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Review article

Antiparasitic activity of ivermectin: Four decades of research into a "wonder drug"

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ABSTRACT

Parasitic diseases still pose a serious threat to human and animal health, particularly for millions of people and their livelihoods in low-income countries. Therefore, research into the development of effective antiparasitic drugs remains a priority. Ivermectin, a sixteen-membered macrocyclic lactone, exhibits a broad spectrum of antiparasitic activities, which, combined with its low toxicity, has allowed the drug to be widely used in the treatment of parasitic diseases affecting humans and animals. In addition to its licensed use against river blindness and strongyloidiasis in humans, and against roundworm and arthropod infestations in animals, ivermectin is also used "off-label" to treat many other worm-related parasitic diseases, particularly in domestic animals. In addition, several experimental studies indicate that ivermectin displays also potent activity against viruses, bacteria, protozoans, trematodes, and insects. This review article summarizes the last 40 years of research on the antiparasitic effects of ivermectin, and the use of the drug in the treatment of parasitic diseases in humans and animals.

1. Introduction

Ivermectin is a mixture of two semi-synthetic macrocyclic lactones and is widely used as an antiparasitic drug for the treatment of intestinal roundworm infestation in veterinary medicine. It has also a few applications in human medicine, in particular for the treatment and control of onchocerciasis (river blindness), and therefore, is on the World Health Organization's (WHO) model list of essential medicines [1]. There are only a few drugs that can claim the title of "Wonder Drug". Alongside penicillin and aspirin, two drugs that probably had the greatest medicative impact on human health and well-being, ivermectin is also a worthy contender for this title as its effect on global health to date has been extraordinary. Firstly, ivermectin played an important role in global food production by fighting roundworm infestation in livestock, and secondly, the drug was paramount in relieving the burden of filarial diseases from millions of people living in the poorest countries, which can be regarded as the most successful public-private partnerships in global health [2]. Although ivermectin has been studied for over 40 years, the mechanism of its action and resistance are not fully established, mainly because the drug exhibits a wide range of diverse effects in many different organisms. The versatility of ivermectin makes this drug an interesting compound to be investigated as a medication for other diseases and a potential source for derivatization to improve its activity and efficacy. The focus of this review article is a comprehensive literature appraisal on the licensed, "off-label" and experimental uses of ivermectin in humans and domestic animals.

2. Discovery and mode of action of ivermectin

Ivermectin is a sixteen-membered macrocyclic lactone obtained as a 22,23-dihydro derivative of avermectin by selective hydrogenation using rhodium-based Wilkinson's catalyst (Fig. 1) [3]. Avermectins were first isolated from a *Streptomyces* sp. strain in Japan in 1967 [4]. Ivermectin is a mixture of two forms – B1a with an ethyl group at the C-26 position, and B1b with a methyl group at this position (Fig. 1). This mixture contains at least 80% ivermectin B1a and a maximum of 20% ivermectin B1b [5]. Ivermectin exhibits a wide spectrum of anti-helminthic activities and is therefore used in the treatment of various diseases caused by parasitic nematodes [6]. The approval of ivermectin for use in humans in 1987 significantly improved the quality of life of many people in sub-Saharan Africa, India, and elsewhere, enabling the treatment of diseases that had previously been devastating

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[2]. The success of ivermectin is also due to the fact that its use is generally safe with LD_{50} values ranging between 24 mg kg^{-1} (monkeys [7]) and 80 mg kg^{-1} (beagle [7]), while the maximum treatment dose in animals and humans is around 200 μg kg^{-1}.

The first person to discover a microorganism capable of producing avermectin was Satoshi Ōmura, a microbiologist working at the Kitasato Institute in Japan. The researcher focused on *Streptomyces* bacteria, which are commonly found in soil and are known for producing various biologically active substances [8]. He isolated and characterized a new strain of *Streptomyces* from soil samples and successfully cultured these bacteria [8]. Starting from a few thousand samples, he was able to narrow down the sample size to about 50 strains that looked most promising in terms of producing novel bioactive metabolites [9]. One of these strains (NRRL 8165–a) would later be called *Streptomyces avermitilis* [9]. The second scientist who contributed to the discovery of the unusual biological activity of avermectin was William Campbell, who worked as a biologist and parasitologist at the Merck Shape and Dome Research Laboratories (MDRL) in New Jersey, USA. He investigated Ōmura's bacterial broths for their biological properties and activities [6,10,11]. One of Campbell's collaborators, Thomas Miller, was the first to chemically characterize avermectin, the active component of Omura's sample NRRL 8165–a [11]. Campbell conducted a number of studies that confirmed the high antiparasitic activity of avermectin against many worms in domestic animals [12,13]. Then, together with other MDRL scientists, they chemically modified avermectin to obtain ivermectin, which turned out to exhibit even stronger antiparasitic activity [14]. According to Campbell, this molecule showed extraordinary biological activity against many parasites, was active even against benzimidazole-resistant nematodes, and was well-tolerated by the host species [15]. This discovery was the cornerstone that changed the world in the fight against helminthic diseases.

For the discovery of ivermectin, Satoshi Ōmura and William Campbell were awarded the Nobel Prize in Physiology/Medicine in 2015, specifically, "(…) for their discoveries concerning a novel therapy against infections caused by roundworm parasites" [16]. Ivermectin, thanks to its high efficacy, versatility, and safety of use, has so significantly influenced medical treatments, that many scientists call it a "wonder drug", comparing ivermectin to aspirin or penicillin [17].

Mechanistically, ivermectin acts as a positive allosteric modulator that selectively opens inhibitory glutamate-gated chloride ion channels (GluCl) of muscle and nerve cells of microfilariae, female reproductive tracts, and the excretory/secretory pores of nematodes, as well as of muscles and nerves of insects (Fig. 2) [7,18,19]. GluCl channels consist of five subunits, each of which has four transmembrane α-helices: M_1, M_2, M_3, and M_4 [20,21]. Their mode of action relies on glutamate binding to the orthosteric agonist site of the channels, which leads to the opening of the channel and subsequent flow of ions [20,21]. Ivermectin, in turn, binds to the allosteric site of the channels (Fig. 2). The drug, due to its lipophilicity, can insert deeply into the subunits of the channels, which stabilizes the open-pore conformation and thus extends its opening time [7,22]. The binding between the drug and the channel is characterized by high affinity and leads to an increased influx of chloride ions, and subsequently to hyperpolarization, paralysis, and death of the parasite [7,18,19].

Moreover, ivermectin has also the ability to inhibit the conductance of γ-aminobutyric acid (GABA) channels in *Ascaris suum* at concentrations of <0.2 μM [22]. This additional action may, together with its binding to GluCl channels, synergistically enhance the antiparasitic activity of the drug [7]. What is important, ivermectin does not cross the blood-brain barrier, and therefore, does not affect mammals, including humans, in which GABA receptors are located mainly in the central nervous system [17]. Nevertheless, accumulation of ivermectin in the human brain has been observed after administration of doses about 100 times higher than the recommended one [23]. Such an overdose of the drug may lead to coma and subsequent death of the patient [23]. Oral administration of doses several times higher than recommended was found to be lethal to mice and rats as well [24]. The symptoms of an overdose of ivermectin manifest as significant ataxia, bradypnea, decreased activity, and mydriasis [24]. In addition to overdosing, ivermectin can also enter the brain when mutated multi-drug-resistance transporters present in the blood-brain barrier are unable to effectively eliminate drugs from the plasma [7]. It has been noted that ivermectin, in addition to binding to GABA receptors in the mammalian brain, also targets glycine receptors (GlyRs) and nicotinic acetylcholine receptors (nAChRs) [25–27].

Ivermectin has also been found to be effective against *Plasmodium falciparum*, the parasite species responsible for the most severe form of malaria (see section 5.1.3 for details). The drug inhibits the signal recognition particle (SRP) nuclear import in malaria cells by blocking the motility of the heterodimer carrier IMPα/β, which leads to the subsequent death of the parasite [28]. SRPs are eukaryote ribonucleoprotein complexes that are present in *P. falciparum* cells and are responsible for targeting proteins to the endoplasmic reticulum [28].

3. Licensed use of ivermectin

Ivermectin was introduced for use in humans about 20 years after its discovery [29]. The extremely high microfilaricidal activity of ivermectin and its extraordinary safety in human use, which have been confirmed in many studies, enabled the implementation of this compound in healthcare systems. However, the turning point came in 1987, when Dr. Roy Vagelos (CEO of Merck & Co., Inc.) decided to donate ivermectin "as much as needed, for as long as needed, to anyone who needed it" [29]. This decision greatly improved the quality of life of people living in sub-Saharan regions of Africa, India, and elsewhere, where people could not afford the drug. The introduction of ivermectin made it possible to treat diseases that had affected the poorest people in the world. In particular, ivermectin has been pivotal in the fight against river blindness (*Onchocerca volvulus*) (Table 1). The drug is also used to treat strongyloidiasis (*Strongyloides stercoralis*) and scabies (*Sarcoptes scabiei* var. *hominis*) infections in humans (Table 1) [30].

In addition to being greatly important for human medicine, ivermectin's widespread use in veterinary medicine should be emphasized. Ivermectin and other macrocyclic lactones are commonly used in the treatment and prevention of parasitic diseases in livestock and pets. They are one of the most frequently used anthelmintics in the UK sheep

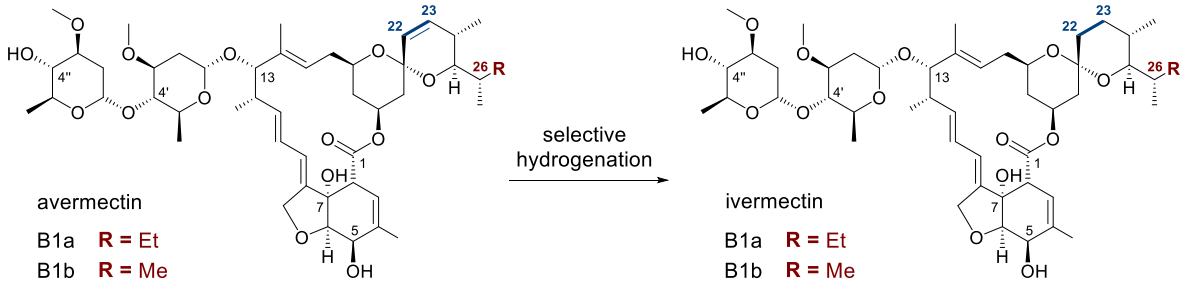

Fig. 1. Chemical structure of avermectin and ivermectin.

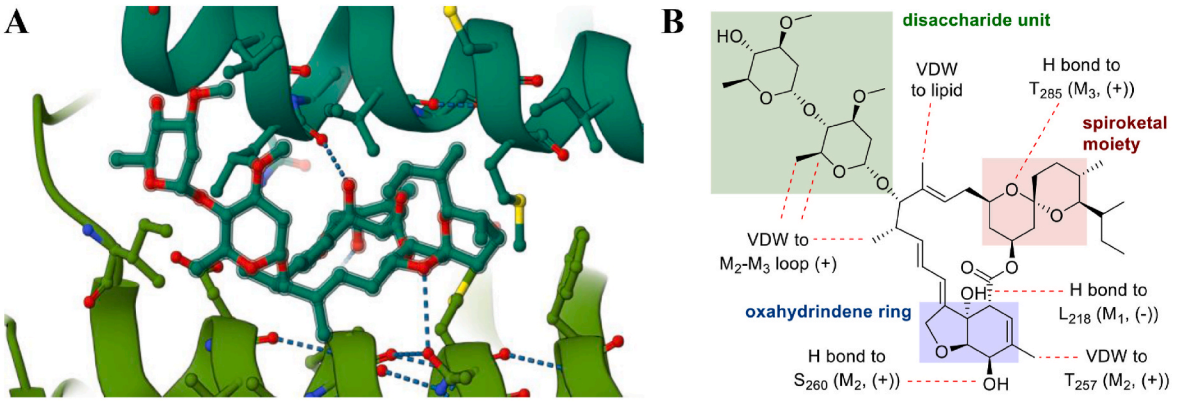

Fig. 2. (**A**) Ivermectin-binding site of a glutamate-gated chloride ion channel (GluCl) subunit. Ribbons are part of the GluCl while the stick molecule is ivermectin; (**B**) Interactions between the ivermectin molecule and GluCl. VDW, van der Waals interactions [20].

industry and the US cattle industry [2,31,32]. There are many animal parasitic diseases for which ivermectin is the drug of first choice. Parasitic diseases treated with ivermectin include heartworm disease, intestinal roundworm infestations, eye worm infestation, lungworm infestation, equine onchocerciasis, mange, lice infestation, myiasis, and gastric myiasis (Table 1).

3.1. In humans

3.1.1. River blindness

River blindness (onchocerciasis) is a helminthic disease caused by the nematode *Onchocerca volvulus*. This filarial worm is transmitted by infected blackflies (*Simulium* spp.). In the human body, the adult worms produce embryonic larvae (microfilariae) which migrate to the eyes, skin, and other organs, consequently causing the clinical symptoms of the disease, which include severe itching, various skin changes, and eye lesions that can lead to permanent blindness [33]. According to the WHO, more than 99% of people affected by river blindness live in 31 sub-Saharan African countries [33]. An estimation by the Global Burden of Disease Study indicated that at least 220 million people required preventive chemotherapy against river blindness in 2017, with 14.6 million individuals who already had skin disease and 1.15 million vision loss [33].

Mass drug administration (MDA) with ivermectin remains the main strategy in combating river blindness. In 2008, Basáñez et al. [34] performed a systematic review of individual and population-based ivermectin trials to examine the temporal dynamics of the microfilaricidal and embryostatic efficacy after single-dose administration at 150 μg kg^{-1} of the drug. Analysis of the data collected from 26 microfilarial and 15 macrofilarial studies was supported by a mathematical model, describing the dynamics of potentially fertile female worms to skin microfilariae [34]. According to the authors, 2 days after treatment with ivermectin, the dermal microfilarial load was reduced by 78% [34]. After 3 days, this value increased to 90%, after 7–8 days to 92–95%, and after 14–60 days to ~98% [34]. The combination of meta-analysis and mathematical modeling suggested that the placebo-corrected microfilaricidal efficacy of ivermectin was 92–99% [34].

Combination therapies of ivermectin with other drugs have been also tested to establish whether these may increase the effectiveness of the treatment. Such studies indicated that 30 years of monotherapy with ivermectin resulted in the emergence of drug-resistant variants of *O. volvulus* [35]. It has been confirmed that in some communities, adult female worms did not respond or were resistant to the anti-fecundity effect of ivermectin-based treatment [36]. Unfortunately, the efficacy of doxycycline-ivermectin co-therapy to target also adult worms remained unclear [37]. It should be noted that the survival of adult worms of *O. volvulus* depends on symbiotic *Wolbachia* bacteria that can be killed with the antibiotic doxycycline. Although in a 6-month follow-up, more patients in the ivermectin plus doxycycline group showed improvement in iridocyclitis and punctate keratitis than those in the ivermectin alone group, the authors concluded that the results are of insufficient quality, and thus cannot be treated as decisive [37]. In another randomized, open-label clinical trial the effectiveness of ivermectin plus albendazole co-therapy was evaluated [38]. The results demonstrated that the combination of ivermectin and albendazole was not better than ivermectin alone in sterilizing and killing adult worms, or achieving sustained microfilariae clearance [38]. Nevertheless, it was found that after 36 months, a 6-monthly treatment regimen was superior compared to a yearly treatment regimen in achieving sustained clearance of *O. volvulus* microfilariae from the skin [38].

3.1.2. Strongyloidiasis

Strongyloidiasis is a chronic parasitic disease caused by nematodes from the genus *Strongyloides*, with *S. stercoralis* being mainly responsible for the human variant of the disease. This parasite belongs to the group of soil-transmitted helminths, i.e., microfilariae released into the soil directly penetrate the skin of the human host [39]. The main symptoms of the disease are intermittent or persistent diarrhea, pruritus, coughing, and wheezing. It is estimated that around 30–100 million people are suffering from strongyloidiasis worldwide [39].

Currently, the most effective treatment option for strongyloidiasis is the use of ivermectin, thiabendazole, or albendazole [39]. However, ivermectin is better tolerated than thiabendazole and more effective in achieving larval clearance than albendazole [40–42]. The standard treatment regimen for uncomplicated *S. stercoralis* infections in the US is oral ivermectin at a dose of 200 μg kg^{-1} per day for two consecutive days, but some specialists suggest repeating the cycle after 2 weeks to prevent possible autoinfections [42,43]. In severe cases of strongyloidiasis, the parasite can appear as two different clinical entities, which is known as hyperinfection syndrome [44]. In this situation, the classic life cycle of the parasite is exaggerated, resulting in an increase in the parasitic burden as a result of autoinfections [44]. In such cases, it is suggested that ivermectin should be administered daily at 200 μg kg^{-1} per day for at least 2 weeks [42]. If needed, treatment should be extended until no more larvae are found in stool specimens [42].

In 2004, Igual-Adell et al. [45] compared the effectiveness of ivermectin and thiabendazole in the treatment of strongyloidiasis. A total of 88 patients were treated using the following protocols: 31 patients – thiabendazole 25 mg kg^{-1} every 12 h for 3 consecutive days; 22 patients – ivermectin 200 μg kg^{-1} as a single dose; and 35 patients – ivermectin 200 μg kg^{-1} for 2 consecutive days [45]. The criterium for cure was the absence of parasites in the feces of three samples collected every other day [45]. Among the 31 patients treated with thiabendazole, 25 (78%) met the criteria for a cure, and 5 (16%) experienced side effects, such as

Table 1
Licensed use of ivermectin in humans and animals.

Species to be treated	Disease	Parasitic species (type)
Humans	River blindness	*Onchocerca volvulus* (nematode)
	Strongyloidiasis	*Strongyloides stercoralis* (nematode)
	Scabies	*Sarcoptes scabiei* var. *hominis* (mite)
Dogs, cats	Heartworm disease	*Dirofilaria immitis* (nematode)
Cattle, sheep, goats (ruminants)	Intestinal roundworm infestation	*Bunostomum phlebotomum*, *Chabertia ovina*, *Cooperia curticei*, *C. oncophora*, *C. pectinata*, *C. punctata*, *Haemonchus contortus*, *H. placei*, *Nematodirus battus*, *N. helvetianus*, *N. spathiger*, *Oesophagostomum columbianum*, *Oe. radiatum*, *Oe. venulosum*, *Ostertagia circumcincta*, *Os. ostertagi*, *Os. lyrata*, *Strongyloides papillosus*, *Trichostrongylus axei*, *T. colubriformis*, *Trichuris ovis* (nemotodes)
	Eye worm infestation	*Thelazia* sp. (nematodes)
	Lungworm infestation	*Dictyocaulus filaria*, *D. viviparus* (nematodes)
	Mange	*Psoroptes ovis*, *Sarcoptes scabiei* var. *bovis*, *S. s.* var. *ovis* (mites)
	Lice infestation	*Haematopinus eurysternus*, *Linognathus africanus*, *L. ovillus*, *L. pedalis*, *L. stenopsis*, *L. vituli*, *Solenopotes capillatus* (lice)
	Myiasis	*Hypoderma bovis*, *H. lineatum*, *Oestrus ovis* (flies)
Horses	Intestinal roundworm infestation	*Craterostomum* sp., *Cyathostomum* sp., *Cyliocyclus* sp., *Cyliodontophorus* sp., *Cyliostephanus* sp., *Gyalocephalus* sp., *Habronema megastoma*, *H. microstoma*, *H. muscae*, *Oesophagodontus* sp., *Oxyuris equi*, *Parascaris equorum*, *Poteriostomum* sp.,*Strongyloides westeri*, *Strongylus edentatus*, *S. equinus*, *S. vulgaris*, *Tristrongylus* sp. (nematodes)
	Lungworm infestation	*Dictyocaulus arnfieldi* (nematode)
	Equine onchocerciasis	*Onchocerca cervicalis*, *Camellia reticulata* (nematodes)
	Eye worm infestation	*Thelazia* sp. (nematodes)
	Gastric myiasis	*Gasterophilus haemorrhoidalis*, *G. intestinalis*, *G. nasalis* (flies)
Swine	Intestinal roundworm infestation	*Ascaris suum*, *Hyostrongylus rubidus*, *Oesophagostomum brevicaudatum*, *O. dentatum*, *O. quadrispinulatum*, *Strongyloides ransomi* (nematodes)
	Lungworm infestation	*Metastrongylus apri*, *M. pudendotectus*, *M. salmi* (nematodes)
	Mange	*Sarcoptes scabiei* var. *suis* (mite)
	Lice infestation	*Haematopinus suis* (louse)

asthenia, epigastralgia, and disorientation [45]. Of the 22 patients treated with a single dose of ivermectin, 17 (77%) met the criteria for a cure, and only 2 (9%) reported side effects, like dizziness and dyspepsia [45]. Among the 35 patients treated with ivermectin on 2 consecutive days, all patients were cured and no one experienced side effects [45]. This outcome showed that the treatment regimen with ivermectin was the most effective and safe. Moreover, in a study that compared the effectiveness of ivermectin versus albendazole, it was found that parasitological cure was higher in the ivermectin group and that ivermectin was as well tolerated as albendazole [46].

Ivermectin was also shown to be effective in the treatment of strongyloidiasis in primary school children. With a single dose of 200 μg kg^{-1}, a cure rate of ~95% was achieved in the pupils, with no side effects [47]. Moreover, ivermectin has also been tried in the treatment of strongyloidiasis in human immunodeficiency virus (HIV)-positive men [48]. After 3 weeks of oral administration of the drug, no changes were observed [48]. However, a high plasma concentration of ivermectin was achieved after parenteral administration resulting in a rapid disappearance of the parasite from biological samples and a significant improvement in the clinical condition of the men without any adverse reaction [48].

3.1.3. Scabies

Scabies is a parasitic skin condition that is caused by the *Sarcoptes scabiei* var. *hominis* mite in humans. The main symptoms of the disease are severe itching, linear burrows, and vesicles around the finger webs, wrists, upper and lower limbs, and belt area [49]. Scabies is one of the most common dermatological diseases in the world, and it is estimated that more than 200 million people suffer from it at any time [49]. Current treatment methods are based on the use of 5% permethrin, 0.5% malathion lotion, 10–25% benzyl benzoate emulsion, or 5–10% sulfur ointment [49]. In addition, oral administration of ivermectin at a dose of 200 μg kg^{-1} is also very effective in treating scabies [50]. However, as ivermectin seems not to be immediately effective against all forms of the parasite, it was found that taking a second dose 7–10 days after the first dose can increase the cure rate [50].

In 2018, Rosumeck et al. [51] analyzed the results of 13 studies comprising 1456 patients to evaluate the effectiveness of systemic ivermectin versus permethrin. Oral administration of ivermectin at a dose of 200 μg kg^{-1} led to slightly lower rates of complete clearance of the mites after one week than topical treatment with 5% permethrin cream (extrapolated cure rates: permethrin 65%, ivermectin 43%) [51]. However, after two weeks, no significant difference in the rates of complete clearance was observed (extrapolated cure rates: permethrin 74%, ivermectin 68%) [51]. Considering the life cycle of the scabies mite (10–17 days), the authors suggested repeating the treatment to increase the effectiveness of the therapy, because ivermectin, unlike permethrin, only affects the adult mites, but not the eggs [51].

According to the WHO, the safety of ivermectin in children under 15 kg body weight has not been established [49]. An observational study performed by Levy et al. [52] in 2020 suggested that ivermectin is safe and effective for the treatment of scabies in infants and young children [52]. Data were collected from 170 infants and children aged 1–64 months, with a body weight of 4–14.5 kg, who were treated with oral ivermectin [52]. The administered dose was 223 μg kg^{-1}, and a second dose was given to 89% of the young patients [52]. Mild adverse events were reported in 7 children (4%) [52]. At the follow-up visit, 139 children (85%) were completely cured [52]. In addition, ivermectin may also be an effective drug in the treatment of scabies in patients with HIV infection [53]. In an open-label study, 11 otherwise healthy patients and 11 HIV patients with scabies were treated with a single oral dose of 200 μg kg^{-1} ivermectin [53]. After 4 weeks, all 11 healthy patients had fully recovered with no evidence of the parasite [53]. Ten of the 11 HIV patients (91%) also showed no evidence of scabies 4 weeks after having been treated with ivermectin [53]. Moreover, ivermectin seems to be effective in treating patients with therapy-resistant scabies too, as some studies report successful interventions with ivermectin in patients with previous treatment failures [54].

3.2. In animals

3.2.1. Heartworm disease

Heartworm disease is caused by the nematode *Dirofilaria immitis*. It is a very serious parasitic disease in dogs and cats that can lead to severe lung damage, heart failure, other organ damage, and death [55]. The infectious larvae of *D. immitis* are transmitted by infected mosquitoes. The average worm burden in dogs is about 15 worms, but the number can vary from 1 up to 250 [55].

Ivermectin administered subcutaneously at a dose of 200 μg kg^{-1} was shown to be effective against *D. immitis* [56]. For example, 90% of dogs treated with ivermectin (pre-treated with sodium thiacetarsamide at a dose of 2.2 mg kg^{-1} twice daily for 2 days) showed no signs of microfilariae in their blood 21 days after starting the therapy [56].

Interestingly, other studies have shown that ivermectin is even effective against *D. immitis* larvae at much lower doses [57]. Larvicidal activity of ivermectin was fully achieved at a dose of 3.0 μg kg^{-1}, while lower doses of 0.5 μg kg^{-1}, 1.0 μg kg^{-1}, and 2.0 μg kg^{-1} showed incomplete anti-larval activities [57]. These results have been confirmed by other authors. For example, a group of 42 dogs was injected with 50 infective larvae of *D. immitis* [58]. The animals were then divided into six groups: group 1 was a vehicle-treated control, groups 2–5 were treated with oral ivermectin at doses of 0.3 μg kg^{-1}, 1.0 μg kg^{-1}, 2.0 μg kg^{-1}, and 3.3 μg kg^{-1}, respectively, 30 days after infection while group 6 was given ivermectin at a dose of 2.0 μg kg^{-1} 45 days after being inoculated with the parasite [58]. The efficacies for preventing heartworm maturation were 0% (group 2), 53% (group 3), 97% (group 4), 98% (group 5), and 64% (group 6), demonstrating that therapies with orally administered doses of 2.0 μg kg^{-1} or 3.3 μg kg^{-1} ivermectin 30 days after *D. immitis* infection were the most effective treatment regimens [58].

Ivermectin was also successfully used in the form of subcutaneous implants, providing long-term prevention of *D. immitis* infection in dogs [59]. A study by Genchi et al. [59] evaluated whether implants consisting of an ethylcellulose matrix containing ivermectin had prophylactic properties. At necropsy, all control dogs were found to be infected, however, implanted dogs were negative for the presence of microfilaria and *D. immitis* antigens [59]. The implants protected dogs against the parasite for at least one year without side effects [59]. It should be noted that ivermectin and other macrocyclic lactones are highly potent against *D. immitis*, but in some cases, the efficacy of ivermectin can be reduced due to emerging drug resistance in this parasite [60].

3.2.2. Intestinal roundworm infestations

There are numerous nematodes responsible for causing intestinal roundworm infestations in livestock (Table 2). The most common roundworms in northern Europe are *Ostertagia ostertagi* and *Cooperia oncophora*, but all intestinal nematodes can be a serious threat to animal breeding, as they can reduce growth rates by up to 30% [61]. Ivermectin has been successfully used in the treatment and prevention of intestinal roundworm infestations in livestock (cattle, sheep, goats, horses, and swine) in various formulations [62].

With respect to ruminants, ivermectin administered in the form of a paste at a dose of 200 μg kg^{-1} to calves experimentally infected with *Bunostomum phlebotomum* 18 and 60 days after infection proved to be very effective, with 100% and 99.8% cure rates, respectively [62]. In another study with calves, ivermectin at the dose of 200 μg kg^{-1} was 100% effective against a resistant variant of *C. oncophora* [63]. At the same dose administered subcutaneously to cattle infected with different nematode species (*B. phlebotomum*, *Cooperia pectinata*, *C. punctata*, *Haemonchus placei*, *Oesophagostomum radiatum*, *Ostertagia ostertagi*), ivermectin showed an efficacy of 80% against all the roundworms in 80% of the treated animals after 7 or 9 days of treatment [64]. Sustained-release ivermectin delivering approximately 8 mg of the drug per day for the duration of 120 days protected 100% of cattle when challenged with infective larvae of *B. phlebotomum*, *H. placei*, *O. radiatum*, *O. ostertagi*, and *Trichostrongylus axei* 4–6 weeks after the bolus administration [65].

Ivermectin has also been given to infected sheep in the form of a controlled-release capsule which delivers the drug at the rate of 1.6 mg per day for 100 days [66]. This technique worked successfully against numerous parasites with an effectiveness of ≥99% [66]. The results suggested that the controlled-release formulation of the drug for sheep may be an effective method in fighting nematode infestations [66]. Oral administration of ivermectin to sheep at a dose of 200 μg kg^{-1} to clear away larvae and adult worms of other nematode species, including benzimidazole-resistant strains achieved 80% efficacy in more than 80% of the treated animals within 9–43 days [67]. Worrying, however, is the emergence of ivermectin-resistant variants in some nematode species. For instance, it has been found that ivermectin treatment of lambs reduced the level of *Ostertagia circumcincta* and *Cooperia curticei* by only

Table 2
Licensed use of ivermectin in the treatment of intestinal roundworm infestations.

Animals	Dose and formulation of ivermectin	Parasitic species	Efficacy	Ref.
Calves	paste, 200 μg kg^{-1}	*Bunostomum phlebotomum*	100% cure rate after 18 days and 99.8% cure rate after 60 days	[62]
Calves	subcutaneous administration, 200 μg kg^{-1}	*Cooperia oncophora*	100% cure rate after 7 and 14 days	[63]
Cattle	subcutaneous administration, 200 μg kg^{-1}	*Bunostomum phlebotomum*, *Cooperia pectinata*, *C. punctata*, *Haemonchus placei*, *Oesophagostomum radiatum*, *Ostertagia ostertagi*,	80% effective in 80% of the treated animals after 7 or 9 days	[64]
Cattle	sustained-release, 8 mg per day for 120 days	*Bunostomum phlebotomum*, *Haemonchus placei*, *Oesophagostomum radiatum*, *Ostertagia ostertagi*, *Trichostrongylus axei*	100% efficacy	[65]
Sheep	controlled-release capsule, 1.6 mg per day for 100 days	*Chabertia ovina*, *Cooperia curticei*, *Dictyocaulus filaria*, *Haemonchus contortus*, *Nematodirus battus*, *N. filicollis*, *Oesophagostomum venulosum*, *Ostertagia circumcincta*, *O. pinnata*, *O. trifurcata*, *Protostrongylus rufescens*, *Strongyloides papillosus*, *Trichostrongylus axei*, *T. colubriformis*, *T. vitrinus*, *Trichuris ovis*, *T. skrjabini*	≥99% cure rate after 21, 28, 35 and 56 days	[66]
Sheep	oral administration, 200 μg kg^{-1}	*Chabertia ovina*, *Dictyocaulus filaria*, *Gaigeria pachyscelis*, *Haemonchus contortus*, *Nematodirus spathiger*, *Oesophagostomum circumcincta*, *Oe. columbianum*, *Trichostrongylus colubriformis*, *Trichuris* spp.	80% effective in more than 80% of the treated animals after 9–43 days	[67]
Horses	oral 2% ivermectin formulation, 200 μg kg^{-1}	*Coronocyclus ulambajari*, *Craterostomum acuticaudatum*, *Cyathostomum catinatum*, *C. pateratum*, *Cylicocyclus brevicapsulatus*, *C. insigne*, *C. leptostomum*, *C. nassatus*, *C. ultrajectinus*, *Cylicocyclus* spp., *Cylicostephanus calicatus*, *C. longibursatus*, *C. poculatus*, *Habronema muscae*, *Habronema* spp., *Oxyuris equi*, *Parascaris equorum*, *Poteriostomum imparidentatum*, *Triodontophorus* spp.	100% efficacy after 5 days, 99% after 14 days and 100% after 19 days	[68]
Ponies	paste, 200 μg kg^{-1}	*Coronocyclus coronatus*, *C. labiatus*, *C. labratus*, *Craterostomum acuticaudatum*,	reduction in the number of parasites from 94% to >99%	[69]

(*continued on next page*)

Table 2 (*continued*)

Animals	Dose and formulation of ivermectin	Parasitic species	Efficacy	Ref.
		Cyathostomum catinatum, *C. pateratum*, *Cylicocyclus ashworthi*, *C. elongatus*, *C. insigne*, *C. leptostomum*, *C. nassatus*, *C. radiatus*; *Cylicodontophorus bicoronatus*, *Cylicostephanus asymetricus*, *C. bidentatus*, *C. calicatus*, *C. goldi*, *C. longibursatus*, *C. minutus*, *Gasterophilus intestinalis*, *Gyalocephalus capitatus*, *Habronema* spp., *Oxyuris equi*, *Parapoteriostomum euproctus*, *P. mettami*, *Parascaris equorum*, *Petrovinema poculatum*, *Poteriostomum imparidentatum*, *P. ratzii*, *Strongylus edentatus*, *S. vulgaris*, *Triodontophorus brevicauda*, *T. serratus*	after 14 or 15 days	
Foals	intramuscular administration, 200 μg kg^{-1}	*Strongyloides westeri*	≥99% reduction in the number of parasites after 21 days	[70]
Pigs	feed formulation, 100 μg kg^{-1} or 200 μg kg^{-1} per day	*Ascaris suum*, *Ascarops strongylina*, *Hyostrongylus rubidus*, *Macracanthorhynchus hirudinaceus*, *Metastrongylus* spp., *Oesophagostomum* spp.	efficacy from 86% to 100%, depending on the type of the parasite	[71]
Pigs	100 μg kg^{-1} per day	*Ascaris suum*, *Hyostrongylus rubidus*, *Metastrongylus salmi*, *Strongyloides ransomi*	95% cure rate after 14 days	[72]

37% and 19%, respectively [73].

Ivermectin was also shown to be effective in treating intestinal roundworm infestations in horses. For example, 20 horses naturally infected with 19 different nematode species were divided into an ivermectin-treated group (single oral dose of 200 μg kg^{-1}) and a control group [68]. The efficacy of the treatment on days 5, 14, and 19 post-infection was 100%, 99%, and 100%, respectively [68]. Similar results were obtained when ivermectin was administered as a paste at a dose of 200 μg kg^{-1} on ponies naturally infected with small and large strongyle nematodes [69]. A reduction in the number of parasites between 94% and 99% was observed [69]. At a dose of 200 μg kg^{-1}, ivermectin was also effective against the *Strongyloides westeri* in naturally infected foals [70]. Intramuscular injection of the drug reduced the number of parasite egg output by more than 99% [70].

The effectiveness of ivermectin has also been confirmed in the treatment of pigs infected with roundworms when the drug was administered to the animals in feed for 7 days [71]. At a concentration that provided a dose of 100 μg kg^{-1} per day, the efficacy against naturally acquired and induced (fourth-stage larvae) roundworm infections ranged between 90% and 100%, depending on nematode species [71]. At a quantity that afforded a dose of 200 μg kg^{-1} per day, ivermectin was found to be particularly potent in eliminating *Ascaris suum*, *Ascarops strongylina*, and *Metastrongylus* spp [71]. The effectiveness of ivermectin in the treatment of swine was also confirmed in another study in which animals were given either ivermectin or abamectin (avermectin B1) at a dose of 100 μg kg^{-1} per day for 7 days [72]. Both drugs were more than 95% effective against *A. suum*, *Hyostrongylus rubidus*, *Metastrongylus salmi*, and *Strongyloides ransomi* [72].

3.2.3. Eye worm infestation

Eye worm infestation (thelaziasis) is a disease caused by nematodes of the genus *Thelazia*, which affects cattle and horses worldwide. These roundworms are transmitted by face flies [74]. Thelaziasis causes inflammation of the eye with symptoms ranging from lacrimation, epiphora, conjunctivitis, and ulcers, to blindness. The drugs used to treat eye worm infestation are ivermectin, doramectin (an ivermectin derivative), and levamisole [74].

Kennedy et al. [75] have performed a study to test the effectiveness of ivermectin in a pour-on formulation on cattle naturally infected with *Thelazia* sp. The drug (IVOMEC®, 0.5% w/v ivermectin) was applied topically at 1.0 mL per 10 kg body weight [75]. After 14 days, the total elimination of *T. gulosa* worms and a 97% reduction in the number of *T. skrjabini* worms were observed, compared to the control group [75]. Total elimination of *T. skrjabini* nematodes was also observed 2 weeks after subcutaneous administration of ivermectin at a dose of 200 μg kg^{-1} to experimentally infected calves [76]. Similar results have been reported after subcutaneous administration of the drug at the same dose to cattle naturally infected with *T. rhodesii* [77]. The parasite reduction exceeded 99%, reaching 100% in two-thirds of the cases [77].

3.2.4. Lungworm infestation

Lungworm infestation (verminous bronchitis, verminous pneumonia) is a disease of the lower respiratory tract in livestock caused by various nematodes. The disease in cattle, sheep, goats, and horses is induced by *Dictyocaulus* spp, while in swine it is caused by *Metastrongylus* spp [78]. The most common symptoms are coughing and dyspnea, however, the condition of the animal can get worse due to simultaneous bacterial or viral infections. A commonly used treatment involves the use of anthelmintics [78].

In a study by Pouplard et al. [79], the effectiveness of ivermectin was compared to that of levamisole in the treatment of calves infected with *D. viviparus* larvae. One group of calves was given levamisole at a dose of 10 mg kg^{-1}, while the other group was administered ivermectin at a dose of 200 μg kg^{-1} [79]. Ivermectin turned out to be more effective than levamisole [79]. These results were confirmed in another study with calves experimentally infected with *D. viviparus* larvae [80]. One group was given an injectable formulation of ivermectin at a dose of 200 μg kg^{-1}, while the second and third groups were treated with a pour-on formulation of levamisole at 10 mg kg^{-1} or ivermectin at a dose of 500 μg kg^{-1} [80]. The fourth group was left untreated (control group) [80]. After 28 days, the presence of *D. viviparus* worms was checked in 2 calves from each group [80]. On day 35, the remaining calves were re-infected [80]. Levamisole treatment was ~95% effective, while both ivermectin treatment regimens eradicated 100% of the parasites [80]. In addition, the calves treated with ivermectin were protected from reinfection, which subsequently became an issue in the control calves and those treated with levamisole [80]. Ivermectin has also been shown to be effective in treating calves infected with inhibited larvae of *D. viviparous* [81]. After subcutaneous treatment at a dose of 200 μg kg^{-1}, no traces of adult worms or inhibited L5 stages of *D. viviparus* were found in the lungs of the treated animals [81].

Ivermectin was also successfully used in the treatment of lungworm infections in ponies caused by *D. arnfieldi* [82]. Oral administration of the drug in the form of a paste at a single dose of 200 μg kg^{-1} resulted in a complete cure of the infected ponies [82]. The possibility of using ivermectin in the treatment of *Metastrongylus* spp. responsible for lungworm infestation of swine was also studied. A dose of 100 μg kg^{-1} allowed the elimination of the parasite with an efficacy of 95% or better, while a double dose was 100% effective [71,72].

3.2.5. Equine onchocercosis

Equine onchocercosis is a skin disease in horses caused by

microfilariae produced by *Onchocerca* sp. adult worms. The parasites are transmitted by different species of biting flies. Unfortunately, there is no treatment that is effective against the adult worms of the parasite [83]. However, ivermectin is commonly used in the fight against *O. cervicalis* and *O. reticulata* microfilariae.

In a study, a group of 40 horses who were infected with microfilariae of *O. cervicalis* and suffering from dermatitis, alopecia, and pruritus, were given a single injection of 200 μg kg^{-1} of ivermectin [84]. Skin snips were taken from all horses after 4 and 33 days post-treatment [84]. All samples were found to be negative for the presence of *O. cervicalis* microfilariae [84]. Significant clinical improvement in health was observed within 2–3 weeks after treatment when the lesions were replaced by healthy skin and new hair [84]. Ivermectin at a single dose of 200 μg kg^{-1} in injectable paste formulation was also effective against microfilariae of *O. cervicalis* in naturally infected horses [85]. The number of microfilariae was reduced to zero 21 days after treatment in 19 out of 20 horses [85]. Active lesions improved or completely disappeared within 63 days after treatment [85]. Another study compared the efficacy of moxidectin (a macrocyclic lactone related to ivermectin) 2% oral gel (dose 400 μg kg^{-1}) with the efficacy of ivermectin 2% oral paste (dose 200 μg kg^{-1}) in horses infected with *O. cervicalis* [86]. After analyzing skin snipes taken 14 days after treatment, it was concluded that both drugs were 100% effective when used as a single oral dose [86].

3.2.6. Mange

Mange is a disease caused by parasitic mites. Species of the genera *Chorioptes*, *Demodex*, *Psorobia* (formerly *Psorergates*), *Psoroptes*, and *Sarcoptes*, are the main pathogens responsible for mange in domestic animals. However, the widespread use of macrocyclic lactones over the last 30 years has reduced the risk of mite infestation [87,88]. Ivermectin is commonly used in the treatment of mange in ruminants (cattle, sheep, and goats), especially against *Psoroptes ovis*, *Sarcoptes scabiei* var. *bovis*, and *S. scabiei* var. *ovis*. The drug is also used in the treatment of mange in swine.

The efficacy of a controlled-release formulation of ivermectin in the treatment and prevention of *P. ovis* in sheep has been described by Forbes et al. [89]. The results clearly indicated that an intraruminal controlled-delivery system (bolus) to release ivermectin at a rate of 20–40 μg kg^{-1} per day for 100 days completely eliminated the parasite [89]. The prophylactic effect was maintained throughout the active life of the bolus [89]. Another study investigated how effectively a long-acting injectable formulation of the drug protects cattle against *P. ovis* [90]. The animals were divided into 5 groups, including one control group that was not treated with any drug [90]. The treatment groups were administered with ivermectin at a dose of 630 μg kg^{-1}, 56, 42, or 35 days prior to infection, or with doramectin (a macrocyclic lactone closely related to ivermectin) at a dose of 200 μg kg^{-1}, 35 days prior infection [90]. Then, all animals were challenged with *P. ovis* [90]. Viable mites were present in 33%, 67%, and 83% of the controls after 14, 21, and 28 days of infection, respectively [90]. However, no parasites were present in animals treated with ivermectin, indicating that a long-acting injectable formulation of this drug may protect cattle against the disease for at least 56 days [90]. On the other hand, doramectin showed no prophylactic effect 35 days after treatment [90]. Ivermectin was also successfully applied topically at 500 μg kg^{-1} against *S. scabiei* var. *bovis* in cattle [91]. Out of 12 cattle naturally infected with *S. scabiei* var. *bovis*, only in one case three mites were recovered on day 28 [91]. In the remaining cases, no mites were found in scrapings from ivermectin-treated animals after 2 weeks [91].

Ivermectin can also be successfully used to treat *S. scabiei* var. *suis* in pigs. When administered by esophageal intubation at doses of 300 μg kg^{-1}, 400 μg kg^{-1}, or 500 μg kg^{-1}, a significant reduction in the number of mites was observed in pigs [92]. Of the 18 pigs treated with ivermectin, 10 were found to be mite-free after a week [92]. This number increased to 16 pigs after 14 days and to 18 pigs after 21 days, respectively, and then decreased to 16 pigs after 28 days [92]. In another study, sows infected with *S. scabiei* var. *suis* were treated with a single subcutaneous injection of ivermectin at doses of 75 μg kg^{-1}, 150 μg kg^{-1}, or 300 μg kg^{-1} [93]. There was a significant decline in the number of mites, especially in the animals treated with the highest dose [93]. In the latter case, almost all mites and eggs were eradicated after one week of ivermectin treatment [93]. The drug was also tried in the form of a single subcutaneous injection at a dose of 300 μg kg^{-1} on a commercial herd of 146 pigs, 80% of which were infected with the mite [94]. Ivermectin was administered to all animals, except 6 which served as controls [94]. At 28 and 42 days post-treatment, no parasites were found in the scrapings of ivermectin-treated pigs [94]. In contrast, live mites were present in the scrapings of all control animals [94].

3.2.7. Lice infestation

Lice infestation is a big problem in livestock farming, especially in winter, when animals are crammed together. It affects, among others, cattle and swine, leading to skin and hair damage, weight loss, and decreased milk production [95,96]. The disease in ruminants is mainly caused by the following lice species: *Haematopirus eurysternus*, *Linognathus africanus*, *L. ovillus*, *L. pedalis*, *L. stenopsis*, *L. vituli*, and *Solenoptes capillatus*. In swine, the disease is caused by the *H. suis* louse (Table 1).

Ivermectin has been successfully used to combat the lice species listed above. Both subcutaneous and oral drug administration at a dose of 200 μg kg^{-1} allowed complete elimination of sucking lice (*L. vituli*) from infected cattle as early as 3 or 4 days post-treatment [97]. The high efficacy of ivermectin was also confirmed in other studies. The drug completely eliminated *L. vituli* and *S. capillatus* from heavily infested cattle [98]. The efficacy of a combination of ivermectin with the antiparasitic drug triclabendazole was also evaluated in cattle [99]. Two combined formulations providing ivermectin at a dose of 200 μg kg^{-1} and triclabendazole at a similar dose of 10 mg kg^{-1} or 12 mg kg^{-1}, respectively, were tested orally or subcutaneously [99]. Both formulations proved to be effective against three different lice species [99]. The efficacy against *L. vituli* was greater than 99% after 7 days of treatment [99]. For *S. capillatus* and *H. eurysternus*, the efficacy was 100% and 98% and thus equally high after one week of treatment [99]. Subcutaneous administration of ivermectin was also highly effective against *H. suis* in swine [100]. The drug was given at a dose of 20 μg kg^{-1}, 100 μg kg^{-1}, or 200 μg kg^{-1}, and the efficacy range between 99% and 100% [100].

3.2.8. Myiasis

Myiasis is a disease of cattle and other livestock caused by cattle grubs (*Hypoderma bovis* and *H. lineatum*) and the sheep bot fly (*Oestrus ovis*). The larvae of these flies enter the host's body, causing increased susceptibility to other diseases, poor growth rate, decreased meat and milk production, and thus significant economic losses [101]. Macrocyclic lactones, including ivermectin, are being used in the treatment of myiases.

IVOMEC® is a type of ivermectin formulation that can be used in the fight against myiasis in cattle [102]. The formulation (0.5% ivermectin) is used at the dose of 1 mL per 10 kg body weight [102]. Studies indicated that it is 100% effective against migrating first-instar larvae of *H. lineatum* for 3 weeks after administration [102]. After 4 weeks, its efficacy was still high (96%) [102]. Another study conducted on cattle selected from herds with a history of cattle grubs has shown that long-acting formulation of ivermectin administered subcutaneously at a dose of 630 μg kg^{-1} was 100% effective in treating the animals naturally infected with *H. bovis* and *H. lineatum* [103]. A study on yaks was conducted to establish the lowest effective dose of ivermectin against *Hypoderma* spp [104]. The drug was administered to the animals subcutaneously at doses of 1 μg kg^{-1}, 5 μg kg^{-1}, and 10 μg kg^{-1}, respectively [104]. After 4 and 6 months, no warbles were found on treated animals, although they were present in the control group [104]. This study showed that ivermectin at a relatively low dose of 1 μg kg^{-1} was sufficiently effective to protect animals against *Hypoderma* spp. larvae

[104].

Ivermectin can also be used to treat effectively sheep infected with *O. ovis*. Oral administration of the drug at a dose of 200 μg kg^{-1} showed 100% efficacy in combating *O. ovis* larval infestations [67,105]. As mentioned above, ivermectin in the form of a controlled-release capsule that delivered the drug at the rate of 1.6 mg per day for 100 days showed ≥99% efficacy against *O. ovis* larvae [66]. In a study by Bello et al. [106], the prophylactic effect of ivermectin and closantel to control *O. ovis* infestation in sheep was compared. Ten sheep each were assigned to the following groups: control, treated with ivermectin given subcutaneously at a dose of 200 μg kg^{-1}, and treated with closantel given orally at a dose of 10 mg kg^{-1} [106]. All animals were kept together, and after examination, it was found that 7 of the control lambs were found to be infected with *O. ovis* larvae [106]. The botfly larvae were intact and active [106]. Three of the lambs treated with ivermectin had *O. ovis* larvae, but they were dead, while no botfly larvae were found in animals treated with closantel [106]. According to the authors, both drugs showed high efficacy against *O. ovis* [106].

3.2.9. Gastric myiasis

Gastric myiasis is a disease of horses caused by *Gasterophilus* spp. maggots. Adult females lay eggs on single hairs of the horse's front legs, abdomen, flanks, and shoulders. After the larvae have hatched, they are ingested by the horse and bury themselves in the tongue, gums, or lining of the mouth. The second stage larvae move into the stomach and can cause inflammatory reactions and in large numbers blockages and colics [107]. Ivermectin is the treatment of choice as it shows efficacy against both oral and gastric stages [107].

In one study, the efficacy of ivermectin in treating ponies naturally or experimentally infected with *G. intestinalis* was investigated [108]. The drug was administered at a dose of 200 μg kg^{-1} by intravenous injection, by intramuscular injection, or as oral paste [108]. After 21 days of treatment, no maggots were found in the ponies treated with ivermectin [108]. The drug showed 100% efficacy against oral and gastric stages of *Gasterophilus* spp [108]. However, one pony that was given the drug intravenously had an anaphylactic reaction, resulting in its death [108]. This effect was also seen in a control pony given the vehicle intravenously, while no adverse reactions occurred in ponies treated orally or intramuscularly [108]. The high potential of ivermectin in treating ponies was also confirmed in two other studies. In one study, the drug was administered at a dose of 200 μg kg^{-1} in the form of an injectable micelle solution administered intramuscularly or in the form of an oral paste formulation [109]. In both cases, the efficacy of ivermectin was higher than 98% against *G. intestinalis* and *G. nasalis* larvae [109]. In the second study, it was shown that ivermectin was ≥97% effective against *G. intestinalis* larvae when administered intramuscularly to ponies [110]. The study tested ivermectin at doses of 200 μg kg^{-1}, 300 μg kg^{-1}, and 500 μg kg^{-1}, and the effect was similar for each dosage [110].

4. "Off-label" use of ivermectin

In addition to the licensed use of ivermectin for the treatment of onchocerciasis, strongyloidiasis, and scabies in humans, as well as nematodiases in veterinary medicine, this semi-synthetic macrocyclic lactone was also found to be effective against a number of other parasitic nematodes and arthropods for which the drug has not been officially approved. This practice is known as "off-label" use, which refers to the use of a pharmaceutical drug for an unlicensed indication or in an unlicensed dosage or route of administration [111]. Generally, healthcare authorities may prescribe a drug for unlicensed use when they judge that it is medically appropriate for their patients [112]. The "off-label" use is more common when the patients are less likely to be included in clinical trials (for example, those suffering from neglected tropical diseases), as well as in veterinary medicine, as the available pharmacopeia for veterinarians is smaller than for human practitioners. Unlicensed use of ivermectin involves certain intestinal roundworm infestations, mansonellosis, cutaneous larva migrans, gnathostomiasis, demodicosis, and lice infestations in humans, and mange, ear mites, and certain intestinal roundworm and lungworm infestations in animals (Table 3).

4.1. In humans

4.1.1. Intestinal roundworm infestations

Numerous nematodes are responsible for causing intestinal roundworm infestations in humans. Ascariasis, caused by *Ascaris lumbricoides*, is one of the most commonly neglected soil-transmitted helminth infections of major public health importance [113]. This human parasite is mainly distributed in tropical and subtropical regions, with more than a billion individuals affected worldwide [114]. According to the data published by the Global Burden of Diseases Study, 446 million cases of *A. lumbricoides* infections were reported worldwide in 2019 [115]. *Trichuris trichiura*, also known as the human whipworm is another example of a soil-transmitted nematode species. Both ascariasis and trichuriasis are classified as neglected tropical diseases.

Ascariasis may cause shortness of breath and fever at the beginning of the disease, while abdominal swelling and pain combined with diarrhea are the symptoms during the advanced stage of the parasitosis. Trichuriasis is typically asymptomatic [116], but individuals with heavy infections may have gastrointestinal problems, growth retardation, or other mild pathologies [116]. The current treatment for ascariasis and trichuriasis in humans is based on the administration of benzimidazoles (Fig. 3). Unfortunately, the effectiveness of benzimidazoles in the treatment and prophylaxis of soil-transmitted helminthiases is limited, and thus the search for new treatment options is a priority. In this context, ivermectin has been investigated as an alternative treatment and prevention option for these human parasitic nematodes.

In a randomized, double-blind, multicenter clinical trial to evaluate the efficacy and side effects of ivermectin and albendazole against *A. lumbricoides*, the cure rates of the drugs at a dose of 0.1 mg kg^{-1} and 6.7 mg kg^{-1}, were found to be 100% (102/102 individuals) and 99% (101/102 individuals), respectively [117]. In addition to a lower effective dose of ivermectin compared with albendazole, the use of the macrocyclic lactone resulted only in rare, mild, and transient side effects, with no special treatment required [117]. Importantly, the elimination of the worms was faster in the ivermectin-treated group as well [117], which was suggested to be a consequence of the different antiparasitic mechanisms of action of the two drugs. The better efficacy of ivermectin was also reported by other authors. For example, single doses

Table 3
"Off-label" use of ivermectin in humans and animals.

Species to be treated	Disease	Parasitic species (type)
Humans	Intestinal roundworm infestation	*Ascaris lumbricoides, Trichuris trichiura, T. vulpis* (nematodes)
	Mansonellosis	*Mansonella ozzardi, M. perstans, M. streptocera* (nematodes)
	Cutaneous larva migrans	*Ancylostoma brazilliensis, A. caninum, A. tubaeforme, Gnathostoma hispidum, G. spinigerum* (nematodes)
	Gnathostomiasis	*Gnathostoma spinigerum* (nematode)
	Demodicosis	*Demodex folliculorum* (mite)
	Lice infestation	*Pediculus humanus capitis, P. h. corporis, Phthirus pubis* (lice)
Dogs, cats	Ear mite infestation	*Notoedres cati, Otodectes cynotis* (mites)
	Mange	*Cheyletiella blakei, C. yasguri, Demodex canis, D. cati, D. gatoi, Sarcoptes scabiei* var. *canis* (mites)
Dogs	Intestinal roundworm infestation	*Ancylostoma caninum, Toxascaris leonine, Toxocara canis* (nemotodes)
	Lungworm infestation	*Capillaria aerophila* (nematode)
Rabbits, guinea pigs	Ear mite infestation	*Notoedres cati, N. muris* (mites)
	Mange	*Cheyletiella parasitovorax, Chirodiscoides caviae, Psoroptes cuniculi, Trixacarus caviae* (mites)

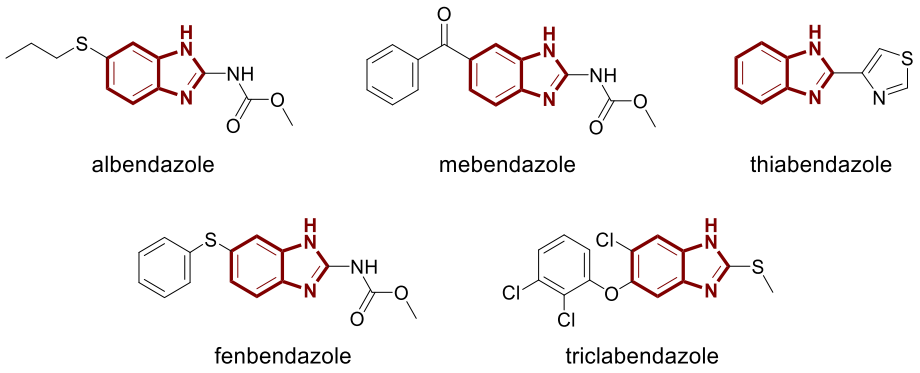

Fig. 3. Chemical structures of the antiparasitic drugs from the benzimidazole group. The benzimidazole scaffold present in the molecules is highlighted in red.

of albendazole (400 mg once a day), mebendazole (500 mg once a day), and ivermectin (0.1–0.4 mg kg^{-1}) were found to produce comparable effects against infection with *A. lumbricoides*, resulting in a high parasitological cure, i.e., the elimination of the parasite from stool samples, without serious side effects [118]. Of note, treatment failure after single-dose administration was the lowest with ivermectin [118]. A 100% overall cure rate in ascariasis-positive patients was also reported after ivermectin administration by Naquira et al. [119] and others [120].

A promising strategy to fight intestinal roundworm infestation seems also to be a combination therapy of ivermectin with albendazole [121–126]. Although an MDA trial with ivermectin/albendazole (200 μg kg^{-1} of ivermectin plus 400 mg of albendazole) revealed that the combination therapy had little effect on the prevalence of *A. lumbricoides*, it showed that the intensities of infections were reduced [121]. On the other hand, combinational treatment with ivermectin was shown to be not superior to albendazole alone against *A. lumbricoides*, but increased the effectiveness of the benzimidazole drug against *T. trichiura* [122,127]. A similar effect of ivermectin in enhancing the efficacy of albendazole was also confirmed by other authors [125,126]. This finding is of importance, as benzimidazoles are known to be less effective against trichuriasis than against ascariasis or hookworm infestations, and as there are concerns that benzimidazole monotherapies could lead to the emergence of resistant intestinal roundworms in patients.

There is also an urgent need for up-to-date knowledge on the prevalence and intensity of soil-transmitted helminth infections in children in general and, in particular, in children under the age of five. If soil-transmitted helminthiases are not controlled in children, youngsters can constitute a human reservoir for the geoparasites and thus may contribute to the spread of the diseases to the general population. For example, in a study by Nana-Djeunga et al. [128] including 421 children aged 2–4 years, it was found that the overall prevalence of infections with *A. lumbricoides* and *T. trichiura* was ~10% (95% CI 6.5–13.9), with a maximum infection rate of ~30% in a specific district. Although Moncayo et al. [129] have shown that the administration of ivermectin to school-age children had no significant impact on *A. lumbricoides* or hookworm infections, the drug was effective against infections caused by *T. trichiura*. Moreover, combination therapy of this drug with albendazole seems to be a highly effective and well-tolerated treatment strategy against *T. trichiura* infections in children and adolescents [130–132]. Interestingly, Knopp et al. [133] have found that the addition of ivermectin improves the therapeutic outcome of both albendazole and mebendazole in the fight against trichuriasis, with the ivermectin-mebendazole combination producing a higher reduction in egg output (97%, 95% CI 95%–98%) than the ivermectin-albendazole combination (91%, 95% CI 87%–94%). It has also been shown that ivermectin can be safely administered to preschool-aged children infected with trichuriasis [134]. The pharmacokinetic properties of ascending doses of ivermectin (100–600 μg kg^{-1}) studied in *T. trichiura*-infected children aged 2–12 years showed a lower exposure profile of the drug in children compared with adults [135]. However, in an ivermectin/albendazole combination MDA study with 228 pupils in Tanzania, it was found that the prevalence of *A. lumbricoides* and *T. trichiura* had only insignificantly decreased from 0.9 to 0.7% ($p = 0.84$) [136].

Analysis of the long-term benefits of treating ascariasis with ivermectin suggests that the efficacy of the drug to control this intestinal nematode may also depend on the geographical region (i.e., different geographical strains) [117,137] and on the genetic disposition of the individuals living in local communities [138]. Similar conclusions regarding the effectiveness of anthelmintic drugs used alone or in combination were also reached for other roundworm infestations [139–142].

4.1.2. Mansonellosis

Mansonellosis is a filarial disease caused by three species, *Mansonella ozzardi*, *M. perstans*, and *M. streptocera*. The three species vary in their geographic distribution and location within their human host [143]. The parasites are transmitted by the bite of infected midges. While the adult worms of *M. perstans* reside in body cavities (pleural and peritoneal cavities, pericardium), adult worms of *M. ozzardi* and *M. streptocera* live in subcutaneous tissue and dermis, respectively. The microfilariae of the three *Mansonella* species enter the peripheral circulation, and in the case of *M. streptocera* also the skin [143]. The main common symptoms of mansonellosis are pruritus, arthralgias, headaches, and fever. There is no standard treatment for mansonellosis but the most commonly used drug to treat this filarial disease is diethylcarbamazine [144].

Although the ineffectiveness of single dose of ivermectin treatment has been independently confirmed for *M. ozzardi* and *M. perstans* filariasis [145,146], in a double-blind, randomized, placebo-controlled study, a single oral dose of the drug (150 μg kg^{-1}) led to an almost complete reduction (99.9%) of the *M. ozzardi* microfilaraemia in infected people [147], suggesting that the drug has some effect on female worm survival or fertility. Filaricidal activity of ivermectin against *M. ozzardi* microfilariae, which could last for up to one year, has also been reported by other authors [148–150]. When using ivermectin, the possibility of early adverse reactions, including the Mazzotti reaction (severe, potentially life-threatening allergic response), should always be taken into account, but in most studies evaluating the effectiveness of the drug in the treatment of mansonellosis, nearly all patients recovered rapidly without any additional antiallergic therapy required [147,148,151].

Human mansonellosis caused by *M. perstans* is usually regarded as the most difficult to treat among the three forms of the disease [144]. Ivermectin has been shown to reduce the motility of microfilariae *in vitro* to 50–65%, irrespective of the concentration of the drug [152]. Specifically, both 5 μg mL^{-1} and 10 μg mL^{-1} of ivermectin had almost the same effect on microfilariae survival (~50%) by day 5, but its activity was lower than those of mefloquine and artesunate [152]. Ivermectin

generally produced no significant changes in microfilaraemia *in vivo*, suggesting it is inefficient against *M. perstans* infections when used alone [153,154]. However, the efficacy of ivermectin treatment against this parasite may be strictly related to cumulative doses of the drug. A 3-year trial showed that the microfilariae loads were only reduced by two-thirds in patients treated with the standard dose (150 μg kg^{-1} annually), while in another group treated with high doses (two doses of 400 μg kg^{-1}, followed by ten doses of 800 μg kg^{-1} 3-monthly) the reduction was 97%, and in two other groups treated with medium doses (one dose of 400 μg kg^{-1}, followed by two doses of 800 μg kg^{-1} or 150 μg kg^{-1} every three months) the reduction was 85% [155]. Ivermectin has also been successfully used in the treatment of infections caused by *M. streptocerca* [156,157]. Moreover, the same authors showed that a single dose of ivermectin (150 μg kg^{-1}) can lead to long-lasting suppression of *M. streptocerca* microfilariae, with almost half of the patients displaying no detectable microfilariae in skin biopsies one year after the therapy [157].

Worth mentioning is that a combination treatment with ivermectin and albendazole was found to slightly decrease the microfilariae load in patients infected with *M. perstans* [158,159]. A randomized, double-blind study performed by Asio et al. [139] showed that the combination of ivermectin (150–200 μg kg^{-1}) with albendazole (once 400 mg) appears more effective than ivermectin alone, but the differences were small and not statistically significant. The combination treatment regimens including ivermectin, albendazole, and doxycycline were found to be effective in two cases of *M. perstans* infections imported to Europe [160].

4.1.3. Cutaneous larva migrans

Cutaneous larva migrans (creeping disease) is a neglected parasitic skin disease that is widespread worldwide, particularly in low-income countries with tropical or subtropical climates [161]. This syndrome may be caused by larval forms of nematodes, including *Ancylostoma* and *Gnathostoma* spp. In humans, the larvae cannot penetrate the basement membrane of the epidermis, and therefore the larvae keep migrating within the skin, causing local inflammation and intense itching [162]. For multiple lesions or severe infestation, ivermectin is a first-line systemic treatment option.

Ivermectin was found to be ~40–50 times and 300 times more effective against *Ancylostoma ceylanicum* larvae than against *Necator americanus* larvae *in vitro* [163] and *in vivo* (hamster model) [164], respectively. While complete clearance of *A. ceylanicum* was achieved with a single dose of 100 μg kg^{-1} of the drug [164], the clinical cure of an 18-year-old patient with extensive cutaneous larva migrans was accomplished with a single dose of 200 μg kg^{-1} of ivermectin [165]. Numerous cases of successful ivermectin-based therapy for creeping disease have also been documented by other authors [166–169]. In a prospective study performed by Bouchaud et al. [166], 64 patients with cutaneous larva migrans were enrolled and treated with a single dose of 200 μg kg^{-1} ivermectin, which resulted in a 77% cure rate. The overall cure rate increased to 97% after one or two supplementary doses [166]. Caumes [167] reported that a similar single dose of ivermectin (once 12 mg) was effective in achieving a cure of 98% in French tourists suffering from cutaneous larva migrans.

A prospective open-labeled study showed that ivermectin when given orally at dosages of up to 200 μg kg^{-1} was safe in patients diagnosed with cutaneous gnathostomiasis, with no serious adverse events [170]. In a placebo-controlled study on 17 patients with a serologically confirmed diagnosis of cutaneous gnathostomiasis, 41% of individuals responded to the therapy when treated with 200 μg kg^{-1} of ivermectin [171]. A higher cure rate (76%) was observed by Karavichian et al. [168], when a group of 17 patients suffering from cutaneous gnathostomiasis was treated with the same dose of the antiparasitic drug. Ivermectin proved also to be successful in a returning traveler with cutaneous gnathostomiasis when the initial albendazole therapy failed [172].

4.1.4. Gnathostomiasis

Human gnathostomiasis is a food-borne parasitic disease that is caused by several species of the genus *Gnathostoma*. Definitive hosts are dogs, cats, and wild mammals, but humans can also be accidental hosts after ingesting third-stage larvae [173]. People become infected primarily by eating raw or undercooked fish, frogs, lobsters, crabs, snakes, and poultry or drinking contaminated water [174]. Moreover, gnathostomiasis is increasingly reported among travelers returning from endemic areas. The *Gnathostoma* larvae typically cause migratory swelling, but the parasites can also enter other tissues, resulting in vision loss or blindness, nerve pain, paralysis, coma, and death. If the nematodes can be easily removed, surgical intervention is recommended. Otherwise, ivermectin can be used as a non-invasive drug against gnathostomiasis.

After two rounds of ivermectin therapy (200 μg kg^{-1}), followed by a 3-week course of albendazole (400 mg, twice per day), a patient diagnosed with invasive gnathostomiasis was lesion-free at 40 weeks post-initial administration [175]. In a comparative treatment study, ivermectin showed slightly greater activity than albendazole, with a cure rate of ~95% and ~94%, respectively [176]. In the ivermectin-treated group, the side effects were hypotension, dizziness, weakness, and diuresis [176]. Similarly, higher values of cure rate after ivermectin administration (0.2 mg kg^{-1} for 2 days) compared with that after albendazole therapy (400 mg twice daily for 21 days) have been further confirmed by the same research team [177], but the difference between the two drugs was statistically insignificant.

4.1.5. Demodicosis

Demodicosis is a skin disease of the pilosebaceous units, involving predominantly the face and head [178]. In humans, the disease is caused by *Demodex* mites (*D. folliculorum* and *D. brevis*) [179]. Demodicosis may have a primary or secondary form, with a rosacea-like presentation, and itching, hair loss, and inflammation as the most common symptoms. In immunocompromised patients, the disease may be more frequent and severe, and therefore, systemic therapy is usually needed to achieve a clinical cure. Worth mentioning is that ivermectin has potent acaricidal activity and therefore may be useful in the treatment of human demodicosis [180], particularly in HIV-positive patients [181,182].

Oral administration of ivermectin, followed by topical application of 5% permethrin cream, demonstrated good therapeutic effects in the fight against demodicosis [183,184]. In a single clinical case, three months after the initiation of the co-therapy, the facial eruption had completely resolved in a 6-year-old child with acute leukemia during chemotherapy [185]. Interestingly, there is growing evidence that the pathogenesis of rosacea may involve *Demodex* mites [186]. According to Brown et al. [187], the causative role of *D. folliculorum* should be considered in immunocompetent children with rosacea or rosacea-like refractory eruptions. In such cases, ivermectin-based treatment should be safe and beneficial [187]. Other formulations of ivermectin or combinations with other antiparasitic drugs for the treatment of demodicosis have been reported by some authors. For example, single or double application of ivermectin in the form of 1% cream was not only well tolerated but also highly effective in reducing or eliminating the characteristic sleeves – the primary clinical sign of *D. folliculorum* infestation of the eyelids [188]. In a randomized, single-blind, controlled clinical trial it was found that a combination therapy of ivermectin with metronidazole was superior in decreasing the *D. folliculorum* count compared to ivermectin monotherapy [189]. After 4 weeks, 72% of individuals in the combined therapy group showed complete remission of the disease, while only 45% of patients from the monotherapy group fully recovered [189].

4.1.6. Lice infestation

Human pediculosis can be caused by two species of obligate blood-sucking lice, *Pediculus humanus*, and *Phthirus pubis*. The infestation affects people in both developing and developed countries. *Pediculus*

humanus occurs in two ecotypes, the head louse (*P. h. capitis*) and the body louse (*P. h. corporis*) [190]. *Phthirus pubis*, the crab or pubic louse resides mainly in the pubic hair. The parasites spread most frequently from person to person by close contact, and symptoms include itching and scratching, which can lead to secondary bacterial infections [191]. In recent years, a growing problem seems to be the development of drug-resistant lice, including double and cross-resistance to insecticides [192–195]. Treatment of lice infestations generally involves shampoos and creams usually containing insecticides (pyrethrins, permethrin, and malathion). Also, both topical and oral ivermectin have been found promising for the treatment of all forms of pediculosis [196–201].

Ivermectin in the form of 0.5% lotion was approved by the Food and Drug Administration (FDA) in 2012 for topical use against head lice infestation (pediculosis capitis) in patients aged ≥6 months [197]. The efficacy of this treatment is generally about 75% [202,203], but this value varied between studies. For instance, in a study by Hamedanian et al. [204], about 91% of individuals who were treated with ivermectin lotion had no head lice one month after the intervention. Additionally, ivermectin given orally may be an alternative way of drug administration against lice infestation [205]. In a multicenter, cluster-randomized, double-blind controlled trial, eradication of head lice was achieved by day 15 in more than 95% of patients when treated orally on days 1 and 8 with ivermectin at a dose of 400 μg kg^{-1} [206]. Similarly, oral ivermectin used at the standard dose of 200 μg kg^{-1}, administered on days 1 and 8, reduced the burden of active pediculosis capitis [207]. A reduction of ~89% and ~71% was achieved at 2-week and 3-month follow-ups, respectively [207]. Ahmad et al. [208] have shown that both topical and oral ivermectin are characterized by high efficacy and tolerability in the treatment of head lice infestation. It should, however, be noted that the authors of this study compared the effects of a high 1% topical ivermectin formulation with the standard oral dose of 200 μg kg^{-1} ivermectin. The co-therapy of ivermectin with diethylcarbamazine or albendazole was found to successfully reduce head lice infestation in endemic rural communities [209].

In a laboratory study, it was shown that 81%–100% of nymphs and females of the human body louse (*P. h. humanus*) died after artificial feeding on blood containing ivermectin at concentrations ranging from 2.5 to 10 ng mL^{-1} [210]. Using toxicity bioassays, Lamassiaude et al. [211] further confirmed the activity of ivermectin against *P. h. humanus*. A combination of ivermectin with various antibiotics (doxycycline, erythromycin, rifampicin, and azithromycin) demonstrated synergistic effects in the killing of body lice, which should be of great value when considering drug-resistant lice populations [212]. Moreover, oral ivermectin at a dose of 250 μg kg^{-1} was successfully used in the treatment of *P. pubis* infestations, with no side effects or recurrences [213,214].

4.2. In animals

4.2.1. Intestinal roundworm infestations

Bhanjadeo et al. [215] have documented a 100% efficiency of ivermectin against the canine hookworm *Ancylostoma caninum* when used at oral doses of 200 μg kg^{-1}. The compound was found to remove all adult worms after the initial dose, bringing down the fecal egg count from 1725 ± 331 to zero on days 15 and 30 [215]. Even lower single doses of 10–100 μg kg^{-1} ivermectin were reported to successfully eliminate *A. caninum* in dogs [216]. The ivermectin therapy was actually superior compared to treatments with the anti-hookworm agent albendazole [216]. An efficacy of ≥96% was observed for ivermectin at a dosage of 24 μg kg^{-1} in the treatment of *A. caninum* and *Uncinaria stenocephala* infections in pups, regardless of the administration route (subcutaneous or oral) [217]. Closer inspection of the results revealed that the estimated oral doses of ivermectin required to achieve maximal efficacy ranged from 14 μg kg^{-1} for adult worms of *A. caninum* to 44 μg kg^{-1} for fourth-stage larvae of *U. stenocephala* [217]. Anderson and Roberson [218] have evaluated the activity of ivermectin not only against hookworms (*A. caninum*, *A. braziliense*) but also against dog roundworms (*Toxocara canis*, *T. leonina*) and whipworms (*Trichuris vulpis*), as well as experimentally induced infections caused by fourth-stage larvae of *A. caninum* and *T. canis*. Single subcutaneous injections of 50 μg kg^{-1}, 100 μg kg^{-1}, 200 μg kg^{-1}, or 400 μg kg^{-1} of ivermectin expelled >99% of the adult forms of both species of *Ancylostoma* hookworms as well as intestinal larval forms of *A. caninum* [218]. At a dose of 200 μg kg^{-1}, ivermectin was found to be effective against larval stages of *T. canis* (97%), but only marginally efficacious (up to ~69%) against *T. leonine* [218]. The effect of ivermectin on preventing transplacental transmission of reactivated encysted *T. canis* larvae to pups during pregnancy in female greyhounds was studied by Payne and Ridley [219]. The strategic use of the drug at a dose of 300 μg kg^{-1} in the female dogs on days 0, 20, and 60 of gestation reduced the worm burden in puppies by 90% [219].

In a study by Heredia Cardenas et al. [220], the efficacy of a combined therapy of ivermectin (200 μg kg^{-1}) and praziquantel (5 mg kg^{-1}) was evaluated in 100 dogs with confirmed diagnosis of *Toxocara* spp. infestation. After a single dose of the drug combination, the number of parasite eggs decreased by 71% and 88% on day 14 and 28 post-treatment, respectively [220]. In another study, the combination of ivermectin (6 μg kg^{-1}) and pyrantel (as pamoate salt, 5 mg of active drug kg^{-1}) in a chewable formulation, was shown to be 100% effective in preventing the development of *Dirofilaria immitis* larvae in dogs, while the efficacy of the combination therapy against *A. caninum*, *T. canis*, *T. leonina*, and *U. stenocephala* was 98.5%, 90.1%, 99.2%, and 98.7%, respectively [221]. The formulation was also effective against *A. caninum* and *U. stenocephala* in experimentally infected dogs and reduced the worm burden in the animals by 99.6% without any adverse side effects [222]. The ivermectin/pyrantel combination therapy was tested for its efficacy against *A. braziliense* in Beagles as well and 100% efficacy was observed against the adult form of this hookworm species [223].

4.2.2. Lungworm infestation

Capillaria aerophila is among the most frequently diagnosed parasites of the respiratory system in carnivorous mammals. The nematode settles in the mucous membrane mainly of the trachea and bronchi. Most infections caused by *C. aerophila* are asymptomatic and only periodically can lead to mild catarrhal inflammation. Severe infestations cause irritation that can obstruct the lumen of the airways, which can be followed by a chronic cough, by occasional shortness of breath, and by secondary bacterial bronchitis.

A single dose of ivermectin administered orally was found to efficaciously eliminate *C. aerophila* infecting the nasal passages in a dog [224]. No side effects of the treatment were observed [224]. Ivermectin (300 μg per 100 g body weight) was also shown to be an effective and well-tolerated treatment against *Capillaria* spp. of hedgehogs, providing 100% efficacy against the nematodes [225]. In adult gray foxes naturally infected with *C. aerophila*, ivermectin together with febantel and fenbendazole, effectively eliminated the lungworm, and the activity of the drug combination was higher than that of mebendazole [226].

4.2.3. Ear mite infestation

Ear mite infestations, caused by *Notoedres cati*, *N. muris*, and *Otodectes cynotis*, are frequently diagnosed in cats, dogs, rabbits, and other pet animals. The parasites are usually found in the ear canal, but they can also live on the skin surface, causing intense itching, which triggers scratching at the affected ear(s) and can finally lead to serious bacterial infections. Most older ear mite treatment products contain insecticides and are applied topically. However, these products must be used for at least 3 weeks as they do not kill the eggs. Modern topical ear mite medications include isoxazolines (fluralaner and sarolaner) or macrocyclic lactones (selamectin, moxidectin, and ivermectin). Only ivermectin-based preparations can be administered orally or subcutaneously.

Administration of 0.5 mL of 0.01% ivermectin otic suspension

removed ear mites in kittens more effectively than the related macrocyclic lactone selamectin [227]. Importantly, no evidence of toxicity was observed with the preparation [227]. Noteworthy is that the formulation even prevented the hatching of *O. cynotis* larvae from eggs in *in vitro* tests [228]. A complete clinical recovery was also found in cats after four doses of ivermectin administered orally (200 μg kg^{-1}), along with supportive daily therapy, i.e., multi-vitamin and mineral syrup [229].

On the other hand, ivermectin given subcutaneously at a dosage of 200 μg kg^{-1} twice at 3-weekly intervals was shown to be effective against *O. cynotis* infestation in the American red foxes (*Vulpes fulva*), with an efficacy of about 97% [230]. Toxic side effects associated with the drug administration were not observed, even after increasing the dose to 1.0 mg kg^{-1} [230]. In addition, the activity of ivermectin to eliminate *N. muris* has been confirmed in marsh rats [231]. In a therapeutic trial study it was found that 6 days after treatment with ivermectin (400 μg kg^{-1}, single subcutaneous injection), a complete visual shedding of lesions was observed in a group of 15 rabbits infected with *N. cati* var. *cuniculi* [232]. In another study, it was shown that ivermectin injected subcutaneously at weekly intervals for 4 weeks resulted in remission of clinical signs and improvement of the health condition in rabbits with mixed infestations of *N. cati*, *Sarcoptes cuniculi*, and *Psoroptes cuniculi* [233].

4.2.4. Mange

In addition to the licensed use of ivermectin to treat mange in ruminants and swine (see section 3.2.6 and Table 1 for details), the drug can also be used "off-label" against a series of other parasitic mites. Ivermectin-based therapy was found to be effective in the fight against feline and canine cheyletiellosis, especially when large numbers of animals are involved [234,235]. For example, the subcutaneous injection of the drug at the dose of 300 μg kg^{-1} twice, at a 3-weekly interval, resulted in a complete cure of adult dogs infected with *Cheyletiella yasguri* with no adverse reactions [234]. In a retrospective treatment study of cheyletiellosis in rabbits, 2–3 subcutaneous injections of ivermectin at doses ranging between 200 and 476 μg kg^{-1} in intervals of 11 days, resulted in remission of almost 82% of the animals [236]. The effective elimination of these mites is important, as infected pet animals can become a source of *Cheyletiella* dermatitis in humans [237,238].

On the basis of the literature evidence, oral daily administration of ivermectin (300 μg kg^{-1}) can be recommended for the treatment of generalized canine demodicosis, but the administration of the drug should be initiated at lower doses and animals need to be monitored for possible adverse reactions [239]. A slightly lower dose of ivermectin (250 μg kg^{-1}) every other day was used in a study on two cats suffering from feline demodicosis [240]. This treatment regimen was found to be effective in both cases in eradicating *Demodex gatoi* from the skin, but after 4 months of therapy, neurological symptoms were observed in one animal, confirming the need for close veterinary monitoring during the treatment [240]. Demodicosis caused by *D. canis* and *D. cornei* was also successfully treated with ivermectin in dogs by daily oral administration of 500 μg kg^{-1} of the drug together with external application of amitraz (non-systemic acaricide) as well as a supportive therapy [241]. Complete recovery from the disease was achieved in 45 days without any side reactions [241]. The successful use of ivermectin to treat canine demodicosis has also been confirmed by other authors [242]. In a blinded, randomized three-phase clinical trial with 58 dogs, ivermectin was found to be more effective than 2.5% moxidectin plus 10% imidacloprid [243]. Interestingly, Saridomichelakis et al. [244] have shown that systemic treatment using a combination of ivermectin and cephalexin led to a complete resolution of the skin lesions and the disappearance of demodectic mites in two dogs after two months. On the other hand, topical use of the drug (1.5 mg kg^{-1} of 0.5% pour-on ivermectin) was found to have a rather limited efficacy in the treatment of chronic generalized demodicosis in dogs [245].

Effective treatment of the mange mite *Sarcoptes scabiei* var. *canis* with ivermectin was also confirmed in animals [246]. A progressive clinical improvement of mange lesions was observed in foxes, whereby the best results were obtained when ivermectin was given subcutaneously at the initial dose of 400 μg kg^{-1}, followed by a subsequent dose of 200 μg kg^{-1} of the drug after 2 or 3 weeks of the initial treatment [246]. Nevertheless, it should be noted that canine scabies resistant to the action of ivermectin-based therapy have been reported [247].

Ivermectin has also been shown to be effective against *Psoroptes* mites. At a single dose of 400 μg kg^{-1} and regardless of the injection route (intramuscularly or subcutaneously), the drug eliminated completely *Psoroptes cuniculi* and *P. ovis* mites in rabbits [248]. In a study by McKellar et al. [249] it was found that 400 μg kg^{-1} of ivermectin given subcutaneously, significantly reduced the clinical score in rabbits infected with *P. cuniculi*, while a slightly higher dose (500 μg kg^{-1}) resulted in a clinical cure in guinea pigs suffering from mange due to *Trixacaurus caviae*. Other studies confirmed that rabbits naturally infested with *P. cuniculi* can be effectively treated with ivermectin [250–252]. For example, Pandey [251] reported that the administration of a single dose of the drug of 200 μg kg^{-1} and 400 μg kg^{-1} injected subcutaneously, led to the elimination of *P. cuniculi* in rabbits within 6 days and that the animals remained negative for the presence of the mite until the end of the trial. Nevertheless, the regression of lesions was faster in rabbits who received twice the dose of the drug [251]. Although ivermectin seems to have no direct effect on the immune response of mite-infested rabbits [253], it can enhance the production of specific antibodies, particularly in weakly-infested animals [254]. A clinical trial with guinea pigs revealed that subcutaneous injection of ivermectin at a dose of 400 μg kg^{-1} led to the elimination of *T. caviae* mites within 40 days [255]. The promising use of ivermectin to treat and control *T. caviae* infestations in guinea pigs has also been confirmed in another study [256].

5. Experimental use of ivermectin

As described above, ivermectin is widely used in the treatment of many parasitic diseases, both in licensed and "off-label" use. In many cases, the drug is the first choice, due to its high efficiency at low dosage (usually 200 μg kg^{-1}). Taking into consideration that the use of ivermectin in humans and animals is very safe, this drug has also been tested as experimental therapy against other parasitoses and diseases, such as viral and bacterial infections, and cancer [4,257]. Although drug repurposing can be a useful strategy to find new therapeutic applications for existing medications, it should only complement the process of drug discovery but not be its alternative [257].

Taking into account the constant need for new antiparasitic drugs due to the growing problem of the emergence of parasites that are resistant to commonly available therapeutics, ivermectin should be considered as an alternative drug in the treatment of many parasitic diseases, including leishmaniasis, trypanosomiasis, malaria, schistosomiasis, and trichinosis. Ivermectin may also be useful in the fight against bedbugs, which feed on human blood [4,258].

5.1. In protozoans

5.1.1. Leishmaniasis

Leishmaniasis is caused by *Leishmania* parasites, which are transmitted by the bites of infected female phlebotomine sandflies [259]. There are over twenty *Leishmania* species and three main forms of the disease – visceral (the most serious, fatal without treatment), cutaneous (causing skin ulcers), and mucocutaneous (affecting mouth, nose, and throat) [259]. There are an estimated 700,000 to one million new cases of the disease annually [259]. Several drugs are available for the treatment of the different forms of leishmaniasis (including amphotericin B and paromomycin) [260], but ivermectin has also been shown to exhibit antileishmanial activity.

The *in vitro* and *in vivo* activity of ivermectin was evaluated against

L. infantum [261]. The *in vitro* testing of the drug against promastigotes of *L. infantum* and macrophages gave IC_{50} (50% *Leishmania* inhibitory concentration) and CC_{50} (50% macrophage inhibitory concentration) values of 3.64 ± 0.48 μM and 427.50 ± 17.60 μM, respectively, and thus a selectivity index (SI) of around 117 [261]. For comparison, the corresponding values for amphotericin B were: IC_{50} = 0.12 ± 0.05 μM, CC_{50} = 1.06 ± 0.23 μM, and SI ~9 [261]. Although the *in vitro* activity of ivermectin was lower than that of amphotericin B, the macrocyclic lactone showed a more promising selectivity [261]. In addition, this drug showed prophylactic activity by inhibiting macrophage infection with pre-treated parasites [261]. Importantly, ivermectin in free format or incorporated in polymeric micelles (5 mg kg^{-1} every two days for 10 days) could significantly reduce the parasite load in mice infected with *L. infantum* [261]. In a study by Rifaat et al. [262], the authors evaluated the antileishmanial activity of ivermectin against *L. donovani* infections in hamsters and mice. The activity of the drug was compared with that of other medicaments, including pentostam, levamisole, and thymic extract [262]. Ivermectin was administered at a dose of 300 μg per 100 g body weight every day for 10 days [262]. At the end of the study, it was found that the reduction in parasite burden was ~89% and ~76% in hamsters and mice, respectively [262]. Compared with pentostam, levamisole, and pentostam/thymic extract treatment regimens, ivermectin administration gave the best results [262].

Freitas et al. [263] tested the leishmanicidal activity of ivermectin against *L. amazonensis* and *L. donovani* in infected macrophages, using different drug concentrations (1 μg mL^{-1}, 5 μg mL^{-1}, and 10 μg mL^{-1}). Amphotericin B was used as a reference at the concentrations of 1 μg mL^{-1}, 2 μg mL^{-1}, and 5 μg mL^{-1} [263]. The results indicated a similar decrease in the percentage of infected macrophages after treatment with increasing concentrations of both drugs (Fig. 4) [263]. In addition, the authors showed that ivermectin incorporated into polymeric micelles and administered to chronically infected mice may cause a better cellular and humoral response than in animals treated with free ivermectin [263].

In the prevention of leishmaniasis, it is also important to control the phlebotomine sandfly vectors. To determine the insecticidal activity of ivermectin against sandflies, the drug was administered subcutaneously to hamsters at a dose of 200 μg kg^{-1} or 400 μg kg^{-1} [264]. Then, *Phlebotomus papatasi* infected with *L. major* were allowed to blood-feed on ivermectin-treated hamsters at various times post-treatment (4 h, days 1, 2, 6, and 10) [264]. The highest mortality rate was recorded in the sandflies that fed closest to the time of drug administration [264].

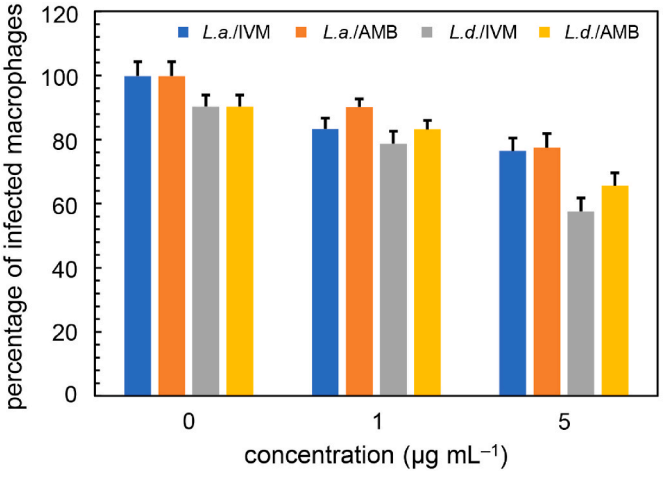

Fig. 4. Effect of ivermection (IVM) and amphotericin B (AMB) on the infection of macrophages with *L. amazonensis* (*L.a.*) and *L. donovani* (*L.d.*). The percentage of infected macrophages after 48 h incubation with the drugs at 0 μg mL^{-1}, 1 μg mL^{-1}, and 5 μg mL^{-1} is shown. Figure created using data published by Freitas et al. [263].

While the average survival rate of control insects that fed on non-treated hamsters was 11.5 days, the survival of sandflies that fed on hamsters treated with a dose of 400 μg kg^{-1} ivermectin after 4 h, 1 day, or 2 days was 1.6, 2.1 and 2.7 days, respectively [264]. Sandflies that fed on low-dose (200 μg kg^{-1}) treated hamsters still showed higher mortality rates than the controls [264]. However, it was also found that *L. major* promastigotes in sandflies that survived feeding on ivermectin-treated hamsters were unaffected by the drug [264]. Therefore, the findings of this study indicate that ivermectin can be considered as an agent for vector control to prevent leishmaniasis.

5.1.2. Trypanosomiasis

Trypanosomiasis comprises diseases caused by parasites from the genus *Trypanosoma*, including human African trypanosomiasis (sleeping sickness) caused by *T. brucei gambiense* and *T. b. rhodesiense*, human American trypanosomiasis (Chagas disease) caused by *T. cruzi*, and animal trypanosomiasis (nagana disease) caused by *T. b. brucei, T. evansi*, *T. congolense*, and *T. vivax* [265,266]. African trypanosomes are transmitted by tsetse flies (*Glossina* sp.), and mainly affect humans and animals in sub-Saharan Africa [265]. The parasites that cause Chagas disease are transmitted by triatomine bugs, but humans can get also infected by consuming contaminated food and beverages, by transfusion of contaminated blood products, during pregnancy from mother to child, and by laboratory accidents [266]. Chagas disease mainly affects people living in rural regions of Central and South America [266]. If left untreated, trypanosomiasis can lead to death in humans and animals [265,266]. Treatment of trypanosomiasis depends on a few drugs that have limited efficacy and can cause serious side effects [265,266]. Vector control plays also an important role in the prevention of trypanosomiasis [265,266]. Due to the emergence of drug-resistant trypanosome strains, it is necessary to search for new trypanocidal drugs. In this context, the potential antitrypanosomal activity of ivermectin may be of interest.

Fraccaroli et al. [267] have evaluated the activity of ivermectin against various strains and life cycle stages of *T. cruzi*. The EC_{50} values for epimastigotes were determined after 72 h of culture, while those for trypomastigotes and amastigotes after 24 h [267]. It was found that the EC_{50} values for epimastigotes ranged between 5.3 μM and 12.5 μM, whereas those for amastigotes and trypomastigotes were 0.3 μM and 10.4 μM, respectively [267]. Noteworthy is that the activity of ivermectin against amastigote and trypomastigote stages was better than that of the commonly used drugs benznidazole and nifurtimox [267]. Moreover, the SI of ivermectin calculated for *T. cruzi* amastigotes was 12, which meets the criteria for candidates for infectious disease drugs (SI > 10) [267,268]. The study also determined whether the effects of ivermectin on *T. cruzi* were trypanostatic or trypanocidal [267]. A drug is considered trypanostatic when the proliferation of the parasite recovers after transfer into a drug-free medium, while it is trypanocidal when the drug irreversibly affects the proliferation of the parasites [267, 269]. It has been shown that ivermectin can exhibit both trypanostatic and trypanocidal activity depending on the dose used [267]. At a dose of 50 μM (4 × EC_{50}), epimastigote proliferation was recovered by removing the drug after incubation for up to an hour, while at twice the dose (8 × EC_{50}), the drug irreversibly inhibited the proliferation of the epimastigotes [267].

The *in vitro* activity of ivermectin against the *T. evansi* bloodstream forms was also investigated [270]. An IC_{50} value of 13.82 μM was determined for the drug and an SI value ranging from ~1.3 to ~1.6 was established with mammalian cells [270]. The antitrypanosomal activity of ivermectin was also confirmed in a study on mice infected with *T. brucei* [271]. A dose of 300 μg mL^{-1} per kg body weight was most effective for both treatment and prophylaxis, increasing the average survival time of infected mice from 5 to 12 days [271]. Further research is, however, needed to determine whether the appropriate form of treatment should be a single dose (as in the study), multiple doses, or a combination with other drugs [271].

In addition to the antitrypanosomal activity of ivermectin, another important aspect of the drug is whether it can also be used in the control of the vectors that transmit trypanosomes. In a study by Pooda et al. [272], cows were injected with a therapeutic dose of ivermectin (200 μg kg^{-1}) or a 10 times higher dose (2 mg kg^{-1}). Then, tsetse flies (*Glossina palpalis gambiensis*) were allowed to feed on treated and control cattle [272]. A significant decrease in the survival rate of the insects that fed on the ivermectin-treated cows was observed [272]. After 8 days, the reduction in survival ranged from ~21% to ~84% for tsetses that fed on cattle treated with 200 μg kg^{-1}, and after 14 days from ~78% to ~94% for flies that fed on cattle treated with 2 mg kg^{-1} [272]. Ivermectin also led to 100% mortality in adult teneral males, mature males, and fertile females of *G. morsitans* when feeding on a single meal of defibrinated pig blood containing the drug at concentrations of 0.1 μg mL^{-1}, 1.6 μg mL^{-1} or >1.6 μg mL^{-1}, respectively [273]. The lethal dose was <0.04 μg mL^{-1} for teneral males when fed repeatedly on treated blood [273]. Moreover, after oral administration of ivermectin to a horse at a dose of 400 μg kg^{-1}, the drug concentration in the blood reached 0.14 μg mL^{-1} within 24 h, which reduced the fecundity of tsetse flies to zero after a single meal [273].

5.1.3. Malaria

Malaria is still one of the most life-threatening parasitic diseases to humans. According to WHO data, nearly half of the world's population was at risk of malaria in 2021 [274]. In humans, the disease is mainly caused by 5 malaria species, *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*, with the first two being the most dangerous [274]. Malaria parasites are transmitted by infected female *Anopheles* mosquitoes, but humans can get also infected via blood transfusion and contaminated needles [274]. The initial symptoms of the disease include fever and headache, and thus, the infection is often mistaken for flu. However, if left untreated, the disease can lead to extreme tiredness and fatigue, abnormal bleeding, and subsequent death [274]. The drugs commonly used to treat malaria are chloroquine, primaquine, and artemisinin-based combination therapies [274]. Importantly, the first malaria vaccine was approved for use in humans in 2021 [274].

Ivermectin has been shown to exhibit antimalarial activity and has been used in experimental therapies for malaria. In a study performed by Kobylinski et al. [275], the effect of ivermectin on the survival and re-feeding of *A. darlingi* as well as the development of *P. vivax* in the mosquito were evaluated. Different concentrations of the drug were mixed with human blood and fed to *A. darlingi* whose viability was monitored for the next 7 days [275]. After this time, the LC_{50}, LC_{25}, and LC_5 values were determined, which were 43.2 ng mL^{-1}, 27.8 ng mL^{-1}, and 14.82 ng mL^{-1}, respectively [275]. In the next step, the sporontocidal activity of ivermectin against *P. vivax* in *A. darlingi* was determined [275]. For this purpose, blood samples were taken from malaria patients and administered to mosquitoes with or without ivermectin at doses corresponding to the LC_{50}, LC_{25}, or LC_5 values [275]. The drug was found to be sporontocidal to *P. vivax* in *A. darlingi* at the LC_{50} and LC_{25} concentrations, reducing the prevalence by ~23% and ~17%, respectively, but it showed no activity at the LC_5 concentration [275]. To investigate whether ivermectin inhibits re-feeding, estimated concentrations of the drug occurring after a single oral dose of 200 μg kg^{-1} were given to *A. darling* [275]. For the next 12 days, the mosquitoes had the opportunity to re-feed on a volunteer [275]. It was found that the drug significantly delayed the time of re-feeding at predicted 4-h (48.7 ng mL^{-1}) and 12-h (26.9 ng mL^{-1}) concentrations [275]. Other studies have also confirmed that ivermectin is sporontocidal to *P. falciparum* in mosquitoes at sub-lethal concentrations to *A. gambiae* [276]. Sprorogony was inhibited in *A. gambiae* when the mosquitoes ingested ivermectin at a concentration of 10.7 ng mL^{-1} together or after the uptake of the parasites [276]. Mendes et al. [277] have demonstrated the effectiveness of ivermectin against the liver stage of the parasite in both *in vitro* and *in vivo* experiments. The drug was found to reduce *P. berghei* infection in human hepatoma cells *in vitro*, with similar efficacy as primaquine, the only licensed liver-stage antiplasmodial drug (IC_{50} = 2.1 μM and 2.4 μM, respectively) [277,278]. Worth mentioning is that ivermectin given to mice at a dose of 10 mg kg^{-1} reduced liver infections by 80% after 44–46 h post parasite infection [277]. In a study by Batiha et al. [279] it was shown that ivermectin has also the potential to be an alternative remedy in inhibiting the growth of the malaria-related parasite *Babesia* sp. and *Theileria* sp. both *in vitro* and *in vivo*.

Various studies have shown that ivermectin also exhibits mosquitocidal and larvicidal activities, and therefore, may be used to control the spread of malaria vectors. In a study by Pampiglione et al. [280], the effectiveness of ivermectin against four mosquito species was determined. The drug showed larvicidal properties against *Culex pipiens* (LC_{50} = 3.94 ppb), *A. stephensi* (LC_{50} = 5.85 ppb), and *A. aegypti* (LC_{50} = 23.41 ppb) [280]. When given to adult female mosquitoes (*A. stephensi*, *A. aegypti*, and *C. quinquefasciatus*) at a concentration of 2.8 mg L^{-1} (in sucrose), ivermectin killed the insects within 60 h [280]. *In vivo* studies were also conducted using mice injected subcutaneously with ivermectin at a dose of 82 mg of active ingredient per kg body weight [280]. After 12 h, female mosquitoes were allowed to blood-feed on the treated mice [280]. After 36 h, 100% mortality was observed for *A. stephensi*, 60% mortality for *A. aegypti*, and 50% mortality for *C. quinquefasciatus* [280]. The mosquitocidal properties of ivermectin administered orally to dogs at various doses (10 μg kg^{-1}, 500 μg kg^{-1}, 1000 μg kg^{-1}, and 2500 μg kg^{-1}) were also studied [281]. *A. quadrimaculatus* mosquitoes were allowed to blood-feed on treated dogs or were given blood previously collected from one of the dogs [281]. Mosquito mortality was observed 24 h and 48 h after feeding [281]. More than 90% of mosquitoes from the groups that fed on dogs died, while the mortality of mosquitoes that fed on the blood collected from a dog treated with 10 μg kg^{-1} was ~65% [281]. In another study, a volunteer took ivermectin at a single dose of 250 μg kg^{-1} and then allowed *A. farauti* mosquitoes to blood-feed on him [282]. High mosquito mortality was observed, with at least 80% of insects dying within 3 days [282].

A major problem in the use of ivermectin as a prophylactic agent is the limited retention time of therapeutic concentrations in the blood [283]. This problem can be overcome by using a sustained-release formulation of the drug. In a study by Chaccour et al. [284], rabbits were given silicone implants with ivermectin, deoxycholate, and sucrose, which made it possible to maintain a concentration of ivermectin in the blood of the animals at a level corresponding to the LC_{50} value against *A. gambiae* for at least 12 weeks [284]. Mathematical modeling based on the experimental data predicted a 98% reduction in infectious vector density by using a long-lasting ivermectin formulation for 12 weeks [284]. An oral long-lasting drug formulation was also developed by encapsulation of ivermectin in poly(ε-caprolactone) [285]. In a swine model, it was shown that the long-lasting formulation maintained therapeutic concentrations of ivermectin for up to 2 weeks, which was supposed to have a significant impact on malaria transmission [285]. The antimalarial activity of ivermectin and its derivatives has been recently comprehensively reviewed [286].

5.2. In helminths

5.2.1. Schistosomiasis

Schistosomiasis is a parasitic disease caused by blood flukes of the genus *Schistosoma* [287]. According to WHO data, in 2021, at least 251.4 million people required preventive treatment against schistosomiasis [287]. The intermediate hosts of the disease are different species of freshwater snails that release free-swimming larvae (cercariae) into the water. Infection occurs when cercariae from infested water penetrate the human skin [287]. The symptoms of the disease are diarrhea and blood in the stool or urine (depending on the schistosome species), among others, and they are mainly related to the body's reaction to the eggs of the parasite [287]. Praziquantel is mainly used to treat the disease, but albendazole and ivermectin should be considered as therapeutic agents

as well [287,288].

A study by Taman et al. [289] was conducted to test the effectiveness of ivermectin against *S. mansoni* in experimentally infected mice. The drug was administered 42 days after infection in two regimens, a single dose of 25 mg kg^{-1} given orally and the same dose for two consecutive days [289]. In both cases, a significant decrease in the number of female worms, hepatic tissue eggs, and early immature eggs was observed [289]. The use of the same dose for 2 days significantly reduced the number of male worms and intestinal tissue egg load [289]. However, another study questioned the effectiveness of ivermectin in treating *S. mansoni*-infected mice [290]. Ivermectin was administered orally at a lower dose of 1 mg kg^{-1} alone, or in combination with other drugs (cobicistat or elacridar), 3 days before infection [290]. It was found that ivermectin alone or in combination with cobicistat or elacridar showed no prophylactic activity against infection by *S. mansoni* cercariae [290]. In addition, mice treated with ivermectin and elacridar displayed severe neurotoxic adverse effects [290]. Thus, it seems to be necessary to perform further studies to validate the effectiveness and safety of ivermectin in the treatment of schistosomiasis.

One strategy to prevent infections with schistosomes is the control of the intermediate host snails with molluscicides. However, the treatment of freshwater bodies with pesticides may be harmful to other organisms living in the environment. Katz et al. [291] evaluated the effects of ivermectin on three *Biomphalaria* species (*B. glabrata*, *B. tenagophilia*, *B. straminea*), on *B. glabrata* infected with *S. mansoni*, and on snail egg-masses, miracidia, and cercariae, as well as on guppies (*Poecilia reticulata*). According to the authors, the calculated LD_{50} and LD_{90} doses for the three species of snails ranged between 0.03 and 0.13 μg mL^{-1} and 0.3–1.0 μg mL^{-1}, respectively [291]. *B. glabrata* snails that were shedding cercariae died already when exposed to the drug at a concentration of only 0.01 μg mL^{-1} [291]. Interestingly, only ivermectin B1b, which constitutes a maximum of 20% of the commercially available drug, was responsible for the death of snails [291]. Regarding the life-cycle stages of the parasite, ivermectin at a dose of 0.2 μg mL^{-1} was sufficient to kill 50% and 90% of the cercariae and miracidia within 5 min and 30 min, respectively [291]. Of concern is the observation that guppies were also very sensitive to the action of ivermectin. At the concentrations of 0.5 μg mL^{-1} and 0.01 μg mL^{-1}, the mortality rates after 24 h of exposure were 100% and 30%, respectively [291]. Thus, at the low concentration of 0.01 μg mL^{-1} that was sufficient to kill 100% of schistosome-infected snails, ivermectin still killed 30% of the guppies [291]. Furthermore, ivermectin was ineffective against snail egg masses up to 100 μg mL^{-1}, the highest concentration tested [291].

5.2.2. Trichinosis

Trichinosis (trichinellosis) is a disease caused by roundworms of the genus *Trichinella*. Infection in humans occurs most often as a result of eating undercooked meat (mainly pork) infected with larvae of the parasite [292]. There are about 10,000 infections annually worldwide, and initial symptoms are gastrointestinal problems, such as diarrhea or vomiting, when the ingested larvae develop into adult worms in the small intestine [292]. After several weeks, the adult worms produce larvae that migrate through the body to reach striated muscle tissue. Once larvae have entered the muscle tissues, patients can experience muscle aches and pain, muscle stiffness, and muscle weakness [292]. The disease may also affect any mammals and even birds can be experimentally infected with trichinae. For the treatment of the disease in humans, albendazole and mebendazole are used, which are effective in eliminating adult worms, but unfortunately, are ineffective in combating encysted larvae residing in the muscles [292]. Thus, it is necessary to investigate the activity of other drugs against trichinae.

A study by Soliman et al. [293] compared the efficacy of ivermectin and doramectin (a derivative of ivermectin) at the dose of 200 μg kg^{-1}, along with levamisole at the dose of 7.5 mg kg^{-1} against *T. spiralis* in experimentally infected rats [293]. The drugs were tested against adult worms on day 4 post-infection, migrating larvae on day 10 post-infection, and encysted larvae on day 35 post-infection [293]. Both macrocyclic lactones were shown to be highly effective in eliminating mature worms and migrating larvae with efficacies of ~98% and ~86% for doramectin and 95% and ~84% for ivermectin, respectively [293]. However, both drugs were ineffective in killing encysted larvae residing in the diaphragm [293]. In another study, the effectiveness of ivermectin and verapamil in eliminating intestinal adult worms and encysted muscle larvae was examined [294]. Ivermectin was orally administered to mice at a dose of 4 μg per mouse per day on days 1, 5, 15, and 35 post-infection, while verapamil was given to the animals from 1 to 35 days post-infection at a dose of 30 μg per mouse per day in the form of intraperitoneal injections [294]. Verapamil was found to be ineffective against adult worms but it was highly effective in reducing the number of encysted muscle larvae by ~94% [294]. In contrast, ivermectin was active against both life-cycle forms and reduced adult worm count by ~85% and muscle larval count by ~98% [294]. The combined use of ivermectin and verapamil resulted in a reduction in adult worms by ~69% and in muscle larvae by 99% [294]. Elmehy et al. [295] compared the effectiveness of ivermectin administered in two different formulations, i.e., 200 μg kg^{-1} in a single oral dose of nanocrystalline ivermectin and 200 μg kg^{-1} in a single oral dose of niosomal ivermectin [295]. The study was conducted on mice infected with different life-cycle stages of *T. spiralis* (adult worms, migrating larvae, and encysted larvae) [295]. In each case, the niosomal administration of ivermectin was more effective than the nanocrystalline formulation [295]. The percentages of reduction were ~92% and ~73% for adult worms, ~70% and ~35% for migrating larvae, and ~63% and ~51% for encysted larvae, for niosomal and nanocrystalline ivermectin, respectively [295]. Moreover, ivermectin was also effective in treating monkeys and baboons infected with *T. zimbabwensis* [296].

5.3. In bedbugs

Bedbugs are parasitic wingless insects that feed on the blood of humans and animals during sleep [297,298]. Although the insects do not spread diseases, they can cause itching and severe allergic reactions in some people that may lead to subsequent bacterial skin infections [297,298]. There are two species that mainly feed on humans, *Cimex lectularius* and *C. hemipterus* [297]. Preventive measures include controlling the spread of the insects, for which ivermectin seems to be an effective tool.

To determine the mortality and morbidity of *C. lectularius* after ivermectin intervention, an artificial feeding membrane, and pre-treated mice and humans were used in the tests [299]. The results indicated that after 13 days of feeding on mouse blood containing ivermectin at a concentration of 260 ng mL^{-1} through an artificial membrane, the bedbugs mortality rate was 98%, while the mortality rate in the control group (just mouse blood) was 0% [299]. Similar results (86% mortality) were observed with bedbugs that fed on mice treated with 200 μg kg^{-1} ivermectin [299]. In addition, bedbugs that fed on a human who had been given 200 μg kg^{-1} of oral ivermectin 3 h earlier, showed a mortality rate of 63% after 20 days (mortality rate of the control was 8%) [299]. Thus, it seems that ivermectin may be useful in controlling bedbugs. Similar results were obtained in a study by Ridge et al. [300], in which a rabbit was treated with subcutaneous ivermectin at a dose of 300 μg kg^{-1}, and *C. lectularius* bedbugs were allowed to feed on the animal (before and after drug administration) [300]. At blood concentrations of ~2 ng mL^{-1}, a reduction in bedbug fecundity was observed, while blood concentrations of ~8 ng mL^{-1} led to the death of the insects or long-term morbidity, including a reduction in refeeding, mobility, and molting [300]. A relationship between the concentration of the drug in the blood and the reaction of bedbugs has also been demonstrated by other authors [301]. The mortality rate of *C. lectularius* bedbugs that fed on blood containing ivermectin or moxidectin (an ivermectin-like macrocyclic lactone) at a concentration as little as 25 ng mL^{-1} was 100% after 13 days, compared to 0%–6% mortality of the control [301].

Bedbugs that survived blood meals containing ivermectin at a concentration of 2.5 ng mL^{-1} showed reduced fecundity, feeding difficulty, and incomplete ecdysis [301].

González-Morales et al. [302] have determined the LC_{50} and LC_{90} values of ivermectin against bedbugs of the Harlan strain. Ivermectin was dissolved in DMSO and added to human blood, and the insects were fed using an artificial feeding system. LC_{50} and LC_{90} values were determined to be 61.0 ng mL^{-1} and 114.9 ng mL^{-1}, respectively [302]. However, in *in vivo* studies, ivermectin did not show high efficacy [302]. Chickens were injected with ivermectin at the dose of 200 μg kg^{-1}, but it did not result in the killing of the bedbugs that fed on the treated animals [302]. When administered orally at the same dose, mortality was achieved only for a few insects (5–11 out of 15 bedbugs per replicate), and a relatively low bioavailability of ivermectin in chicken blood may explain the low efficacy of the drug in this animal model [302]. It was also found that drug levels in bedbugs decreased rapidly during the first week of treatment but remained relatively constant between weeks 1 and 4 [302]. This observation was confirmed in another study in which it was discovered that ivermectin can persist in the blood of bedbugs for up to one month after a blood meal [303]. The long retention time of ivermectin in bedbugs may explain why those insects that survived the treatment exhibit long-term morbidity [302].

5.4. In other diseases

In addition to the broad antiparasitic potency, ivermectin also exhibits biological activities against bacteria, viruses, and cancer cells [4]. Previously it was believed that ivermectin did not have antibacterial properties, but reports from the last decade have shown that the drug is effective against *Chlamydia trachomatis*, *Mycobacterium tuberculosis,* and *M. ulcerans* [304–306], although some studies could not confirmed the antimycobacterial activity of the drug [307,308]. Thus, additional studies are needed to validate the real antibacterial potential of this compound. Regarding the antiviral activity of ivermectin, the drug effectively inhibited the replication of the yellow fever virus and other flaviviruses [309]. Ivermectin exhibits also activity against RNA viruses, such as HIV-1 and dengue viruses [310]. In recent years, the drug has gained popularity as a potential treatment option against COVID-19. For example, ivermectin at a concentration of 5 μM allowed for an approximately 5000-fold reduction of the SARS-CoV-2 virus in cell culture after 48 h [311]. However, despite many clinical trials, ivermectin has never been introduced as a treatment for COVID-19.

Several recently published reports described the high anticancer activity of ivermectin against various types of tumors, including colorectal, breast, glioblastoma, head and neck, leukemia, melanoma, pancreatic, and prostate cancers [257,312]. The mechanism of anticancer activity of ivermectin is extremely diverse and affects many biochemical processes. Briefly, the drug can inhibit the synthesis of proteins responsible for multi-drug resistance (MDR) and the AKT/mTOR pathways, which are the main regulators of ovarian cancer progression, but it can also block the Wnt/TCF pathway responsible for the proliferation process of cancer cells [5,312]. Moreover, the mode of action of ivermectin is associated with the degradation of PAK-1, the main kinase responsible for the process of carcinogenesis, as well as with an increase in the level of reactive oxygen species (ROS) in tumor cells, leading to oxidative stress and subsequent DNA damage [5,312]. Ivermectin has also been shown to significantly reduce the number of cancer stem cells, a small subpopulation of cancer cells (5%–10% of the tumor mass), whose presence is associated with the progression, metastasis, and recurrence of cancer [5,312]. Importantly, ivermectin can reach clinically relevant concentrations to inhibit tumor growth in humans [312]. Further studies are necessary to demonstrate whether ivermectin can be used in anticancer therapy.

6. Opportunities and challenges of ivermectin

Ivermectin is one of the most extensively used antiparasitic drugs worldwide against various nematode, insect, and acarine parasites. The drug may be administered at relatively low doses via different routes (orally, topically, or subcutaneously). However, the limited retention time of therapeutic concentrations of ivermectin in the blood is a major problem in its use as a prophylactic agent [283]. For example, it has been shown that the mosquitocidal concentration of ivermectin against *A. gambiae* lasts for 2–3 days after a single standard dose of the drug (200 μg mL^{-1}) in the blood meal [283,313,314], which clearly illustrates the need for multiple doses of the drug to achieve appropriate concentration levels for longer times. To increase the half-life of ivermectin in the blood, sustained or slow-release formulations of the drug should be introduced. This issue has been extensively studied recently [284,315–317], showing that relatively stable mosquitocidal plasma levels of the drug can be safely sustained in animals for months. Although such techniques seem to be very promising, their safety and efficacy need to be validated in humans. As ivermectin is readily metabolized in the liver by the 3A subfamily of cytochrome P450 (CYP3A) enzymes system [318], it is also postulated that an increase in the plasma levels of ivermectin can be achieved by the use of inhibitors to these specific enzymes, such as ketoconazole [319–322].

Ivermectin is well-tolerated in most mammals, has minimal side effects, and can be administered even by non-medical personnel with appropriate training, as long as it is used at recommended doses. The Mazzotti reaction and other early adverse side effects should always be considered after ivermectin administration, but neurological dysfunction and other systemic symptoms may occur following an ivermectin overdose [23,323,324]. It has been documented that >100 times the normal dose of ivermectin may result in the accumulation of the drug in the brain, leading to coma and even death [23]. Ivermectin is classified by the FDA as a Pregnancy Category C drug [24], and therefore, pregnant women are typically excluded from receiving this drug due to potential adverse effects on the fetus, but potential benefits may warrant its use in pregnant women despite the potential risks. However, the available data regarding the safety of ivermectin in pregnancy are limited and ambiguous [325,326]. Thus, more studies are needed to carefully evaluate the risk ivermectin may pose during pregnancy. With respect to the potential brain-damaging effects of ivermectin, Mealey et al. [327] have found that the drug induces neurotoxic reactions in collies carrying a deletion mutation of the MDR1 gene. Mutations of this gene lead to an incomplete synthesis of the P-glycoprotein (P-gp) [327], which plays a pivotal role in the process by which the blood-brain barrier limits the uptake of drugs into the brain. Therefore, the lack of the P-gp causes an increase in the level of ivermectin which explains why the drug displays severe neurotoxic effects in animals with MDR1 gene deletion.

A growing problem in veterinary medicine is the emergence of drug-resistant parasites. This refers also to ivermectin-resistant parasite strains that developed as a consequence of the MDA-approach of the drug to protect all animals considered “at risk”. In addition, the incomplete understanding of the underlying mechanisms of ivermectin resistance and the lack of diagnostic resistance markers may all have a negative impact on current as well as future parasite control strategies. There are some options to overcome these limitations, which include the combination of ivermectin with albendazole or other antiparasitic drugs in novel treatment regimens, or systematic modification of the multifunctional structure of ivermectin to obtain derivatives with improved activity and selectivity. The sixteen-membered macrocyclic system is necessary for maintaining the high antiparasitic activity of ivermectin and other avermectin derivatives, as is the presence of the hydroxyl group at the C-5 position of the oxahydrindene (hexahydrobenzofuran) ring (Fig. 1) [328]. The disaccharide unit seems to also be important for retaining the antiparasitic activity, wherein the chemical modification of the C-4" hydroxyl group (Fig. 1) is recognized as one of the promising sites to possibly improve the overall activity profile of the native

structure [328]. Of note, Singh et al. [329,330] have shown that the replacement of the disaccharide unit of ivermectin with rationally selected pharmacophores may lead to molecular hybrids exhibiting potent antimalarial activity. Nevertheless, more work is needed to develop new antiparasitic drug candidates based on the ivermectin molecule.

7. Conclusions

The macrocyclic lactone ivermectin has revolutionized the treatment of roundworm infestations in domestic animals when it was introduced to the animal health market in 1981. The success of the drug is based on its high efficacy against a broad range of nematode and arthropod parasites, its activity at low dosages, and its low toxicity in mammals, as well as on the possibility that the drug can be delivered via diverse routes of administration. Eventually, ivermectin was also introduced for the therapy of a few human parasitic diseases. The use of ivermectin against river blindness was a breakthrough in the treatment and control of this insidious disease that caused blindness in so many people in tropical Africa. In particular, the mass administration of ivermectin from the 1990s had an impressive impact so that in most endemic foci, river blindness is no longer a health problem. Over 40 years of intensive research on ivermectin has led not only to its approval for the treatment of river blindness and strongyloidiasis in humans, and roundworm and arthropod infestations in animals, but also to the effective use of this drug against many other worm-related parasitic diseases in "off-label" practice and experimental therapy. The drug has even the potential as medication for disease other than parasitoses. However, the massive use of ivermectin increases the risk of the development of drug-resistant parasite strains. This problem may be overcome by combining ivermectin with other drugs in treatment regimens. Another possibility is the systematic derivatization of ivermectin to enhance its activity and specificity, a research area which has been explored too little so far.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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