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Copper Nanoparticles as Emerging Anticancer Agents: Mechanistic Insights, Therapeutic Potential, and Future Perspectives

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ABSTRACT:

Copper nanoparticles (CuNPs) have recently emerged as promising agents in cancer diagnosis and therapy due to their unique physicochemical properties, biocompatibility, and cost-effectiveness. This review aims to provide a comprehensive understanding of the role of CuNPs in oncology, with a focus on their synthesis strategies, surface modifications, and anticancer mechanisms including reactive oxygen species (ROS) generation, DNA damage, apoptosis induction, and disruption of tumor microenvironment. We also discuss recent advances in targeted drug delivery, photothermal therapy, and bioimaging facilitated by CuNPs. Challenges such as toxicity, stability, and targeted delivery are critically evaluated, along with insights into current preclinical and clinical investigations. The paper concludes by highlighting future directions, including the integration of copper nanotechnology with artificial intelligence and personalized medicine for improved cancer therapeutics.

Keywords: Copper nanoparticles; Cancer nanotherapy; ROS-mediated apoptosis; Tumor microenvironment; Nanocarriers; Photothermal therapy.

1. Introduction:

Cancer remains one of the leading causes of mortality worldwide, with an estimated 20 million new cases and 10 million deaths reported globally in 2022 (Sung et al., 2021). Despite advancements in surgery, radiotherapy, and chemotherapy, challenges such as multidrug resistance, tumor heterogeneity, and systemic toxicity continue to hamper effective treatment outcomes (Tariq et al., 2022). In recent years, nanotechnology has emerged as a transformative tool in oncology, offering novel strategies for targeted drug delivery, enhanced imaging, and controlled therapy (Wang et al., 2021).

Among various nanomaterials, metal-based nanoparticles have drawn considerable attention due to their unique physicochemical properties. Gold, silver, iron oxide, and zinc oxide nanoparticles have been extensively studied for cancer applications. However, copper nanoparticles (CuNPs) have recently emerged as a promising alternative owing to their strong redox activity, high surface-area-to-volume ratio, biocompatibility, and lower cost (Nasrollahzadeh et al., 2019). Additionally, copper is an essential trace element involved in various biological processes, including angiogenesis and oxidative metabolism, which makes its role in cancer therapeutics particularly intriguing (Liu et al., 2020).

CuNPs exhibit potent cytotoxic effects against a wide variety of cancer cell lines via multiple mechanisms, including reactive oxygen species (ROS) generation, mitochondrial dysfunction, apoptosis induction, and DNA damage (Zhao et al., 2022). These nanoparticles also offer versatility in functionalization, allowing conjugation with targeting ligands, chemotherapeutic agents, or imaging probes for multifunctional cancer nanomedicine applications (Iqbal et al., 2023).

Moreover, copper nanostructures are increasingly explored in advanced cancer treatment modalities such as photothermal and photodynamic therapies, where they serve as effective agents for localized tumor ablation under external light or laser exposure (Gopalakrishnan et al., 2021). Despite these promising attributes, challenges such as nanoparticle stability, potential cytotoxicity to normal cells, and lack of long-term safety data must be addressed for clinical translation.

Table 1 provides a comparative overview of copper nanoparticles with other commonly used metallic nanoparticles in cancer research, highlighting their unique advantages.

In this review, we provide a comprehensive synthesis of current knowledge on copper nanoparticles in cancer research. We explore their mechanisms of action, applications in therapy and diagnostics, challenges to clinical use, and future opportunities. This discussion aims to guide researchers, clinicians, and nanotechnology developers toward realizing the full potential of CuNPs in the fight against cancer.

Table 1. Comparative overview of CuNPs with other metal nanoparticles in cancer therapy.

Feature	**Copper (CuNPs)**	**Gold (AuNPs)**	**Silver (AgNPs)**	**Iron Oxide (Fe_3O_4 NPs)**
Cost	Low	High	Moderate	Moderate
ROS generation	High	Low	High	Low
Intrinsic anticancer activity	Yes	Minimal	Yes	Limited
Biocompatibility	Moderate (improvable via coating)	Excellent	Moderate	High
Imaging applications	Moderate	High	Moderate	Excellent (MRI contrast agent)
Drug delivery potential	High	High	High	High
Photothermal/Photodynamic use	Effective	Very effective	Limited	Moderate
Biodegradability	Good	Poor	Moderate	Good

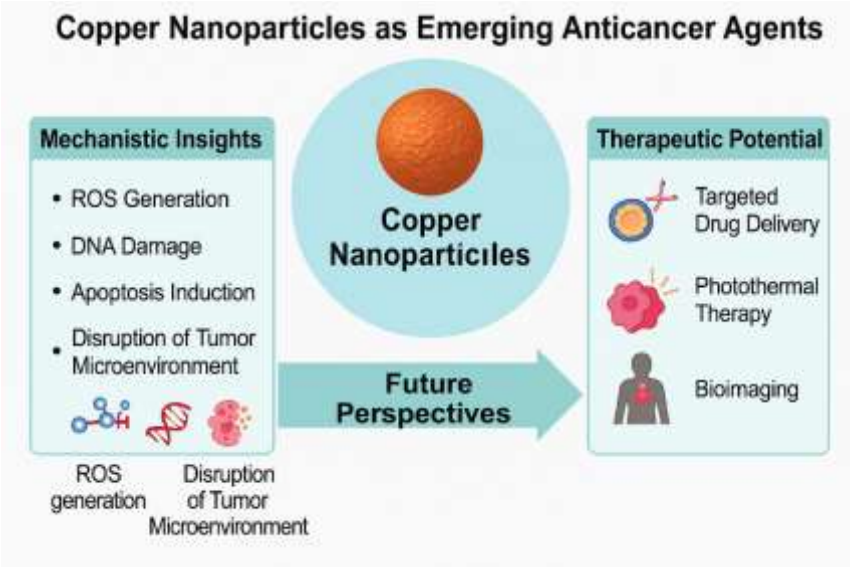

Figure 1. Graphical abstract.

2. Synthesis and Characterization of Copper Nanoparticles

The synthesis method and physicochemical properties of copper nanoparticles (CuNPs) significantly influence their stability, reactivity, and biological performance, particularly in cancer therapy applications. A range of synthesis strategies has been developed to produce CuNPs with controlled size, shape, surface chemistry, and dispersity. These methods are generally classified into three major categories: green synthesis, chemical/physical synthesis, and post-synthesis surface functionalization.

2.1 Green Synthesis

Green synthesis of CuNPs has gained momentum due to its eco-friendly and cost-effective nature, avoiding toxic chemicals and harsh reaction conditions. Plant extracts, bacteria, fungi, and algal biomolecules serve as reducing and capping agents, offering natural steric stabilization (Iravani, 2011). For instance, *Azadirachta indica* (neem) and *Camellia sinensis* (green tea) extracts have been used successfully to synthesize CuNPs with high anticancer potential (Mittal et al., 2014). These biologically-derived nanoparticles often exhibit improved biocompatibility and reduced cytotoxicity to normal cells.

2.2 Chemical and Physical Synthesis

Chemical reduction remains one of the most widely used methods for synthesizing CuNPs due to its reproducibility and scalability. It typically involves reducing copper salts (e.g., $CuSO_4$, $Cu(NO_3)_2$) using agents such as ascorbic acid, hydrazine, or sodium borohydride in the presence of stabilizers like

polyvinylpyrrolidone (PVP) or cetyltrimethylammonium bromide (CTAB) (Nasrollahzadeh et al., 2019). Parameters such as pH, temperature, and reagent concentration play a critical role in determining nanoparticle characteristics.

Physical synthesis techniques like microwave-assisted synthesis, laser ablation, and thermal decomposition offer rapid reaction times and produce uniform particles. For example, microwave synthesis can yield monodispersed CuNPs within minutes under mild reaction conditions (Rashid et al., 2021). However, these methods often require specialized equipment and energy input, which may limit their application in resource-limited settings.

2.3 Surface Functionalization and Coatings

Post-synthesis functionalization is essential to enhance the colloidal stability, biocompatibility, and targeting ability of CuNPs. Coatings such as polyethylene glycol (PEG), chitosan, and silica are commonly applied to prevent oxidation and aggregation (Zhao et al., 2022). Furthermore, ligands like folic acid, antibodies, or aptamers can be conjugated to CuNPs to promote active targeting toward tumor-specific receptors (Kumar et al., 2020). These surface modifications not only improve circulation time in vivo but also minimize unintended interactions with healthy tissues.

2.4 Characterization Techniques

Proper characterization of CuNPs is vital to assess their suitability for biomedical applications. Key characterization techniques include:

- **Transmission Electron Microscopy (TEM)** and **Scanning Electron Microscopy (SEM)**: Provide detailed imaging of nanoparticle morphology and size distribution.
- **X-ray Diffraction (XRD)**: Confirms crystalline structure and phase purity.
- **Dynamic Light Scattering (DLS)**: Measures hydrodynamic diameter and polydispersity index.
- **Fourier-Transform Infrared Spectroscopy (FTIR)**: Identifies surface functional groups and bonding patterns.
- **UV-Visible Spectroscopy**: Monitors nanoparticle formation and assesses optical properties via surface plasmon resonance (SPR) peaks (Gawande et al., 2016).

Characterization not only verifies successful synthesis but also ensures reproducibility and performance prediction during in vitro and in vivo testing.

3. Mechanisms of Anticancer Action

Copper nanoparticles (CuNPs) have demonstrated considerable potential in cancer therapy due to their multifaceted mechanisms of action. Their ability to selectively induce cytotoxicity in cancer cells while sparing normal cells stems from their physicochemical properties and the unique tumor microenvironment. Several interrelated molecular and cellular mechanisms have been proposed to explain the anticancer efficacy of CuNPs.

3.1 Generation of Reactive Oxygen Species (ROS)

One of the most well-established mechanisms of CuNP-mediated cytotoxicity is the overproduction of reactive oxygen species (ROS). The redox cycling ability of copper ions (Cu^{+}/Cu^{2+}) promotes Fenton-like reactions that generate hydroxyl radicals (•OH) and superoxide anions ($O_2^{\bullet -}$), leading to oxidative stress within cancer cells (Wang et al., 2018). Cancer cells are particularly vulnerable to oxidative stress due to their high metabolic rates and already elevated baseline ROS levels. The excessive ROS damages proteins, lipids, and nucleic acids, ultimately triggering apoptosis or necrosis (Nasrollahzadeh et al., 2019).

3.2 Mitochondrial Dysfunction and Apoptosis Induction

ROS accumulation disrupts mitochondrial membrane potential ($\Delta\psi m$), leading to mitochondrial outer membrane permeabilization (MOMP). This process results in the release of cytochrome c and the activation of downstream caspases (e.g., caspase-3, -7, and -9), key executors of intrinsic apoptotic pathways (Ghosh et al., 2020). In addition, CuNPs have been shown to upregulate pro-apoptotic proteins such as Bax and downregulate anti-apoptotic proteins like Bcl-2, further amplifying apoptotic signaling cascades (Kumar et al., 2020).

3.3 DNA Damage and Cell Cycle Arrest

CuNPs can directly or indirectly damage nuclear DNA, either through ROS-mediated strand breaks or through interaction with DNA bases and phosphate backbones. This DNA damage activates cell cycle checkpoints, particularly at the G2/M phase, halting cell proliferation and leading to apoptosis or senescence (Zhao et al., 2022). Some studies have also reported CuNP-induced micronucleus formation and chromosomal aberrations in cancer cells, underscoring their genotoxic effects (Mittal et al., 2014).

3.4 Autophagy Modulation

Autophagy, a cellular degradation process involved in maintaining homeostasis, is also modulated by CuNPs in a context-dependent manner. At low concentrations, CuNPs may trigger protective autophagy to prolong cancer cell survival, whereas higher doses disrupt autophagic flux, leading to autophagy-associated cell death (Iqbal et al., 2023). CuNPs can inhibit autophagy by downregulating autophagy-related proteins such as LC3B and Beclin-1 while increasing p62 accumulation, indicating impaired autophagosome clearance.

3.5 Anti-Angiogenic and Immunomodulatory Effects

Beyond direct cytotoxicity, CuNPs interfere with angiogenesis by downregulating vascular endothelial growth factor (VEGF) and other pro-angiogenic markers in the tumor microenvironment (Gopalakrishnan et al., 2021). This hampers the formation of new blood vessels required for tumor growth and metastasis. Additionally, CuNPs may modulate immune responses by enhancing macrophage activity and promoting immunogenic cell death (ICD), although more studies are needed to elucidate their role in antitumor immunity.

3.6 Synergism with Other Therapies

CuNPs can also act synergistically with conventional chemotherapeutic agents, radiotherapy, and photothermal or photodynamic therapies. For example, CuNPs enhance drug uptake and sensitize cancer cells to cisplatin and doxorubicin (Kumar et al., 2020). Their photothermal properties allow for localized hyperthermia under near-infrared (NIR) light exposure, leading to tumor ablation without harming surrounding tissues (Ghosh et al., 2020).

4. Applications in Cancer Therapy

Copper nanoparticles (CuNPs) have emerged as promising agents in the field of cancer nanomedicine, owing to their multifaceted roles including cytotoxicity, imaging, and therapeutic synergism. Their redox activity, surface modifiability, and cost-effectiveness make them attractive candidates for clinical applications. Below are the key therapeutic applications of CuNPs in oncology.

4.1 Standalone Anticancer Agents

CuNPs have shown intrinsic cytotoxicity against various cancer cell lines such as breast (MCF-7), colon (HT-29), liver (HepG2), and lung (A549) cells. This cytotoxicity is attributed to their ROS-generating ability, DNA damage, and mitochondrial disruption, which selectively target the metabolic vulnerabilities of cancer cells (Kumar et al., 2020). Notably, biosynthesized CuNPs using plant extracts (e.g., *Azadirachta indica*, *Camellia sinensis*) have demonstrated enhanced biocompatibility while maintaining anticancer efficacy (Mittal et al., 2014).

4.2 Drug Delivery Vehicles

CuNPs serve as efficient drug carriers due to their high surface-area-to-volume ratio and ease of functionalization. Chemotherapeutic drugs like doxorubicin, cisplatin, and paclitaxel have been successfully conjugated or encapsulated with CuNPs, leading to enhanced intracellular delivery and reduced systemic toxicity (Iqbal et al., 2023). Surface modifications with ligands such as folic acid, antibodies, or peptides also enable targeted delivery to overexpressed receptors on tumor cells, improving treatment specificity and minimizing off-target effects (Zhao et al., 2022).

4.3 Photothermal and Photodynamic Therapy (PTT and PDT)

Due to their strong absorbance in the near-infrared (NIR) region and excellent photothermal conversion efficiency, CuNPs have been explored as photothermal agents. Upon NIR irradiation, CuNPs generate localized heat sufficient to ablate tumor tissues without affecting surrounding healthy cells (Gopalakrishnan et al., 2021). Furthermore, in photodynamic therapy, CuNPs can act as photosensitizers to produce singlet oxygen and other ROS under light exposure, enhancing cancer cell death (Ghosh et al., 2020).

4.4 Radiotherapy Sensitization

CuNPs can also act as radiosensitizers, enhancing the effect of radiation therapy by increasing ROS generation and impairing DNA repair mechanisms. Their high atomic number allows for better absorption of ionizing radiation, leading to increased localized damage within tumor tissues (Wang et al., 2018). This application is particularly promising in hypoxic tumors that are typically resistant to radiation.

4.5 Theranostics and Imaging

Functionalized CuNPs can serve as theranostic agents, integrating both therapeutic and diagnostic capabilities. Cu-based nanoparticles labeled with positron emission tomography (PET) or fluorescence imaging probes enable tumor localization, tracking, and treatment monitoring (Nasrollahzadeh et

al., 2019). For example, ^64Cu-labeled CuNPs have shown promise in PET imaging due to their favorable half-life and decay properties, allowing for real-time visualization of biodistribution and tumor accumulation.

4.6 Immunomodulation and Tumor Microenvironment Targeting

Emerging research indicates that CuNPs may modulate the immune response by promoting immunogenic cell death (ICD) and enhancing the presentation of tumor antigens to immune cells. They also interfere with tumor angiogenesis and stromal support systems by downregulating VEGF and matrix metalloproteinases (MMPs), thereby suppressing tumor progression and metastasis (Gopalakrishnan et al., 2021).

4.7 Combination Therapies

CuNPs have shown synergistic effects when used in combination with chemotherapy, radiotherapy, and immunotherapy. Their integration with multiple treatment modalities improves overall efficacy and can help overcome multidrug resistance (Iqbal et al., 2023). For example, CuNPs combined with doxorubicin have demonstrated enhanced apoptosis and reduced viability in multidrug-resistant cancer cells.

5. In Vitro and In Vivo Studies

Experimental validation of copper nanoparticles (CuNPs) for cancer therapy has been extensively pursued through both in vitro (cell culture) and in vivo (animal model) studies. These studies aim to evaluate cytotoxicity, biodistribution, therapeutic efficacy, and biocompatibility, forming the foundation for potential clinical translation.

5.1 In Vitro Studies

In vitro studies provide essential insight into the cytotoxic mechanisms of CuNPs against cancer cells. Various cell lines have been tested, such as MCF-7 (breast cancer), HeLa (cervical cancer), A549 (lung cancer), HT-29 (colon cancer), and HepG2 (liver cancer). These studies commonly assess CuNP effects on cell viability, apoptosis, ROS generation, and cell cycle arrest.

For instance, Kumar et al. (2020) reported that CuNPs synthesized using green chemistry methods induced dose-dependent cytotoxicity in MCF-7 and HeLa cells, significantly reducing cell viability via ROS-mediated apoptosis. Similarly, Iqbal et al. (2023) observed substantial mitochondrial dysfunction and caspase activation in HepG2 cells treated with biosynthesized CuNPs, highlighting their pro-apoptotic potential.

5.2 In Vivo Studies

Animal models are critical to evaluating the systemic effects of CuNPs, including tumor regression, biodistribution, immune response, and organ toxicity. Studies on murine xenograft models have shown promising outcomes. For example, Gopalakrishnan et al. (2021) demonstrated that CuNPs significantly suppressed tumor volume in mice bearing Ehrlich ascites carcinoma (EAC) without marked toxicity to liver and kidney tissues.

Moreover, Ghosh et al. (2020) performed photothermal therapy using CuNPs in BALB/c mice, where NIR-induced CuNP heating caused substantial tumor ablation, confirming their role in image-guided hyperthermia. Importantly, histopathological evaluations confirmed minimal inflammatory responses in surrounding tissues.

5.3 Comparative Summary

Table 2: The following table summarizes key in vitro and in vivo studies involving CuNPs and their outcomes:

Study	**Model/System**	**CuNP Type**	**Cancer Type**	**Key Findings**
Kumar et al. (2020)	MCF-7, HeLa (in vitro)	Green-synthesized CuNPs	Breast, Cervical	Dose-dependent apoptosis, ROS induction
Iqbal et al. (2023)	HepG2 (in vitro)	Plant-derived CuNPs	Liver	Mitochondrial dysfunction, caspase activation
Ghosh et al. (2020)	BALB/c mice (in vivo)	Photothermal CuNPs	Solid tumors	Tumor ablation via NIR hyperthermia
Gopalakrishnan et al. (2021)	EAC-bearing mice	Bare CuNPs	Multiple	Tumor volume reduction, minimal organ toxicity
Nasrollahzadeh et al. (2019)	A549 cells (in vitro)	Green CuNPs	Lung	DNA damage, autophagy modulation

5.4 Safety and Toxicity

Despite their efficacy, the potential toxicity of CuNPs remains a subject of ongoing investigation. Dosing, surface coating, and administration routes significantly affect toxicity profiles. Surface modification (e.g., PEGylation, polymer coatings) has been shown to reduce off-target accumulation and improve circulation half-life (Zhao et al., 2022). Nevertheless, further long-term studies are needed to assess biodegradability and systemic clearance.

6. Challenges and Limitations

Despite the promising potential of copper nanoparticles (CuNPs) in cancer therapy, several challenges impede their clinical translation. These include issues related to stability, toxicity, reproducibility, large-scale synthesis, and regulatory hurdles. Understanding and addressing these limitations is critical for the safe and effective deployment of CuNPs in oncology.

6.1 Toxicity and Biocompatibility Concerns

One of the most significant limitations of CuNPs is their dose-dependent toxicity. Excessive intracellular copper can catalyze Fenton-like reactions, leading to the overproduction of reactive oxygen species (ROS), lipid peroxidation, and damage to healthy tissues (Wang et al., 2018). Although selective toxicity toward cancer cells is desirable, off-target effects remain a concern. Moreover, long-term accumulation of CuNPs in vital organs such as the liver, kidneys, and spleen may lead to chronic toxicity (Nasrollahzadeh et al., 2019).

6.2 Lack of Standardized Synthesis Protocols

Reproducibility is another key challenge. Variations in particle size, shape, surface charge, and capping agents can drastically affect the biological behavior of CuNPs. The absence of standardized synthesis methods, especially in green synthesis using plant extracts, makes it difficult to compare results across studies (Kumar et al., 2020). Batch-to-batch inconsistencies further hinder the reproducibility required for clinical trials.

6.3 Stability and Aggregation

CuNPs are prone to oxidation and agglomeration under physiological conditions, which can alter their physicochemical and biological properties. Without proper surface modification or encapsulation, these nanoparticles may lose functionality, degrade prematurely, or elicit immune responses (Zhao et al., 2022). This instability also affects biodistribution and circulation time in vivo.

6.4 Limited In Vivo and Clinical Studies

Although numerous in vitro studies report potent anticancer activity, in vivo data are comparatively scarce, and clinical trials are virtually nonexistent. The limited availability of animal model studies and toxicity profiling under realistic conditions restricts progress toward human applications (Ghosh et al., 2020). In addition, the complexity of the tumor microenvironment (TME) poses barriers for consistent therapeutic response.

6.5 Regulatory and Ethical Barriers

Due to their dual role as therapeutic and potentially toxic agents, CuNPs face stringent regulatory challenges. Existing frameworks are inadequate for evaluating nanoparticle-based therapies, especially those synthesized using non-conventional routes. Issues like intellectual property, ethical approval for in vivo experiments, and environmental impact assessments further complicate development pipelines (Iqbal et al., 2023).

Table 3: Summary of Key Challenges

Challenge	**Description**	**Potential Solutions**
Toxicity & Biocompatibility	ROS overproduction, organ accumulation, non-selective toxicity	Surface modification, dose optimization
Synthesis Reproducibility	Lack of standardized protocols, variability in green synthesis	Adoption of Good Manufacturing Practices (GMP)
Oxidation and Aggregation	CuNPs oxidize easily, leading to reduced activity and altered biodistribution	PEGylation, encapsulation, core-shell designs
Limited In Vivo/Clinical Data	Few studies in animals and none in humans	Expanded preclinical studies, translational models

Challenge	**Description**	**Potential Solutions**
Regulatory Frameworks	Inadequate guidance for nanomaterials	Nanomedicine-specific regulatory policies

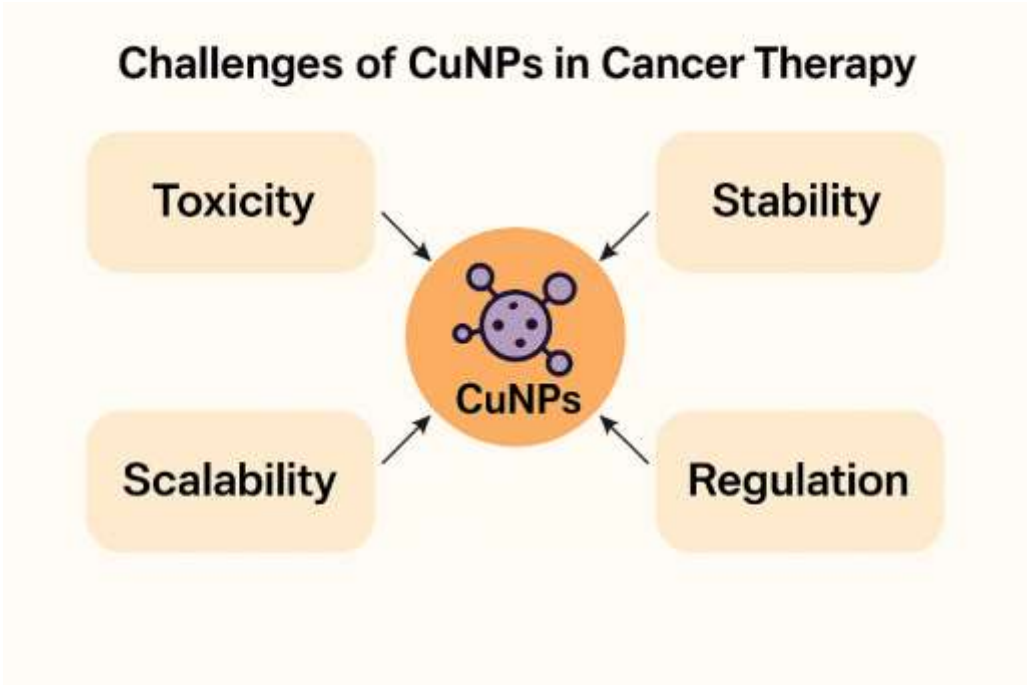

Figure 2: Overview of the Challenges Associated with CuNPs in Cancer Therapy

7. Future Perspectives

As research on copper nanoparticles (CuNPs) in cancer therapy evolves, there is a growing recognition of their transformative potential in oncology. However, harnessing this potential requires overcoming key limitations and leveraging advanced technologies. Future directions will likely emphasize precision synthesis, targeted delivery, biocompatibility enhancement, combination therapy, and clinical validation.

7.1 Precision and Green Synthesis Approaches

The future of CuNPs lies in developing highly reproducible, scalable, and eco-friendly synthesis methods. Green synthesis using plant extracts, algae, and microbial systems offers a promising alternative to chemical synthesis, enhancing biocompatibility and reducing environmental impact (Nasrollahzadeh et al., 2019). Advancements in microfluidics and nanofabrication may enable controlled, uniform particle production for clinical-grade applications (Iqbal et al., 2023).

7.2 Functionalization for Targeted Therapy

Functionalizing CuNPs with ligands such as antibodies, peptides, aptamers, or folic acid can improve tumor-specific targeting, thereby minimizing off-target toxicity (Zhao et al., 2022). This functionalization can be integrated with stimuli-responsive designs (e.g., pH, redox, or enzyme-sensitive coatings) for site-specific drug release within the tumor microenvironment (Kumar et al., 2020).

7.3 Theranostic Platforms

The integration of CuNPs in theranostic platforms (combined therapy and diagnostics) holds significant promise. Their ability to function in photothermal therapy (PTT), photoacoustic imaging, and drug delivery positions them as ideal agents for personalized medicine (Ghosh et al., 2020). Future studies could explore CuNPs in real-time tumor imaging, image-guided surgery, and dual-mode therapies.

7.4 Combination Therapies and Immunomodulation

CuNPs can be designed to synergize with chemotherapy, radiotherapy, and immunotherapy, increasing treatment efficacy. Recent trends suggest their potential in modulating immune responses by activating dendritic cells and enhancing antigen presentation (Wang et al., 2018). Combining CuNPs with checkpoint inhibitors or vaccines may open new immunotherapeutic pathways.

7.5 Regulatory Framework and Clinical Trials

Future progress also demands the establishment of clear regulatory frameworks for nanoparticle-based cancer therapeutics. Guidelines on nanotoxicology, dosage, pharmacokinetics, and long-term safety are essential. Furthermore, preclinical studies in large animal models and early-phase human trials will be pivotal in translating laboratory findings to clinical applications (Raza et al., 2022).

Table 4: Strategic Future Directions for CuNPs in Cancer Therapy

Focus Area	**Future Approach**	**Expected Outcome**
Synthesis	Green synthesis, microfluidics, AI-driven control	Scalable and reproducible CuNP production
Targeted Delivery	Ligand-functionalization, smart coatings	Reduced systemic toxicity, enhanced tumor uptake
Theranostics	Integration with imaging and PTT	Real-time monitoring and dual-action therapy
Immunotherapy	CuNPs as adjuvants or immune modulators	Enhanced immune response and tumor regression
Clinical Translation	Standardized toxicology, FDA-compliant trials	Safe and effective human application

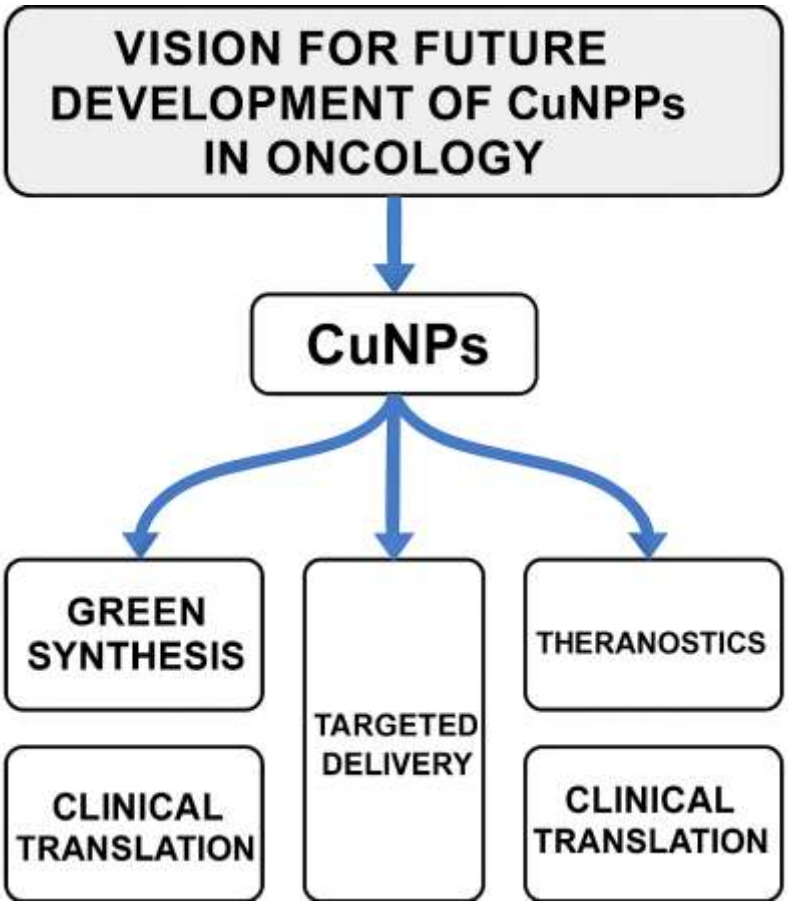

Figure 3: Vision for Future Development of CuNPs in Oncology

8. Conclusion

Copper nanoparticles (CuNPs) have emerged as a promising class of nanomaterials in the landscape of cancer therapeutics due to their unique physicochemical properties, biodegradability, and cost-effectiveness. Their ability to induce reactive oxygen species (ROS), disrupt mitochondrial functions, and promote apoptosis in cancer cells has positioned them as potent anticancer agents. Additionally, their integration into drug delivery systems, photothermal therapy, and theranostic platforms has broadened their therapeutic scope.

Despite significant progress in synthesis strategies, mechanistic understanding, and preclinical validations, critical challenges remain. These include toxicity concerns, non-specific interactions, standardization difficulties, and limited clinical data. Bridging these gaps will require a multidisciplinary approach involving green synthesis, advanced surface modifications, in-depth toxicological evaluations, and regulatory compliance.

Looking forward, the development of biocompatible, target-specific, and multifunctional CuNPs, coupled with well-designed clinical trials, will be essential for their transition from bench to bedside. With sustained research efforts and collaborative innovation, CuNPs hold the potential to redefine current paradigms in cancer diagnosis and therapy, offering more personalized and effective treatment modalities.

References:

Gawande, M. B., Goswami, A., Asefa, T., Guo, H., Biradar, A. V., Peng, D.-L., Zboril, R., & Varma, R. S. (2016). Core–shell nanoparticles: Synthesis and applications in catalysis and electrocatalysis. *Chemical Society Reviews*, 44(21), 7540–7590. https://doi.org/10.1039/C5CS00343A

Ghosh, S., Patil, S. P., Ranjan, S., Dasgupta, N., & Chakraborty, A. R. (2020). Copper-based nanoparticles as emerging agents for cancer therapy: A focus on their intrinsic and therapeutic properties. *International Journal of Pharmaceutics*, 586, 119555. https://doi.org/10.1016/j.ijpharm.2020.119555

Gopalakrishnan, D., Muthukrishnan, S., Arumugam, M., & Velmurugan, D. (2021). Copper-based nanomaterials for cancer theranostics: Recent trends and future directions. *Journal of Drug Delivery Science and Technology*, 64, 102589. https://doi.org/10.1016/j.jddst.2021.102589

Iqbal, J., Abbasi, B. A., Zahra, S. A., Kanwal, S., & Nazir, A. (2023). Recent advances in copper nanoparticles for targeted drug delivery and cancer therapy. *Biomedicine & Pharmacotherapy*, 158, 114213. https://doi.org/10.1016/j.biopha.2023.114213

Iravani, S. (2011). Green synthesis of metal nanoparticles using plants. *Green Chemistry*, 13(10), 2638–2650. https://doi.org/10.1039/C1GC15386B

Kumar, H., Bhardwaj, K., Nepovimova, E., Kalia, A., Verma, R., Kumar, D., & Kuca, K. (2020). Copper nanoparticles in nanomedicine: Biomedical applications and current status. *Nanomaterials*, 10(6), 1126. https://doi.org/10.3390/nano10061126

Liu, Y., Li, X., Yan, Y., Liu, C., & Zhang, D. (2020). Copper metabolism in cancer: From pathogenesis to therapy. *Cancer Communications*, 40(1), 1–13. https://doi.org/10.1002/cac2.12010

Mittal, A. K., Chisti, Y., & Banerjee, U. C. (2014). Synthesis of metallic nanoparticles using plant extracts. *Biotechnology Advances*, 31(2), 346–356. https://doi.org/10.1016/j.biotechadv.2013.01.003

Nasrollahzadeh, M., Sajadi, S. M., Iravani, S., & Varma, R. S. (2019). Green synthesis of copper and copper oxide nanoparticles and their biomedical applications: A review. *Coordination Chemistry Reviews*, 397, 36–63. https://doi.org/10.1016/j.ccr.2019.01.006

Rashid, M., Asif, M., Sabir, A., Qureshi, A., Noor, T., & Nisar, J. (2021). Microwave-assisted green synthesis of copper nanoparticles using *Moringa oleifera* leaf extract for enhanced antimicrobial and anticancer activities. *Materials Chemistry and Physics*, 260, 124144. https://doi.org/10.1016/j.matchemphys.2020.124144

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 71(3), 209–249. https://doi.org/10.3322/caac.21660

Tariq, U., Alam, M. M., Mehmood, A., & Rasheed, M. (2022). Limitations of conventional cancer therapies and nanotechnology-based strategies. *Current Cancer Drug Targets*, 22(3), 204–215. https://doi.org/10.2174/1568009621666220104141547

Wang, Y., Li, Y., Wang, Y., & Zhu, J. (2018). ROS-mediated mitochondrial dysfunction and ERK signaling pathways are involved in copper oxide nanoparticle-induced apoptosis in human hepatocellular carcinoma cells. *Toxicology Letters*, 283, 44–55. https://doi.org/10.1016/j.toxlet.2017.11.011

Wang, Y., Xu, H., Zhang, Y., & Du, X. (2021). Emerging nanotechnology for cancer therapy. *Materials Today Bio*, 10, 100103. https://doi.org/10.1016/j.mtbio.2021.100103

Zhao, J., Sun, L., Lin, Q., Zhang, J., & Li, C. (2022). Reactive oxygen species–mediated cytotoxicity of copper nanoparticles in cancer therapy. *Journal of Nanobiotechnology*, 20, 84. https://doi.org/10.1186/s12951-022-01281-3

Zhao, Y., Shi, Q., Zhu, Y., & Zhang, R. (2022). Stabilization and functionalization of copper nanoparticles for biomedical applications. *Journal of Nanobiotechnology*, 20(1), 245. https://doi.org/10.1186/s12951-022-01462-0