

## Emerging Role of Benzimidazole-Loaded Nanoparticles in Targeted Drug Delivery and Cancer Therapy: A review

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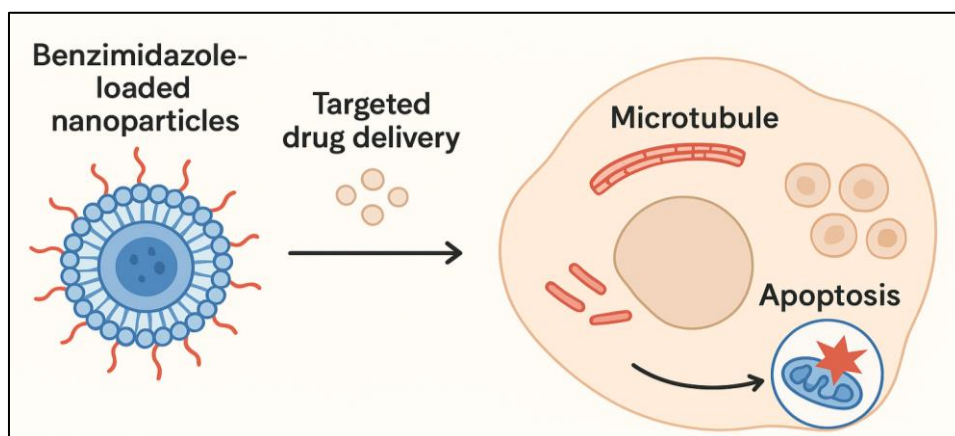
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### Abstract

Benzimidazole derivatives are a privileged heterocyclic scaffold with well-established pharmacological activities, including antimicrobial, antiviral, and anticancer properties. Despite their therapeutic promise, many benzimidazole compounds face challenges such as poor aqueous solubility, limited bioavailability, and off-target toxicity, which hinder their clinical translation. Recent advances in nanotechnology have provided innovative solutions to these limitations through the development of benzimidazole-loaded nanoparticles. Nanoparticle-based formulations improve the solubility, stability and pharmacokinetic profile of benzimidazoles while enabling targeted and sustained delivery to tumor tissues. This review provides a comprehensive analysis of the emerging role of benzimidazole-loaded nanoparticles in drug delivery and cancer therapy. It covers the pharmacological significance of benzimidazoles, nanocarrier platforms, targeting mechanisms, preclinical evidence, clinical outlook, challenges, and future perspectives. Emphasis is placed on how nanotechnology enhances the therapeutic performance of benzimidazoles through improved bioavailability, tumor targeting via passive and active strategies, and controlled drug release.

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

### Graphical Abstract



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## 1. Introduction

Cancer continues to be one of the leading causes of morbidity and mortality worldwide, with an estimated 19.3 million new cases and 10 million deaths reported in 2020 <sup>[1]</sup>. Chemotherapy remains a cornerstone of treatment, but conventional chemotherapeutic agents often suffer from poor selectivity, systemic toxicity, and resistance development <sup>[2]</sup>. These limitations highlight the urgent need for novel therapeutic scaffolds and advanced drug delivery strategies.

Benzimidazole derivatives have gained attention as promising anticancer candidates due to their ability to interact with diverse biological targets, particularly microtubules and kinases <sup>[3]</sup>. Drugs such as albendazole, mebendazole, and thiabendazole, originally developed as anthelmintics, have demonstrated potent anticancer effects in preclinical models <sup>[4]</sup>. However, the clinical translation of these agents has been restricted by poor aqueous solubility and low oral bioavailability <sup>[5]</sup>.

Nanoparticle-based drug delivery systems (DDS) offer a potential solution to these barriers. Nanocarriers can encapsulate benzimidazoles, enhance their solubility and circulation time, and preferentially deliver them to tumour tissues via the enhanced permeability and retention (EPR) effect <sup>[6]</sup>. Additionally, surface modification allows active targeting of tumour-specific receptors, improving therapeutic outcomes while reducing systemic toxicity <sup>[7]</sup>. This review critically discusses the pharmacological importance of benzimidazoles, recent advances in nanoparticle-based delivery, and their translational relevance for targeted cancer therapy.

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## 2. Benzimidazole Pharmacology and Anticancer Potential

### 2.1. Structure and pharmacophore

Benzimidazole is a bicyclic heteroaromatic scaffold consisting of a fused benzene and imidazole ring <sup>[8]</sup>. The presence of two nitrogen atoms confers the ability to form hydrogen bonds and interact with diverse biomolecular targets. Structural modifications at the C-2 and C-5 positions often lead to improved pharmacological activity <sup>[9]</sup>.

### 2.2. Mechanism of anticancer action

Several benzimidazole derivatives, particularly albendazole and mebendazole, exert anticancer activity through disruption of microtubule polymerization <sup>[10]</sup>. This leads to mitotic arrest, inhibition of cell proliferation, and induction of apoptosis. Other mechanisms include inhibition of angiogenesis, modulation of signalling pathways such as Wnt/ $\beta$ -catenin, PI3K/AKT, and induction of reactive oxygen species (ROS) <sup>[11]</sup>.

### 2.3. Clinical limitations

Despite their broad pharmacological spectrum, benzimidazoles suffer from poor oral absorption due to low aqueous solubility and extensive first-pass metabolism <sup>[12]</sup>. Their plasma concentrations are often insufficient to achieve therapeutic anticancer effects, limiting their clinical utility. This pharmacokinetic drawback underscores the need for advanced drug delivery systems <sup>[13]</sup>.

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## 3. Nanoparticle-based drug delivery

### 3.1. Rationale for nanoparticles

Nanoparticles (NPs) provide multiple advantages over conventional formulations: enhanced solubility, prolonged circulation, tumour targeting, and controlled drug release <sup>[14]</sup>. Particle size (50–200 nm) allows accumulation in tumour tissues via the EPR effect, while surface modifications enable receptor-mediated targeting <sup>[15]</sup>.

### 3.2. Types of nanocarriers for benzimidazoles

#### 3.2.1. Polymeric nanoparticles

Biodegradable polymers such as PLGA, PEG, and chitosan have been widely used to encapsulate albendazole and mebendazole <sup>[16]</sup>. Polymeric NPs offer sustained release and protection from enzymatic degradation.

### 3.2.2. Lipid-based carriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been developed for benzimidazoles to improve solubility and oral bioavailability [17]. These carriers mimic physiological lipids and are biocompatible.

### 3.2.3. Protein-based carriers

Albumin nanoparticles, such as Abraxane®, serve as a clinically validated platform. Encapsulation of benzimidazoles in albumin NPs enhances tumour accumulation through albumin-mediated uptake [18].

### 3.2.4. Inorganic and hybrid nanocarriers

Metal–organic frameworks (MOFs), mesoporous silica nanoparticles, and carbon-based nanostructures have emerged as novel carriers. Their high surface area allows high drug loading and stimuli-responsive release [19].

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## 4. Targeting Strategies for Benzimidazole Nanoparticles

### 4.1. Passive Targeting via the Enhanced Permeability and Retention (EPR) Effect

One of the major rationales for using nanocarriers in oncology is the enhanced permeability and retention (EPR) effect, which is particularly pronounced in rapidly growing tumours. Unlike healthy tissues, tumours typically exhibit leaky vasculature due to aberrant angiogenesis, as well as defective lymphatic drainage. These structural abnormalities facilitate the preferential accumulation of nanoparticles within tumour tissues compared to normal tissues [20]. In the context of benzimidazole-based drugs such as albendazole (ABZ) and mebendazole (MBZ), which suffer from poor aqueous solubility and low bioavailability, the use of nanoparticles allows higher local drug concentrations at the tumour site, improving therapeutic efficacy. Passive accumulation minimizes systemic exposure and reduces dose-limiting toxicities, which are common with conventional administration of benzimidazoles. Furthermore, nanoparticles ranging between 50–200 nm are most effective in exploiting the EPR effect, as they can extravasate through fenestrated tumour vasculature while avoiding rapid renal clearance. Despite its potential, it is important to note that the magnitude of the EPR effect can vary widely among patients and tumour types, potentially influencing therapeutic outcomes [20].

### 4.2. Active Targeting

While the EPR effect provides a baseline mechanism for nanoparticle accumulation, active targeting strategies have been developed to further enhance the selectivity and uptake of benzimidazole-loaded nanoparticles. This is typically achieved by functionalizing the nanoparticle surface with ligands, antibodies, peptides, or small molecules that specifically recognize overexpressed receptors on cancer cells [21]. Examples of commonly used ligands include:

- Folic acid: Many cancers (e.g., ovarian, breast, lung) overexpress folate receptors. Folic acid-conjugated albendazole nanoparticles have demonstrated enhanced cytotoxicity in folate receptor-positive cells compared to non-targeted systems [22].
- Transferrin: Leveraging the overexpression of transferrin receptors in proliferating tumour cells, transferrin-modified benzimidazole nanoparticles enable receptor-mediated endocytosis, increasing intracellular drug delivery.
- RGD peptides (integrin ligands): Targeting integrins such as  $\alpha_v\beta_3$  allows benzimidazole nanocarriers to bind specifically to angiogenic endothelial cells, thereby disrupting tumour vasculature.

Incorporating such targeting moieties not only improves cellular uptake and retention of benzimidazole drugs but also reduces the required therapeutic dose, lowering systemic toxicity. Importantly, active targeting strategies can overcome some of the heterogeneity associated with the EPR effect by facilitating receptor-mediated endocytosis independent of vascular permeability [21,22].

### 4.3. Stimuli-Responsive Delivery

Beyond passive and active targeting, stimuli-responsive nanoparticles represent a cutting-edge approach in drug delivery systems. These nanoparticles are designed to release benzimidazoles in response to intrinsic or extrinsic stimuli characteristic of the tumour microenvironment (TME).

- pH-responsive systems: Tumours are often more acidic (pH ~6.5) compared to normal tissues (pH ~7.4). Albendazole-loaded pH-sensitive liposomes have been engineered to remain stable in systemic circulation but rapidly release their payload in acidic conditions, thereby improving drug penetration into tumour tissues [23].

- Enzyme-responsive systems: Certain enzymes, such as matrix metalloproteinases (MMPs), are upregulated in tumours. Incorporating enzyme-cleavable linkers enables benzimidazole release specifically at tumour sites.
- Redox-responsive systems: Due to the higher glutathione (GSH) concentration inside tumour cells, nanoparticles containing disulfide linkages can undergo intracellular degradation, leading to controlled release of benzimidazoles within malignant cells.
- External stimuli: Light, heat, and magnetic fields are being investigated to trigger benzimidazole release from engineered nanocarriers in a spatiotemporally controlled manner.
- Stimuli-responsive systems hold promise in achieving precision medicine, as they ensure that the drug is released only at the site of disease, minimizing off-target effects [23].

## 5. Preclinical Evidence

### 5.1. Albendazole Nanoparticles

Albendazole (ABZ), a potent benzimidazole derivative, has shown antimitotic and anti-angiogenic activity by binding to  $\beta$ -tubulin and disrupting microtubule polymerization. However, its poor solubility and extensive first-pass metabolism severely limit its clinical use as an anticancer agent. Formulation into poly (lactic-co-glycolic acid) (PLGA) nanoparticles, lipid nanoparticles, and nanostructured lipid carriers (NLCs) has resulted in dramatic improvements in pharmacokinetics and therapeutic efficacy. In preclinical xenograft models of breast and lung cancer, ABZ-loaded nanoparticles demonstrated

- Higher tumour accumulation due to EPR effect.
- Greater antitumor efficacy compared to free ABZ.
- Significant inhibition of tumour angiogenesis and micro vessel density.
- Reduced systemic toxicity and improved tolerability [24]. These findings highlight the ability of nano formulation to repurpose ABZ from an antiparasitic agent into a promising anticancer candidate.

### 5.2. Mebendazole Nanoparticles

Mebendazole (MBZ) is another benzimidazole derivative with reported anticancer activity, particularly in glioblastoma, colorectal cancer, and melanoma. Its mechanism includes microtubule disruption, apoptosis induction, and inhibition of angiogenesis. However, like ABZ, MBZ suffers from poor oral bioavailability. Polymeric micelles, solid lipid nanoparticles, and nanosuspensions have been developed to address this limitation. In glioblastoma models, MBZ encapsulated in polymeric micelles showed:

- Dramatic improvement in aqueous solubility.
- Increased blood-brain barrier (BBB) penetration, which is critical for brain tumour therapy.
- Enhanced cytotoxicity against glioblastoma cells compared to free MBZ [25].
- These results support the potential of MBZ nanoparticles as a repurposed anticancer therapy for otherwise treatment-resistant tumours.

### 5.3. Thiabendazole Nanoparticles

Thiabendazole (TBZ), while historically used as an antifungal agent, has gained attention for its potential anticancer effects. Studies show that TBZ can act as an antiangiogenic agent by targeting vascular endothelial growth factor (VEGF)-mediated pathways. TBZ-loaded lipid nanoparticles have demonstrated:

- Improved oral absorption and pharmacokinetic profile.
- Enhanced antifungal and anticancer activity compared to free TBZ.
- Better therapeutic index due to controlled release and reduced systemic toxicity [16].
- Although less extensively studied than ABZ and MBZ, TBZ nanoparticles represent an intriguing area for further research.

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## 6. Clinical Potential and Challenges

### 6.1. Clinical Translation

The preclinical evidence strongly supports the anticancer potential of benzimidazole-loaded nanoparticles, but their clinical development remains in early stages. Nonetheless, the success of Abraxane® (albumin-bound paclitaxel) provides a proof of concept that poorly soluble drugs can be reformulated into clinically approved nanomedicines with significant therapeutic and commercial success [18]. Similarly, benzimidazole derivatives could benefit from this approach, transforming them from neglected antiparasitic agents into novel oncology therapeutics. Moreover, the possibility of combining benzimidazole nanoparticles with standard chemotherapies, immunotherapies, or radiotherapy offers avenues to overcome drug resistance and improve patient outcomes. For example, albendazole nanoparticles co-delivered with doxorubicin have demonstrated synergistic cytotoxic effects in preclinical studies, suggesting combinatorial strategies may be viable in clinical settings.

### 6.2. Challenges

Despite encouraging results, several hurdles remain in the translation of benzimidazole nanoparticles from bench to bedside

- Manufacturing challenges: Scale-up of nanoparticle synthesis must ensure batch-to-batch consistency, stability, and reproducibility, which can be technically demanding and cost-intensive [19].
- Regulatory hurdles: Regulatory agencies require comprehensive data on nanoparticle safety, stability, and long-term toxicity. The relatively limited clinical experience with benzimidazole nanomedicines poses a barrier.
- Safety concerns: Nanoparticles may accumulate in organs such as the liver, spleen, or kidneys, leading to long-term toxicity. Immunogenicity of functionalized nanocarriers must also be evaluated.
- EPR variability: The EPR effect is highly heterogeneous among patients, depending on tumour type, stage, and vascularization. This variability limits the universal applicability of passive targeting and may necessitate patient stratification [20].
- Cost and accessibility: Developing nanomedicines is significantly more expensive than conventional drugs, which may limit their use in resource-constrained healthcare settings.
- Addressing these challenges requires a multidisciplinary effort, integrating advances in nanotechnology, pharmacology, oncology, and regulatory science to enable the clinical adoption of benzimidazole-loaded nanoparticles.

### *Future Perspectives*

Future research should focus on hybrid nanocarriers combining polymeric and lipid components, personalized nanomedicine approaches based on tumor biomarkers, and clinical evaluation of benzimidazole nano formulations. Integration of artificial intelligence and machine learning for nanoparticle design and optimization may accelerate translation [21].

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## 7. Conclusion

Benzimidazole derivatives represent a valuable yet underutilized class of anticancer agents. Their clinical limitations, particularly poor solubility and bioavailability, can be effectively addressed by nanoparticle-based drug delivery systems. Nanocarriers not only improve pharmacokinetics but also enable targeted and controlled delivery to tumours, significantly enhancing therapeutic efficacy. Preclinical studies demonstrate encouraging results, and with further optimization and clinical evaluation, benzimidazole-loaded nanoparticles could emerge as a novel class of targeted cancer therapeutics.

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## Compliance with ethical standards

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*Disclosure of conflict of interest*

All authors declare there are no conflicts of interest.

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