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Advances in metal oxide nanoparticles for cancer therapy and their potential in combating COVID-19

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Nanoparticles hold potential as versatile tools for combating both cancer and COVID, offering targeted therapies and innovative diagnostic approaches. Recently, nano medicines have received much attention due to their role in the treatment of different types of cancer and viral infections. Nanoparticles can be useful for the treatment of cancer alone or along with other anticancer drugs. In the last couple of years, there has been a rapid and remarkable evolution in the field of nano medicine, primarily fueled by the urgent worldwide demand for innovative technologies aimed at offering preventive and curative solutions against coronavirus disease 2019 (COVID-19). Among different types of nanoparticles, metal and metal oxide nanoparticles have gained significant importance. Different types of therapies are used for the treatment of cancer, but one of the main problems is their side effects on normal healthy cells. Metal oxide nanoparticles have the ability to target only abnormal tumor cells and produce toxicity in them. Metal oxide nanoparticles work through different types of antitumor mechanisms including the generation of ROS, apoptosis, necrosis and interfering in signaling pathways of p53 and other related genes. In this review, we aim to provide an overview of the current knowledge and advancements regarding the potential use of metal oxide nanoparticles for the treatment of cancer and viral infections including COVID-19. We have discussed the strategies employed to enhance nanoparticle targeting, drug delivery and therapeutic efficacy for cancer therapy and viral infections. Furthermore, we have addressed the challenges, safety considerations and future directions for the use of metal oxide nanoparticles as potential therapeutic agents.

Keywords: Cancer; Zinc oxide nanoparticles, Copper oxide nanoparticles; Iron oxide nanoparticles; COVID-19

INTRODUCTION

Nano medicine is the convergence of nanotechnology, pharmaceuticals and biomedical sciences and has developed rapidly with the design of new nano formulations for therapeutic purposes, imaging agents and agnostic applications. Nano formulations were defined by the Food and Drug Administration (FDA) as products in combination with nanoparticles ranging from 1–100 nanometers (nm); or other formulations outside this range showing dimension-dependent properties (Ventola et al. 2017). Cancer is a major problem worldwide and it is rapidly increasing with an increased number of cases. According to WHO, cancer is the second leading cause of death around the world (S. Ullah et al., 2023; Wiesmann, Tremel, & Brieger, 2020). Cancer is a genetic disease that arises due to abnormalities of genes, mainly tumor suppressor genes and protein-coding(Anwar et al., 2023). It involves a series of events at the molecular level, which ultimately leads to malfunctioning of the cell division process, which results in uncontrolled cell division. Many risk factors are associated with cancer, including aging, obesity, consumption of alcohol, lack of physical activity, and use of junk food (Iqbal et al., 2019). Cancer can be treated through various techniques, i.e., chemotherapy, radiotherapy, hormonal, and immunotherapy (Abbasi et al., 2018; S. Ullah et al., 2022). Chemotherapy-based treatments are mostly used for the treatment of cancer, but these drugs have severe side effects. These drugs can be harmful to heart, kidney, skin tissue etc. Therefore, there is a need for a treatment strategy that should be effective for various types of cancer and not toxic to normal cells (Chow, 2010). Great advancement has been made in cancer research in recent years but it is still a major problem and requires the innovation of new techniques and therapies. For these reasons,

nanomedicine can be an effective tool for cancer therapy (Chow, 2010).

Nanoparticles can be used in the treatment of cancer through different methods either directly or indirectly. Among different types of nanoparticles, metal and metal oxide nanoparticles have gained much attention in recent years (Abbasi et al., 2019). Metal oxide nanoparticles can be synthesized through different methods. Chemical methods include toxic chemicals, so they may be harmful for humans and the environment (Iqbal et al., 2019). Nanoparticles can also be prepared by a green method, which is an ecofriendly and economical method. These nanoparticles possess many properties including antibacterial, antifungal, catalytic, cytotoxic and UV-filtering (Abbasi et al., 2019). Nanoparticles used for cancer treatment have the advantage over other cancer treatments that they can easily be directed to tumor cells by covalent bonds due to their particulate nature (Vinardell & Mitjans, 2015).

In this review, anticancer properties of important metal oxide nanoparticles i.e zinc oxide nanoparticles, copper oxide nanoparticles and iron oxide nanoparticles are considered along with their mechanism of action and both *in vivo* and in vitro effects. We have also discussed the antiviral properties of metal oxide nanoparticles and their role in COVID treatment.

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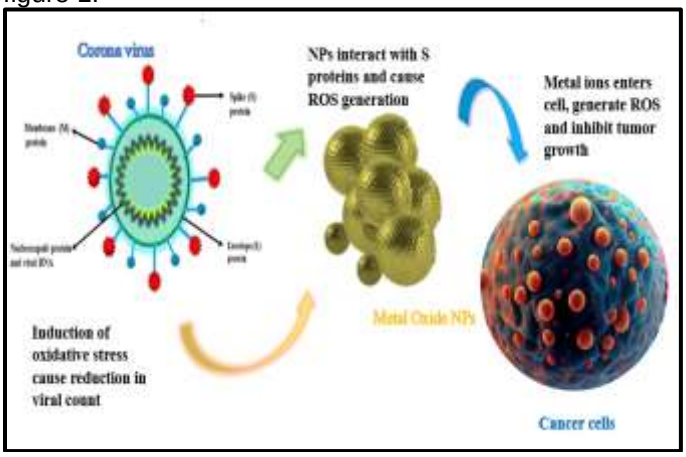

Figure: 1. Metal oxide nanoparticles show promise in dual applications, acting as potential agents for cancer therapy and combating COVID-19. Their unique properties enable targeted drug delivery and enhanced antiviral effects, offering a versatile approach to addressing both health challenges. Ongoing research explores their efficacy and safety for innovative treatments in these critical areas.

Mechanism of Action

Metal oxide nanoparticles have gained significant

attention in medicine in the past few years (Hussain et al., 2023). Metal oxide nanoparticles have shown several mechanisms of action in cancer treatment (Fig 2). Metal oxide nanoparticles such as titanium dioxide (TiO2), iron oxide (Fe2O3) and zinc oxide (ZnO) can generate ROS when exposed to light or other forms of energy. ROS can cause oxidative damage to cancer cells, leading to apoptosis or cell death (Chen, McMillan-Ward, Kong, Israels, & Gibson, 2008). Reactive oxygen species (ROS) have been identified as potential therapeutic agents for cancer treatment. ROS are molecules that contain oxygen and are highly reactive due to the presence of unpaired electrons. They are produced during normal cellular metabolism and play an important role in various cellular processes such as signaling, gene expression, and immune defense. However, excessive ROS production can cause oxidative damage to cells, leading to cell death or senescence (Vinardell & Mitjans, 2015).

In cancer cells, the balance between ROS production and scavenging is disrupted, leading to increased levels of ROS. This is due to several factors such as mutations in oncogenes and tumor suppressor genes, altered metabolism, and mitochondrial dysfunction. This high ROS level can make cancer cells more vulnerable to ROS-induced cell death or senescence (W. Lu, Ogasawara, & Huang, 2007). Metal oxide nanoparticles can be used in photodynamic therapy (PDT), a non-invasive cancer treatment that uses light to activate a photoensitizer that generates ROS leading to cell death (Fahmy, Azzazy, & Schaefer, 2021).

Metal oxide nanoparticles can also be used as carriers to deliver drugs directly to cancer cells, reducing toxicity and improving efficacy (Wahajuddin & Arora, 2012). Metal oxide nanoparticles have emerged as promising drug delivery systems for cancer therapy due to their unique physicochemical properties such as small size, high surface area, and biocompatibility (Ranghar, Sirohi, Verma, & Agarwal, 2014). Metal oxide nanoparticles can be functionalized with targeting ligands such as antibodies, peptides or aptamers that can recognize and bind to specific receptors or antigens on the surface of cancer cells. This can improve the selectivity and specificity of drug delivery, reducing toxicity to normal cells (Tietze et al., 2015). Another mechanism is that iron oxide nanoparticles can generate heat when exposed to an alternating magnetic field leading to hyperthermia, which can damage cancer cells and enhance the effects of chemotherapy and radiation therapy (Shah, Davis, Glover, Nikles, & Brazel, 2015).

Metal oxide nanoparticles can modulate the immune system by stimulating the production of cytokines and activating immune cells such as macrophages, dendritic cells, and T cells, leading to enhanced anti-tumor activity. Immunomodulation is the process of manipulating the immune system to enhance or suppress its activity. Immunomodulation has emerged as a promising approach to stimulate the immune system to recognize and attack cancer cells (Blank et al., 2011). The immune system has a complex network of cells, tissues, and molecules that work together to protect the body from foreign invaders such as viruses, bacteria, and cancer cells. However, cancer cells can evade the immune system by various means such as downregulating the expression of antigens, inducing immune tolerance, and secreting immunosuppressive factors (Rabinovich, Gabrilovich, & Sotomayor, 2007). Immune checkpoint inhibitors are monoclonal antibodies that block the interaction between immune checkpoints such as programed cell death protein 1 (PD-1) and its ligand (PD-L1), leading to the activation of T cells and the recognition of cancer cells (Pandey et al., 2022). Metal oxide nanoparticles can accumulate in tumor tissues due to the EPR (enhanced permeability and retention) effect, which is characterized by leaky vasculature and impaired lymphatic drainage of tumors. This can increase the concentration of drugs or other therapeutic agents in tumor tissue, improving their efficacy (Kalyane et al., 2019).

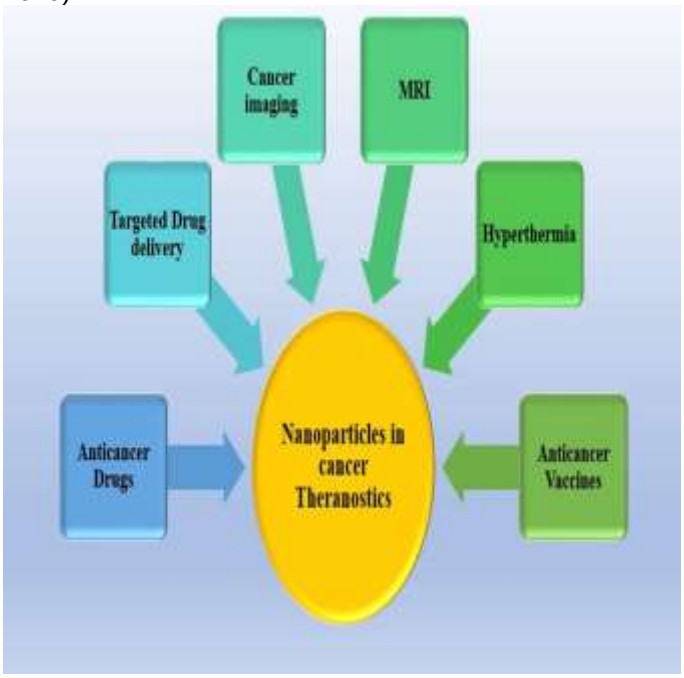

Figure: 2. Role of nanoparticles in cancer treatment and therapy. Different type of techniques and mechanism of actions involved in treatment of cancer

Copper Oxide Nanoparticles

Copper oxide is a chemical compound composed of two elements: copper and oxygen. These elements are categorized as d-block and p-block elements in the periodic table, respectively. Within crystal structure, each copper ion is surrounded and coordinated by four oxygen ions. Both copper (Cu) and copper oxide (Cu2O) nanoparticles have garnered significant interest due to the essential role copper plays in modern

technologies and its widespread availability (Guajardo-Pachecoa MJ et al. 2010). Copper is involved in many biological processes including catalytic activity and electron transfer. Copper can eliminate cancer cells due to the induction of oxidative stress (Tardito & Marchio, 2009).Copper oxide nanoparticles are toxic to a wide range of cells due to the generation of ROS and involvement in the induction of other cellular stresses (Akhtar et al., 2016).Copper oxide nanoparticles synthesized from *Azadirachta indica* leaves by a green process can be used as anticancer drugs. When these green synthesized nanoparticles were used against two cancer cell lines, Hela cells and MCF-7, they entered cancer cells and produced imbalance in NO and ROS generation. Higher levels of NO and ROS lead to DNA fragmentation. Pro-apoptotic protein expression and pro-inflammatory cytokinine levels of cancer cells were also increased, which in turn led to cell death (Dey et al., 2019). Copper oxide nanoparticles synthesized from *Ficus religiosa* leaf extract were toxic against A549 cells (lung cells) due to ROS generation. ROS generation in A549 triggered apoptosis by disturbing mitochondrial functions. The toxicity of copper nanoparticles against A549 lung cells was determined in a dose-dependent manner (Sankar, Maheswari, Karthik, Shivashangari, & Ravikumar, 2014).

An important species of bacteria, *Lactobasillus casei, has* been used for the synthesis of different types of nanoparticles, particularly metal oxide nanoparticles, due to its efficient ability to reduce metal ions (Kalaiarasi et al., 2018). (Kouhkan, Ahangar, Babaganjeh, & Allahyari-Devin, 2020) conducted a study in which they synthesized copper oxide nanoparticles from *Lactobasillus cases* and used these nanoparticles against human gastric carcinoma cells (AGS) and human colon carcinoma cell line (HT-29). After the treatment of nanoparticles on AGS and HT-29 cell line, levels of nitric oxide were abnormally high. The elevated levels of nitric oxide were responsible for oxidative stress, which in turn led to cell death.

The role of copper oxide nanoparticles was studied against human breast cancer cells (Laha et al., 2014). Copper nanoparticles induce autophagy in human breast cancer MCF7 cells. Autophagy inhibition in breast cancer cells leads to apoptosis induction by interfering in signaling pathways. Combining copper oxide nanoparticles along with autophagy inhibitor induces cell death (Laha et al., 2014). Copper oxide nanoparticles synthesized from *Ormocarpum cochinchinense* leaves were toxic against human colon cancer cell lines (HCT-116) (Gnanavel, Palanichamy, & Roopan, 2017).

Fungi *Trichoderma* produces several important metabolites and has been used for the synthesis of metallic nanoparticles having pathogenic properties (Saravanakumar & Wang, 2018). A study was conducted in which copper oxide nanoparticles were synthesized from the fungi species *Trichoderma perellum* and the toxicity of these nanoparticles was evaluated against human A549 cells. Copper nanoparticles synthesized from *Trichoderma asperellum* were highly toxic against cancer cells and induced photothermolysis by ROS generation and nuclear damage, which leads to cell death. It was observed that cas-3 proteins were higher in cells treated with copper oxide nanoparticles (Saravanakumar et al., 2019).

Zinc oxide NPs

Zinc oxide nanoparticles have small size and large surface area like other nanoparticles. Due to these properties and high reactive nature, it generates reactive oxygen species, which is crucial to destroy tumor cells (Fu, Xia, Hwang, Ray, & Yu, 2014). ROS generation is induced due to high levels of zinc ions (H. Müller et al., 2010). An illustration has been shown in Fig 3 how zinc oxide nanoparticles destroy cancer cells. Zinc oxide nanoparticles have cancer cell targeting potential so they can be used as therapeutic agent against cancer(Ng et al., 2011) Zinc oxide nanoparticles were toxic against human colon cancer cells and reduced growth of tumor cells. High levels of LDH enzymes were observed in tumor cells treated with zinc oxide nanoparticles with an average size of 32.11 nm(D. S. Vimala et al., 2019). Photoexcited zinc oxide nanoparticles induce cell death in head and neck cancer tumor cells at different doses (Hackenberg et al., 2010). Human head and neck squamous cell carcinoma (HNSCC) cell lines HLaC 78, UD-SCC 7A and pOMCs (primary oral mucosa cells) were initially incubated with zinc oxide nanoparticles and then treated with UVA-1. A significant reduction in viability was observed in these cells. Zinc oxide nanoparticles induce necrosis and apoptosis in tumor cells due to their photocatalytic properties.

Rod shaped zinc oxide nanoparticles synthesized from palm fruit extract showed significant activity against MCF-7 and HT-29 cells in a dose-dependent manner. The effect of zinc oxide nanoparticles along with anticancer drug Dox was also studied on MCF-7 and HT-29 cells. In vivo study carried out on murine model system revealed that zinc oxide nanoparticles along with anticancer drug Dox have less effect and showed less toxicity. This rod shaped zinc oxide nanoparticles can be used for an efficient drug delivery method (K. Vimala, Sundarraj, Paulpandi, Vengatesan, & Kannan, 2014). Zinc oxide nanoparticles were cytotoxic against three human squamous cell carcinoma (HNSCC) cell lines including HLaC 78 (lymph node metastasis of a laryngeal squamous cell carcinoma), Cal-27 (human tongue squamous cell carcinoma) and PJ 41 (human oral squamous cell carcinoma). In this study, these cancer cell lines were incubated with zinc oxide nanoparticles for 24 h along with ultraviolet radiation and chemotherapy drugs for cancer, i.e. paclitaxel or cisplatin. This combination approach targeted tumor cells through different mechanisms disturbing microtubule dynamics, DNA crosslinks and inducing apoptosis and cytotoxicity. A high

amount of tumor cell death was recorded due to the simultaneous use of chemotherapy and phototherapy (Hackenberg et al., 2012).

In a study conducted by (Ng et al., 2011)zinc oxide nanoparticles were applied to human bronchial epithelial cells (BEAS-2B) and human neonatal fibroblasts (BJ). They observed that zinc oxide nanoparticles interfere in the p53 pathway, which is a tumor suppressor. Zinc oxide nanoparticles cause the activation of p53, which in turn causes double-strand DNA damage. Another study was conducted by (Hassan, Mansour, Abo-Youssef, Elsadek, & Messiha, 2017) in which the effect of zinc oxide nanoparticles was evaluated against three cell lines, i.e. human hepatocellular carcinoma (HEPG2), human prostate cancer (PC3) and none- small cell lung cancer (A549) Zinc oxide nanoparticles showed remarkable activity against these three cell lines due to apoptosis and high expression of caspase 3. These nanoparticles also showed antitumor properties against diethylnitrosamine (DENA)- induced HCC in adult male rats and were helpful to testament to HCC.

Zinc oxide nanoparticles conjugated with phenylboronic acid were synthesized and then loaded with quercitin which is a bioflavonoid commonly found in plants. These nanoparticles showed good results for reducing tumors (MCF-7) in mice in an in vivo study. Quercitin as a natural anticancer drug can be a good alternative for chemically synthesized drugs. Nanoformulation of zinc oxide used for drug delivery enhanced its effect on tumor cells. Moreover, these nanoparticles were toxic only for tumor cells but showed no toxicity against the vital organs (Sadhukhan et al., 2019).

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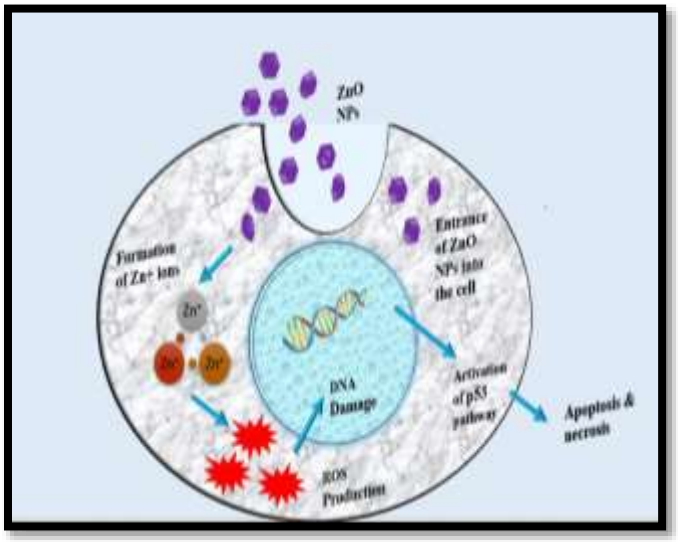

Figure: 3. General mechanism showing how ZnO nanoparticles destroy cancer cells (Ng et al., 2011).

Iron Oxide NPs

Iron oxide nanoparticles were synthesized by the green method using *Juglans regia* green husk extract with an average size of 5.77 nm. Dose dependent cytotoxic effect of these green synthesized nanoparticles were evaluated against normal and cancerous cell lines. These nanoparticles were cytotoxic against cervical cell lines with concentrations equal to or higher than 1000 µg/ml (Izadiyan et al., 2020). FDA (Food and Drug Administration) approved iron supplement fermumoxytol, which is synthesized from superparamagnetic iron oxide nanoparticles, was used for the treatment of lung, liver, and mammary cancer. This treatment increases the activity of caspase 3 when treated with adenocarcinoma cells. In vivo experiments were also conducted in mice in which pro-inflammatory M1 macrophages were increased in cancer cells after this treatment and reduced the development of liver cancer (Zanganeh et al., 2016).

Iron oxide nanoparticles coated with hyaluronic acid were synthesized using a hydrothermal method. This hyaluronic acid coating served for both purposes, one as coating layer and another as ligand for CD44 receptors. In breast cancer cells, these CD44 receptors were overexpressed. These hyaluronic acid coated iron oxide nanoparticles were highly toxic against MDA-MB-231 breast cancer cells while showed no toxicity against normal cells. These nanoparticles were specific to CD44 receptors due to the ligand-mediated endocytosis pathway and receptor-mediated endocytosis (Soleymani, Velashjerdi, Shaterabadi, & Barati, 2020). Surface functionalized and hydrophilic super paramagnetic iron oxide nanoparticles were synthesized for the treatment of liver cancer. These SPIONs were surface functionalized using different molecules such as 1,4 diaminobenzene, 3, 4 diamino benzoic acid and some other molecules.

Table 1: Previous literature showing *invitro* and *invivo* studies to evaluate the role of nanoparticles against different types of cancer.

No	Metal Oxide	Target Cells	Experiment Conditions	Type of NP Synthesis	Size of NP	Reference
1	Copper Oxide	MCF-7 & HeLa cells	In-vivo & invitro	Green (plant)	36 ± 8 nm	(Dey et al., 2019)
2	Copper Oxide	Human and lung cells	Invitro	Green (plant)	577nm	(Sankar et al., 2014)
3	Copper Oxide	Human AGS & HT-29	Invitro	Green (Bacteria)	200nm	(Kouhkan et al., 2020)
4	Copper Oxide	Human breast, Cancer cells and (MCF7)	Invitro	Chemical	300nm	(Laha et al., 2014)
5	Copper Oxide	(HeLa cells)	invitro	Green (plant)	26.6nm	(Nagajyothi, Muthuraman, Sreekanth, Kim, & Shim, 2017)
6	Copper oxide	Hela cells	invitro	Green (plant)	3.54 nm	(Elemike, Onwudiwe, & Singh, 2020)
7	Copper oxide	HCT-116	Invitro	Green (plant)	2.1 microm	(Gnanavel et al., 2017)
8	Copper oxide	A549 cells	Invitro	Green (fungi)	110 nm	(Saravanakumar et al., 2019)
9	Copper oxide	HEPG-2, MCF-7, CaCO-2 and Human cell lines	Invitro	Chemical	50± nm	(Elsayed et al., 2021)
10	Copper oxide	Liver cell, HEPG2	Invitro	Green (plant)	15-16 nm	(Fakhar-e-Alam et al., 2021)
11	Zinc oxide	HEPG2, PC3 an & A549	Invitro	Chemical	35 nm	(Hassan et al. 2017)
12	Zinc oxide	HT29 (Colon Cancer cell line)	Invitro	Chemical	32.11 nm	(D. S. Vimala et al., 2019)
13	Zinc oxide	MCF-7 & HT-29	Invitro	Green (plant)	55 nm	(K. Vimala et al., 2014)
14	Zinc oxide	Murine model System	Invivo	Green (plant)	55 nm	(K. Vimala et al., 2014)
15	Zinc oxide	HLaC 78, Cal-27 & PJ 41	Invitro	Chemical	66±25 nm	(Hackenberg et al., 2012)
16	Zinc oxide	Skin fibroblasts	Invitro	Chemical	22.5 ± 4.9 nm	(Ng et al., 2011)
17	Zinc oxide	MCF-7	Invivo	Chemical	40 nm	(Sadhukhan et al., 2019)
18	Zinc oxide	Hepatocellular Carcinoma, Carcinoma (adult rats)	Invivo	Chemical	35nm	(Hassan et al., 2017)
19	Zinc oxide	A549, HeLa, T24, HNSCCUM-02T	Invitro	Chemical	15-18 nm	(Wiesmann et al., 2019)
20	Zinc oxide	MCF-7 cells	Invitro	Chemical	80 nm	(Khorsandi & Farasat, 2020)
21	Iron oxide	cervical cell Lines	invitro	Green (plant)	5.77 nm	(Izadiyan et al., 2020)
22	Iron oxide	MCF-7, MDA-MB-231	Invivo	Chemical	12±3 nm	(Kossatz et al., 2015)

23	Iron oxide	Human melanoma cells	Invitro	Chemical	9 nm	(Petri-Fink, Chastellain, Juillerat-Jeanneret, Ferrari, & Hofmann, 2005)
24	Iron oxide	Lung & colon Cancer	Invitro	Chemical	10 ±2 nm	(Piktel et al., 2020)
25	Iron oxide	Human breast Cancer Cells	invitro	Chemical	8.5 nm & 23.4 nm	(Soleymani et al., 2020)
26	Iron oxide	4T1 & C26	Invitro	Green (plant)	50 nm	(Farshchi et al., 2018)
27	Iron oxide	A549 & HeLa cell lines	Invito	Chemical	10-20 nm	(Reinhard, Khanum, & Daniel, 2022)
28	Iron oxide	HeLa & MCF-7	Invitro	Chemical	70-100 nm	(Alangari et al., 2022)
29	Iron oxide	MCF-7	Invitro	Laser Pyrolysis	8-10 nm	(Marcu et al., 2013)
30	Iron oxide	CD47 positive Pancreatic cancer Cells	Invitro	Chemical	12±3 nm	(Trabulo, Aires, Aicher, Heeschen, & Cortajarena, 2017)

SPIONs were used for treatment of liver cancer by magnetic fluid hyperthermia (MFH) based thermotherapy. SPIONs coated with 3,4 diaminobenzoic acid were very toxic against liver tumor cells (HepG2) (Kandasamy, Sudame, Luthra, Saini, & Maity, 2018).

The medicinally important plant *Rosmarinus officials***,** which contains various phytochemicals, was used to synthesize iron oxide nanoparticles. Rosemary synthesized iron oxide nanoparticles were cytotoxic against 4T1 and C26 cancer cell lines (Farshchi, Azizi, Jaafari, Nemati, & Fotovat, 2018). Iron oxide nanoparticles coated on macrophage membrane showed biocompatibility with immune cells. They were effective for breast cancer cells by photothermal therapy in *invivo* experiments on mice (Zanganeh et al., 2016). Recently, research has been conducted for the development of vaccines from nanoparticles. Many FDA (Food and Drug Administration) approved vaccines are available for clinical use, which are synthesized from iron oxide nanoparticles. A vaccine was developed from super paramagnetic iron oxide nanoparticles and their effect was studied both in vitro and in vivo. The effect of the SPION-synthesized vaccine on cytokine expression was also studied. They found that these vaccines played an important role in immune cell activation and production of cytokines (Zhao, Zhao, Cheng, Guo, & Yuan, 2018). The role of metal oxide nanoparticles against different types of cancer has also been shown in Table 1.

Cancer and COVID-19

While cancer and COVID-19 are distinct medical conditions, there is a link between them in terms of their impact on patients and healthcare systems. Cancer patients, particularly those undergoing treatments such as chemotherapy, radiation therapy, or immunotherapy, may have weakened immune systems, making them more susceptible to infections, including COVID-19 (Mohseni Afshar et al., 2022). The presence of cancer can also contribute to a higher risk of severe illness and complications if a patient also get COVID-19 (Curigliano et al., 2020). The COVID-19 pandemic has necessitated modifications in cancer treatment approaches. In some cases, treatment plans have been adjusted to minimize hospital visits, reduce the risk of exposure to the virus, and optimize patient safety (Schrag, Hershman, & Basch, 2020). This may involve delaying non-essential treatments, using telemedicine for follow-up visits, and prioritizing the most critical cases (Yuen et al., 2020).

In addition, COVID-19 has disrupted cancer diagnosis and screening efforts. The focus on controlling the spread of the virus and diverting healthcare resources has led to delays in cancer screenings, reduced access to diagnostic tests, and a backlog of cases (Ranganathan et al., 2021). Consequently, cancer diagnoses may be delayed, potentially affecting treatment outcomes and prognosis (Tsibulak et al., 2020). Both cancer and COVID-19 can have significant psychological and social impacts on patients(S Ullah, Ullah, RahmanW, Ahmad, & Ullah, 2020). Dealing with cancer diagnosis and treatment is already a challenging experience, and the added fear and uncertainty brought about by the pandemic can exacerbate emotional distress (Hill, Frost, & Martin, 2021).

Nanotechnology and COVID-19

The field of nanotechnology has shown immense promise in revolutionizing various aspects of healthcare including diagnosis and treatment of diseases (Prasad et al., 2018). Metal oxide nanoparticles have gained significant attention for their potential applications in both cancer treatment and management of viral infections, such as COVID-19 (Mbatha, Akinyelu, Chukwuma, Mokoena, & Kudanga, 2023). These nanoparticles possess unique physicochemical properties that can be harnessed to target and combat cancer cells and viruses, offering new avenues for improved therapeutic strategies

(Liu, Jiang, Nam, Moon, & Kim, 2018). In the COVID-19 pandemic, the need for effective antiviral strategies has become paramount (Banerjee & Rao, 2020). While vaccines have played a crucial role in disease prevention, the development of targeted therapies for treating COVID-19 is still underway (Marian, 2021). Metal oxide nanoparticles offer potential applications in combating viral infections, including the SARS-CoV-2 virus responsible for COVID-19 (Abo-Zeid, Ismail, McLean, & Hamdy, 2020). Metal oxide nanoparticles can be used to inhibit viral attachment and entry into host cells, disrupt viral replication, or modulate the host immune response to counteract viral infection (Alavi, Kamarasu, McClements, & Moore, 2022).

Advances in Metal Oxide Nanoparticles for Cancer Therapy and Their Potential in Combating COVID-19

Metal oxide nanoparticles have unique properties that make them attractive for various applications including catalysis, electronics, energy and biomedicine (Joudeh & Linke, 2022). Metal oxide nanoparticles have a diameter of less than 100 nanometers, which allows them to interact with biological systems such as cells, proteins, and DNA at the nanoscale level. Metal oxide nanoparticles have a high surface area-to-volume ratio, which enhances their reactivity and adsorption capacity. This can be exploited for applications such as catalysis, gas sensing, and drug delivery (S. Sarkar, Guibal, Quignard, & SenGupta, 2012). Metal oxide nanoparticles can be synthesized with different compositions and crystal structures, such as iron oxide, titanium oxide, zinc oxide and cerium oxide (Murthy, Effiong, & Fei, 2020). Metal oxide nanoparticles are stable under a wide range of conditions, including high temperatures, acidic or basic environments, and oxidative or reducing conditions. This makes them suitable for use in harsh environments or for long-term storage (A. H. Lu, Salabas, & Schüth, 2007). Metal oxide nanoparticles are biocompatible with biological systems because they do not cause any toxicity or inflammation in living organisms (Augustine & Hasan, 2020). This biocompatibility makes them attractive for biomedical applications such as drug delivery, imaging and sensing (Arias et al., 2018). Optical properties of metal oxide nanoparticles fluorescence or plasmonic resonance can be exploited for applications such as biosensing and imaging. Overall, the unique properties of metal oxide nanoparticles make them versatile platform for wide range of applications including catalysis, electronics, energy and biomedicine (Tucek, Kemp, Kim, & Zboril, 2014).

Metal oxide nanoparticles have shown great potential for disease treatment, particularly in the field of biomedicine. Metal oxide nanoparticles can be functionalized with drugs, imaging agents or photodynamic therapy (PDT) agents, which can specifically target cancer cells and induce cell death (Wang et al., 2014). Additionally, metal oxide nanoparticles can be used for gene delivery or immunomodulation, enhancing the efficacy of cancer treatment (Xia et al., 2020). Metal oxide nanoparticles can be functionalized with antimicrobial agents, such as antibiotics, antiviral agents, or antifungal agents, which can target pathogens and inhibit their growth (Alavi & Rai, 2021). Moreover, metal oxide nanoparticles can be used for vaccine development, improving the immune response and reducing the risk of infection (Poon & Patel, 2020). Metal oxide nanoparticles can also be used for diagnostic imaging or sensing, allowing non-invasive detection and monitoring of neurological diseases (Na et al., 2007). They can also be functionalized with drugs or imaging agents which can specifically target the heart or blood vessels. Metal oxide nanoparticles can be used for drug delivery or sensing, improving the efficacy and safety of cardiovascular disease treatment. Overall, metal oxide nanoparticles hold great promise for disease treatment, but their translation into clinical practice requires careful consideration of their safety, efficacy, and regulatory approval (Godin et al., 2010)**.**

Harnessing Metal Oxide Nanoparticles for Cancer Treatment

Metal oxide nanoparticles have emerged as promising tools for cancer treatment, offering several advantages over conventional cancer therapies. Metal oxide nanoparticles can be designed to target cancer cells specifically, which can enhance the efficacy of cancer treatment while minimizing side effects on normal tissues (Zhi, Yang, Yang, Fu, & Zhang, 2020). Metal oxide nanoparticles can also release therapeutic agents such as drugs or photoensitizers in a controlled and sustained manner which can optimize therapeutic efficacy and reduce toxicity. Metal oxide nanoparticles can enhance the efficacy of cancer treatment by increasing the accumulation of therapeutic agents in tumor tissues, reducing drug resistance and energizing with other cancer therapies (Guo, Liu, Tang, & Shubhra, 2022). Metal oxide nanoparticles can be used as imaging agents allowing non-invasive detection and monitoring of tumors. Additionally, metal oxide nanoparticles can be functionalized with targeting ligands such as antibodies or peptides, allowing specific accumulation in tumor tissues (Zhao et al., 2018). They can activate the immune system to recognize and attack cancer cells, offering a promising avenue for cancer immunotherapy (Finn, 2012). Metal oxide nanoparticles can reduce the toxicity of cancer therapies by delivering therapeutic agents specifically to tumor tissues, which can reduce damage to normal tissues. Overall, metal oxide nanoparticles offer a versatile platform for cancer treatment, offering several advantages over conventional cancer therapies. However, their clinical translation requires careful consideration of their safety, efficacy, and regulatory approval (Bañobre-López, Teijeiro, & Rivas, 2013).

Tackling COVID-19 Challenges

Metal oxide nanoparticles play a significant role in enhancing the effectiveness of antiviral drugs. These nanoparticles, such as zinc oxide, titanium dioxide, and copper oxide, possess unique physicochemical properties that make them ideal for antiviral applications (Bhatti & DeLong, 2023). When combined with antiviral drugs, metal oxide nanoparticles can act as carriers, delivering the drugs to specific target sites and improving their bioavailability (Lembo & Cavalli, 2010). Additionally, metal oxide nanoparticles exhibited an intrinsic antiviral activity by disrupting viral replication and inhibiting viral attachment to host cells (Alavi et al., 2022). Their small size and large surface area also enable efficient interaction with viral particles, leading to enhanced antiviral effects. metal oxide nanoparticles can be used as carriers for antiviral drugs and therapeutic agents against COVID-19 (Ibrahim Fouad, 2021). Metal oxide nanoparticles enhance drug efficacy while minimizing potential side effects (Laurent, Saei, Behzadi, Panahifar, & Mahmoudi, 2014).

Antiviral Properties of Metal Oxide Nanoparticles

The antiviral properties of metal oxide nanoparticles stem from their ability to interact with viral components such as viral envelope or capsid and disrupt their structural integrity (Adhikari et al., 2022). Metal oxide nanoparticles have shown the antiviral activity against various viruses, including influenza, herpes simplex virus, and human immunodeficiency virus (HIV) (Yadavalli & Shukla, 2017). Preliminary studies have indicated the potential of metal oxide nanoparticles in inhibiting the infectivity of coronaviruses, including SARS-CoV-2 (DeDiego et al., 2022) (Sadique et al., 2021). By using the unique properties of metal oxide nanoparticles, novel antiviral strategies can be developed to combat viral infections effectively (Carvalho & Conte-Junior, 2021). These nanoparticles can exhibit antiviral effects through multiple mechanisms including direct virucidal activity, the inhibition of viral attachment and disruption of viral replication (Lin et al., 2021). Studies have also shown that metal oxide nanoparticles can inhibit viral infectivity in SARS-CoV-2 (P. K. Sarkar & Das Mukhopadhyay, 2021). Metal oxide nanoparticles can exhibit antiviral effects through multiple mechanisms including direct virucidal activity, inhibition of viral attachment and disruption of viral replication (Lin et al., 2021; Rakowska et al., 2021). Metal oxide nanoparticles have potential for surface coating applications. Metal and metal oxide nanoparticles have demonstrated strong antimicrobial properties and can inactivate viruses and bacteria on contact. By incorporating these coatings into frequently touched surfaces in public spaces, the persistence and transmission of the SARS-CoV-2 virus is potentially reduced (80).

Limitations

Nanoparticles hold great potential in cancer therapy due to their unique properties such as small size, high surface area and ability to encapsulate or conjugate with drugs, genes or imaging agents. However, there are also some challenges that need to be addressed for the successful translation of nanoparticles into clinical practice (Thakor & Gambhir, 2013). Many studies proved that nanoparticles can effectively target tumor cells without harming healthy cells, but still there is some evidence that they can also be cytotoxic to non-cancerous cells. One of the main reasons for their cytotoxicity is their surface area. Due to their high surface to mass ratio they can show adverse effects during delivery. Nanoparticles possess various donors and electron acceptors on their surfaces, which can react with molecular oxygen and therefore ultimately result in the formation of hydrogen peroxides and superoxides. These reactive oxygen species are harmful for healthy cells (Aftab et al., 2018), (Nel, Xia, Mädler, & Li, 2006). The toxicity of nanoparticles also depends upon the size and shape of nanoparticles and their agglomeration (Awasthi et al., 2016). Due to their small size, they can also be deposited in various human organs, which can be lethal to humans(Jiang, Oberdörster, & Biswas, 2009).

Targeted delivery of nanoparticles to cancer cells remains a major challenge due to the heterogeneity and complexity of tumors (J. Li & Burgess, 2020). Nanoparticle-based therapies need to be designed to overcome the physical and biological barriers of the tumor microenvironment, such as the dense extracellular matrix, abnormal blood vessels and immunosuppressive factors (Liang et al., 2020). Combination therapy using nanoparticles with different modalities such as chemotherapy, immunotherapy and photodynamic therapy can enhance the efficacy and reduce the toxicity of cancer treatments. However, the optimal combination and sequence of therapies need to be determined based on the specific characteristics of the tumor and the patient (X. Li, Lovell, Yoon, & Chen, 2020). The development of personalized medicine using nanoparticles requires identification of biomarkers that can predict the response of individual patients to specific treatments. This requires the integration of clinical, genomic and imaging data to develop predictive models for treatment selection and monitoring (Mathema, Sen, Lamichhane, Orešič, & Khoomrung, 2023). The biodistribution and toxicity of nanoparticles need to be thoroughly investigated to understand their potential adverse effects on normal tissues and organs (Arvizo, Bhattacharya, & Mukherjee, 2010). This requires the development of sensitive and accurate methods for nanoparticle detection and characterization. Extensive research is needed before their application to humans. All physical and chemical properties should be analyzed, and suitable animal models should be used prior to testing on humans (Awasthi et al., 2016).

CONCLUSIONS

We concluded that metal oxide nanoparticles are very useful for the treatment of tumor cells. They are highly toxic to cancer cells alone or in combination with different drugs. Moreover, they are not harmful for normal healthy cells. Many studies have been carried out on the treatment of cancer by nanoparticles under in vitro conditions; however, in vivo studies still require extensive research. Apart from a lot of advantages, some studies also showed their harmful effect on noncancerous cells, which might be due to the generation of reactive oxygen species. Avoiding harmful chemicals in their synthesis process and using ecofriendly green methods could be effective in reducing their harmful effects. Furthermore, while preliminary studies are promising, further research is needed to fully understand the potential of metal oxide nanoparticles as antiviral agents against coronaviruses.

Supplementary materials

Not applicable

Author contributions

SA designed, proofread and reviewed the whole manuscript. NA, SH, SR, SM & MI wrote different parts of manuscript. WA & GA made the tables and figures. LK and MR corrected grammatical mistakes & reviewed the manuscript.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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