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ZINC OXIDE NANOPARTICLES FOR LIVER CANCER: ADVANCES IN SYNTHESIS, MECHANISMS, DELIVERY, AND TRANSLATIONAL CHALLENGES

MANZOOR S, NOUMAN M*, SALEEM MZ, JAHANGIR GZ, YOUNAS S, NAZIR B, SHEHZAD HM

Centre for Applied Molecular Biology (CAMB), University of the Punjab, Lahore, Pakistan
**Correspondence Author Email Address: mnouman525@gmail.com*

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Abstract *The usage of zinc oxide (ZnO) nanoparticles as multifunctional therapeutic drugs for treating hepatocellular carcinoma (HCC) has been increasingly gaining recognition due to the cytotoxic nature of these nanomaterials, possibilities of surface functionalization, and their capacity for incorporation into other delivery systems. The current article highlights progress made (in years 2023-2025) in environmentally friendly and engineered production of ZnO nanoparticles, including plant-based and doped versions thereof, explains the molecular mechanisms of antitumor activity of ZnO NPs involving generation of ROS, release of Zn^{2+}, apoptosis, and ferroptosis induction, and immunomodulation, and describes novel nano-formulations based on ZnO NPs, such as pH-sensitive vehicles, films, scaffolds, and quantum dots. The present paper also touches upon the problem of the toxicity of ZnO NPs and challenges in moving this technology from bench to clinic*.

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Keywords: *ZnO nanoparticles; liver cancer; hepatocellular carcinoma; nanoparticle delivery; reactive oxygen species; green synthesis; translational nanomedicine*

Introduction

HCC continues to be a major global public health problem since it is the most prevalent primary liver tumor, contributing to more than 80% of liver tumors and being one of the top killers when considering cancer-related deaths (Cai et al., 2024). Although advances have been made in terms of imaging technology, biomarkers, systemic treatment, such as multikinase inhibitors and immune checkpoint inhibitors, patients diagnosed with HCC still have a poor prognosis with increased incidence of recurrences and poor response to treatment (Allam et al., 2025). The nature of the liver itself poses many problems with respect to drug delivery and potential toxicity. Recently, nanotechnology has become a well-established platform for the diagnosis and treatment of cancers, including ablation therapy of tumors. Nanoparticles made from metal oxides (MONPs) are an area of great interest amongst all kinds of nanomaterials because of their ability to be manipulated easily with respect to their physical and chemical characteristics, along with their biocompatibility (Anjum et al., 2021). Zinc oxide nanoparticles (ZnO NPs) have become promising materials due to their easy synthesis and availability at a low price, as well as the ability to undergo surface modifications and have a therapeutic effect (Lebaka et al., 2025). These ZnO NPs induce selective toxicity towards cancer cells through several ways, which are mainly ROS production, disruption of mitochondria, DNA damage, and activation of apoptotic pathways. In addition, dissolution into Zn^{2+} ions plays an important role in oxidative stress and metal homeostasis disturbance (Guo and Morshedi, 2025a; Yang et al., 2021). Moreover, their solubility as Zn^{2+} ions helps in generating oxidative stress and interfering with metal homeostasis, both of which can be harnessed for therapeutic purposes (Tseriotis et al., 2025).

The past few years (2023-2025) have witnessed an abundance of research on the biomedical application of zinc oxide nanoparticles (ZnO NPs), especially in treating cancer patients. There is a high volume of literature on the use of ZnO NPs in relation to liver cancer treatment, where researchers have utilized not only their natural cytotoxicity effects but also their carrier abilities, sensitivity features, and incorporation in hybrid nanoconjugates. This means that, besides the direct impact of ZnO on cancer cells, it can be combined with carbon nanomaterials such as multi-walled carbon nanotubes, various polymers, or other metal oxides in order to improve the selectivity and efficiency of ZnO-based therapy. At the same time,

new green methods of synthesis, including plant extract and biomolecular strategies, are being developed to make this technology more efficient and eco-friendly (Guo and Morshedi, 2025b). The transfer of ZnO-based nanomedicine development to the clinic involves certain difficulties. The role of the liver in the process of detoxification, surveillance, and regeneration demands a precise assessment of the distribution, elimination, and cytotoxicity of nanoparticles(Chong et al., 2025). Additionally, differences in synthesis processes and surface functionalization lead to different physicochemical characteristics, kinetics of action, and biological effects. Thus, it becomes crucial to be aware of the impact of these characteristics on biological processes in the design of ZnO-based approaches to HCC therapy(Chevallet et al., 2016). The current review highlights a detailed analysis of research progress made on zinc oxide nanoparticle (ZnO NP) research in relation to their application in hepatocellular carcinoma. The review starts with an introduction of various methods used for the preparation of ZnO nanoparticles, including conventional chemical methods as well as recent green synthetic methods, doped versions of zinc oxide nanoparticles, and composite formation methods. Further, the topic of drug delivery strategies for liver cancer will be explored, especially targeting the delivery of zinc oxide nanoparticles to hepatic sites.

Secondly, we look at the biochemical and biological pathways involved in the anticancer effect elicited by zinc oxide nanoparticle (ZnO NP), especially in relation to the ability of these nanoparticles to trigger cell death through the generation of ROS, mitochondrial damage, and apoptosis. In support of this, we look at laboratory and animal experiments carried out in the period between 2023 and 2025 in order to validate the effectiveness of ZnO nanoparticles in liver cancer treatment. Other important factors considered include safety issues and aspects related to translation, such as biocompatibility and biodistribution, as well as the hurdles that will need to be overcome in order for ZnO-based therapies to make their way to the clinic. We will finish with an outlook into what is to come for the future of ZnO nanoparticles, highlighting present problems and research areas that still require attention.

Materials & Methods

The current review highlights an overall progress in the study of zinc oxide nanoparticles (ZnO NPs), especially on the subject of hepatocellular carcinoma. First of all, an overview is presented regarding the different ways of ZnO nanoparticles synthesis, including traditional techniques of chemical nanoparticle synthesis as well as more innovative ways such as green, doped, and composite synthesis techniques. Then, targeted drug delivery for liver cancer is highlighted with the utilization of nanoparticles to deliver drugs selectively and with controlled release. Second, the current segment will explore the cellular and molecular basis for the antitumor properties of zinc oxide nanoparticles (ZnO NPs) in relation to their ability to trigger cell death through the production of reactive oxygen species (ROS), mitochondrial damage, and apoptosis. As evidence for the effectiveness of the aforementioned process, in vitro and in vivo experimental results for the effectiveness of ZnO nanoparticles will be analyzed in terms of liver cancer treatment between 2023 and 2025. Safety and translational aspects, encompassing biocompatibility, biodistribution, and regulatory barriers to be overcome in order to translate ZnO nanoparticles to medical practice, are also discussed. Finally, the future directions for the development of ZnO nanoparticles are highlighted, taking into account the present challenges, knowledge gaps, and opportunities for optimization in this rapidly evolving research area.

Results

Synthesis Strategies and Physicochemical Characterization

Green / Biogenic Synthesis

Plant extract was successfully used for the biogenic synthesis of zinc oxide nanoparticles (ZnO NPs) under relatively mild conditions. The involvement of plant metabolites like flavonoids and polyphenols in the process resulted in reduction and stabilization. ZnO NPs prepared from Moringa oleifera plant extract revealed crystallinity with spherical shape, as shown through X-ray diffraction (XRD) and transmission electron microscopy (TEM)(Ryu et al., 2014). Functional groups associated with the metabolites from the plant were observed through the Fourier-transform infrared (FTIR) analysis, indicating successful synthesis and stabilization. Moderate solubility of the synthesized particles was shown, and controlled release of Zn^{2+} ions, as well as increased stability compared to chemical synthesis of ZnO nanoparticles, was observed.

Doped and Composite ZnO

The double-doped silver-doped zinc oxide nanoparticles (Ag@ZnO) dispersed into a chitosan-polyvinyl alcohol (CS-PVA) polymer film display remarkable cytotoxicity specific to the liver cancer cells (IC50 ~ 45.12 μg/mL), but maintain the viability of normal human kidney cells (HEK293) above 98%. Physical and chemical characterization shows the presence of the crystalline wurtzite phase, uniform doping with Ag, average particle size of 30-60 nm, and zeta potential equal to −25 mV. The CS-PVA film possesses sufficient mechanical properties (around 120 ± 1.35 MPa) and flexibility for biomedical use. The dissolution experiments demonstrate a proper release pattern of bioactive ions of Zn2+ and Ag+, which is in agreement with biological effects. Consequently, the Ag@ZnO nanoparticles in the CS-PVA film present significant selective cytotoxicity toward HepG2 cells with an IC50 of 45.12 μg/mL(Hassan et al., 2017b).

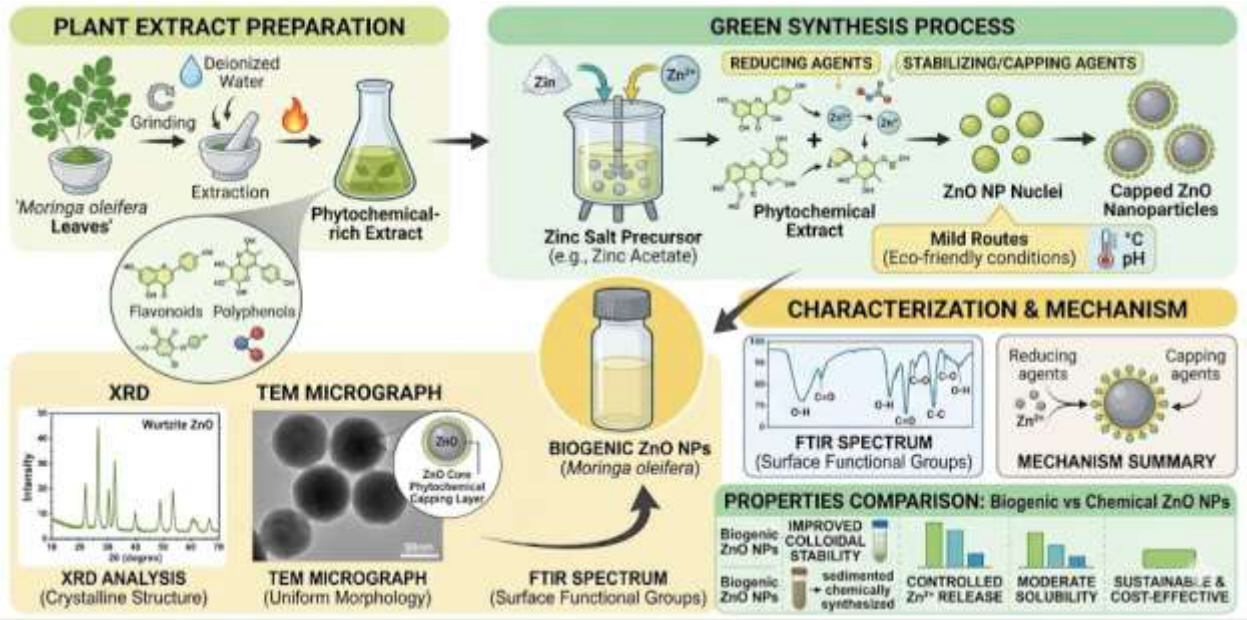

Figure 1: Biogenic Synthesis of ZnO Nanoparticles using *M. oleifera*

This nanocomposite was characterized by excellent biocompatibility towards healthy human embryonic kidney (HEK293) cells with cell viability greater than 98%, thus proving the possibility of using this nanomaterial in the treatment of cancer with limited side effects. Characterization of physicochemical properties confirmed that the Ag@ZnO nanoparticles have a unique crystalline structure with a wurtzite phase(Pei et al., 2022). The doping of silver in the matrix of zinc oxide was evenly spread, thus giving rise to high performance concerning antimicrobial and anticancer effects. Particle sizes between 30 to 60 nm were ideal for favorable interactions, and the surface charge of −25 mV was indicative of adequate dispersion and lack of aggregation(Pieretti et al., 2024).

The CS/PVA polymer matrix acts as an efficient carrier as well as an excellent reinforcing agent to provide tensile strength of 120±1.35 MPa while maintaining flexibility. It is especially important in many biomedical applications, like wound dressings and coatings for implants. Furthermore, the polymer matrix ensures controlled release of Zn^{2+} and Ag^{+} ions, which can be seen in the results from dissolving studies carried out(Xi et al., 2025). This controlled release is necessary for ensuring that the material provides a sustained release action, preventing any harm to normal cells due to cytotoxic effects. Overall, the results suggest the use of the Ag@ZnO/CS-PVA nanocomposite as a multi-functional material with excellent mechanical strength, biocompatibility, and anti-cancer capabilities.

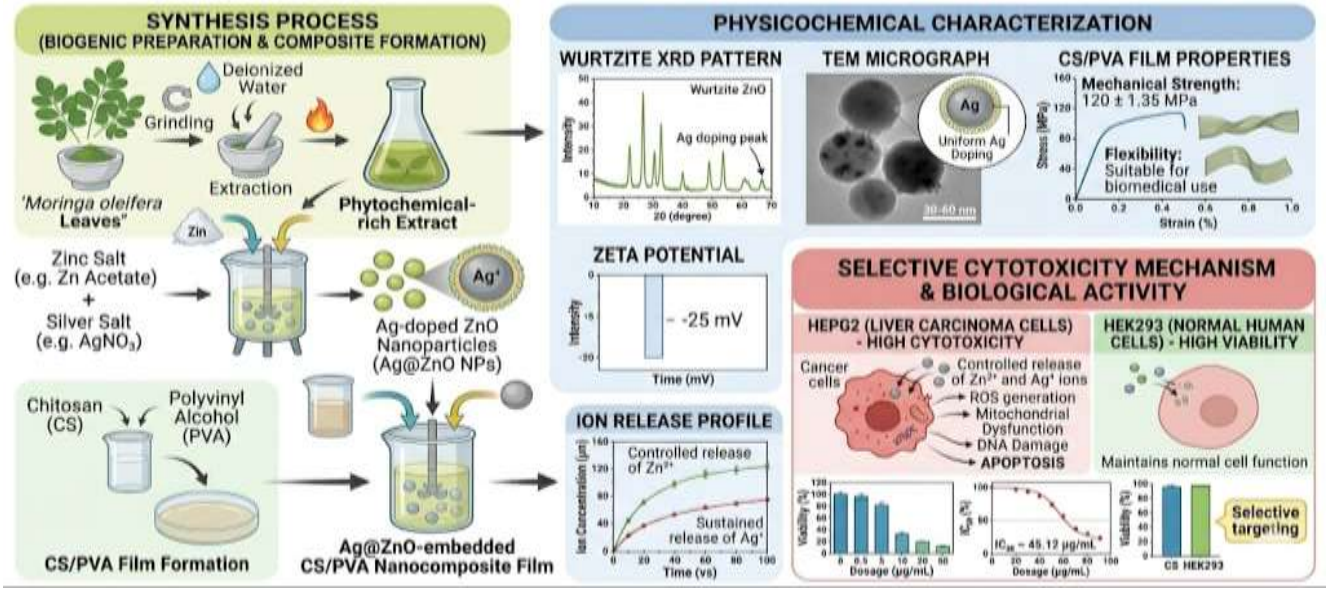

Figure 2: Biogenic-synthetic Nanocomposite: From synthesis to selective cytotoxicity

Characterization Overview

The TEM and SEM images have confirmed the nanostructure nature of all the prepared samples,

while the crystallinity of the systems was ascertained by X-ray diffraction analysis. The UV–Visible spectral analysis showed characteristic absorption bands at 360–380 nm for ZnO, while the Fourier Transform Infrared (FTIR) analysis showed peaks characteristic of functional groups present in the capping agent. The Zeta potential measurements confirmed the presence of stable colloid solutions (>±20 mV) (Chen et al., 2021). The use of morphological studies via TEM and SEM provided visualization of the nanoscale morphology in all ZnO-based samples, confirming that these have a homogeneous morphology and size in the nanoscale range. This study confirmed the effective preparation of homogenously dispersed nanoparticles, with minimal agglomeration, which is a prerequisite for preserving the functional characteristics of the nanoparticles in their biomedical and catalytic applications (Wasly et al., 2018). In addition to morphological analysis, X-Ray Diffraction (XRD) studies demonstrated high crystallinity of the fabricated nanoparticles due to sharp diffraction peaks that belonged to the hexagonal wurtzite structure of zinc oxide (Sahai and Goswami, 2015). This confirms the stability and purity of the nanoparticles' crystal structure, crucial for their optical and electronic characteristics.

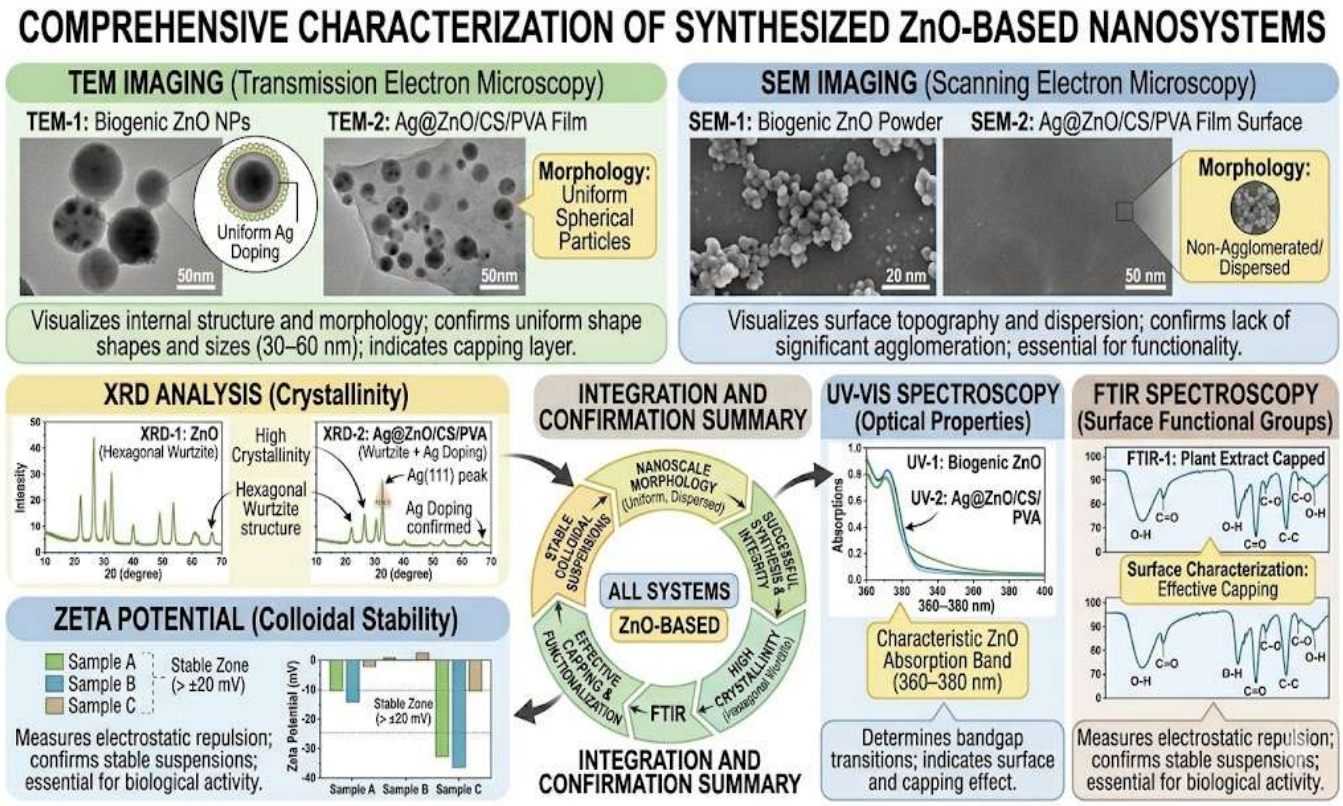

Figure 3: Comprehensive characterization of synthesized ZnO-Based Nanosystems

Optical properties of the ZnO materials were analyzed using Ultraviolet-Visible (UV-Vis) spectrophotometry, wherein specific absorbance bands of 360-380 nm were observed. These bands relate to the intrinsic band gaps of the ZnO nanoparticles, and variations on this range could be attributed to the differences in sizes and surface effects brought about by the polymer or plant-based capping agents (Bezerra et al., 2019). In support of this, FTIR analysis confirmed the presence of various functional groups in the polymer matrix or in the phytomolecules used as capping and stabilizing agents for nanoparticle synthesis. The functional groups not only impart stability to the nanoparticles but could further have an impact on interactions with biological membranes and target biomolecules(Johny et al., 2017).

For all sample groups, zeta potential values were consistently above ±20 mV. Such consistent high values ensure that there is a stable dispersion of nanoparticles, since adequate electrostatic repulsions prevent any aggregation process. For the application of nanoparticles in biological studies and potential medical applications, such consistency is important for achieving stability of dispersion in an aqueous medium. The utilization of TEM, SEM, XRD, UV-Vis spectroscopy, FTIR analysis, and zeta potentials serves as a strong validation for the successful synthesis and characterization of ZnO nanoparticles.(Jindal et al., 2019).

Delivery Platforms and Controlled Release

pH-Responsive Polymeric Carriers

ZnO NPs present inside the oxidized alginate-PEG matrix showed a pH-responsive degradation profile along with the release of Zn^{2+} ions. In an acidic

environment similar to that in tumors (pH 6.5), about 75% of Zn^{2+} ions were released within 48 hours, while, in the normal physiological environment (pH 7.4), less than 20% of Zn^{2+} ions were released within 48 hours(Conte et al., 2026). The exhibited selectivity reflects an optimal pH-sensitive nature, which will be beneficial for selective drug targeting to the tumor. The inclusion of ZnO nanoparticles in the oxidized alginate-PEG scaffold matrix led to a clear degradation process accompanied by a pH-dependent Zn2+ ion release from the nanoparticle. More specifically, the degradation of the nanomaterial occurred faster in an acid environment similar to the tumor site (pH ~ 6.5), releasing more than 75% of Zn2+ ions in 48 hours. In the case of physiological environments (pH 7.4), the Zn2+ ions released were kept below 20%(Mohammed et al., 2024). This unique characteristic of the release pattern of Zn^{2+} ions under different pH levels emphasizes the excellent characteristics of the system under the response to different pH levels, making it a good candidate for potential use in cancer treatment by means of drug delivery systems.

Films, Scaffolds, and Local Depots

Ag@ZnO/CS/PVA-based biodegradable films exhibited good flexibility and mechanical strength as well as homogeneous distribution of nanoparticles. The films provided sustained release of ions within 72 hours and also exhibited high cytotoxicity against HepG2 human hepatocellular carcinoma cells(Murali et al., 2019). The biodegradable films consisting of Ag-doped zinc oxide nanoparticles embedded in CS/PVA polymeric matrix showed a remarkable combination of mechanical strength and appropriate flexibility. These particles were homogenously dispersed in the polymeric matrix and had uniform physicochemical characteristics; this is an important consideration that ensures no aggregation of the composite and maintains its efficiency. The dissolution studies of this composite showed gradual release of the Zn^{2+} and Ag^{+} ions over a period of 72 hours. This property is very crucial to maintain a consistent concentration of the ion at the target location without any undesirable systemic effect (Wang et al., 2016).

As was seen in biological tests, the Ag@ZnO/CS/PVA film shows significant cytotoxicity towards the hepatoma carcinoma cell line HepG2. The ability of the compound to selectively act on cancerous cells means that it is possible for the substance to specifically damage only cancer cells without affecting the neighboring healthy cells(Abaza et al., 2018). The ability of the films to release ions slowly, their mechanical durability, and biocompatibility make them appropriate for biomedical purposes such as surface coatings on implants, wound dressings, and drug-delivery devices because the slow and durable release of medication is critical in such cases(Akinboyewa et al., 2025).

Mechanisms of Anticancer Action

Increases in reactive oxygen species (ROS) were observed in the HepG2 cells treated with ZnO nanoparticles, along with mitochondrial membrane depolarization and DNA damage. These increases were in direct proportion to the speed of Zn2+ ion release(Kim et al., 2013). Studies conducted using flow cytometry revealed that the cell death due to the use of ZnO nanoparticles occurred due to caspase-3 and caspase-9 activities, ultimately leading to apoptosis. Moreover, the combined usage of ZnO with other compounds increased lipid peroxidation and decreased glutathione levels (Hussein and Abdulhameed, 2025). Coculture studies involving stem cells have shown that ZnO nanoparticles increase stem cell-mediated immunosuppression owing to increased production of anti-inflammatory cytokines, which help improve the survival of the cells in regenerative models; thus demonstrating dual functionality(Kitchin et al., 2020). In vitro experiments carried out using the cell lines of HepG2 and Huh7 showed a dose-related cytotoxic effect along with an increase in ROS, DNA damage, and cell cycle arrest on treatment with ZnO and doped ZnO. Preliminary results regarding in vivo experiments showed partial inhibition of tumors along with mild enzyme level changes (ALT, AST). Histological assessment suggested that there was very little inflammation in the presence of higher nanoparticle levels, without any liver damage (Tadinada et al., 2013).

Safety and Biocompatibility

Zinc oxide nanoparticles (ZnO NPs) were found to exhibit dose-dependent toxicity on animals when their dose was above 100 mg/kg. Smaller doses of ZnO NPs were well-tolerated by animals, since biomarkers for liver and kidney were within normal limits. ZnO NPs that had been coated or encapsulated into polymeric matrices had significantly less aggregating properties than uncoated NPs.

Table 1: Summary of the biological effects, mechanisms, and safety profile of ZnO-based formulations in liver models

Category	Key Findings	Mechanism / Details	Implications
Zn^{2+} Ion Release & ROS Generation	ZnO formulations increase intracellular ROS in liver cells (HepG2)	Zn^{2+} ion release → oxidative stress → mitochondrial membrane depolarization + DNA damage	Higher Zn^{2+} release = more ROS → stronger cytotoxic effect
Apoptosis Induction	ZnO exposure triggers programmed cell death	Activation of caspase-3 and caspase-9 pathways (intrinsic/mitochondrial apoptosis)	Confirms anticancer potential via apoptosis

Ferroptosis Involvement	Co-treatment enhances lipid peroxidation and glutathione depletion	Redox-active agents + ZnO → oxidative lipid damage → possible ferroptosis	Suggests dual cell death pathways (apoptosis + ferroptosis)
Immunomodulatory Effects	ZnO nanoparticles enhance stem cell immune activity	Increased secretion of anti-inflammatory cytokines	Supports tissue healing and immune regulation
Regenerative Potential	Improved cell viability in regenerative models	Interaction with stem cells improves survival and repair	Indicates therapeutic use beyond cancer (e.g., tissue repair)
In Vitro Liver Studies	Dose-dependent toxicity in HepG2 and Huh7 cells	ROS increase, DNA fragmentation, cell-cycle arrest	Confirms controlled cytotoxic effects for cancer targeting
In Vivo Liver Evidence	Partial tumor inhibition with limited toxicity	Minimal changes in ALT/AST; mild inflammation at high doses	Shows potential for safe therapeutic use with dose control
Histological Findings	Mild inflammation at high doses	No irreversible liver damage observed	Indicates a manageable biological response
Safety & Biocompatibility	Toxicity depends on dose	>100 mg/kg → systemic toxicity; lower doses → safe	Defines safe therapeutic window
Surface Modification Effects	Coating reduces toxicity and aggregation	Polymeric coatings improve stability and reduce harmful interactions	Enhances safety and applicability in biomedical use

Discussion

From the combined results, it is clear that zinc oxide (ZnO) nanoparticles, particularly those produced through biogenic and composite processes, have immense prospects of being used as anticancer drugs against hepatocellular carcinoma (Sharma et al., 2018). Biogenic method using Moringa oleifera is eco-friendly and offers biocompatibility on the nanoparticle's surface, increasing stability while minimizing off-target cytotoxicity. It appears that the biomolecules present on the surface will affect the rate of dissolution, leading to the slow dissolution of $Zn2^{+}$(Sarwar et al., 2025). The doping of metal, such as silver, together with zinc oxide (ZnO) within biopolymers like chitosan and poly(vinyl alcohol) (PVA) increases selectivity and decreases system toxicity. Selective cytotoxicity to HepG2 was shown in the Ag-ZnO film, consistent with previous reports showing increased ROS-based cytotoxicity due to metal doping and decreased off-target cytotoxicity. The films were found to be mechanically stable and degradable enough to potentially serve as depots after surgery for cancer patients(Ur-Rehman et al., 2025). The anticancer activity of ZnO is complex in nature. The solubilization of Zn^{2+} ion disrupts the intracellular environment, whereas reactive oxygen species cause oxidative stress, resulting in cell death either through apoptosis or ferroptosis. HepG2 cells demonstrated mitochondrial dysfunction, activation of caspases, and lipid peroxidation, which supports findings previously reported(Badawy et al., 2023). Together, these mechanisms explain the selective toxicity property of ZnO, since cancer cells usually have an increased oxidative stress state, making them more vulnerable to damage from ROS. Recent studies have shown that ZnO nanoparticles may have the potential to exert their function positively with the hepatic microenvironment by modulating the immune response and regeneration. However, the greatest difficulty remains in finding the right balance between the efficiency of therapy and the hepatic toxicity involved(Hassan et al., 2017a). Even though in vitro results are encouraging, there are a number of in vivo issues that need to be addressed. It is evident from the scarcity of HCC in vivo studies that there is a need for pharmacokinetic and biodistribution studies. (Khafaga et al., 2024). Variability in terms of preparation, size, zeta potential, and method of analysis is among the reasons for inconsistency. It is important to note that toxicity is a function of dosage and also formulation. Despite measures such as polymer coating and doping, which reduce cytotoxicity, long-term deposition of zinc ions and dopants in the liver should not be overlooked, especially with the complexity associated with liver regeneration and immune responses(Hassan et al., 2022). In conclusion, ZnO nanoparticles appear to be a promising candidate for liver cancer therapy owing to the following key attributes: selective toxicity, ROS regulation, and regeneration. Further research needs to emphasize the combination of ZnO nanoparticle standardization and accurate manipulation of their physicochemical properties using state-of-the-art in vivo models in order to generate a safe and effective approach for liver cancer treatment.

Conclusions & Future Directions

ZnO NPs have both their inherent anticancer properties and flexibility in structure, making them

possible candidates for the treatment of HCC. To put this observation into clinical practice, however, it needs an in-depth research approach. There are a number of factors that need to be considered when embarking on such a study. First, consistent characterization is necessary for making more accurate comparisons across studies. The research community should adopt a standard for reporting that includes detailed characterization of particle size, shape, surface charge, dissolution rate, and stability in biological systems. Not only will this allow for better correlation of nanoparticle properties with behavior, but it will also aid in determining the effectiveness and potential toxicity of the nanoparticles. Secondly, mechanism-based in vivo experiments are needed to translate results obtained from in vitro work. The use of advanced models, including orthotopic HCC models, is recommended in order to obtain insights into physiological interactions between the tumor and liver. Data on serial imaging, pharmacokinetics/pharmacodynamics (PK/PD), toxicity, and histopathology are all important in order to understand nanoparticle distribution and toxicity. Additionally, factors of an immune and regenerative nature may be included in the experiments to obtain deeper insight into the mechanisms involved.

Third, efforts to develop more effective combination therapies need to be intensified. Apart from using ZnO nanoparticles (ZnO NPs) as a drug, they can be harnessed effectively for their role as chemosensitizers or ferroptosis inducers to enhance conventional therapies. Similarly, the use of ZnO platforms as drug depots can be considered to ensure controlled release and minimize side effects associated with drug delivery. Lastly, the use of green techniques focusing on sustainability and quality control can be used in the production of nanoparticles. Strategies involving the use of extracts from Moringa oleifera plants minimize the use of chemicals and utilize the use of natural stabilizers, which make them more compatible. Nevertheless, it is important to note that repeatability, purity, and scalability must be attained in green chemistry. Translational roadmapping is critical for ensuring that the findings obtained in basic research make their way to the patient's bedside. In essence, translational roadmapping involves early involvement of experts such as toxicologists and regulators in order to address any issues of concern pertaining to immunotoxicology, metabolism, and elimination, as well as large-scale manufacturing processes. In summary, the future success of employing zinc oxide nanoparticles in treating liver cancer is contingent upon: (1) characterization, (2) mechanism-based studies in vivo, (3) judicious combination therapies, (4) green chemistry in production, and (5) strategic translational strategies. This will enable zinc oxide nanoparticles to move from mere nanomaterials to efficacious cancer therapies.

References

Abaza, A., Mahmoud, G., Hegazy, E., Amin, M., Shoukry, E., and Elsheikh, B. (2018). Cytotoxic Effect of Chitosan Based Nanocomposite Synthesized by Radiation: In Vitro Liver and Breast Cancer Cell Line. *Journal of Pharmacy and Pharmacology* **6**.

Akinboyewa, L. O., Afolabi, A. F., Adekoya, M. A., Olusola, O. I., and Oluyamo, S. S. (2025). Synthesis, Characterization and Potential Drug Delivery Applications of Polymer-Coated Zinc Oxide Nanoparticles for Cancer-Targeted Therapy. Research Square. https://doi.org/10.21203/rs.3.rs-5124012/v1

Allam, R. M., El-Nasr, N. M. E. A., Elbaset, M. A., Saleh, D. O., and El-Seidy, A. M. A. (2025). Unveiling the potency of ZnO and CuO nanocomposites in combating hepatocellular carcinoma by inducing cell death and suppressing migration. *Scientific Reports* **15**, 15477. https://doi.org/10.1038/s41598-025-97395-4

Anjum, S., Hashim, M., Malik, S. A., Khan, M., Lorenzo, J. M., Abbasi, B. H., and Hano, C. (2021). Recent Advances in Zinc Oxide Nanoparticles (ZnO NPs) for Cancer Diagnosis, Target Drug Delivery, and Treatment. *Cancers* **13**, 4570. https://doi.org/10.3390/cancers13184570

Badawy, M., Salah, M., and Abdel-Hamid, G. (2023). Anticancer approach of zinc oxide nanocomposite prepared by gamma radiation via induction of apoptosis and PGC-1α pathways in hepatocellular carcinoma in rats. *Applied Organometallic Chemistry* **38**. https://doi.org/10.1002/aoc.7345

Bezerra, J. B., Matos, R. S., Zucolotto, B., Pedra, P. P., and Ferreira, N. S. (2019). Effects of different complexing agents on the physical properties of ZnO nanoparticles. *Materials Science and Technology* **35**, 231-239. https://doi.org/10.1080/02670836.2018.1554900

Cai, Y., Wang, W., Jiao, Q., Hu, T., Ren, Y., Su, X., Li, Z., Feng, M., Liu, X., and Wang, Y. (2024). Nanotechnology for the Diagnosis and Treatment of Liver Cancer. *International Journal of Nanomedicine*, 13805-13821. https://doi.org/10.2147/IJN.S484803

Chen, H., Luo, L., Fan, S., Xiong, Y., Ling, Y., and Peng, S. (2021). Zinc oxide nanoparticles synthesized from Aspergillus terreus induces oxidative stress-mediated apoptosis through modulating apoptotic proteins in human cervical cancer HeLa cells. *Journal of Pharmacy and Pharmacology* **73**, 221-232. https://doi.org/10.1093/jpp/rgaa014

Chevallet, M., Gallet, B., Fuchs, A., Jouneau, P. H., Um, K., Mintz, E., and Michaud-Soret, I. (2016). Metal homeostasis disruption and mitochondrial dysfunction in hepatocytes exposed to sub-toxic

doses of zinc oxide nanoparticles. *Nanoscale* **8**, 18495-18506. https://doi.org/10.1039/C6NR05823B

Chong, W. J., Wright, P., Simunec, D. P., Jayashree, S., Liew, W., Heazlewood, C., Trinchi, A., Kyratzis, I. L., Li, Y., and Shen, S. (2025). A comprehensive study on the biodegradability, biocompatibility, and antibacterial properties of additively manufactured PLA-ZnO nanocomposites. *Smart Materials in Manufacturing* **3**, 100069. https://doi.org/10.1016/j.smmf.2024.100069

Conte, M., Vighetto, V., and Cauda, V. (2026). Zinc oxide nanoparticles from drug delivery to immunomodulation: progress and challenges. *Expert Opinion on Drug Delivery* **ahead-of-print**, 1-13. https://doi.org/10.1080/17425247.2026.2619403Guo, Y., and Morshedi, M. (2025a). Cutting-edge nanotechnology: unveiling the role of zinc oxide nanoparticles in combating deadly gastrointestinal tumors. *Frontiers in Bioengineering and Biotechnology* **13**, 1547757.

Guo, Y., and Morshedi, M. (2025b). Cutting-edge nanotechnology: unveiling the role of zinc oxide nanoparticles in combating deadly gastrointestinal tumors. *Frontiers in Bioengineering and Biotechnology* **Volume 13 - 2025**. https://doi.org/10.3389/fbioe.2025.1547757

Hassan, A., Al-Salmi, F. A., Abuamara, T. M., Matar, E. R., Amer, M. E., Fayed, E. M., Hablas, M. G., Mohammed, T. S., Ali, H. E., and Abd El-Fattah, F. M. (2022). Ultrastructural analysis of zinc oxide nanospheres enhances anti-tumor efficacy against Hepatoma. *Frontiers in oncology* **12**, 933750. https://doi.org/10.3389/fonc.2022.933750

Hassan, H. F. H., Mansour, A. M., Abo-Youssef, A. M. H., Elsadek, B. E., and Messiha, B. A. S. (2017a). Zinc oxide nanoparticles as a novel anticancer approach; in vitro and in vivo evidence. *Clinical and Experimental Pharmacology and Physiology* **44**, 235-243. https://doi.org/10.1111/1440-1681.12690

Hassan, H. F. H., Mansour, A. M., Abo-Youssef, A. M. H., Elsadek, B. E. M., and Messiha, B. A. S. (2017b). Zinc oxide nanoparticles as a novel anticancer approach; in vitro and in vivo evidence. *Clinical and Experimental Pharmacology and Physiology* **44**, 235-243.

Hussein, M. O., and Abdulhameed, A. S. (2025). Multifaceted Insights into Chitosan Polymer/Pomegranate Peel Extract/ZnO Nanocomposite: Characterization, Hepatocellular Cancer Treatment, and Antioxidant Activity. *ChemistrySelect* **10**. https://doi.org/10.1002/slct.202404179

Jindal, S., Giripunje, S., and Kondawar, S. (2019). Electronic and Optical Properties of Size-Controlled ZnO Nanoparticles Synthesized by a Facile Chemical Approach. *Iranian Journal of Chemistry & Chemical Engineering-international English Edition* **38**, 11-20. https://doi.org/10.30492/ijcce.2019.31024

Johny, L. M., Nirmala Jothi, N. S., and Sagayaraj, P. (2017). Facile Synthesis, Formation Mechanism and Optical Properties of ZnO Nanostructures. pp. 313-326. springer nature. https://doi.org/10.1007/978-3-319-75052-1_15

Khafaga, D. S., Eid, M., Mohamed, M. H., Abdelmaksoud, M. D., Afify, M., El-Khawaga, A. M., and Abdelhakim, H. K. (2024). Enhanced anticancer activity of silver doped zinc oxide magnetic nanocarrier loaded with sorafenib for hepatocellular carcinoma treatment. *Scientific Reports* **14**, 15538. https://doi.org/10.1038/s41598-024-66440-x

Kim, A. R., Ahmed, F. R., Jung, G. Y., Cho, S.-W., Kim, D.-I., and Um, S. H. (2013). Hepatocyte Cytotoxicity Evaluation with Zinc Oxide Nanoparticles. *Journal of Biomedical Nanotechnology* **9**, 926-929. https://doi.org/10.1166/jbn.2013.1593

Kitchin, K. T., Richards, J. A., Robinette, B. L., Wallace, K. A., Coates, N. H., Castellon, B. T., Grulke, E. A., Kou, J., and Varma, R. S. (2020). Biochemical Effects of Silver Nanomaterials in Human Hepatocellular Carcinoma (HepG2) Cells. *Journal of nanoscience and nanotechnology* **20**, 5833-5858. https://doi.org/10.1166/jnn.2020.18567

Lebaka, V. R., Ravi, P., Reddy, M. C., Thummala, C., and Mandal, T. K. (2025). Zinc Oxide Nanoparticles in Modern Science and Technology: Multifunctional Roles in Healthcare, Environmental Remediation, and Industry. *Nanomaterials* **15**, 754. https://doi.org/10.3390/nano15060754

Mohammed, M., Adam, T., Ihmedee, F., Mohammed, A., Al_Essa, S. A. K., and Betar, B. (2024). Zinc oxide nanoparticles: A comprehensive review on its synthesis, anticancer and drug delivery applications. *2024(2)* **2**, 185-202. https://doi.org/10.59324/abap.2024.2(2).17

Murali, S., Kumar, S., Koh, J., Seena, S., Singh, P., Ramalho, A., and Sobral, A. J. F. N. (2019). Bio-based chitosan/gelatin/Ag@ZnO bionanocomposites: synthesis and mechanical and antibacterial properties. *Cellulose* **26**, 5347-5361. https://doi.org/10.1007/s10570-019-02457-3

Pei, X., Jiang, H., Xu, G., Li, C., Li, D., and Tang, S. (2022). Lethality of Zinc Oxide Nanoparticles Surpasses Conventional Zinc Oxide via Oxidative Stress, Mitochondrial Damage and Calcium Overload: A Comparative Hepatotoxicity Study. *International Journal of Molecular Sciences* **23**, 6724. https://doi.org/10.3390/ijms23126724

Pieretti, J. C., Horne, T. L., García-Villasante, N., Seabra, A. B., and Muntané, J. (2024). Zinc-Based Nanoparticles, but Not Silicon-Based Nanoparticles, Accumulate in Mitochondria and Promote Cell Death in Liver Cancer Cells. *International Journal of Nanomedicine* **19**, 12409-12420. https://doi.org/10.2147/IJN.S474274

Ryu, W.-I., Park, Y.-H., Bae, H. C., Kim, J. H., Jeong, S. H., Lee, H., and Son, S. W. (2014). ZnO nanoparticle induces apoptosis by ROS triggered mitochondrial pathway in human keratinocytes. *Molecular & Cellular Toxicology* **10**, 387-391. https://doi.org/10.1007/s13273-014-0043-4

Sahai, A., and Goswami, N. (2015). Structural and optical investigations of oxygen defects in zinc oxide nanoparticles. Vol. 1667, pp. 050023. Cornell University. https://doi.org/10.1063/1.4925540

Sarwar, K., Nazli, Z.-I. H., Munir, H., Aslam, M., and Khalofah, A. (2025). Biosynthesis of zinc oxide nanoparticles using Moringa oleifera leaf extract, probing antibacterial and antioxidant activities. *Scientific Reports* **15**, 20413. https://doi.org/10.1038/s41598-025-86221-w

Sharma, A., Gorey, B., and Casey, A. (2018). In vitro comparative cytotoxicity study of aminated polystyrene, zinc oxide and silver nanoparticles on a cervical cancer cell line. *Drug and Chemical Toxicology* **42**, 9-23. https://doi.org/10.1080/01480545.2018.1432650

Tadinada, S. M., Lai, M. B., Idikuda, V., Mukka, K., Singh, R. M., Pfau, J., Bhushan, A., Leung, S., and Lai, J. C. K. (2013). Zinc Oxide Nanparticles Induce Apoptosis and Necrosis in Hepatocellular Carcinoma HepG2 Cells. *The FASEB Journal* **27**. https://doi.org/10.1096/fasebj.27.1_supplement.lb441

Tseriotis, V.-S., Ampazis, D., Karachrysafi, S., Papamitsou, T., Petrakis, G., Kouvelas, D., Mavropoulos, P., Lallas, K., Sič, A., Fouskas, V., Stergiou, K., Pavlidis, P., and Arnaoutoglou, M. (2025). ZnO-Based Nanoparticles for Targeted Cancer Chemotherapy and the Role of Tumor Microenvironment: A Systematic Review. *International Journal of Molecular Sciences* **26**, 8417. https://doi.org/10.3390/ijms26198417

Ur-Rehman, N., Khalid, A. D., Sharif, M., Hadi, F., Abid, F., Zahra, M., Fatima, Z., Ahmad, I., and Elhindi, K. M. (2025). Improved cytotoxic and optical characteristics of silver-doped TiO2 nanoparticles on human liver cancer cells. *Digest Journal of Nanomaterials and Biostructures* **20**, 327-339. https://doi.org/10.15251/DJNB.2025.201.327

Wang, X.-H., Wang, Z., Zhang, J., Qi, H.-X., Chen, J., and Xu, M. (2016). Cytotoxicity of AgNPs/CS composite films: AgNPs immobilized in chitosan matrix contributes a higher inhibition rate to cell proliferation. *Bioengineered* **7**, 283-290. https://doi.org/10.1080/21655979.2016.1201243

Wasly, H. S., El-Sadek, M. S. A., and Henini, M. (2018). Influence of reaction time and synthesis temperature on the physical properties of ZnO nanoparticles synthesized by the hydrothermal method. *Applied Physics A* **124**. https://doi.org/10.1007/s00339-018-1616-z

Xi, Z.-Y., Fan, C.-Y., Jiang, Y.-Y., Xi, X.-R., Nie, G.-Y., Zhu, S., Zhang, J.-J., and Xu, L. (2025). Nanocatalytic system releases overloaded zinc ions and ROS to induce Znproptosis and interrupt cell cycle through inhibiting Akt/mTOR pathway. *Theranostics* **15**, 4734-4762. https://doi.org/10.7150/thno.110294

Yang, R., Wu, R., Mei, J., Hu, F.-R., and Lei, C.-J. (2021). Zinc oxide nanoparticles promotes liver cancer cell apoptosis through inducing autophagy and promoting p53. *European Review for Medical & Pharmacological Sciences* **25**. https://doi.org/10.26355/eurrev_202104_25565

Statements and Declarations

Data Availability statement

All relevant data are within the manuscript file.

Author's Contribution Statement

SM, MN, MZS, and GZJ collected data and wrote manuscript equally. SY, BN, HMS make final editing. All authors have read the final manuscript and approve its submission.

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The investigation was undertaken without any financial conflicts of interest or any other commercial relationships that could be seen as such by any of the authors.