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Advancing Cancer Treatment to Overcome Conventional Therapy Limitations Through Zinc-Based Nanoparticles: A Review

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ABSTRACT:
Cancer is one of the issues that afflict many individuals. Physicians treat cancer through chemotherapy, radiotherapy and surgery. Such therapies do not necessarily work. They may also damage the body not only the cancer cells. Cancer stands one among the major causes of death and illnesses worldwide is still cancer. Scientists have been considering nanotechnology as a method of improving cancer treatment in the past few years. Of interest to them are, especially, zinc-made particles. These particles are good since they can combat cancer and they are cheap. They are non-toxic to people and animals. In such a way, zinc particles may be used to treat cancer. They are able to produce types of oxygen which kill cancer cells. They are also capable of causing cancer cells to die which is known as apoptosis. Zinc particles have the ability of damaging DNA of cancer cells to prevent their growth and release ions that interfere with the balance of cancer cells. The good thing with zinc particles is that, they are able to kill cancer cells independently. Cancer drugs can also be administered using them straight to the cancer cells. This implies that the drug is able to hit on the cancer cells precisely thus minimizing the damage to normal tissues. Zinc particles have been utilised in combination with other treatments such as chemotherapy and radiotherapy. They have been examining the effectiveness of this combination with various forms of cancers. This paper is, concerning the properties of zinc particles make them how they fight cancer and how harmless they are. It also discusses the way zinc particles can be utilized in future to cure cancer. Zinc particles can be a better treatment of cancer.

Keywords: Zinc nanoparticles (Zn-NPs), nanoparticles based drug delivery system (DDs), targeted delivery, green synthesis, reduced toxicity to healthy tissues

I. INTRODUCTION:

Cancer affects people of all age and gender, it has become one among the leading causes of fatality worldwide. Genetic, environmental or cellular imbalances are some of the causes [1]. Cancer is characterised by the unmanageable proliferation of cells that metastasis across the body and violates the normal body signals. Therefore, cancer is fundamentally a genomic disease, caused by the progressive build up of genetic mutations and epigenetic alterations which damages the normal cellular functions [2]. These irregularities impair the checkpoints responsible for cell division, DNA repair, and apoptosis processes enabling the cancerous cells to divide freely. Cancer has key characteristics like avoiding proliferation inhibitors, resistance to programmed cell death, sustaining proliferative signalling, allowing cells to divide repeatedly without limits, helping in the formation of new blood vessels and leading to invasion and spread to other parts of the body [3]. Moreover, the current global trends like an aging population along with rising risk factors such as smoking, obesity, and exposure to environmental pollutants convey that both the number of cases and death rates would continuously increase [4]. Cancer remains one of the major global health challenges in the 21st century. As stated by the world health organization, cancer is now a leading cause of death worldwide, causing nearly 10 million deaths each year and with around 20 million new cases annually [5].

The conventional cancer treatment methods including surgery, radiotherapy and chemotherapy offer certain drawbacks, The main failure of the systemic chemotherapy is the inability to differentiate between cancerous and normal cells [6] . This method causes the killing of healthy tissues, and this prevents the administration of the maximum tolerated dose safely to a patient [7]. Due to the free circulation of conventional drugs in the blood, they have off-target effects such as myelosuppression,

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cardiotoxicity, and neurotoxicity. These undesirable effects will result in missed treatment, dose adjustment, or discontinuation of the treatment, which affects the patient survival [8]. Additionally, multidrug resistance (MDR) may develop due to increased activity of efflux pumps that are actively used to push drugs out of the cell [9]. Moreover, the genetic instability of cancerous cells is high, and thus they develop mutations that avoid the particular metabolic pathways that are targeted by chemotherapy agents [10]. These limitations lead to the development of more precise and less toxic therapeutic techniques, nanomedicine is one such emerging technique.

The term nanomedicine refers to nanotechnology (usually between 1-100 nm) as a way to enhance disease diagnosis, treatment and monitoring [11]. The Enhanced Permeability and Retention (EPR) effect phenomenon where the build up of the agent is preferential in tumours because of the porous character of tumour vascularity and the dysfunctional lymphatic drainage and NPs depend on this [12]. Also the encapsulation of cytotoxic drugs in nanoparticles prevents he premature drug release into the bloodstream. The toxic effects on the organs such as liver and bone marrow are minimized [13].

Among the various other available nanoparticles, Zinc (Zn) nanoparticles have emerged as best means of therapeutic agent for cancer therapy. They are more biocompatible and biodegradable than heavy metals, such as silver, they dissolve into Zn2+ ions which are safely taken up by the cellular metabolism [14]. ZnO-NPs show selective cytotoxicity with cancer cells, which disperse into Zn2+ ions that are harmlessly absorbed by the cellular metabolism [14]. ZnO-NPs, unlike gold or platinum, are inexpensive and are abundant. Moreover, ZnO-NPs can be readily produced by the application of plant extracts through the green chemistry technique that minimizes the manufacturing expenses and reduces the environmental footprint [15]. This review aims to detail the physiochemical characteristics, preparation methods, the anticancer activity and their potential as drug delivery system, the toxicity and biocompatibility and the applications of Zn-NPs in cancer therapy

II. PHYSIOCHEMICAL CHARACTERISTICS OF Zn NANOPARTICLES:

Zn NPs are widely studied due to their unique physiochemical properties which are influenced by parameters such as particle size, surface area and their crystal structure which are responsible for their functional performance [71].

2.1. Structure of ZnO Nanoparticles:

Although both elemental zinc (Zn) and zinc oxide (ZnO) nanoparticles have been studied, ZnO nanoparticles (ZnO-NPs) is the most common type in the study of cancer therapy due to its semiconducting properties [16]. It crystallizes into a hexagonal wurtzite structure with covalent bonding, which is responsible for the piezoelectric properties, chemical stability and optical behaviour [17].

2.2. Size and Morphology:

ZnO Nanoparticles can be synthesized in different geometrical shapes and sizes, allowing them to be tailored specifically to the biological applications. Among the various shapes spherical nanoparticles generally show higher anticancer efficiency due to their ability to be internalised [18]. Because of their relatively high surface area to surface-to-volume ratio, the nanoparticle possess increased possibility of endocytosis. They also produce reactive oxygen species that induce oxidative stress [19].

2.3. Surface Charge and Modification:

At the isoelectric point of 7.5
(physiological pH), the zinc oxide nanoparticles possess a positive surface charge. This enables an electrostatic attraction between the negatively charged phospholipids present on the cancer cell membrane[20]. The nanoparticles undergo modifications in use of stabilizing agents and ligands like plant based extracts and polymers, folic acids and antibodies to in order to increase the target specificity of the nanoparticles [21][22].

2.4. Stability in Biological Systems

The important factor that influences the successful delivery of anticancer drugs is the stability of ZnO-NP2 observed in the bloodstream and in intracellular environments Unmodified ZnO-NPs when in aqueous media and aggregate due to high surface energy. However, ZnO-NPs can be highly dispersed by the use of biosurfactants [23]. At physiological pH (7.4) ZnO- NPs are relatively stable, but they dissolve rapidly in the acidic environment of tumour tissues. This disintegration is one of the therapeutic mechanisms because the abrupt release of the zinc ions results in the mitochondrial failure [22].

III. SYNTHESIS OF ZnO NANOPARTICLES:

The particle size along with surface characteristics of nanoparticles heavily influences the cellular uptake and toxicity, thereby making synthesis approach of ZnO-NPs play an important role in determining the biological functionality of the nanoparticles [24]. Scientists apply three major types of synthesis chemical, physical, and green/biological with their advantages being different in regards to their scalability, purity, and environmental impact [25].

3.1. Chemical Methods:

Chemical method stands out to be the commonly used approach in synthesis of ZnO-NPs. This method is highly favoured due to high yield and increased control over the morphological properties of the particles [26].

3.1.1 Sol-Gel Method

Precursors such as zinc acetate that are subjected to hydrolysis followed by condensation and are used in sol-gel method. As a result they form colloidal solution called "sol" developing further into gel that is later cured. One of the major advantage involved in employment of this method is the immense control over the particle size, homogeneity and purity.It is extremely useful for creating nanoparticles with accurate nanoparticles with sizes ranging between 15-30 nm and improved functional properties for various application [27][28].

3.1.2 Hydrothermal Synthesis

This process is performed in a closed system where the crystalline ZnO nanostructures are obtained directly from aqueous solutions. This is performed under high pressure and temperature and does not require high temperature calcination. Defect free crystals with improved electronic properties can be synthesized by this method due to its precise control over the morphology and crystallinity, [29][30]

3.1.3 Co-precipitation

It is a fast and inexpensive method, in which a base such as KOH or NaOH is added to a solution of zinc salt, this results in the formation of zinc hydroxide precipitate which is subsequently subjected to heating to produce ZnO. Co-precipitation is a suitable method for large scale production if ZnO nanoparticles [31].

3.2. Physical Methods

Physical techniques mostly rely on the top-down strategies wherein a bulk material is milled or heat treated down to the nanoscale using external physical forces [32].

3.2.1 High-Energy Ball Milling:

This is a mechanochemical process that requires no solvent and relies on mechanical force to produce uniform nanoparticles, the size of the nanoparticle can be managed by controlling the milling time. In this method coarse Zn or ZnO are continuously hit by hard balls causing the refinement of particles into nanoscale structures. [33].

3.2.2 Laser Ablation:

ZnO target is immersed in a liquid or gas medium and is focused by a high powered laser beam. This results in the vaporisation of the material leading to rapid condensation of nanoparticles. The technique is very desirable in the generation of highly pure ligand-free nanoparticles less than 10 nm, which are suitable in sensitive biomedical applications [34].

3.2.3 Gas Condensation:

This method involves the vaporization of metallic zinc in an inert environment which is then cooled rapidly to create nanoparticles. It offers excellent control of particles stoichiometry, size and surface purity. Although it can be used to provide excellent stoichiometry control, it needs complex and energy-demanding equipment [35].

3.3. Green/Biological Synthesis

This method is an environmental friendly and more sustainable option compared to traditional methods of nanoparticle synthesis. Plants are employed as biological factories to produce Zn nanoparticles which minimizes the use of toxic reagents [36]

3.3.1 Plant Mediated Synthesis:

The extracts of medicinal plants (e.g., Centella asiatica or Myristica fragrans) reduce Zn2+ ions to ZnO nanoparticles. This is due to their function as natural reducing as well as capping reagents, that enables the reduction of metal ions. The nanoparticles are stabilized by phytochemicals that include flavonoids, polyphenols, and terpenoids, which typically provide the final product with other antioxidant and anticancer effects [37]. This technique often produces NPs with enhanced biological activities such as antimicrobial and antioxidant properties [38].

3.3.2 Microbial Synthesis:
Microbial synthesis involves organisms like bacteria, fungi, and algae which help in reducing metal salts intracellularly or extracellularly via certain enzymes secreted by them. One ability of fungi especially is the ability to synthesize in large quantities extracellular enzymes which enable the scalable synthesis of nanostructures [39][40].

IV. MECHANISM OF ANTICANCER ACTIVITY

Zinc oxide nanoparticles have gained attention in cancer due to their unique physiochemical and selective cytotoxicity towards tumour cells. These mechanisms enable ZnO NPs to effectively target cancer cells while reducing the toxic side effects [46]

4.1. Reactive Oxygen Species (ROS):

Oxidative stress occurs because of the increased production of ROS within cancer cells. This is possible due to the semiconductor nature of the ZnO nanoparticle surface. When the ZnO-NPs are internalised the semiconducting properties lead to electron- hole pair formation which reacts with the water and oxygen to create oxidative stress within the cell that disrupts cellular balances and destroys the biomolecules [41].

4.2. Induced Apoptosis:

When the ROS levels are rise, they trigger the intrinsic apoptotic signalling pathway. When activated this results a decrease in mitochondrial membrane potential along with the release of cytochrome c into the cytoplasm which further initiates a cascade of reaction. Ultimately, this leads to programmed death of the tumour cell [42].

4.3. DNA damage and cell cycle arrest

ZnO-NPs can cause the breakage of both single and double stranded DNA due to their genotoxic property. When such damage is caused, it becomes irreparable due to the inhibition of the repair enzymes by the action if Zn ions. Further the DNA adduct formation and DNA damage subsequently lead activation of checkpoints which in turn leads to cell cycle arrest and prevention the rapid proliferation of the tumour mass [43][44].

4.4. Zn2+ ion release and cellular

The tumours create a microenvironment that supports its proliferation and prevents the immune mechanism of the body. This microenvironment is usually acidic, and when the ZnO-NPs enter, they dissolve and release Zn2+ ions which is absorbed by the cancer cells. This uptake disrupts the cellular mechanism and the metabolic enzymes causing protein denaturation leading to autophagic death [45]

4.5. Selective Cytotoxicity to Cancer Cells

ZnO-NPs offers better advantage than traditional drugs due to the selective cytotoxic activity towards the tumour cells. The cancer cells are usually have higher metabolic activity and more acidic nature, this increases the dissolution rate of ZnO-NP than healthy cells. Moreover, antioxidants in malignant cells are typically lower, which exposes them to the ROS-burst of zinc-based materials [46][47].

V. Zn NANOPARTICLE AS DRUG DELIVERY SYSTEMS:

As a novel application, ZnO-NPs also have a great potential in the form of highly efficient Drug Delivery System (DDS), as it is no longer a simple toxic agent but a specialized carrier [48].

5.1. Drug Loading and Release:

ZnO nanoparticles posses a relatively high surface area compared to their volume, permits high loading of hydrophobic drugs such as Paclitaxel or Doxorubicin. A large surface area in relation to volume ensures that drugs adsorb via electrostatics or covalent bonding [49]. The release of the drug is pH-dependent, and it happens quickly in the acidic microenvironment of the tumour and is maintained in the neutral bloodstream [50].

5.2. Targeted Delivery:

To increase the accuracy, the surface of ZnO-NPs is functionalized by ligands, which bind to those receptors (FRa or CD44) overexpressed on cancer membranes [51]. This active targeting improves the drug accumulation in tumour tissues and reduces the non-specific binding to the healthy tissues [23].

5.3. Reduced Side Effects:

ZnO-NPs will reduce the cytotoxic exposure of healthy tissues to systemic cytotoxic drugs, which will significantly reduce numerous adverse side effects, which are associated with cytotoxic drugs and their delivery methods [52].

VI. APPLICATION OF ZnO-NPs IN CANCER THERAPEUTICS:

Zn NPs are used as drug delivery systems for the targeted delivery of the anticancer agents.

Since these nanoparticles can be easily functionalized with biomolecules to enhance the tumour targeting and controlled drug release making it suitable for cancer treatment [72]

6.1. Breast Cancer

ZnO nanoparticles have demonstrated strong cytotoxic effects against both oestrogen receptor-positive (MCF-7) and triple-negative breast cancer (MDA-MB-231) cell lines by inducing oxidative stress [69] [70]. Their main function is to cause p53-mediated apoptosis and inactivating anti-apoptotic factors such as Bcl-2 that is frequently overexpressing in aggressive breast tumours. The recent applications with ZnO/Graphene Oxide (GO) nanocomposites, these platforms have shown the ability to improve the toxicity of the chemotherapeutic drug, Paclitaxel, by more than 10-folds over that of the free drug, mainly by enhancing the production of the ROS species [53][54].

6.2. Lung cancer

In lung cancer, ZnO-NPs suppress the tumour growth by targeting the MAPK/ERK and P13K pathways which play a role in the cancer cell proliferation and survival. Additionally, they cause G2/M phase arrest in the cell cycle, which slows down tumour progression. Zn-NPs cause ROS generation which subsequently leads to mitochondrial dysfunction resulting in cell apoptosis [55]. When ZnO-NPs are conjugated with ligands or polymers they show better accumulation in mung tumours via the ERP effect. Furthermore, these nanoparticles have shown the ability to reverse epithelia;-mesenchymal transition (EMT) which helps reduce the metastasis in lung cancer [56][57].

6.3. Liver Cancer

In hepatocellular cancer, ZnO-NPs act as anti-proliferative agents by disrupting glycolysis and mitochondrial respiration of the liver cells. They induce DNA damage and ROS mediated apoptosis due to the elevated Zn2+ levels in cells. Furthermore, when ZnO-NPs are doped with Cobalt and Manganese they have shown enhanced ROS effect and improved selectivity towards cancer cells [58]

6.4. Combination Therapy

Zn-NPs improve the efficacy of chemotherapy by enhancing the drug accumulation, stability ,tumour targeting and inhibits the activity of efflux pumps. When Zn-NPs are combined with chemotherapeutic drugs like 5-Fluorouracil, Cisplatin they show strong cytotoxic activity while reducing the toxic side effects [59][60].

Zn-NPs have high atomic number and electron density and can act as radiosensitizers, enhancing the effective radiation absorption. When the nanoparticles are exposed to X-ray, they generate a secondary electron cascade, leading to excessive ROS production which ultimately targets and breaks the double stranded DNA in cancer. This results in enhanced destruction of the tumour cell with limited radiation exposure reducing the side effects to the surrounding healthy tissues [61].

VII. TOXCITY, SAFETY AND BIOCOMPATABILITY:

The toxicity, safety and biocompatibility of ZnO nanoparticles are important factors which determine the suitability for various application [73]

7.1. Effect on Normal Cells

The major issue with ZnO-NP therapy is that the tendency of selective toxicity on the cancer cells should not be applied to normal tissues [62]. Usually, normal cells, like human dermal fibroblasts and healthy T-cells, show a resistance to ZnO-NPs that is higher than that of malignant cells, which is due to their superior antioxidant capability and neutral surface charge that reduces adhesion to nanoparticles. However, excessive concentrations can cause mitochondrial dysfunction in healthy cells [63]

7.2. In Vitro vs. In Vivo Observations

In Vitro: Most cultures reports high generation of ROS, but they could also be due to the sedimentation of particles onto static cell monolayer

In Vivo: It is observed that, in living organisms (mice/rats), acute toxicity is cleared by the systemic clearance mechanisms of the liver and the spleen (Taylor and Francis, 2025). Although oral/IV administration can temporarily cause elevations in liver enzymes, the body generally is able to eliminate the dissolved zinc ions, so long as the dose is not administered in excess [64].

7.3. Long-term safety

The long-term safety of ZnO-NPs has to do with potential bioaccumulation and neurotoxicity. Continuous exposure can lead to the accumulation of zinc ions in kidneys and pancreas causing changes like inflammatory cell infiltration. Furthermore, emerging evidence suggests that circulating ZnO nanoparticles are capable of crossing the blood-brain barrier (BBB) and can accumulate in regions like the

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hippocampus and cerebellum, which can cause a memory impair in the long term exposure [65]. However, since these NPs are biodegradable they can degrade and integrate into the zinc pool of the body, but a close monitoring is necessary [66].

7.4. Dose Dependency

Zn-NPs dose dependent effects, where at low concentrations (<10 µg/mL), they are generally biocompatible and may support the normal cellular functions by supplying Zn ions. On the other hand, high concentrations result in excessive Zn ions leading to apoptosis through the caspase signalling pathways. Additionally, nanostructures of Zn exhibits greater toxicity mainly because of its large surface area and increased reactivity [67][68].

VIII. CONCLUSION:

Zinc nanoparticles are indeed wonderful in costing us with the cancer treatment issues. Their surface and size and stability influence the manner in which they interact with living things and their effectiveness in use as medicine. Zinc nanoparticles are effective in damaging cancer cells. Do not injure healthy organs so much. This is in contrast to chemotherapy and radiation treatments that may cause damage to the body and not only the cancer. Among the things about the zinc nanoparticles, they can combat cancer in some manner. They have the ability to produce objects that kill cancer cells. They are able to promote the death of cancer cells. They are capable of releasing zinc ions in cells that interfere with the functioning of cells. They are able to prevent proliferation of cancer cells. This implies that cancer cells will not be prone to develop resistance towards the treatment. This is also possible with zinc nanoparticles that can be used to deliver medicine in a better way and reduce the side effects. Zinc nanoparticles aid in the delivery of the medicine to the location during the right time. Zinc nanoparticles are able to treat cancers such as breast, lung, liver, and colon cancer The treatment would be even better using zinc nanoparticles with medicines. The novel methods of producing zinc nanoparticles which are environmentally and body-safety are being developed. This would make them better in the treatment of cancer. Problems are yet to be resolved. We should ensure that zinc nanoparticles are not harmful in the long run. We must have methods of producing and testing zinc nanoparticles in a manner that we can get confident with the findings. We should consider the reasons why laboratory results occasionally may vary, with human body results. In order to determine whether zinc nanoparticles can be used as a means of treating cancer we must study and test them on humans. One of the ways of treating cancer is through short zinc nanoparticles as they can be safe and effective. Should we fix the issues and conduct research zinc nanoparticles may alter the treatment of cancer. One method of treating cancer is by using zinc nanoparticles and with work they could be quite useful. Zinc nanoparticles have a great potential in assisting us in dealing with cancer.

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