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Prospects and genesis of the versatile antiparasitic drug Ivermectin and its unsurpassed beneficial impact in Human and Veterinary Medicine

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ABSTRACT

Ivermectin is a naturally-derived dihydro derivative of avermectin originating exclusively from a single microorganism isolated from Japanese soil displaying an exceptionally wide range of antiparasitic efficacy against internal and external parasites of human and domestic animals. At the outset introduced as veterinary drugs of commercial livestock and companion animals but it was quickly discovered to be ideal in tackling two of the world's most distressing and disfiguring diseases such as river blindness and elephantiasis which have besieged African countries for centuries. The kinetics of ivermectin is characterized in general terms by a slow absorption process, a broad distribution in the organism, low metabolism, and slow excretion. The pharmacokinetic parameters of ivermectin vary extensively and in accordance with many factors that can all influence the drug's plasma concentration. These factors, which include the animal species, route of administration, vehicle used in the commercial formulation, bodyweight, body condition, age, physiological status, and amount and type of nutrition, all of which contribute to differences in drug efficacy. Currently, ivermectin is one of the most important drugs for the control of endectoparasitic infection in human and veterinary medicine and was the joint focus of the 2015 Nobel Prize, some 3 decades after its remarkable discovery. Although best described for its activity on glutamate-gated chloride channels in parasites, understanding much of its therapeutic mechanism and wide array of novel targets remains to be elucidated. Today, ivermectin is continuing to surprise and excite scientists, with an extensive use and an enormous success as well as showing novel promise against a diverse range of human and animal diseases round the globe.

Keywords: Ivermectin, Discovery, Genesis, Ectoparasitics, Endoparasitics, Pharmcokinetics, Interactions, New Targets, Efficacy

INTRODUCTION

Ivermectin is one of the best known and most extensively used antiparasitic drugs in human and veterinary medicine. The discovery and synthesis of this wonder drug traced back to 1970 when renowned Japanese Microbiologist Dr. Satoshi Omura collected a soil sample from forest close to a golf course in Kawana, on the south east coast of Honshu, Japan [1]. Omura isolated and cultured a Gram-positive bacterium, a then unknown species of *Streptomyces*. After initial laboratory evaluation at Tokyo's Kitasato Institute, this mysterious species of *Streptomyces* as well as 50 other promising bioactive strains of *Streptomyces* which seemed unusual in appearance or culture characteristics were then sent to Dr. William Campbell at Merck laboratory, USA for further in vivo testing. Cultures showed potent activity against *Nematospiroides dubius* (now *Heligomosoides polygyrus*) infection in mice, and the active components were purified, revealing a family of macrocyclic lactones. These naturally occurring compounds were named the avermectins and the bacterium, *Streptomyces avermitilis* to reflect the vermin (worm)-free 'averminous' conditions they produced [2, 3].

The safer and more effective derivative, ivermectin, was subsequently commercialized, entering the veterinary, agricultural and aquaculture markets in 1981 by USA based world's largest pharmaceutical company Merck Sharp and Dohme (MSD), as an antiparasitic agent [4], and it remains the leading worldwide antiparasitic agent for livestock. It is a highly lipophilic substance that dissolves in most organic solvents like methylene chloride, ethanol etc, but is practically insoluble in water (0.0004% m/v). It has exceptional potency against endo- and ectoparasites at extremely low doses (doses recommended are expressed as µg/kg); this accounts

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for its larger margin of safety. The drug's potential in human health was confirmed a few years later and it was registered in 1987 and immediately supplied for treating disease free of cost branded as Mectizan®. Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found [5]. Dr. William C. Campbell of Merck Laboratories, USA and Japanese Microbiologist Dr. Satoshi Ōmura were awarded 2015's Nobel prize in medicine or physiology for discovering avermectin, the derivatives of which drastically lowered the incidence of river blindness and lymphatic filariasis, as well as showing efficacy against an expanding number of other ecto and endo parasitic diseases [1].

In 1975, only two drugs were available for the treatment of onchocerciasis: diethylcarbamazine (DEC) and suramin. The use of both was highly unsatisfactory. DEC, which was known to kill microfilariae, caused violent and even dangerous hypersensitivity reactions in the human host. Suramin, developed 50 years previously for treatment of Sleeping Sickness, was the only drug considered for killing adult worms but was highly toxic, often causing severe and occasionally fatal reactions. Moreover, parasitological cure of patients using DEC and suramin required lengthy and expensive treatment given under medical supervision. Therefore, ivermectin proved to be virtually purpose-built to combat Onchocerciasis, which has two main manifestations, dermal damage resulting from microfilariae in the skin and ocular damage arising from microfilariae in the eye. Intriguingly, ivermectin has a diverse range of effects in many different organisms, far beyond the endoparasites and ectoparasites it was developed to control. For example, ivermectin has been shown to regulate glucose and cholesterol levels in diabetic mice [6], to suppress malignant cell proliferation in various cancers [7], to inhibit viral replication in several flaviviruses [8], and to reduce survival in major insect vectors of malaria and trypanosomiasis [9, 10]. Clearly, much remains to be learned about this versatile drug, but the promise of more sustainable strategies for current helminth-control programmes and novel applications to improve human and animal health are compelling arguments to pursue this cause. This paper highlights some important but unresolved questions regarding the most important aspects of genesis, pharmacokinetics, interactions, potentials and prospects of the wonder drug ivermectin in human and veterinary medicine.

CHEMICAL STRUCTURE AND SYNTHESIS

Naturally produced avermectins are a mixture of four compounds, avermectin A_1, A_2, B_1 and B_2, each of which exists as two variants, a and b [11]. The 'A' and 'B' designations describe the presence of methoxy or hydroxy groups at position C5, while the subscripts 1 and 2 refer to the presence of a double bond between C22 and C23 or hydrogen at C22 and hydroxy group at C23, respectively. The 'a' variants have secbutyl at C25, while the 'b' variants have isopropyl. These subtle differences in chemical structure were found to have significant functional consequences; while initial trials found that all four avermectins showed some efficacy against gastrointestinal nematodes of sheep, avermectins of the 'B' series showed highest activity [12]. Further, when given orally, avermectin B_1 was more active than B_2, while with parenteral administration, avermectin B2 was more active than B1[11]. On this basis, development of a commercial anthelmintic focused on the 'B' series and the chemical structure at the C22 and C23 positions. IVM is a chemically modified derivative of naturally produced avermectin B_1, comprised of about 80% 22,23-dihydro-avermectin B_{1a} and almost 20% 22,23-dihydro-avermectin B_{1b}, with potent activity against a broad spectrum of parasitic nematodes after both oral and parenteral administration [3, 11]. Ivermectin is not active against flukes or tapeworms, but does have activity against various arthropods, including lice, mites, and some ticks. Ivermectin has a wide safety margin in most mammals, although some dogs with a deletion mutation in MDR1, a P-glycoprotein that functions in the blood–brain barrier, are susceptible to neurological effects [13].

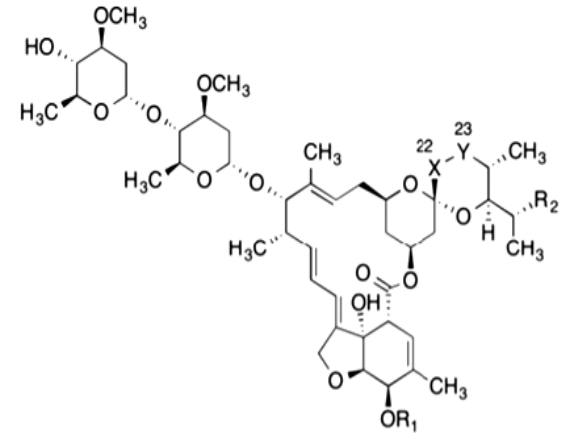

Figure: The molecular structure of avermectin, a complex of several compounds, which then underwent chemical modification to produce ivermectin, a combination of two dihydroderivatives: 22, 23-dihydroavermectin B_{1a}(where the R group is ethyl) and B_{1b}(the R group is methyl) in a ratio of 80:20 [14].

MECHANISM OF ACTION

In the beginning, researchers working on the development of ivermectin believed that it blocked neurotransmitters, acting on GABA-gated chloride channels, exhibiting potent disruption at GABA receptors in invertebrates and mammals. GABA is recognized as the primary inhibitory neurotransmitter in the somatic neuromuscular system of nematodes. Subsequently, they discovered that it was in fact glutamate-gated chloride channels (GUCl) that were the target of ivermectin and related drugs. GABA-related channels are commonplace throughout nematodes and insects, whereas in mammals, GABA receptors and neurons are restricted to the central nervous system [15]. After being bound ivermectin disrupt neurotransmission in nerve and muscle cells of the parasites, causing hyperpolarisation of the neuronal membrane, inducing paralysis of somatic muscles, particularly the pharyngeal pump, killing the parasites. At least one study, however, seems to suggest a depolarizing rather than hyperpolarizing role for ivermectin on the glutamate-gated chloride channel [16]. However, in either case, the end result is the deactivation of the channel by manipulation of chloride levels. Ivermectin, while paralyzing body-wall and pharyngeal muscle in nematodes and ectoparasites it has no such impact on mammals, as it cannot cross the blood-brain barrier into the mammalian central nervous system, where GABA receptors are located.

PHARMACOKINETICS AND INTERACTIONS

The route of administration and the formulation strongly affect ivermectin's pharmacokinetics. The drug can be administered by oral, intramuscular (IM), subcutaneous (SC), or topical (pour on) routes, depending on the species. But the oral route is the only approved route for ivermectin administration in humans. The greatest bioavailability was achieved with the SC injection, followed by the oral route. Ivermectin's extremely low water solubility and its precipitation in SC tissues favor slow absorption from the injection site, resulting in a prolonged presence in the bloodstream. Even if the dose was increased from 200 to 500 µg/kg the bioavailability was obtained lowest after topical (pour on) administration. Parenteral administration delays ivermectin's absorption compared to the oral route, but leads to an overall higher availability in plasma, a longer duration of activity, and better efficacy [17]. In ruminant species, intraruminal (IR) administration yields a lower systemic availability resulting shorter duration of activity against gastrointestinal nematodes and lesser efficacy against ectoparasites [18].

Pour-on formulations are used in cattle, as their application is less stressful for handlers and animals. Bioavailability is low and does not exceed 15% of that for SC injection possibly due to wastage or the drug being trapped in the skin and released very slowly over a longer period of time [19]. Thus, the choice of a SC or pour-on route could be important clinically, as topical formulations (with a longer action) would be more effective against most sensitive parasite species (*D. viviparous* or *Oesophagostomum radiatum*), whereas SC administration should be considered for less sensitive nematodes (*Nematodirus helvetianus* or *Trichostrongylus colubriformis*). With topical application, attention should be paid to the animal's licking behaviour.Thus, with licking, a substantial amount of topically applied ivermectin could access the systemic circulation via oral consumption resulting in sub-therapeutic concentrations in untreated and licked animals, which can contribute to the development of resistance.

In healthy human being received 12 mg of ivermectin as ethanolic oral solution had approximately twice the systemic availability than had the similar amount in tablets or capsules form [20]. In healthy human and onchocerciasis patients treated with 150 µg/kg, no significant differences were found in the pharmacokinetic parameters calculated. Due to its high lipophilic nature, ivermectin is extensively distributed with broad volumes of distribution in all species. It tends to accumulate in fat tissue, which acts as a drug reservoir and the highest levels of ivermectin are found in liver and fat, and the lowest in brain tissue whilst comparable distributions were also observed in skin, nodular tissues and worms as well as the lowest concentrations found in the subcutaneous fascia [21, 22]. The widespread binding to lipoproteins could affect the delivery of ivermectin to fat tissue and consequently relate to its extended presence in the body. Binding studies in dogs have shown that ivermectin binds extensively to plasma albumin and lipoproteins [23], and this should be considered in undernourished animals or in diseases in which plasma proteins decrease, as there would be a higher free fraction of the drug. Ivermectin persists in the body for a prolonged period, due not only to low plasma clearance but also to this accumulation in fat tissue. Plasma clearance appears to be greater in pigs than in polygastric species (goats > sheep > cattle).

Ivermectin undergoes little metabolism; most of the dose is excreted unchanged. Metabolic studies have been performed in rats, cattle, sheep, goats, and pigs. The major metabolites isolated in vivo are 24-OH-H2B1a and 24-OH-H2B1b in cattle, sheep, and rats [24], whereas in pigs O-demethylation derivatives are the major metabolites that have been isolated (3''-O-desmethyl-H2B1a and 3''-O-desmethyl-H2B1b); 3-O-desmethyl metabolite was found in goats. Studies regarding the metabolism of ivermectin in humans are scarce. This drug is extensively metabolized by human liver microsomes by cytochrome P450. Ivermectin is mainly eliminated in the feces in all species regardless of the route of administration, and fecal excretion accounts for 90% of the dose administered with <2% of the dose excreted in urine. Bile is the main route of

excretion. Ivermectin is also excreted through human and animal milk. As P-glycoprotein is also present in

for 6 weeks), kept the microfiladermia levels low more time than did ivermectin alone. Doxycycline

Table: Ivermectin spectrum of activity in several domestic animals [17].

Animal	Nematodes(endoparasites)	Arthropods	Dose
Cattle	*Hemonchus spp.* *Ostertagia* spp. *Cooperia spp.* *Trichostrongylus* spp. *Strongyloides papillosus*; *Bunostomum* spp. *Nematodirus* spp. *Trichuris* spp. *Oesophagostomum* spp. *Dictyocaulus viviparus*	*Hypoderma spp.* *Sarcoptes bovis* *Psoroptes ovis* *Linognathus* spp. *Haematopinus* spp.	200 µg/kg subcut & oral, 500
Sheep	*Haemonchus* spp. *Chabertia ovina* *Ostertagia* spp. *Cooperia* spp. *Trichostrongylus* spp. *Strongyloides papillosus* *Bunostomum* spp. *Nematodirus* spp. *Trichuris* ovis *Oesophagostomum* spp. *Dictyocaulus filaria*	*Oestrus ovis* *Sarcoptes scabiei* *Psoroptes ovis* *Melanophagus ovinus*	200 µg/kg subcut & oral
Goat	*Haemonchus* spp. *Chabertia ovina* *Teladorsagia* spp. *Cooperia* spp. *Trichostrongylus* spp. *Strongyloides papillosus* *Oesophagostomum* spp. *Dictyocaulus filaria*	*Sarcoptes* spp. *Psoroptes* ovis	200 µg/kg subcutaneous
Pig	*Ascaris suum* *Hyostrongylus rubidus* *Strongyloides ransomi* *Oesophagostomum* spp. *Metastrongylus* spp. *Stephanurus dentatus* *Trichinella spiralis*	*Sarcoptes scabiei* *Haematopinus suis*	300 µg/kg subcutaneous
Horse	*Strongylus* spp. *Parascaris equorum* *Oxyuris equi* *Draschia* spp. *Habronema* spp. *Trichostrongylus axei* *Parascaris equorum* *Strongyloides westeri* *Dictyocaulus arnfieldi* *Onchocerca* spp.	*Gasterophilus* spp. *Sarcoptes scabiei*	200 µg/kg oral
Dog	*Dirofilaria immitis* (microfilaria and fourth-stage *Toxocara canis* *Toxascaris leonine* *Ancylostoma caninum* *Uncinaria stenocephala* *Trichuris vulpis*	*Sarcoptes scabiei* *Otodectes cynotis*	6 µg/kg oral

biliary canalicules, it could contribute to the drug's high fecal excretion [25]. Ivermectin is also excreted by the mammary gland in dairy cows, sheep, and goats; this mode of excretion is related to its high lipophilicity.

To interrupt the transmission of onchocerciasis in humans, the combination of ivermectin and doxycycline is highly effective as, in infested patients, the ingestion of the anthelmintic (200 µg/kg, single dose) and the antibacterial (100 mg/kg, daily

enhanced ivermectin-induced suppression of microfiladermia, as it sterilizes adult female worms for a few months by depletion of symbiotic endobacteria of filariae, *Wolbachia* spp [26]. Albendazole (400 mg) and ivermectin (200 µg/kg) appears to be highly effective against trichuriasis (*Trichuris trichiura*) in human [27]. Thus, interactions of ivermectin with concurrently administered drug can take place.

IVERMECTIN IN ANIMAL HEALTH

The market for Ivermectin has remained exceptionally strong in the livestock industry, particularly for the control of wide spectrum of ecto and endoparasites. Ivermectin is highly active against a broad range of nematode species, including most larvae and adult forms; it is also highly effective against many arthropod parasites of domestic animals (Table 1). All important gastrointestinal and lung nematodes are susceptible to the drug, including sensitive mites, ticks, biting flies, and parasitic dipteran larvae [28, 18]. In dogs, ivermectin is also active against developing larvae of *Dirofilaria immitis* and is used in heartworm prophylaxis. Many rumino-reticular delivery systems, as well as oral, topical, and injectable formulations of ivermectin, are currently available at the dosage recommended by manufacturers, namely, 200 µg/kg (500 µg/kg for pour on) in large and small ruminants also equines, 300 µg/kg in pigs, and 6 µg/kg in dogs [17]. A number of derivatives,such as eprinomectin (topical application for farm animals, with extended activity and no milk withdrawal [29], and selamectin (topical application for small animals, with a wider safety margin than ivermectin in dogs with the MDR1 mutation [30], have been developed since, to great commercial success. Two additional macrocylic lactones of commercial importance, moxidectin and milbemycin oxime, belong to a closely related but distinct family of Streptomyces-derived anthelmintics called the milbemycins [31].

IVERMECTIN IN HUMAN HEALTH

The origins of ivermectin as a human drug are inextricably linked with Onchocerciasis (or River Blindness), a chronic human filarial disease caused by infection with Onchocerca volvulus worms. The parasites are transmitted via the bite of infected blackflies of the genus Simulium, which breed in highly-oxygenated, fast-flowing rivers and watercourses. In the human body, immature larval forms of the parasite create nodules in subcutaneous tissue, where they mature into adult worms. After mating, female worms can release up to 1000 microfilariae a day for some 10–14 years. These move through the body, and when they die they cause a variety of conditions, including skin rashes, lesions, intense itching, edema and skin depigmentation. Microfilariae also invade the eye, causing visual impairment and loss of vision, onchocerciasis being the second leading cause of blindness caused by an infectious disease [32]. The disease causes visual damage for some 1–2 million people, around half of who will become blind [33]. In the early-1970s, the disease was endemic in 34 countries: 27 in Africa; 6 in the Americas; and 1 in the Arabian Peninsula. The World Health Organization (WHO) later estimated that 17.7 million people were infected worldwide, of whom some 270,000 were blind, and another 500,000 severely visually disabled. The burden of onchocerciasis was particularly extreme in the hyper-endemic belt across sub-Saharan Africa. Communities in these areas exhibited high rates of visual disability caused by Onchocerciasis, up to 40% in some areas, which caused immeasurable negative impact on individual and community health, reducing economic capacity and productivity, and leading to the abandonment of fertile agricultural lands [34].

Lymphatic Filariasis, also known as Elephantiasis, is another devastating, highly debilitating disease that threatens over 1 billion people in more than 80 countries. Over 120 million people are infected, 40 million of whom are seriously incapacitated and disfigured. The disease results from infection with filarial worms, *Wuchereria bancrofti*, *Brugia malayi* or *B. timori*. The parasites are transmitted to humans through the bite of an infected mosquito and develop into adult worms in the lymphatic vessels, causing severe damage and swelling (lymphoedema). Adult worms are responsible for the major disease manifestations, the most outwardly visible forms being painful, disfiguring swelling of the legs and genital organs. The psychological and social stigmas associated with the disease are immense, as are the economic and productivity losses it causes. Indeed, the field trials had confirmed that ivermectin in combination with Albendazole or diethylcarbamazine (DEC) were 99% effective in getting rid of the microfilariae of *Wuchereria bancrofti* and others. Following the advancement in diagnosis and treatment, lymphatic filariasis has been taken as one of the six “potentially eradicable” public health diseases [35].

Today, ivermectin is being increasingly used worldwide to combat other diseases in humans, such as Strongyloidiasis which infects some 35 million each year , scabies which causes 300 million cases annually, Pediculosis and Gnathostomiasis as well as new and promising properties and uses for ivermectin and other avermectin derivatives are continuing to be found [36]. Ivermectin has a significant impact on Myiasis, an infestation of fly larvae that grow inside the host (man and animal). Surgical removal of parasites is often the only remedy but unavailable to many of the needful people who live in poor, rural tropical communities where myiatic flies thrive. Oral myiasis has been successfully treated with ivermectin, which has also been used effectively as a noninvasive treatment for orbital myiasis, a rare and preventable ocular morbidity [37]. Globally, approximately 11 million individuals are infected with roundworm *Trichinella*. Ivermectin kills *Trichinella spiralis*, the species responsible for most of these infections [38]. Ivermectin is highly effective in killing a broad range of insects. Comprehensive testing against 84 species of insects showed that avermectins were toxic to almost all the insects tested. At sub-lethal doses, ivermectin inhibits feeding and disrupts mating behavior, oviposition, egg hatching and development [39]. Mosquitoes (*Anopheles gambiae*) that transmit *Plasmodium falciparum*, the most dangerous

malaria-causing parasite, can be killed by the ivermectin present in the human bloodstream after a standard oral dose [40, 41]. Ivermectin has been proposed as a possible rodent-bait feed-through insecticide to help control the Phlebotomine sandfly vectors that transmit *Leishmania* parasites. Experiments to test the impact of ivermectin on one blood-feeding sandfly vector, *Phlebotomus papatasi*, demonstrated that they die if the blood feed is 1–2 days Tse Tse flies (*Glossina palpalis*) fed on ivermectin-treated animals die within 5 days, demonstrating that ivermectin could help controlling these flies which acts as vectors for African trypanosomiasis or sleeping sickness in human [45, 46]. In case of American trypanosomiasis (Chagas disease), when dogs infected with *Trypanosoma cruzi* parasites suffered a tick infestation, ivermectin treatment eliminated the ticks but had no impact on either the dogs or their infection. Schistosoma species are the causative agent of schistosomiasis, a disease afflicting more than 200 million people worldwide. Praziquantel is the sole drug available for controlling schistosomiasis, with schistosome-resistant parasites now becoming an increasingly worrying problem [47]. Ivermectin is a potent agonist of glutamate-gated chloride channels and as glutamate signaling has been recorded in schistosomes, there may be an ivermectin target in the tegument [48, 49]. Ivermectin is used to treat diseases associated with Demodex mites, such as blepharitis and demodicosis, oral ivermectin, in combination with topical permethrin, being a safe and effective treatment for severe demodicosis [50]. It is also known that the prevalence of head lice is markedly reduced in children taking ivermectin tablets [51]. Ivermectin 1% cream is more effective and safer than all current topical treatment for rosacea lesions, a chronic skin condition that manifests as recurrent inflammatory lesions [52]. Studies of long-term treatment with ivermectin to control Onchocerciasis have shown that use of the drug is additionally associated with significant reduction in the prevalence of infection with any soil-transmitted helminth parasites (including Ascaris, Trichuris and hookworm), most or all of which are deemed to be major causes of the morbidity arising from poor childhood nutrition and growth [53].

Nodding syndrome is a mysterious and problematic form of epilepsy that occurs in parts of South Sudan and northern Uganda. It is also endemic in a locus in Tanzania but, there, the prevalence is low and stable. The condition has serious socioeconomic implications and, like other forms of epilepsy, generates profound social stigma [54]. The obvious outward feature of nodding syndrome, which afflicts children and adolescents, is a paroxysmal bout of forward and downward head movement, the nodding episodes representing epilepsy seizures. Children with this syndrome display varying levels of mental retardation, often alongside notable stunted growth and failure to develop secondary sexual characteristics (hyposexual dwarfism). Many neurological disorders, such as motor neuron disease, arise due to cell death initiated by excessive levels of excitation in central nervous system neurons. A proposed novel therapy for these disorders involves silencing excessive neuronal activity using ivermectin. A number of early studies discovered that, at high doses, ivermectin increases the chloride conductance of mammalian neuronal cells. On this basis, high-dose ivermectin (up to 1.6 mg/kg) has previously been used successfully for symptomatic treatment of severe muscle spasticity in patients with spinal cord injuries [55].

More recently, ivermectin was shown to induce intracellular chloride flux in human leukaemia cells in vitro [56]. This was associated with an increase in the production of intracellular reactive oxygen species (ROS), leading to cell death in leukaemia cells, but not in normal hematopoietic cells. This difference in susceptibility may reflect an increased expression of chloride channels on malignant cells or an increased susceptibility to ROS, both of which have been reported previously. Ivermectin was also effective at slowing tumor growth in vivo in three mouse models of leukaemia, suggesting promise as a cancer chemotherapeutic [56]. Other potential parasite target for ivermectin is bedbugs. Bed bugs are parasitic insects in the Cimicidae family that exclusively feed on blood. *Cimex lectularius*, the common bedbug, feeds on human blood, with infestations increasing significant in poor households across North America and Europe. During the 20th century, bed bug populations diminished, at least in the U.S. and Europe, due to the use of potent pesticides and other interventions. However, bed bugs have staged a resurgence starting in the 1980s, partly due to increasing levels of insecticide resistance. Ivermectin is highly effective against bedbugs, capable of eradicating or preventing bedbug infestations [57].

Concluding remarks and future directions

Ivermectin has essentially remain a drug of choice in veterinary and human medicine for nearly three decades but still much to learn about this enigmatic drug. The precise mode of action and interactions of the drug is still unrevealed, but the relationship between host immunity and drug efficacy is intriguing and worthy of further study. Similarly, in-depth pharmacokinetic, pharmacodynamic and drug resistance mechanisms are unclear, and determining the genetic basis of resistance remains a pressing issue. However, the availability of multiple parasite genomes for comparative analysis, and the application of high-throughput sequencing technologies to classical genetic approaches may provide answers to some of the questions soon. While ivermectin has already lifted the burden of onchocerceriasis and lymphatic filariasis from millions of people, as well as a range of endo and ectoparsites from various domestic animals and pets it is also likely that ivermectin novel derivatives may

prove valuable in the treatment of other important diseases. Further, the incredibly broad range of effects of ivermectin in a wide variety of systems may offer new insights into its therapeutic effects in the target species.

Contribution and conflict of Interest:
MMR had the leading contribution to the critical thinking, primary writing and editing of this article. All other authors significantly contributed to the eventual completion of this paper. The authors declare that there are no commercial or financial relationships with this manuscript that could be construed as a potential conflict of interest.

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