Repurposed drugs

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Ivermectin, a Molecular Swiss Army Knife: A Review of Mechanisms, Indications and Safety Concerns in Drug Repurposing

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Abstract

Ivermectin, originally developed for the treatment of parasitic diseases such as onchocerciasis (river blindness), has earned its title of "wonder drug" due to its broad-spectrum therapeutic activity. Ivermectin's potential to address unmet global health challenges makes it an important focus for future medical research. This review explores ivermectin's mechanisms of action and its expanding therapeutic applications, including in parasitic, bacterial and viral infections, and cancer among other disorders. It demonstrates a robust safety profile, and wide scale studies have found a low rate of adverse events. This review highlights the ongoing research and emphasizes the need for careful consideration of both the benefits and risks of ivermectin. Further studies are required to support its repurposing for new indications.

Introduction

The discovery of ivermectin was serendipitous and fortuitous, it is a story in which the discovery could have easily been missed, and billions of people deprived of its benefits. Ivermectin's illustrious story begins in 1972, when Dr. Satoshi Ōmura launched a research project to bioprospect for antibiotics from organisms in natural environments (**Figure 1**). (1) Ōmura of the Kitasato Institute in Japan formed a collaboration the next year with the laboratories of Merck, Sharpe and Dohme (MSD) in the United States, led by Dr. William Campbell.

Between 1973 and 1974, Ōmura collected soil samples to screen for the biological activity of compounds. One of these samples, collected at a golf course in Kawana, about 80 miles outside Tokyo, was sent to the MSD laboratories for testing as an antihelminthic agent. (2) Sample number MA-4680 showed potent anthelmintic activity across a broad range of concentrations, with crude extracts potently inhibiting roundworms at concentrations as low as 0.0003%. (3) The compound appeared safe, as the toxicity observed in the *in vivo* tests was attributable to a microbial metabolite, which could be removed in subsequent isolation. (3) The anthelminthic compound was named avermectin, and the bacterial species which produced it was named *Streptomyces avermitilis.* The discovery of *Streptomyces avermitilis by* Ōmura was extremely fortunate, it wasn't until 1992 that another isolate of the same species was found in a field sample in Italy. (4) Since then, the bacterium has been discovered only a handful more times from soil samples, underscoring its rarity. (5,6)

Ivermectin (IVM) has been widely used throughout

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Africa and South America to treat its primary indication of river blindness, a disease caused by infection with helminth worms. Its efficacy for river blindness was established with clinical trials in the 1980's. (7)

Since ivermectin's discovery in 1975, it has saved hundreds of thousands of lives. It is estimated to have saved at least 19.1 million Disability Adjusted Life Years (DALYs) between 1995 and 2010 alone through the African Program for Onchocerciasis Control, with an additional 500 000 DALYs saved from non-target diseases. (8) Ivermectin is widely used, with 1.3 billion doses being distributed between 1987 and 2013. (9,10) The broad applications of ivermectin culminated in Satoshi Ōmura being awarded the Nobel Prize in Physiology or Medicine in 2015 for his contributions to its discovery. (11)

Ivermectin's potential was explored beyond its antiparasitic properties. In 2004, studies showed its antitumor effects, (12) and in 2011, it was found to effectively treat allergic asthma symptoms in mice. (13) Ivermectin was repurposed to treat Covid-19 during the recent pandemic. (14,15)

Ivermectin's shows a very broad therapeutic spectrum across parasites, (11) bacteria, (16) viruses, (17) cancer, (18) and other indications. (13,19,20) This review explores the indications and mechanisms by which ivermectin has a therapeutic effect, both as an established therapeutic and an agent with therapeutic potential. This review aims to present a balance view for the therapeutic potential of ivermectin and a guide to potential health hazards.

Antiparasitic and antibacterial use

Mechanism

Ivermectin's antiparasitic action is typically attributable to its effect on glutamate channels, which causes a rapid polarization in neurons, leading to death of parasitic organisms. (21) Fortunately, human receptors have very low affinity for IVM and so any neurotoxicity is highly selective against non-mammalian glutamate receptors. This is the main mechanism of antiparasitic activity of ivermectin. (10,21,22) **Figure 2** (reproduced from [23] under a Creative Commons Attribution Non-Commercial license) shows the IVM binding site and its structural determinants in GluCl and GlyR.

Indications

Ivermectin is broadly useful as an antiparasitic and against bacterial infections. (3)

Onchocerciasis (river blindness)

Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus*, which affects approximately 37 million people, (24,25) with 100 million at risk of infection. (24,25) It can cause visual impairment and blindness, with 500,000 people suffering significant vision loss and 270,000 becoming blind. (26) Ivermectin is the standard treatment for this condition, (27) reducing parasite loads and preventing new infections. The drug works by activating mast cells, which play a role in the host's immune response. (28)

Myiasis

Myiasis, caused by botflies from the *Oestridae* and *Callihoridae* families, is rare in humans but more common in livestock and wild animals. (29) Ivermectin is considered a standard treatment alongside albendazole and clindamycin. (30) The drug works through the Glutamate-gated Chloride Channels (GGCC) mechanism, (31) with studies showing its effectiveness in controlling *Haemonchus contortus* infections. (32)

Trichinosis

Trichinosis, caused by *Trichinella spp.*, affects approximately 11 million people globally. (10) Ivermectin serves as a first-line treatment, (33) with its antiparasitic action linked to GGCC activation. (34) In addition to reducing parasitic activity, ivermectin has the potential to decrease NF-κB, tissue Nitric Oxide (NO), and myogenin expression, (35) enhancing its therapeutic benefits.

Trichuriasis (whipworm infection)

Trichuris trichiura, the whipworm responsible for trichuriasis, infects an estimated 429 to 508 million individuals globally. (36) Clinical data supports the efficacy of ivermectin, (37) with the likely mechanism involving GGCC, which disrupts the neural function of the parasites.

Malaria

Malaria, caused by *Plasmodium spp.* and transmitted by *Anopheles* mosquitoes, affects 249 million people globally, with 608,000 deaths in 2022. (38) Ivermectin has shown promise in reducing malaria transmission by killing the mosquito host, (39) reducing transmission by 35%. (40) Its mechanisms include the activation of GGCC in mosquitoes and inhibition of Importin alpha (IMPα) in *Plasmodium*. (14-17)

Toxoplasmosis

Toxoplasmosis, a parasitic disease caused by *Toxoplasma gondii*, affects approximately 25.7% of the global population. (45) Though ivermectin's use in treating toxoplasmosis is still in the preclinical

phase, (46-48) studies suggest that it inhibits IMPα in *Toxoplasma gondii* (44) and increases local expression of GABA, (47) contributing to its antiparasitic effects.

Neurocysticercosis
Taenia solium causes neurocysticercosis, affecting populations in Latin America, Asia, and Sub-Saharan Africa. (49) Case reports (50) and preclinical data suggest that ivermectin, (51,52) possibly through GGCC activation, may be effective in managing this condition when used in combination with other treatments like albendazole.

Leishmaniasis
Leishmaniasis, caused by *Leishmania spp.*, results in approximately 0.9 to 1.6 million cases annually. (53) Preclinical studies indicate that ivermectin may act by inducing oxidative stress, (54,55) leading to plasma membrane rigidity and mitochondrial alterations in the parasite, (56,57) offering potential as a therapeutic agent. (58)

African trypanosomiasis (sleeping sickness)
African trypanosomiasis, caused by *Trypanosoma brucei* and transmitted by the *tsetse fly*, claims around 100,000 lives annually. (32,33) Although no human trials have been conducted, (60) preclinical evidence (61) suggests that ivermectin may enhance host defense by improving packed cell volume (62,63) and anemia while also controlling the *tsetse fly* vector. (38,39)

American trypanosomiasis (Chagas disease)
Chagas disease, also caused by *Trypanosoma brucei*, affects 5-18 million people and causes over 10,000 deaths annually. (66) Preclinical data supports (67) ivermectin's potential in targeting the importin alpha/beta pathway in *Trypanosoma* species, though no human trials have yet been conducted. (62,63)

Schistosomiasis
Schistosomiasis, caused by *Schistosoma spp.*, affects more than 200 million people worldwide. (10) Preclinical studies suggest (68) that ivermectin may activate GGCC channels, though results remain conflicting, (69) and no human trials have confirmed its efficacy for this indication. (68,70,71)

Bedbugs
Bedbug infestations, caused by *Cimex lectularius*, affect an estimated 78% of the global population. (72) Ivermectin has demonstrated efficacy against bedbugs, (73) potentially by targeting GGCC channels, contributing to their morbidity and mortality.

Epilepsy (nodding syndrome)
Nodding syndrome, associated with *Onchocerca volvulus* infection, affects fewer than 10,000 people globally. (74) The distribution of ivermectin has been linked to a reduction in incidence, (75,76) and ongoing trials suggest its potential to modulate neuroinflammation and other pathways involved in epilepsy. (77)
Ivermectin is believed to work by modulating glutamate-gated chloride channels (GGCC) and potentially interacting with neuroinflammatory, opioidergic pathways, (19,78,79) and potassium channels. However, a completed trial for treating this syndrome with ivermectin has not yet shown conclusive results. (78)

Tuberculosis
Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, affects 10 million people annually, with 1.4 million deaths reported in 2019. (80) Ivermectin has shown preclinical promise against TB, (16,81) particularly as an inhibitor of the DprE1 enzyme, (82) which is critical for the bacterial cell wall synthesis. While ivermectin is not a standard treatment for TB, ongoing research suggests potential benefits in combination with traditional therapies. (82)

Buruli ulcer
Buruli ulcer is a necrotizing skin disease caused by *Mycobacterium ulcerans* and affects approximately 4,000 people each year, particularly in tropical regions. (83) While there is preclinical evidence supporting the effectiveness of ivermectin in managing this condition, (84) its exact mechanism of action remains unknown. Ivermectin's role in treating Buruli ulcer may expand as more studies are conducted.

Strongyloidiasis
Strongyloidiasis is an intestinal parasitic infection caused by *Strongyloides stercoralis*, affecting 30 to 100 million people annually. (85) Ivermectin is commonly used as a treatment, with several case studies demonstrating its effectiveness. (86-89) The drug works by disrupting parasitic neurological function, leading to their paralysis and death.

Demodecidosis
Demodecidosis, caused by the mites *Demodex folliculorum* and *Demodex brevis*, can lead to skin irritation and inflammation. These mites are found in about 18% of adults. (90) Ivermectin has been used to treat demodecidosis, with case reports showing

that it can reduce mite populations and alleviate symptoms, such as itching and redness. (91)

Loiasis
Loiasis, caused by *Loa Loa*, is a parasitic infection that affects about 3.7 million people. (92) In regions where ivermectin has been administered for other conditions, the prevalence of Loiasis has significantly decreased. Ivermectin's ability to target and kill the *Loa Loa* microfilariae contributes to its effectiveness. (93)

Scabies
Scabies is caused by *Sarcoptes scabiei* mites, leading to intense itching, rash, and skin irritation. It affects over 204 million people globally. (94) Ivermectin is considered a standard treatment for scabies and works by paralyzing the mites, (95) leading to their death.

Pediculosis (head lice)
Pediculosis, or head lice infestation, primarily affects children, with around 19% of school-aged children experiencing infestations. (96) Ivermectin has been shown to be highly effective in clinical trials, (97) killing lice through neural disruption that leads to paralysis and death.

Lymphatic filariasis
Lymphatic filariasis, caused by *Wuchereria bancrofti* and transmitted by *Culex* mosquitoes, affects about 120 million people globally, with 76 million suffering from severe lymphatic and renal damage. (98) Ivermectin, often used in mass drug administration programs, has been shown to reduce the incidence of infection and halt disease progression through its action on parasitic microfilariae. (99)

Impetigo
Impetigo, a bacterial skin infection primarily caused by *Staphylococcus aureus*, (100) affects around 162 million children worldwide. (101) Ivermectin has shown efficacy in treating impetigo, with clinical data supporting its use, especially in areas where co-infection with parasitic diseases is common. (102) **Table 1** shows the worldwide burden of parasitic diseases, mechanisms of ivermectin, and status of repurposing research for antiparasitic indications.

Viral diseases
Mechanisms
Ivermectin is effective against a wide variety of viruses. (17,104-106) One property of ivermectin is that the mechanism which act against viruses are somewhat delineable from those that act against parasites. While ivermectin's primary mode of action against parasites is that of GGCC channel activation, the most common mode of action of ivermectin against viruses is by inhibition of nuclear import. (63,107)
Nuclear import is a biological process that is hijacked during viral infection and viral takeover of this process is often crucial for successful infection. (63,108-110) Viral hijacking of the nuclear transport process impacts the host innate immune response, and can be crucial for evasion during infection. (108) Regulation of host nuclear transport is common to many viruses, including most DNA viruses, which typically replicate in the nucleus of the infected cell, and require nuclear transport for entry, as well as some RNA viruses, a minority of which replicate in the host cell nucleus, and a greater proportion who replicate in the cytoplasm, yet rely on nuclear transport at some stage of infection. (109) This mechanism is common to many viruses, and is also considered as a potential anti-cancer target. (111) **Figure 3** (reproduced from [112] under a Creative Commons Attribution 4.0 International [CC BY 4.0] license) shows the inhibition of nuclear import by ivermectin.

Indications
HIV (human immunodeficiency virus)
HIV is a retrovirus that affects approximately 1.99 million people worldwide, (113) with 864,000 deaths annually. (113) The virus integrates its genome into the host's DNA in the nucleus, leading to a chronic infection that weakens the immune system over time, causing AIDS if untreated. Symptoms include fever, fatigue, and swollen lymph nodes in the early stages, progressing to life-threatening infections and cancers. Preclinical studies suggest that ivermectin inhibits importin α/β-mediated nuclear import, (114) a crucial process for HIV-1 replication. This mechanism offers potential for repurposing ivermectin in HIV treatment, although more clinical data is needed. (44,115)

Influenza virus
Influenza is a widespread virus, with about 1 billion infections and 389,000 deaths reported annually (from 2002 to 2011). (5,6) Influenza attacks the respiratory system, causing fever, cough, body aches, and, in severe cases, pneumonia or death, particularly in vulnerable populations. (118) The virus replicates in the nucleus, with viral RNA entering and exiting the nucleus. (5,6) Preclinical evidence shows that ivermectin affects the NS1 protein, (116) a key viral component involved in immune evasion and replication, (8,9) though clinical efficacy is yet

to be established.

Dengue virus

Dengue affects 59.22 million people globally and is transmitted by mosquitoes. (121) It causes flu-like symptoms such as high fever, severe headache, pain behind the eyes, and, in severe cases, hemorrhagic fever or shock. (122,123) If untreated, severe dengue can be fatal. Preclinical data show that ivermectin inhibits importin α/β-mediated nuclear import in dengue virus replication, (2,3,13-15) and while clinical efficacy is limited, one study demonstrated that ivermectin shortened the clearance time of NS1 antigenemia. (127,128) Ongoing trials aim to determine its full potential. (18,19)

Zika virus

Zika virus, primarily transmitted by mosquitoes, caused 169,734 cases in 2021. It typically causes mild symptoms, including fever, rash, and conjunctivitis, but is of significant concern due to its link to birth defects such as microcephaly. Preclinical data suggest that ivermectin blocks nuclear import via importin α/β inhibition, (131-134) affecting the viral NS5 protein, (135) although conflicting results have been reported. (25,26) Further research is needed to clarify its potential in Zika treatment.

Chikungunya virus

Chikungunya, a mosquito-borne virus, caused 271,824 cases in Brazil alone in 2016. (28) It results in fever and severe joint pain, which can persist for months. If untreated, chronic arthritis-like symptoms may develop. Preclinical studies have shown that ivermectin reduces RNA production and viral protein expression, (134,140,141) and while trials have been completed, no results are currently available. (142)The mechanism involves inhibition of capsid protein interactions. (27,32)

Hepatitis B virus (HBV)

Hepatitis B affects 356 million people globally, causing liver infection, (94) which can lead to cirrhosis, liver failure, or liver cancer if untreated. The virus enters the nucleus to replicate. Preclinical data demonstrate that ivermectin decreases the expression of HBV core protein and the nuclear transporter karyopherin α2 (KPNA2), (144) suggesting a potential role in treatment. However, clinical evidence is still lacking.

Hepatitis E virus (HEV)

Hepatitis E causes 20 million infections and 3 million symptomatic cases globally each year. (145) It typically results in acute liver disease with symptoms such as jaundice, fatigue, and abdominal pain. Untreated cases can lead to liver failure, especially in pregnant women. Preclinical evidence suggests that ivermectin may inhibit HEV replication through importin α1, (146) although further research is needed to confirm this.

Herpes simplex virus (HSV-2)

Herpes simplex virus type 2 (HSV-2) affects 491.5 million people worldwide, (147) causing painful genital sores. The virus enters the nucleus for replication and establishes lifelong latency. If untreated, HSV-2 can lead to recurrent outbreaks and complications such as neonatal herpes. Ivermectin has shown preclinical efficacy in inhibiting importin α/β-mediated nuclear import, though more clinical data are required. (134)

COVID-19 (SARS-CoV-2)

COVID-19 has affected over 700 million people, (148,149) causing 7 million deaths between 2020 and 2024. (150) Symptoms range from mild respiratory illness to severe pneumonia and death. Ivermectin has been deployed in treatment, with preclinical and clinical studies showing efficacy. (14) Mechanistically, it is suggested that it disrupts the importin heterodimer complex (IMPα/β1), (14,15,151) downregulates STAT3, (44,45) and affects viral proteins such as the spike protein (153) and 3CL protease. (112,154,155)

Venezuelan equine encephalitis virus (VEEV)

VEEV occasionally causes outbreaks in Latin America, with a notable outbreak of 75,000 to 100,000 cases in Colombia in 1995. (56-59) The virus causes flu-like symptoms and can progress to encephalitis, which can be fatal if untreated. Preclinical data indicate that ivermectin inhibits importin α/β-mediated nuclear import, (56,57,60) a key step in VEEV replication. (158,159)

West Nile virus (WNV)

WNV, a mosquito-borne virus, caused 1,267 cases and 119 deaths in the U.S. in 2013. (160) It can cause flu-like symptoms, but severe cases can lead to encephalitis or meningitis. Preclinical studies suggest that ivermectin inhibits viral replication by targeting the NS5 and NS3 proteins. (62,63,65,66) However, its efficacy in humans remains to be demonstrated. (162)

Semliki forest virus (SFV)

SFV is an alphavirus that primarily affects humans in Africa, with outbreaks being rare but infection potentially common, as indicated by seroprevalence

studies. (163) Symptomatically, SFV often presents with fever, headache, muscle pain, and sometimes neurological symptoms such as encephalitis. If untreated, severe cases can progress to chronic neurological damage, though fatalities are rare. Preclinical studies have shown a slight effect of ivermectin on the virus in cell lines, (143) but the exact mechanism remains unclear. Possibly, the mechanism is due to disruption of the nuclear imported protein nsp2. (164)

Yellow fever virus

Yellow Fever is a serious viral disease transmitted by mosquitoes, primarily in Africa and South America. In 2021, there were 86,509 reported cases. (121) Symptoms include fever, chills, severe headache, back pain, nausea, and vomiting. In more severe cases, patients may develop jaundice, bleeding, and multi-organ failure, which can lead to death if untreated. Preclinical data using cell lines have explored ivermectin's effects on the virus, (143) though the precise mechanisms remain unknown, (165) and clinical efficacy is yet to be demonstrated.

Sindbis virus

Sindbis virus is a mosquito-borne virus with outbreaks primarily in Finland, where the incidence rate is estimated at 7 to 9 per 100,000 people. (166) The virus causes fever, rash, and arthritis, with symptoms usually subsiding after several weeks. However, arthritis can become chronic if untreated. Preclinical studies have shown only slight effects of ivermectin on the virus in cell lines, (143) with no clear mechanism identified for its action.

Adenovirus

Adenoviruses are common globally, affecting 47% of the U.S. (167) population at some point. They can cause a wide range of illnesses, including respiratory infections, gastroenteritis, conjunctivitis, and even severe pneumonia in immunocompromised individuals. If untreated, adenovirus infections can lead to severe complications such as bronchitis and pneumonia, especially in children and those with weakened immune systems. Preclinical studies have demonstrated that ivermectin inhibits nuclear import, (168) which is crucial for adenovirus replication, but further research is needed to establish clinical efficacy. (72,74) **Table 2** contains an overview of viruses affecting human health, ivermectin's mechanisms of inhibition, and current repurposing status for antiviral use.

Cancer

Ivermectin’s antitumor properties were first elucidated in 2004. (12) Since then, research has discovered ivermectin’s multiple different anticancer mechanisms. (181-184) Clinical evidence is still limited, but the repurposing of ivermectin as an anticancer drug is highly promising and early clinical data shows benefit. (182) **Table 3**, which is adapted from (184) with additional mechanisms added (18), shows the antitumour mechanisms of ivermectin.
Two clinical trials using ivermectin for cancer treatment are posted on clinical trials.gov. (201,202) Currently, the evidence for ivermectin’s efficacy in cancer is mostly limited to preclinical data.

Other indications

Mechanisms

Ivermectin has action as an anti-inflammatory, which is useful for several other conditions. It also interacts with several human receptors, which may be useful for treatment. (23)

Indications

Alcohol use disorder

Ivermectin has shown potential therapeutic benefits across a range of conditions. Alcohol use disorder effects 12.7% of adults in the USA in 2013, (203) and 5.1% of the global population. (204) Preclinical data in mice suggests that ivermectin can antagonize ethanol’s inhibition on purinergic P2X4 receptors, providing a possible mechanism for its use. This supports the positive results shown in a pilot study of alcohol use disorder in adults.

Amyotrophic lateral sclerosis (ALS)

For Amyotrophic Lateral Sclerosis (ALS), which has a global prevalence of 4.42 per 1 million people, preclinical studies suggest ivermectin may inhibit AMPA-mediated toxicity through its antagonistic effects on P2 receptors, presenting a possible therapeutic role.

Asthma

Asthma, affecting 4.3% of the global adult population, also shows potential for ivermectin as an anti-inflammatory treatment. Though evidence is currently limited to preclinical data and case reports, these findings point to further avenues for research.

Rosacea

In rosacea, an inflammatory skin condition which impacts 5.5% of the global adult population, ivermectin’s efficacy has been established through multiple clinical trials. Its anti-inflammatory effects include inhibiting IL-8, IL-6, and MCP-1 secretion, as well as inhibiting KLK5 and CAMP, making it a promising treatment option.

Atopic dermatitis

Another skin condition, atopic dermatitis, with a global prevalence of 2,690 per 100,000 persons (or 221 million people), has also shown a potential response to ivermectin in preclinical studies due to its anti-inflammatory properties.

Post COVID -19 vaccination syndrome

For COVID-19 post-vaccination syndrome, which affects up to 3% of vaccine recipients, ivermectin has been used by 18% of patients. Its mechanisms include binding to the spike protein, anti-inflammatory effects, and modulation of α7nAChR and GABA pathways, indicating potential utility in managing these post-vaccine symptoms.

Table 4 contains an overview of other indications for which ivermectin demonstrates repurposing potential.

Drug safety

As with any pharmaceutical, the risk of adverse events is inherent in ivermectin treatment, and these risks must be weighed against the potential benefits of the drug. While it is crucial to limit adverse effects, delaying treatment can result in greater harm, particularly in regions where parasitic diseases are endemic. Pharmacovigilance plays a critical role in ensuring ongoing drug safety and addressing post-marketing concerns. (231) Several drugs have been approved and later recalled due to unforeseen safety issues, which underscores the importance of continuous monitoring and improving treatment protocols to reduce the risk of adverse events.

Ivermectin's use is concentrated primarily in developing nations where parasitic infections remain endemic, while its use in the developed world remains relatively uncommon. In 2022, ivermectin was only the 314th most prescribed medication in the United States, despite its use for acute Covid-19. (232) Worldwide, hundreds of millions of people have received ivermectin. (233) Over the past three decades, a substantial body of clinical reports and review articles has documented adverse events occurring during clinical trials or following ivermectin prescriptions. (234)

Commonly reported side effects include headache, muscle pain, cough, nausea, vomiting, diarrhea, blurred vision, dyspnea, postural hypotension, and disorientation. Additionally, anecdotal symptoms such as significant skin reactions and edematous swelling have been observed in clinical trials and observational studies. (235) Non-neurological adverse effects related to ivermectin use, including nephropathy, (236) cutaneous reactions, (237) mental disorder, (238) hepatic diseases, (239) and multiorgan dysfunction syndrome, (240) have also been reported.

Despite these side effects, ivermectin has a well-established safety profile, with serious adverse effects being rare, especially considering it has been administered over a billion times globally. (9,10) During treatment for *Strongyloides stercoralis* infection, 13% of patients reported fatigue, 9% experienced headaches, 10% noted dizziness and drowsiness, 12% reported itching, and 9% experienced lightheadedness. (241,242) In another study, dysmenorrhea was reported by 6% of patients, throat pain by 2%, and diarrhea by 2%. (243)

The highest doses studied in human volunteers have been up to ten times the maximum FDA-approved dose of 200 μg/kg, with limited adverse effects. (22) In animal models, the LD50 in mice exceeds 27 mg/kg. (244). Ivermectin's half-life ranges from 12 to 36 hours in human blood. (245)

Reproductive adverse effects

Reproductive adverse effects from high doses of ivermectin have been observed in animal (246-253) and insect models, (254,255) motivating the study of adverse reproductive effects in humans. Larger animals, show conflicting results, with some studies showing no adverse reproductive effects of ivermectin, (256,257) while others show negative impacts. (258) Ivermectin is classified by the US FDA as pregnancy category C, meaning "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks". (259) The World Health Organization African Programme for Onchoceriasis Control also advises pregnant women to withhold IVM treatment until one week after childbirth, but notes that "pregnancy is not considered a specific contraindication". (260) Currently, there are few large scale trials in humans, though the present meta-analyses in humans show no ill effects. (261,262)

One meta-analysis involving 893 mothers during pregnancy found no neonatal deaths, preterm births, or low birthweight. (261) Another study on ivermectin taken during pregnancy for the treatment of onchoceriasis, shows that at least in the circumstance of acuteonchoceriasis, the benefits of IVM treatment outweigh potential risks. (262) However, the data which exist are inadequate to declare IVM safe in pregnancy, given the teratogenicity shown in rabbit models at repeated doses as low as 0.2 times the maximum human recommended dose per bodyweight. (259,263) A pharmacovigilance study of

667 ivermectin related adverse drug reactions found 9 reports of pregnancy related complications and 9 reproductive related complications. (264) Given that the drug has been given an estimated 1.3 billion times by 2013, (9,10) this is a low rate of reproductive adverse events.

Neurological adverse events

Serious neurological adverse events associated with ivermectin are rare, (265) but there is potential danger for individuals with polymorphisms in the ABCB1 gene, which encodes the P-glycoprotein transporter. (266,267) These gene variants can compromise the blood brain barrier, which is typically impermeable to ivermectin. (265) A plurality of serious neurological adverse events reported with ivermectin occur during treatment for onchocerciasis. (265)

In rare cases, poisoning from high doses of veterinary formulations has resulted in symptoms such as rash, edema, headache, dizziness, nausea, vomiting, diarrhea, and asthenia. (242,268) More severe symptoms such as seizures, dyspnea, paresthesia, urticaria, abdominal pain, and contact dermatitis have also been documented. Additionally, treatment for *Onchocerca volvulus* infections has been associated with neurological effects in humans, including encephalopathy, disorientation, stupor, and coma, particularly in reports from African nations. (269) In human clinical trials, neurological effects such as headaches (0.2%) during treatment for onchocerciasis and dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), and tremor (0.9%) during strongyloidiasis treatment were observed. (270,271)

Ivermectin's potential to cause serious neurological effects may be exacerbated in cases of infection with *Loa loa*. While the mechanism is poorly understood, density of *Loa loa* microfilarial density is correlated with adverse event severity after IVM treatment. (265,272) Vulnerability in *Loa loa* infection may be related to P-glycoprotein polymorphisms with reduced mdr-1 expression. (267)

Environmental impacts of ivermectin

Ivermectin is widely used globally as an antiparasitic drug in pets and livestock, and its environmental impacts are a growing concern due to the large-scale veterinary applications. (273) Widespread use of ivermectin presents potential risks to ecosystems on land and in water. Ivermectin exhibits high toxicity to crustaceans, both acutely and chronically, while in fish, it induces lethargy, darkened skin, and reduced feeding activity. (274)

Drug resistance from ivermectin

Ivermectin was the first broad-spectrum endectocide of the avermectin/milbemycin class, widely used in parasitic disease management. (275) However, drug resistance is a growing concern, especially in parasitic nematodes. For example, resistance to ivermectin in the sheep nematode *Haemonchus contortus* has been linked to P-glycoprotein expression. Studies have shown that the efficacy of ivermectin and related drugs like moxidectin can be enhanced in *H. contortus* strains when coadministered with verapamil, a multidrug resistance-reversing agent. (276) These findings suggest that P-glycoproteins may play a crucial role in resistance to ivermectin and other macrocyclic lactones, posing challenges for the long-term management of parasitic diseases.

Conclusion

In conclusion, ivermectin stands as a versatile therapeutic agent with an impressive history of treating parasitic diseases such as onchocerciasis and its potential applications beyond its traditional scope. From viral infections to cancer and neurological disorders, the drug's wide-ranging mechanisms of action provide hope for various medical challenges. However, despite its vast benefits, there remain significant concerns, particularly regarding its safety in individuals with ABCB1 polymorphisms (266,267) and its environmental impact. Additionally, while clinical trials and preclinical data continue to support its repurposing, careful consideration of its side effects, resistance development, and specific populations at risk is essential for ensuring the safe and effective use of ivermectin in future applications. The ongoing monitoring and study of ivermectin's capabilities are crucial as it continues to influence global health.

Further research will expand ivermectin's repertoire of repurposed conditions, as well as improve treatment standards by finding synergistic interventions to improve treatment efficacy for a wide variety of conditions. Depending on the choice of milestone, the 50th anniversary of ivermectin is approaching, and given its demonstrable record of success, we believe this is only the beginning of this versatile drug.

Table 1. Worldwide burden of parasitic diseases, mechanisms of ivermectin, and status of repurposing research for antiparasitic indications

Indication	Organism	Number affected worldwide	State of repurposing evidence	Mechanisms	Interaction model
Myiasis	Botflies of family Oestridae and Callihoridae	Rare in humans (29), more common in livestock and wild animals	IVM considered standard treatment alongside albendazole and clindamycin(30)	GGCC (31)	Mechanism shown in H. contortus (32)
Trichinosis	*Trichinella* spp.	Approximately 11 million (10)	First line treatment (33)	GGCC (34) Potential: Decrease NK-κB, tissue NO, and myogenin expression (35)	
Trichuriasis (whipworm infection)	Trichuris trichiura	429 to 508 million infections (36)	Clinical data (37)	Likely GGCC	
Malaria	*Plasmodium* spp. Host: Anopheles mosquitos	249 million people affected and 608 000 deaths in 2022 (38)	Reduces transmission of malaria by 35% through killing host mosquitos (39) Reduces malaria (40)	Potential: GGCC in host Anopheles (41-43) IMPα in Plasmodium (44)	GGCC (42) IMPα (44)
Toxoplasmosis	Toxoplasma gondii	25.7% of the global population has an infection (45)	Preclinical data (46-48)	IMPα in Toxoplasma gondii (44) increase the level of GABA local expression (47)	
Neurocysticercosis	Taenia solium	Latin America: 4% to 24% Asia: 2% to 13% Sub-Saharan Africa: 6% to 22% (49)	Case reports (50) Preclinical data (51,52)	Possibly GGCC	
Leishmaniasis	*Leishmania* spp.	0.9 to 1.6 million cases per year (2012) (53)	Preclinical data (54,55)	Potential: Oxidative stress → plasma membrane rigidity (56,57) Alterations in parasite mitochondria (58)	
African trypanosomiasis (Sleeping sickness)	Trypanosoma brucei Host: *Glossina tachinoides*	100 000 deaths per year (2002) (59). World Health Organization claims 70 million people at risk (103)	No human trials as of February 2023 (60) Preclinical data (61)	Potential: IMPα/β1 (62,63) Possible improvement of host defense capacity through improvement in packed cell volume and state of anemia. (64) Vector control of Tsetse fly (65)	

American trypanosomiasis (Chagas disease)	Trypanosoma brucei	5-18 million current infections, more than 10 000 deaths annually (66)	Preclinical data (67) No human trials as of August 22, 2024.	Potential: IMPα/β1 (62,63)	
Schistosomiasis	*Schistosoma* spp.	Over 200 million (10)	Preclinical data (68) Conflicting results (69) No human trials as of August 22, 2024	Potential: GGCC (68,70)	(71)
Bedbugs	Cimex lectularius	78% of global population, or approximately 6.4 billion people (72)*	Efficacy against bedbugs demonstrated (73)	Possibly GGCC	
Epilepsy (Nodding Syndrome)	Onchocerca volvulus (associated with Nodding Syndrome)	<10 000 cases <1000 deaths (2013) (74)	Distribution of IVM associated with drop in Nodding Syndrome incidence (75,76) Completed trial without results (77)	GGCC (19,78,79) Potential: modulation of neuroinflammation, opioidergic pathways and potassium channels interaction with nitrergic system (78)	
Tuberculosis	Mycobacterium tuberculosis	10 million cases 1.4 million deaths (2019) (80)	Preclinical data (16,81)	Inhibitor of DprE1 enzyme (82)	(82)
Buruli ulcer	Mycobacterium ulcerans	~4000 cases reported per year (2015) (83)	Preclinical data (84)	Unknown	
Strongyloidiasis	Strongyloides *stercoralis*	30-100 million people yearly (85)	Case studies (86-89)	Unknown	
Demodecidosis	Demodex folliculorum and Demodex brevis	Mites found in 18% of adults in Hungarian survey (2011) (90)	Case reports (91)	Likely GGCC	
Onchocerciasis (river blindness)	Onchocerca volvulus	37 million with active disease (24,25) 100 million at risk of new infection (24,25) 500,000 individuals with significant visual impairment (26) 270,000 blind (26)	Standard treatment (27)	Mast cell activation (28)	
Loaisis	Loa loa	3.7 million people (1995) (92)	Decreased prevalence in IVM treated communities (93)	Likely GGCC	

Scabies	Sarcoptes scabiei	204 151 700 (2015) (94)	Considered a standard treatment (95)	Likely GGCC	
Pediculosis (head lice)	Pediculus humanus capitis	19% of school aged children (96)	Efficacy shown in clinical trial (97)	Likely GGCC	
Lymphatic filariasis	Wuchereria bancrofti Vector: Culex quinquefasciatus	120 million infected 76 million with damaged lymphatic and renal systems (98)	Clinical data (99)	Likely GGCC	
Impetigo	Staphylococcus aureus (100)	162 million children (101)	Clinical data (102)	Likely GGCC	

Legend: GGCC=glutamate-gated chloride channel; IMPα=importin alpha.
*Based on a weighted average (by population) of the survey results for bedbug incidence in different continents. 95% of respondents in USA, 98% of respondents in Canada, 92% of respondents in Europe, 90% of respondents in Africa and the Middle East, 73% of respondents in Asia, and 59% of respondents in Latin America. (72)

Table 2. Overview of viruses affecting human health, ivermectin's mechanisms of inhibition, and current repurposing status for antiviral use

Virus and genome type	Replication site	Viral elements transported across nuclear membrane or interacting with nuclear transport machinery	Number affected worldwide	State of repurposing evidence	Mechanism	Interaction model
HIV (ssRNA (+), retrovirus)	Cytoplasm & nucleus	Viral genome enters nucleus for integration	1 989 000 world-wide (113) 864 000 deaths (113)	Preclinical data (114)	Inhibits importin α/β-mediated nuclear import in HIV-1 replication (44,115)	
Influenza virus (ssRNA (-), segmented)	Nucleus	Viral RNA enters nucleus, mRNA exits Ribonucleoprotine particles and NS1 protein (116)	1 billion cases (2019) (117) 389 000 deaths per year (period 2002-2011) (118)	Preclinical data (119)	NS1 protein (120)	(120)
Dengue virus (ssRNA (+))	Cytoplasm	NS5 (122,123)	59 220 428 (2021) (121)	Preclinical data (114,124-126) Clinical efficacy not observed, but IVM shortened clearance time of NS1 antigenemia (127,128) Completed trial, results not available (129) Trial (status unknown) (130)	Inhibits importin α/β-mediated nuclear import in dengue replication (115)	
Zika Virus (ssRNA (+))	Cytoplasm	NS5 (135)	169 734 cases (2021)	Preclinical data (131-134) Conflicting results (136)	Blocking nuclear import by importin α/β inhibition (137)	
Chikungunya virus (ssRNA (+))	Cytoplasm	Capsid protein (138)	271 824 (2016 in Brazil alone) (139)	Preclinical data (134,140,141) Completed trial (no results available) (142)	Decreased RNA production and protein expression (143)	

Hepatitis B virus (dsDNA, partially double-stranded)	Nucleus & cytoplasm	Viral genome enters nucleus	356 083 400 (94)	Preclinical data (144)	Decreased the expression of HBV core protein and the nuclear transporter karyopherin α2 (KPNA2) in the nuclei of HepG2-hNTCP-C4 cells (144)	
Hepatitis E virus (ssRNA (+))	Cytoplasm	Unknown	20 million infections 3 million symptomatic cases (2023) (145)	Preclinical data (146)	Likely importin α1 (146)	
Herpes simplex virus (Type 2) (dsDNA)	Nucleus	Viral genome enters nucleus	491.5 million people infected (2016) (147)	Preclinical cell data (134)	Unknown. Proposed inhibition of importin α/β (134)	
COVID-19 (SARS-CoV-2) (ssRNA (+))	Cytoplasm	ORF6 disrupts nuclear import (148,149)	700 million cases 7 million deaths (2020 through 2024) (150)	Preclinical and clinical data (14,15,151) Veterinary data in murine coronavirus (152)	Nsp13 helicase (170) Disrupting the Importin heterodimer complex (IMPα/β1) (112,154,155) Downregulating STAT3 3CL Protease Spike protein (153) CD147 (153) α7nAChr (153)	Spike protein (153) CD147 (153) α7nAChr (153) IMPα (171-173) ACE2 (human) $3CL^{pro}$ PL^{pro} SARS unique domain (SUD) (174,175) NF-κB, MAPK10, and MAPK14 (human) (176)
Venezuelan equine encephalitis virus (ssRNA (+))	Cytoplasm	Capsid protein interacts with nuclear transport (156,157)	Occasional outbreaks in Latin America. Outbreak of 75 000 to 100 000 cases in humans in Colombia in 1995 (177,178)	Preclinical cell line data (158)	Inhibitor of importin α/β-mediated import (158,159)	
West Nile virus (WNV) (ssRNA (+))	Cytoplasm	NS5 (179,180)	1267 Cases 119 deaths (2013, USA only) (160)	Preclinical cell line data (63,161)	Inhibitor of importin α/β-mediated import (63) NS3 helicase (161) Host control (162)	(161)

Semliki forest virus (ssRNA (+))	Cytoplasm	nsP2 (164)	Rare outbreaks in humans in Africa (163). Infection may be common based on seroprevalence studies, but disease rare (163)	Slight effect in cell lines (143)	Unknown	
Yellow fever virus (ssRNA (+))	Cytoplasm	NS5 (165)	86,509 (2021) (121)	Preclinical data: cell line (143)	Unknown	
Sindbis virus (ssRNA (+))	Cytoplasm	No known nuclear cargo	Incidence rate in Finland 7 to 9 per 100 000 (166)	Slight effect in cell lines (143)	Unknown	
Adenovirus (dsDNA)	Nucleus	Viral genome enters nucleus, mRNA exits (169)	47% of US civilians (167)	Preclinical data (168)	Inhibition of nuclear import (168)	

Table 3. Antitumour mechanisms of ivermectin

Target	Effect	Reference
MDR protein	Inhibition	(185)
Chloride channel	Increase of activity	(186)
Akt/mTOR pathway	Inhibition	(187)
P2X7/P2X7 receptors	Activation	(188,189)
PAK1 protein	Inhibition	(190,191)
WNT-TCF pathway	Inhibition	(192,193)
SIN3 domain	Inhibition	(194)
NS3 DDX23 helicase	Inhibition	(195)
Nanog/Sox2/Oct4 genes	Downregulation	(196)
YAP1	Inhibition	(197)
TFE3 reporter	Activation	(198)
Tubulin polymerization	Increase of activity	(199)
VEGF and GST	*Inhibition*	(200)

Table 4. An overview of other indications for which ivermectin demonstrates repurposing potential

Indication	Number affected	State of repurposing evidence	Mechanism	Interaction model
Alcohol use disorder	12.7% of adults (USA, 2013) (203) 5.1% of global population (204)	Pilot study shows efficacy (20) Preclinical data in mice (205)	Antagonist of ethanol inhibition on purinergic P2X4 receptors (206-210)	(211)
Amyotrophic lateral sclerosis	4.42 per 1 million people worldwide (212)	Preclinical data (213)	Potential: inhibits AMPA-mediated toxicity through antagonism with P2 receptors (213)	(211)
Asthma	4.3% of global adult population has doctor-diagnosed asthma (214)	Preclinical data (215) Limited case reports (216)	Anti-inflammatory (13,217,218)	NF-kB (176)
Rosacea	5.5% of global adult population (219)	Efficacy established in multiple clinical trials (220)	Potential: Anti-inflammatory (inhibits IL-8, IL-6 and MCP-1 secretion) and inhibits KLK5 and CAMP (221,222)	
Atopic dermatitis	Prevalence 2690 per 100 000 persons, or 221 million people (223)	Preclinical data (224)	Anti-inflammatory (224)	
Covid-19 post-vaccination syndrome	Up to 3% of recipients of Covid-19 vaccine dose*	Mechanistic basis (227) Used by 18% of patients (228)	Spike protein binding (153,229) Anti-inflammatory (218) α7nAChr modulation (153,230) GABA modulation (230)	Spike protein binding (153,229)

Legend: *Based on a Vaccine Adverse Event Reporting System (VAERS) reporting rate of 0.1% (225) and an under-reporting factor of 31 (226).

Figure 1. A timeline of the history of Ivermectin discovery and application worldwide

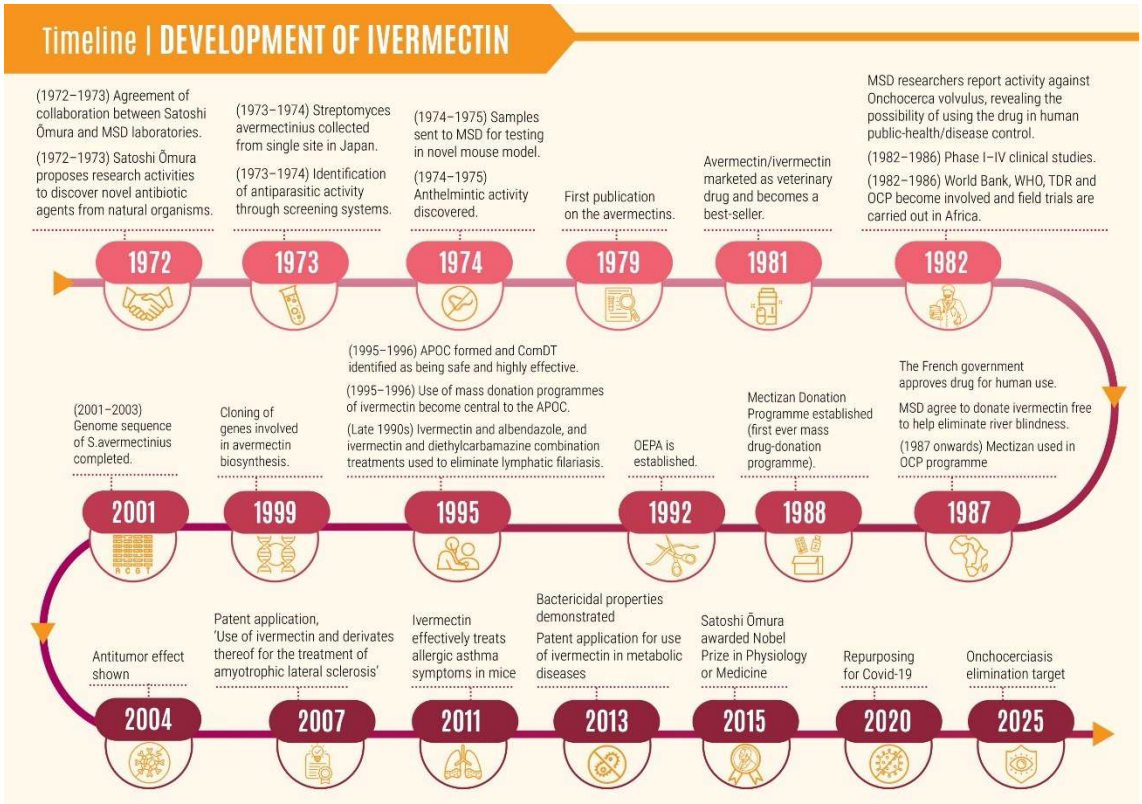


Figure 2. IVM binding site and its structural determinants in GluCl and GlyR

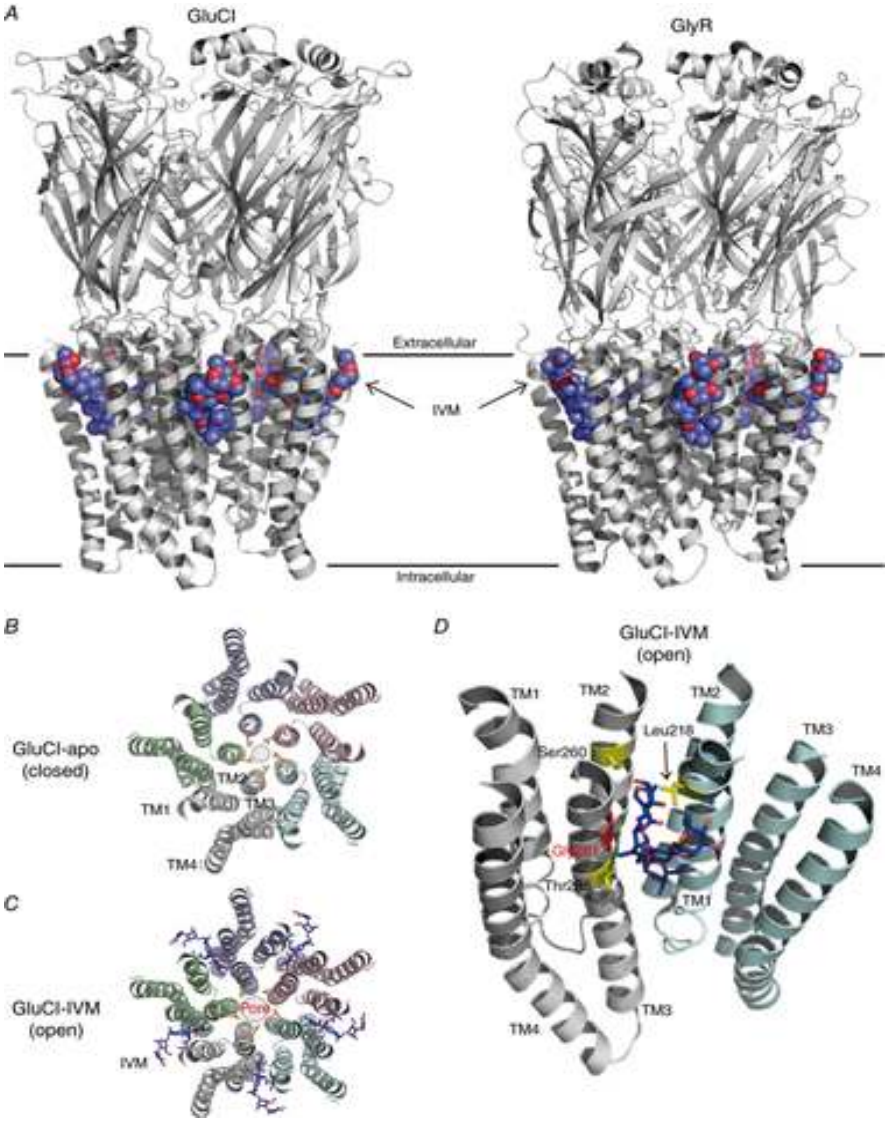
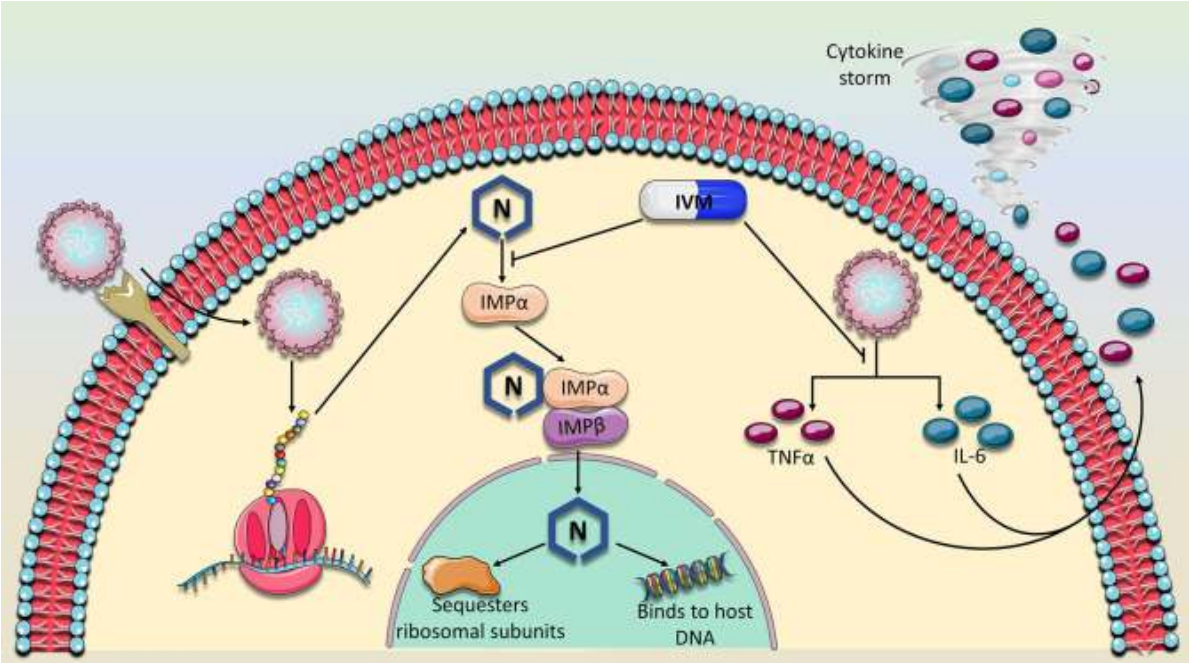


Figure 3. Inhibition of nuclear import by ivermectin



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