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Repurposing Broad-spectrum Anthelmintics for Colorectal Cancer Treatment: A Mini Review

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ABSTRACT

Albendazole (ABZ) and Mebendazole (MBZ), well-known for their broad-spectrum anti-parasitic properties, have emerged as promising candidates for cancer therapy, particularly in colorectal cancer (CRC). This mini review examines the anti-cancer potential of ABZ and MBZ, focusing on their mechanisms of action, clinical efficacy, and pharmacokinetic challenges. Both drugs inhibit microtubule polymerization, inducing apoptosis in cancer cells, and have demonstrated significant tumor suppression in preclinical and clinical studies. Despite their established safety profiles, the low bioavailability of ABZ and MBZ limits their therapeutic potential, necessitating the development of advanced formulations to enhance drug absorption and efficacy. Current clinical trials continue to explore their effectiveness in CRC, highlighting the potential of these repurposed anthelmintic drugs as cost-effective, safe, and efficient alternatives for cancer treatment. Further research is essential to optimize their clinical use and confirm their therapeutic benefits in oncology.

Keywords: Albendazole; Mebendazole; Colorectal Cancer; Drug Repurposing; Anthelmintic; Microtubule Inhibitors

Abbreviations: EMR: Endoscopic Mucosal Resection; TEM: Transanal Endoscopic Microsurgery; LAR: Low Anterior Resection; CRC: Colorectal Cancer; CNS: Central Nervous System; ABZ: A Study Exploring the use of Albendazole; HCC: Hepatocellular Carcinoma; AUC: Area Under the Concentration-Time Curve; NAC: N-Acetyl Cysteine; HUVECs: Human Umbilical Vein Endothelial Cells

Introduction

Cancer occurs when the body's cells regenerate uncontrollably and spread to other internal organs. Normally, cells divide and grow in a controlled way to create new cells when needed, but this process can sometimes malfunction, causing damaged or abnormal cells to proliferate. These cells can form tumors, which may be either malignant (cancerous) and capable of spreading or benign (non-cancerous) and typically do not spread. Cancer is fundamentally a genetic disease caused by mutations in genes that regulate cell growth and division. These mutations can arise from cell division errors, DNA damage due to environmental factors like smoking or UV rays, or be inherited from parents. The body's ability to eliminate DNA-damaged cells diminishes with age, increasing the risk of cancer. Lung, prostate, stomach, and liver cancers are more common in men, whereas breast, colorectal, lung, cervical, and thyroid cancers are more common in women (Cancer, n.d.). The major classifications of cancer include carcinoma, lymphoma, myeloma, sarcoma, and leukemia. Carcinoma, the most common type, originates in the cells lining internal organs or external surfaces, affecting organs such as the breast, lungs, bladder, colon, and prostate (Cancer, n.d.). Lymphoma is a blood cancer impacting the immune system, originating in the lymphatic system and leading to abnormal growth of lymphocytes, which can affect lymph nodes in various body parts.

Myeloma arises in plasma cells in the bone marrow and is often called multiple myeloma due to the presence of multiple bone lesions, affecting the body's ability to produce healthy blood cells. Sarcoma

develops in connective and supportive tissues such as fat, muscles, bones, and cartilage, with examples including osteosarcoma (bone cancer) and chondrosarcoma (cartilage cancer). Leukemia is a group of blood cancers that affect the bone marrow, leading to the overproduction of immature white blood cells, which impairs the immune system. Cancers can also be classified based on their location, such as breast, colorectal, lung, prostate, blood, bladder, cervical cancers, and more (Carbone, et al. [1]).

Clinical Aspects and Treatment Options for Colorectal Cancer

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide, affecting people of all ages and professions (Daaboul, et al. [2]). CRC typically starts in the rectum and progresses to the colon, originating from polyps in the colon lining that become cancerous. Early detection through colonoscopy is crucial, as lifestyle choices, such as low fiber intake, high-fat diets, smoking, lack of physical activity, diabetes, and alcohol consumption, significantly impact CRC development and progression. Adenocarcinoma is the most common type of CRC, beginning in mucus-producing cells in the colon and rectum. CRC is classified into five stages based on the tumor's invasiveness, which helps in determining the prognosis and treatment plan (Daaboul, et al. [2]).

Treatment by Stage

1. Stage I: Often treated with surgical resection, such as endoscopic mucosal resection (EMR) or transanal endoscopic microsurgery (TEM). Low anterior resection (LAR) may be performed for upper rectal cancer, followed by adjuvant chemoradiotherapy using 5-fluorouracil (5-FU) or capecitabine.
2. Stage II: The role of adjuvant chemotherapy is unclear, but 5-FU remains central. Neoadjuvant chemotherapy and radiation therapy are used to reduce tumor size before surgery, especially if the tumor has invaded nearby tissues.
3. Stage III: Characterized by lymph node metastasis. Treatment typically involves partial colectomy and adjuvant chemotherapy with drugs like oxaliplatin, 5-FU, or folinic acid. For high-risk local recurrence, additional therapies are recommended.
4. Stage IV: The most severe, with metastasis to other organs. Treatment involves surgery to remove tumors, potentially followed by chemotherapy and radiation. Systemic chemotherapy with drugs like 5-FU, capecitabine, irinotecan, and oxaliplatin is commonly used (Daaboul, et al. [2]).

Drawbacks of Existing Treatments

Diagnosis of CRC often occurs at advanced stages, limiting the effectiveness of treatments. Chemotherapy and targeted therapies offer limited survival benefits due to resistance and side effects. Immune checkpoint inhibitors show low response rates in patients with microsatellite instable high tumors. Advanced CRC treatments include chemotherapy combinations and monoclonal antibodies, but issues like drug resistance and side effects persist. Despite advances, the five-year survival rate for metastatic CRC remains low, around 12% (van der Jeught et al., 2018; Xie, et al. [3]). Monoclonal antibodies, while beneficial, can cause significant side effects, such as severe rashes from Cetuximab (Erbitux) targeting the EGFR protein (Xie, et al. [3]).

Drug Repurposing in Cancer Treatment

Drug repurposing has emerged as a valuable strategy in cancer treatment due to the high costs and lengthy processes associated with developing new medications. The rising incidence of new cancer forms and the limitations of current treatments, such as severe side effects and low selectivity, underscore the need for innovative approaches. Drug repurposing offers a cost-effective solution by finding new uses for existing drugs. For example, Albendazole, an antiparasitic drug, is being considered for colorectal cancer treatment due to its potential for fewer side effects and better selectivity compared to traditional chemotherapy and anticancer antibiotics.

Aim and Objectives

The review focuses on the potential of anthelminthic drugs, specifically albendazole and mebendazole, to improve responses to microtubule inhibitors in colorectal cancer (CRC) treatment. The main aim is to highlight recent advances that enhance the effectiveness of these drugs in selectively inhibiting CRC cancer cells with fewer side effects.

Methodology

For this review study, data were gathered through a comprehensive literature search using reliable sources, including peer-reviewed papers and online academic databases. The search included journals, review papers, research databases, clinical trial databases, and official websites to collect crucial information on repurposing albendazole and mebendazole, two benzimidazole derivatives, for colorectal cancer (CRC) therapy. Reputable data sources such as Google Scholar, ScienceDirect, PubMed, and Scopus were utilized, and clinical trial data were obtained from clinicaltrails.gov. Figures and structures were generated using biorender.com. Relevant publications were identified using keywords related to drug repurposing, the use of albendazole and mebendazole in cancer treatment, and nanoparticle delivery systems. Out of 109 articles initially evaluated based on title and keywords, 78 articles remained after abstract review. Ultimately, 61 publications were carefully selected and analyzed for the study. Proper and ethical referencing was ensured using Mendeley software.

Characteristics of Albendazole and Mebendazole

Albendazole (ABZ) and Mebendazole (MBZ) are benzimidazole derivatives originally developed as broad-spectrum anti-helminthic

medications. They are being repurposed for cancer treatment due to their well-documented pharmacokinetic and pharmacodynamic profiles, good safety records, and low cost. Both drugs work by binding to the colchicine-binding site on tubulin, preventing microtubule polymerization, which is essential for cell division. This mechanism not only disrupts glucose uptake in helminthic cells but also induces apoptosis in cancer cells by depolymerizing their microtubules and causing condensed nuclei, thus inhibiting tumor growth, angiogenesis, and cell proliferation (Petersen, et al. [4]).

Antiparasitic Mechanism

ABZ and MBZ block the microtubule networks in both parasites and mammalian cells, leading to cell death by inhibiting glucose absorption and transport. These drugs are effective against a range of parasitic infections, including nematode, trematode, and protozoan diseases. They prevent the assembly of alpha and beta tubulin dimers, essential for microtubule formation, which inhibits parasite growth and leads to their death due to immobilization and lack of glucose uptake.

Pharmacokinetics and Clinical Potential

Despite their effectiveness, ABZ and MBZ have low bioavailability, limiting their full potential in cancer therapy. Clinical studies indicate that ABZ has a bioavailability of less than 5%, while MBZ ranges from 5-10% (Hegazy et al. [5]). Efforts are underway to develop formulations with higher bioavailability to enhance their therapeutic potential in colorectal cancer (CRC), particularly in advanced stages (Son, et al. [6]). These drugs have shown promise in clinical and pre-clinical trials as safe and efficient options for CRC treatment, with ongoing research aimed at maximizing their efficacy (Howard, et al. [7]). Albendazole (ABZ) has a median half-life of 1.5 hours and reaches its maximum concentration (Cmax) of 12.5 to 26.5 ng/ml within 2 hours. The area under the concentration-time curve (AUC) ranges from 44 to 78 ng/h/ml. Its absorption is enhanced by consuming a fatty meal. ABZ is capable of crossing the blood-brain barrier, affecting the central nervous system (CNS). Excretion of ABZ is predominantly biliary (~98%), with minimal urinary excretion (<1%). The drug is metabolized by CYP2J2 and CYP2C19 enzymes from the CYP450 family.

Mebendazole (MBZ) exhibits a bioavailability of 5 to 10% at a dose of 10 mg/kg in a normal patient, regardless of physiological or pathological conditions, although liver or kidney impairment may affect these values. MBZ has a high protein-binding capacity, potentially requiring higher doses for effective formulation. It is metabolized by the same CYP450 enzymes (CYP2J2 and CYP2C19) as albendazole (ABZ). MBZ is primarily excreted in feces (~90%), with minimal urinary (<2%) and biliary excretion. High-fat meals significantly enhance the absorption of both ABZ and MBZ, doubling their area under the concentration-time curve (AUC) and maximum concentration (Cmax) compared to low-fat meals (Son, et al. [6]; Ochoa et al., 2021). Use of Albendazole and Mebendazole in Colon Cancer Treatment Albendazole (ABZ) interacts with microtubules similarly to paclitaxel. It binds to tubulin, preventing its polymerization and promoting microtubule depolymerization, which leads to apoptosis in cancer cells (Al-Bassam & Corbett, n.d.). Research shows that ABZ causes the compacted nuclei typical of apoptosis and disrupts microtubule structure by depolymerizing acetylated-alpha-tubulin and alpha-tubulin, contrasting with paclitaxel, which stabilizes microtubules.

Regulation of Apoptosis and Autophagy in Cancer Cells

ABZ significantly reduces carcinogenesis in colorectal cancer (CRC) cell lines by upregulating apoptosis and autophagy. Studies using human colon adenocarcinoma cell lines (HCT-15, HCT-116, HT-29, and SW480) found that ABZ enhances late apoptotic cells, promotes apoptosis, and induces cell cycle arrest in the subG1 phase (Jung, et al. [8]). ABZ also reverses the reduction of apoptosis and autophagy induced by the antioxidant N-acetyl cysteine (NAC) in CRC cells.

Selective Apoptotic Cell Death

ABZ selectively kills cancer cells, particularly effective in the colorectal cancer cell line HT-29, with an IC50 of less than 1 μM at 48 hours. Both ABZ and mebendazole (MBZ) induce classical apoptosis, characterized by caspase-3 activation, phosphatidylserine exposure, DNA fragmentation, mitochondrial membrane permeability, and reactive oxygen species production. They also cause cell cycle arrest in the G2/M phase and disrupt tubulin polymerization (Petersen, et al. [9]).

Cell Cycle Arrest in Cancer Cells

Research on HT-29 CRC cells shows that ABZ causes significant cell cycle arrest in the G2/M phase, similar to paclitaxel. After 24 hours of treatment, the G2/M phase increased to 58.68% with ABZ, compared to 62.42% with paclitaxel. This was accompanied by reductions in the G1 and S phases (Petersen & Baird, 2021).

Inducing DNA Fragmentation in Cancer Cells

ABZ causes apoptosis in CRC cells by inducing DNA fragmentation, evidenced by an increase in cells with sub-G1 DNA content after 24 and 48 hours of treatment. This DNA damage is partly due to oxidative stress, which provides therapeutic prospects for cancer treatment (Hosoya & Miyagawa, 2014; Mikhed et al., 2015).

Mebendazole's Mode of Action on Cancer Cells

MBZ inhibits tubulin polymerization, angiogenesis, and interacts with ionizing radiation, chemotherapeutic drugs, and the immune system's antitumor response. It prevents tubulin dimers from forming microtubules, causing mitotic arrest and inhibiting cancer cell proliferation and migration. In vivo studies show significant tumor growth inhibition and enhanced antiproliferative effects when combined with chemotherapy agents like 5-FU (Guerini et al., 2019).

Inhibition of Angiogenesis

MBZ inhibits angiogenesis, a crucial factor in CRC growth and metastasis. In vivo studies using mouse models and human umbilical vein endothelial cells (HUVECs) show MBZ suppresses angiogenesis in a dose-dependent manner and increases p53 levels, aiding in cell cycle arrest (Bai, et al. [10,11]).

Antitumor Immune Response Induction

MBZ boosts the immune system's response against CRC metastasis. It promotes proinflammatory (M1) macrophage activity, which enhances phagocytic, antigen-presenting, and cytotoxic functions, and activates T lymphocytes and natural killer cells. MBZ upregulates genes associated with cytokines, surface markers, and chemokines, inducing a tumor-suppressive effect in co-culture setups with differentiated THP-1 macrophages and HT-29 colon cancer cells. It also inhibits the enzyme DYRK1B, modulating the immune response (Blom, et al. [12-14]).

Clinical Evidence of Anti CRC Activity of ABZ and MBZ

Albendazole (ABZ), known for its efficacy and safety in treating parasitic infections, shows promising anticancer properties, although more clinical trials are needed to fully uncover its potential. Clinical evidence supports its effectiveness in treating colorectal cancer (CRC), liver cancer, gastrointestinal (GI) tract cancer, pancreatic cancer, lung cancer, ovarian cancer, prostate cancer, biliary cancer, and other untreatable malignant forms (Chai, et al. [15]). In a notable clinical trial, a 74-year-old patient with metastatic colon cancer showed significant improvement after six weeks of monotherapy with Mebendazole (MBZ) at 100 mg twice daily. The patient experienced almost complete remission of metastases in the lungs and lymph nodes and a partial remission in the liver, with no adverse side effects apart from a temporary increase in liver enzymes (Nygren, et al. [16-32]). Currently, six active and recruiting clinical trials are evaluating MBZ's therapeutic effectiveness, with three specifically focused on CRC treatment. ABZ is also undergoing clinical trials for CRC and refractory solid tumors, with three ongoing studies. Detailed clinical trial data are available on the clinicaltrials.gov website, summarized in Tables 1 & 2. A study exploring the use of albendazole (ABZ) for colorectal cancer (CRC) and hepatocellular carcinoma (HCC) began with seven patients receiving 10 mg of ABZ daily Tables 3 & 4.

Table 1: Summarization of albendazole clinical use for CRC.

Drug	Disease condition	Number of Patients	Drug regimen	Side effects	Summary of findings	References
Albendazole	CRC and HCC	7 patients	10 mg/day	Neutropenia in patients 1, 2 and 8	ABZ use showed an extensive tumor biomarker stabilization	Chai, et al. [15]
Albendazole	Refractory solid tumor	36 patients	400mg-1200mg/day (Oral)	Fatigue, mild GI upset	1 patient, stable marker response, 16% tumor marker responses with drops of 50% or more	Morris, et al. [26]
Albendazole	CRC	12 patients	800mg/day	No severe side effects	Maximum acceptable dose of ABZ determined (Phase I)	Pourgholami, et al. [29]
Albendazole	Malignant Disease, CRC	250 patients	Not mentioned	No severe side effects	Phase 2 clinical trial	Son, et al., [31]

Table 2: Summarization of albendazole clinical use for CRC.

Drug	Disease condition	Number of Patients	Drug regimen	Side effects	Summary of findings	References
Mebendazole	CRC	1	200mg/day for 42 days	No severe side effects	Near complete remission	Nygren, et al. [16]
Mebendazole	CRC (Stage 4)	40	Given as an adjuvant therapy	No severe side effects	Phase 3 clinical trial	Hegazy, et al. [5]
Mebendazole	Variable cancers	207	100mg/day	No severe side effects	Phase 3 clinical trial	Son, et al. [6]
Mebendazole	Malignant Disease, CRC	250 patients	Not mentioned	No severe side effects	Phase 2 clinical trial	Son, et al. [6]

Table 3: Pharmacokinetics of Albendazole.

Pharmacokinetics	Albendazole	Reference
Absorption		
Data types	Values	
Bioavailability	<5%	(Schulz, et al. [30])
C_{max}	12.5-26.5 ng/mL	
T_{max}	2-5 µg	
AUC	44-78 ng.h/ml	
Impact of food	Fatty meal speeds absorption	
Distribution		
Vd	10mg/kg	(Bloom & Ryan, 2012)
Plasma protein binding	70%	
Blood brain barrier (BBB) crossing	Yes	
Metabolism	CYP2J2 and CYP2C19	(Wu, et al. [32])
Excretion		
Clearance	<1%	(Schulz, et al. [30])
Half-life (t1/2)	~1.5 hr	
Excretion of the drug	Urine <1%, Bile ~98%	

Table 4: Pharmacokinetics of Mebendazole.

Pharmacokinetic parameters	Mebendazole (Approved in US in 1974)	Reference
Absorption		
Data types	Values	
Bioavailability	5-10%	Guerrj et al., 2019a
C_{max}	17.5-500 ng/mL	
T_{max}	1.5 hr (.5-3hr range)	
AUC	207.2 ng.h/ml	
Impact of food	Fatty meal speeds absorption	
Dosage	10mg/kg	
Distribution		
Vd	1-2L/kg	Bethesda, et al. [17]
Plasma protein binding	90-95%	
Blood brain barrier (BBB) crossing	Yes	
Metabolism	CYP2J2 and CYP2C19	Hong, et al. [23]
Excretion		
Clearance	<1%	Pawluk et al., 2014
Half-life (t1/2)	3-6 hr	
Excretion of the drug	Urine <2%, Bile -, Feces ~90%	

Three patients experienced neutropenia, but the drug stabilized tumor markers. In another study involving 36 patients with resistant solid tumors, ABZ was administered in doses of 400–1200 mg daily. Common side effects included fatigue and mild gastrointestinal discomfort. The trial found that 16% of the 24 evaluable patients had significant tumor marker responses, with declines of at least 50% from baseline levels, and one patient showed a sustained marker response. In a phase 1 clinical trial for CRC, 12 patients received 800 mg/day of ABZ with no serious adverse effects. Another phase 2 clinical study with 250 patients is ongoing to determine ABZ's impact on malignant diseases. Mebendazole (MBZ) is being studied for CRC in a single-patient trial. The patient took 200 mg per day for 42 days without serious side effects and achieved near-complete remission. In another study, MBZ was used as adjuvant therapy for 40 stage 4 CRC patients, with no serious adverse effects. A phase 3 clinical study involving 207 patients with various malignancies is administering 100 mg of MBZ daily. Additionally, MBZ is undergoing a phase 2 clinical trial for malignant diseases and CRC with 250 patients. Clinical studies on ABZ and MBZ are ongoing for various types and stages of cancer. Preliminary in vivo and in vitro data have shown positive outcomes for CRC treatment with both drugs. However, further trials are necessary to confirm the therapeutic efficacy of ABZ and MBZ in CRC treatment.

Conclusion

Albendazole (ABZ) and Mebendazole (MBZ) are potent, broad-spectrum anti-parasitic and anti-cancer drugs. They effectively treat human intestinal helminthiases (nematodes and cestodes), tissue helminthiases, filarial nematode infections, liver and intestinal trematode infections, and various protozoan disorders. Recently, these drugs have garnered attention for their anti-cancer properties demonstrated in vitro and in vivo in animal models, as well as in some clinical studies. However, more extensive testing is needed before considering them as viable treatments for colorectal cancer (CRC). When used as prescribed, ABZ and MBZ are highly safe anti-parasitic medications. Nonetheless, caution is necessary as liver damage can rarely occur with a single dose. Increasing instances of parasites developing resistance to ABZ have been reported. While both drugs are well-established and secure in the market, their efficacy in treating CRC at both early and later stages remains uncertain. Current studies focusing on ABZ for early-stage CRC and MBZ for later-stage CRC may uncover their full potential. Both medications have very poor bioavailability, necessitating research to develop new methods to enhance their effectiveness.

Limitations

Solubility is crucial for medication absorption, bioavailability, and therapeutic response. The low solubility of Albendazole (ABZ) limits its application, but formulating it into nanostructures can enhance its solubility, bioavailability, and delivery effectiveness. Currently, six different types of ABZ nano formulations have been developed, including host-guest nanocomplexes, liposomes, various polymeric

nanoparticles, and solid lipid nanoparticles (Movahedi et al., 2017). These nanostructures have successfully increased ABZ's solubility. An in vivo experiment using Ehrlich ascites carcinoma-bearing mice demonstrated the anticancer activity of ABZ. The study showed that treatment with ABZ (20 mg/kg) and methotrexate (MTX, 2 mg/kg) inhibited tumor growth by 32%, while MTX alone resulted in a 55% decrease in tumor growth. Both treatments also extended the animals' survival times (Castro et al., 2016). To further enhance ABZ's bioavailability and therapeutic effectiveness, pharmacokinetic and structural activity studies are necessary to address the issues related to its limited absorption.

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