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Review

Oral Fenbendazole for Cancer Therapy in Humans and Animals

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Abstract. *Fenbendazole is a benzimidazole anthelmintic agent commonly used to treat animal parasitic infections. In humans, other benzimidazoles, such as mebendazole and albendazole, are used as antiparasitic agents. Since fenbendazole is not currently approved by the FDA or EMA, its pharmacokinetics and safety in humans have yet to be well-documented in medical literature. Despite this, insights can be drawn from existing in vitro and in vivo animal studies on its pharmacokinetics. Given the low cost of fenbendazole, its high safety profile, accessibility, and unique anti-proliferative activities, fenbendazole would be the preferred benzimidazole compound to treat cancer. To ensure patient safety in the repurposing use of fenbendazole, it is crucial to perform clinical trials to assess its potential anticancer effects, optimal doses, therapeutic regimen, and tolerance profiles. This review focuses on the pharmacokinetics of orally administered fenbendazole and its promising anticancer biological activities, such as inhibiting glycolysis, down-regulating glucose uptake, inducing oxidative stress, and enhancing apoptosis in published experimental studies. Additionally, we evaluated the toxicity profile of fenbendazole and discussed possibilities for improving the bioavailability of the drug, enhancing its efficacy, and reducing potential toxicity.*

Fenbendazole, also known as methyl N-(6-phenylsulfanyl-1H-benzimidazole-2yl), is currently used as an antiparasitic therapeutic agent in dogs and other animals. In humans, other benzimidazoles, such as mebendazole and albendazole, are used as antiparasitic agents (1). Fenbendazole exerts its antiparasitic effects primarily in the anterior intestine by depolymerizing microtubules, inhibiting intestinal secretory vesicle transport. Fenbendazole binds to beta-tubulin in parasites, causing microtubule destabilization and hindering tubulin polymerization. This destabilization disrupts cellular function, such as glucose uptake, thereby affecting the energy management of parasites. Due to its poor absorption by oral administration, fenbendazole is particularly effective for targeting intestinal parasites (2).

In August 2016, fenbendazole garnered global attention as a potential anti-cancer therapy following the complete recovery success story of Joe Tippens, who was diagnosed with small-cell lung cancer. At the time, Tippens was undergoing a clinical trial for a novel anti-cancer drug. Meanwhile, under the guidance of a veterinarian, Tippens began self-administering 222 mg fenbendazole orally, along with vitamin E supplements, CBD oil, and bioavailable curcumin. After three months of self-administration, a PET scan revealed no detectable cancer cells in his body. Notably, Tippens was the only patient cured of cancer among the 1,100 clinical trial participants (3). While the Joe Tippens case is compelling, it remains an anecdotal report. It underscores the need for rigorous clinical trials to validate the efficacy and safety of fenbendazole as an anti-cancer therapy.

The anti-cancer activity of fenbendazole has been studied across many cell lines, demonstrating anti-tumor effects against multiple cancer types (Table I) (4-7). Additionally, fenbendazole has shown efficacy against 5-FU, paclitaxel, and docetaxel-resistant cancer cells (5, 8, 9). Compared to albendazole, fenbendazole was more effective against 5-FU-resistant colorectal cells, likely due to its intervention in glycolysis (5).

Although fenbendazole exhibits promising anti-cancer effects, experimental studies indicated its poor water solubility has hindered its therapeutic performance. When

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Table I. *Studies of fenbendazole in vivo and in vitro cell lines.*

Cancer type; Cell lines	Experimental model	Fenbendazole dose	Results	References
Skin cancer; A375	*In vitro*	1,2, and 4 μM for 24-48 hours	Increased levels of γH2AX, indicating DNA damage. Confirmation of antiproliferative activity of fenbendazole, microtubule disruption, induced cell cycle arrest at G_2/M phase. Increase of p53 activity by down-regulating Mdm2 and MdmX expression.	(35)
Lung cancer; A549, H460, and H1299 cells	*In vitro*	0.001, 0.01, 0.1, 1, 10, and 100 μM for 48 hours.	50% tumor inhibition at 1 μM. Tubulin destabilization activity was observed at 1 and 10 μM. Induced cell cycle arrest in the G_2/M phase.	(10)
Non-small cell lung cancer; H460 and A549 cells in *nu/nu* mice	*In vitro* and *in vivo*	*In vitro*: 1 μM for 48 hours *In vivo*: 1 mg/mouse, *p.o.*, every second day for 12 days	Significant reduction in number of tumor cell colonies. Reduction of tumor size and weight. Confirmation of microtubule disruption, induced cell cycle arrest in G_2/M phase.	(4)
Non-small cell lung cancer; A549, H460	*In vitro*	1 μM for 48 hours	Observed tumor growth inhibition and apoptotic cancer cell death, possibly by inhibiting proteasomal function. Fenbendazole demonstrated cytotoxicity towards tumor cells but retained non-toxicity to normal cells. Observed p53 induction and up-regulation of p53 target genes.	(58)
Cervical cancer; HeLa, C-33A, CaSki	*In vitro*	0.1, 1, 10 μM for 48 hours	Fenbendazole inhibited tumor colony formation and induced cell apoptosis and arrest. It was more toxic to HeLa cells and less toxic to normal cells. Down-regulation of MMP2 and MMP9 expression inhibited HeLa cell migration and invasion.	(37)
Colorectal cancer; SNU-C5	*In vitro*	0.50 μM for 3 days	Triggered cancer cell apoptosis through mitochondrial injury and the caspase 3-PARP pathway. Increased p53 expression, leading to p53-mediated apoptosis.	(5)
Colorectal cancer; SNU-C5/5-FU resistant cells	*In vitro*	4.09 μM for 3 days	Triggered cancer cell apoptosis without affecting p53 expression. Enhanced p53-independent apoptosis and ferroptosis-augmented apoptosis.	(5)
Lymphoma; P493-6B cells in SCID mice	*In vivo* and *in vitro*	150 ppm fenbendazole, with diet and/or with vitamins	Observed low anti-cancer effect when fenbendazole was administered alone. Tumor growth inhibition was higher in mice administered fenbendazole with a vitamin-supplemented diet.	(59)
Leukemia; HL60 in mice	*In vivo* and *in vitro*	0.1, 0.2, and 0.5 μM for 1-6 days	Higher concentrations of fenbendazole led to apoptosis. In as little as 3 days, lower concentrations (0.1 μM) caused leukemia cells to convert to granulocytes and induced apoptosis. At 72 hours, fenbendazole exhibited 14.5-fold selectivity in killing HL60 cells over healthy human bone marrow stem (BMSC) cells.	(6)
Hepatocellular carcinoma; H4IIE cells	*In vitro*	1.25 μM for 48 hours	Growth suppression in cancer cells actively growing. Induced p21-mediated apoptosis in tumor cells.	(7)
Breast cancer; MCF-7	*In vitro*	1,2, and 4 μM for 48 hours	Increased levels of γH2AX, indicating DNA damage. Confirmation of antiproliferative activity of fenbendazole, microtubule disruption, induced cell cycle arrest at G_2/M phase. Increase of p53 activity by down-regulating Mdm2 and MdmX expression.	(35)

Table I. *Continued*

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Cancer type; Cell lines	Experimental model	Fenbendazole dose	Results	References
Breast cancer; EMT6 mouse mammary tumor cells in female BALB/cRw mice	*In vitro* and *in vivo*	0.11, 0.33, 1.0, and 3.0 μM for 8 days *in vitro* 150 ppm in diet and 50 mg/kg/day, *i.p.* for 2 days *in vivo*	Higher drug concentrations demonstrated cytotoxicity towards tumors and high tumor inhibition. Tumor appearance also changed, suggested to be due to disruption of tubulin microtubule equilibrium. No change in tumor growth or metastatic pattern. No change in tumors with radiation.	(27)

administered orally, fenbendazole struggles to reach systemic circulation and, subsequently, the therapeutic levels necessary to impact tumors (10-12). Addressing pharmacokinetic limitations is crucial to repurposing fenbendazole for cancer treatment.

This review focuses on the pharmacokinetics of fenbendazole when administered orally and its promising anticancer biological activities, such as inhibiting glycolysis, down-regulating glucose uptake, inducing oxidative stress, and enhancing apoptosis. In addition, we evaluate the toxicity profile of fenbendazole and discuss possibilities for improving the bioavailability of the drug, enhancing its efficacy, and reducing potential toxicity. This comprehensive review aims to provide a detailed understanding of fenbendazole's potential as a repurposed anti-cancer agent and outline the necessary steps for its clinical application.

Anti-cancer Mechanisms and Targets of Fenbendazole

Studies attribute the anti-cancer mechanisms of fenbendazole to increasing p53 activation, inhibiting the GLUT1 transporter and hexokinase, and reducing glucose uptake in cancer cells (4). Enhanced glycolysis is a crucial signal of tumor progression (13-15). Under anaerobic conditions, glycolysis produces lactate, which increases acidification in the tumor microenvironment and leads to drug resistance (16). Metabolic disturbances, such as glutamine overuse, further enhance glycolysis, creating a feedback loop for tumor growth (15, 17). Fenbendazole has been found to inhibit glucose uptake, resulting in reduced lactate levels (4). Thus, fenbendazole can serve as a viable treatment for drug-resistant cancer cells.

Fenbendazole exhibits several other mechanisms contributing to its anti-cancer effects, primarily by disrupting energy metabolism. It functions as a microtubule destabilizing agent, impairs proteasomal function, and inhibits glucose metabolism. Glucose, a primary energy source for tumor cells, is metabolized through aerobic glycolysis and delivered across the cell membrane *via* the GLUT1 transporter (18). Unlike normal cells, cancer cells perform glycolysis to metabolize glucose to lactate even under aerobic conditions (13, 16, 19). Although aerobic glycolysis is not an efficient method of supplying energy and appears to produce less ATP than oxidative phosphorylation, it provides essential materials for tumor cell growth, such as nucleotides, amino acids, and lipids (20, 21). Additionally, the ATP/ADP and NADH/NAD+ ratios in tumor cells remain high, indicating sufficient ATP supply through glycolytic tumor metabolism (22).

The GLUT1 transporter has been highly expressed in 99% of patients with squamous cell carcinoma and 50% of patients with adenocarcinoma (23-25), leading to being proposed as a promising therapeutic target in cancer therapy (26). Fenbendazole induces mitochondrial translocation of p53, indicating activation of the p53-p21 pathway, which inhibits GLUT transporter expression and prevents glucose uptake in cancer cells (4). Through p53 activation, fenbendazole is believed to impede hexokinase II (HKII) (4, 7), the first glycolytic pathway enzyme critical for cancer cell growth. However, another study did not observe inhibition of HKII activity at 1 and 10 μM fenbendazole (10). As a primary enzyme in glucose metabolism, the inhibition of HKII would prevent tumor development (4, 27, 28). Therefore, fenbendazole's actions on HKII warrant further exploration. Thus, through targeting GLUT1, HKII, and glycolysis, fenbendazole can lead to cancer cell starvation and reverse drug resistance, aiding cancer treatment.

In addition to glycolysis inhibition, fenbendazole induces apoptosis in cancer cells (4-7). In colorectal cancer (CRC) cells, fenbendazole triggers apoptosis through mitochondrial injury and the caspase 3-PARP pathway. In wild-type CRC, fenbendazole activates p53-mediated apoptosis by increasing p53 expression. Additionally, it induces necrosis, autophagy, and ferroptosis. In 5-FU-resistant CRC, fenbendazole triggers apoptosis without affecting p53 expression, likely enhancing p53-independent ferroptosis-augmented apoptosis (5).

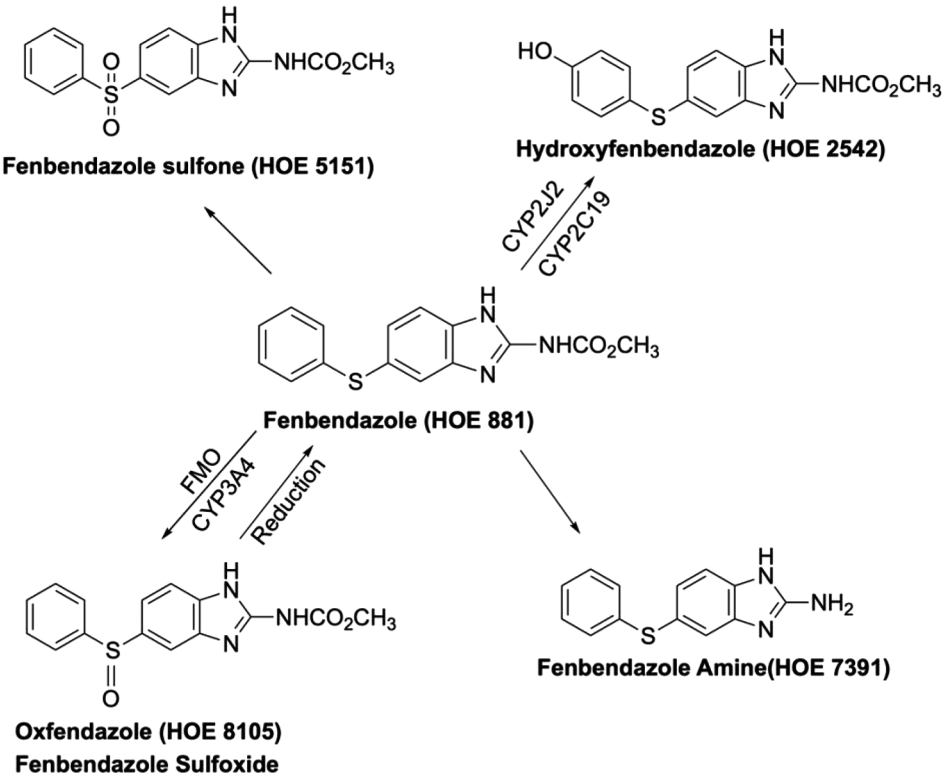

Figure 1. *The metabolites of fenbendazole. Structures based on the metabolic scheme shown in the Fenbendazole UN FAO document (42).*

Fenbendazole also acts as a microtubule destabilizing agent. Microtubule-targeting agents are promising cancer treatments due to the microtubules' roles in mitosis, cell structure maintenance, and other cellular events (29-33). Some cancer therapy drugs inhibit microtubule polymerization (vincristine, vinblastine), while others stabilize microtubules (paclitaxel, docetaxel), leading to apoptosis and metaphase arrest (34). Fenbendazole shows microtubule depolymerizing activity in human cancer cell lines and demonstrates anticancer effects *in vitro* and *in vivo* (4, 10, 35). Fenbendazole induces cell cycle arrest in the G_2/M phase (4, 36) and demonstrates tubulin destabilization activity at concentrations of 1 and 10 μM, with more cell cycle arrest demonstrated at higher concentrations (10 μM) (10).

When administered orally at micromolar concentrations, fenbendazole induces cytotoxicity and effectively blocks cancer cell growth. Fenbendazole also causes oxidative stress and activates the MEK3/6-p38MAPK pathway, inhibiting cancer cell proliferation and enhancing apoptosis. Fenbendazole reduces toxicity to normal cells while maintaining its anti-cancer effects of impairing energy metabolism and restraining cancer cell migration and invasion (37). Beyond oncology, fenbendazole shows potential in treating pulmonary fibrosis by inhibiting the progression of bleomycin-induced lung fibrosis (36).

Pharmacokinetics of Fenbendazole

Given that fenbendazole has not been approved for regulatory use in humans, pharmacokinetic data for this drug is limited. While no clinical trials have tested fenbendazole in humans, insights can be drawn from *in vitro* and *in vivo* animal studies. The FDA recently granted a fast-track designation for developing oxfendazole, a major metabolite of fenbendazole, to treat human trichuriasis. Pharmacological studies of oxfendazole can help supplement the understanding of fenbendazole's pharmacokinetics in humans.

Fenbendazole undergoes partial absorption in the liver, where it is rapidly metabolized by flavin-monooxygenase (FMO) and CYP3A4 enzymes to become its sulfoxide derivative, oxfendazole (fenbendazole sulfoxide) (38, 39). Additionally, CYP2J2 and CYP2C19 enzymes metabolize fenbendazole into hydroxyfenbendazole (40). Another metabolic pathway converts fenbendazole into fenbendazole sulfone (41, 42) by pre-systemic and systemic metabolism (43). Although fenbendazole sulfone predominates in the plasma following administration (41), oxfendazole is the primary metabolite responsible for the biological activity of fenbendazole (44). Through systemic metabolism (43), oxfendazole is reduced back to fenbendazole (44) rather than first-pass metabolism (Figure 1) (45).

Table II. *Pharmacokinetic profile of fenbendazole when administered orally to male rats at a dose of 10 mg/kg. After the peak concentration, the drug concentration remained lower than 0.1 μg/ml (10).*

Parameter	Oral Fenbendazole (10 mg/kg)
T_{max}(h)	0.25±0.00
$T_{1/2}$	8.23±2.49
C_{max} (μg/ml)	0.32±0.24
AUC_{last} (μg·h/ml)	0.73±0.05
AUC_{∞} (μg·h/ml)	0.88±0.17

In male rats, the maximum concentration of fenbendazole was observed to be 0.32 μg/ml (Table II) (10). After hepatic metabolism, fenbendazole and its metabolites are excreted *via* the feces and urine. A study performed in cattle found that 36% of orally administrated fenbendazole was recovered in the feces, with none in urine. When administered intravenously, over 50% of the fenbendazole dose was excreted as hydroxyfenbendazole (46).

Due to its low water solubility and permeability of 0.3 μg/ml (11), fenbendazole struggles to reach systemic circulation at levels sufficient to affect tumors. Its drug release rate is 5% within 15 min and 81% within an hour (12).

Safety and Toxicity

In animals, fenbendazole demonstrated a high safety margin and low toxicity. A safety profile study of fenbendazole administered to cattle found that fenbendazole was well-tolerated, even when administered at six times the prescribed dose and three times the recommended duration (47). In rodents, its lethal dose (LD_{50}) exceeded 10 g/kg, which is 1,000 times the therapeutic level. Lifetime studies in rats indicated no maternal or reproductive toxicity and no carcinogenesis. However, morphologic changes in hepatocellular hypertrophy and hyperplasia were observed (48).

Table III. *Studies exploring various vehicles to improve the solubility of fenbendazole.*

Vehicle	Description & Study Results	Reference
PLGA nanoparticles (FZ-PLGA-NPs)	Fenbendazole-encapsulated poly(D,L-lactide-co-glycolide) acid (PLGA) nanoparticles (FZ-PLGA-NPs) have shown increased anti-cancer effects of fenbendazole on epithelial ovarian cancer (EOC) cells both *in vitro* and *in vivo*. In xenograft mouse models, *i.v.* injections of FZ-PLGA-NPs significantly reduced tumor weight compared to the control group. FZ-PLGA-NPs decreased cancer cell proliferation in patient-derived xenograft models as well.	(8)
DMSO (100% DMSO) or DNTC (DMSO, NMP, Tween-80 and Cremophor mix in 1:3:2:2 ratio)	Fenbendazole-DNTC and Fenbendazole-DMSO demonstrated significantly higher cytotoxicity than control groups of DNTC and DMSO alone. DNTC and DMSO can be vehicles to improve the solubility of fenbendazole. Fenbendazole alone significantly inhibited tumor growth more than paclitaxel. Moreover, Fenbendazole-DNTC was found to be significantly more cytotoxic than paclitaxel. Fenbendazole itself was the only drug more significantly cytotoxic and apoptotic in both paclitaxel-resistant prostate cancer cell lines compared to paclitaxel, clofazimine, fluspirilene, suloctidil, and niclosamide.	(41, 53)
Methyl-β-cyclodextrin	Fenbendazole complexed with methyl-β-cyclodextrin at a 1:1 ratio. Methyl-β-cyclodextrin, when complexed with fenbendazole, can increase the water solubility of fenbendazole to 20.21 mg/ml.	(11)
Fenbendazole-loaded Soluplus® micelles	Fenbendazole was encapsulated in low-toxicity Soluplus® micelles for injection. *In vitro* pharmacokinetic studies showed that fenbendazole-loaded Soluplus® micelles had lower total clearance and volume of distribution, along with higher AUC and plasma concentration at T_0. Fenbendazole-loaded Soluplus® micelles released fenbendazole more gradually than the Fen-25% Cremophor El®/EtOH solution. At ≤72 h, the release rate for Fenbendazole-loaded Soluplus® micelles was 50.4% and 75.1% for the Fen-25% Cremophor El®/EtOH solution. An *in vivo* toxicity assay revealed that Fen-loaded Soluplus® micelles did not induce severe toxicity to normal cells.	(60)
Supplementary vitamins (A/Retinol, D3/Cholecalciferol, E, K3, B1, B2, B6, B12, folate, niacin, pantothenic acid, biotin)	Twenty-four-week-old SCID (human lymphoma cell line) mice were divided into four treatment groups: standard diet only, diet with fenbendazole, vitamin-supplemented diet, and vitamin-supplemented diet with fenbendazole. The group of SCID mice treated with a vitamin-supplemented diet with fenbendazole exhibited significant inhibition of tumor growth. This is believed to be due to the antimicrotubular activity of fenbendazole. Additionally, taking fenbendazole with food may have increased its absorption.	(59)
Cocrystals (cinnamic, benzoic, and salicylic acids)	Among the tested cocrystals, fenbendazole-salicylic acid exhibited the highest cumulative drug release of 38% in 15 min. In under 1 h, fenbendazole-salicylic showed a 100% drug release, while pure fenbendazole had a drug release of 81% at 1 h.	(12)

Oxfendazole, a major metabolite of fenbendazole, is well tolerated in humans. A randomized, double-blind, placebo-controlled, phase I study conducted in 70 healthy participants evaluated multiple ascending oral doses of oxfendazole, from 0.5 to 60 mg/kg. The dose study found acceptable safety and tolerability profiles, even after 5 repeated daily doses of up to 15 mg/kg. This clinical trial also characterized the disposition of fenbendazole, describing the drug as a one-compartment model with formation rate-limited elimination (43).

Although studies of the pharmacokinetics of oxfendazole can give insight into the safety of fenbendazole, it should be noted that the solubility of oxfendazole is 44.12 μg/ml (49), demonstrating much higher pharmacokinetic exposure than the solubility of fenbendazole at 0.3 μg/ml (11), even after the same oral dose (50). Further clinical studies using fenbendazole are needed to accurately assess its safety, toxicity, and therapeutic dose in humans.

Increasing Fenbendazole Solubility and Absorption

A significant challenge in using fenbendazole is its low water solubility and bioavailability. Improving the water solubility is essential, as it would reduce the amount of drug needed to reach the same therapeutic effect. With this increase in solubility, fenbendazole can also meet the requirements for use as a systemic anticancer drug. Several studies have investigated various vehicles to overcome this low solubility limit (Table III).

Among the discussed vehicles for increasing the bioavailability of oral fenbendazole, it would be worthwhile to focus on dimethyl sulfoxide (DMSO), Salicylic acid, and methyl-β-cyclodextrin. DMSO and DNTC (DMSO, NMP, Tween-80, and Cremophor mix in a 1:3:2:2 ratio) are highly promising solvents that warrant further exploration. DMSO inhibits several cytochrome P450 subtypes (2C9, 2C19, 2E1, and 3A4) in a concentration-dependent manner (51, 52). Since 2C19 and 3A4 are known CYP450 subtypes that metabolize fenbendazole, inhibiting these enzymes would allow fenbendazole to stay in circulation at higher concentrations for longer periods. Through this increase in bioavailability, fenbendazole can prolong its effects on cancer cells. Fen-DMSO and Fen-DNTC have also been found to be cytotoxic and induce apoptosis in paclitaxel-resistant cells (53). Due to their enhanced cytotoxicity, DMSO or DNTC formulations could be beneficial in treating drug-resistant cancer types.

Another method to improve the solubility of fenbendazole would be to complex it with methyl-β-cyclodextrin at a 1:1 ratio. When fenbendazole is complexed with methyl-β-cyclodextrin, the complex can significantly increase the drug's water solubility to 20.21 mg/ml, which is 60,000 times better than the average solubility of fenbendazole. With this complex, fenbendazole can meet the water solubility requirements (5-10 mg/ml) and could be tested in future clinical trials as a potential anti-cancer drug. Additionally, methyl-β-cyclodextrin increases the drug release rate of fenbendazole to 75% in 15 min, compared to 5% for pure fenbendazole (11).

Salicylic acid would also be an excellent vehicle to improve the drug release rate of fenbendazole. Fenbendazole-salicylic acid performed exceptionally well, achieving a 100% drug release rate in under 1 hour and a 1.052 mg/ml solubility. This significant drug release rate improvement could offer immediate therapeutic action. The enhancement in solubility is suggested to be due to intermolecular interactions such as carboxylic-carboxylic or carboxylic-amino groups forming hydrogen bonds (12).

Fenbendazole as a Cancer Therapy in Humans

Despite the lack of regulatory approval and extensive clinical trials for fenbendazole as a cancer treatment in humans, some cancer patients have self-administered the drug, as documented in case studies. Table IV discusses four case reports where fenbendazole has led to a reduction in tumor size (54, 55) and two cases (56, 57) where patients experienced drug-related hepatic dysfunction (Table IV). In both cases, despite the hepatotoxicity, patients' liver function recovered rapidly upon discontinuing fenbendazole.

Due to its accessibility over the counter at a relatively low price, patients have turned to fenbendazole as an at-home treatment for cancer. As the published case reports observed, the most common self-administered regimen involves taking 1 gram of fenbendazole orally once daily for three consecutive days, followed by four days off treatment (54-57). However, the use of fenbendazole for cancer therapy in humans requires further pilot and extensive clinical trials to establish effective doses and regimens. Patients with compromised liver function, liver cirrhosis, or liver cancer should use fenbendazole with caution. Additionally, combining fenbendazole with glycolysis inhibitors and hepatoprotective pharmaceutical or nutraceutical agents can lead to synergic therapeutic activity while reducing potential liver toxicity.

Conclusion and Perspectives

Fenbendazole's disruptive effects on energy metabolism are fascinating areas of study that could lead to significant advancements in cancer treatment. Various studies in cell lines and animals have demonstrated the efficacy of fenbendazole in inhibiting tumors and targeting drug-resistant cancer cells through glycolysis inhibition. By increasing p53 expression and impacting multiple cellular pathways that act on GLUT and HKII, fenbendazole down-

Table IV. *Summarized patient case reports on the self-administration of fenbendazole for cancer.*

Patient case; Cancer type	Treatment	Results	Evaluation of findings	Reference
83-year-old male patient; Stage IVa diffuse large B-cell lymphoma (DLBCL)	First 6 months: 1g fenbendazole, administered orally once per day (based on self-research). He adjusted his doses between 1 and 6 tablets/day depending on his symptoms. Months 7 and 8: Due to peripheral neuropathy, the patient reduced doses to 1-three tablets of fenbendazole, taken orally once daily. Repeated PET/CT scans revealed smaller mediastinal lymph nodes. Month 9: Followed up with oncology and had a repeated PET/CT scan, which showed improved lymphadenopathy. Months 10, 11, 12: The patient continued tapering down fenbendazole, reducing to three tablets per week. Another PET/CT scan revealed further improvement with no new lesions observed.	Repeated PET/CT scans over 12 months revealed that the patient's lymphadenopathy improved compared to previous scans. In addition, no new lesions were observed.	Physicians speculated that the regression of the patient's stage IVa DLBCL might be due to fenbendazole. However, whether this improvement is directly related to fenbendazole or other factors remains uncertain.	(54)
63-year-old Caucasian male; high-grade clear cell renal cell carcinoma (mRCC)	800 mg pazopanib was initiated; the patient had intolerable side effects and required discontinuation. Cabozantinib was initiated next, but it had limited effectiveness and intolerable side effects, requiring discontinuation. Nivolumab was initiated (three treatments of 240 mg, over one month); the patient had intolerable side effects and required discontinuation. Patient initiated 1g fenbendazole, administered orally once/day for three days/week.	Due to the side effects of immunotherapies, fenbendazole was taken as an alternative treatment. Interval MRI imaging revealed near complete resolution of left renal mass and a decrease in pancreatic head/body and right posterior iliac spine lesions.	Fenbendazole significantly reduced tumor size and had no reported side effects. At the time of the report, the patient had been taking fenbendazole with no new lesions observed for about 10 months without further continuing immune checkpoint inhibitor therapy (nivolumab).	(55)
72-year-old Caucasian male; high-grade urothelial carcinoma (HGUC)	Gamma knife radiotherapy, carboplatin, paclitaxel, and pembrolizumab combination treatments. Gemcitabine and cisplatin for six cycles over four months. Alternative therapy of 1g fenbendazole administered orally once/day for three days/week, 800 mg vitamin E orally once/day, 600 mg curcumin orally once/day, and CBD oil.	Initial combination therapies addressed the patient's brain and pulmonary metastases. However, while on pembrolizumab maintenance, the patient developed progressive retroperitoneal disease. Gem/cisplatin therapy was initially effective, leading to a near complete response. However, interval CT revealed an increase in aortocaval node size. After initiation of alternative therapy with 1g fenbendazole, serial CTs from the past nine months showed a decrease in tumor size.	Alternative therapy with fenbendazole resulted in a decrease in tumor size, achieving a complete radiographic response.	(55)

Table IV. *Continued*

Table IV. *Continued*

Patient case; Cancer type	Treatment	Results	Evaluation of findings	Reference
63-year-old Caucasian female; urothelial carcinoma of the bladder	Transurethral resection of bladder tumor (TURBT). Accelerated Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (AMVAC) for six cycles over four months, along with concurrent 1 g fenbendazole administered orally once/day for three days/week.	Follow-up CT revealed no evidence of disease and minimal residual thickening.	Follow-up CT showed that AMVAC/Fenbendazole therapy effectively decreased disease size. The patient remains on surveillance with no disease progression.	(55)
80-year-old female with advanced non-small-cell lung cancer (NSCLC) with brain metastases	Pembrolizumab monotherapy was initiated for nine months. 1g fenbendazole was administered once/day orally for three days, followed by four days off. The patient self-administered fenbendazole for one month. After fenbendazole was discontinued, pembrolizumab therapy recommenced.	The patient's liver function tests indicated severe hepatic dysfunction, with a Naranjo Adverse Drug Reaction Probability score of 6, suggesting that fenbendazole was the probable cause. A chest CT showed no antitumor effects on the patient's lung cancer before and after 1 month of fenbendazole administration. Due to increased tumor size in her lung, pembrolizumab monotherapy was terminated.	After discontinuation of fenbendazole, the patient's liver dysfunction was resolved. No hepatic disorder relapse was observed; therefore, fenbendazole was likely responsible for the liver dysfunction. However, it is possible that pembrolizumab, in combination with fenbendazole, enhanced hepatotoxicity.	(56)
67-year-old female; history of colon cancer post-resection.	Fenbendazole is administered orally three days/week for one year to cure a precancerous skin lesion. Drug strength unknown.	A liver biopsy revealed severe drug-induced liver injury (DILI) with a RUCAM score of 9, suggesting a high probability that fenbendazole was the cause. Consequently, fenbendazole was discontinued.	Histology confirmed that fenbendazole was likely responsible for the patient's severe DILI. After discontinuation of fenbendazole, the patient's hepatocellular injury pattern improved.	(57)

regulates glucose uptake, causing cancer cell starvation and enhancing apoptosis. Through this mechanism, fenbendazole effectively eliminates cancer cells while exhibiting no or acceptable minimal toxicity to normal cells.

Improving the solubility of fenbendazole is crucial for enhancing its bioavailability and reducing the drug needed to reach therapeutic effects. Future studies could compare these vehicles and test various concentrations to optimize fenbendazole's solubility and drug release. Additionally, combining fenbendazole with hepatoprotective pharmaceutical, nutraceutical, and glycolysis inhibitors can be a promising approach to improving the drug's effectiveness while reducing its potential reversible liver toxicity.

With its high safety profile, affordability, and minimal side effects, fenbendazole stands out as a potential option for cancer therapy. Moreover, fenbendazole is easy to acquire and can be administered orally, offering a less invasive treatment that can increase patient adherence. Furthermore, by inhibiting glycolysis in cancer cells and preventing lactate buildup, fenbendazole surpasses albendazole and mebendazole in treating drug-resistant cells, making it the benzimidazole of choice for cancer therapy.

Despite numerous success stories using fenbendazole and the extensive research performed *in vitro* and *in vivo*, repurposing fenbendazole for cancer treatment remains non-suggested by conventional medical institutions and oncologists. Clinical trials should be funded and performed to promote the possible application of fenbendazole as an inexpensive, well-characterized, and widely available anticancer therapeutic in animals and humans.

Conflicts of Interest

All Authors declare no conflicts of interest in writing and publishing the manuscript.

Authors' Contributions

JN: Conceptualization, Visualization, Writing – original draft, Writing – review & editing; TQN: Conceptualization, Writing – review & editing; BH: Prepared the references, Writing – review & editing; BXH: Conceptualization, Supervision, Writing – review & editing. All Authors read the manuscript before submission.

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