Veterinary Antiparasitic to Human Anticancer

Subjects: Oncology

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Cancer is an extensive disease and the most common cause of morbidity and mortality worldwide. It is characterized by a deregulation of the cell cycle, which primarily results in a progressive loss of control of cellular growth and differentiation. The repurposing of veterinary antiparasitic drugs for the treatment of cancer is gaining traction, as supported by existing literature. A prominent example is the proposal to implement the use of veterinary antiparasitics such as benzimidazole carbamates and halogenated salicylanilides as novel anticancer drugs. These agents have revealed pronounced anti-tumor activities and gained special attention for “double repositioning”, as they are repurposed for different species and diseases simultaneously, acting via different mechanisms depending on their target. As anticancer agents, these compounds employ several mechanisms, including the inhibition of oncogenic signal transduction pathways of mitochondrial respiration and the inhibition of cellular stress responses.

Keywords: drug repurposing ; antiparasitic ; benzimidazole carbamates ; halogenated salicylanilides ; cancer therapy

1. Introduction

Cancer is an extensive disease and the most common cause of morbidity and mortality worldwide. It is characterized by a deregulation of the cell cycle, which primarily results in a progressive loss of control of cellular growth and differentiation [1]. Although there are numerous ongoing studies on anticancer therapy, with many lead candidates at various phases of preclinical or clinical research, only 5% of potential anticancer therapies entering phase I clinical trials have been approved and have entered the market [2]. The standard cancer treatments include surgery, immunotherapy, radiation, and chemotherapy. Currently, chemotherapy is one of the most efficient and potent strategies used to treat malignant tumors. However, the development of multidrug resistance to chemotherapeutics has become a huge impediment to successful cancer treatment. Clearly, new therapeutic alternatives are required to improve cancer diagnosis and treatment. Prior to being marketed as a new drug, the lead compounds face many hurdles during preclinical and clinical studies to ensure their quality, safety, dosage, and efficacy. Clinical trials are costly and time-consuming, requiring ten to fifteen years of dedicated research. The entire development process of getting a single candidate compound onto the market is hindered by the exorbitant costs (approximately $1–$2.5 billion) associated with the necessary trials required for U.S. Food and Drug Administration (FDA) approval [3].

Drug repurposing has gained recognition in the last decade, enabling existing pharmaceutical products to be reconsidered for alternative applications. It has reduced the risk of a drug failing to reach the market, owing to the low burden of adverse effects, the attenuation of the economic load, and the expedition of the approval process [4]. It can also offer an improved risk versus reward trade-off as it shortens the timeline of the drug development process and is also economically feasible when compared to other drug development strategies [5]. Additionally, the preclinical results obtained from the use of repurposed drugs may expedite the process of the preclinical to clinical translation of cancer treatment [6].

2. BZ Carbamates

BZ antiparasitics are a group of heterocyclic aromatic organic compounds that are extensively used in both human and veterinary medicines to inhibit internal parasites. Some important BZ drugs include MZ, albendazole (ABZ), fenbendazole (FZ), flubendazole (FLU), triclabendazole, parbendazole, oxibendazole, and ricobendazole. In the last few years, some of these have been successfully investigated for various types of cancers worldwide.

2.1. Mechanism of Action of BZ Carbamates

The molecular mode of action of BZ carbamates involves inhibiting the polymerization of tubulin and facilitating the disruption of microtubules in parasite cells (**Figure 1**) [7]. An in vitro study using the extracts of helminthic and mammalian tubulin has implicated tubulin as the leading molecular target of BZ carbamates [8]. Tubulin is pivotal to cell motility,

proliferation, and division; the intercellular transport of organelles; the maintenance of cell shape; and the secretion process of cells in all living organisms [9]. By blocking microtubule elongation in worms, BZ carbamates perturb glucose uptake in cells. Eventually, the glycogen reserves are exhausted, and their energy management mechanisms are depleted, culminating in the death of the parasites [10].

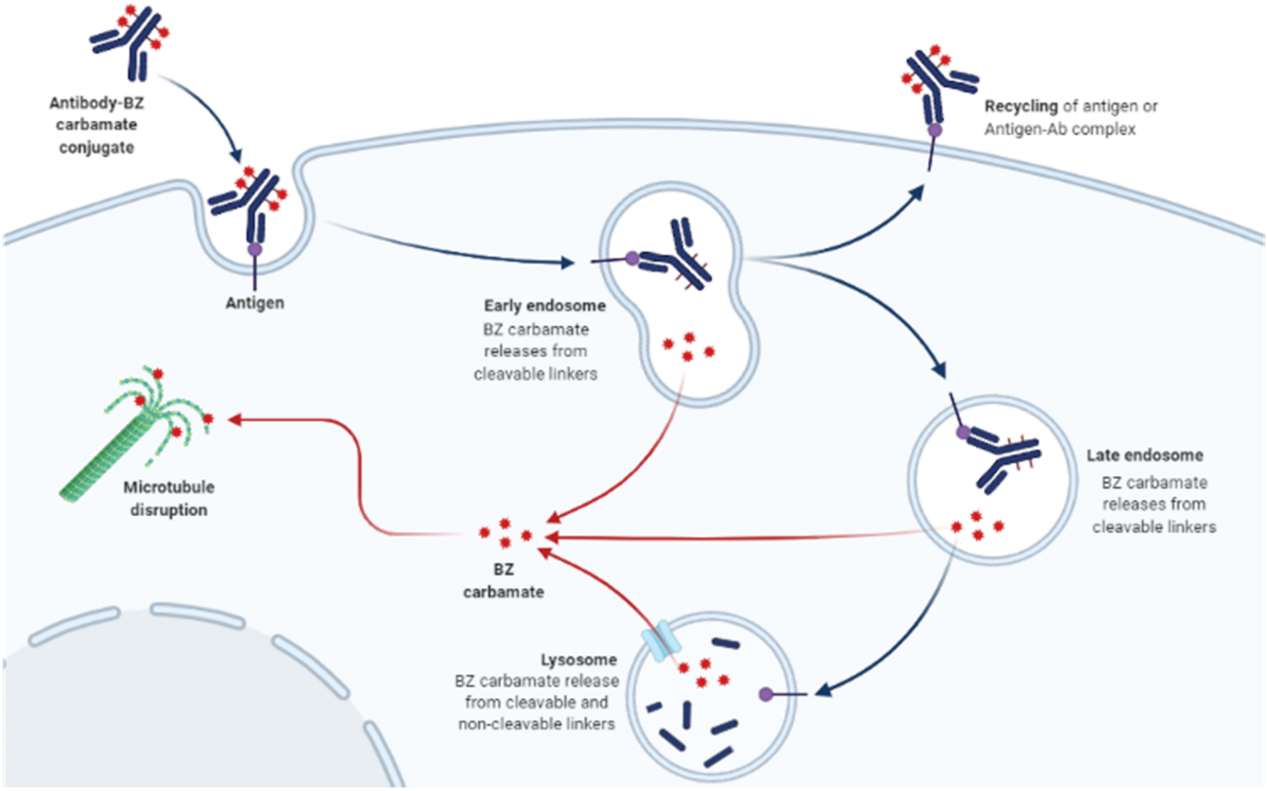

Figure 1. Mechanism of action of benzimidazole (BZ) carbamates targeting tubulin. Tubulin is the leading molecular target of BZ carbamates. They selectively bind to parasitic β-tubulin, promoting their immobilization and death. dapted from "Antibody-Drug Conjugate Drug Release", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates, accessed on 10 March 2022.

2.2. Anticancer Activity of BZ Carbamates

BZ carbamates are cancer cell-selective, causing minimal cytotoxicity in normal cells but increased cytotoxicity in different tumor cells. Several studies have reported that BZ carbamates inhibit the polymerization of mammalian tubulin in vitro. Whether the same effect would be observed in human cells, and if so, whether such targeted efforts could be effective against tumors, are some questions raised by these reports. Lacey et al. first addressed the activity of BZ carbamates against mouse leukemia cells L1210 in 1985 [11]. A more thorough inquiry into the antitumor effects of BZ carbamates was carried out; the most promising outcomes of this inquiry are summarized in **Table 1**. The general pharmacokinetic properties of BZ carbamates are as follows: slow absorption; wide distribution throughout the body; extensive hepatic metabolism; and excretion via urine and feces (**Figure 2**a). Their common side effects are fever, nausea, vomiting, abdominal discomfort, and hepatotoxicity. The low intestinal absorption rate of BZ carbamates may make it difficult for them to reach concentrations in the systemic circulation effective in treating cancers in humans. Increased bioavailability is necessary to enhance their antitumor effect, making them safe and well tolerable in human and veterinary use.

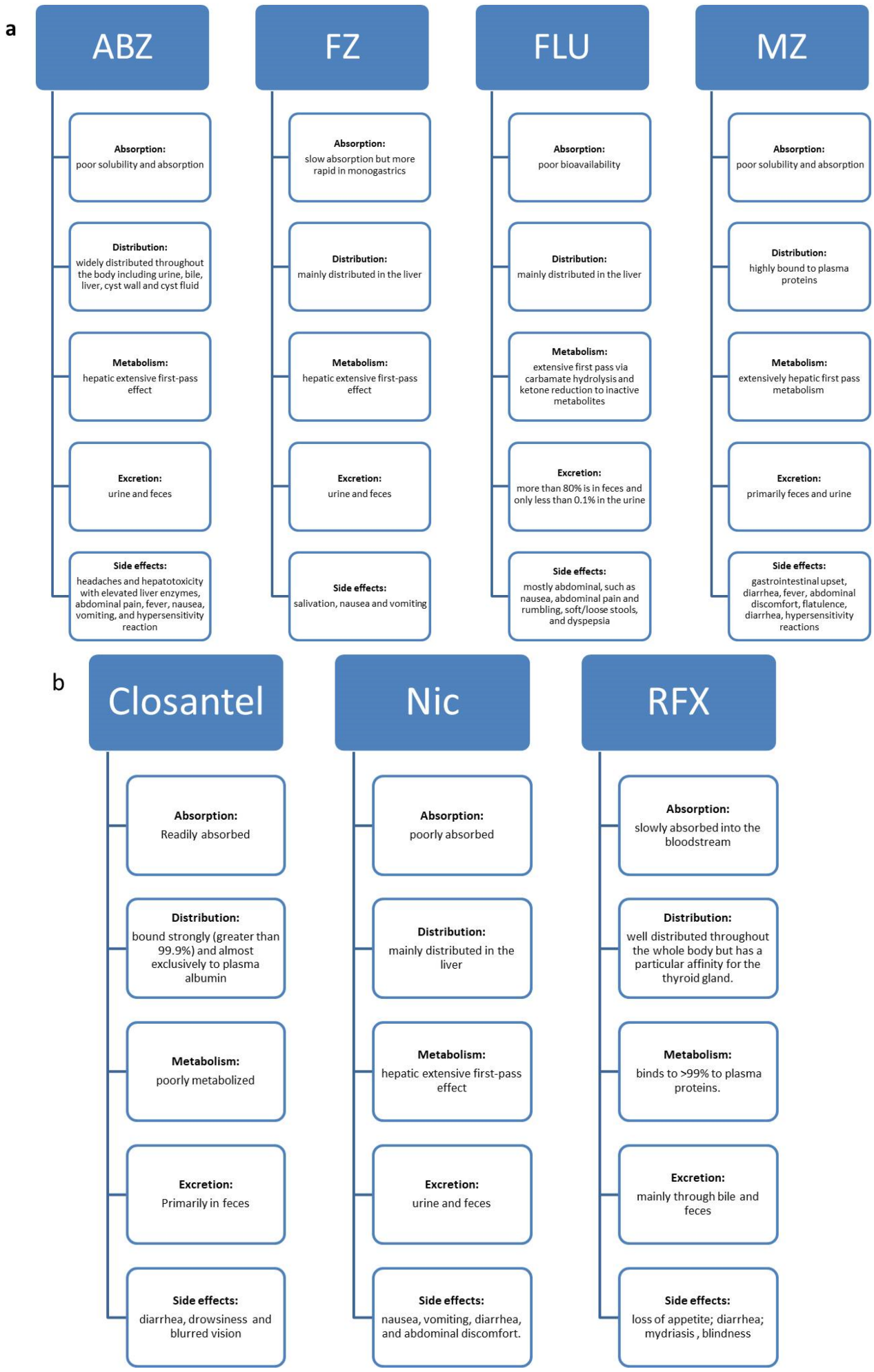

Figure 2. Pharmacokinetic properties and side effects of veterinary antiparasitic drugs. (**a**) The BZ carbamate drugs are poorly absorbed; have a wide distribution in the body; show extensive hepatic metabolism; and are excreted via feces and

urine. (**b**) The halogenated salicylanilides (HS) antiparasitic drugs show poor absorption, distribution throughout the body, are poorly metabolized and are excreted in bile, feces, or urine.

Table 1. Anticancer activity of BZ carbamates.

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	Hep G2 and Hep3B	in vitro	*Mice*	ABZ	HCC	Cytotoxicity	[12]
Human	Hep G2 and Hep3B, PLC/PRF/5 and SKHEP-1	in vitro					
	SKHEP-1	in vivo	*Mice*	ABZ	HCC	Tubulin disruption	[13]
Rat	HTC, Novikoff	in vitro					
Mice	Hep1-6	in vitro					
Human	SW480, SW620, HCT8 and Caco2	in vitro	*Mice*	ABZ, RBZ, FLU	Intestinal cancer	Tubulin disruption	[14]
Human	HT-29	in vitro	*Mice*	ABZ	CRC	Apoptosis	[15]
Human	CEM/dEpoB300	in vitro	*Mice*	ABZ	Leukemia	Apoptosis	[16]
Human	1A9Pc TX22	in vitro	*Mice*	ABZ	OC	Apoptosis	[17]
Mouse	EMT6	in vitro in vivo	*Mice*	FZ	Mammary carcinoma	Cytotoxicity	[18]
Human	H460 and A549	in vitro in vivo	*nu/nu mice*	FZ	LC	microtubule disruption, p53 activation and down regulation of pivotal glycolytic enzymes	[19]
Human	P493-6	in vitro in vivo	*SCID mice*	FZ	Lymphoma	Tubulin disruption	[20]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Mice	EMT6	in vitro in vivo	*BALB/c Rw mice*	FZ	Mammary carcinoma	Tubulin disruption	[21]
Human	OCI-AML-2	in vitro in vivo	*SCID mice*	FLU	Leukaemia and Myeloma	Tubulin disruption	[22]
Human	MDA-MB-231, BT-549, SK-BR-3 and MCF-7	in vitro in vivo	*Mice*	FLU	BC	Tubulin disruption	[23]
Human	TNBC cell lines MDA-MB-231 and MDA-MB-468	in vitro in vivo	*Mice*	FLU	BC	Apoptosis	[24]
Human	BT474, SK-BR-3, MDA-MB-453, JIMT-1	in vitro in vivo	*BALB/c mice*	FLU	BC	Tubulin disruption Apoptosis	[25]
Human	HCT116, RKO and SW480	in vitro in vivo	*BALB/c mice*	FLU	CRC	Apoptosis	[26]
Human	H295R and SW-13	in vitro	*Mice*	MZ	Adrenocortical carcinoma	Apoptosis	[27]
Human	H460, A549, H1299 and WI-38	in vitro in vivo	*Mice*	MZ	LC	Tubulin disruption, Apoptosis	[28]
Human	HCT 116 and RKO	in silico	-	MZ	CC	Tubulin disruption	[29]
Human	DLD-1, HCT-116, HT-29 and SW480	in vitro	*Mice*	MZ	CC	Tubulin disruption	[30]
Human	ACP-02, ACP-03 and AGP-01	in vitro in vivo	*Mice*	MZ	GC	Tubulin disruption	[31]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Mouse	GL261	in vitro in vivo	*C57BL6 Mice*	MZ	Brain tumour	Tubulin disruption Apoptosis	[32]
Human	GBM U87-MG, D54, H80, H247, H392, H397, H502 and H566	in vitro in vivo	*C57BL/6 mice*	MZ	Brain cancer	Apoptosis	[33]
Mouse	GL261						
Human	D425 MB	in vivo	*p53 mice*	MZ	Medullo-blastoma	Tubulin disruption	[34]
Human	293T and hTERT-RPE1	in vitro in vivo	*nu/nu* athymic mice	MZ	Medullo-blastoma	Hedgehog inhibitor	[35]
Murine	CP2 and SP1	in vitro in vivo	*BALB/c mice*	MZ	PC	Tubulin disruption	[36]
Human	KKU-M213	in vitro in vivo	*Nude mice*	MZ	Bile duct Cancer	Apoptosis	[37]
Human	PANC-1	in vitro	*Mice*	MZ	Pancreatic cancer	-	[38]
Human	CAL27 and HCC15	in vitro in vivo	*Nude mice*	MZ	Head and neck cancer	Apoptosis	[39]
Human	SK-Br-3	in vivo	*Mice*	MZ	BC	Tubulin disruption	[40]
Human	M-14 and SK-Mel-19	in vitro	*Mice*	MZ	Melanoma	Tubulin disruption	[41]
Human	MM622, MM540, D08, MM329, D17, and UACC1097	in vitro in vivo	*Mice*	MZ	Melanoma	Tubulin disruption	[42]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	$NRAS^{Q61K}$	in vitro in vivo in silico	*Athymic mice*	MZ	Melanoma	Apoptosis	[43]
Human	GL261	in vitro in vivo	*C57BL/6 mice*	MZ	Brain cancer	Tubulin disruption	[44]
Human	Burkitt's lymphoma Ramos cells, Hela cells, PANC-1 cells, and HepG2 cells	in vivo	*Zebra-fish*	Closantel	Lymphoma, cervical cancer, PC, and LC	Suppression of antiangiogenesis and Closantel	[45]
Human	Du146	in vitro	*Mice*	Nic	PC	Inhibition of STAT3 Pathway	[46]
Human	HEK293 cells	in vitro	*Mice*	Nic	PC and BC	Inhibition of Wnt/β-catenin Pathway	[47]
Human	MCF7 and MDA-MB-231	in vitro in vivo	*NOD/SCID mice*	Nic	BC	Apoptosis and downregulation stem pathways	[48]
Human	MDA-MB-231	in vitro in vivo	*BALB/c nude mice*	Nic and cisplatin	BC	Apoptosis and inhibition of Akt, ERK, and Src pathways	[49]
Human	MDA-MB-468 and MCF-7	in vitro	*Mice*	Nic	BC	Inhibition of cell motility and STAT3 activity	[50]
Human	TNBC MDA-MB-231, MDA-MB-468 and Hs578T	in vitro in vivo	*Athymic nude mice*	Nic	BC	Inhibition of Wnt/β-catenin Pathway	[51]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Mouse	4T1	in vitro in vivo	*BALB/c mice*	Nic	BC	Apoptosis and suppression of cell migration and invasion	[52]
Human	MDA-MB-231, MDA-MB-468 and MCF-7	in vitro					
Human	2LMP, SUM159, HCC1187, and HCC1143	in vitro in vivo	*NOD/ SCID mice*	Nic	BC	Cytotoxicity	[53]
Human	K562 and KBM5-T315I cells	in vitro in vivo	*NOD mice*	Nic	Chronic myelogenous leukemia	Inhibition of FOXM1/β-catenin Pathway	[54]
Human	HL-60, U937, OCI-AML3, Molm13, MV4-11, and U266 cells	in vitro in vivo	*BALB/c mice*	Nic	Acute myelogenous leukemia	Apoptosis and Inhibition of NF-κB pathway	[55]
Human	MCF7	in vitro	*Mice*	Nic	Adeno-carcinoma	Inhibition of PI3K-dependent signalling	[56]
	HCC1954				Carcinoma		
	BT-474	in vivo			Ductal Carcinoma		
	MDA-MB-361 and				Adeno-carcinoma		
	SKBR3 cell	in silico			Adeno-carcinoma		
Human	HCT116, SW620, and HT29	in vivo	*Mice*	Nic	CC	Inhibition of STAT3 phosphorylation	[57]
Human	HCT116, SW480, DLD1 and 293 cells	in vitro in vivo	*APC-MIN mice*	Nic	CC	Inhibition of Wnt/Snail-mediated EMT	[58]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	HCT116, SW620, LS174T, SW480, and DLD-1	in vitro in vivo in situ	*NOD/SCID mice*	Nic	CC	Inhibition of S100A4-induced metastasis formation	[59]
Human	HT29, HCT116, CaCO2 and MCF-10A	in vitro in vivo	*NOD/SCID mice*	Nic	CC	Inhibition of Wnt/ β-catenin Pathway	[60]
Human	HEK293T, U2OS, WIDR, DLD-1, CRC 240, COLO205, CRC57 and HCT116	in vitro	*Mice*	Nic	CC	Induction of autophagy and inhibition of Wnt/ β-catenin Pathway	[61]
Human	SW480 and SW620	in vitro	*Mice*	Nic	CC	Reduction of Wnt activity	[62]
Rodent	CC531	in vivo					
Murine	MC38	in vitro in vivo					
Human	HCT116	in vitro	*APC$^{min/+}$ mouse*	Nic-EN and oxyclozanide	CC	Mitochondrial uncoupling	[63]
Rodent	C2C12	in vitro in vivo					
Human	SKOV3 and CP70	in vitro in vivo	*SCID mice*	Nic	OC	Induction of metabolic shift to glycolysis	[64]
Human	OVCAR-3, SKOV-3 and A2780	in vitro in vivo	*NOD/ SCID mice*	Nic	OC	Inhibition of CP70sps and primary OTICs	[65]
Human	SKOV3.ip1	in vitro in vivo	*Mice*	Nic	OC	Inhibition of Wnt/ β-catenin Pathway	[66]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	SKOV3 and HO8910	in vitro in vivo	*Athymic Nude mice*	Nic	OC	Mitochondrial Respiration and aerobic glycolysis	[67]
Human	A2780ip2, A2780cp20, and SKOV3Trip2	in vitro in vivo	*SCID mice*	Nic	OC	Inhibition of Wnt/β-catenin, mTOR and STAT3 pathways	[68]
Human	Tumorspheres	in vitro in vivo	*Mice*	Nic and its analogs in combination with carboplatin	OC	Cytotoxicity	[69]
Human	HepG2 and QGY7701	in vitro	*Mice*	Nic	HCC	Apoptosis and suppression of ATF3 expression	[70]
Human	NSCLC, NCI-H1299 and HCT116	in vitro	*Mice*	Nic	LC	Apoptosis through ROS-mediated p38 MAPK-c-Jun activation	[71]
Human	SK-Hep-1 and Huh7	in vitro	*Mice*	Nic	HCC	Inhibition of metastasis of HCC, and CD10	[72]
Human	HCC827, H1650, and H1975	in vitro in vivo	*Nu/Nu nude mice*	Nic	LC	Inhibition of STAT3 phosphorylation	[73]
Human	A549/DDP	in vitro	*Mice*	Nic combined with cisplatin (DDP)	Cisplatin-resistant LC	Apoptosis and reduction of c-myc protein	[74]
Human	HepG2, QGY-7703 and SMMC-7721	in vitro	*Mice*	Nic	HCC	Inhibition of cell growth and STAT3 pathway	[75]

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	Lung adenocarcinoma (549, EKVX, H358, Hop62, H322M, H522, H838, and H23), large cell lung carcinoma (H460, Hop92), NCSLC (H1299, H810) and small cell LC (H82)	in vitro	*Mice*	Nic	LC	Reduction in proliferation and inhibition of S100A4 protein	[76]
Human	U-87 MG	in vitro	*Mice*	Nic	Glioblastoma	Cell toxicity and inhibition of Wnt/β-catenin, PI3K/AKT, MAPK/ERK, and STAT3	[77]
Human	TS15-88, GSC11	in vitro in vivo	*Athymic nude mice*	Nic and/or temo-zolomide	Glioblastoma	Inhibition of the expression of epithelial-mesenchymal transition-related markers, Zeb1, N-cadherin, and β-catenin	[78]
Human	LN229, T98G, U87(MG), U138, and U373(MG)	in vitro in vivo	*Rag2$^{-/-}$Il2rg$^{-/-}$ and SCID/ Beige mice*	Nic	Glioblastoma	Cytotoxicity and diminished the pGBMs' malignant potential	[79]
Human	C4-2B, LNCaP and DU145	in vitro	*Mice*	Nic with enzalutamide	Enzalutamide resistance PC	Inhibition of migration, invasion and IL6-Stat3-AR pathway	[80]
Human	LNCaP, VcaP, CWR22Rv1, PC3 and HEK293	in vitro in vivo	*SCID mice*	Nic with enzalutamide	Castration-resistant PC	Inhibition of AR variant and enzalutamide-resistant tumor growth	[81]

Cell Origin	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	CaLo, HeLa, SiHa, CasKi, DoTc2, ViBo and C-33A	in vitro and in vivo	*SCID mice*	Nic	Cervical cancer	Inhibition of mTOR signaling	[82]
Human	ESO26, FLO-1, KYAE-1, OE33, SK-GT-4, and OE19	in vitro and in vivo	*SCID mice*	Nic	Esophageal cancer	Inhibition of Wnt/β-catenin	[83]
Human	BE3, CE48T/VGH and CE81T/VGH	in vitro	*Mice*	Nic	Esophageal cancer	Inhibition of cell proliferation and STAT3 pathway	[84]
Human	Osteosarcoma cells	in vitro and in vivo	*Mouse*	Nic	Osteosarcoma	Apoptosis and target multiple signaling pathways	[85]
Human	NCI-H295R and SW-13	in vitro and in vivo	*Nu*$^{+}$/*Nu*$^{+}$ *mice*	Nic	Adrenocortical Carcinoma	Induction of G_1 cell-cycle arrest mitochondrial uncoupling	[86]
Human	A498 and Caki-1	in vitro and in vivo	*Athymic nude mice*	Nic	Renal cell carcinoma	Inhibition of cell proliferation, migration and cell cycle progression	[87]
Human	SCC4 and SCC25	in vitro and in vivo	*Mice*	Nic	Oral cancer	Inhibition of cancer stemness, extracellular matrix remodeling, and metastasis through dysregulation Wnt/β-catenin signaling pathway	[88]
Human	H929, MM1S, U266 and BMSC	in vitro and in vivo	*BALB/c nude mice*	RFX	Multiple myeloma	Apoptosis and inhibition of DNA synthesis	[89]

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PubMed, Google Scholar, and CTD databases were used to summarize the data for the antitumor effects of BZ carbamates (ABZ—albendazole, BC—bromocriptine, CC—colon cancer, FLU—flubendazole, GBC—gallbladder cancer, HCC—hepatocellular carcinoma, ICD—immunogenic cell death, LC—lung cancer, MZ—Mebendazole, Nic—Niclosamide, Nic-EN—Niclosamide ethanolamine, OC—ovarian cancer, PC—prostate cancer, RBZ—Ricobendazole, RFX—Rafoxanide.

2.3. Anticancer Activity of BZ Carbamates in Clinical Models

A pilot study of the effect of ABZ in seven patients with advanced hepatocellular carcinoma and CRC with hepatic metastases refractory to other forms of therapy was performed for 28 days. Patients received ABZ orally (10 mg/kg/day) in two divided doses. The levels of tumor markers, carcinoembryonic antigen, and a-fetoprotein were measured routinely. The parameters of hematological and biochemical indices were also obtained to monitor bone marrow, kidney, and liver toxicities. The results of this research further confirm the tolerance for ABZ in patients, with the only side effect of concern being acute neutropenia in three of the patients. Moreover, ABZ significantly reduced the tumor markers in two patients, while in three other patients the markers were stabilized, demonstrating that ABZ possesses antitumor effects in humans [94].

At present, no clinical study on FLU and FZ in human malignancies has been conducted. A more thorough report on clinical trials documenting the antitumor effects of antiparasitic drugs is summarized in **Table 2**.

Table 2. Application of veterinary antiparasitic drugs in clinical trials used to treat different types of cancers.

Cell Source	Cell Lines	Procedure of Study	Species	Antiparasitics	Cancer Type	Target Pathway	Reference
Human	A431 and A375	in vitro	*BALB/c nude mice*	RFX	Skin cancer	Inhibition of CDK4/6	[90]
		in vivo					
Human	HCT-116 and HT-29	in vitro	*Apc$^{min/+}$* mice	RFX	CRC	Inhibition of cell proliferation	[91]
		in vivo					
Human	HCT-116 and DLD1 cells	in vitro	*BALB/c nude mice*	RFX	CRC	Induction of ICD of CRC cells	[92]
		in vivo					
Human	SGC-7901 and BGC-823, GES-1	in vitro	*BALB/c nude mice*	RFX	GC	Apoptosis and inhibition of PI3K/Akt/mTOR signaling pathway	[93]

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Antiparasitics	Cancer Type	Title	Phase	Purpose	Status/Result	Identifier/Ref
ABZ	HCC or CRC	Pilot Study Of Albendazole In Patients With V600E Advanced Malignancy. Effect On Serum Tumor Markers/High Incidence Of Neutropenia	I	Evaluation of anticancer activity	Stabilization of the disease, but because of neutropenia, treatment was stopped on day 19	[95]
ABZ	Solid tumors	Oral Albendazole In Patients With Advanced Cancer	I	To characterize the pharmacokinetics and preliminary evidence of efficacy.	Well tolerated, and the associated adverse effects of MZ are basic mechanisms of	[96]
MZ	Adreno-cortical carcinoma	Long-Term Disease Control in Metastatic Adrenocortical Carcinoma	CS	To describe successful long-term tumor control	No disease-related symptoms were found.	[97]
MZ	GC	Repositioning Drug From Bench To Bedside: Tumour Remission By The Antihelmintic Drug Mebendazole In Refractory Metastatic Colon Cancer	CS	Repositioning drugs for use in advanced CC		
MZ	Glio-blastoma	Mebendazole In Newly Diagnosed High Grade Glioma Patients Receiving Temozolomide (Mebendazole)	1	To find the highest dose and the efficiency of MZ to slow the growth of the brain tumor	Active, not recruiting	NCT01729260
Refractory Solid tumors	Mixed Tumors	Phase I Clinical Trial To Determine Tolerated Dose Of Oral Albendazole	I	To determine the safety, tolerability, and the maximal tolerated dose.	2400 mg/day from 1200 mg bid. Decreased plasma VEGF and 16% patients stabilized tumor marker response with a fall of at least 50%	[94]

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Antiparasitics	Title	Phase	Purpose	Status/Result	Identifier/Ref
Type					
MZ	A Phase I Study of Mebendazole for the Treatment of Pediatric Gliomas	1	To determine the safety and efficacy of MZ	Recruiting	NCT01837862
Pediatric Gliomas					
MZ	A Clinical Safety and Efficacy Study of Mebendazole on GI Cancer or Cancer of Unknown Origin	1	To determine the safety and efficacy of MZ (ReposMZ)	Terminated (Lack of effect)	NCT03628079
GI Cancer					
MZ		2			
Cancer of Unknown Origin					
(ReposMZ)					
CC, PC and ovarian epithelial cancer	Safety, Tolerability and Efficacy of Metabolic Combination Treatments on Cancer (METRICS)	1	To determine the effectiveness of a regimen of selected metabolic treatments for cancer patients and to perform exploratory analysis on the relationship between the degree of response and changes in biochemical markers	Not yet recruiting	NCT02201381
MZ					
MZ	Mebendazole as Adjuvant Treatment for Colon Cancer	3	MZ as adjuvant treatment for colon cancer	Recruiting	NCT03925662
CC					
Nic	A Study of Niclosamide in Patients With Resectable Colon Cancer	1	To determine the maximum tolerated dose (MTD)	Terminated (low accrual)	NCT02687009
CC					
Nic	Drug Trial to Investigate the Safety and Efficacy of Niclosamide Tablets in Patients With Metastases of a Colorectal Cancer Progressing After Therapy (Nikold)	2	To evaluate the safety and efficacy of oral appliqued Nic	Unknown	NCT02519582
CRC					

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Antiparasitics	Cancer Type	Title	Phase	Purpose	Status/Result	Identifier/Ref
Nic	PC	Niclosamide and Enzalutamide in Treating Patients With Castration-Resistant, Metastatic PC	1	To determine the side effects and best dose of Nic	Completed (No result posted)	NCT02532114
Nic	Metastatic PC	Enzalutamide and Niclosamide in Treating Patients With Recurrent or Metastatic Castration-Resistant PC	1	To determine the best dose and side effects of Nic when given together with enzalutamide	Recruiting	NCT03123978
Nic	Recurrent PC	Abiraterone Acetate, Niclosamide, and Prednisone in Treating Patients With Hormone-Resistant PC	2	To determine the side effects and how well abiraterone acetate, Nic, and prednisone work in treating patients with hormone-resistant PC	Recruiting	NCT02807805
Nic	Stage IV PC	Niclosamide in Treating Patients With Stage IV PC	1	To determine the best dose and side effects of Nic	Recruiting	NCT03506373

NCBI database was used to inquire about the clinical trials on antitumor effects of antiparasitic drugs. ABZ—albendazole; MZ—mebendazole, Nic—niclosamide, CS—clinical study; CC—colon cancer; CRC—colorectal cancer; HCC—hepatocellular carcinoma; PS—pilot Study.

3. HS

Salicylanilides are a very large group of compounds that show efficient activity against certain types of parasites. Their basic chemical structure consists of a salicylic acid ring and an anilide ring. Examples of HS drugs with potent antihelminthic activity are Nic, rafoxanide (RFX), and closantel.

3.1. Mechanism of Action of HS

The primary mechanism of action of HS was investigated in vitro using houseflies and rat liver mitochondria. The authors found an association with the uncoupling of oxidative phosphorylation that halts the production of ATP. This seems to happen through the suppression of the activity of two enzymes, succinate dehydrogenase and fumarate reductase, and thus impairs the motility of parasites and eventually causes death [98]. Several researchers have subsequently confirmed the proposed mechanism in vivo [45][99].

3.2. Anticancer Activity of HS

Several HS group drugs have been investigated for their effect on cancer in experimental and preclinical models. The pharmacokinetic properties and common side effects of HS drugs are shown in **Figure 2**b.

3.3. Anticancer Activity of HS in Clinical Models

Nic underwent clinical trials in patients with resectable colon cancer in 2017, but was terminated because of the low enrolment rate (NCT02687009). Two other clinical studies are currently underway to test the anticancer effects of Nic in patients with FAP (NCT04296851) and progression of metastases of colorectal cancer after therapy (NCT02519582). Although a phase I trial of Nic administered together with enzalutamide in patients with castration-resistant prostate cancer has concluded, anticipating the commencement of a phase 2 trial (NCT02532114), another phase I clinical trial is investigating the potent dose and side effects of Nic in combination with enzalutamide to treat castration-resistant prostate cancer patients (NCT03123978). A phase II clinical trial is also ongoing to evaluate the efficacy of abiraterone acetate, Nic, and prednisone in treating patients with hormone-resistant prostate cancer (NCT02807805).