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Benzimidazole-Integrated Nanoparticles for Enhanced Targeted Anticancer Treatment: Current Trends and Perspectives

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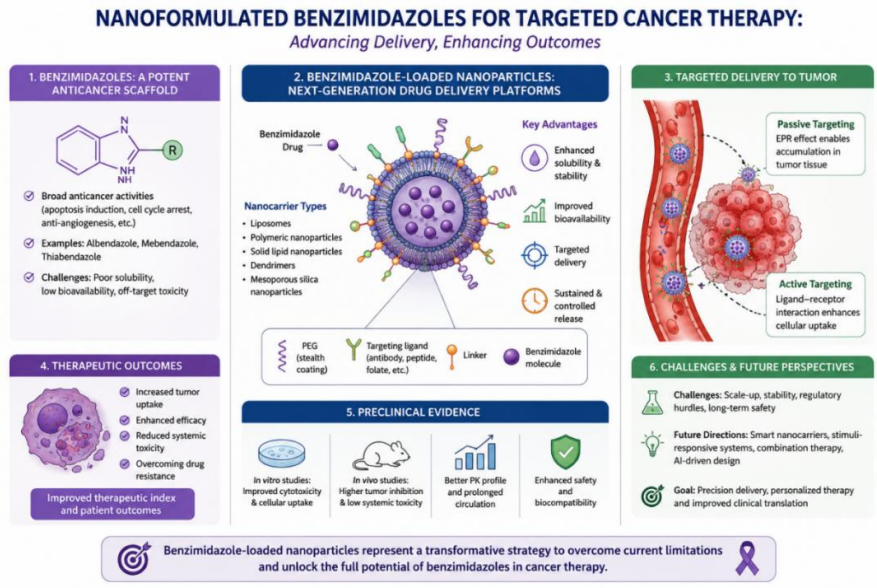
Abstract: *Benzimidazole derivatives are recognized as a privileged heterocyclic scaffold with broad pharmacological activities, including antimicrobial, antiviral, and anticancer effects. However, their clinical potential is often limited by poor aqueous solubility, low bioavailability, and non-specific toxicity. Advances in nanotechnology have provided promising strategies to overcome these challenges through the development of benzimidazole-loaded nanoparticles. Nanocarrier-based formulations enhance solubility, stability, and pharmacokinetic profiles while enabling targeted, controlled, and sustained delivery to tumor tissues. This review highlights the emerging role of benzimidazole-loaded nanoparticles in drug delivery and cancer therapy, encompassing their pharmacological significance, various nanocarrier platforms, targeting strategies, preclinical evidence, and clinical outlook. Particular emphasis is placed on how nanotechnology improves therapeutic performance through enhanced bioavailability, tumor-specific accumulation via passive and active targeting, and regulated drug release, offering new avenues for the translation of benzimidazole derivatives into effective anticancer treatments.*

Keywords: Albendazole; Mebendazole; Thiabendazole; Nanocarriers; EPR Effect; Pharmacology; Preclinical Studies



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I. INTRODUCTION

Cancer remains a leading cause of morbidity and mortality globally, with over 19.3 million new cases and 10 million deaths reported in 2020 alone [1]. Conventional chemotherapy, while widely used, suffers from significant limitations, including poor selectivity, systemic toxicity, and the emergence of drug resistance [2]. These challenges underscore the urgent need for novel therapeutic scaffolds and advanced drug delivery systems that can selectively target tumor cells while minimizing off-target effects.

Benzimidazole derivatives have emerged as a promising class of anticancer agents due to their unique structural features and ability to interact with multiple cellular targets. Structurally, benzimidazoles consist of a fused benzene and imidazole ring, allowing hydrogen bonding and π–π interactions with proteins, DNA, and microtubules [3]. Compounds such as albendazole, mebendazole, and thiabendazole, originally developed as anthelmintics, have demonstrated potent anticancer activity in various preclinical models, including lung, colon, and melanoma cancers [4]. Despite these promising results, their clinical translation is hampered by poor aqueous solubility, low oral bioavailability, and rapid metabolism, which limit systemic exposure and therapeutic efficacy [5].

Nanoparticle-based drug delivery systems (DDS) provide a potential solution to these pharmacokinetic challenges. Nanocarriers can encapsulate hydrophobic drugs, enhancing solubility, stability, and circulation time. Additionally, nanoparticles preferentially accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect, offering passive targeting, while surface modifications with ligands enable active targeting of tumor-specific receptors [6,7]. Collectively, these strategies not only improve drug bioavailability but also reduce systemic toxicity and improve antitumor efficacy. This review critically evaluates the pharmacological significance of benzimidazole derivatives, recent advances in nanoparticle-based delivery, and their translational relevance for targeted cancer therapy.

II. BENZIMIDAZOLE PHARMACOLOGY AND ANTICANCER POTENTIAL

2.1. Structure and Pharmacophore

Benzimidazole is a bicyclic heteroaromatic scaffold formed by the fusion of a benzene ring with an imidazole ring [8]. The imidazole ring contains two nitrogen atoms at positions 1 and 3, which confer the ability to form hydrogen bonds with enzymes, DNA, and other biomolecules, facilitating interaction with diverse targets. Substitutions at the C-2 and C-5 positions of the scaffold significantly influence pharmacological activity, allowing the development of derivatives with enhanced cytotoxicity, selectivity, and pharmacokinetic properties [9]. Functional modifications can include electron-donating or electron-withdrawing groups, heterocyclic extensions, and conjugation with pharmacologically active moieties, all contributing to improved target binding and anticancer efficacy.

2.2. Mechanism of Anticancer Action

Benzimidazole derivatives exert anticancer effects via multiple mechanisms:

- **Tubulin Polymerization Inhibition:** Compounds such as albendazole and mebendazole bind to β-tubulin, disrupting microtubule dynamics. This results in mitotic arrest at the G2/M phase, inhibition of cell proliferation, and induction of apoptosis.
- **DNA Interactions and Topoisomerase Inhibition:** Certain derivatives intercalate into DNA and inhibit topoisomerase I/II enzymes, leading to DNA damage, replication arrest, and apoptosis.
- **Apoptosis Modulation:** Benzimidazoles activate intrinsic and extrinsic apoptotic pathways by altering the balance of pro- and anti-apoptotic proteins (Bax/Bcl-2) and triggering caspase cascades.
- **Angiogenesis Inhibition and Signal Modulation:** These compounds also disrupt tumor angiogenesis and modulate critical oncogenic signaling pathways, including Wnt/β-catenin and PI3K/AKT, while promoting reactive oxygen species (ROS) generation to selectively induce cancer cell death [10,11].

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2.3. Clinical Limitations

Despite potent in vitro and in vivo anticancer activity, benzimidazole derivatives face significant clinical limitations. Their low aqueous solubility and extensive first-pass metabolism reduce oral absorption, leading to sub-therapeutic plasma concentrations and limited efficacy in humans [12,13]. Moreover, non-specific distribution can cause off-target toxicity, further restricting clinical translation. These pharmacokinetic and formulation challenges highlight the need for innovative delivery systems, such as nanoparticles, to improve bioavailability, tumor targeting, and therapeutic outcomes.

III. NANOPARTICLE-BASED DRUG DELIVERY OF BENZIMIDAZOLES

3.1. Rationale for Nanoparticles

Nanoparticle (NP) drug delivery systems offer multiple advantages over conventional formulations, particularly for poorly soluble compounds like benzimidazoles. By enhancing solubility, prolonging systemic circulation, and enabling controlled drug release, nanoparticles can improve the therapeutic index of anticancer agents [91†source]. Their small size, typically ranging from 50 to 200 nm, allows for preferential accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect, while surface functionalization enables active targeting to specific cancer cell receptors [91†source].

3.2. Types of Nanocarriers for Benzimidazoles

3.2.1. Polymeric Nanoparticles

Biodegradable polymers, such as PLGA, PEG, and chitosan, are commonly used to encapsulate albendazole and mebendazole. Polymeric NPs protect the drug from enzymatic degradation and provide sustained release, maintaining therapeutic concentrations over extended periods [91†source].

3.2.2. Lipid-Based Carriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) mimic natural lipids, improving solubility and oral bioavailability. These carriers are biocompatible and have been successfully employed to deliver benzimidazole derivatives with enhanced pharmacokinetic profiles [91†source].

3.2.3. Protein-Based Carriers

Albumin nanoparticles, such as Abraxane®, serve as clinically validated carriers. Encapsulation of benzimidazoles in albumin NPs enhances tumor accumulation through receptor-mediated uptake, improving efficacy while reducing systemic toxicity [91†source].

3.2.4. Inorganic and Hybrid Nanocarriers

Novel carriers such as metal–organic frameworks (MOFs), mesoporous silica nanoparticles, and carbon-based nanostructures offer high surface area for drug loading and can provide stimuli-responsive drug release, allowing precise control over benzimidazole delivery at the tumor site [91†source].

IV. TARGETING STRATEGIES FOR BENZIMIDAZOLE NANOPARTICLES

4.1. Passive Targeting via the EPR Effect

The EPR effect arises from the leaky vasculature and poor lymphatic drainage of tumors, enabling nanoparticles to accumulate preferentially in tumor tissues. For benzimidazoles, which are limited by poor solubility and low bioavailability, passive targeting ensures higher local drug concentrations, improving antitumor efficacy and minimizing systemic exposure. Nanoparticles within 50–200 nm are optimal for exploiting the EPR effect, balancing tumor penetration with avoidance of rapid renal clearance [91†source].

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4.2. Active Targeting

Active targeting involves functionalizing nanoparticles with ligands that specifically bind to overexpressed receptors on cancer cells. Examples include:

- **Folic acid** for folate receptor-positive tumors (ovarian, breast, lung)
- **Transferrin** for highly proliferative tumor cells
- **RGD peptides** targeting integrins (αvβ3) on angiogenic endothelial cells

Active targeting enhances cellular uptake, increases intracellular drug retention, reduces required doses, and helps overcome heterogeneity in the EPR effect [91†source].

4.3. Stimuli-Responsive Delivery

Advanced stimuli-responsive nanoparticles are designed to release benzimidazoles in response to specific triggers in the tumor microenvironment (TME):

- **pH-responsive systems:** Exploit the acidic tumor milieu (~pH 6.5) to release drugs preferentially at the tumor site.
- **Enzyme-responsive systems:** Utilize overexpressed enzymes such as MMPs to cleave linkers and release the payload.
- **Redox-responsive systems:** Leverage higher intracellular glutathione (GSH) levels to trigger disulfide bond cleavage and drug release.
- **External stimuli:** Light, heat, and magnetic fields can be applied to control drug release spatially and temporally.

These strategies collectively enhance precision, minimize off-target effects, and improve the therapeutic performance of benzimidazole-loaded nanoparticles.

V. PRECLINICAL EVIDENCE

5.1. Albendazole Nanoparticles

Albendazole (ABZ) is a benzimidazole derivative known for its antimitotic and anti-angiogenic activity, primarily through binding to β-tubulin and disrupting microtubule polymerization. Its poor aqueous solubility and extensive first-pass metabolism have limited clinical application as an anticancer agent. Encapsulation in polymeric nanoparticles such as PLGA, lipid nanoparticles, and nanostructured lipid carriers (NLCs) significantly improves pharmacokinetics and therapeutic efficacy. Preclinical xenograft models of breast and lung cancer demonstrated that ABZ-loaded nanoparticles:

- Accumulate preferentially in tumor tissues via the EPR effect.
- Exhibit greater antitumor efficacy than free ABZ.
- Reduce microvessel density and inhibit tumor angiogenesis.
- Show lower systemic toxicity and enhanced tolerability.
- These studies illustrate the potential to repurpose ABZ as a targeted anticancer therapy using nanoparticle formulations.

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5.2. Mebendazole Nanoparticles

Mebendazole (MBZ) has demonstrated anticancer activity against glioblastoma, colorectal cancer, and melanoma through microtubule disruption, induction of apoptosis, and inhibition of angiogenesis. Poor oral bioavailability has been a major barrier to its clinical application. Nanoparticle strategies, including polymeric micelles, solid lipid nanoparticles, and nanosuspensions, have improved solubility, BBB penetration, and cytotoxicity in preclinical models. For example, MBZ encapsulated in polymeric micelles:

- Dramatically improves aqueous solubility.
- Enhances penetration of the blood–brain barrier, critical for brain tumors.
- Increases cytotoxicity against glioblastoma cells relative to free MBZ.

These findings suggest MBZ-loaded nanoparticles could be an effective therapy for resistant and hard-to-treat tumors.

5.3. Thiabendazole Nanoparticles

Thiabendazole (TBZ), historically used as an antifungal, has shown potential anticancer effects, particularly via anti-angiogenic mechanisms targeting VEGF-mediated pathways. TBZ-loaded lipid nanoparticles enhance oral absorption, improve pharmacokinetics, and increase therapeutic index by controlled drug release and reduced systemic toxicity. Although less extensively studied, TBZ nanoparticles represent a promising avenue for further preclinical research.

VI. CLINICAL POTENTIAL AND CHALLENGES

6.1. Clinical Translation

Preclinical evidence strongly supports the anticancer potential of benzimidazole-loaded nanoparticles. Although clinical development remains in early stages, the success of albumin-bound paclitaxel (Abraxane®) demonstrates that poorly soluble drugs can be reformulated as nanomedicines with high therapeutic and commercial success. Similar strategies could transform benzimidazole derivatives into effective oncology therapeutics. Furthermore, combinatorial approaches with conventional chemotherapy, immunotherapy, or radiotherapy may overcome resistance and enhance efficacy. For instance, co-delivery of albendazole nanoparticles with doxorubicin has shown synergistic cytotoxic effects in preclinical studies.

6.2. Challenges

Despite promising results, several challenges remain in translating benzimidazole nanomedicines:

- **Manufacturing:** Scaling up nanoparticle synthesis requires consistent batch-to-batch quality, stability, and reproducibility.
- **Regulatory hurdles**: Comprehensive data on safety, long-term toxicity, and pharmacokinetics are required for approval.
- **Safety concerns**: Nanoparticles may accumulate in organs such as liver, spleen, and kidneys, potentially causing toxicity. Immunogenicity of functionalized carriers must be carefully evaluated.
- **EPR variability:** The enhanced permeability and retention effect varies among patients and tumor types, affecting passive targeting efficiency.
- **Cost and accessibility:** Nanomedicine development is more expensive than conventional drugs, potentially limiting widespread application.

Addressing these challenges will require multidisciplinary efforts, integrating nanotechnology, pharmacology, oncology, and regulatory expertise.

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VI. FUTURE PERSPECTIVES

Future research should focus on hybrid nanocarriers that combine polymeric and lipid-based systems, personalized approaches guided by tumor biomarkers, and clinical evaluation of benzimidazole nanoformulations. Integration of artificial intelligence and machine learning can accelerate rational nanoparticle design, optimize targeting efficiency, and predict pharmacokinetic profiles. Innovations in tumor-targeted delivery, stimuli-responsive release, and combination therapies could further enhance efficacy and reduce toxicity.

VII. CONCLUSION

Benzimidazole derivatives are a versatile and underutilized class of anticancer agents. Their limitations, particularly poor solubility and bioavailability, can be effectively overcome through nanoparticle-based delivery. Nanocarriers enhance pharmacokinetics, enable targeted and controlled release, and improve tumor accumulation, leading to superior antitumor activity in preclinical models. With continued optimization, clinical evaluation, and integration with modern technologies, benzimidazole-loaded nanoparticles hold great promise as a novel class of targeted cancer therapeutics

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