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The Antitumor Potentials of Benzimidazole Anthelmintics as Repurposing Drugs

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
ABZ, albendazole; AFP, alpha-fetoprotein; AKT, protein kinase B; ALDH1, aldehyde dehydrogenase 1; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AP-1, activator protein 1; ATF, activating transcription factor; BAD, Bcl-2 associated agonist of cell death; Bax, Bcl-2-associated X protein; Bcl-2, B-cell

ABSTRACT

The development of refractory tumor cells limits therapeutic efficacy in cancer by activating mechanisms that promote cellular proliferation, migration, invasion, metastasis, and survival. Benzimidazole anthelmintics have broad-spectrum action to remove parasites both in human and veterinary medicine. In addition to being antiparasitic agents, benzimidazole anthelmintics are known to exert anticancer activities, such as the disruption of microtubule polymerization, the induction of apoptosis, cell cycle (G2/M) arrest, anti-angiogenesis, and blockage of glucose transport. These antitumorigenic effects even extend to cancer cells resistant to approved therapies and when in combination with conventional therapeutics, enhance anticancer efficacy and hold promise as adjuvants. Above all, these anthelmintics may offer a broad, safe spectrum to treat cancer, as demonstrated by their long history of use as antiparasitic agents. The present review summarizes central literature regarding the anticancer effects of benzimidazole anthelmintics, including albendazole, parbendazole, fenbendazole, mebendazole, oxibendazole, oxfendazole, ricobendazole, and flubendazole in cancer cell lines, animal tumor models, and clinical trials. This review provides valuable information on how to improve the quality of life in patients with cancers by increasing the treatment options and decreasing side effects from conventional therapy.

Keywords: Benzimidazole; Anthelmintics; Cancer; Therapeutics

INTRODUCTION

Benzimidazole anthelmintics have a chemical structure of benzimidazole with broad anthelmintic activity and are extensively used in both human and veterinary medicine to control internal parasites. Due to their low cost and high efficacy, benzimidazole anthelmintics have been used throughout the world since their introduction in the 1960s (1). Benzimidazole anthelmintics are well-tolerated without severe side effects, and their decades of use provide a basis for safety in humans. Benzimidazole anthelmintics selectively bind to β-tubulin of parasitic worms, causing their immobilization and death. The binding of benzimidazole anthelmintics to nematode tubulin had a 250–400-fold greater inhibition compared with that of mammals (2), indicating selective toxicity toward parasites. Due to the selective interaction with microtubules, benzimidazole anthelmintic drugs have been extensively studied as antitumor agents to disrupt tubulin

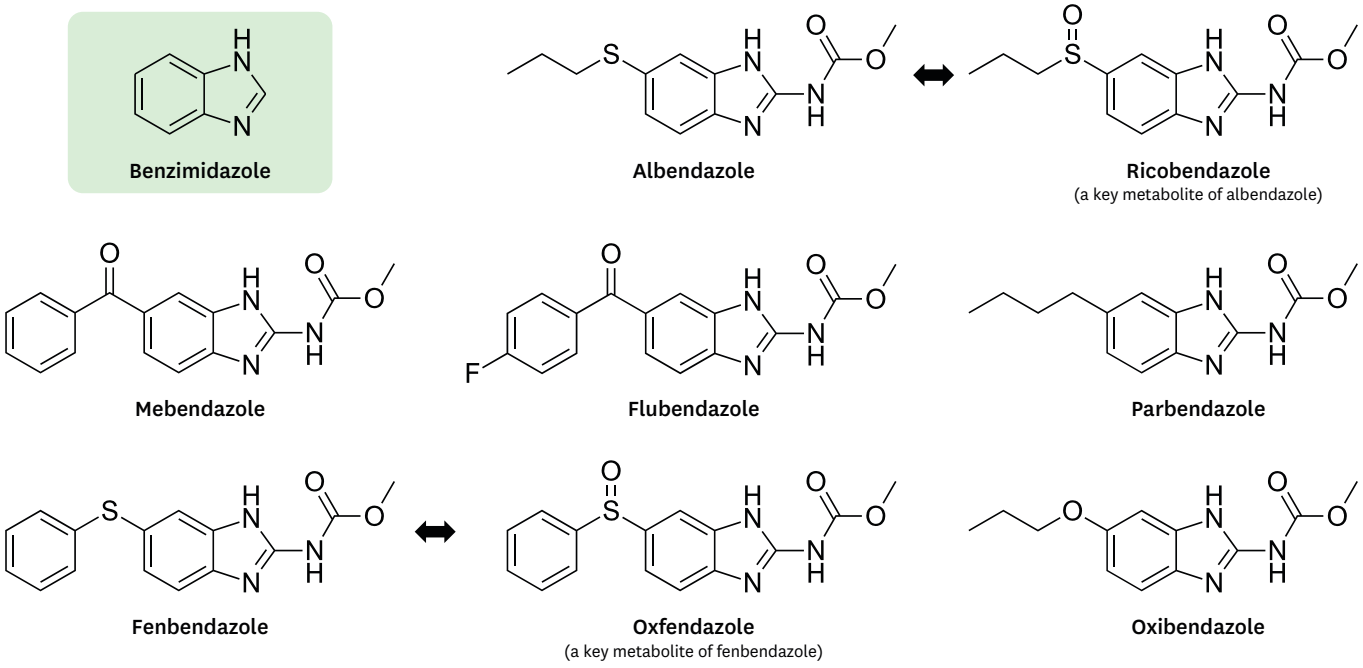

Figure 1. Structures of benzimidazole anthelmintics.

lymphoma 2; BSA-ABZ, BSA-albendazole; CA, cancer antigen; CEA, carcinoembryonic antigen; CHOP, C/EBP homologous protein; c-MYC, a human homology with the viral gene v-myc; COX-2, cyclooxygenase-2; DEN, N-nitrosodiethylamine; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; FDA, Food and Drug Administration; FGF, fibroblast growth factor; GLUT, glucose transporter; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; HIF, hypoxia-inducible factor; HK, hexokinase; i.p., intraperitoneal injection; i.t., intratumoral injection; i.v., intravenous injection; IC50, half maximal inhibitory concentration; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; JNK, c-Jun N-terminal kinases; KRAS, Kirsten rat sarcoma viral oncogene homolog; LC3, microtubule-associated protein 1 light chain 3; Mcl-1, myeloid cell factor-1; Mdm2, mouse double minute 2 homolog; MdmX, mouse double minute 4; MDSC, myeloid-derived suppressor cell; miR, microRNA; MMP, matrix metalloproteinase; Nab-ABZ, nano albumin formulation of albendazole; p, phosphorylated; p.o., oral administration; PARP, poly(ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PFS, progression-free survival;

polymerization for drug repurposing. In this review, we focus on the antitumor effects of the following benzimidazole anthelmintics for human or veterinary use: albendazole, parbendazole, oxibendazole, ricobendazole, mebendazole, fenbendazole, oxfendazole, and flubendazole (**Fig. 1**).

Conventional cancer therapy, including chemotherapy and radiation therapy, appears to have severe toxic effects, such as normal cell death, neurotoxicity, cardiotoxicity, gastrointestinal toxicity, and immune suppression, resulting in a diminished quality of life in patients with cancer (3). Furthermore, chemotherapeutic drugs most often are associated with resistance and eventual evasion of their cytotoxic effects. The benzimidazole anthelmintics are known to be effective in inhibiting paclitaxel and doxorubicin-resistant cancer cells (4), overcoming multidrug resistance. Based on antitumor activity in cancer cells, benzimidazole anthelmintics may provide adjuvant and neoadjuvant therapy in combination with conventional therapy, leading to increased treatment success and decreased risk of recurrence. As benzimidazole anthelmintics have a strong safety profile, combination therapy may decrease the toxic effects of conventional therapy by adjusting the dosage of chemotherapeutics with high doses of these anthelmintics. However, all benzimidazoles have low aqueous solubility and poor absorption from the gastrointestinal tract; the low bioavailability of benzimidazole anthelmintics may significantly improve their absorption by coadministration with a fatty meal (5). Strategies to overcome the low bioavailability of benzimidazole anthelmintics help to increase the antitumor effects by adopting various formulations, including the use of liposomes, nanoparticles, and cyclodextrins. This review article covers the antitumor activity of benzimidazole anthelmintics in cell lines, animal tumor models, and clinical trials. Finally, the pharmacokinetic properties and side effects of benzimidazole anthelmintics are briefly summarized based on reviews and websites, providing a basic understanding to improve the use of benzimidazole anthelmintics in the cancer field. Furthermore, additional benzimidazole derivatives that have been developed for other purposes, such as anticancer, antimicrobial, and antidiabetic agents, are excluded in this review, as they are out of scope.

pH3, phospho-Histone H3; PK, pyruvate kinase; PP2A, protein phosphatase 2A; PSA, prostate-specific antigen; PUMA, p53 upregulated modulator of apoptosis; RAF, rapidly accelerated fibrosarcoma (a family of three serine/threonine-specific protein kinases); RB, retinoblastoma protein; s.c., subcutaneous injection; SIRT, sirtuin; SOX2, SRY (sex determining region Y)-box 2; SRF, serum response factor; TCF4, T-cell factor-4; TIMP, tissue inhibitor of metalloproteinase; TMZ, temozolomide; TNIK, TRAF2- and NCK-interacting kinase; TTP, tristetraprolin; TUNEL, transferase dUTP nick end labeling; VEGFR2, vascular endothelial growth factor receptor 2; XIAP, X-linked inhibitor of apoptosis protein.

Author Contributions

Conceptualization: Son DS; Data curation: Son DS, Lee ES, Adunyah SE; Formal analysis: Son DS, Lee ES; Funding acquisition: Son DS, Lee ES, Adunyah SE; Investigation: Son DS; Methodology: Son DS; Supervision: Son DS; Validation: Son DS, Lee ES, Adunyah SE; Visualization: Son DS; Writing - original draft: Son DS; Writing - review & editing: Son DS, Lee ES, Adunyah SE.

ANTITUMORIGENIC EFFECTS OF BENZIMIDAZOLE ANTHELMINTICS IN CANCER CELLS

Supplementary Table 1 (4,6-80) summarizes the antitumorigenicity of benzimidazole anthelmintics on cancer cell lines. Benzimidazole anthelmintics inhibit the progression of cancer through a variety of mechanisms. The most common antitumor effects of benzimidazole anthelmintics are: inhibited cell viability, migration, and invasion; reduced colony formation, disrupted tubulin polymerization, induced apoptosis and autophagy, increased sub G1, G2/M cell cycle arrest, induced differentiation and senescence, multinucleation, reduced angiogenesis, inhibited drug resistance and transporters, and impaired glucose utilization. Benzimidazole anthelmintics have been shown to inhibit cell viability in a variety of cancer cell lines, appearing as a promising medication (14). The half maximal inhibitory concentrations (IC50s) of flubendazole were well described in 461 cancer cell lines. Cell growth inhibition above 5 μM of fenbendazole are as follows: hepatocellular carcinoma (HCC) 70, HCC1143, HCC1937, and MCF-7 cells in breast cancer; LN405, TU132, U138MG, and U87MG cells in glioma; HUH6 clone5, HUH7, and SK-HEP-1 cells in hepatocellular carcinoma; P12-ICHIKAWA cells in leukemia; DMS79, H2228, and NCI-H146 cells in lung cancer; ONS76 cells in medulloblastoma; Rh28 cells in rhabdomyosarcoma; and T24 cells in urothelial carcinoma (14). These results indicate that some cancer cell lines may be less sensitive to benzimidazole anthelmintics. Even the same cell lines have differences in IC50s among benzimidazole anthelmintics, as well as laboratories which evaluated the IC50s (**Supplementary Table 1**). Identifying resistant and sensitive cancer cells is critical for the therapeutic application of benzimidazole anthelmintics in cancer types. Normal human lung fibroblasts and human umbilical vein endothelial cells have less sensitivity to mebendazole compared with lung cancer cells (56,57). Mebendazole had no effects on normal fibroblasts compared with adrenocortical carcinoma cells (79). The inhibitory effect of flubendazole was limited in normal human liver cells and cardiomyocytes compared with colorectal cancer cells (34). Fenbendazole showed little effect on normal human bronchial epithelial cells, normal immortalized human prostate cells, and primary mouse fibroblasts compared with lung cancer cells, as the IC50 values for fenbendazole were several fold higher in these normal cells compared with cancer cell lines (38). These results indicate that benzimidazole anthelmintics are relatively non-toxic to normal cells, increasing specific sensitivity to cancer cells. The benzimidazole anthelmintics usually decreased signaling proteins related to cell proliferation and survival, such as phosphorylated (p)HER2/3, PI3K/protein kinase B (AKT), rapidly accelerated fibrosarcoma (a family of three serine/threonine-specific protein kinases) (RAF)/MEK/ERK, mTOR, and Ki-67. Interestingly, fenbendazole inhibited PI3K/AKT and RAF/MEK/ERK in Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant lung cancer cells but had no effects in KRAS-wild-type H-1650 lung cancer cells despite inhibited cell viability (53). Fenbendazole also had no effects on cell viability in some p53 mutant lung cancer cells (55). These findings indicate that mutation conditions in cancer cells may affect the sensitivity of benzimidazole anthelmintics differentially.

Among MAPK signaling, benzimidazole anthelmintics inhibited ERK activation (14,51) but increased p38 and c-Jun N-terminal kinases (JNK) activations (38,55). As benzimidazole anthelmintics increased ELK1/serum response factor (SRF) to activate the Fos family, AP-1 also was activated, likely due to the activation of the Jun family from increased pJNK with the activated Fos family (45).

Benzimidazole anthelmintics inhibited cell migration and invasion, which are related to an epithelial-to-mesenchymal transition (EMT). The benzimidazole anthelmintics decreased

N-cadherin, vimentin, FAK, and matrix metalloproteinase (MMP) 2, leading to inhibition of the mesenchymal phase followed by reduced metastasis. The benzimidazole anthelmintics decreased β-tubulin in cancer cells. Although having a 250–400-fold greater inhibition in the tubulin of parasites compared with that of mammals (2), benzimidazole anthelmintics disrupted tubulin polymerization broadly in cancer cells, leading to a lethal effect in rapidly dividing cells. The disruption of tubulin polymerization brings multinucleation and mitotic catastrophe in cancer cells. Interestingly, albendazole had no effects on tubulin depolymerization in HCT116 colorectal cancer cells despite its inhibited cell viability (36,37).

Benzimidazole anthelmintics induced autophagy as they increased autophagic proteins, such as microtubule-associated protein 1 light chain 3 (LC3) and Beclin-1. Mebendazole induces autophagy in endothelial cells (81), likely impairing angiogenic activity via decrease in Wnt/β-catenin axis and VEGFR-2 levels (82). Autophagy has a dual role in tumorigenesis regulation (83). Although autophagy facilitates cell survival in tumor initiation, it suppresses tumor promotion through mTOR and ROS downregulation after tumor formation (83,84). Autophagy promotes invasion of cancer stem cells through TGF-1β dependent epithelial-mesenchymal transition (85). However, autophagy inhibitors have not yet shown survival improvements in clinical trials (86). Further studies require to clarify mechanisms by which benzimidazole anthelmintics induce autophagy.

Above all, benzimidazole anthelmintics induced apoptosis by increasing sub G1 phase, caspase-3/7/8/9 activity and cleaved poly(ADP-ribose) polymerase (PARP), B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax; pro-apoptotic), cytochrome c, p53 upregulated modulator of apoptosis (PUMA), and γH2AX, while decreasing Bcl-2 (anti-apoptotic), truncated Bid (pro-apoptotic), pBAD (anti-apoptotic), myeloid cell factor-1 (Mcl-1), X-linked inhibitor of apoptosis protein (XIAP), and survivin (14,46).

The benzimidazole anthelmintics arrested G2/M phase specifically in the cell cycle by increasing phospho-Histone H3 (pH3), cyclin B1, and p27Kip1, while decreasing cyclin A, cyclin D1, cyclin E, CDC25c, and protein phosphatase 2A (PP2A) cα. Although parbendazole arrested G2/M phase, it decreased cyclin B1 in pancreatic cancer cells (68). The benzimidazole anthelmintics reduced angiogenesis-related proteins, such as hypoxia-induced hypoxia-inducible factor (HIF)-1α and VEGF (54). The benzimidazole anthelmintics induced differentiation and senescence, attributing to increased Keratin 18 and p53 tumor suppressor. The p53 wild-type cancer cells have a higher sensitivity to benzimidazole anthelmintics compared with the p53 mutant cells (38). Benzimidazole anthelmintics increased pp53, p53, and p21 but decreased mutant p53, mouse double minute 2 homolog (Mdm2; sometimes increased), mouse double minute 4 (MdmX), CDK4, CDK6, and pRB (22,23,58,59).

The benzimidazole anthelmintics induced cellular stress through the accumulation of ubiquitylated proteins and increased ROS levels, C/EBP homologous protein (CHOP), activating transcription factor (ATF) 4, and caspase-4/12 as endoplasmic reticulum (ER) stress markers (72).

They also reduced colony formation and inhibited stemness in cancer cells, attributing to decreased a human homology with the viral gene v-myc (c-MYC), OCT4, SRY (sex determining region Y)-box 2 (SOX2), NANOG, aldehyde dehydrogenase 1 (ALDH1) activity, the $CD24^{low}/CD44^{high}$ and $CD24^{high}/CD49^{high}$ subpopulation as stem-like cells, and CD44 as stem cell markers (20).

Benzimidazole anthelmintics impaired glucose utilization, decreasing glucose transporter (GLUT)-1, ATP production, hypoxia-induced glycolysis, GLUT-4, and hexokinase II. These decreases indicate that benzimidazole anthelmintics may inhibit the Warburg effect in cancer. Furthermore, benzimidazole anthelmintics increased AMP-activated protein kinase (AMPK) activation (15), which negatively regulate the Warburg effect. However, fenbendazole had no change in glucose uptake in OCI-AML2 leukemia cells (30), indicating that effects of benzimidazole anthelmintics on glucose metabolisom are a cell-type-specific manner. The benzimidazole anthelmintics inhibited genes related to drug resistance and transporters, such as MDR1, ABCB1, ABCC1, SLC47A1, and p62 (41-43).

The benzimidazole anthelmintics inhibited NF-κB signaling by decreasing phospho-p65 and the nuclear translocation of NF-κB and by increasing the half-life of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). However, albendazole-induced sirtuin 3 (SIRT3) degradation elicited ROS-mediated p38 MAPK activation, leading to pyruvate kinase M2-mediated tristetraprolin (TTP) degradation, followed by TNF-α upregulation in human leukemia cells (46). The benzimidazole anthelmintics inhibited hedgehog signaling, likely leading to reduced metastasis, inhibited angiogenesis, and increased apoptosis. The benzimidazole anthelmintics inhibited pSTAT3 and nuclear translocation of STAT3, resulting in decreased proliferation, increased apoptosis, reduced angiogenesis, downregulated stemness, increased chemosensitivity, and immune surveillance (34,38). On the other hand, they increased STAT1/2, inducing cell death. The benzimidazole anthelmintics inhibited c-Src activation, resulting in decreased tumor growth and metastasis. Flubendazole decreased PD-1 in melanoma cells (76), likely inhibiting tumor growth.

The benzimidazole anthelmintics decreased β-catenin, maintaining the Wnt-off state. Mebendazole is a novel TRAF2- and NCK-interacting kinase (TNIK) inhibitor (87). As TNIK is an activating kinase for the T-cell factor-4 (TCF4) and β-catenin transcriptional complex (88), benzimidazole anthelmintics may impede the Wnt signaling by inhibiting TNIK. The benzimidazole anthelmintics increased AMPK activation, likely resulting in inhibited mTOR, decreased cyclin D1, and increased p53 and p21. Oxibendazole increased microRNA (miR)-24a and miR-204 in prostate cancer cells (71). Although miR-24a repressed apoptosis in the developing neural retina (89), miR-204 inhibits invasion and EMT in esophageal cancer (90). The effects of benzimidazole anthelmintics on miRNA signature in cancer are still immature. Fenbendazole is a more effective cytotoxic agent as compared with cisplatin and taxol (at IC50 concentration) and had similar effects also with the Food and Drug Administration (FDA)-approved proteasomal inhibitor bortezomib (38). The benzimidazole anthelmintics decreased proteasome activity, acting as a proteasomal inhibitor.

Mebendazole had little or no effect on clustering and cytokine release in non-activated PBMCs, but increased clustering and released proinflammatory cytokines, including TNF-α, IL-1β, IFN-γ, and IL-6 in CD3/IL2-activated PBMCs, potentiating both tumor cell reduction and apoptosis (91). Mebendazole induced a proinflammatory (M1) phenotype of monocytic cells (THP-1) via ERK1/2 and TLR8-dependent inflammasome activation (48). The differentiated THP-1 macrophages enhanced the suppressive effects of mebendazole in leukemia cells. These results may be relevant to explain the anticancer activity of benzimidazole anthelmintics.

Benzimidazole anthelmintics sensitize cancer cells to conventional therapy, such as chemotherapeutics and radiation, enhanceing antitumor potentials when used in

combination. Benzimidazole anthelmintics show synergistic antitumorigenicity in combination with temozolomide, vinblastine, fluorouracil, doxorubicin, docetaxel, gemcitabine, paclitaxel, cisplatin, and trametinib.

Epothilone-paclitaxel resistant leukemic cells are sensitive to albendazole (49). These facts indicate that benzimidazole anthelmintics may be adjuvant therapeutics in cancer cells resistant to conventional chemotherapy. However, fenbendazole had no change in cytotoxicity in combination with docetaxel in EMT6 mouse mammary tumor cells (29). Albendazole showed antagonistic effects in combination with paclitaxel and vinblastine in HCT-116 colorectal cancer cells and DU145 prostate cancer cells (36). Mebendazole had antagonistic and additive cytotoxicity in combination with trametinib in STU ($BRAF^{V600K}$/$NRAS^{WT}$) melanoma cells in a dose-dependent manner (75). These facts indicate the different sensitivity of benzimidazole anthelmintics in a cancer cell-type-specific manner, requiring the careful application of benzimidazole anthelmintics with conventional chemotherapy.

ANTITUMORIGENIC EFFECTS OF BENZIMIDAZOLE ANTHELMINTICS IN ANIMAL TUMOR MODELS

We summarized the antitumorigenicity of benzimidazole anthelmintics in animal tumor models (**Supplementary Table 2**) (4,8,11-17,20,27-30,34-37,39,45,47,51,52,54-57,61,63-66,69-71,74-76,78-80,92-94). Benzimidazole anthelmintics have been shown to inhibit the tumor growth in animals, which have been well-tolerated without significant side effects during the experimental period. Based on **Supplementary Table 2**, the most common antitumor effects of benzimidazole anthelmintics in animal tumor models appear as follows: prolonged overall survival and progression-free survival; inhibited tumor growth; reduced vessel formation; decreased tumor volume and weight; and reduced metastasis. The antitumor effects of benzimidazole anthelmintics in animal tumor models (**Supplementary Table 2**) share similar mechanisms with those in cancer cells (**Supplementary Table 1**). The benzimidazole anthelmintics in animal tumor models have shown the following mechanistic effects: decreased human epidermal growth factor receptor (HER) 2, pMEK, pERK1/2, pmTOR, fibroblast growth factor (FGF) 2, Ki-67, and proliferating cell nuclear antigen (PCNA) to inhibit tumor growth; increased LC3 and Beclin-1 to induce autophagy; increased caspase-3/9, Bax (pro-apoptotic), DNA fragmentation, apoptotic cells (transferase dUTP nick end labeling [TUNEL] staining) and p53+ cells, and decreased Bcl-2 (anti-apoptotic) and XIAP to trigger apoptosis; increased pH3 and decreased cyclin D1 to arrest cell cycle; decreased HIF-1α, VEGF, vascular endothelial growth factor receptor (VEGFR) 2 kinase activity, FGF2, and CD31 to reduce angiogenesis; reduced activities of hexokinase (HK), pyruvate kinase (PK), and LDH to impair glucose utilization; decreased vimentin, TGF-β, MMP2, MMP9, and MMP2/tissue inhibitor of metalloproteinase (TIMP) 1 ratio related to the inhibition of mesenchymal phase to reduce metastasis; decreased MYC, ALDH1A1, CD49f, and CD44 as stem cell markers to inhibit stemness; increased keratinocyte differentiation markers, p53, and p21 to induce differentiation and senescence; and decreased cyclooxygenase-2 (COX-2), TNF-α, IL-6, and IL-1B to inhibit NF-κB signaling. As shown in cancer cells, the benzimidazole anthelmintics in animal tumor models inhibited pSTAT3, resulting in decreased tumor growth, increased apoptosis, reduced angiogenesis, and downregulated stemness. They reduced hedgehog signaling, leading to reduced metastasis, inhibited angiogenesis, and increased apoptosis. The benzimidazole anthelmintics decreased G-CSF, GM-CSF, PD-1, and CD11b+Gr1+ myeloid-derived suppressor cell (MDSC) levels, inhibiting tumor growth with a good prognosis.

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Benzimidazole anthelmintics decreased cancer markers, such as cancer antigen 125 (CA125), in an ovarian cancer model (65) and prostate-specific antigen (PSA) in a prostate cancer model (71), requiring further studies for other cancer markers. Mebendazole decreased serum alanine aminotransferase (ALT) and alpha-fetoprotein (AFP) in N-nitrosodiethylamine (DEN)-induced hepatocellular carcinoma (51), improving hepatic function, inflammation, and fibrogenesis. Although oxibendazole has increased miR-24a and miR-204 in prostate cancer (71), the effects of benzimidazole anthelmintics on miRNA signature in cancer are still immature, and the benzimidazole anthelmintics may act as specific miRNA regulators to affect cancer prognosis.

Certain formulated-mebendazole and benzimidazole anthelmintics, such as thiabendazole, flubendazole, oxfendazole, and fenbendazole, had no effects on survival in intracranial implantation models of brain cancer cells (92). The intracranial xenograft model of temozolomide-resistant glioblastoma multiforme responded well to mebendazole, but not to albendazole (8). These facts indicate the structure-dependent manner of benzimidazole anthelmintics. Intradermal models of EMT6 mouse mammary tumor cells did not respond to fenbendazole alone or in combination with radiation (28,29). This result indicates the cell-type-specific manner of benzimidazole anthelmintics, identifying sensitive and resistant cancer cells. BSA-albendazole (BSA-ABZ) and nano albumin formulation of albendazole (Nab-ABZ) inhibited tumor weight, ascites fluid, and VEGF in ovarian cancer models, whereas free albendazole had no effects (63). The formulation-dependent effectiveness of albendazole provides a clue to overcoming the low bioavailability of benzimidazole anthelmintics. Furthermore, flubendazole decreased tumor volume in MDA-MB-435 cell-bearing mice after intraperitoneal injection, but not after intratumoral injection (76). This result indicates that the route of benzimidazole anthelmintics administration may be critical for therapeutic application.

Benzimidazole anthelmintics enhanced survival in tumor-bearing animals in combination with temozolomide, elacridar, radiation, sulindac, vincristine, sorafenib, trametinib, and docetaxel. These findings confirm that benzimidazole anthelmintics may be adjuvant therapeutics in combination with conventional chemotherapy. Moreover, albendazole had no synergistic effect with paclitaxel in the ovarian cancer model, indicating that benzimidazole anthelmintics must be used carefully in combination with conventional chemotherapy to maximize therapeutic potential (94). Fenbendazole decreased tumor weight in mammary fat pads of trastuzumab-resistant JIMT-1 cells, providing a possibility of benzimidazole anthelmintics to overcome cancers resistant to conventional chemotherapeutics and recurrent cancers (20).

Despite the safety profile of benzimidazole anthelmintics, some animal studies with mebendazole alone and in combination with vincristine and elacridar showed side effects, such as weight loss and neuropathy. Mebendazole with 100 mg/kg daily administration caused weight loss, whereas the dose of 50 mg/kg did not show adverse effects in C57BL6 mice (8). A combination of mebendazole with vincristine appeared to increase the emergence of neuropathy with rapid weight loss (11). The prolonged treatment course with elacridar and mebendazole increased toxicity in mice, as evidenced by weight loss and mortality (92). These findings require further safety monitoring for the application of benzimidazole anthelmintics alone or in combination with anticancer drugs. We describe the side effects of benzimidazole anthelmintics in the following sections.

ANTITUMORIGENIC EFFECTS OF BENZIMIDAZOLE ANTHELMINTICS IN CLINICAL ASPECTS

The antitumorigenicity of benzimidazole anthelmintics in clinical aspects is summarized (**Table 1**) (95-98). Clinical trials of benzimidazole anthelmintics have insufficient data to evaluate theier use in treating cancer. As benzimidazole anthelmintics have been given to patients with refractory solid tumors, metastatic tumors, and failure of conventional chemotherapy, the antitumor effects of benzimidazole anthelmintics on primary tumors are worth clarifying.

Table 1. Antitumorigenicity of benzimidazole anthelmintics in clinical aspects

Stage	Cancer type	Purpose	Methods	Results and ongoing	Ref.
Phase 1	36 patients with refractory solid tumors	Maximum-tolerated dose	Albendazole: p.o. on a day 1–14 of a 3-weekly cycle, from 400 mg b.d. to 1,200 mg b.d.	2,400 mg/day from 1,200 mg b.d. Decreased plasma VEGF Patients (16%) had a tumor marker response with a fall of at least 50% Adverse effects: myelosuppression, fatigue and mild gastrointestinal upset	(95)
Case report	74-year-old man with metastatic colon cancer	Treatment for significant progression in the lungs and abdominal lymph nodes with new partly, poorly defined liver metastases	Mebendazole: 100 mg b.d. for 6 wk	Near complete remission of the metastases in the lungs and lymph nodes and a good partial remission in the liver	(96)
	48-year-old man with adrenocortical carcinoma	Treatment for failure or intolerance to conventional treatments with mitotane, 5-fluorouracil, streptozotocin, bevacizumab, and radiation therapy	Mebendazole: 100 mg b.d. for 19 months	Regression of hepatic metastatic lesions and subsequently remained stable for 19 months, but progressed after 24 months No clinically adverse effects; quality of life was satisfactory	(97)
Phase 1	A patient with hepatocellular carcinoma with metastasis	Evaluation of albendazole	Albendazole: 10 mg/kg/day, p.o. in 2 divided doses for 28 days	Stabilization of the disease, but because of neutropenia, treatment was stopped on day 19	(98)
	8 patients with colorectal cancer with metastasis			Decreased carcinoembryonic antigen (CEA) in 2 patients and stabilized in 3 patients, an initial stabilization (5–10 days) in 2 patients No significant changes in liver and kidney function tests, but neutropenia in 2 patients	(98)
Phase 1 NCT01729260	24 high-grade glioma	Mebendazole in newly diagnosed high-grade glioma patients receiving temozolomide	Mebendazole: 500 mg chewable tablets with meals, p.o. 3 times every day on 28-day cycle	Study period: April 4, 2013 to September 2025 Location: The Johns Hopkins Hospital, Baltimore, Maryland, United States	
NCT02644291	21 high-grade glioma	Phase I study of mebendazole therapy for recurrent/ progressive pediatric brain tumors	Mebendazole: 500 mg chewable tablets, 3 divided doses with meals	Study period: May 2016 to June 2022 Location: Johns Hopkins All Children's Hospital Saint Petersburg, Florida, United States Johns Hopkins University School of Medicine Baltimore, Maryland, United States	
Phases 1/2 NCT01837862	36 low- and high-grade glioma	A phase I study of mebendazole for the treatment of pediatric gliomas	Mebendazole: 50, 100, and 200 mg/kg/day, p.o. and b.d. for 70 wk for low-grade glioma patients and 48 wk for high-grade glioma patients	Study period: October 22, 2013 to April 2020 Location: Cohen Children's Medical Center of New York, New Hyde Park, New York, United States	
Phase 2 NCT02366884	250 patients with malignant disease that is considered untreatable, progressive and fatal	Clinical evaluation of a new form of cancer therapy based on the principles of atavistic metamorphosis (atavistic chemotherapy)	Anti-bacterial, anti-fungal, anti-protozoal agents: anti-cancer properties of albendazole and mebendazole	Study period: July 2011 to December 31, 2023 Location: Dr. Frank Arguello Cancer Clinic San Jose del Cabo, Baja California Sur, Mexico Instituto de Ciencia y Medicina Genomica Torreon, Coahuila, Mexico	
Phase 3 NCT03925662	40 patients with stage 4 colorectal cancer	Mebendazole as adjuvant treatment for colon cancer	Mebendazole	Study period: April 1, 2019 to December 2028 Location: Sherief Abd-Elsalam, Cairo, Egypt	
NCT02201381	207 participants with cancer	Study of the safety, tolerability and efficacy of metabolic combination treatments on cancer (METRICS)	Mebendazole: 100 mg, p.o. and u.i.d. for study duration	Study period: May 22, 2017 to May 22, 2022 Location: Care Oncology Clinic, London, United Kingdom	

b.d., twice daily; p.o., oral administration; u.i.d., once daily dosage.

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Thirty-six patients with refractory solid tumors were tolerant of albendazole, even with 2,400 mg/day, resulting in decreased plasma VEGF and tumor markers by 16%. Some patients experienced side effects, such as myelosuppression, fatigue, and mild gastrointestinal upset (95). A patient with metastatic colon cancer responded well to mebendazole, showing nearly complete remission of the metastases in the lungs and lymph nodes and a good partial remission in the liver (96). A patient with adrenocortical carcinoma in failure or intolerance to conventional treatments had taken mebendazole for 19 months. The patient having the regression of hepatic metastatic lesions remained stable for 19 months but progressed after 24 months. No clinically adverse effects were observed, and quality of life was satisfactory (97). Although a patient with metastatic hepatocellular carcinoma remained stable after albendazole doses, treatment was stopped on day 19 due to neutropenia (98). The antitumor effects of albendazole in eight patients with metastatic colorectal cancer were as follows: decreased carcinoembryonic antigen (CEA) in two patients; stabilization in three patients; an initial stabilization (5–10 days) in two patients; no significant changes in liver and kidney function tests in all patients; and neutropenia in 2 patients (98). Based on ClinicalTrials.gov (https://clinicaltrials.gov), we have summarized ongoing clinical trials of albendazole and mebendazole for phases 1, 2, and 3, including low- and high-grade glioma, malignant disease under untreatable, progressive and fatal conditions, and stage 4 colorectal cancer (**Table 1**). Joe Tippens, a lung cancer survivor, used fenbendazole as a dog de-worming drug to eliminate late-stage small cell lung cancer (https://www.dailymail.co.uk/health/article-6965325/Oklahoma-grandfather-claims-drug-DOGS-cured-cancer-tumor-free.html). Fenbendazole for veterinary use has yet to be established as safe for human use. Albendazole and mebendazole have a priority for clinical trials, rather than other benzimidazole anthelmintics, due to approvals for human use. Clinical trials in the near future will clarify the availabilty of benzimidazole anthelmintics to use as adjuvant and neoadjuvant therapeutics for cancer treatments.

PHARMACOKINETIC PROPERTIES AND SIDE EFFECTS OF BENZIMIDAZOLE ANTHELMINTICS

As benzimidazole anthelmintics have a long history for human and veterinary use, the pharmacokinetic properties and side effects of these anthelmintics are well established based on many studies. **Table 2** (5,99-110) briefly summarizes the pharmacokinetic properties and side effects of benzimidazole anthelmintics using extracted literature reviews and websites, including www.drugs.com and PARASITIPEDIA.net, emphasizing some issues of these anthelmintics as repurposed drugs for cancer treatment.

The general pharmacokinetic properties of benzimidazole anthelmintics are as follows: poor absorption; wide distribution in the body; extensive hepatic metabolism; and excretion via feces and urine (**Table 2**). The absorption of benzimidazole anthelmintics is poor, resulting in low bioavailability. The oral absorption of albendazole is about 20%–30% in mice and rats, about 50% in cattle, and about 1%–<5% in humans (5). The low water solubility and low intestinal absorption rate of benzimidazole anthelmintics may make it difficult to achieve effective concentrations in the systemic circulation to treat cancer in humans. A fatty meal enhances absorption up to 5-fold in humans and animals. Micro-emulsifying delivery systems and increased lipid solubility in dosing benzimidazole anthelmintics help to maximize the therapeutic efficacy. The bioavailability of albendazole in fasted calves was markedly greater than that in calves fed ad libitum (111), indicating better bioavailability in

fasting conditions. Various formulation strategies attempt to circumvent the low solubility and poor bioavailability of benzimidazole anthelmintics through the use of organic co-solvents, liposomes, surfactants, nanoparticles, microspheres, and cyclodextrins.

Table 2. Pharmacokinetic properties and side effects of benzimidazole anthelmintics

Drug	Dosage	Pharmocokinetic properties	Side effects	Ref.
Albendazole FDA approval (1996): category C	Human and veterinary use, 400 mg/day, p.o. and b.d. for 1 to 6 months in *Echinococcus* infection	Absorption: poor solubility and absorption (<5% in humans and 50% in cattle); increase up to 5 times when administered with a fatty meal Distribution: widely distributed throughout the body including urine, bile, liver, cyst wall, cyst fluid, and CSF Metabolism: Hepatic extensive first-pass effect; rapid sulfoxidation to active metabolite albendazole sulfoxide and finally inactive albendazole sulfone, hydrolysis, and oxidation Excretion: urine (<1% as active metabolite) and feces, hepatic clearance = 18.2 ml/min/kg Time to peak = 2–5 h for albendazole sulfoxide in serum t1/2 = 8–12 h for albendazole sulfoxide Protein binding = 70%	Common: headaches and hepatotoxicity with elevated liver enzymes Few: abdominal pain, nausea, vomiting, fever, and hypersensitivity reaction, such as hives and pruritus Rare: alopecia, telogen effluvium Other: leukopenia, anemia, thrombocytopenia, pancytopenia Avoid during pregnancy: teratogenic effects in the offspring of rats, but pregnant patients who received albendazole did not show an increased risk of teratogenicity No risk of aneuploidy for conventional therapeutic use of albendazole in human	(5,99-102)
Mebendazole approved in the United States in 1974	Human and veterinary use Some experts recommend: 200 to 400 mg, p.o. and t.i.d. for 3 days, then 400 to 500 mg, p.o. and t.i.d. for 10 days for trichinosis	Absorption: poor solubility and absorption, 5%–10% in humans and 1%–2% after a high dose, enhanced by eating high-fat meals distribution: Vd = 1–2 L/kg Metabolism: extensively hepatic first pass metabolism involving keto-reduction and decarbamylation, followed by conjugation Excretion: primarily feces (as unchanged drug and primary metabolite) and urine (<2%) t1/2 = 3–6 h Protein Binding = 90%–95% Pass through the blood–brain barrier	Anthelmintic spectrum and adverse effect profile of mebendazole is almost identical to albendazole Relatively non-toxic, well-tolerated Side effects are uncommon with rare cases, such as gastrointestinal upset, fever, diarrhea, abdominal pain, discomfort, flatulence, diarrhea, hypersensitivity reactions, such as rash, urticaria, and angioedema High doses may induce anemia and hepatotoxicity with rare instances of neutropenia, marrow aplasia, alopecia Rodents showed fetal toxicity and teratogenicity at high doses, but not other species including rabbits, horses, sheep, and swine Contraindicated for pregnancy Aneuploidy in *in vitro* and *in vivo* experiments but not considered to be a risk to humans receiving conventional therapy	(5,101,103,104)
Fenbendazole	Veterinary use	Metabolism: extensively hepatic first pass to the active metabolite fenbendazole sulfoxide (active form) and finally fenbendazole sulfone Excretion: primarily feces and urine	A nontoxic drug in rodents: LD50 exceeds 10 g/kg (a dose 1,000 times the therapeutic level) Lifetime studies in rats: lack of carcinogenesis, no maternal and reproductive toxicity Morphologic changes of hepatocellular hypertrophy and hyperplasia in rats No observed adverse effect in mice Myelosuppression in dogs and birds, but not in rodents	(105,106)
Ricobendazole (albendazole sulfoxide)		Absorption: poor bioavailability and enhanced hydrosolubility Vd = 0.67–1.2 L/kg in cattle and sheep Metabolism: absorbed oxfendazole is partly and reversibly reduced to albendazole both in the liver and in the rumen Excretion: feces and urine t1/2 = 8–12 h in man Protein binding = 70% Crosses the blood–brain barrier Ricobendazole enantiomers have a species difference in pharmacokinetic profiles	Ricobendazole is a key metabolite of albendazole; may have side effects similar to albendazole	(5,105)

(continued to the next page)

Table 2. (Continued) Pharmacokinetic properties and side effects of benzimidazole anthelmintics

Drug	Dosage	Pharmocokinetic properties	Side effects	Ref.
Oxfendazole (fenbendazole sulfoxide)	Veterinary use	Enhanced hydrosolubility Distribution throughout the body Metabolism: absorbed oxfendazole is partly and reversibly reduced to fenbendazole both in the liver and in the rumen Excretion: 80% through bile and feces in ruminants t1/2 = 8–12 h in human (NCT03035760, NCT02234570) Oxfendazole enantiomers have a species difference in pharmacokinetic profiles	Well-tolerated in most species Main symptoms of intoxication after high oral doses: loss of appetite, diarrhea, fever, cramps, nausea, vomit and convulsions Hepatic and epicardial hemorraghe can also happen Mutagenic effects, embryotoxicity, teratogenicity in mice	(105,107)
Flubendazole	Veterinary use	Absorption: poor bioavailability Metabolism: extensive first pass via carbamate hydrolysis and ketone reduction to inactive metabolites Excretion: more than 80% of p.o. dose in feces and only very small amounts of unchanged drug (less than 0.1%) in the urine t1/2 in tissues = 1–2 days	Well-tolerated without adverse effects Not be used in pregnant or lactating queens, nor in puppies younger than 1 year	(108)
Oxibendazole	Veterinary use	Absorption: poor bioavailability but increased bioavailabiblity in sheep and goats splitting the therapeutic dose during 3 consecutive days (each day 1/3 of the recommended dose) Metabolism: little information but expected broken down in the liver to metabolites without anthelmintic activity	Well-tolerated in most species No acute toxicity with single oral doses in mice (4–32 g/kg of body weight), sheep (230–600 mg/kg), and cattle (600 mg/kg) No subacute toxicity with multiple doses for 5 days in cattle (30–75 mg/kg/day) and sheep (10–50 mg/kg/day) No chronic effects with 3–30 mg/kg for 98 days in rats and dogs No teratogenicity in mice, rats, sheep at 30 mg/kg and cattle at 75 mg/kg during pregnancy Main symptoms after high oral doses: vomiting, depression, trembling	(109)
Parbendazole	Veterinary use	Peak blood levels = 6–8 h after administration	Pregnant animals are contraindicated: teratogenicity is largely skeletal Laxation (soft dung/diarrhea), anorexia, listlessness	(110)

LD50, lethal dose, 50%; p.o., oral administration; t1/2, half-life time; t.i.d., three times a day; Vd, volume of distribution.

Nanoformulations of albendazole and conjugated albendazole with nano-carriers improve solubility and increase drug delivery to tumor cells (112). This increased bioavailability will enhance the antitumor potential of benzimidazole anthelmintics, which are generally safe and well-tolerated in human and veterinary use. The common side effects of benzimidazole anthelmintics are as follows: headaches and hepatotoxicity in common; leukopenia and anemia occasionally; and issues in the gastrointestinal tract, such as laxation and anorexia (**Table 2**). Although albendazole has hepatotoxicity, liver function in patients recovered rapidly on the withdrawal of albendazole (113). Benzimidazole anthelmintics must be used with caution in patients with reduced liver function and with liver cirrhosis and liver cancer. Although albendazole stabilized cancer conditions in a patient with metastatic hepatocellular carcinoma, the treatment was stopped due to neutropenia (98). Albendazole is known to be a teratogen and a fetal toxicant in rodents (114), indicating contraindication during pregnancy. Netobimin, a prodrug of albendazole, increased resorption and skeletal malformations and decreased fetal body weight in pregnant rats (115). However, it does not appear to induce a teratogenic action in humans, even in women dosed during pregnancy (5). The differential toxicity of benzimidazole anthelmintics among species indicates species-specific effects. Although fenbendazole may be considered a nontoxic drug in rodents (106), benzimidazole anthelmintics for veterinary use have not led to enough evidence of safety for human use, requiring further studies.

SUMMARY

Benzimidazole anthelmintics induce minimal cytotoxicity in normal cells but high cytotoxicity in tumor cells, exerting a cancer cell-specific selectivity. The antitumor effects of benzimidazole anthelmintics are exerted through various biological actions, such as inhibited cell viability, migration, and invasion, reduced colony formation, disrupted tubulin polymerization, induced apoptosis and autophagy, G2/M cell cycle arrest, induced differentiation and senescence, reduced angiogenesis, inhibited drug resistance and transporters, and impaired glucose utilization. Specific signaling pathways related to these biological actions of these compounds support the antitumorigenicity of benzimidazole anthelmintics (**Fig. 2**). In addition to *in vitro* cancer cell lines, benzimidazole anthelmintics have shown antitumor effects in *in vivo* animal tumor models, such as prolonged overall survival and progression-free survival, inhibited tumor growth, reduced vessel formation, and reduced metastasis, all of which share signaling pathways shown in cancer cell models (**Fig. 2**). Almost all animals tolerated benzimidazole anthelmintics without significant side effects. These benzimidazole anthelmintics have demonstrated the synergistic and enhanced antitumorigenicity in combination with conventional chemotherapeutics and radiation, appearing to be a promising candidate for adjuvant and neoadjuvant therapy with low cost. Some cancer cells have tendency for resistence to benzimidazole anthelmintics, requiring mechanistic studies to explain the cause. Clinical trials for the antitumor effects of benzimidazole anthelmintics have insufficient data to demonstrate the availability to treat human cancers. Despite the limited data, some patients with metastatic late-stage cancers responded well to albendazole and mebendazole showing reduced

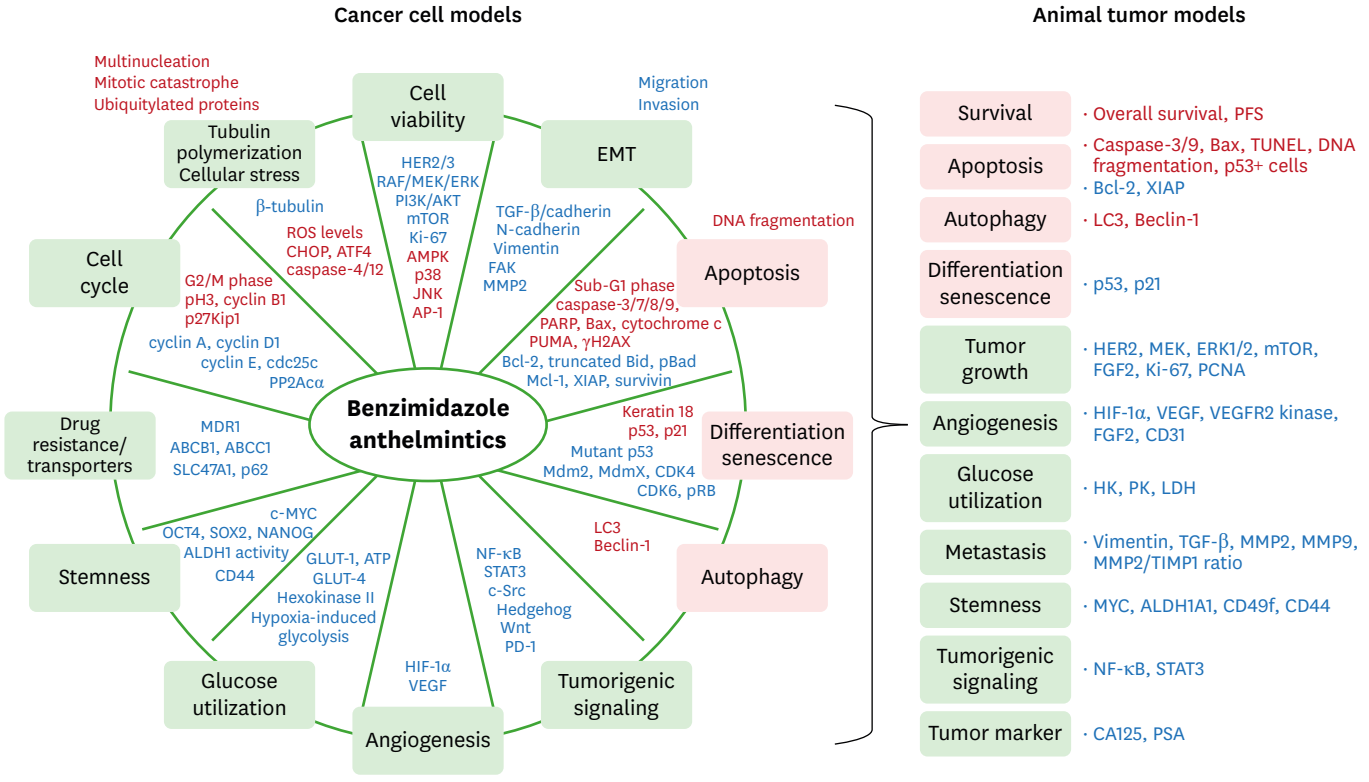

Figure 2. Summarized schemes for the antitumorigenicity of benzimidazole anthelmintics in cancer. Light green boxes, inhibited biological aspects; pink boxes, induced biological aspects; red letters, upregulated signalings and reactions; blue letters, downregulated signalings and reactions. See **Tables 1** and **2** for genes and proteins.

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tumor markers and metastasis and stabilized disease. Ongoing clinical trials will provide insight to benzimidazole anthelmintics for primary and metastatic cancer treatments in the near future. Although benzimidazole anthelmintics have a broad safety spectrum, the poor bioavailability of these anthelmintics is the main hindrance, requiring better formulation strategies and fatty meals to increase the solubility. Increased bioavailability of benzimidazole anthelmintics may improve antitumorigenesis and prolong overall survival. Although benzimidazole anthelmintics for veterinary care have well-known safety, the safety has not been established for human use, requiring further studies.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Antitumorigenicity of benzimidazole anthelmintics on cancer cell lines

Click here to view

Supplementary Table 2

Antitumorigenicity of benzimidazole anthelmintics in animal tumor models

Click here to view

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