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Review Article | 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.

Key Words:

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).

Table I.

View inline

Studies of fenbendazole in vivo and in vitro cell lines.

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

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).

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).

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Figure 1.

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

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).

Table II.

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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).

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

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).

Table III.

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Studies exploring various vehicles to improve the solubility of fenbendazole.

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.

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.

Table IV.

View inline

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

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-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

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.

Footnotes

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

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Keywords

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