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Review

Anthelmintics for drug repurposing: Opportunities and challenges

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ABSTRACT

Drug repositioning is defined as a process to identify a new application for drugs. This approach is critical as it takes advantage of well-known pharmacokinetics, pharmacodynamics, and toxicity profiles of the drugs; thus, the chance of their future failure decreases, and the cost of their development and the required time for their approval are reduced. Anthelmintics, which are antiparasitic drugs, have recently demonstrated promising anticancer effects *in vitro* and *in vivo*. This literature review focuses on the potential of anthelmintics for repositioning in the treatment of cancers. It also discusses their pharmacokinetics and pharmacodynamics as antiparasitic drugs, proposed anticancer mechanisms, present development conditions, challenges in cancer therapy, and strategies to overcome these challenges.

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Contents

1. Introduction	435
2. Physicochemical properties of anthelmintics	435
2.1. Pharmacokinetics and pharmacodynamic	435
2.1.1. Metabolism and excretion	436
3. Efficacy and spectra of activity of anthelmintics	436
3.1. Benzimidazoles and pro-benzimidazoles	436
3.2. Imidazothiazoles and tetrahydropyrimidines	437
3.3. Macrocyclic lactones	437
4. Mode of action as anti-cancer agents	437
4.1. Anthelmintics under clinical trials	437
4.1.1. Albendazole	437
4.1.2. Ivermectin	437
4.1.3. Levamisole	438
4.1.4. Mebendazole	439
4.1.5. Niclosamide	439
4.2. Anthelmintics with promising anti-cancer effects	439
4.2.1. Flubendazole	439
4.2.2. Rafoxanide	439
4.2.3. Nitazoxanide	439
4.2.4. Praziquantel	440

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4.2.5.	Pyrvinium pamoate	440
4.2.6.	Piperazine	440
4.2.7.	Eprinomectin	440
5.	Challenges with anthelmintics in cancer therapy	440
6.	Strategies to overcome these challenges	441
6.1.	Nanoparticles for improving the solubility of anthelmintics	441
6.2.	Pro-drug formulations	441
6.3.	Production of solid dispersions	441
7.	Conclusion and future perspectives	443
	Funding	443
	Declaration of Competing Interest	443
	References	443

1. Introduction

Cancer, with rapidly increasing incidence (18.1 million new cases and annual incidence of 3–5%, 2018) and mortality (9.6 million patients, 2018), is one of the most critical health issues throughout the world (Hassankhani, Rahmani, Taleghani, Sanaat, & Dehghannezhad, 2020; J. Zhang et al., 2019). Many efforts have been made to develop anti-cancer agents, and various lead candidates have been developed at preclinical and clinical stages; however, only 5% of compounds that enter phase I clinical trials receive the end approval (Kato et al., 2015).

Generally, to develop a novel anti-neoplastic agent, various natural-based compounds derived from microorganisms, animals, and plants are evaluated by a variety of pharmacological and biochemical analyses, that often continue with the whole chemical synthesis or modification of determined individual compounds (Čáňová, Rozkydalová, & Rudolf, 2017). Further, this process of drug development has been complemented by screening the assays of libraries of all recognized and determined compounds to select the potentially appropriate candidates for further assessment. However, these strategies are associated with several difficulties, such as financial burden, laboriousness, and longer duration for drug development (Čáňová et al., 2017). Currently, the development of a new drug takes 10–15 years, and the success rate is negligible (approximately 2%). As the cost of clinical trials has recently increased, the number of new drugs, approved by Food and Drug Administration (FDA) has been decreased (Laudisi, Marônek, Di Grazia, Monteleone, & Stolfi, 2020; Scannell, Blanckley, Boldon, & Warrington, 2012). Between 2004 and 2012, on average 2–3 billion US dollars were spent for a pharmaceutical clinical trial, and considering the inflation, this value would be higher now (Sertkaya, Wong, Jessup, & Beleche, 2016). Companies have recently claimed that developing new drugs is unfavorable and risky (Laudisi et al., 2020); therefore, new strategies are required to optimize the development of novel and efficacious anti-neoplastic agents. One of the favorite strategies is drug repositioning (or repurposing) (Čáňová et al., 2017).

Drug repositioning is a process by which a new application for an existing drug can be provided (Yaseen & Akram, 2019). This is a promising approach since many existing drugs are developed by standardized constructing techniques and have well-known pharmacokinetics, pharmacodynamics, and toxicity profiles; therefore, the chance of their future failure decreases owing to their adverse effects. Also, the cost of the development of a repositioned drug (50–60% compared to new drugs) and the required time (3–12 years) for its approval are reduced (Armando, Mengual Gómez, & Gomez, 2020; Čáňová et al., 2017). In addition, while approximately 10% of new drug applications reach the market, this value for repositioned drugs is approximately 30%, encouraging pharmaceutical companies to reposition the existing assets (Ashburn & Thor, 2004). Currently,

more than 270 drugs are being assessed for their potential anti-tumor activity (Armando et al., 2020), and from these, approximately 57% have demonstrated anti-tumor effects in human clinical trials (Xue, Li, Xie, & Wang, 2018). One of the important groups of drugs, which have demonstrated anti-tumor activity, is anthelmintic agents.

Anthelmintics are a series of compounds, demonstrating anti-infectious activity against helminths, which settle in the human intestine (Laudisi et al., 2020). These therapeutics were initially developed for the treatment of veterinary parasites and have subsequently been used for patients, suffering from helminthiasis. Anthelmintics have a variety of chemical entities and function through changing the parasite (worm) metabolism or paralyzing the parasite, in which the parasite can be eliminated by the host immune system (Laudisi et al., 2020; Rajagopal et al., 2019). It has been demonstrated that some of the anthelmintics are able to inhibit critical oncogenic pathways, such as Wnt/ β -catenin, signal transducer and activator of transcription proteins 3 (STAT3), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (Laudisi et al., 2020); therefore, their application for cancer treatment has been considered.

This literature review provides an overview of the updated information about anthelmintics with anti-cancer activity and their possible use as anti-cancer agents (i.e., repositioned drugs). These anthelmintics are characterized, in terms of their i) structural analysis, ii) tumor type-specific effects, iii) mode of action, and iv) up to date data about the clinical trials. It also discusses the challenges for their applications as anti-cancer agents, such as low water solubility and low bioavailability, and strategies to overcome these challenges, such as nanocarrier-based formulations, pro-drug formulations, and solid dispersions (SDs).

2. Physicochemical properties of anthelmintics

2.1. Pharmacokinetics and pharmacodynamic

According to chemical structures and pharmacological properties, there are seven classes of modern anthelmintics, including benzimidazoles (BZDs; cambendazole, parbendazole, thiabendazole, mebendazole, fenbendazole, oxfendazole, oxibendazole, albendazole, ricobendazole, and triclabendazole), probenzimidazoles (pro-BZDs; netobimin, febantel, and thiophanate), tetrahydropyrimidines (THPs; pyrantel pamoate, pyrantel tartrate, and morantel), imidazothiazoles (IMTs; levamisole), iso-quinolines, salicylanilides (closantel, niclosamide, and rafoxanide), and macrocyclic lactones (MLs, avermectins and milbemycins or endectocides; ivermectin, abamectin, moxidectin, doramectin, eprinomectin, selamectin, and milbemycin oxime) (Barbosa, Löbenberg, de Araujo, & Bou-Chacra, 2019; Gokbulut & McKellar, 2018).

The pharmacokinetics of anthelmintics, including their absorption, distribution, and biotransformation/elimination pattern, are critical factors, which determine the time to a maximum effect-site concentration of the drugs (anti-parasitic) in the body. Pharmacokinetics, as a determinant factor for drug exposure in the parasitic location, are strongly correlated with pharmacodynamics (drug effect) (Lanusse et al., 2018). Anthelmintics are administered by oral drench (as a general route), slow-release bolus, injection, or in-feed (Taylor, 1999).

According to previous studies (Davis et al., 2020; Lalthanpuui & Lalchhandama, 2020), transcuticular/tegumental diffusion is an appropriate route for drug entrance into parasitic worms. Drug entrance into the parasite is determined by drug lipophilicity, as a critical physicochemical factor, in which by increasing the drug lipophilicity, a higher amount of the drug can be penetrated and consequently accumulated within the parasite (Lifschitz, Lanusse, & Alvarez, 2017). Therefore, drug entrance and accumulation into a parasitic worm are crucial factors to achieve the optimal therapeutic outcome. Also, other factors, such as i) the balance among drug entry (influx), ii) the capacity of the parasite to metabolize and inactivate the drug, and iii) the drug efflux capacity of the parasite, determine the drug accumulation within a parasite (Lanusse, Lifschitz, & Alvarez, 2015). The exposure time of parasite to active drug concentrations is a critical factor that affects the efficacy and/or durability of activity of most anthelmintics used in ruminants. Overall, these factors are responsible to determine the ultimate anthelmintic activity (Lanusse et al., 2018).

2.1.1. Metabolism and excretion

2.1.1.1. Benzimidazoles and Pro-benzimidazoles. Ricobendazole is the active metabolite of albendazole and the only available injectable BZD. In the host body, the gastrointestinal microflora and liver are responsible to metabolize pro-BZDs into active BZD drugs, in which febantel, thiophanate, and netobimin are metabolized into fenbendazole, luxabendazole, and albendazole, respectively (Gokbulut & McKellar, 2018). BZDs are metabolized in the liver to various molecules, such as albendazole sulfoxide and albendazole sulfone for albendazole (Yang, Liu, Chen, & Zhihua, 2016).

Hydroxylation is one of the crucial metabolic pathways of BZDs. In sheep, it has been shown that hydroxy oxfendazole and hydroxy fenbendazole were the main hepatic metabolites of fenbendazole following intraruminal administration that are excreted through the bile as free or conjugated metabolites (Gokbulut & McKellar, 2018).

2.1.1.2. Imidazothiazoles and tetrahydropyrimidines. Levamisole is metabolized in the liver and kidney into several components, such as aminorex, and mostly excreted via the kidneys. Depending on the animal species, it has a plasma elimination half-life of 5–6 h (Handley, Belsey, Couchman, & Flanagan, 2019; Kolanović et al., 2018). Pyrantel is mostly metabolized into metabolites with higher polarity in various animals through different metabolic pathways, including the oxidation of the thiophene ring, the oxidation of the tetra-pyrimidine ring, and conjugation to mercapturic acid. The polar metabolites of pyrantel are supposed to be eliminated by the kidneys (Gokbulut & McKellar, 2018).

2.1.1.3. Macrocytic lactones. MLs are partially metabolized by the animal and are mainly excreted via feces (Tydén, Jansson, & Ringmark, 2019). Ivermectin, as a member of MLs, is metabolized in the liver by the cytochrome P450 system. The blood concentration of the drug reaches the peak 4 h after administration, and after that, the concentration decreases slowly. The metabolites concentration in the blood increases for a longer time when it is compared with the parent compound, which can be resulted from the hetero-

hepatic recycling. The drug can be detected in various sites, including the nodules, and subcutaneous fascia. A single oral dose (12 mg) of ivermectin reaches the peak 8 h after administration in various sites, such as sebum, and forehead, and starts to decrease after 24 h (El-Saber Batiha et al., 2020).

2.1.1.4. Other anthelmintics. Closantel

Closantel is a salicylanilide compound and normally used for veterinary purposes (Gokbulut & McKellar, 2018; Venkatesh, Pereira, Aseem, & Yadav, 2019). It is poorly metabolized, in which around 80% of the administered dose is eliminated through the feces. Approximately 45% of the orally administered dose is excreted 48 h after administration; however, this value for intramuscular injection is approximately 10%. Closantel has an elimination half-life of 2–3 weeks. In dairy cows, approximately 1% of the administered dose is eliminated through the milk without any change (Venkatesh et al., 2019).

Praziquantel

Praziquantel is an isoquinoline compound, and while in laboratory animals, it is metabolized to glucuronide and sulfuric conjugates, which are less active compared to the parent compound. In human, the absorption of praziquantel occurs quickly and mostly (90%) after administration and then quickly eliminated with a plasma clearance equal to 28 L/kg (Gokbulut & McKellar, 2018).

Trichlorfon

Trichlorfon is an organophosphate that is quickly absorbed after oral administration. It is metabolized in the liver by phosphatases in a host species-specific manner, and the metabolites are then eliminated through the urine (Gokbulut & McKellar, 2018).

Piperazine

Piperazine is a hexahydropyrazine compound. It is absorbed slightly and variably from the gastrointestinal tract, and probably the un-absorbed drug from the gastrointestinal tract is responsible for anti-parasitic activity (Gokbulut & McKellar, 2018).

3. Efficacy and spectra of activity of anthelmintics

Anthelmintics were primarily generated for the treatment of veterinary parasites, and their application has then been expanded for the treatment of human patients. They have a variety of chemical entities and act through several modes of action. For example, BZDs are bound selectively to β -tubulin of nematodes, cestodes, and fluke and block the formation of microtubule and cell division (Hamilton & Rath, 2017). Mebendazole and flubendazole, two members of BZDs, cause the loss of cytoplasmic microtubules of helminths, resulting in the loss of transport of secretory vesicles, a decrease in the uptake of glucose, and an increase in the use of stored glycogen (Hamilton & Rath, 2017). The salicylanilides drugs, such as radoxanide, oxyclozanide, and closantel, are proton ionophores (Hamilton & Rath, 2017; Hu et al., 2013) or proton carriers to help to transfer protons from the aqueous phase into the lipophilic membrane (Mahmoud, Saad, Elzanfaly, Amer, & Essam, 2020). Other anthelmintics are functionally classified as nicotinic, glutamate-gated chloride channel potentiators, or macrolides (Hamilton & Rath, 2017).

3.1. Benzimidazoles and pro-benzimidazoles

BZDs demonstrate a significant difference, in terms of efficacy, against various species of parasites (Gokbulut & McKellar, 2018). In various studies, the efficacy of these drugs was evaluated against various types of gastrointestinal nematodes, such as *Strongylus* species and *Parascaris* species (Salem et al., 2020; Yuriadi,

Tjahajati, Indarjulianto, & Widiyono, 2019). Yuriadi *et al.* (Yuriadi *et al.*, 2019), in one study, evaluated the efficacy of oxfendazole (7.5 mg/kg) on a group of infected horses. The results demonstrated that oxfendazole was completely effective (100%) to kills *Strongylus* and *Parascaris* worms. Salem *et al.* (Salem *et al.*, 2020), in another study, investigated the efficacy of fenbendazole on the prevalence of gastrointestinal nematode infections in working horses to measure the resistance of strongyle to the drug using faecal egg count reduction testing (FECRT). The results demonstrated that the drug was highly potent, in which the Strongyle FECR was found to be 100%.

3.2. Imidazothiazoles and tetrahydropyrimidines

Regarding the anti-parasitic effects of pyrantel pamoate, it has been demonstrated that this drug is a potent anthelmintic drug against *Strongylus* worms (Yuriadi *et al.*, 2019), in which an oral dose of the drug (20 mg/kg) caused a reduction in the eggs per gram (EPG) of feces to zero for *Strongylus* worms, 12 days after administration in horses. It also demonstrated 95–97% potency against adult cyathostomins, *Parascaris equorum*, and *Strongylus vulgaris*, and moderate antiparasitic effects towards *Strongylus edentatus* (70%) and *Oxyuris equi* (65%, a gastrointestinal parasite) (Gokbulut & McKellar, 2018). Also, the oral administration of pyrantel pamoate, as a paste formulation and at a dosage of 13.2 mg/kg, caused the parasitocidal activity of 95–98% against mature infections of *Anoplocephala perfoliata* (a tapeworm in equids) in horses and ponies (Slocombe, 2004). Hamed *et al.* (Hamed, El-Allawy, & Hassnein, 2019) evaluated the anti-parasitic potency of pyrantel (single dose, oral administration, 1 g/10 kg) in parasite-infected donkeys using EPG of feces. The egg count was performed on days 7, 14, 21, and 28 after the drug administration. The results demonstrated that the mean EPG% in pyrantel treated animals was less than 90% throughout 28 days of the treatment.

3.3. Macrocyclic lactones

MLs are one of the most favorite anthelmintics, used to control parasitic worms and arthropods of domestic animals and livestock (Yilmaz, Gerst, McKay-Demeler, & Krücken, 2019). Of these compounds, moxidectin was found significantly potent towards equine nematodes (Gokbulut & McKellar, 2018). Katre *et al.* (Radha Katre, 2020) evaluated the efficacy of ivermectin and moxidectin against gastrointestinal nematode (*Strongylus* species, and *Parascaris* species) infection in horses using faecal egg count (FEC). The horses received a single oral dose of ivermectin (0.2 mg/kg) and moxidectin (0.4 mg/kg). The results demonstrated that both the drugs caused a reduction in the FEC for both the parasites by 100% on the 14th-day post-treatment. However, the FEC was more rapidly reduced in moxidectin receiver horses compared to those received ivermectin (Radha Katre, 2020). In the other study, Shashank *et al.* (Shashank & Ayodhya, 2019) evaluated the efficacy of ivermectin against goats positive for gastrointestinal nematodal infestation and compared the results with levamisole using the FEC method. FEC, at day 0, was 1520 ± 156.20 and 1310 ± 126.88 in ivermectin and levamisole receiver groups, respectively. The *Strongyles*, *Trichuris*, and *Strongyloides* species were the gastrointestinal nematodes that are recognized in these animals. The results of the evaluation demonstrated that ivermectin caused a reduction of 86.22, 100 and 100% on day 3, 5 and 7 post-treatment, respectively, in FEC, while these values for levamisole were 77.38, 97.20, and 100%, respectively. The study suggested that ivermectin could be an ideal anthelmintic drug against both single and mixed gastrointestinal nematodal infestation in goats.

4. Mode of action as anti-cancer agents

Anthelmintics have exerted anti-cancer activity against various types of cancers, in particular cancer stem cell-like subpopulations (Hamilton & Rath, 2017). The anti-cancer activities of mebendazole, pyrinium pamoate, and niclosamide were reported by Mukhopadhyay *et al.* (Mukhopadhyay, Sasaki, Ramesh, & Roth, 2002), in 2002, Esumi *et al.* (Esumi, Lu, Kurashima, & Hanaoka, 2004), in 2004, and Wang *et al.* (Wang *et al.*, 2009), in 2009, respectively. Since then, several studies (Ashburn & Thor, 2004; Pantziarka *et al.*, 2014) have demonstrated that anthelmintics could exert anti-cancer effects *in vitro*, *in vivo*, and in first clinical trials. Various mechanisms, such as down-regulating the P-glycoprotein (P-gp) expression via the inhibition of the epidermal growth factor receptor (EGFR) (Armando *et al.*, 2020), the disruption of microtubule polymerization, the induction of apoptosis, inhibition of cell cycle progression (G2/M), anti-angiogenesis, the blockage of the transport of glucose, and uncoupling the oxidative phosphorylation in mitochondria (Barbosa *et al.*, 2019; Son, Lee, & Adunyah, 2020), have been identified for the anti-cancer activity of anthelmintics (Fig. 1) (Armando *et al.*, 2020; Son *et al.*, 2020). Overall, anthelmintics can be divided into two groups; those progressed in clinical trials (Table 1) and others that are not.

4.1. Anthelmintics under clinical trials

4.1.1. Albendazole

Albendazole has demonstrated *in vitro* anti-tumor effect against hepatocellular carcinoma (HCC) and colorectal carcinoma (CRC) and *in vivo* anti-tumor effect against a xenograft model of peritoneal carcinomatosis. This drug has also shown anti-proliferative activity against tumor cells (e.g., leukemia and ovarian cancer cells) which are resistant to other microtubule-targeted drugs (Armando *et al.*, 2020). In addition to interfering in microtubule function, albendazole seems to inhibit the production of vascular endothelial growth factor (VEGF) and angiogenesis in the peritoneal ovarian tumor in animal model (mice) (Armando *et al.*, 2020; Pourgholami, Cai, Lu, Wang, & Morris, 2006). Currently, the anti-cancer effect of albendazole is being investigated in a clinical trial (clinical trial no. NCT02366884) (Table 1).

4.1.2. Ivermectin

Ivermectin exerts its anti-parasitic effects by increasing the parasite cell membrane permeability, resulting in paralysis and death. It has also demonstrated some preliminary anti-cancer effects (Armando *et al.*, 2020). Ivermectin can inhibit proliferation, metastasis, and angiogenic activity in various tumor and cancer cells. These activities may result from its ability to regulate various signaling pathways through p21-activated kinase 1. Also, ivermectin helps programmed cell death, such as apoptosis, autophagy, and pyroptosis. In addition, it is capable of sensitizing multidrug-resistant cells to chemotherapeutics and causes an optimal effect when used in combination with other chemotherapeutics (Tang *et al.*, 2020). Jiang *et al.* (Jiang, Wang, Sun, & Wu, 2019) demonstrated that ivermectin was potent to reverse the resistance of tumor cells to anti-cancer drugs. The drug functions mainly by reducing the P-gp expression through the inhibition of the EGFR. Ivermectin inhibits ERK/Akt/NF- κ B pathway through binding to the extracellular domain of EGFR and inhibiting its activation. The restriction of NF- κ B causes a reduction of P-gp transcription. Ivermectin also causes the restriction of yes associated protein 1 (YAP1), which functions as the transcription activator for those genes related to cell proliferation and suppression of apoptosis (Armando *et al.*, 2020). Moreover, ivermectin blocks the karyopherin β 1 (KPNB1, encoding nuclear transport factors) function.

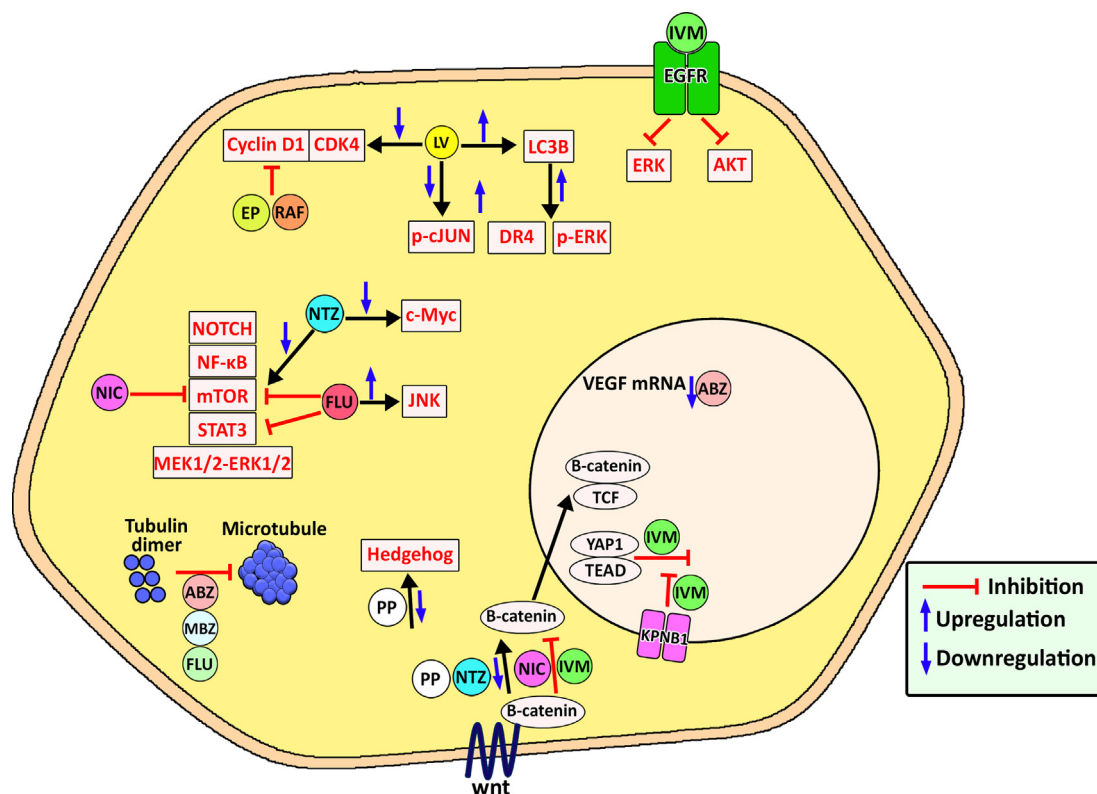


Fig. 1. Mode of action of albendazole (ABZ), ivermectin (IVM), levamisole (LV), mebendazole (MBZ), niclosamide (NIC), flubendazole (FLU), rafoxanide (RAF), nitazoxanide (NTZ), pyrinium pamoate (PP), and eprinomectin (EP).

Kodama *et al.* (Kodama *et al.*, 2017) demonstrated that ivermectin inhibited the function of KPNB1 in ovarian cancer cells, resulting in apoptosis and cell cycle arrest. Ivermectin, in combination with paclitaxel, caused synergistic anti-cancer effects *in vivo* as well (Kodama *et al.*, 2017). Ivermectin can also inhibit the canonical wnt (wingless-related integration site) signaling pathway that influences a transcriptional factor of the T-cell factor (TCF) family, resulting in the inhibition of colon and lung cancer proliferation (Armando *et al.*, 2020). Ivermectin is also able to modulate those genes involved in the epithelial mesenchymal transition and maintenance of a cancer stem cell (CSC) phenotype in triple-negative breast cancer (TNBC), and consequently causes dysfunction in clonogenic self renewal *in vitro*, and the restriction

of tumor growth and metastasis *in vivo* (Kwon *et al.*, 2015). In addition, ivermectin can cause anti-tumor effects through a variety of mechanisms. It can interact with various targets, such as multidrug resistance (MDR) protein (Juarez, Schcolnik-Cabrera, & Dueñas-Gonzalez, 2018).

4.1.3. Levamisole

Levamisole has been identified with various functions, such as anti-tumor activity (Qiao *et al.*, 2020). In particular, it is used as an adjuvant of 5-fluorouracil (5-FU) and in combination with 5-FU for the treatment of colon cancer (stage III) (Qiao *et al.*, 2020). Costa e Silve *et al.* (Costa, Celani, Azevedo, & Medeiros, 2019) compared the efficacy of levamisole with cisplatin in the treatment of

Table 1
List of anthelmintics, which have demonstrated anti-cancer effects and are repositioning in oncology.

Drug	Phase	Type of cancer	Study ID number or reference
Albendazole	II	Colorectal cancer, leukemia, liver and ovarian cancers	NCT02366884
Ivermectin	II	triple-negative breast cancer, colorectal cancer, lung and ovarian cancers	NCT02366884
Levamisole	III	Hepatocellular carcinoma	NCT03950518
Levamisole	III	Intrahepatic cholangiocarcinoma	NCT03940378
Mebendazole	III	Colon cancer	NCT03925662
Mebendazole	Terminated (lack of effect)	Gastrointestinal cancer	NCT03628079
Mebendazole	II	Colorectal cancer	NCT03925662
Niclosamide	Terminated (low accrual)	Colorectal cancer	NCT02687009
Niclosamide	II	Colorectal cancer	NCT02519582
Niclosamide	II	Familial adenomatous polyposis	NCT04296851
Niclosamide	II	Tumors of neuroendocrine origin, lung cancer (non small cell), breast cancer (triple-negative), acute myeloid leukemia, osteosarcoma, adrenocortical carcinoma, glioma tumors, ovarian, prostate, lung, and head and neck cancers	NCT02807805

urethane-induced lung tumors in rats using *ex vivo* fluorescence imaging. The results demonstrated that while the mean fluorescence intensity (MFI) was 245 ± 15 in the levamisole treated group, this value was 277 ± 28 in the animals receiving cisplatin. The MFI in the saline-treated group was 680 ± 57 , which was considerably higher than that in the other groups ($p < 0.05$). The results of the study demonstrated that levamisole had a positive effect on the treatment of urethane-induced lung tumors in rats (Costa et al., 2019). Qiao et al. (Qiao et al., 2020) assessed the anti-cancer effects of levamisole in lung cancer, both *in vitro* and *in vivo*, and the results demonstrated that levamisole caused a reduction in the proliferation of lung cancer cells and inhibited the cell cycle arrest in G0/G1 phase. Also, levamisole caused an increase in the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced death receptor 4 (DR4)-independent apoptosis rate through the restriction of the phosphorylation of c-Jun N-terminal kinase (JNK). In addition, it was found that levamisole caused an increase in the expression of LC3B (a component of LC3B-DR4/ErK as a cellular protective pathway) and subsequently activated the phosphorylation of ErK and increased the DR4 expression. Currently, levamisole has been evaluated in two clinical trials (phase III), in terms of efficacy and safety. The first trial is evaluating the therapeutic effects of a levamisole in combination with arginine hydrochloride in the patients, suffering from advanced hepatocellular carcinoma (HCC) (NCT03950518). The second one is assessing levamisole hydrochloride for the treatment advanced intrahepatic cholangiocarcinoma (NCT03940378) (Laudisi et al., 2020).

4.1.4. Mebendazole

Mebendazole can be an appropriate repositioned drug as it has a proper and proven toxicity profile and pharmacokinetics, making the drug suitable for therapeutic purposes. Also, it is an inexpensive drug that can be administered easily. Mebendazole causes the inhibition of various factors contributing to tumor progressions (e.g. polymerization of tubulin, angiogenesis, pro-survival pathways, and matrix metalloproteinases). Mebendazole causes direct cytotoxic effects, has synergistic effects with ionizing radiations and various chemotherapeutics, and motivates anti-tumoral immune responses. Mebendazole, as a single agent or in combination with chemotherapeutics, causes a reduction or complete inhibition of tumor growth, a significant decrease in the metastatic spread, and an increase in survival time (Guerini et al., 2019). The therapeutic effects of mebendazole against various cancers have been demonstrated in various studies (X.-h. Chen et al., 2019; L. Zhang et al., 2019). Chen et al. (X.-h. Chen et al., 2019) demonstrated that mebendazole caused the induction of apoptosis in c-Maf (a vital oncogenic transcription factor that participates in myelomagenesis)-expressing myeloma cells. Also, an oral dose of the drug caused a delay in the growth of human myeloma xenografts (nude mice) without inducing any evident toxicity. Zhang et al. (L. Zhang et al., 2019) showed that mebendazole, at the concentration of $0.7 \mu\text{M}$, was potent to inhibit the mammosphere formation from non-sorted cells in two human breast cancer SUM159PT and MDA-MB-231 cells by approximately 86 and 88%, respectively, compared to the control group. At present, mebendazole is in progress in various phases of clinical trials (II and III) for the treatment of different cancers, including colon cancer and CRC (NCT03925662).

4.1.5. Niclosamide

The mechanism of action of niclosamide against parasites comprises uncoupling the oxidative phosphorylation in mitochondria, resulting in a disruption in the metabolism of parasites (Barbosa et al., 2019). MacDonald et al. (MacDonald et al., 2006) may be the first who identified the probable repositioning of niclosamide for cancers when observed unexpected results for this drug. They

evaluated protein–protein interactions in human embryonic kidney 293 (HEK-293) cells using protein-fragment complementation assays (PCA) to detect hidden or not expected biological functions from a wide variety of compounds, belonging to various therapeutic categories. PCA can identify unexpected anti-proliferative effects when using niclosamide, observed in various types of cancer cells, including a human prostate cancer cell (PC-3) (Samy et al., 2020), a human lung cancer cell (A549) (Özdemir, Turanli, Çalışkan, Arka, & Banoglu, 2020), a human pancreatic cancer cell (MiaPaCa) (Lee, Lee, Sim, & Kim, 2020), a human colon cancer cell (LOVO) (Lee et al., 2020), and a human glioblastoma cell (U87MG) (Arzani et al., 2019), with an inhibitory concentration of 50 (IC_{50}) at the mean concentrations of $0.6 \mu\text{M}$ (MacDonald et al., 2006). Since then, various preclinical studies (L. Chen, Wang, Shen, Lin, & Li, 2017; Suliman et al., 2016; Zhou, Jin, Jin, Liu, & Pan, 2017) demonstrated that niclosamide exerts its anti-cancer effects through the inhibition of signaling pathways, including NOTCH, NF- κB , and mammalian target of rapamycin (mTOR). In addition, the potency of the drug to inhibit other oncogenic pathways, such as Wnt/ β -catenin, STAT3, and MEK1/2-ERK1/2, has been demonstrated against various types of cancer cells, such as esophageal, ovarian, and melanoma, in several preclinical studies (Shangguan et al., 2020; Wei, Liu, Yuan, & Yao, 2020; Zhu et al., 2019). Currently, the anti-cancer effects of niclosamide have been evaluated in several clinical trials (NCT02687009, NCT02519582, NCT04296851, and NCT02807805).

4.2. Anthelmintics with promising anti-cancer effects

4.2.1. Flubendazole

Flubendazole has demonstrated anti-tumor effects against various cancer cells, including leukemia, neuroblastoma, multiple myeloma, melanoma, and breast cancer cells (Armando et al., 2020; Hou et al., 2015). It functions through i) the induction of changes in microtubule structure, ii) the induction of apoptosis, iii) the restriction of angiogenesis, iv) the induction of cell differentiation, v) the restriction of cell migration, and vi) the induction of reactive oxygen species (ROS) activating autophagy (Armando et al., 2020; Hou et al., 2015). Currently, there are no clinical trials considering the anti-tumor effects of flubendazole against human malignancies (Armando et al., 2020).

4.2.2. Radoxanide

Radoxanide is a halogenated salicylanilide and can effectively inhibit the oncogenic BRAF V600E mutant protein, prevalently developed in melanomas and CRCs, and linked with a poorer prognosis (Laudisi et al., 2020). While it restricts the proliferation of CRC cells, it has no effects on normal colonic epithelial cells. Radoxanide down-regulates the expression of cyclin D1 protein and causes cell accumulation in the G0/G1 phase. These processes depend upon the selective induction of the endoplasmic reticulum stress response, resulting in caspase-dependent cell death (Grazia et al., 2020). Also, it has been found that radoxanide inhibits the proliferation of human gastric cancer SGC-7901 and BGC-823 cells *in vitro* via the restriction of the activity of the PI3K/Akt/mTOR signaling pathway. This process induces autophagy and apoptosis in cancerous cells (Liu et al., 2019).

4.2.3. Nitazoxanide

The anti-cancer effects of nitazoxanide have been reported against various cancers, such as ovarian and colon cancers (Laudisi et al., 2020; Pal, Nandave, & Kaithwas, 2020). Nitazoxanide has exceptional pharmacokinetic and safety profiles. It can cause CRC cells apoptosis in a glutathione-S-transferase P1 (GSTP1)-dependent manner. In HCT-116 and HT-29-derived spheroids, nitazoxanide caused a reduction in c-Myc, mTOR, and Wnt signaling

pathways (0.1–17 $\mu\text{mol/L}$), while it activated the AMPK pathway. These findings were confirmed *in vivo*, where nitazoxanide (100 mg/kg), in combination with irinotecan (40 mg/kg), induced a strong suppression in the tumor growth of a human xenograft colorectal cancer in NMRI nu/nu mice compared to irinotecan alone (Laudisi et al., 2020). It has been demonstrated that, in breast cancer xenograft mouse models, nitazoxanide functions through various pathways, such as AMPK, mTOR, and Wnt signaling. Also, in these models, nitazoxanide acts through the downregulation of c-Myc (Pal et al., 2020). Pal et al. (Pal et al., 2020), in one study, evaluated the anti-cancer effects of nitazoxanide (50 mg/kg) compared to those of tamoxifen (tamoxifen) against mammary gland carcinoma induced by N-methyl-N-nitrosourea (MNU) in experimental rats. The results demonstrated that nitazoxanide restored the histological architecture in the animals and caused a reduction in the alveolar buds and a downregulation in the oxidative stress markers, such as glutathione, protein carbonyl, and catalase, and inflammatory markers, such as nitric oxide, hydrogen sulphide, cyclooxygenase, and lipoxygenase. The results suggested that nitazoxanide could be exploited as a potential chemoprophylactic agent against mammary gland carcinoma developed by MNU.

4.2.4. Praziquantel

Praziquantel is an anthelmintic drug, and its function has not yet been well understood; however, it can function through the blockage of Ca^{2+} channels, resulting in an increase in the intracellular concentration of Ca^{2+} and the induction of muscular contractions (Laudisi et al., 2020). It has been demonstrated that praziquantel at the concentration of 20–40 μM can increase the cytotoxicity of paclitaxel. Especially, praziquantel in combination with paclitaxel can synergistically inhibit cell proliferation and causes apoptosis in various cancer cells, such as CRC DLD-1 (Laudisi et al., 2020). Praziquantel in combination with paclitaxel is also able to impair the X-linked inhibitor of apoptosis protein (XIAP) expression as an anti-apoptotic protein, that functions as an effective inhibitor of caspase activity (Laudisi et al., 2020).

4.2.5. Pyrvinium pamoate

Pyrvinium pamoate is able to kill various cancer cells, especially CSC. The drug functions through the reduction of WNT- and Hedgehog-dependent signaling pathways (Dattilo et al., 2020). It also causes an inhibition in the mitochondria respiration and can inhibit oncogenic PI3K-dependent signaling (Dattilo et al., 2020). Dattilo et al. (Dattilo et al., 2020) demonstrated the anti-cancer effects of pyrvinium pamoate against triple-negative breast CSC that caused a reduction in the metastases of CSC by affecting the lipid anabolism. The drug caused a disruption in the anabolic flux from glucose to cholesterol and fatty acids. Nair et al. (Nair et al., 2020) evaluated the anti-cancer activity of pyrvinium pamoate against human B cell acute lymphoblastic leukemia cells, including REH and RS4. Also, the metabolic function of these cells was evaluated by measuring the rates of extracellular acidification and oxygen consumption. The results demonstrated that pyrvinium pamoate showed anti-leukemia effects against all cell lines with the IC_{50} of 0.17 and 1 μM for REH and RS4 cells, respectively. Also, the effects of the drug on the REH cell cycle were evaluated, and the results demonstrated a significant reduction in the cell number in the S (by ~26%) and M phases (by ~50%) compared to the control group (Nair et al., 2020). The anti-tumor activity of pyrvinium pamoate was also evaluated in a xenograft model of human pancreatic cancer PANC1 cells (Laudisi et al., 2020). The oral administration of pyrvinium pamoate (100 and 200 μg) caused a reduction in tumor growth and inhibited the Akt phosphorylation. It was found that pyrvinium pamoate (0.1 and 0.3 μM) inhibited the transcription of two critical chaperons (i.e. GRP78 and GRP94), thereby restricted the unfolded protein response due to glucose depriva-

tion. The drug also inhibits other UPR pathways (e.g. XBP-1 and ATF4) stimulated by glucose starvation (Laudisi et al., 2020).

4.2.6. Piperazine

The anti-cancer effects of piperazine and its derivatives against various types of cancer cells have been demonstrated in various studies (Evren, Yurttaş, Ekselli, & Akalin-Ciftci, 2019; Mongre et al., 2019). The piperazine derivative AK301 at the concentration of 5 μM could cause a critical impairment in the tubulin polymerization and a mitotic arrest in human colorectal adenocarcinoma HT-29 and HCT-116 cells (Laudisi et al., 2020). In parallel, AK301 induced the expression of tumor necrosis factor receptor 1 (TNFR1) therefore caused an increase in the susceptibility of cancer cells to apoptosis by TNF- α (Laudisi et al., 2020). Özdemir et al. (Özdemir et al., 2020) developed a series of benzimidazole-piperazine hybrids and evaluated their toxicity effects against human lung cancer A549 and human breast cancer MCF-7 cells. The results demonstrated that most of the hybrids had anti-proliferative activity against A549 cells with the IC_{50} of 2.8–7.8 μM . Also, one compound demonstrated the most balanced cytotoxicity effect towards A549 and MCF-7 cells with the IC_{50} of 5.4 and 4.2 μM , respectively. Mechanistically, these compounds caused a cleavage in PARP-1 and activate caspase 7, resulting in morphological changes, such as bleb formation in the treated cells, and a significant increase in the nuclear fragmentation. Considering all the results, these findings demonstrate that these compounds (benzimidazole-piperazine hybrids) exert their cytotoxicity through the apoptotic cell death induction (Özdemir et al., 2020).

4.2.7. Eprinomectin

Eprinomectin is a member of avermectin drugs, demonstrating exceptional broad-spectrum anti-parasitic activity. Samy et al. (Samy et al., 2020) evaluated its anti-cancer effects against PC-3 cells. The results demonstrated that eprinomectin caused a significant reduction in PC-3 cell viability as well as suppression in colony formation and wound healing abilities. Eprinomectin exerted its cytotoxicity effects through inducing ROS and the activation of apoptosis. The drug also could affect the cyclin-dependent kinase 4 (CDK4), causing an arrest in the G0/G1 phase of the cell cycle, resulting in the induction in PC-3 cells. Furthermore, eprinomectin could restrain the expression of various markers related to cancer stem cells (e.g. ALDH1, Nanog, and CD44) and pluripotent stem cells (e.g. alkaline phosphatase). In addition, it was found that the drug caused the translocation of β -catenin from the nucleus to the cytoplasm, resulting in the inhibition of Wnt/ β -catenin signaling pathway. In addition, the results of western blot analysis displayed that eprinomectin caused a reduction in the expression of the crucial cell cycle (e.g. cyclin D3, and c-Myc) and anti-apoptotic markers (e.g., Mcl-1, XIAP, c-IAP1, and survivin). In contrast, eprinomectin could activate p21, Bad, caspases 9, and 3. It also caused a cleavage in PARP1. These findings demonstrated that eprinomectin can be considered as a promising compound for the treatment of advanced PCa cells through regulating apoptosis signaling (Samy et al., 2020).

5. Challenges with anthelmintics in cancer therapy

Low water solubility is a problem that limits the use of anthelmintics (P. Li, Rios Coronado, Longstaff, Tarashansky, & Wang, 2018). Drug insolubility can influence both the pharmacokinetic and pharmacodynamic profiles of drugs. The low water solubility of drugs can cause: i) a reduction in the drug absorption and permeation that in combination with the rapid drug degradation could result in an inadequate *in vivo* drug concentration and failure to achieve the therapeutic dose and thus the appropriate pharma-

cological effects, and ii) the oscillation in the drug plasma levels that results in the unforeseeable levels of bioavailability. To solve these problems, the dosage forms can be increased; however, increasing the dosage to achieve the therapeutic effects can result in: i) an increase in the costs of treatment, ii) incomplete absorption of the drug *in vivo* and its removal from the environment, and iii) the emergence of the drug toxicity (Khalikov & Dushkin, 2020). Therefore, the development of strategies to solve these problems-related to anthelmintics is of great importance.

6. Strategies to overcome these challenges

There are various shortcomings in the use of anthelmintics, such as low water solubility and low bioavailability, resulting in a reduction in the potency of these drugs for cancer therapy. To overcome these challenges, various strategies could be suggested as follow that enhance anti-cancer effects of anthelmintics.

6.1. Nanoparticles for improving the solubility of anthelmintics

Nanoparticles are known with high surface to volume ratio, meaning that by reducing the size, the higher surface area is provided (Barbosa et al., 2019). Increasing the surface area causes an increase in the dissolution rate of the particles (Barbosa et al., 2019). Also, nanoparticles take advantage of the ease of surface modification, allowing them to target specific cancer cells, expressing specific surface receptors (Ghaferi, Asadollahzadeh, Akbarzadeh, Ebrahimi Shahmabadi, & Alavi, 2020; Ghaferi, Koochi Moftakhari Esfahani, et al., 2020) (Fig. 2A).

Particle size also impacts the diffusion layer thickness and saturation solubility (Barbosa et al., 2019; Fontana et al., 2018; Peltonen & Hirvonen, 2018). Increased saturation solubility and dissolution rate are the two critical factors of nanoparticles to enhance the drug absorption and bioavailability of the drugs with poor water solubility (Barbosa et al., 2019). Using nanostructures provides various advantages, such as i) drug protection from degradation in the organism, ii) improved drug absorption in tumor tissue, and iii) the modification of the drug pharmacokinetic properties, compared to the free administration of the drugs (Ebrahimi Shahmabadi et al., 2014; Ghaferi, Amari, et al., 2020; Vieira & Gamarra, 2016). Also, drug encapsulation into nanoparticles can improve the efficacy of the drug and reduce its side effects (Alavi, Esfahani, Ghassemi, Akbarzadeh, & Hassanshahi, 2014; Alavi, Muflih Al Harthi, Ebrahimi Shahmabadi, & Akbarzadeh, 2019). In addition, nanocarrier-based drug delivery systems cause an increase in drug economic life (Movahedi, KOOHI, Alavi, & Akbarzadeh, 2013). Researchers have used various nanocarriers to improve the bioavailability of anthelmintics (Paredes, Llabot, Sanchez Bruni, Allemandi, & Palma, 2016; Rehman, Khan, Khan, Shafique, & Khan, 2018). Rehman et al. (Rehman et al., 2018) synthesized niclosamide-loaded solid lipid nanoparticles (SLNs) and could increase the bioavailability of the drug by 11.1-folds. This finding indicated that the drug absorption significantly increased by taking up SLNs, as a drug delivery system, from the gastrointestinal wall, resulting in an increase in the drug bioavailability. Also, Paredes et al. (Paredes et al., 2016) synthesized self-dispersible nanocrystals of albendazole and could increase the dissolution rate of the drug by 4-fold that could increase the drug bioavailability. Nanocrystals have a very enlarged surface area, which results in a rapid saturation in the dissolution layer around the particles, and as a result an increase in the dissolution rate (Paredes et al., 2016). In addition, Darwish et al. (Darwish, Bayoumi, & El-Kolaly, 2018) synthesized nitazoxanide-loaded liposome nanoparticles using the membrane extrusion method and evaluated their biodistribution in ehrlich ascites carcinoma-

bearing swiss albino mice using gamma scintillation counter. The results demonstrated a rapid and higher accumulation of the nanoformulation in the tumor sites. This could result from the disruption of lipid bilayer due to the photosensitization process and the singlet oxygen species as a result.

6.2. Pro-drug formulations

Prodrugs are chemically modified drug molecules that are inactive or partially inactive. They are converted to the active parent drug on or near the target site *in vivo* by chemical and/or enzymatic biotransformation to exert the therapeutic effects (Fig. 3).

The prodrug approach can resolve various unsuitable features, such as poor aqueous solubility, poor oral or local absorption, short half-life, and toxicity (Jornada et al., 2016). There are two major classes of prodrugs, including carrier-linked prodrugs and bioprecursors (Jornada et al., 2016). Carrier-linked prodrugs are composed of a drug linked to a promoity, which is eliminated through a chemical or enzymatic reaction, leading to the drug release (Jubehe, Breijjeh, & Karaman, 2020), while bioprecursor prodrugs have no carrier and are quickly converted to an active drug through oxidation or reduction reactions (Jornada et al., 2016; Jubehe et al., 2020).

Prodrug design is a powerful tool to improve various properties of drugs, such as solubility, and bioavailability (Sanchez & Ferreira, 2019). Researchers, in various studies (Chassaing et al., 2008; Flores-Ramos et al., 2017; L. Nielsen, Bundgaard, & Falch, 1992; L. S. Nielsen, Sløk, & Bundgaard, 1994; Zimmermann et al., 2018), have developed various prodrugs of anthelmintics to improve their aqueous solubility. Nielsen et al. (L. Nielsen et al., 1992) synthesized an N-(4-amino-methylbenzoyl)oxymethyl prodrug of thiabendazole, demonstrating a 300-fold higher water-solubility compared to the parent compound. Nielsen et al. (L. S. Nielsen et al., 1994), in another study, synthesized a prodrug of mebendazole (N-alkoxycarbonyl), which was exceptionally more soluble compared to mebendazole (solubility rate of 2.7×10^5 vs. 1.7×10^{-6} M for the prodrug and mebendazole, respectively). Chassaing et al. (Chassaing et al., 2008) synthesized a highly water-soluble prodrug of fenbendazole, in which its aqueous solubility was extraordinarily increased by 195-fold compared to when the parent drug was used. Also, Flores-Ramos et al. (Flores-Ramos et al., 2017) synthesized a phosphate salt prodrug of triclabendazole (MFR-5) and demonstrated that its water solubility was exceptionally increased by 88000-fold compared to that of the parent compound. In addition, Zimmermann et al. (Zimmermann et al., 2018) synthesized an N substituted prodrug of mebendazole, and the results showed that the prodrug had more than 10000-fold aqueous solubility compared to when mebendazole was used.

6.3. Production of solid dispersions

SDs strategy is a promising approach to improve drug solubility. It is composed of two or more different components, including a hydrophobic drug and a hydrophilic matrix (Fig. 4) (Khalikov & Dushkin, 2020; Wagh & Wagh, 2015).

SDs of drugs are delivery systems for drug molecules and can improve the biopharmaceutical properties of drugs, such as increasing the solubility and bioavailability, decreasing the toxicity, and increasing the stability of the drugs during storage. SDs can increase the drug solubility through the following mechanisms: i) decreasing the size of the particles, ii) improving the wettability, and iii) increasing the level of drug dispersion in a polymeric matrix (Khalikov & Dushkin, 2020). Various SDs, such as disodium salt of glycyrrhizic acid (Na₂GA) (Metelva et al., 2019), polyvinylpyrrolidone (Arkhipov et al., 2019), poloxamer 407 (Real, Orzan, Leonardi, & Salomon, 2020), polyethylene

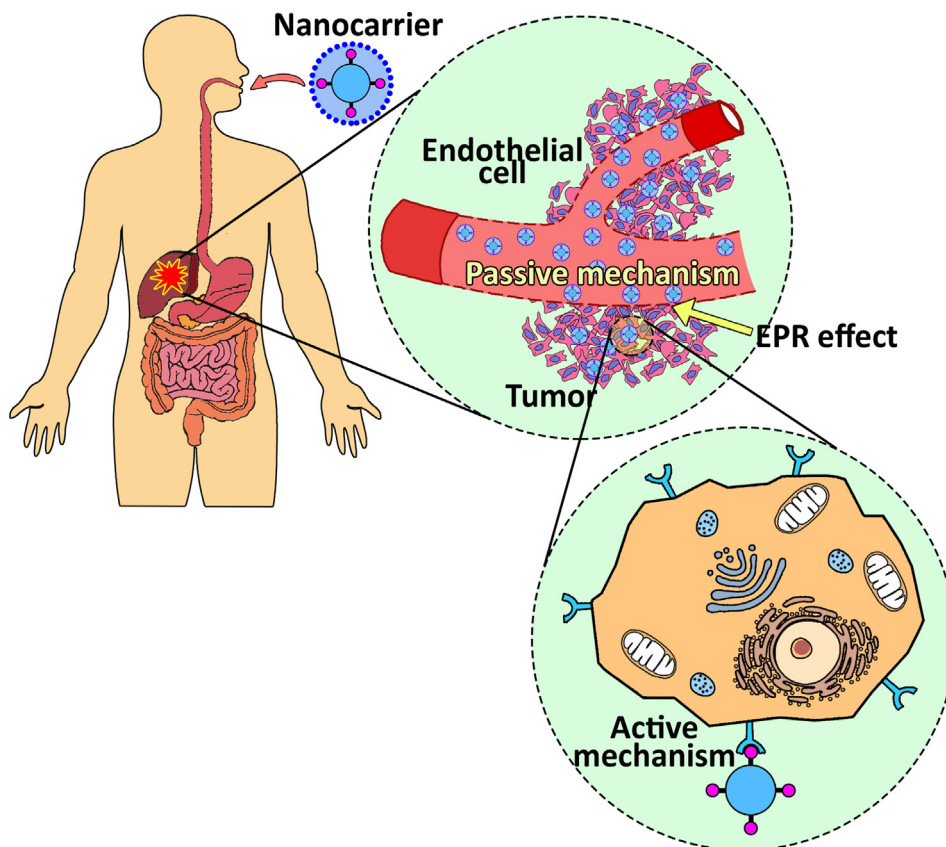


Fig. 2. Using nanocarriers for improving drug solubility. A poor soluble drug can be loaded into a tumor cell-targeted nanocarrier and administered orally. The nanoformulation is adsorbed through the gastrointestinal tract and deposited into the tumor tissue (e.g., liver tumor) through the Enhanced Permeation and Retention (EPR) effect, resulting from the increased vascular permeability in the tumor tissue (passive mechanism). As the nanoformulation is targeted against tumor cells, it can specifically interact with its specific receptor on the surface of tumor cells and internalized into the cells (active mechanism).

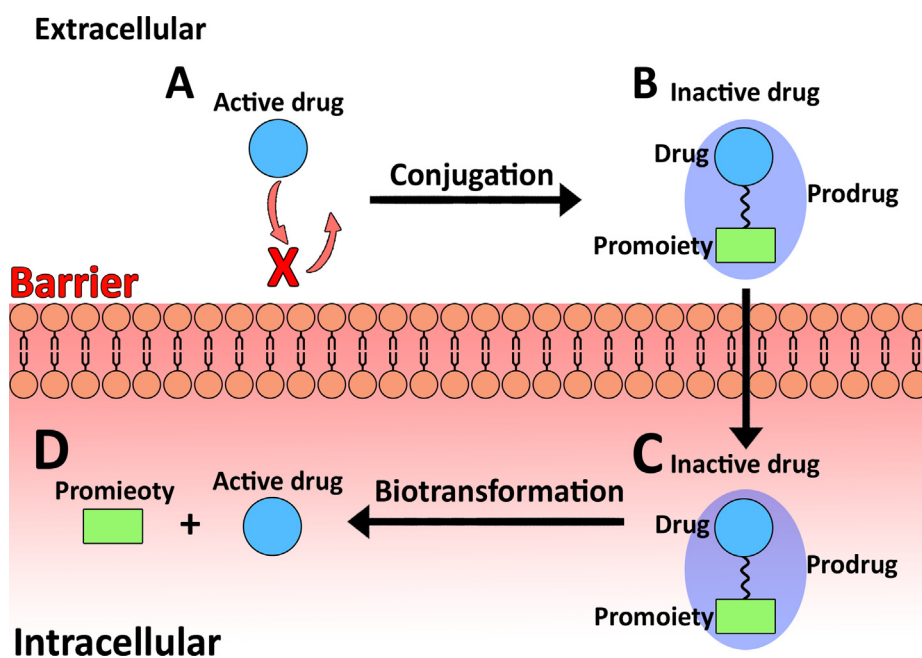


Fig. 3. Using prodrug for improving drug solubility to cross biological barriers. **A)** Due to low solubility, some drugs cannot cross biological barriers, and as a result, their therapeutic effects cannot be observed or are decreased. **B)** This shortcoming can be resolved using the prodrug approach (carrier-linked prodrug), **C)** after crossing the barrier, **D)** the prodrug is biotransformed, and the active drug is produced in the cell and demonstrates the optimized effect.

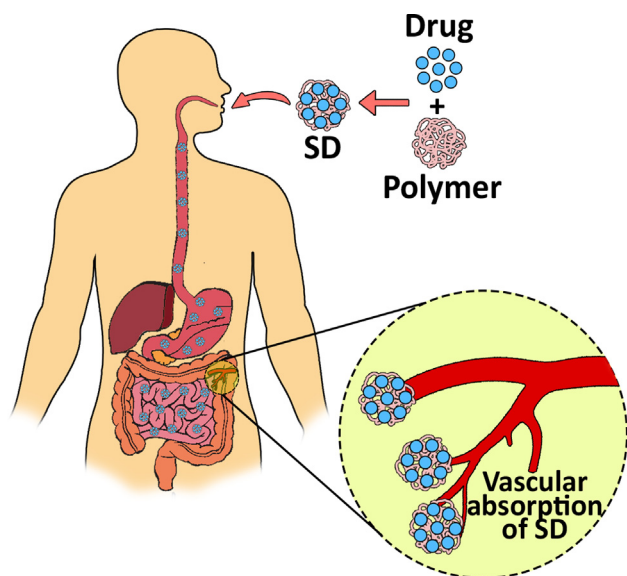


Fig. 4. Solid dispersion (SD) approach is a successful method to improve the oral absorption of poorly soluble drugs, such as anthelmintics. It can be prepared using polymers and drugs. An SD formulation can be administered orally and absorbed through the gastrointestinal tract, resulting in an increase in the blood concentrations of the drugs.

glycol-6000 (PEG 6000)/ Poloxamer 188 (P 188) (Dong et al., 2020), and povidone (M. Li et al., 2020), have been used to increase the solubility of anthelmintics. Meteleva et al. (Meteleva et al., 2019) provided an SD of praziquantel using Na₂GA and could increase the solubility of the drug by 3.5-folds. Also, Arkhipov et al. (Arkhipov et al., 2019) prepared an SD of fenbendazole using polyvinylpyrrolidone, and the results demonstrated an increase in the drug solubility by 2.8-fold. In another study, Real et al. (Real et al., 2020) provided an SD of triclabendazole using poloxamer 407 that could increase the solubility of triclabendazole by 41.5-fold. In addition, Dong et al. (Dong et al., 2020) prepared an SD of albendazole using PEG 6000/P 188 that increased the solubility of albendazole by 3.3-fold. Li et al. (M. Li et al., 2020), in the other study, synthesized an SD of rafoxanide using povidone, and the results showed an increase in the solubility of the drug by 7000-fold.

7. Conclusion and future perspectives

The drug (approved and abandoned) repositioning is increasingly used as a favorite and cost-effective strategy in oncology. These drugs can reach the clinic more quickly as their safety and pharmacological profiles have already been approved (Sleire et al., 2017). Some of the anthelmintics have shown promising results for cancer therapy. They can be administered as monotherapy or in combination with other anti-cancer drugs to enhance the anti-cancer effects *in vitro* and in preclinical studies. These drugs have received considerable attention, as they can interfere with key oncogenic pathways. These properties cause some anthelmintics to be undergone clinical trials (phase II/III) for cancer treatment (Laudisi et al., 2020). They are mainly administered orally, resulting in their higher content in the gastrointestinal tract; however, their concentration in the circulation is usually very low mainly due to low water solubility (Khalikov & Dushkin, 2020; Laudisi et al., 2020). In this literature review, we discussed the repositioning of anthelmintics in oncology, and the shortcomings for their success to reach the clinic. As discussed, the main issue that limits their use *in vivo* is low water solubility, resulting in their

low bioavailability. The strategies to overcome these shortcomings (i.e., nanocarriers-based formulation, prodrug design, and SDs) were also discussed. These strategies can be used to improve the solubility, bioavailability, toxicity profile, and the cost-effectiveness of anthelmintics in oncology. However, these need to be optimized, in terms of toxicity profile and safety issues, demanding further studies in future. Overall, the available data have demonstrated that the repositioning of anthelmintics in cancer therapy is a promising approach and can be considered as a less expensive and faster strategy for extending the repository of approved drugs. However, to perform the repositioning, there are some challenges that must be addressed to provide a real conception of whether a repositioning project is a valuable opportunity. Consequently, further studies are required to better understand the pharmacokinetic and dynamic profile of the upcoming formulations in our body. In our opinion, the generation of effective formulations of anthelmintics, as an anti-cancer, might require strong interdisciplinary collaborations between chemists, material scientists, and pharmacists. We hypothesize that listing those anthelmintics that are currently under clinical trial or under investigation in research laboratories with their promising anti-cancer effects as well as their challenges and potential strategies in one place, in this review, will generate a greater interest in anthelmintics and can help to formulate their anti-cancer effective formulations soon.

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References

- Alavi, S.E., Esfahani, M.K.M., Ghassemi, S., Akbarzadeh, A., Hassanshahi, G., 2014. *In vitro* evaluation of the efficacy of liposomal and pegylated liposomal hydroxyurea. *Indian J. Clin. Biochem.* 29 (1), 84–88.
- Alavi, S. E., Muflih Al Harthi, S., Ebrahimi Shahmabadi, H., & Akbarzadeh, A. (2019). Cisplatin-loaded polybutylcyanoacrylate nanoparticles with improved properties as an anticancer agent. *International journal of molecular sciences*, 20(7), 1531.
- Arkhipov, I.A., Khalikov, S.S., Sadov, K.M., Dushkin, A.V., Meteleva, E.S., Varlamova, A. I., Danilevskaya, N.V., 2019. Influence of mechanochemical technology on anthelmintic efficacy of the supramolecular complex of fenbendazole with polyvinylpyrrolidone. *J. Adv. Veterinary Anim. Res.* 6 (1), 133.
- Armando, R.G., Mengual Gómez, D.L., Gomez, D.E., 2020. New drugs are not enough—drug repositioning in oncology: an update. *Int. J. Oncol.* 56 (3), 651–684.
- Arzani, H., Adabi, M., Mosafer, J., Dorkoosh, F., Khosravani, M., Maleki, H., Kamali, M., 2019. Preparation of curcumin-loaded PLGA nanoparticles and investigation of its cytotoxicity effects on human glioblastoma U87MG cells. *Biointerface Res. Appl. Chem.* 9 (5), 4225–4231.
- Ashburn, T.T., Thor, K.B., 2004. Drug repositioning: identifying and developing new uses for existing drugs. *Nat. Rev. Drug Discovery* 3 (8), 673–683.
- Barbosa, E.J., Löbenberg, R., de Araujo, G.L.B., Bou-Chacra, N.A., 2019. Niclosamide repositioning for treating cancer: Challenges and nano-based drug delivery opportunities. *Eur. J. Pharm. Biopharm.* 141, 58–69.
- Čáňová, K., Rozkydalová, L., Rudolf, E., 2017. Anthelmintic flubendazole and its potential use in anticancer therapy. *Acta Medica Hradec Kralove Czech Repub* 60 (1), 5–11.
- Chassaing, C., Berger, M., Heckerth, A., Ilg, T., Jaeger, M., Kern, C., Uphoff, M., 2008. Highly water-soluble prodrugs of anthelmintic benzimidazole carbamates: synthesis, pharmacodynamics, and pharmacokinetics. *J. Med. Chem.* 51 (5), 1111–1114.
- Chen, L., Wang, L., Shen, H., Lin, H., Li, D., 2017. Anthelmintic drug niclosamide sensitizes the responsiveness of cervical cancer cells to paclitaxel via oxidative stress-mediated mTOR inhibition. *Biochem. Biophys. Res. Commun.* 484 (2), 416–421.

- Chen, X.-H., Xu, Y.-J., Wang, X.-G., Lin, P., Cao, B.-Y., Zeng, Y.-Y., Zhang, T., 2019. Mebendazole elicits potent antimyeloma activity by inhibiting the USP5/c-Maf axis. *Acta Pharmacol. Sin.* 40 (12), 1568–1577.
- Costa, A.L., Celani, L.M.S., Azevedo, Í.M., Medeiros, A.C., 2019. Levamisole in treatment of urethane-induced pulmonary carcinoma in rats. *J. Surg. Clin. Res.* 10 (2), 54–64.
- Darwish, W.M., Bayoumi, N.A., El-Kolaly, M.T., 2018. Laser-responsive liposome for selective tumor targeting of nitazoxanide nanoparticles. *Eur. J. Pharm. Sci.* 111, 526–533.
- Dattilo, R., Mottini, C., Camera, E., Lamolinara, A., Auslander, N., Doglioni, G., Ercolani, C., 2020. Pyrvinium pamoate induces death of triple-negative breast cancer stem-like cells and reduces metastases through effects on lipid anabolism. *Cancer Res.*
- Davis, C.N., Winters, A., Milic, I., Devitt, A., Cookson, A., Brophy, P.M., Morphew, R.M., 2020. Evidence of sequestration of triclabendazole and associated metabolites by extracellular vesicles of *Fasciola hepatica*. *Sci. Rep.* 10 (1), 1–11.
- Dong, C.-L., Zheng, S.-D., Liu, Y.-Y., Cui, W.-Q., Hao, M.-Q., God'spower, B.-O., ... Li, Y.-H. (2020). Albendazole solid dispersions prepared using PEG6000 and Poloxamer188: formulation, characterization and in vivo evaluation. *Pharmaceutical development and technology*, 1-10.
- Ebrahimi Shahmabadi, H., Movahedi, F., Koohi Moftakhari Esfahani, M., Alavi, S. E., Eslamifard, A., Mohammadi Anaraki, G., & Akbarzadeh, A. (2014). Efficacy of Cisplatin-loaded polybutyl cyanoacrylate nanoparticles on the glioblastoma. *Tumor Biology*, 35(5), 4799–4806.
- El-Saber Batiha, G., Alqahtani, A., Ilesanmi, O.B., Saati, A.A., El-Mleeh, A., Hetta, H.F., Magdy Beshbishy, A., 2020. Avermectin derivatives, pharmacokinetics, therapeutic and toxic dosages, mechanism of action, and their biological effects. *Pharmaceuticals* 13 (8), 196.
- Esumi, H., Lu, J., Kurashima, Y., Hanaoka, T., 2004. Antitumor activity of pyrvinium pamoate, 6-(dimethylamino)-2-[2-(2, 5-dimethyl-1-phenyl-1H-pyrrol-3-yl) ethenyl]-1-methyl-quinolinium pamoate salt, showing preferential cytotoxicity during glucose starvation. *Cancer Sci.* 95 (8), 685–690.
- Evren, A.E., Yurttaş, L., Ekselli, B., Akalin-Ciftci, G., 2019. Novel tri-substituted thiazoles bearing piperazine ring: Synthesis and evaluation of their anticancer activity. *Lett. Drug Des. Discovery* 16 (5), 547–555.
- Flores-Ramos, M., Ibarra-Velarde, F., Jung-Cook, H., Hernández-Campos, A., Vera-Montenegro, Y., Castillo, R., 2017. Novel triclabendazole prodrug: A highly water soluble alternative for the treatment of fasciolosis. *Bioorg. Med. Chem. Lett.* 27 (3), 616–619.
- Fontana, F., Figueiredo, P., Zhang, P., Hirvonen, J.T., Liu, D., Santos, H.A., 2018. Production of pure drug nanocrystals and nano co-crystals by confinement methods. *Adv. Drug Deliv. Rev.* 131, 3–21.
- Ghaferi, M., Amari, S., Mohrir, B.V., Raza, A., Shahmabadi, H.E., Alavi, S.E., 2020a. Preparation, Characterization, and Evaluation of Cisplatin-Loaded Polybutylcyanoacrylate Nanoparticles with Improved In Vitro and In Vivo Anticancer Activities. *Pharmaceuticals* 13 (3), 44.
- Ghaferi, M., Asadollahzadeh, M.J., Akbarzadeh, A., Ebrahimi Shahmabadi, H., Alavi, S. E., 2020b. Enhanced efficacy of PEGylated liposomal cisplatin: In vitro and in vivo evaluation. *Int. J. Mol. Sci.* 21 (2), 559.
- Ghaferi, M., Koohi Moftakhari Esfahani, M., Raza, A., Al Harthi, S., Ebrahimi Shahmabadi, H., & Alavi, S. E. (2020). Mesoporous silica nanoparticles: synthesis methods and their therapeutic use-recent advances. *Journal of Drug Targeting* (just-accepted), 1-67.
- Gokbulut, C., McKellar, Q.A., 2018. Anthelmintic drugs used in equine species. *Vet. Parasitol.* 261, 27–52.
- Grazia, A.D., Laudisi, F., Fusco, D.D., Franzè, E., Ortenzi, A., Monteleone, I., Stolfi, C., 2020. Rifaxonide Induces Immunogenic Death of Colorectal Cancer Cells. *Cancers* 12 (5), 1314.
- Guerini, A.E., Triggiani, L., Maddalo, M., Bonù, M.L., Frassine, F., Baiguini, A., Pasinetti, N., 2019. Mebendazole as a candidate for drug repurposing in oncology: An extensive review of current literature. *Cancers* 11 (9), 1284.
- Hamed, M.I., El-Allawy, T.A., Hassnein, E., 2019. Prevalence and anthelmintic resistance of Strongyle infection of donkeys in El-Wadi El-Gadid, Egypt. *J. Adv. Veterinary Res.* 9 (4), 144–150.
- Hamilton, G., Rath, B., 2017. Repurposing of anthelmintics as anticancer drugs. *OncoImmunology* 2, 142–149.
- Handley, S.A., Belsey, S.L., Couchman, L., Flanagan, R., 2019. Plasma and urine levamisole in clinical samples containing benzoyllecgonine: absence of aminorex. *J. Anal. Toxicol.* 43 (4), 299–306.
- Hassankhani, H., Rahmani, A., Taleghani, F., Sanaat, Z., Dehghannezhad, J., 2020. Palliative care models for cancer patients: Learning for planning in nursing. *J. Cancer Educ.* 35 (1), 3–13.
- Hou, Z.-J., Luo, X., Zhang, W., Peng, F., Cui, B., Wu, S.-J., Long, Z.-J., 2015. Flubendazole, FDA-approved anthelmintic, targets breast cancer stem-like cells. *Oncotarget* 6 (8), 6326.
- Hu, Y., Ellis, B.L., Yiu, Y.Y., Miller, M.M., Urban, J.F., Shi, L.Z., Aroian, R.V., 2013. An extensive comparison of the effect of anthelmintic classes on diverse nematodes. *PLoS ONE* 8, (7) e70702.
- Jiang, L., Wang, P., Sun, Y.-J., Wu, Y.-J., 2019. Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF- κ B pathway. *J. Exp. Clin. Cancer Res.* 38 (1), 1–18.
- Jornada, D.H., dos Santos Fernandes, G.F., Chiba, D.E., De Melo, T.R.F., Dos Santos, J.L., Chung, M.C., 2016. The prodrug approach: a successful tool for improving drug solubility. *Molecules* 21 (1), 42.
- Juarez, M., Scholnik-Cabrera, A., Dueñas-Gonzalez, A., 2018. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. *Am. J. Can. Res.* 8 (2), 317.
- Jubeih, B., Breijyeh, Z., Karaman, R., 2020. Antibacterial Prodrugs to Overcome Bacterial Resistance. *Molecules* 25 (7), 1543.
- Kato, S., Moulder, S.L., Ueno, N.T., Wheler, J.J., Meric-Bernstam, F., Kurzrock, R., Janku, F., 2015. Challenges and perspective of drug repurposing strategies in early phase clinical trials. *Oncoscience* 2 (6), 576.
- Khalikov, S., Dushkin, A., 2020. Strategies for Solubility Enhancement of Anthelmintics. *Pharm. Chem. J.*, 1–5.
- Kodama, M., Kodama, T., Newberg, J.Y., Katayama, H., Kobayashi, M., Hanash, S.M., Rangel, R., 2017. In vivo loss-of-function screens identify KPNB1 as a new druggable oncogene in epithelial ovarian cancer. *Proc. Natl. Acad. Sci.* 114 (35), E7301–E7310.
- Kolanović, B.S., Bilandžić, N., Varenina, I., Luburić, Đ.B., Varga, I., Cvetnić, L., Pavliček, D., 2018. Estimation of the withdrawal time of levamisole in eggs after oral administration to laying hens. *J. Food Prot.* 81 (10), 1627–1634.
- Kwon, Y.-J., Petrie, K., Leibovitch, B.A., Zeng, L., Mezei, M., Howell, L., Yang, S., 2015. Selective inhibition of SIN3 corepressor with avermectins as a novel therapeutic strategy in triple-negative breast cancer. *Mol. Cancer Ther.* 14 (8), 1824–1836.
- Lalthanpuui, P., Lalchandama, K., 2020. Scanning electron microscopic study of the anthelmintic effects of some anthelmintic drugs on poultry nematode *Ascaridia galli*. *Adv. Anim. Vet. Sci.* 8 (8), 788–793.
- Lanusse, C., Canton, C., Virkel, G., Alvarez, L., Costa-Junior, L., Lifschitz, A., 2018. Strategies to optimize the efficacy of anthelmintic drugs in ruminants. *Trends Parasitol.* 34 (8), 664–682.
- Lanusse, C., Lifschitz, A., Alvarez, L., 2015. Basic and clinical pharmacology contribution to extend anthelmintic molecules lifespan. *Vet. Parasitol.* 212 (1–2), 35–46.
- Laudisi, F., Marònek, M., Di Grazia, A., Monteleone, G., Stolfi, C., 2020. Repositioning of anthelmintic drugs for the treatment of cancers of the digestive system. *Int. J. Mol. Sci.* 21 (14), 4957.
- Lee, J., Lee, J., Sim, W., Kim, J.-H., 2020. Differential dependency of human pancreatic cancer cells on targeting PTEN via PLK 1 expression. *Cancers* 12 (2), 277.
- Li, M., Meng, F., Tsutsumi, Y., Amoureux, J.-P., Xu, W., Lu, X., 2020. Understanding Molecular Interactions in Rifaxonide-Povidone Amorphous Solid Dispersions from Ultrafast Magic Angle Spinning NMR. *Molecular Pharmaceutics*.
- Li, P., Rios Coronado, P.E., Longstaff, X.R.R., Tarashansky, A.J., Wang, B., 2018. Nanomedicine Approaches Against Parasitic Worm Infections. 7, (13). <https://doi.org/10.1002/adhm.201701494>
- Lifschitz, A., Lanusse, C., Alvarez, L., 2017. Host pharmacokinetics and drug accumulation of anthelmintics within target helminth parasites of ruminants. *New Zealand Veterinary Journal* 65 (4), 176–184.
- Liu, J.-Z., Hu, Y.-L., Feng, Y., Guo, Y.-B., Liu, Y.-F., Yang, J.-L., Xue, W.-J., 2019. Rifaxonide promotes apoptosis and autophagy of gastric cancer cells by suppressing PI3K/Akt/mTOR pathway. *Exp. Cell Res.* 385, (2) 111691.
- MacDonald, M.L., Lamerdin, J., Owens, S., Keon, B.H., Bilter, G.K., Shang, Z., Minami, T., 2006. Identifying off-target effects and hidden phenotypes of drugs in human cells. *Nat. Chem. Biol.* 2 (6), 329–337.
- Mahmoud, A.M., Saad, M.N., Elzanfaly, E.S., Amer, S.M., Essam, H.M., 2020. An electrochemical sensing platform to determine tetrahydrozoline HCl in pure form, pharmaceutical formulation, and rabbit aqueous humor. *Anal. Methods*.
- Meteleva, E.S., Chistyachenko, Y.S., Suntsova, L.P., Khvostov, M.V., Polyakov, N.E., Selyutina, O.Y., Dushkin, A.V., 2019. Disodium salt of glycyrrhizic acid—a novel supramolecular delivery system for anthelmintic drug praziquantel. *J. Drug Delivery Sci. Technol.* 50, 66–77.
- Mongre, R.K., Mishra, C.B., Prakash, A., Jung, S., Lee, B.S., Kumari, S., Lee, M.-S., 2019. Novel Carbazole-Piperazine hybrid small molecule induces apoptosis by targeting BCL-2 and inhibits tumor progression in lung adenocarcinoma in vitro and Xenograft Mice model. *Cancers* 11 (9), 1245.
- Movahedi, F., KOOHI, M. E. M., Alavi, S. E., & Akbarzadeh, A. (2013). Cytotoxicity assessment of nanoliposomal Paclitaxel and nanoliposomal Hydroxyurea in MCF-7 cells.
- Mukhopadhyay, T., Sasaki, J.-I., Ramesh, R., Roth, J.A., 2002. Mebendazole elicits a potent antitumor effect on human cancer cell lines both in vitro and in vivo. *Clin. Cancer Res.* 8 (9), 2963–2969.
- Nair, R.R., Piktel, D., Hathaway, Q.A., Rellick, S.L., Thomas, P., Saralkar, P., Gibson, L.F., 2020. Pyrvinium pamoate use in a B cell acute lymphoblastic leukemia model of the bone tumor microenvironment. *Pharm. Res.* 37 (3), 43. <https://doi.org/10.1007/s11095-020-2767-4>.
- Nielsen, L., Bundgaard, H., Falch, E., 1992. Prodrugs of thiabendazole with increased water-solubility. *Acta pharmaceutica nordica* 4 (1), 43–49.
- Nielsen, L.S., Sløk, F., Bundgaard, H., 1994. N-alkoxycarbonyl prodrugs of mebendazole with increased water solubility. *Int. J. Pharm.* 102 (1–3), 231–239.
- Özdemir, A., Turanlı, S., Çalişkan, B., Arka, M., Banoglu, E., 2020. Evaluation of cytotoxic activity of new benzimidazole-piperazine hybrids against human MCF-7 and A549 cancer cells. *Pharm. Chem. J.*, 1–11.
- Pal, A.K., Nandave, M., Kaithwas, G., 2020. Chemoprophylactic activity of nitazoxanide in experimental model of mammary gland carcinoma in rats. 3. *Biotech* 10 (8), 1–12.
- Pantziarka, P., Bouche, G., Meheus, L., Sukhatme, V., Sukhatme, V. P., & Vikas, P. (2014). The repurposing drugs in oncology (ReDO) project. *ecancermedicallscience*, 8.

- Paredes, A.J., Llabot, J.M., Sanchez Bruni, S., Allemandi, D., Palma, S.D., 2016. Self-dispersible nanocrystals of albendazole produced by high pressure homogenization and spray-drying. *Drug Dev. Ind. Pharm.* 42 (10), 1564–1570.
- Peltonen, L., Hirvonen, J., 2018. Drug nanocrystals—versatile option for formulation of poorly soluble materials. *Int. J. Pharm.* 537 (1–2), 73–83.
- Pourgholami, M.H., Cai, Z.Y., Lu, Y., Wang, L., Morris, D.L., 2006. Albendazole: a potent inhibitor of vascular endothelial growth factor and malignant ascites formation in OVCAR-3 tumor-bearing nude mice. *Clin. Cancer Res.* 12 (6), 1928–1935.
- Qiao, X., Wang, C., Wang, W., Shang, Y., Li, Y., Ni, J., Chen, S.-Z., 2020. Levamisole enhances DR4-independent apoptosis induced by TRAIL through inhibiting the activation of JNK in lung cancer. *Life Sci.* 257, 118034.
- Radha Katre, S.W., Pajai, K.S., Hajare, S.W., Sajid Ali, S., Game, Harshada, 2020. Comparative efficacy of ivermectin and moxidectin against gastrointestinal nematode infection in horses. *Int. J. Chem. Stud.* 8 (3), 1761–1763. <https://doi.org/10.22271/chemi.2020.v8.i3x.9452>.
- Rajagopal, P., Linsha, K., Sreejith, K., Premaletha, K., Parthasarathy, I. A., & Aneeshia, S. (2019). Anthelmintic studies on the leaves of *Urena lobata* Linn.
- Real, D., Orzan, L., Leonardi, D., Salomon, C.J., 2020. Improving the dissolution of triclabendazole from stable crystalline solid dispersions formulated for oral delivery. *AAPS PharmSciTech* 21 (1), 16.
- Rehman, M.U., Khan, M.A., Khan, W.S., Shafique, M., Khan, M., 2018. Fabrication of Niclosamide loaded solid lipid nanoparticles. *In Vitro characterization and comparative in vivo evaluation.* *Artif. Cells Nanomed. Biotechnol.* 46 (8), 1926–1934.
- Salem, S.E., Abd El-Ghany, A.M., Hamad, M.H., Abdelaal, A.M., Elsheikh, H.A., Hamid, A.A., Ras, R., 2020. Prevalence of gastrointestinal nematodes, parasite control practices and anthelmintic resistance patterns in a working horse population in Egypt. *Equine Vet. J.*
- Samy, A.L.P.A., Bakthavachalam, V., Vudutha, M., Vinjamuri, S., Chinnappa, S., Munirathinam, G., 2020. Eprinomectin, a novel semi-synthetic macrocyclic lactone is cytotoxic to PC3 metastatic prostate cancer cells via inducing apoptosis. *Toxicol. Appl. Pharmacol.* 401. <https://doi.org/10.1016/j.taap.2020.115071>
- Sanches, B.M., Ferreira, E.I., 2019. Is prodrug design an approach to increase water solubility?. *Int. J. Pharm.* 568, 118498.
- Scannell, J.W., Blanckley, A., Boldon, H., Warrington, B., 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discovery* 11 (3), 191.
- Sertkaya, A., Wong, H.-H., Jessup, A., Beleche, T., 2016. Key cost drivers of pharmaceutical clinical trials in the United States. *Clinical Trials* 13 (2), 117–126.
- Shangguan, F., Liu, Y., Ma, L., Qu, G., Lv, Q., An, J., Cao, Q., 2020. Niclosamide inhibits ovarian carcinoma growth by interrupting cellular bioenergetics. *J. Can.* 11 (12), 3454.
- Shashank, J., & Ayodhya, S. (2019). Evaluating the efficacy of ivermectin and levamisole against gastrointestinal nematodes in goats.
- Sleire, L., Førde, H.E., Netland, I.A., Leiss, L., Skeie, B.S., Enger, P.Ø., 2017. Drug repurposing in cancer. *Pharmacol. Res.* 124, 74–91.
- Slocombe, J.O., 2004. A modified critical test for the efficacy of pyrantel pamoate for *Anoplocephala perfoliata* in equids. *Can J Vet Res* 68 (2), 112–117.
- Son, D.-S., Lee, E.-S., Adunyah, S.E., 2020. The antitumor potentials of benzimidazole anthelmintics as repurposing drugs. *Immune Network* 20 (4).
- Suliman, M.A., Zhang, Z., Na, H., Ribeiro, A.L., Zhang, Y., Niang, B., Zuo, Y., 2016. Niclosamide inhibits colon cancer progression through downregulation of the Notch pathway and upregulation of the tumor suppressor miR-200 family. *Int. J. Mol. Med.* 38 (3), 776–784.
- Tang, M., Hu, X., Wang, Y., Yao, X., Zhang, W., Yu, C., Fang, Q., 2020. Ivermectin, a potential anticancer drug derived from an antiparasitic drug. *Pharmacol. Res.* 105207.
- Taylor, M., 1999. Use of anthelmintics in sheep. *Practice* 21 (5), 222–231. <https://doi.org/10.1136/inpract.21.5.222>.
- Tydén, E., Jansson, A., Ringmark, S., 2019. Parasites in horses kept in a 2.5 year-round grazing system in nordic conditions without supplementary feeding. *Animals* 9 (12), 1156.
- Venkatesh, R., Pereira, A., Aseem, A., Yadav, N., 2019. Commentary: closantel; a lesser-known evil. *Indian J. Ophthalmol.* 67 (10), 1771–1772. https://doi.org/10.4103/ijoo.IJO_1150_19.
- Vieira, D.B., Gamarra, L.F., 2016. Advances in the use of nanocarriers for cancer diagnosis and treatment. *Einstein (Sao Paulo)* 14 (1), 99–103.
- Wagh, V., Wagh, R., 2015. Solid dispersion techniques for enhancement of solubilization and bioavailability of poorly water soluble drugs – a review. *Int. J. Pharm. Technol.* 6, 3027–3045.
- Wang, A.M., Ku, H.H., Liang, Y.C., Chen, Y.C., Hwu, Y.M., Yeh, T.S., 2009. The autonomous notch signal pathway is activated by baicalin and baicalein but is suppressed by niclosamide in K562 cells. *J. Cell. Biochem.* 106 (4), 682–692.
- Wei, W., Liu, H., Yuan, J., Yao, Y., 2020. Targeting Wnt/β-catenin by anthelmintic drug niclosamide overcomes paclitaxel resistance in esophageal cancer. *Fundamental & Clinical. Pharmacology.*
- Xue, H., Li, J., Xie, H., Wang, Y., 2018. Review of drug repositioning approaches and resources. *Int. J. Biol. Sci.* 14 (10), 1232.
- Yang, S., Liu, H., Chen, G., Zhihua, Y., 2016. Confirmatory Method for Detecting Multi-Benzimidazoles. *Probenzimidazoles and their Metabolites in Animal Products, IAEA TECDOC SERIES*, p. 201.
- Yaseen, S., Akram, S., 2019. Drug repositioning, an approach for identification of new. *J. Nat. Appl. Sci. Pakistan* 1 (2), 192–200.
- Yilmaz, E., Gerst, B., McKay-Demeler, J., Krücken, J., 2019. Minimal modulation of macrocyclic lactone susceptibility in *Caenorhabditis elegans* following inhibition of cytochrome P450 monooxygenase activity. *Exp. Parasitol.* 200, 61–66.
- Yuriadi, Y., Tjahajati, I., Indarjulianto, S., Widiyono, I., 2019. The Efficacy Study of Duramectin, Oxfendazole, Piperazine, and Pyrantel pamoate Against Gastrointestinal Worms In Horses In Yogyakarta Special Region*). 2019, 37(1), 9. doi:10.22146/jsv.42969.
- Zhang, J., Chen, L., Shen, B., Chen, L., Mo, J., Feng, J., 2019a. Dual-sensitive graphene oxide loaded with proapoptotic peptides and anticancer drugs for cancer synergetic therapy. *Langmuir* 35 (18), 6120–6128.
- Zhang, L., Dratver, M.B., Yazal, T., Dong, K., Nguyen, A., Yu, G., Bhat, K., 2019b. Mebendazole potentiates radiation therapy in triple-negative breast cancer. *International Journal of Radiation Oncology* Biology* Physics* 103 (1), 195–207.
- Zhou, J., Jin, B., Jin, Y., Liu, Y., Pan, J., 2017. The anthelmintic drug niclosamide effectively inhibits the malignant phenotypes of uveal melanoma in vitro and in vivo. *Theranostics* 7 (6), 1447.
- Zhu, Y., Zuo, W., Chen, L., Bian, S., Jing, J., Gan, C., Hu, W., 2019. Repurposing of the anti-helminthic drug niclosamide to treat melanoma and pulmonary metastasis via the STAT3 signaling pathway. *Biochem. Pharmacol.* 169, 113610.
- Zimmermann, S. C., Tichý, T. s., Vávra, J., Dash, R. P., Slusher, C. E., Gadiano, A. J., . . . Monincová, L. (2018). N-substituted prodrugs of mebendazole provide improved aqueous solubility and oral bioavailability in mice and dogs. *Journal of Medicinal Chemistry*, 61(9), 3918–3929.