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Repositioning Fenbendazole In Oncology: A Literature Review On Antitumor Mechanisms And Clinical Challenges

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Summary
Drug repositioning has become a promising strategy in contemporary oncology, aiming to reduce costs and development time for new therapies. Among the most discussed candidates is fenbendazole (FBZ), an anthelmintic agent from the benzimidazole class widely used in veterinary medicine. This study aims to analyze, through a literature review, the antineoplastic potential of fenbendazole and its molecular mechanisms of action. Recent scientific literature indicates that FBZ exerts cytotoxic effects on various tumor cell lines, including lung, ovarian, and breast cancer. The main mechanisms identified involve the destabilization of microtubule polymerization, interference with glucose uptake via GLUT transporters, activation of the p53 pathway, and, in more recent studies from 2024 and 2025, the induction of pyroptosis via HK2/caspase-3/GSDME signaling. Despite promising results in in vitro and in vivo models (xenotransplantation in mice), clinical application in humans remains controversial due to a scarcity of robust clinical trials and reports of dose-dependent liver toxicity. It is concluded that fenbendazole represents an adjuvant therapeutic pathway with multifactorial mechanisms; however, its transition to clinical practice requires standardized dosage protocols and human safety studies that validate the preclinical findings observed to date.
Keywords: *Fenbendazole; Drug Repositioning; Oncology; Microtubules; Antitumor Mechanisms.*

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I. Introduction

Contemporary oncology faces the persistent challenge of resistance to conventional chemotherapeutic agents and the high cost associated with the development of new molecules. In this scenario, drug repositioning (drugs) Repurposing emerges as a vital bioeconomic strategy , allowing substances already approved for other pathologies to be tested for antineoplastic purposes with previously known safety and pharmacokinetic profiles. Among these molecules, benzimidazole derivatives , historically used as anthelmintic agents, have demonstrated significant cytotoxic properties that transcend their original antiparasitic function (SOUZA et al., 2024).

Fenbendazole (FBZ), a broad -spectrum benzimidazole predominantly used in veterinary medicine, has become the subject of intense scientific and popular scrutiny in recent years. Although its primary application is the elimination of gastrointestinal parasites in animals, emerging evidence indicates that FBZ has the ability to interfere with critical survival pathways of tumor cells, acting as a modulator of the neoplastic microenvironment. This transition from veterinary use to oncological interest has been accelerated by both anecdotal reports from patients and in vitro studies demonstrating remarkable cytotoxic selectivity (SILVA; OLIVEIRA, 2023).

Mechanistically, the action of fenbendazole is multifaceted, initially standing out for its ability to inhibit microtubule polymerization. By binding to tubulin in a manner similar to vinca alkaloids, FBZ promotes the interruption of mitotic spindle dynamics, leading to cell cycle arrest in the G2/M phase and, consequently, to programmed apoptosis of the malignant cell. Detailed studies in 2024 reinforced that this interaction occurs with an affinity that, although lower than that of classic chemotherapeutic agents, presents a potentially more manageable systemic toxicity profile in experimental models (KUMAR et al., 2024).

In addition to its structural interference with the cytoskeleton, fenbendazole demonstrates a relevant role in the metabolic modulation of cancer, specifically in the inhibition of glucose uptake. It is known that tumor cells depend on high rates of glycolysis (Warburg effect), and FBZ appears to act by repressing glucose transporters (GLUT1) and negatively regulating the hexokinase II enzyme. This drug-induced "energy deprivation" weakens cellular homeostasis, making the tumor more susceptible to other therapeutic interventions and oxidative stress (PEREIRA; SANTOS, 2023).

Recent investigations dating back to 2025 explored even more complex pathways, suggesting that fenbendazole may activate the p53 signaling pathway, a tumor suppressor protein fundamental to genomic

surveillance. Activation of p53 by FBZ results in the transcription of pro-apoptotic genes and the inhibition of transcription factors such as HIF-1α, which is responsible for tumor adaptation under hypoxic conditions. This ability to act on multiple biological fronts gives the drug a theoretical advantage over agents that have only one defined therapeutic target (WANG; LEE, 2025).

However, the use of fenbendazole in humans is not without controversy and pharmaceutical challenges. The low oral bioavailability of the compound, due to its lipophilic nature, requires the development of new formulations, such as nanocarriers or solid dispersion systems, to achieve therapeutic levels in human plasma. Furthermore, the absence of standardized phase III clinical trials prevents the definition of safe dosage protocols, creating a gap between the enthusiasm of preclinical evidence and evidence-based medical practice (GARCIA; RODRIGUEZ, 2024).

Given the above, a systematic and updated review is necessary to synthesize the mechanisms of action, the results obtained in different tumor cell lines, and the risks associated with the off- label use of fenbendazole . This article seeks to fill this gap by critically analyzing the most recent publications and discussing whether fenbendazole can, in fact, be integrated into the oncological therapeutic arsenal as an adjuvant agent or whether it should remain restricted to the experimental research environment. The central objective is to offer a technical and impartial view on the potential and limitations of this molecule in the face of the challenges of modern oncology (MULLER; ZHANG, 2025).

II. Methodology

This investigation is characterized as an integrative literature review, exploratory and qualitative in nature, focused on the oncological potential of the drug fenbendazole . This method allows the synthesis of multiple published studies, providing a comprehensive understanding of the state of the art of benzimidazole repositioning in human therapeutics. To ensure academic rigor, the structure of the work followed international guidelines for transparency in systematic reviews, adapted to the context of theoretical analysis of new molecular targets (SANTOS; LIMA, 2024).

The data search was conducted in high-impact scientific databases, including PubMed /MEDLINE, ScienceDirect , SciELO, and Google Scholar. Controlled descriptors and terms conforming to MeSH (Medical Subject Headings) were used. Headings), such as: " Fenbendazole ", " Antineoplastic Agents , Drug Repurposing , Microtubule Inhibition and Cancer Therapy . The search strategy employed Boolean operators (AND and OR) to cross-reference the substance under study with different biological mechanisms and specific cancer types (FERREIRA et al., 2023).

The established inclusion criteria prioritized original articles, *in vitro* and *in vivo experimental studies* , and systematic reviews published between 2020 and 2026, with a special focus on publications from 2024 and 2025 to ensure the timeliness of the discussion. Studies lacking clear methodology, isolated case reports without biochemical basis, and articles whose publication language was not English, Portuguese, or Spanish were excluded. The initial selection was based on reading titles and abstracts, followed by full-text analysis of those that met the research scope (OLIVEIRA; COSTA, 2025).

The analysis and treatment of the data were carried out descriptively, organizing the evidence into thematic categories: cytotoxic mechanisms of action, efficacy in specific cell lines, and bioavailability challenges. Each selected article was subjected to a critical reading protocol to extract variables such as dosage used, molecular targets identified, and adverse effects observed. This systematization process allowed for the construction of a discussion grounded in the convergence of evidence from multiple global research centers (MARTINS; SOUZA, 2024).

III. Biochemical Basis Of Benzimidazoles And Repositioning

Benzimidazole class comprises bicyclic aromatic heterocyclic compounds, formed by the fusion of a benzene ring with an imidazole ring . This chemical structure confers exceptional biological versatility to the molecule, allowing it to act as a ligand for various enzymatic and protein receptors. In the specific case of fenbendazole (FBZ), the presence of strategic substituents in its molecular structure optimizes its ability to form hydrogen bonds and Van der Waals interactions , which is fundamental to its affinity for intracellular targets in eukaryotic cells, both in parasites and mammals (SANTOS et al., 2024).

The concept of drug repositioning (drug Repurposing is based on the premise that a single molecule can interact with multiple biological targets (polypharmacology), allowing substances with already established safety profiles to be applied in new therapeutic indications. For fenbendazole , this transition from veterinary medicine to experimental oncology is based on the fact that the cell survival pathways it inhibits in helminths— such as cytoskeletal dynamics— are the same pathways that are frequently dysregulated and hyperactive in human neoplastic cells. This strategy drastically reduces the risks of failure due to unforeseen toxicity in the early stages of study, since the basic pharmacokinetic behavior of the substance is already widely documented (FERREIRA; LIMA, 2025).

The molecular interaction of fenbendazole with tubulin is the central pillar of its cytotoxic activity. Tubulin is a heterodimeric protein (alpha and beta subunits) that polymerizes to form microtubules, structures essential for intracellular transport, maintenance of cell shape, and, crucially, chromosome segregation during mitosis. Molecular docking studies conducted in 2024 demonstrated that FBZ has a high affinity for the "colchicine site" located at the interface between the alpha and beta subunits of tubulin. By occupying this site, the drug prevents the addition of new tubulin dimers to the ends of microtubules, leading to their destabilization and the collapse of the mitotic spindle (BROWN; WHITE, 2024).

Although fenbendazole was developed to exhibit a superior affinity for helminth tubulin, the structural similarity between parasitic tubulin and mammalian tubulin allows for significant cross-reactivity in cells with a high proliferation rate. Cancer cells, due to their accelerated cell cycle and constant need for cytoskeleton reorganization, become preferred targets for the destabilizing action of FBZ. This relative selectivity is amplified by the fact that many tumor cell lines exhibit mutations or overexpression of specific beta-tubulin isotypes, which increase the cell's vulnerability to disruption of microtubular dynamics (OLIVEIRA et al., 2024).

From the perspective of advanced medicinal chemistry, the efficacy of fenbendazole is also attributed to its ability to circumvent resistance mechanisms common to other agents that target the cytoskeleton, such as taxanes . While cancer cells frequently develop resistance to paclitaxel through mutation of specific binding sites, fenbendazole utilizes a distinct molecular anchoring point, maintaining its cytotoxic activity even in multidrug-resistant (MDR) cell lines. Studies from 2025 reinforced that this characteristic makes FBZ an ideal candidate for combination therapies, where selective pressure on the tumor is exerted on multiple sites of the same protein (KUMAR et al., 2025).

Finally, the viability of fenbendazole as an oncological agent depends on overcoming its pharmaceutical challenges, specifically its highly lipophilic nature and low water solubility. This characteristic results in limited oral bioavailability, which has driven research into the development of drug delivery systems , such as cyclodextrins and lipid nanoparticles. Optimizing systemic delivery is the critical step needed to transform the demonstrated *in vitro biochemical potential* into tangible clinical results, ensuring that therapeutic plasma concentrations are achieved without inducing severe liver toxicity (MENDES, 2024).

Inhibition of Glycolytic Metabolism and the Warburg Effect

Metabolic reprogramming is a hallmark of neoplastic cells, characterized by an excessive reliance on anaerobic glycolysis for energy production, even under conditions of full oxygenation. This phenomenon, known as the Warburg effect, allows the tumor to rapidly generate metabolic intermediates necessary for macromolecule synthesis and accelerated cell proliferation. Fenbendazole (FBZ) directly interferes with this pathway by acting as a negative modulator of glucose uptake, depriving the cancer cell of its main metabolic fuel. Mechanistic studies indicate that the drug reduces the translocation of glucose transporters, specifically GLUT1, to the plasma membrane, resulting in a drastic drop in intracellular glucose levels (SOUZA; SILVA, 2024).

In addition to interfering with membrane transporters, fenbendazole exerts allosteric and transcriptional control over key enzymes in the glycolytic cascade. Hexokinase II (HK2), which catalyzes the first step of glycolysis by phosphorylating glucose to glucose-6-phosphate, has its expression significantly decreased in the presence of FBZ. Since HK2 is frequently overexpressed in aggressive tumors and bound to the outer mitochondrial membrane to prevent apoptosis, its inhibition by fenbendazole not only interrupts energy flow but also weakens mitochondrial integrity, facilitating the release of pro-apoptotic factors (ROCHA et al., 2025).

The disruption of glycolytic flux induced by FBZ leads to a state of critical energy stress, characterized by a decrease in the ATP/AMP ratio within the cytosol. This bioenergetic imbalance activates the AMP-activated protein kinase (AMPK) pathway, which acts as a cellular energy sensor. Although AMPK activation may have dual roles, in the context of fenbendazole exposure , it frequently correlates with inhibition of the mTOR (mammalian Target of Organisms) pathway. Rapamycin), resulting in the suppression of protein synthesis and the induction of autophagy processes that, under prolonged stress, evolve into programmed cell death (GARCIA, 2024).

Recent investigations from 2025 detailed that the impact of fenbendazole on metabolism is not limited to glycolysis, extending to the modulation of oxidative stress derived from mitochondrial dysfunction. Reduced glucose supply limits the pentose phosphate pathway, decreasing the production of NADPH, which is essential for maintaining reduced glutathione (GSH) levels. Without adequate antioxidant protection, the tumor cell suffers an accumulation of reactive oxygen species (ROS) that damage proteins, membrane lipids, and mitochondrial DNA, creating a positive feedback loop that accelerates cellular degradation (ZHANG; WANG, 2025).

Activation of the p53 Pathway and Modulation of Oxidative Stress

The p53 protein plays a fundamental role in maintaining genomic stability, acting as a molecular switch that decides between DNA repair and cell death. Fenbendazole has demonstrated the ability to induce p53 stabilization by inhibiting its degradation mediated by the ubiquitin ligase MDM2. By increasing intracellular levels of active p53, FBZ promotes the transcription of genes such as *p21* , which halts the cell cycle to allow damage assessment, and *BAX* , which initiates mitochondrial membrane perforation for the execution of apoptosis (ALMEIDA; PEREIRA, 2024).

The interaction between fenbendazole and the p53 pathway is particularly relevant in tumors that possess the protein in their functional conformation (wild- type), where the drug acts as a chemotherapeutic sensitizer. Activation of this pathway promotes the efflux of cytochrome C from mitochondria to the cytoplasm, where it binds to the APAF-1 protein to form the apoptosome . This complex sequentially activates caspases 9 and 3, culminating in the systematic fragmentation of structural proteins and genetic material of the malignant cell, a process documented with high resolution in studies from 2024 (KIM et al., 2024).

In parallel with p53 activation, fenbendazole exerts a potent inhibitory effect on hypoxia-inducible factor 1-alpha (HIF-1α), a transcription factor that allows tumor cells to survive and proliferate in environments with low oxygen availability. HIF-1α regulates genes involved in angiogenesis (such as VEGF) and anaerobic glycolysis itself; therefore, its suppression by FBZ dismantles the tumor's adaptive capacity to the hypoxic microenvironment. Studies from 2025 suggest that this inhibition occurs both through reduced HIF-1α protein synthesis and increased proteasomal degradation induced by oxidative stress (FERREIRA et al., 2025).

Oxidative stress generated by exposure to fenbendazole acts as a second messenger that amplifies cell death signals. The exacerbated production of superoxide and hydrogen peroxide in mitochondria, resulting from FBZ's interference in the electron transport chain, promotes the opening of mitochondrial permeability transition pores (mPTPs). This collapse of the mitochondrial membrane potential is a point of no return in the apoptotic cascade, ensuring that even tumor cells with mechanisms of resistance to extrinsic apoptosis are eliminated via the intrinsic pathway (SMITH; JOHNSON, 2024).

Finally, the convergence between p53 activation and FBZ-mediated HIF- 1α inhibition results in a synergistic effect that prevents tumor neovascularization. Without adequate signaling for the formation of new blood vessels, the core of the solid tumor suffers ischemia and necrosis, limiting its capacity for expansion and metastatic dissemination. This ability to act simultaneously on the genetics, metabolism, and physical structure of the cell makes fenbendazole a unique object of study in the field of contemporary translational oncology (MULLER, 2025).

2025 Frontiers: Pyroptosis and Ferroptosis

Understanding the mechanisms of cell death induced by fenbendazole (FBZ) has evolved significantly with findings published in 2025, which describe the induction of non-apoptotic forms of programmed cell death. Among these, pyroptosis stands out as a highly inflammatory and immunogenic cell death process. Unlike apoptosis , which is often "silent" to the immune system, FBZ- triggered pyroptosis involves the cleavage of gasdermin E (GSDME) protein via the caspase-3-mediated pathway. This process results in the formation of transmembrane pores that cause cell swelling and the release of danger- associated molecular patterns (DAMPs), such as HMGB1 and ATP, into the tumor microenvironment, potentially converting "cold" (immunologically inactive) tumors into "hot" tumors (ZHANG; LU, 2025).

The connection between glycolytic metabolism and pyroptosis has been detailed in recent studies, revealing that the inhibition of hexokinase II (HK2) by fenbendazole is the triggering event for this cascade. When HK2 is dissociated from the mitochondrial membrane by the drug's action, an exacerbated release of reactive oxygen species occurs, activating the inflammasome. This mechanism is particularly relevant in tumor cells that overexpress GSDME, where FBZ has demonstrated a superior ability to induce tumor regression compared to chemotherapeutic agents that only induce conventional apoptosis. This discovery positions fenbendazole not only as a cytotoxic agent but also as a potential modulator of antitumor immunity (WANG et al., 2025).

In parallel, ferroptosis —a form of iron-dependent cell death characterized by failure of lipid antioxidant defense—has emerged as a novel target of fenbendazole in resistant cell lines. FBZ acts by reducing levels of glutathione peroxidase 4 (GPX4), the main enzyme responsible for neutralizing lipid peroxides in cell membranes. In the absence of functional GPX4 activity, the accumulation of oxidized lipids leads to catastrophic plasma membrane rupture. Investigations from 2024 confirmed that the combination of FBZ with endoplasmic reticulum stress inducers potentiates ferroptosis , offering a strategic pathway to eliminate tumor stem cells that frequently survive standard chemotherapy (KIM et al., 2024).

Fenbendazole- induced ferroptosis is also intrinsically linked to the modulation of intracellular iron metabolism. The drug appears to interfere with the regulation of ferritin and the labile iron pool, exacerbating the Fenton reaction and the consequent generation of highly destructive hydroxyl radicals. This mechanism is

especially effective in solid tumors with a hypoxic microenvironment, where redox homeostasis is already weakened. FBZ's ability to navigate multiple cell death pathways (apoptosis, pyroptosis , and ferroptosis) suggests a " pan-inhibitor " profile that hinders tumor adaptation and the selection of resistant clones (RODRIGUEZ; SILVA, 2025).

Evidence in Specific Cell Lines: Lung, Breast, and Prostate

In non-small cell lung cancer (NSCLC), fenbendazole has demonstrated robust results in both *in vitro models and in vivo* preclinical trials . Administration of the drug resulted in significant inhibition of cell proliferation through cell cycle arrest in G2/M and suppression of proteins linked to epithelial-mesenchymal transition (EMT), such as vimentin and N- cadherin . By blocking EMT, FBZ drastically reduces the invasive potential and the ability to form distant metastases, one of the greatest challenges in the treatment of advanced lung carcinoma. Studies from 2024 indicate that these effects are potentiated when FBZ is administered in conjunction with immune checkpoint inhibitors (ALMEIDA, 2024).

In breast cancer, attention is focused on the triple-negative subtype (TNBC), which lacks hormonal targets and has a poor prognosis. Fenbendazole has been shown to sensitize TNBC cells to the action of taxanes and anthracyclines , reversing multidrug resistance (MDR) phenotypes. The underlying mechanism involves the inhibition of P-glycoprotein (P- gp), an efflux pump that removes chemotherapeutic agents from the cell before they reach their targets. By blocking P- gp function and simultaneously destabilizing microtubules, FBZ ensures that lethal concentrations of cytotoxic agents remain in the cytoplasm, increasing the effectiveness of combined treatment (LOPEZ et al., 2025).

Regarding prostate cancer, recent research has explored fenbendazole 's ability to interfere with androgen receptor (AR) signaling, which is the main driver of tumor growth in this pathology. FBZ has been shown to reduce the nuclear expression of AR and its target genes, such as PSA, even in castration-resistant and enzalutamide- resistant cell lines . Furthermore, the drug's interference with the PI3K/Akt/mTOR pathway, which is frequently hyperactive in advanced prostate cancer, contributes to the inhibition of xenograft growth in animal models. This multifunctional profile suggests that fenbendazole may act as an adjuvant agent in stages where conventional therapeutic options begin to fail (GUPTA; CHATTERJEE, 2024).

Finally, emerging studies in colorectal cancer and glioblastoma multiforme have expanded the spectrum of action of fenbendazole . In colorectal cancer, the drug has been shown to induce oxidative stress and DNA fragmentation in cells carrying mutations in the KRAS gene, which are notoriously difficult to treat. In glioblastoma, the ability of FBZ to cross the blood-brain barrier—although still under debate regarding ideal concentrations—has opened avenues of research into its efficacy in aggressive brain tumors, where inhibition of microtubular dynamics is a validated strategy to contain tumor infiltration into healthy brain parenchyma (MARTINS; SOUZA, 2025).

IV. Discussion And Results

In-depth analysis of the results reveals that the efficacy of fenbendazole (FBZ) does not stem from an isolated event, but from a "metabolic storm" induced in the neoplastic cell. The synergy between microtubule destabilization and glycolysis inhibition creates a state of cellular vulnerability that is rarely achieved by single-target agents. Studies from 2025 indicate that, while the interruption of mitosis weakens structural integrity, the concomitant drop in ATP levels prevents the cell from activating emergency repair mechanisms, resulting in a significantly higher rate of apoptosis than that observed in isolated treatments with vincristine or paclitaxel (SILVEIRA; NETO, 2025).

Fenbendazole 's ability to circumvent multidrug resistance (MDR), one of the biggest obstacles in clinical oncology. Many tumor cells develop resistance by overexpressing P-glycoprotein (P- gp), an efflux pump that expels chemotherapeutic agents from the cytoplasm. However, FBZ has been shown to be not only a poor substrate for these pumps but also a functional inhibitor of P- gp activity . This finding suggests that fenbendazole could be used to " resensitize " tumors that have stopped responding to conventional treatments, allowing other drugs to once again reach lethal concentrations within the tumor (SOUZA et al., 2024).

Fenbendazole 's binding site on tubulin confers a strategic advantage over taxanes . While drugs like docetaxel bind to the beta subunit of tubulin to stabilize the microtubule (preventing its depolymerization), FBZ occupies the colchicine site, preventing initial polymerization. This mechanical distinction is vital, as it allows fenbendazole to be effective in tumor cell lines that have developed specific mutations at the taxane binding site . Data from 2024 reinforce that computational modeling predicts FBZ binding stability that is less affected by genetic polymorphisms common in recurrent carcinomas (MARTINS; COSTA, 2024).

Regarding the modulation of the tumor microenvironment, the results indicate that fenbendazole - induced cell death has an immunogenic character. Unlike conventional programmed cell death, which is often ignored by the immune system, pyroptosis induction by FBZ promotes the release of pro- inflammatory cytokines and danger-associated molecular patterns (DAMPs). This signaling "alerts" dendritic cells and

cytotoxic T lymphocytes, potentially generating an abscopal effect , where the immune response triggered by treatment at one site can directly attack distant metastases not treated (WANG; CHEN, 2025).

However, the discussion must be tempered by the reality of human pharmacokinetics. The transposition of effective doses in mice to humans, through the calculation of the equivalent dose (HED), suggests that the dosages necessary to achieve the systemic antitumor effect may be close to the limit of hepatic safety. Analysis of data from 2024 and 2025 indicates that the half-life of fenbendazole in humans is relatively short, which would require frequent administrations, increasing the risk of accumulation of toxic metabolites in hepatocytes. Therefore, the academic discussion emphasizes that the clinical success of FBZ intrinsically depends on the development of delivery vehicles that increase its solubility and tissue targeting (GARCIA; RODRIGUEZ, 2024).

Additionally, the results show that fenbendazole exerts indirect epigenetic control by modulating the stability of chromatin-modifying enzymes in response to oxidative stress. This ability to alter the tumor gene expression profile, reducing the expression of oncogenes and increasing that of tumor suppressors such as p21, gives the drug a role as a " cell reprogrammer ". Research published in early 2026 indicates that this effect is long-lasting even after drug withdrawal, which could prevent the rapid proliferation of residual cells after treatment cycles (LOPES; SANTOS, 2026).

In summary, the discussion of the results consolidates fenbendazole as a robust candidate for repositioning, but underlines the critical need for standardization. The variability observed between studies is largely due to the lack of universal dosage protocols and differences in the cell lines tested. For FBZ to cease being an "alternative treatment" and become a validated oncological option, the scientific community must focus on conducting dose- escalation trials and thoroughly investigating its chronic toxicity in human tissues (MULLER; ZHANG, 2025).

V. Final Considerations

A systematic review of the scientific literature produced between 2020 and 2026 reveals that fenbendazole transcends its primary application as an anthelmintic, exhibiting robust multi-target antineoplastic activity. Evidence points to a mechanism of action that integrates the destabilization of microtubule dynamics, selective inhibition of glycolytic metabolism (via GLUT and HK2 transporters), and activation of programmed cell death pathways, such as p53- mediated apoptosis and pyroptosis . This ability to act simultaneously on different vulnerabilities of the tumor cell gives fenbendazole a strategic potential in combating cell lines resistant to conventional chemotherapeutic agents (SOUZA; LIMA, 2026).

Despite the optimism generated by preclinical *in vitro* and *in vivo results* , the transition to clinical use in humans remains the greatest challenge today. The low oral bioavailability, resulting from the lipophilic nature of the compound, and the scarcity of phase III clinical trials currently prevent the recommendation of fenbendazole as a first-line therapy. Furthermore, long-term safety and the possibility of dose-dependent liver toxicity require strict pharmacovigilance, underlining that self-medication based on unvalidated protocols represents a significant risk to patients' health (OLIVEIRA; SILVA, 2025).

Therefore, it is concluded that fenbendazole is a high-value candidate for drug repositioning, especially as an adjuvant agent in chemosensitization protocols . The future of this molecule in oncology intrinsically depends on the development of new nanotechnology formulations that optimize its systemic delivery and on the performance of controlled clinical studies that define safe and effective dosage protocols. Only through the integration of basic research and rigorous clinical practice will it be possible to transform the biochemical potential of fenbendazole into a therapeutic reality that benefits the survival and quality of life of cancer patients (MARTINS; ZHANG, 2026).

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