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Ivermectin: Potential Repurposing of a Versatile Antiparasitic as a Novel Anticancer

Alfonso Dueñas-González and Mandy Juárez-Rodríguez

Abstract

Drug repositioning is an alternative strategy to discover and develop anticancer drugs based on identification of new mechanisms of actions and indications for existing compounds. Ivermectin belongs to the avermectin group of compounds, a series of 16-membered macrocyclic lactone moieties discovered in 1967 and FDA-approved for human use since 1987. Ivermectin has since been used by millions of people worldwide, and have demonstrated a wide margin of clinical safety. Here we summarize the *in vitro* and *in vivo* evidence demonstrating ivermectin's potential as a multitargeting anticancer drug that exerts antitumor effects against different tumor types. Notably, the *in vitro* and *in vivo* antitumor activities of ivermectin are achieved at concentrations that can be clinically achieved based on human pharmacokinetic studies done in the clinical studies. Moreover, repurposed ivermectin safety has been well established recently in clinical studies against COVID-19. Consequently, we believe that ivermectin is an excellent potential candidate drug that can be repurposed for cancer and deserves rigorous evaluation against a variety of cancers in well-designed clinical trials.

Keywords: Drug repurposing, ivermectin, cancer

1. Introduction

Avermectins are a complex of 16-membered macrocyclic lactones produced from soil fermentation of the actinomycete *S. avermitilis* [1, 2]. There exist eight avermectin compounds (A1a, A1b, A2a, A2b, B1a, B1b, B2a, and B2b), of which ivermectin is the most commonly employed due to its semi-synthetic mixture (80% B1a and 20% B1b), and its potent antiparasitic activity as well as its safety [3]. The family of compounds from which Ivermectin is derived was discovered by Nobel laureates Satoshi Omura and William Campbell in the 1970s. The chemical is effective against a wide number of parasites and arthropods - pinworms, mites, lice, heartworms and fleas in dogs, parasitic worms in pasture animals by disrupting the fluid exchange through the insect's cell membrane, and in the past 40 years, ivermectin has been used extensively for agriculture and veterinary purposes [4–7].

The success of ivermectin treatment as antiparasitic is due to its high affinity for the glutamate-gated chloride channels (Glu-Cl) present in parasite cells but absent in vertebrates. The ivermectin-channel-interaction prevents channel closure,

leading to plasma membrane hyperpolarization, paralyzing the target parasite's pharyngeal and somatic muscles, triggering its death [2]. In addition to activating the Glu-Cl parasites channels, ivermectin acts as a dose-dependent positive allosteric regulator of several vertebrate ligand-gated channels, including the γ -aminobutyric acid type-A receptor (GABA receptor), glycine receptor, neuronal α 7-nicotinic receptor, and purinergic P2X4 receptor. The effects of ivermectin over these receptors include the potentiation of agonist-induced currents at low concentrations and channel opening at higher concentrations [8]. However, GABA-sensitive neurons are protected by the blood–brain barrier within the central nervous system, protecting vertebrates against the potentially harmful effects of Ivermectin [3, 6].

2. Drug repurposing in cancer therapy

Effective, safe, and affordable cancer drugs are highly needed to reduce cancer mortality. The field of drug repurposing emerged in the early 1990s as an alternative to the conventional drug discovery model. This model entails targeting discovery and validation, lead identification by high-throughput screening, and lead optimization by medicinal chemistry. Drug repurposing surged to overcome the pharmaceutical industry's limited productivity regarding the number of approved drugs concerning the long time and huge money required to develop a drug. Classical drug discovery requires an average of 15 years of research, whereas drug development by repurposing is portended to be cheaper, faster, and safer. The significant advantage of drug repurposing is that the pharmacokinetics, pharmacodynamics, and toxicity profiles of drugs are, in general, well known; thus, its rapid translation into phase II and III clinical trials is feasible [9]. Among the different drugs currently studied under the focus of therapeutic repositioning, ivermectin is very promising. It has been shown to have antitumor effects *in vitro* and *in vivo* (Figure 1).

3. Antitumor effects of Ivermectin-mechanisms of action and *in vitro* data

Ivermectin has demonstrated antitumor effects in different types of cancers. Among mechanisms of action reported, ivermectin interacts and affects the function of 1) mitochondrial I complex, the multidrug resistance protein (MDR), 2) RNA helicases, 3) the WNT-TCF pathway, 4) chloride channel receptor, 5) immunogenic cell death via ATP- and HMGB1, 6) PAK-1, 7,8) epigenetic signature and self-renewal of stem cells [10]. Preclinical testing have demonstrated inhibition of cell growth, induction of apoptosis in different cancer cell lines and antitumor effects in murine models (Figure 1) [11–19]. The *in vitro* antitumor effects are observed at a median concentration of 5 μ M (0.01–100 μ M), which is clinically attainable according to the pharmacokinetic data in humans shown in Table 1. We present a review of the laboratory results of ivermectin on various cancer cell lines below.

3.1 Ovarian cancer

Ivermectin blocks the oncogenic kinase PAK1 in human ovarian cancer and in NF2-deficient Schwannoma cell lines to suppress their PAK1-dependent growth in cell culture at a half maximal inhibitory concentration (IC50) between 5 and

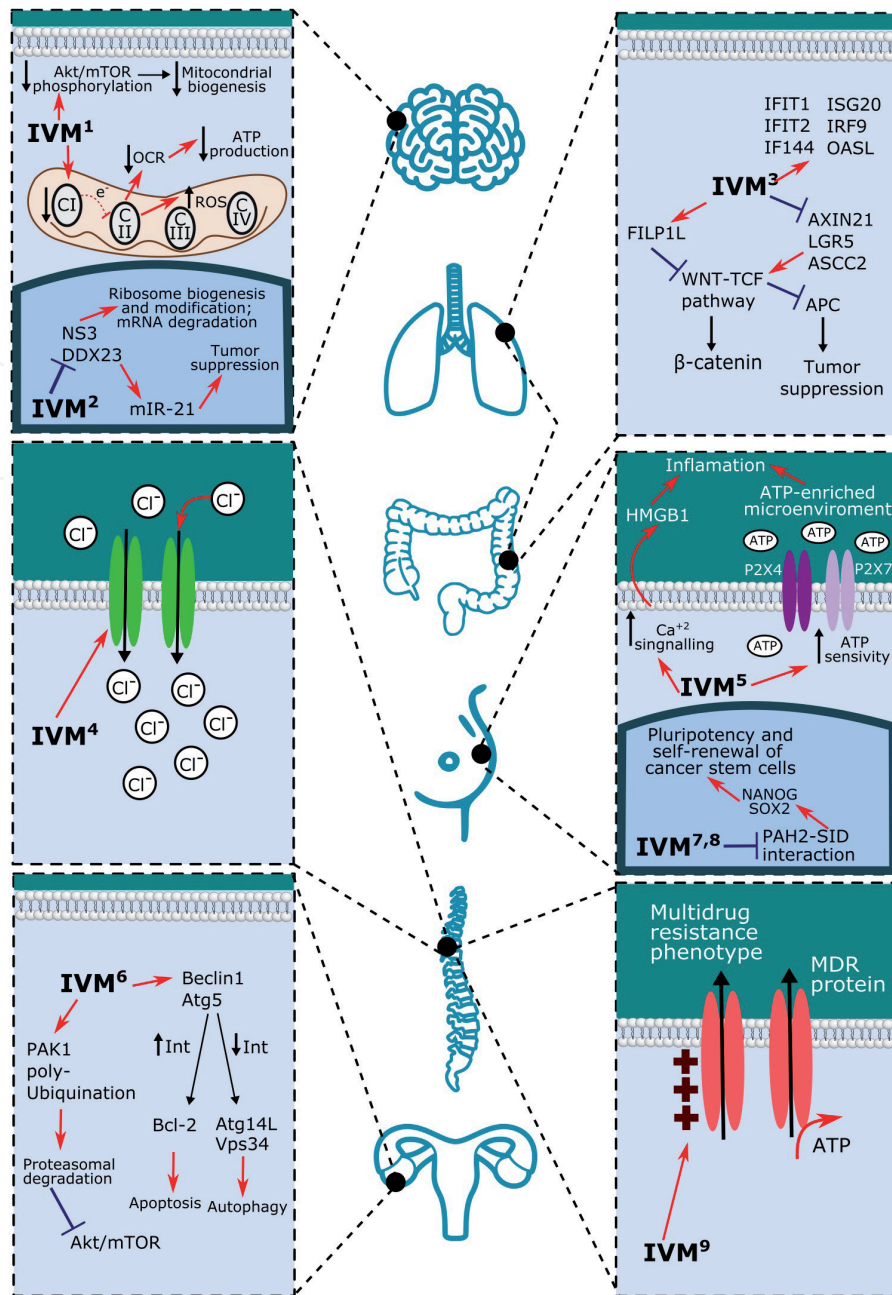


Figure 1.

Cancer targets of ivermectin. 1. Decreasing the function of the mitochondrial complex I, Ivermectin, limits the electronic movement in the oxidative phosphorylation pathway that stimulates oxygen consumption rate to generate ATP for the cell. Low ATP levels are related to a failure in the P-glycoprotein pump to extrude chemotherapy drugs. Concomitantly there is a reduction in the phosphorylation levels of Akt, impacting the mitochondrial biogenesis process. Furthermore, alterations in the mitochondrial machinery are related to increased levels of reactive oxygen species that damage DNA. 2. Ivermectin limits the function of the RNA helicases NS3 and DDX23, both of which are related to ribosome biogenesis and post-transcriptional modifications, as well as with mRNA degradation. DDX23 acts as a promoter of miR-21, which is a well-recognized stimulator of tumor progression. 3. The WNT-TCF pathway, involved in cancer progression and metastases, is inhibited by Ivermectin. Indeed, this compound represses AXIN2, LGR5, and ASCL2, all of them WNT-TCF targets. At the same time, it promotes the repressor of the WNT signaling FILIP1L. Both effects inhibit the ability of WNT-TCF to downregulate the tumor suppressor APC and limit the translocation of β -catenin to the nucleus for epithelial to mesenchymal transition in metastatic events. 4. Ivermectin acts as an ionophore by the up-regulation of chloride channels to generate apoptosis and osmotic cell death. 5. Ivermectin induces immunogenic cell death by stimulating an ATP- and HMGB1-enriched microenvironment, which promotes inflammation. This drug also increases ATP sensitivity and calcium signals in P2X membranaral receptors, particularly P2X4 and P2X7, to induce ATP-dependent immune responses. 6. Ivermectin promotes the poly-ubiquitination of the kinase PAK1, which directs it to degradation in the proteasome. Defective PAK1, in turn, inhibits the Akt/mTOR pathway. At the same time, Ivermectin stimulates the expression of Beclin1 and Atg5, both related to induction of autophagy. Particularly, Beclin1 increases the expression of the positive autophagy regulators Atg14L and Vps34 and reduces the negative regulator of apoptosis Bcl-2. Together, this generates autophagy and apoptosis. 7,8. Ivermectin modifies the epigenetic signature and the self-renewal activity in the malignant cell due to its ability to mimic the SIN3-interaction that binds to the PAH2 motif of the ca.

Illness/Adverse effects	Mild	Intermediate	Severe
Onchocerciasis	Myalgia, skin eruptions, joints swelling, limbs or face, itching, fever and cold	Skin pain and edema, arthralgia, bone pain, severe dizziness, high fever, dyspnea, and hypotension	NA
Filariasis	Headache and nausea	NA	Encephalopathy
Scabies	Nausea	Severe headache, abdominal pain, and tachycardia	NA

Table 1.
Adverse effects caused by Ivermectin.

20 μ M [14]. PAK1 is involved in various signaling pathways that play an essential role in cytoskeletal dynamics, cell adhesion, migration, proliferation, apoptosis, and mitosis. It is required for the growth of approximately 70% of neoplasms [20]. Additionally, cancer stem-like cells derived from SKOV-3 cell line treated with 5 μ M ivermectin showed a significant decrease in cell viability and clonogenic capacity. Also, the expression levels of Nanog, Sox2, and Oct4 are reduced after treatment with ivermectin 5 μ M [11].

3.2 Breast cancer

Ivermectin inhibits the ATK/mTOR pathway in breast cancer cell lines by promoting ubiquitination of PAK1. Ivermectin disrupts the binding of PAK1 protein with AKT, and in turn hinders the phosphorylation and activation of AKT; resulting in AKT/mTOR pathway inactivation. These effects of ivermectin are observed at concentrations above 10 μ M [15]. Additionally, ivermectin preferentially inhibits the viability of cancer stem-like cells enriched populations (CD44+/ CD24-) in the range of 0.2–8 μ M via reducing the expression of maintenance of the pluripotency and self-renewal markers Nanog, Oct4, and Sox2 at both mRNA and protein levels [11]. Separately, a study demonstrated that 1 μ M ivermectin treatment inhibits the function of SIN3 [16], which is part of a complex that positively regulates Nanog and Sox2, leading to a decrease in mammospheres number [21]. Furthermore, ivermectin was reported to induce E-cadherin and Estrogen Receptor 1 expression and the restoration of tamoxifen sensitivity in a triple-negative breast cancer model. According to these observations, ivermectin has potential antitumor effects in triple-negative breast cancer [16]. Another study demonstrated a synergy between ivermectin with docetaxel or cyclophosphamide in estrogen receptor-negative breast cancer cells and a synergistic effect with tamoxifen in estrogen receptor-positive breast cancer cell lines [22].

3.3 Liver cancer

In human combined hepatocellular-cholangiocarcinomas and intrahepatic cholangiocarcinomas (cHC-CCs and ICCs), there is robust YAP1 activation. YAP1 is a transcriptional regulator of genes involved in cell proliferation and suppression of apoptotic genes, and it is inhibited in the Hippo signaling pathway which allows tumor suppression. Nuclear translocation of YAP1/TAZ also increases transcription of TGF- β s [23]. Thus, it is possible that coordinated targeting of YAP1/TAZ and TGF- β signaling may be a treatment for cHC-CCs and ICCs displaying dysregulated Hippo signaling and meanwhile drug screening revealed ivermectin to inhibit YAP1 activation [23].

3.4 Cervical cancer

Ivermectin inhibits the viability of HeLa cells and induces a G1/S cell cycle arrest leading to apoptosis and morphological changes of DNA fragmentation and chromatin condensation of such cells. Additionally, ivermectin can significantly increase intracellular ROS content and inhibit the migration of HeLa cells [24].

3.5 Glioblastoma

Ivermectin inhibits the growth of glioma cells by inducing cell cycle arrest and apoptosis *in vitro* and *in vivo* [25]. Specifically, in glioblastoma and brain endothelial cells, ivermectin has been reported to induce mitochondrial dysfunction. It inhibits cell growth and colony formation and blocks the enzymatic activity of the respiratory chain complex I, thereby decreases mitochondrial respiration, membrane potential, and ATP levels while increasing the generation of superoxides that in turn induces cell death by caspase-dependent apoptosis. Additionally, ivermectin also inhibits angiogenesis at concentrations above 5 μM [12].

3.6 Leukemia and prostate cancer

The treatment of OCI-AML2 cells with ivermectin increased the concentration of intracellular chloride ions, leading to hyperpolarization of the plasma and mitochondrial membranes and ROS production [18]. In contrast, DU145 and PPC-1 cells and primary normal hematopoietic cells that were resistant to ivermectin did not demonstrate changes in their plasma membrane potential when treated with up to 6 μM ivermectin. Moreover, the *in vitro* antitumor effect of ivermectin on various cancer cell lines at a concentration of 5 μM showed that DU145 is only minimally reduced in viability and clonogenic capacity, but when it is treated in combination with docetaxel cells demonstrated strong inhibition [22]. In myeloid leukemia cells ivermectin strongly synergizes with daunorubicin and cytarabine [18].

3.7 Colon and lung cancer

The WNT/TCF signaling pathway is constitutively active in many tumors and it regulates genes for cell growth and proliferation. Ivermectin can inhibit the WNT-TCF signaling pathway by decreasing cyclin D1, which is a direct target in this pathway and ivermectin also affects the phosphorylation of β -catenin, which leads to inhibition of proliferation and increased apoptosis in lung and colon tumor cells at concentrations above 5 μM [13].

4. Antitumor effects of ivermectin-animal data

In a wide-range of pre-clinical studies, rodent models of human xenografts of glioblastoma, leukemia, breast and colon carcinomas, as well as a variety of murine cell lines in syngeneic models have consistently shown ivermectin to possess robust antitumor effect at a median dose of 5 mg/Kg [12, 13, 15, 17, 18]. We present a review of some results of anticancer studies of ivermectin in animal below.

4.1 Glioblastoma

Two independent glioblastoma xenograft SCID mice models were established by subcutaneous injection of U87 or T98G cells, and the rodents were subsequently

treated with intraperitoneal ivermectin at 40 mg/Kg. The treated mice had demonstrated significant tumor growth inhibition but maintained normal behavior and retained their weight [12]. A separate study using 3 mg/Kg of ivermectin showed a 50% decrease in tumor size and there was near complete regression of tumors at 10 mg/Kg. Ki67 staining also confirmed that glioma cell proliferation was decreased in ivermectin-treated animals compared to controls [17].

4.2 Colon and lung cancers

Melotti et al. used H358 human metastatic lung bronchioalveolar carcinoma cells and DLD1 colorectal adenocarcinoma cells to test the antitumor effects of ivermectin. The animals received intraperitoneal injections of cyclodextrin-conjugated ivermectin daily at 10 mg/kg after tumor establishment. Subsequently, it was found that tumors responded to ivermectin with a near 50% reduction of growth and a repressed lung cancer WNT-TCF signature and enhanced p21 levels [13].

4.3 Breast cancer

Ivermectin was evaluated in an orthotopic breast cancer model with human MDA-MB-231 cells subcutaneously injected in the mammary fat pad of NOD-SCID mice. Xenografts treated with ivermectin grew at a slower rate than those of the control group, and the size and weight of control tumors were macroscopically larger than that of ivermectin-treated tumors [15]. Another study tested JC murine breast cancer cells in Balb/c mice treated with a dose of 3 mg/Kg of ivermectin. Treatment reduced tumor size more than 60% with no changes in weight or behavior of the study animals when compared with controls [22]. Recently it was demonstrated the ivermectin at a dose of 5 mg/Kg induces immunogenic cell death hallmarks with large numbers of intratumoral CD44⁺ and CD8⁺ T cells in a 4 T1 murine tumor model. Thus, ivermectin turns cold tumors into hot ones which allows for marked synergy with check point inhibitor nivolumab, leading to major antitumor effects and most importantly, protective immunity [26].

4.4 Leukemia

Human leukemia (OCI-AML2 and K562) and murine leukemia (MDAY-D2) cells were injected subcutaneously into NOD/SCID mice which were subsequently treated with 3 mg/Kg (human equivalent dose of 0.240 mg/Kg) of ivermectin or control in water via oral gavage. Upon follow-up, the treated mice had up to 70% decrease in their tumor burden without any gross sign of organ toxicity, and treatment led to increased apoptosis in OCI-AML2 xenografts [18]. It must be remarked that most of the *in vivo* studies to evaluate the antitumor effects of ivermectin dose ranging from 3 to 10 mg/Kg. These mice doses translate into human to 0.240 to 0.810 mg/Kg which are clinically attainable [27].

5. Clinical experience with ivermectin

As mentioned above, there has been extensive clinical use of ivermectin as an anti-parasitic, and the drug has been repurposed for use against other pathogens and non-parasitic conditions in humans. However, despite considerable preclinical evidence of antitumor effects of ivermectin, it is curious that no clinical studies of ivermectin against cancer have been reported nor clinical trials launched. However, there is a case report on three children with refractory and heavily pretreated acute myeloblastic

leukemia. In the three cases, ivermectin was at 1 mg/Kg either alone or in combination with Ara-C. Two of them had clinical improvement with durable stable disease in one, a and complete hematological response the second. The third one receiving ivermectin alone had no response. Though anecdotic, these data demonstrate that ivermectin can be safely administered at dosis five times higher the recommended dose of 0.200 mg/Kg, and that can show efficacy combined with cytotoxics [28].

Here, we briefly review the clinical experience with ivermectin as an antiparasitic as well as in other repurposed indications, with special attention to its toxicities and safety and its clinical pharmacology, the data of which can be a basis for future clinical trials of ivermectin against cancer.

5.1 Ivermectin use as anti-parasitic

Because of its broad spectrum applicability, ivermectin can be applied to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, ascariasis, scabiasis, and enterobiasis. Since its discovery, ivermectin has been administered to millions of patients with the above parasitic infections around the world. Mild adverse effects of oral ivermectin therapy against certain parasites are common; many of them appear within 24-48 hours of the onset of therapy and are related to ivermectin dose as well as the microfilariae load in the skin in case of filiarasis [29, 30]. Some of these adverse effects include myalgia, skin rashes, joints swelling, limbs or face itching, fever, and chills. These effects are usually transient and do not require treatment [31, 32]. Moderate to severe effects are less common and may include skin edema with the presence of pain, arthralgia, severe dizziness, high fever, dyspnea, and hypotension (Mazzotti's Reaction). It is known that such reaction is not related to the administration of Ivermectin but with the parasite amount present in the host [30, 31]. In addition to Mazzotti's reaction, there have been cases of severe encephalopathy that can be fatal in patients with onchocerciasis and filariasis after treatment with ivermectin. The symptoms of encephalopathy include altered mental status, incontinence, and difficulty standing or walking 48 hours after ivermectin treatment [32, 33]. This effect is again probably due to the obstruction of the cerebral microcirculation due to the accumulation of paralyzed or killed parasites and not by ivermectin itself [34, 35]. Also, toxic effects have been linked to ivermectin's interaction with P-glycoprotein [8]. The absence of P-glycoprotein determines the accumulation of Ivermectin in the brain of transgenic mice who do not express it and dogs with impaired P-glycoprotein function (commonly a 4 base-pair deletion of the MDR-1 gene that produces a stop codon) have increased neurotoxicity to ivermectin [36]. **Table 2** summarizes ivermectin's adverse effects. The dose and schedules vary but human doses are standardized for approved indications within the range of 0.15 to 0.4 mg/Kg. For onchocerciasis, the recommended dose is 0.15 mg/Kg once every 12 months, though patients with heavy ocular infection may require retreatment every 3 or 6 months. Filariasis usually requires a single dose of

Group	Dose (mg/kg)	Drug delivery	Cmax (ng/mL)	Tmax (h)	AUC µg/h/mL
Onchocercosis patients	0.1-0.2	Oral	52.0	5.2	2.852
Healthy volunteers	0.35-0.6	Oral	87.0	4.2	1.444
Healthy volunteers	0.7-1.1	Oral	165.2	3.6	2.099
Healthy volunteers	1.4-2.0	Oral	247.8	4.2	4.547

Table 2.
Pharmacokinetic data of Ivermectin in humans infected with parasites and in healthy volunteers.

0.4 mg/Kg. In strongyloidiasis, a single dose of 0.2 mg/Kg is recommended; however, in immunocompromised (including HIV) patients, the treatment may require repeated administration (i.e. every two weeks) and continued suppressive therapy (i.e. once a month). A single dose of 0.2 mg/Kg is also used to treat ascariasis, while the same dose repeated once at two weeks is recommended for scabiasis [37].

Recently, there has been a growing interest in newer anti-parasitic indications of ivermectin such as against soil-transmitted helminths and malaria, hence doses above 0.4 mg/Kg are being evaluated for achieving higher plasma levels [38, 39].

An example is a pharmacokinetic trial using 18 mg ivermectin tablets in 54 healthy adult volunteers to evaluate the safety of fixed regimens of 18 and 36 mg [40]. A meta-analysis to investigate the safety of higher doses of ivermectin identified four studies for inclusion, and found no differences in the number of individuals experiencing adverse events at higher doses. A descriptive analysis of these clinical trials for a variety of indications also showed no difference in the severity of the adverse events between standard (up to 0.4 mg/Kg) and higher doses of Ivermectin (0.4-0.7 mg/Kg; 0.6 mg/Kg, and 0.8 mg/Kg). Only one trial showed an increase in transient and mild to moderate subjective ocular events such as transitory blurring of vision, itching or pain of the eye, and dyschromatopsia in the higher-dose group in a trial to treat onchocerciasis. Meanwhile, severe adverse events described as life-threatening, was reported in only one out of the four studies with one case of anaphylaxis at the standard dose and another case of QTc prolongation likely due to drug-drug interaction in a higher-dose group [41]. The result of this small meta-analysis is suggestive of relatively safety of higher doses of ivermectin.

5.2 Ivermectin's potential as an anti-viral

Ivermectin exhibits anti-viral activity against viruses both *in vitro* and *in vivo*. The antiviral activity is thought to be related to the inhibition of nuclear translocation of viral proteins, facilitated by mammalian host importin also known as karyopherin α/β -1 heterodimerization [42]. It is partially upon this basis that ivermectin has been tested as a treatment in the current COVID-19 pandemic. A recent meta-analysis and systematic review involving 629 COVID-19 patients from 4 observational studies (3 with control arms and 1 without) found that adding ivermectin led to significant clinical improvement compared to control (OR=1.98, 95% CI: 1.11 - 3.53, $p=0.02$) [43]. However, the authors did caution on the interpretation of their analysis because of the low quality of evidence, and it should be noted that one of the trials included in the analysis was subsequently retracted. Meanwhile, several randomized studies evaluating ivermectin against COVID-19 have recently been published. An Iranian trial demonstrated that a single 0.2 mg/Kg dose of ivermectin was well-tolerated in symptomatic COVID-19 patients, and dyspnea, cough and lymphopenia associated with COVID-19 were significantly improved [44]. In two other randomized trials, the time to viral clearance was statistically reduced. The doses and schedules in these two trials were ivermectin at a fixed 12 mg daily for 5 days [45] and ivermectin at 0.1, 0.2, and 0.4 mg/Kg once at admission [46]. These were underpowered trials so that further evidence is still required to confirm the clinical usefulness of ivermectin under various COVID-19 clinical scenarios.

5.3 Other uses of ivermectin

Ivermectin possesses possible agonistic bioactivity against the γ -aminobutyric acid (GABA) receptor [47] and it was upon this premise that it was used in a patient with severe spasticity caused by spinal cord damage at a dose of 1.6 mg/

Kg subcutaneously twice a week for 12 weeks. The patients had decreased spasm scores, suggesting that ivermectin may reduce spasticity in the spine without adverse effects at this high dose [48].

6. Pharmacokinetics and dose considerations for ivermectin as cancer therapy

Due to its relatively long history of extensive use, the pharmacokinetics of ivermectin has been well studied. The oral route is the only approved for ivermectin administration in humans although it can be given subcutaneously and the intravenous route of administration has also been investigated. Ivermectin is a fat-soluble compound and reaches a peak concentration 4-5 hours after oral administration, and it has a half-life of approximately 19 hours. After administration, it is subsequently extensively metabolized in human liver microsomes by cytochrome P-4503A4, converting the drug to at least ten metabolites, most of them hydroxylated and demethylated derivatives. Its excretion is mainly by the fecal route, and only 1% is excreted in the urine [49]. In healthy individuals and patients infected with onchocerciasis treated with a dose of 0.150 mg /Kg of Ivermectin, significant variability in pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion is not observed [49].

The therapeutic dose for ivermectin as an anti-parasitic compound for human use is between 0.1 and 0.4 mg/ Kg [4-7], resulting in an AUC of 1,444 $\mu\text{g}/\text{h}/\text{mL}$. This drug exposure, which translates to a plasma concentration of 1.65 μM , is however less than concentrations of 5 μM or greater that has been found necessary to inhibit tumor cells *in vitro*. In a phase I pharmacokinetic study done in healthy volunteers, it was demonstrated that doses up to 2 mg/Kg which leads to an AUC of 4,547 $\mu\text{g}/\text{h}/\text{mL}$ can translate into a plasma concentration of 5 μM [50], thus the recommended dose for cancer therapy should likely be 2 mg/kg or higher.

7. Discussion

Currently, various efforts to facilitate the discovery of drug repurposing candidates for cancer and a large number of drug candidates do exist [51]. As an example, the Repurposing Drugs in Oncology (ReDO) Project, which is initiated by a non-profit international collaboration of researchers, clinicians, and cancer patient advocates whose goal is to find efficacious, minimally toxic, and affordable cancer treatments identified a total of 268 drugs that matched the following two criteria: i) the drug is licensed for non-cancer indications in at least one country in the world, and ii) the drug is the subject of one or more peer-reviewed publications showing a specific anticancer effect based on *in vitro*, *in vivo*, or clinical research in one or more malignancies. According to these criteria, ivermectin can be a potential repurposing candidate for cancer. Ivermectin has extensive preclinical *in vitro* and *in vivo* anticancer data and is thus an ideal candidate for clinical trials. An especially promising feature with ivermectin is that its anti-cancer concentration *in vitro* should be attainable clinically, inexpensively, and without undue toxicity.

8. Conclusion

Ivermectin has been administered to millions of patients as an anti-parasitic drug exhibiting a wide margin of clinical safety. There exists a large body of *in vitro*

and *in vivo* evidence demonstrating ivermectin's anti-tumor potential, and ivermectin's anti-tumor efficacy can be demonstrated at concentrations that are clinically attainable based on clinical pharmacokinetics. We thus propose that ivermectin be considered urgently for clinical trials either as a single agent or in combination with existing antineoplastics for cancer.

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