The cytotoxicity of TiO_2 nanoparticles was tested on MCF-7 cells by calculating the percentage of apoptotic cells. After being exposed to TiO_2, malignant cells underwent a number of morphological alterations, including cytoplasmic condensation, cell shrinkage, and the accumulation of dense masses of nuclear chromatin under the nuclear membrane. It was found that with an increase in the concentration of the TiO_2 dose, cell apoptosis increased [28].
DNA damage and apoptosis in mouse liver cells and oxidative stress-mediated apoptosis in human keratinocyte cells, human epidermal cells, and human lung cancer cell lines [29]. Titanium dioxide acts as an important nano sensitizer due to its numerous properties. The sol-gel method is used to create sphere-shaped titanium dioxide nanoparticles that have carbon doping. It has been demonstrated that Pt-doped or Au-doped TiO_2 exhibits therapeutic efficacy and dramatically slows tumor growth. [30].
Melanoma is among the most severe types of skin cancer. Photodynamic therapy (PDT) has overcome some of the side effects of chemo and radiotherapy. Because they can absorb ultraviolet light and produce free electrons and holes, which can react with oxygen (O2) and water (H2O) to form reactive superoxide radicals (O_2•) and hydroxyl radicals (HO•), TiO_2 nanomaterials with excellent biocompatibility, nontoxicity, and high stability have recently been extensively investigated as PDT agents. [31]. TiO_2 NP has a large band gap and shows a fast recombination rate of excited electron-hole pairs. To overcome these things, to enhance the melanoma PDT impact, TiO_2-NP-Au-NC-graphene (TAG) heterogeneous nanocomposites were created. Simulated sunlight, which causes less discomfort for patients, was used as the light source to effectively separate electron-hole pairs and generate enough reactive oxygen radicals. (Figure 13). Photodynamic therapy for melanoma skin cancer uses heterogeneous nanocomposites made of titanium dioxide, gold nanoparticles, and nanoclusters of graphene (TAG)

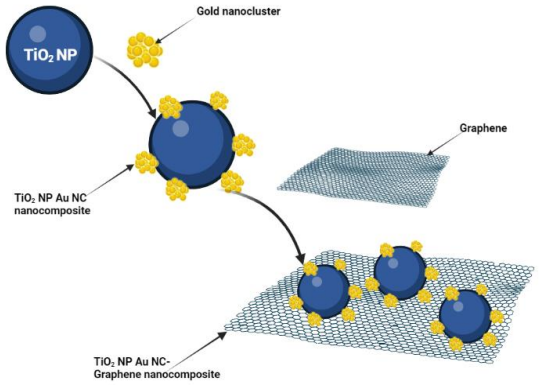

Figure 13: Formation of Titanium dioxide nanoparticle gold nanocluster graphene (TAG)

The TiO_2 NPs-treated tumor-bearing mouse group showed no signs of cardiotoxicity or transformed body weight. The efficient uptake of this TiO_2 NP by the breast cancer cells is necessary to induce ROS-mediated cytotoxicity and genotoxicity in cancerous cells, leading to cell death. The potential cytotoxic effect of TiO_2 NPs was checked by MTT assay in 4T1 mammary carcinoma cells [32]. According to Rao et al., cytotoxicity of Ag-doped TiO2 NPs against the MCF-7 human breast carcinoma cell line was mostly caused by ROS production and oxidative stress [33].

c) Nickel oxide

Metal oxide nanoparticles like nickel oxide (NiO) have cytotoxic activity. NiO nanoparticles were discovered to have anticancer activity against human lung carcinoma cells. Human lung cancer cell (A-549) and human breast cancer cell (MCF-7) MTT assays were conducted to evaluate the efficacy of NiO NPs. With a rise in NiO NP concentration, the cytotoxic activity grew [34].

23.3% of all cancer-related deaths in women are attributable to cervical cancer, making it a leading cause of death in this group. The HeLa cancer cell line was used to test different doses of the NiO NPs' cytotoxicity. To ascertain the cell-killing effect and loss of cell viability after treatment with NiO NPs, an MTT experiment was also performed in relation to the same. It was observed that the more the NiO NPs accumulated in the cancerous cell, the more ROS were liberated [35].

Figure 14 shows that NiO NPs can also be loaded with anticancer drugs such as DOX via electronic interactions, creating a NOP-DOX core, and a BSA shell is also applied via cross-linking. BSA is linked to folic acid. In this system, the NiO NPs can load a high amount of DOX, and BSA provides cancer cell targeting and prevents drug leakage during the trip to the target site [36].

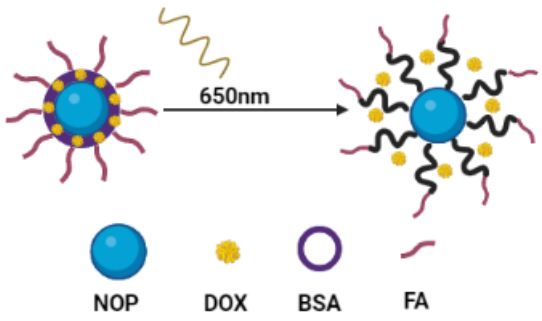

Figure 14: Drug-loaded NP for targeted delivery

Novel flower-like silicon-based NiO nanoparticles were also derived, which showed significant antitumor effectiveness and minimal damage to healthy cells. Through trials testing the survivability of the human breast cancer cell line (MCF-7), the unique silicon NiO nanoflowers' physical and electrochemical properties, as well as their therapeutic potential, were explored. [37]. The two most important feature of these NiO NP is high efficiency and selective toxicity.

Using Curcuma longa root extract, nickel oxide and copper/nickel hybrid NPs were bio-synthesized. Three main mechanisms—their disintegration into functional entities, the production of reactive oxygen species (ROS), and DNA damage—underlie the cytotoxic effects of these materials. [38].
Nickel oxide nanoparticles were also synthesized by *Alhagi sparsifolia* leaf extract. MTT assay was used to assess the cytotoxicity and anti-human breast cancer properties of these NiO NPs on normal (HUVEC) and breast cancer cell lines, including lobular carcinoma of the breast (UACC-3133), inflammatory carcinoma of the breast (UACC732), and metastatic carcinoma (MDA-MB-453). In the presence of NiO nanoparticles, a malignant breast cell line's viability decreased in a dose-dependent manner. [39].
The second-deadliest cancer overall for men and the sixth-deadliest for women is liver cancer. J. Iqbal et al. used fresh *Rhamnus triquetra* leaf broth (RT) to create NiO NPs in a straightforward, environmentally friendly, and economically viable manner. When tested on the HUH7 liver cancer cell line, RT-NiO NPs showed significant anticancer behavior. NiO NPs demonstrated strong enzyme inhibition and modest radical elimination capacities. The metabolic activities of cancerous cells were minimizing when RT-NiO NPs concentration rises. [40].

d) Zinc oxide

In many aspects of daily life, zinc oxide nanoparticles are used, and one of their important functions is seen in the treatment of human hepatocytes and HepG2 cancer cells. The morphologic analysis also revealed that the cells exposed to ZnO NPs fractured, suggesting that necrosis rather than apoptosis may be taking place in the cells. These ZnO NPs can also be eliminated from the body to detoxify after the treatment is complete. A solution for the released Zn^{2+} ions in the cells could be the addition of reagents with a high thiol group content; in cases of severe oxidative stress, a reductant like GSH might be a better option. The removal of ZnO NPs themselves, however, might be one of the direct techniques for cell detoxification. ZnO NPs can be used safely in HepG2 cells if the size and concentration of the particles are controlled, as well as a suitable elimination process.
H. hassan.et.al investigated the potential antitumor activity of ZnO NPs in hepatocellular carcinoma (HCC). The most frequent liver tumor is HCC. ZnO NPs generate a quick release of free zinc ions inside of cells, which upregulates cellular metallothionein [41]. As a result of the ZnO NPs' dissociation, which damages lysosomes and mitochondria, the cellular zinc homeostasis is disturbed. ZnO NPs possess antioxidant effects as well. Reactive oxygen species (ROS) production within cells is increased by ZnO NPs. Using the MTT assay, the cytotoxicity test was run. Cell viabilities were measured after cells were exposed to various doses of ZnO NPs and expressed as a percentage of control.
Human prostate cancer (PC3) is another condition for which ZnO NPs are utilized as an anticancer treatment. For the production of ZnO NPs, R. Priyadarshini et al. described a quick and innovative microwave-mediated approach using the extracts of the macroalga *Gracilariaedulis* (GE). y. To investigate the cytotoxic effects of ZnO NPs on the PC3 cell line, cell viability experiments were performed. According to the research, 62% of the corpses were apoptotic. This strongly suggests that the formed ZnO NPs showed effective anticancer activity against PC3 cell lines [42]. Table 2 shows the activity of numerous metal oxides against different cancer cell types.

Table 2: The action of various metal oxides against different cancer cell types

Sr. No.	Metal oxide	Treatment on in vitro model
1	Magnesium oxide (MgO)	1. MCF-7 breast cancer cell [43] 2. K562 cancer (human leukemia cell line) [44]
2	Silver doped Magnesium Oxide (AgMgO)	3. A549 lung cancer [45] 4. PC-3 Prostate cancer [46]
3	Cadmium oxide (CdO)	1. Hela cancer cells and Saos-2 2. Cells [47]
4	Chromium oxide (Cr_2O_3)	MCF-7 cancer cell [48] HepG2 and Huh-7 cell lines [49] Murine Fibrosarcoma L929 [50]
5	5-FuCrNPs	Murine Fibrosarcoma [51]
6	Cr_2O_3 NPs	3. A549 lung cancer cell line [52]

7	Cerium oxide NPs (CeO_2)	I. L3.6pl (pancreatic cell line) [53] I. HT-29 Colorectal adenocarcinoma [54] II. A375 melanoma cells [55] *I*. SCL-1 Squamous carcinoma cell line [56]
8	Copper oxide	1. Hela cells from cervical tumor 2. HepG2 cells [57] 3. A549 adenocarcinoma cells [58]

*MCF-7*michigan cancer foundation-7, *K562* myelogenous leukemia cell line, *A549* adenocarcinoma human alveolar basal epithelial cells, *PC-3* prostate cancer cell line, *saos-2* sarcoma osteogenic, *HepG2Huh-7* human hepatocellular carcinoma, *CACO-2* colorectal cancer, *L3.6pl* human pancreatic cancer cell, *HT-29* human colorectal adenocarcinoma cell line, *A375* human melanoma cancer cell line, *SCL-1* squamous carcinoma cell line.

V.Covid-19 and cancer

Cancer makes the person mentally and physically weak. The reason behind the immunosuppressed condition of the patient can be due to the cancer itself or to the treatment given for the cancer. Cancer patients are more susceptible to COVID-19 as compared with people without cancer. If a COVID-19-diagnosed person is getting treatment for his or her cancer, then he is at a high risk of developing some serious problems like acute myocardial infarction, septic shock, and acute respiratory distress syndrome. To avoid these issues during cancer treatment, one must go through regular check-ups for COVID-19 infections [59]. The development of COVID-19 vaccines utilizing nanotechnology appears to be a promising field of research, but during vaccine formation, its interaction with the cancerous cells must be kept in mind as it should be effective for immunocompromised patients. It was observed that coronavirus infection led to a 24% mortality rate in cancer patients as compared to 3% in non-cancer patients. The immunity of cancer patients gets reduced mostly due to the treatments they receive, like chemotherapy, in which their bodies must face many heavy doses of chemicals like corticosteroids. During chemotherapy, the cytotoxic medicine causes bone marrow suppression, which leads to thrombocytopenia and neutropenia, which make the patient weaker. In the case of radiation therapy for cancer treatment, the lymphocytes are damaged, which results in lymphopenia, which again elevates COVID-19 to reach the patient. COVID-19 has a negative impact on patients with blood cancers such as leukemia, myelomas, lymphomas, and aplastic anemia.

To overcome these peaks of problems during the treatment of both cancers with COVID-19, nanoparticles have emerged as an ideal tool for their treatment. Nanoparticles have distinct characteristics like very small size, high loading capacity, and surface charge. The nanoparticles can be formed such that they encapsulate the vaccine particles on or in them, resulting in the accurate delivery of the medicine directly to the affected cell without causing any noticeable damage to the healthy cell, thus reducing the risk of immunosuppression. The strategy of treatment for the patients suffering from cancer during COVID-19 is mentioned in following Figure 15.

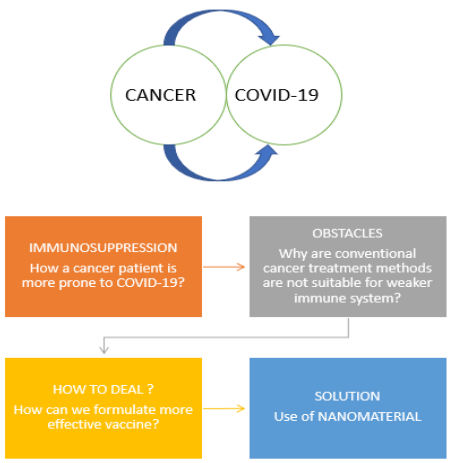

Figure 15: Strategy of treatment for cancer

VI.Conclusions

As discussed in this review, one of the diseases with the fastest rate of growth in contemporary society is cancer. In recent years, conventional cancer treatment methods have come across many objections due to their hazardous effects on the human body. As a solution to this serious problem, nanotechnology has given us a promising tool. Nanomaterials, due to their distinct characteristics, have given us a helping hand in cancer treatment.

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