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Introduction

Back to the Future – Solutions for Parasitic Problems

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1.1 Introduction

Parasites are organisms that range widely in size. Parasites can be bacteria, protists, fungi, viruses, plants or animals. Parasites that live, feed, and harm the host in or on the host organism may be large enough to be visible. It is known that they infect millions of people around the world and cause thousands of deaths. In this respect, parasitic infections are an important health problem worldwide, especially in developing countries [1–3]. Today, parasitic diseases have ceased to be epidemics and have become the problem of the whole world. For example, according to the data of the World Health Organization, 1.5 billion people, in other words, 24% of the world's population, is infected with helminths transmitted from the soil (https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections).

Diseases caused by parasites have not been adequately studied. The displacement of populations has led to the spread of regional parasitic diseases in the world and treatment and preventive health services are needed everywhere.

Parasitic Infections: Immune Responses and Therapeutics, First Edition.
Edited by Abhay Prakash Mishra and Manisha Nigam.
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However, the pharmaceutical industry is still not as interested in developing drugs for the treatment of parasitic infections as in other drugs. Even antiparasitic drugs discovered at the beginning of the twentieth century are still used today. This is important in terms of showing how insufficient are the efforts to develop drugs for parasitic infections. In addition, the COVID-19 pandemic we have been through has also been a risk factor for the spread of parasitic infections. Both the disease itself and the drugs used in the treatment of COVID-19 infection have caused individuals with weakened immunity have become more susceptible to opportunistic parasitic infections.

The treatment of microbial infections or tumoral diseases caused by bacteria, protozoa, fungi, parasites and viruses with drugs is called chemotherapy. In this context, the treatment of infections caused by parasites is also called chemotherapy. Difficulties such as the development of resistance in the treatment of microorganisms other than parasites are also valid for the treatment of infections caused by parasites. Moreover, natural factors such as humidity and temperature also affect the incidence, spread and treatment of some parasitic infections. Mass movements such as travels to these affected regions, and the movement of immigrants also facilitate the spread of parasitic diseases [4–6].

Parasitic infections are most common in tropical climates due to poor hygiene conditions and are less common in developed countries. However, although they affect people who are disadvantaged in many respects, they spread all over the world with mass movements. Thus, parasitic infections affect millions of people around the world every year and can cause deaths. For these reasons, parasitic infections remain current and important as the subjects of drug research and development studies.

Today, there is a need for effective antiparasitic drugs with minimized side effects. In recent years, the factors related to the diseases caused by parasites have been clarified with mechanistic studies of parasitic infections. Thus, more data are available to derive selective and active compounds. With these data, it will be possible to reach new and active drugs having less side effects and increase the success of treatment in the near future.

1.2 Parasite and the Phenomenon of Parasitism

Parasite is a word of Greek origin, and it refers to microorganisms that have evolved to living in or on another organism and feeding by damaging it. Symbiosis is a word of greek origin and means “to live together”. It refers to a long-term and close relationship between two different biological organisms. Parasitism, which is a type of symbiosis, is an opportunistic relationship and expresses the relationship in which one species benefits while the other species is harmed [7–9].

1.3 Role of Parasites in Health and Diseases

The fight against parasites dates back to ancient times with the use of drugs and herbal methods being a success for humanity. According to studies, with the complete eradication of microorganisms such as viruses, bacteria and protozoa, human deaths will decrease and the quality of life will increase [10–13]. However, in a scenario where the parasites are completely destroyed, the ecological role of the parasites in the ecosystem can be better understood. The only parasite that humanity has managed to completely eradicate is variola, the smallpox parasite. Although only one parasite has been eradicated so far, intense efforts are also being made for the eradication of parasitic infections such as leprosy and Chagas disease, which are thought to be eradicated. In certain regions of the world, this eradication has been achieved [14].

In spite of the fact that they are harmful to human health, removing parasites from an ecosystem, especially from ecologically effective species, could be problematic in terms of disturbing the ecological balance. Fighting with parasites is an issue that is almost impossible to completely eradicate and needs to be evaluated in all its dimensions in terms of its consequences. The eradication of one parasite species can lead to the increase or extinction of other parasite species, as well as completely changing the balance of the ecosystem. Although it is thought that as a result of urbanization, healthier and more hygienic conditions will be created, this has not always been the case. In some cases, an increase in parasitic infections has been observed.

However, it is essential to fight parasites and to make efforts for the treatment of parasitic infections, but while doing this, they should not disturb the balance of nature, and strategies should be developed for all species in which life is possible without adversely affecting one another.

1.3.1 Ancient Information of Parasite Towards Health Problems

Medical struggles with microorganisms that cause disease in humans dates back to 3000 BCE. Parasites initially evolved long before the evolution of human beings, and early writings from Egypt mention some such as roundworms and tapeworms. Francesco Redi and Antonie van Leeuwenhoek in the seventeenth century began to research them and created an early version of the branch of parasitology. The pioneer experiments of various great scientists have helped us to understand the pathogenic mechanisms of the parasite.

Our information regarding infections of parasites extend into antiquity, and descriptions of parasites and parasitic infections are observed in the earliest writings and have been confirmed by the discovery of parasites in archaeological

material. Human beings are hosts to approximately 300 different species of worms parasite and more than 70 species of various protozoans, several derived from our ancestors primate condition while others have been acquired from animals. Some parasites cause the most important diseases in the world; certainly these are parasites that have received the great attention. Since most of such parasite diseases occur in tropical regions, the parasitology field has tended to overlap with that of tropical medicine, and consequently the histories of these fields are intertwined. The organized study of parasites started with the rejection of the theory of spontaneous generation and the promulgation of the germ theory. After that, the history of human parasitology continued along two lines: the finding of a parasite and its subsequent connection with particular disease, and the identification of particular disease and the subsequent discovery that it was caused through the infection of the particular parasite.

It is known that many plants are used as chemotherapeutic treatments in Chinese medicine. Avicenna defined microbes and treated the diseases caused by microbes. Galenos tried to treat diseases by using the large plant flora of Anatolia. In the seventeenth and eighteenth centuries, plant extracts began to be used for the treatment of febrile illness. In this period, chemotherapy started with the use of *Cinchona* alkaloids in the treatment of malaria.

Parasites have been defined and characterized depending on a wide variety of factors, from parasite-related factors to host-related factors. Throughout history, humans have been confronted with a large number of parasites, including about 300 species of helminths, and 100 species of protozoa. These microorganisms have caused and continue to cause diseases in humans [10, 15].

1.3.2 Current Information on Parasites Causing Health Problems

Diagnostic methods of parasitic infections have been developed from the past to the present, and many drugs with various chemical compounds have been introduced for treatment. In addition, surgical operations are also performed for the treatment of some parasitic infections. Research on parasites and new drug development studies continue in line with the available data.

The pandemic period we are going through can also be associated with parasitism. COVID-19 treatment has been effective in the diagnosis, treatment and eradication of parasitic infections. For example, cough and dyspnea seen in COVID-19 are also symptoms of some parasitic infections, in which case misdiagnosis or treatment is possible. It is possible to confuse symptoms of parasitic infections, particularly those caused by protozoa, trematodes, and nematodes, with symptoms of COVID-19. In addition, an immune system weakened by parasitic infections can complicate the treatment of COVID-19 [16].

1.4 Control of Parasites

The control and proper treatment of parasites are essential requirements for the health of living beings. In recent years, the inflammatory response resulting from infections caused by parasites has been confirmed by numerous studies. In a study of dogs with visceral leishmaniasis caused by the *Leishmania donovani* complex, inflammatory lesions were observed in the brain, although no parasites were detected. The aim of the studies carried out in recent years were to treat only the infection caused by the parasite and to improve the clinical status. In recent years, mechanistic studies have increased, and all pathways in parasite infections, including the interaction between the host and the parasite, are being investigated. With all these studies, the host–parasite relationship, which involves complex interactions, is increasingly being understood. With the use of new and modern methods such as omic technologies, it will be possible to control parasitic infections in the near future [17, 18]. The control and treatment of parasites has been achieved using different therapeutics approaches.

1.4.1 Herbal Medicines

In the treatment of parasitic infections, herbal medicines as well as synthetic compounds can be the solution. For centuries, mankind has benefited from using plants to treat diseases. Today, some medicines have herbal active ingredients. It is known that many plants such as *Melissa officinalis*, *Citrus limon*, and *Thymus vulgaris* show antiparasitic activity. However, the use of herbal medicines in antiparasitic therapy is limited due to their cytotoxic effects and non-selective activity profiles.

In the current treatment of diseases caused by parasites, the inadequacy of vaccines and the resistance to the drugs used have initiated the search for new treatments. In this search, besides chemical molecules, plants have gained importance because of their secondary metabolites. Secondary metabolites can be effective in parasitism since these metabolites and parasites have common targets such as genetic material, membrane integrity, microtubules and neuronal signal transduction. It is also possible to reach active new derivatives by obtaining synthetic derivatives analogous to these compounds. Many plant products interact with the protein structures and microtubules, which are the main components of the parasite, and cause the death of the parasite. Synthetically derived drugs or herbal compounds must be active and not toxic to the host and compounds with a high selectivity index are needed. The cytotoxicity of herbal and synthetic drugs arises through interaction with genetic material, proteins and biomembranes. Alkylating

agents cause genetic damage by alkylating DNA. This mechanism results in the death of the parasite.

Some secondary metabolites affect genetic mutations by chelating with DNA. In particular, some plants have alkaloids that cause the death of the parasite with this mechanism, such as topoisomerase enzyme inhibitors killing the parasite by disrupting DNA replication.

Destruction of the cell membrane results in impairment of the integrity of the cell. Cytotoxic effects are a result of cell damage, if the cell is a parasite cell, parasite death occurs. It is known that plants containing sesquiterpenes, phenylpropanoids and isothiocyanate structure show antiparasitic activity by this mechanism [4, 19].

1.4.2 Drugs and Drugs Analogs

Wide varieties of drugs and analogs are used for the treatment and management of parasites.

1.4.2.1 Antiprotozoal Drugs

Infections caused by *Plasmodium* species are still an important problem in the world and cause deaths. Alternative treatment methods and more importantly, new synthetic compounds are needed due to the development of resistance to existing treatment drugs. In this context, it is clear that parasite-selective and low-toxicity molecules will have therapeutic success [20].

The life cycle of *Plasmodium* parasites continues on two hosts, *Anopheles* mosquitoes and humans. During blood feeding of infected female *Anopheles*, sporocytes enter the host human and infect liver cells. Sporosides transform into tissue schizonts that cleave and release merosocytes. Merosides pass into the blood and form tarophosites. The trophocytes mature into blood schizonts. These schizonts break down and infect healthy red blood cells [21].

Quinine was the first known antimalarial drug for the treatment of malaria. It was first obtained from the bark of the *Cinchona* tree . The first synthetic antimalarial compound is quinacrine, a 9-aminoacridine derivative. Upon understanding the structure–activity relationships of quinine and its structural similarity with quinacrine, 4-aminoquinoline derivatives (chloroquine and hydroxychloroquine), 8-aminoquinoline derivatives (pamakine and primaquine) were synthesized. In the following years, the synthesis of compounds bearing the pyrimidine ring system continued and attempts were made to vaccinate against the disease.

Antimalarial drugs act by interacting with DNA, inhibiting dihydrofolate reductase, dihydroptereate synthesis, and protein synthesis.

According to their chemical structure, they can be classified as:

1) *Cinchona* alkaloids and analogues;
2) 4-aminoquinoline derivatives;

3) 8-aminoquinoline derivatives;
4) 9-aminoacridine derivative;
5) biguanidine derivatives;
6) diaminopyrimidine derivatives;
7) sesquiterpene lactones;
8) sulfonamides and sulfones; and
9) tetracyclines, clindamycin and azithromycin.

1.4.2.2 *Cinchona* Alkaloids and Analogues

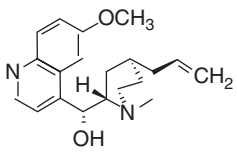
It was known 400 years ago that *Cinchona* bark extract was used to reduce fever and treat malaria. A few centuries later the malaria parasite was discovered. *Cinchona* bark extract, first used by native South Americans, is the prototype for quinine and quinidine used to treat malaria.

For over a hundred years, studies have been carried out for the synthesis of quinine. Since it has four stereogenic centers, it has 16 different configurations, making the synthesis of pure quinine difficult. However, in 2001, the synthesis of pure quinine was achieved [22].

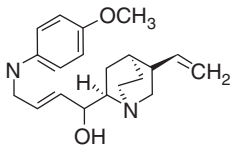
Quinine ((*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo [2.2.2] octan-2-yl]-(6-methoxyquinolin-4-yl)methanol), is mainly used in the treatment of infections caused by *P. falciparum*. In addition, due to its weak analgesic and antipyretic effect, it is used in muscle and joint pain, in the treatment of leg cramps, and rarely to induce labor because it causes uterine contraction. It causes hypotension by relaxing vascular smooth muscle through myocardial depression.

It is used as a sulfate salt in the treatment of malaria, in combination with pyrimethamine, sulfadiazine or tetracycline.

Quinidine ((*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo [2.2.2] octan-2-yl]-(6-methoxy-quinolin-4-yl)methanol), is the (+)-isomer of quinine and is obtained from the bark of the *Cinchona* tree. Although it has antiarrhythmic effects, its use in treatment is almost negligible due to its side effects.



Quinine

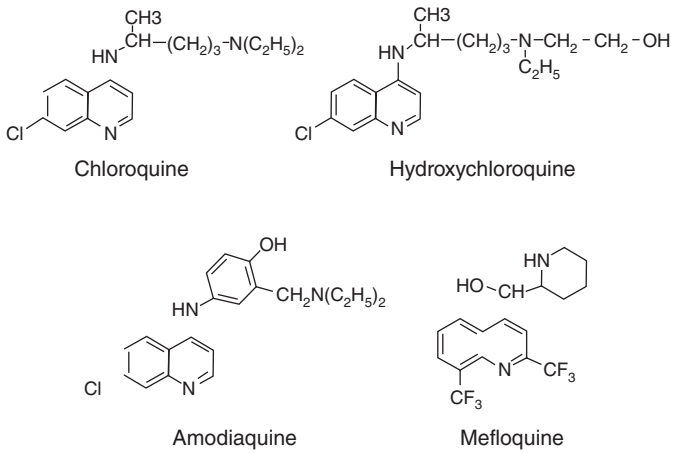


Quinidine

1.4.2.3 4-aminoquinoline Derivatives

Chloroquine (4-*N*-(7-chloroquinolin-4-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine), hydroxychloroquine (2-[4-[(7-chloroquinolin-4-yl) amino] pentyl-ethylamino]

ethanol), amodiaquine (4-[(7-chloroquinolin-4-yl) amino]-2-(diethylaminomethyl) phenol) and mefloquine ([2,8-bis(trifluoromethyl)quinolin-4-yl]-piperidin-2-yl-methanol) are 4-aminoquinoline derivatives available as therapies. These compounds are fast-acting, potent antiprotozoal drugs, especially against *P. falciparum*, acting on blood schizontocytes. However, resistance to these drugs is the most important problem in antiprotozoal therapy. Due to the high toxicity of chloroquine and the resistance of *Plasmodium* species to this drug, the -OH group was introduced, and the hydroxychloroquine synthesized. These drugs are used in the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, and diseases such as anti-phospholipid syndrome, due to their immunomodulatory and antithrombotic properties. Because of their antithrombotic mechanism and their potential to inhibit proinflammatory mediators, these drugs have also been used clinically in the treatment of SARS-CoV-2 infections. It has been argued that these drugs can treat COVID-19 infections by inhibiting the binding of the virus to the host cell membrane and preventing the virus from entering the cell. They are also thought to inhibit the formation and spread of new viral particles. Another proposed antiviral mechanism for chloroquine is to inhibit the zinc ionophores that allow zinc to enter the cell, thereby reducing the intracellular zinc levels of RNA viruses and reducing their pathogenicity. It has also been predicted that chloroquine may inhibit virus-receptor binding by acting on the terminal glycosylation of the ACE-2 enzyme. Due to these features, chloroquine and its hydroxy derivative hydroxychloroquine have been tried in the treatment of COVID-19 infections. However, neither drug has demonstrated significant clinical success. In addition, the side effects of these drugs have led to the abandonment of the use of these compounds in the treatment of COVID-19 [23,24].

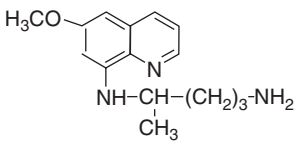


8-aminoquinoline derivatives

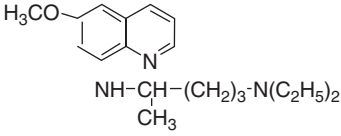
1.4.2.4 8-aminoquinoline Derivatives

8-aminoquinoline derivatives exert their effects by killing hypnozoite forms. Although they have high antiprotozoal activities, their use is limited due to safety problems arising from interactions with glucose-6-phosphate dehydrogenase [25]. Approved by the FDA in 1952 and particularly effective against *Plasmodium vivax* and *Plasmodium ovale* species, primaquine is the prototype of 8-aminoquinoline derivative antimalarial compounds. It is used in combination with chloroquine or artemisinin in the treatment. It is effective against *Plasmodium falciparum* in a single dose and used as phosphate salt in treatment [26].

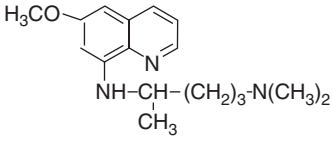
In addition to primaquine (4-*N*-(6-methoxyquinolin-8-yl)pentane-1,4-diamine), 8-aminoquinoline derivatives such as pamaquine (1-*N*,1-*N*-diethyl-4-*N*-(6-methoxyquinolin-8-yl)pentane-1,4-diamine), pentaquine (*N*-(6-methoxyquinolin-8-yl)-*N*′-propan-2-ylpentane-1,5-diamine) and isopentaquine (4-*N*-(6-methoxyquinolin-8-yl)-1-*N*-propan-2-ylpentane-1,4-diamine) are also used in the treatment.



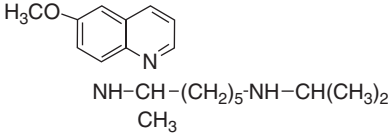
Primaquine



Pamaquine

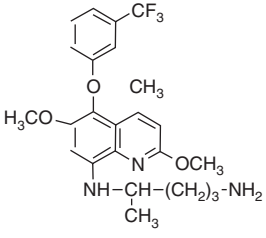


Pentaquine



Isopentaquine

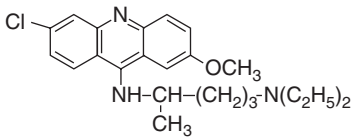
Tafenoquine (4-*N*-[2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy] quinolin-8-yl]pentane-1,4-diamine) is the latest approved 8-aminoquinoline derivative compound. It is a lipophilic derivative of primaquine, with a longer half-life and lower toxicity. It can also be used as a single dose due to its long half-life [27].



Tafenoquine

1.4.2.5 9-aminoacridine Derivative

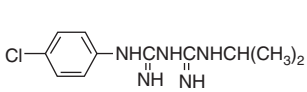
Quinacrine (4-*N*-(6-chloro-2-methoxyacridin-9-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine) is a 9-aminoacridine derivative. It has a higher schizontoside effect than quinine. However, due to its high toxicity, it is not currently used in antiprotozoal therapy. It has toxic effects especially on the central nervous system.



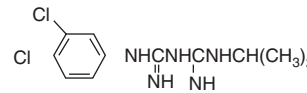
Quinacrine

1.4.2.6 Biguanidine Derivatives

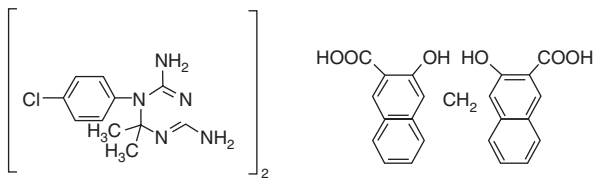
Biguanide derivatives are antimalarial compounds that are frequently used for prophylactic purposes. Proguanil, chlorproguanil, and cycloguanil pamoate are drugs of this group.



Proguanil

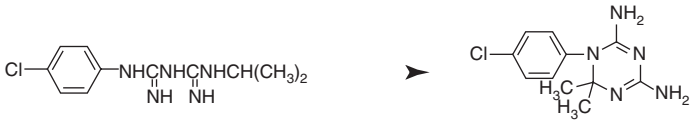


Chlorproguanil



Cycloguanil pamoate

Proguanil (1-[amino-(4-chloroanilino) methylidene]-2-propan-2-ylguanidine) was found while investigating the antimalarial activity of pyrimidine derivatives. Compounds carrying nitrogen heterocycles such as pyrimidine, quinazoline and quinoline with basic side chain and arylamino or arylguanidino substituents have antimalarial activity. The noncyclic biguanide structure has a similar tautomeric system. The antimalarial activity of compounds with biguanide structure showed that the part responsible for the activity in heterocyclic rings was the side chain. Proguanil is a prodrug, its metabolite with dihydrotriazine cycloguanil structure has antimalarial activity.



Proguanil

Sikloguanil (active metabolite)

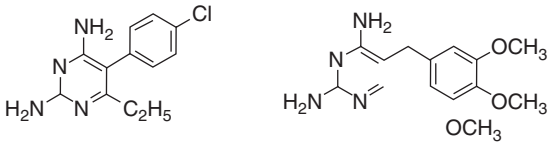
Another antimalarial drug in the biguanide structure is cycloguanil. Since cycloguanil is eliminated very quickly, the pamoate salt (cycloguanil pamoat: 1-(4-chlorophenyl)-6,6-dimethyl-1,3,5-triazine-2,4-diamine 4,4′-methylene-bis[3-hydroxy-2-naftaote] (2:1)) formed with pamoic acid is used as a depot formulation.

Chlorproguanil (1-[amino-(3,4-dichloroanilino) methylidene]-2-propan-2-yl-guanidine), a chlorinated derivative of proguanil, has a similar activity profile and is used in malaria tropica chemoprophylaxis [10, 28, 29].

1.4.2.7 Diaminopyrimidine Derivatives

Pyrimethamine (5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine) and trimethoprim (5-[(3,4,5-trimethoxyphenyl) methyl] pyrimidine-2,4-diamine), which are structurally similar to the pteridine part of dihydrofolic acid, are drugs that show dihydrofolate reductase enzyme inhibitory activity. The prototype of the group is pyrimethamine. Although pyrimethamine is safe at low doses, it causes megaloblastic anemia at high doses. Pyrimethamine inhibits the conversion of dihydrofolate to tetrahydrofolate by irreversibly binding to the enzyme dihydrofolate reductase. The compound shows higher affinity for the dihydrofolate reductase enzyme of *Plasmodium* than for the host dihydrofolate reductase enzyme. This feature makes the compound selective. Inhibition of the conversion of dihydrofolate to tetrahydrofolate reduces the folic acid synthesis required for nucleic acid synthesis in the parasite. Due to the development of pyrimethamine resistance, pyrimethamine-sulfadoxine combination is used in the treatment [10, 30, 31].

Trimethoprim is an antibacterial drug and its antimalarial activity was discovered later. Since it is less selective than pyrimethamine and has a shorter half-life, its use in therapy is limited. It is used in combination with other drugs [10].



Pyrimethamine

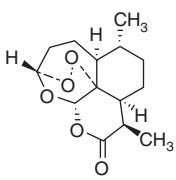
Trimethoprim

1.4.2.8 Sesquiterpene Lactones

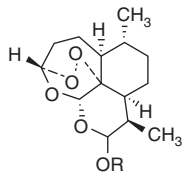
Sesquiterpene lactones are secondary metabolites of more than 5000 compounds, most commonly found in the families Cactaceae, Solanaceae, Araceae, and Euphorbiaceae. Artemisinin ((1*R*,4*S*,5*R*,8*S*,9*R*,12*S*,13*R*)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo [10.3.1.04,13.08,13] hexadecan-10-one) and its derivatives are antimalarial compounds with sesquiterpene lactone structure. These compounds are used in combination with resistant synthetic derivatives. Thus, it is possible to use drug combinations with a longer half-life and to prevent the development of resistance [32].

The antimalarial activity of artemisinin was discovered in China in the mid-twentieth century. Artemisinin and its derivatives are antimalarial compounds with sesquiterpene trioxane lactone structure isolated from *Artemisia annua*. Artemisinin and its derivatives (artemether ((1*R*,4*S*,5*R*,8*S*,9*R*,10*S*,12*R*,13*R*)-10-methoxy-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo [10.3.1.04,13.08,13] hexadecane),arteether((1*R*,4*S*,5*R*,8*S*,9*R*,10*S*,12*R*,13*R*)-10-ethoxy-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.04,13.08,13]hexadecane) and artesunate (4-oxo-4-[[(1*R*,4*S*,5*R*,8*S*,9*R*,10*S*,12*R*,13*R*)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.04,13.08,13]hexadecan-10-yl]oxy]butanoic acid) have been included in antimalarial treatment protocols [33, 34].

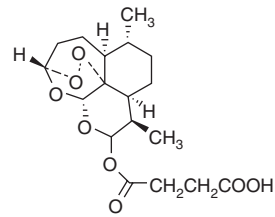
These compounds can be administered in a variety of ways. Its metabolites have a longer half-life and therefore higher activity. The peroxide structure in the 1,2,4-trioxane ring system is essential for antimalarial activity. There is no activity in deoxy compounds that do not have a peroxide structure or in derivatives where one of the peroxide oxygens is replaced by carbon. One of the mechanisms of action predicted for artemisinins is that they show antimalarial activity by endoperoxide and carbon radical mechanism. According to this mechanism, artemisinins can be considered as prodrugs. In the infected erythrocyte, Fe^{2+} is present in the parasite's food vacuole, where hemoglobin is digested and free iron is detoxified by accumulating in hemozoin. Fe^{2+} reacts with endoperoxide to form free oxy radical and Fe^{3+}. The carbon radical formed by the oxy radical kills the *Plasmodium* in the erythrocyte. According to the second proposed mechanism, endoperoxide activation by the iron-dependent mechanism kills the parasite by targeting the parasite's endoplasmic reticulum [35].



Artemisnin



Arthemeter (R: CH_3)
Arteether (R: C_2H_5)



Artesunat

1.4.2.9 Sulfonamides and Sulfones

Sulfonamide and sulfone derivative compounds are used in the treatment of bacterial and fungal infections. These compounds target the folate metabolic pathway, where cofactors for amino acid and DNA synthesis are produced. This group of compounds has a wide variety of activities, including antimalarial activity. These compounds do not have strong antimalarial activity alone and are used in combination with pyrimethamine. While sulfadiazine, sulfadoxine, sulfamethoxypyridazine, sulphalen and sulfisoxazole are counted as antimalarial sulfonamide group compounds, dapsone and diformyldapsone are antimalarial sulfone group compounds.

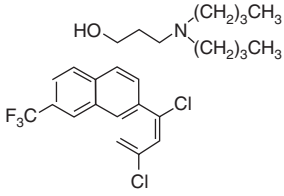
1.4.2.10 Tetracyclines, Clindamycin and Azithromycin

Various antibiotics are used prophylactically alone or in combination with drugs such as quinine and artesunate in antimalarial therapy. Doxycillin, clindamycin, and azithromycin are examples of these antibiotics. These compounds act by inhibiting protein synthesis in the parasite. In addition, halofantrine (3-(dibutylamino)-1-[1,3-dichloro-6-(trifluoromethyl) phenanthren-9-yl] propan-1-ol), lumefantrine (2-(dibutylamino)-1-[(9*Z*)-2,7-dichloro-9-[(4-chlorophenyl) methylidene] fluoren-4-yl] ethanol) and atovaquone (3-[4-(4-chlorophenyl) cyclohexyl]-4-hydroxynaphthalene-1,2-dione) are also antimalarial compounds.

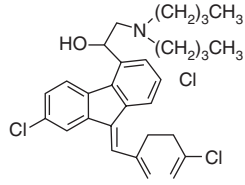
Halofantrine is a 9-phenanthrenemethanol compound. It is used in the treatment of malaria caused by chloroquine-sensitive and chloroquine-resistant *Plasmodium* species. It is taken orally. The most important side effect is cardiac toxicity.

Lumefantrine is an analogous compound to halofantrine. It is used in combination with artemether. It is an erythrocytic schizontocyte.

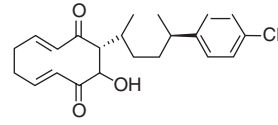
Atovaquone, a naphthoquinone derivative, is also used in combination with proquanil in the treatment of malaria, due to the side effects of existing drugs and resistance to these drugs. Compared to other drugs used in the treatment of malaria, it has fewer side effects [36].



Halofantrine



Lumefantrine



Atovaquone

Entamoeba species settle in the colon and *Entamoeba gingivalis* in the oral mucosa. The term amoebiasis refers to inflammation of the colon caused by *E. histolytica*. Amoebiasis is the most aggressive of the protozoal diseases and ranks second or third among the protozoal diseases that cause death. In infected individuals, amoebae in the colon lumen cause ulceration of the mucosa. The amoeba is excreted in the form of cysts in feces. The infection spreads through these cysts. Water and food contaminated with cysts cause the spread of the disease. Cysts ingested with water and food, pass through the small intestine and reproduce asexually to form trophocytes. The torophosites settle in the colon lumen and mature into amoebae. As a result of weakening of the host's resistance or virulence of the amoeba, the amoeba causes ulceration of the colonic mucosa and ultimately diarrhea in the patient.

In chronic cases, amoebae entering the mucous vessels can be transported to the liver by the portal circulation, causing hepatitis. In addition, they can be carried to the lungs, brain, genital area and form lesions.

Untreated *Entomoeba* infections can become chronic and fatal. Antiamoebic drugs used in the treatment should be effective on both intestinal and extraintestinal forms of the parasite. Extracts obtained from *Cephalis ipecacuanha* were first used in the treatment of the disease. The active ingredient of the extract is emetine, an ipecac alkaloid. Due to the cardiotoxic and gastrointestinal side effects of emetidine, alternative compounds have been discovered and entered into therapy. Later, carbarson and glycobiarsol were synthesized and the antiamoebic effect of chloroquine having antimalarial effect was determined. Following the development of haloquinoline derivatives, haloacetamide derivatives, paromomycin, azomycin, metronidazole, nimorazole, ornidazole and tinidazole have introduced treatment [10, 37, 38].

Antiamoebic drugs are divided into two groups according to their sites of action:

1) tissue amoebicides; and
2) luminal amoebicides.

Tissue amoebicides are drugs that kill amoebae that have settled in tissues such as intestines and liver. These compounds are ineffective against amoebae in the intestinal lumen.

Luminal amoebicides are compounds that act on amoebae in the intestinal lumen.

There are also compounds such as metronidazole that act on amoebae located in both tissue and lumen.

Antiamoebic compounds can be classified according to their chemical structure as follows:

1) 4-aminoquinoline derivatives;
2) antibiotics;

3) haloacetamides;
4) 8-hydroxyquinoline derivatives;
5) ipecac alkaloids;
6) 5-nitroimidazole derivatives;
7) organoarsenic compounds; and
8) other compounds.

1.4.2.11 4-aminoquinoline Derivatives

Chloroquine with 4-aminoquinoline structure, used in the treatment of malaria, also has antiamoebic activity. It has an equivalent activity to emetine in hepatic amoebiasis, since it accumulates in the hepatic parenchyma and reaches high concentrations. It is used orally [10].

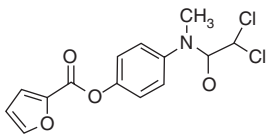
Tetracyclines or paronomycin along with antiamoaebic drugs are used to treat invasive intestinal infection caused by amoebae. These drugs are ineffective in extracolon amobiasis. Tetracyclines have direct and indirect effects, respectively, by killing amoebae and the microorganisms with which amoebae live in symbiosis.

Paromomycin, on the other hand, has an antiamoebic effect by reaching high concentrations in the lumen of the large intestine. It acts by interacting with DNA [10].

1.4.2.12 Haloacetamides

Haloacetamide derivatives have the -N-$COCHCl_2$- structure. Diloxanide furoate ([4-[(2,2-dichloroacetyl)-methylamino] phenyl] furan-2-carboxylate), chlorbetamide (2,2-dichloro-*N*-[(2,4-dichlorophenyl) methyl]-*N*-(2-hydroxyethyl) acetamide), clefamide (2,2-dichloro-*N*-(2-hydroxyethyl)-*N*-[[4-(4-nitrophenoxy) phenyl] methyl] acetamide), etofamide (2,2-dichloro-*N*-(2-ethoxyethyl)-*N*-[[4-(4-nitrophenoxy)phenyl] methyl]acetamide), quinfamide ([1-(2,2-dichloroacetyl)-3,4-dihydro-2*H*-quinolin-6-yl] furan-2-carboxylate) and teclozan (2,2-dichloro-*N*-[[4-[[(2,2-dichloroacetyl)-(2-ethoxyethyl)amino]methyl]phenyl]methyl]-*N*-(2-ethoxyethyl) acetamide) are haloacetamide derivatives. Among the haloacetamide derivatives, the most used compound in therapy is diloxanide furoate.

Diloxanide furoate is used to treat amoebic colitis caused by *Entomoeba histolytica*. It shows activity in the intestinal lumen. Since it has low water solubility, formulations to increase its solubility should be developed. It is a luminal amoebicide, used alone in luminal cases, and in combination with a tissue amoebic drug for tissue amoeba. It acts by disrupting protein synthesis in ribosomes [39].



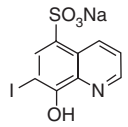
Diloxanide furoate

14.2.13 8-hydroxyquinoline Derivatives

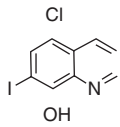
8-hydroxyquinoline derivatives were used as popular oral antiparasitic agents from the 1950s to the 1970s. However, due to its toxic effects, its oral forms were withdrawn from the treatment in 1970, although the topical forms continued to be used. Although the antiamoebic activity of 8-hydroxyquinoline derivatives has been proven, these compounds are not widely used today due to their side effects.

However, although myelo-optic neuropathy was observed, especially in Japanese patients, with the use of chinofon (8-hydroxy-7-iodoquinoline-5-sulfonic acid), clioquinol (5-chloro-7-iodoquinolin-8-ol) was used safely during this period. Topical formulations continue to be used in some countries. Clioquinol has fewer side effects and little is known about resistance to this compound.

Currently, clioquinol is being investigated for new indications beyond its antiamoebic effects [40].



Chiniofon



Clioquinol

1.4.2.14 Ipecac Alkaloids

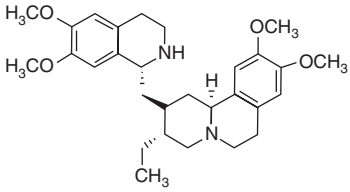
Ipeca is a drug obtained from the plant *Cephalis ipecacuanhae*.

The *Cephaelis* plant was discovered in Brazil in the 1600s and was taken to Paris in the second half of the same century. Used to treat dysentery in France, it was discovered many years later to contain two alkaloids (emetine and cephaline). Emetine and cephaline are obtained from the dried roots and rhizomes of the plant *Cephalis ipecacuanhae*. In the nineteenth century, emetine was found to be effective in treating dysentery caused by amoebae.

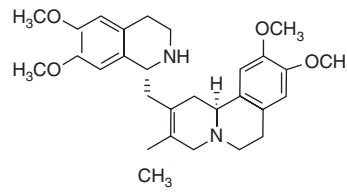
These alkaloids, which have a reversible effect on DNA synthesis, cause cardiotoxicity and muscle weakness in addition to their side effects on the gastrointestinal tract [41, 42].

Emetine ((2*S*,3*R*,11*bS*)-2-[[(1*R*)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl] methyl]-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-benzo[a] quinolizine) is a potent antiamoebic drug that kills trophosides. Although there are many stereoisomers of emetine with asymmetric centers in four positions, the most active isomer is the natural compound (-)-emetine. The active compounds were obtained by quaternizing the nitrogen atom in the emetine and replacing the substituents. Opening of the tetrahydroisoquinoline ring resulted in loss of activity.

The dehydro derivative obtained by saturating second and third positions is as active as emetine. Dehydroemetine ((11*bS*)-2-[[(1*R*)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl] methyl]-3-ethyl-9,10-dimethoxy-4,6,7,11*b*-tetrahydro-1*H*-benzo[a]quinolizine) is used when 5-nitroimidazole derivatives are ineffective or contraindicated. It has cardiovascular, gastrointestinal and neuromuscular side effects.



Emetine



Dehydroemetine

1.4.2.15 5-nitroimidazole Derivatives

Nitroimidazole is an essential and unique ring system discovered in the 1950s. After its discovery, many drug molecules containing this ring system with various activities such as anticancer, antibacterial and antiviral have been synthesized. The most effective drugs used in the treatment of systemic and intestinal amoebiasis are nitroimidazole derivatives. The prototype of the group is metronidazole. This group of compounds shows activity by reductive bioactivation and formation of reactive intermediates. Nitroimidazole derivatives are prodrug and the nitro group is responsible for the activity of the drug. Activity occurs when the nitro group is converted to nitric oxide and reactive nitrogen species. These products inhibit growth by interacting with the cellular components of the protozoa.

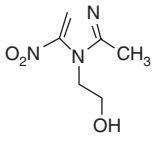
Metronidazole (2-(2-methyl-5-nitroimidazol-1-yl) ethanol) was the first compound found for the treatment of trichomoniasis infections caused by *Trichomonas vaginalis*. Later, it was also used for the treatment of various diseases. Today it is used in the treatment of parasitic infections such as gastrointestinal infections, giardiasis (*G. duodenalis*) and amoebiasis (caused by *E. histolytica*). It is also effective against gram-positive and gram-negative bacteria. Metronidazole is a well tolerated drug and can also be used in pregnant women.

Ornidazole (1-chloro-3-(2-methyl-5-nitroimidazol-1-yl) propan-2-ol) is a 5-nitroimidazole derivative antiprotozoal drug that is successful in 87% of protozoal cases. Although it was first used to treat trichomoniasis, it was later discovered to be broad-spectrum antiprotozoal and antibacterial agent. Ornidazole is used clinically in raceme form.

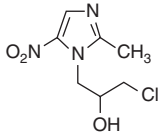
Secnidazole (1-(2-methyl-5-nitroimidazol-1-yl) propan-2-ol) is a well-tolerated drug used in amoebiasis, giardiasis, trichomoniasis and urogenital infections. Its antiamoebic activity is due to the reduction of the nitro group on the imidazole ring.

Tinidazole (1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole) is effective on intestinal amoebiasis activity as well as some other protozoa species and some bacteria. Although its effect profile and side effects are similar to metronidazole, it reaches higher blood levels and has a longer duration of action compared to metronidazole.

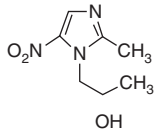
Nimorazole (4-[2-(5-nitroimidazol-1-yl) ethyl] morpholine) is also known as nitrimidazine. Despite its antiinfective and antiamoebic activities, it is mainly used for trichomoniasis infections [10,43].



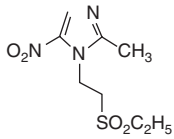
Metronidazole



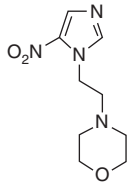
Ornidazole



Secnidazole



Tinidazole



Nimorazole

1.4.2.16 Organoarsenic Compounds

Although carbarsone and glicobiarsol have been used as organoarsenic compounds in the past, today the use of organoarsenic compounds as antiamoebic agents is limited due to the availability of more active and less toxic compounds [10].

1.4.2.17 Other Compounds

Compounds with different chemical structures such as bialamicol and nitazoxanide are also used as antiamoebic. Bialamicol has the hydroxybiphenyl structure. It is used in the treatment of acute and chronic amoebiasis. Nitazoxanide is a thazolide compound, used in the treatment of invasive intestinal amoebiasis.

Leishmaniasis is the general name for infections caused by *Leishmania* species. The parasite is transmitted by the bite of humans by sandflies that feed on infected sources. Thus, infections caused by *Leishmania* occur and an immune response develops. Although cutaneous leishmaniasis is the most common form, visceral leishmaniasis is more serious and dangerous. *Leishmania donovani*, one of the *Leishmania* species that cause visceral leismaniasis or kala-azar and settles in the reticuloendothelial system, especially in the liver and spleen in humans. *L. tropica* causes cutaneous leishmaniasis and settles on the skin. In immunocompromized individuals, *Lesichmania* infections are seen as co-infection [2, 18, 44, 45].

Although many compounds have been synthesized subsequently, there is no definitive cure for the disease. Resistance to antileishmanial drugs reduces the treatment success of infections caused by leishmania by up to 33% [1]. Compounds used in the treatment of *Leishmania* can be classified as:

1) organic antimony compounds;
2) diamidine derivatives;

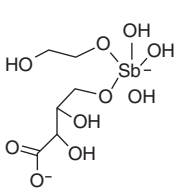
3) antibiotics; and
4) other compounds.

1.4.2.18 Organic Antimony Compounds

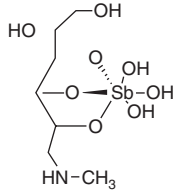
First, antimony potassium tartrate was found to be effective in leishmaniasis, then antimony compounds were studied and sodium stibogluconate (trisodium; (4*R*,5*S*,6*R*)-2-[[(4*R*,5*S*,6*R*)-4-carboxylato-6-[(1*R*)-1,2-dihydroxyethyl]-5-hydroxy-2-oxo-1,3,2λ^5-dioxastibinan-2-yl]oxy]-6-[(1*R*)-1,2-dihydroxyethyl]-5-hydroxy-2-oxo-1,3,2λ^5-dioxastibinane-4-carboxylate;nonahydrate) was synthesized. Among the antimony compounds discovered to date, the two compounds used today are sodium stibogluconate and meglumine antimonate (hydroxy(dioxo)-λ^5-stibane;(2*R*,3*R*,4*R*,5*S*)-6-(methylamino) hexane-1,2,3,4,5-pentol).

The structure of sodium stibogluconate was proven by chromatographic methods and meglumine antimonate structure was clarified by FAB-MS (fast-atom bombardment mass spectrometry) studies. Accordingly, two meglumine molecules are symmetrically coordinated with an Sb atom.

The action mechanism of antimony compounds is not fully known. One of the proposed models is the prodrug model, and antileishmanial activity occurs as a result of the conversion of the pentavalent antimony atom to the trivalent form. The second model explains antileishmanial activity of antimony compounds by the interference of the antimony atom in cellular mechanisms. The third hypothesis proposes that antimony compounds exert antileishmanial activity by activating the host's immune system [45].



Stibogluconate

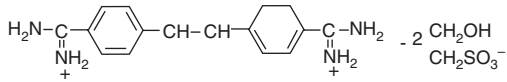


Meglumine antimonate

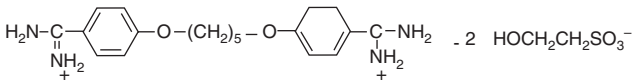
1.4.2.19 Diamidine Derivatives

Diamidines are a very large family of compounds with pharmacological and biological properties. From this group, hydroxystilbamidine isethionate (4-[(*E*)-2-(4-carbamimidoylphenyl) ethenyl]-3-hydroxybenzenecarboximidamide; 2-hydr oxyethanesulfonic acid) and pentamidine isethionate [4-[5-(4-carbamimidoylphenoxy) pentoxy] benzenecarboximidamide; 2-hydroxyethanesulfonic acid] are compounds that show antiprotozoal activity as well as other pharmacological

properties. Diamidine group compounds act by hydrogen bonding of amidine to DNA adenine.



Hydroxstilbamidine isethionate

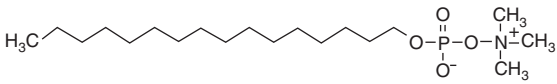


Pentamidine isethionate

1.4.2.20 Antibiotics

In cases where treatment with sodium stibogluconate was unsuccessful, a combination of amphotericin B and pentamidine isethionate is used. Additionally, there are some occasions in which Amphotericin B is used alone. In some cases of leishmaniasis, paronomycin with known antiprotozoal activity is used topically [10].

Other compounds include miltefosine (hexadecyl 2-(trimethylazaniumyl)ethyl phosphate), an alkyl phospholipid analogue developed as an antineoplastic agent, that is used orally for the treatment of visceral leishmaniasis. Due to the high toxicity of antimony compounds, miltefosine has gained importance. Since it does not affect the immune system of the host and is only effective on the parasite, it can be used safely in leishmaniasis infections seen in immunocompromized patients [10, 46].



Miltefosine

Trichomoniasis is a non-viral sexually transmitted disease and one of the most common protozoal diseases worldwide. *Trichomonas* class protozoa produces intestinal and urogenital infections. Thychomoniasis caused by *T. vaginalis* is the most important of these infections and is seen in both men and women. Symptoms can range from asymptomatic to epithelial lesions characterized by foul odor and discharge in women. In addition, there is an increased risk of miscarriage and increased susceptibility to HIV-1 and cervical cancer in pregnant women. Although men can have urethritis, prostatitis, and discharge, the vast majority of infections are asymptomatic. *Trichomonas* infections are a serious problem for

public health because of their symptoms, results, effects on both sexes and high incidence [47].

The drugs used in the treatment of trichomoniasis are classified as systemic compounds and topical compounds

1.4.2.21 Systemic Compounds

In the systemic treatment of trichominiasis, 5-nitroimidazole derivatives are used. Metronidazole is the most commonly used compound from this group. High treatment success can be achieved with metronidazole, which is used in both sexes. Tinidazole is more effective *in vitro* in trichomoniasis infections and has fewer side effects than metronidazole. Tinidazole is used when treatment with metronidazole is unsuccessful. In patients allergic to these compounds, intravaginal administration may be preferred over oral administration. In such cases, it should be noted that the success of the intravaginal application is lower. In addition to metronidazole and tinidazole, there are examples where other 5-nitroimidazole derivatives are used in the treatment of trichomoniasis [47].

1.4.2.22 Topical Compounds

In the treatment of trichomoniasis, there are drugs that are used topically in the form of vaginal tablets or suppositories. These compounds are useful in preventing the recurrence of vaginal infections and normalizing the vaginal flora. Povidone iodine is used in the form of a vaginal tablet or suppository, while iodoquinol is used as a vaginal tablet [10].

Drugs used in the treatment of infections caused by *Trypanosoma* group parasites are called antitrypanosomal drugs. The only alternative therapy is chemotherapy for the treatment of protozoal diseases caused by African trypanosomes (*Trypanosoma brucei*) and South American trypanosomes (*Trypanosoma cruzi*) species. However, like all available chemotherapeutics, these compounds have disadvantages such as low efficacy, high toxicity and development of resistance.

The disease is transmitted by the bite of *Triatoma* insects. The acute period begins following the bite of the insect, while the heart, esophagus, intestine and peripheral nervous system are affected in the chronic period. There are 15–20 years between these two periods. The infection caused by *T. cruzi* is known as Chagas disease because it was first discovered by Brazilian doctor Carlos Chagas. Chagas disease, also known as American trypanosomiasis, is more common in central and south America. The disease can be the cause of some serious conditions such as cardiomyopathy and death in adults. African trypanosomiasis infections caused by the bites of *T. gambiense* and *T. rhodesiense* species are also called "sleeping sickness". If the disease is not treated, it results in death. Benznidazole and nifurtimox are used in the clinic for the treatment of the disease. These compounds are effective in the acute phase of the disease, and treatment is almost impossible in the chronic phase [2].

Both compounds have nitroheterocyclic structure. Benznidazole is a nitroimidazole derivative and shows activity by inducing the oxidation of parasite nucleotides. Nifurtimox, a 5-nitrofuran derivative, creates a nitroanion radical and causes parasite DNA breaks. A change in the nitroreductase enzyme in the parasite causes to resistance to these compounds. Both compounds have limited use due to their serious side effects [1, 10, 48, 49].

Arsenic was first used for the treatment of sleeping sickness after its discovery in 1858. After arsenic was found to be effective against protozoa causing the disease, melarsoprol was synthesized. Later, pentamidine, nitrofurazone, nifurtimox and benznidazole were synthesized.

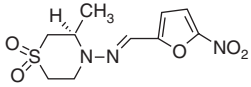
The drugs used in the treatment of trypanomosa infections can be classified as follows:

1) 5-nitrofuran derivatives;
2) urea derivatives;
3) organoarsenic compounds;
4) diamidine derivatives;
5) 2-nitroimidazole derivatives; and
6) amino acid derivatives.

1.4.2.23 5-nitrofuran Derivatives

Nifurtimox ((*E*)-*N*-(3-methyl-1,1-dioxo-1,4-thiazinan-4-yl)-1-(5-nitrofuran-2-yl) methanimine) is the prototype of 5-nitrofuran derivatives. It is the first choice in the treatment of Chagas disease. Although the mechanism of action of nifurtimox has not been fully elucidated, nifurtimox acts by a mechanism based on its metabolism through partial reduction to chemically reactive radicals leading to the production of toxic reduced oxygen species. The formed metabolic products can react with macromolecules such as DNA.

Myalgia, gastric side effects, muscle weakness, weight loss, memory loss, dermatitis and polyneuritis are side effects of nifurtimox [50,51].



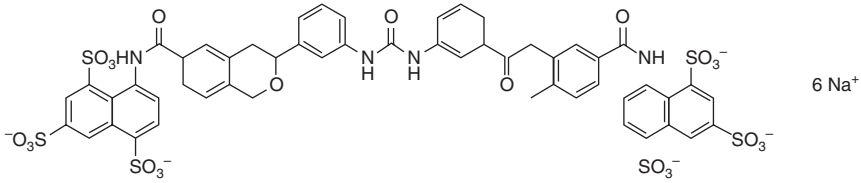
Nifurtimox

1.4.2.24 Urea Derivatives

Suramin sodium (hexasodium;8-[[4-methyl-3-[[3-[[3-[[2-methyl-5-[(4,6,8-trisulfonatonaphthalen-1-yl)carbamoyl]phenyl]carbamoyl]phenyl]carbamoylamino] benzoyl]

amino]benzoyl]amino]naphthalene-1,3,5-trisulfonate) a urea derivative, has been used for 100 years in the treatment of African troponmyosis. After the discovery of the trypan blue dye, a series of potent compounds were synthesized. In the following period, with the synthesis and treatment of suramin, a new era began in African trypanosomiasis chemotherapy. It causes the death of the parasite by binding to the dehydrogenase and kinase enzymes of the protozoa, inhibiting the dihydrofolate reductase and thymidine kinase enzymes necessary for folate biotransformation, and also inhibiting the enzymes necessary for glycolysis.

Although suramin is used for the treatment of various parasitic infections such as *Plasmodium falciparum*, *Trypanosoma brusei*, *Trypanosoma evansi*, *Onchocerca volvulus* infections, ivermectin, with high oral bioavailability and lower toxicity, has now replaced suramin. Nephrotoxicity, dermatitis, anemia, peripheral neuropathy, bone marrow toxicity and hypersensitivity reactions are its side effects [52].

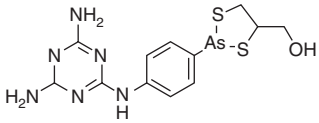


Suramin sodium

1.4.2.25 Organoarsenic Compounds

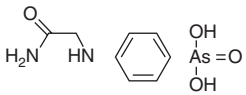
Organoarsenic compounds are selective because they are eliminated by mammalian cells by oxidation to pentavalent compounds, whereas the parasite does not have this mechanism, and this group of compounds has decreased penetration into mammalian cells.

Melarsoprol [2-[4-[(4,6-diamino-1,3,5-triazin-2-yl) amino] phenyl]-1,3,2-dithiarsolan-4-yl] methanol is a classical arsenic-derived compound that shows activity by inhibiting DNA synthesis. It is especially effective when the parasite affects the central nervous system. Melarsoprol shows its biological activity by turning into melarsen oxide when it enters the cell. Melarsoprol reacts with trypanothione to form a complex with the sulfhydryl groups of cysteine and inhibits the enzyme trypanothione reductase. This mechanism, is a proposed mechanism for the action of melapsoprol. In recent years, the clinical importance of melarsoprol has decreased due to the developments in the treatment of trypanosomiasis, especially the treatment success of the nifurtimox eflornithine combination, and the oral use of fexinidazole in tablet form. In order to reduce the toxic effect of melarsoprol, cyclodextrin complex was developed and approved in some countries and entered into treatment [53, 54].



Melarsoprol

Tryparsamide ([4-[(2-amino-2-oxoethyl) amino] phenyl]-hydroxyarsinate) is an arsenic-containing compound used in the treatment of trypanosomiasis. This compound is ineffective in the early stages of the disease. Significant resistance to the compound has developed. It is used in the treatment of meningoencephalitis symptoms caused by the disease in the later stages of infection. It is used in combination with suramin. It has the side effects of organoarsenic derivative compounds [54].



Tryparsamide

1.4.2.26 Diamidine Derivatives

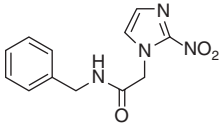
Pentamidine isethionate, which is used in the treatment of leishmaniasis, is a compound that is effective against *Trypanosoma gambiense* and *Trypanosoma rhodesiense* in the early stages of the disease, and ineffective against *Trypanosoma cruzie*. It is a compound with a low therapeutic index and interferes with active transport in the parasite.

1.4.2.27 2-nitroimidazole Derivatives

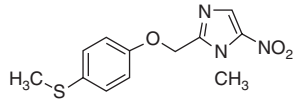
Benznidazole (*N*-benzyl-2-(2-nitroimidazol-1-yl) acetamide) is the second compound approved after nifurtimox for the treatment of infections caused by *T. cruzi*. It is a 2-nitroimidazole derivative compound. The uptake mechanism is assumed to be by passive diffusion. Benznidazole is a prodrug and requires cellular activation to exert its effect. It is effective in acute and chronic phases of infection. Benznidazole activity emerges through electrophilic metabolites produced by the reduction of the nitro group to an amine group by free radicals and nitroreductases. It does not produce reactive oxygen species. The trypanocidal activity of benznidazole is hypothesized to arise by binding the reduced metabolites to the macromolecules of the parasite. It has also been determined that it causes oxidative stress in the parasite.

Fexinidazole (1-methyl-2-[(4-methylsulfanylphenoxy) methyl]-5-nitroimidazole), a 2-substituted 5-nitroimidazole derivative, was discovered as a result of new drug studies for the treatment of human African trypanomososiasis, due to the low

efficacy, toxicity and administration problems of existing drugs. Its mechanism of action is similar to nifurtimox and benznidazole. It is used orally and acts in the acute and chronic stages of the disease [55–58].



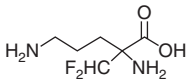
Benznidazole



Fexinidazole

1.4.2.28 Amino Acid Derivatives

Eflornithine (2,5-diamino-2-(difluoromethyl)pentanoic acid) is an alpha-difluoroamino acid derivative compound, and is an inhibitor of the ornithine decarboxylase enzyme. Ornithine decarboxylase is the key enzyme in polyamine production. Polyamines are essential for DNA synthesis and cell proliferation in protozoa. In mammals, it is somewhat ineffective due to rapid turnover of the ornithine decarboxylase enzyme. It is used in the treatment of sleeping disease caused by *T. gambiense*. Its oral bioavailability is not good and high doses are required for treatment. It is also being investigated for cancer treatment as part of the drug repositioning strategy [54,56].



Eflornithine

Intestinal infection caused by *Giardia lamblia* is known as giardiasis or lambliasis. 4-aminoquinoline derivatives, nitroheterocyclic compounds, are used for the treatment of this disease. The most preferred compounds are metronidazole and quinacrine hydrochloride. Pneumocystosis, an infection known as interstitial plasma cell pneumonia, causes death in 50% of cases. Sulfomethoxazole-trimethoprim is used in the treatment. Although combinations of sulfadiazine and sulfapyrazine, tetracyclines, dapsone, pyrimethamine and spiramycin, which are sulfonamide derivatives, can be used in the treatment of toxoplasmosis caused by *Toxoplasma gondii*, pyrimethamine-sulfonamide combination and spiramycin is preferred in pregnant women. *Toxoplasma* infections are the most common parasitic diseases and one-third of all parasitic infections are caused by *T. gondii*. *Toxoplasma* infection in humans is transmitted by eating food contaminated with feces of an infected cat, by eating undercooked food contaminated with toxoplasma cysts, and by transmission from mother to fetus. Immunocompromized individuals are most susceptible to *Toxoplasma* infections [2,59].

1.4.2.29 Antihelmintic Drugs

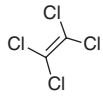
Helminths are parasites that affect millions of people worldwide. The ineffectiveness of the drugs in their treatment, the possibility of developing resistance to these drugs, and the contraindication of existing drugs in some populations, limit the success of anthelmintic therapy. Anthelmintic drugs are drugs used against parasites called helminths that settle in the gastrointestinal tract lumen, blood and lymphatic vessels and some tissues. They show their effects by decomposing the helminth or expelling it from the infected patient's body. Zoologically, helminths are subdivided into helminths, nematodes, cestodes, trematodes, and filariae. The anthelmintic drugs available in the treatment act by paralyzing the parasite, by damaging the worm, causing it to be eliminated by the host immune system, or by altering the parasite's metabolism. Since the metabolic requirements of helminths differ from species to species, drugs that are effective on one type of helminth may be ineffective against other species. Anthelmintic treatment is carried out with the strategy of diagnosis and treatment of patients and administering a single dose of preventive treatment to individuals who are not diagnosed with the disease. Plant extracts were the first anthelmintic medicine, and *Aspidium* is still used. With the discovery of the anthelmintic activity of the piperazine ring, diethylcarbamazine citrate was developed. Later, pyrivinium pamoate, bephenium hydroxynaphthoate, niclosamide, metrifonate, thiabendazole, niridazole, pyrantel pamoate and pyraziquantel were developed and introduced as treatments.

Antihelminthic drugs used in treatment can be classified as follows according to their chemical structures:

1) chlorinated hydrocarbons;
2) phenols and derivatives;
3) cyanine dyes;
4) piperazine derivatives;
5) antimalarial compounds;
6) various heterocyclic compounds:
    i) benzimidazole derivatives;
    ii) imidazothiazole derivatives;
    iii) vinylpyrimidines;
    iv) halogenated salicylanilide derivatives;
    v) quaternary ammonium compounds;
    vi) quinoline derivatives;
    vii) heterocyclic compounds bearing nitro group; and,
    viii) organophosphate compounds;
7) antimony compounds; and
8) natural compounds.

1.4.2.30 Chlorinated Hydrocarbons

Tetrachloroethylene (1,1,2,2-tetrachloroethene), also known as perchlorethylene, is a chlorinated hydrocarbon compound with anthelmintic activity that acts by paralyzing the parasite. The helminth separated from the intestinal wall is excreted with feces. It is used in the treatment of helminthic infections caused by hookworms [10].



Tetrachloroethylene

1.4.2.31 Phenols and Derivatives

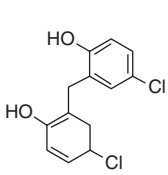
Dichlorophen (4-chloro-2-[(5-chloro-2-hydroxyphenyl) methyl] phenol), bithionol (2,4-dichloro-6-(3,5-dichloro-2-hydroxyphenyl) sulfanylphenol) and hexylresorcinol (4-hexylbenzene-1,3-diol) are anthelmintic compounds with a phenol structure.

Dichlorophen was used before praziquantel and niclosamide in the treatment of infections caused by *Taenia saginata*. In addition to its anthelmintic activity, it also has antifungal and antibacterial activity, and due to these properties, it is included in the structure of soaps and cosmetics. It shows its effect by proteolysis and digestion of the helminth.

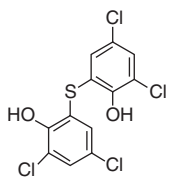
Gastrointestinal side effects such as nausea, vomiting and diarrhea occur in up to one-third of patients following ingestion of a single oral dose. Side effects such as urticaria, contact dermatitis and photosensitivity may also occur.

Bithionol is a compound used as an anthelmintic in the treatment of infections caused by *Fasciola hepatica*. Its effectiveness in the treatment of helminthic infections seen as co-infection in HIV patients has also been investigated [60].

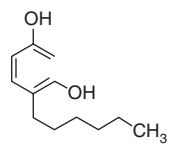
Hexylresorcinol is used in the treatment of hookworm infections. It also has an antibacterial effect [10].



Dichlorophen



Bithionol

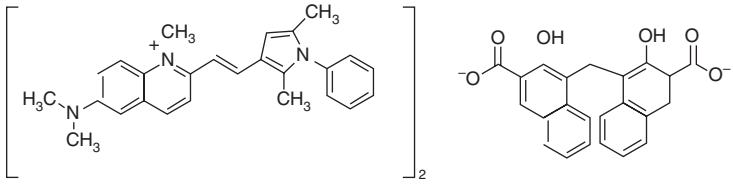


Hexylresocinol

1.4.2.32 Cyanine Dyes

Although pyrvinium pamoate (2-[(*E*)-2-(2,5-dimethyl-1-phenylpyrrol-3-yl) ethenyl]-*N*,*N*,1-trimethylquinolin-1-ium-6-amine) has been used for the treatment of pinworm

infections, especially in children, its low bioavailability has made it the second choice after pyrantel pamoate and mebendazole due to poor absorption from the gastrointestinal tract [61].

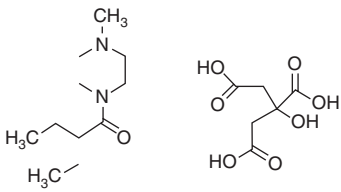


Pryvinium pamoat

1.4.2.33 Piperazine Derivatives

Piperazine, which is used in the treatment of *Ascaris lumbricoides* and *Enterobius vermicularis* infections, polarizes the muscle membrane by disrupting the ion channels at the neuromuscular junction, and reduces the contractile effect of acetylcholine by blocking the impulse transmission. As a result of this effect, the paralyzed helminth is expelled from the intestine. Although it is an alternative medicine in ascariasis, it has lost its importance due to other drugs used in enterobiasis [10].

The mechanism of action of diethylcarbamazine citrate (*N*,*N*-diethyl-4-methyl piperazine-1-carboxamide;2-hydroxypropane-1,2,3-tricarboxylic acid), which has been used as an anthelmintic for over 40 years, is not fully understood. It is an inactive drug *in vitro* and used in filaria infections. It is known that by reducing muscle activity, it provides immobilization of the helminth. Changes are also seen in the surface membrane of the helminth. It increases the adhesion of helminth granulocytes [62].



Diethylcarbamazine citrate

1.4.2.34 Antimalarial Compounds

Although mepacrin, which is used in the treatment of malaria, is used in the treatment of helminthic infections caused by *Taenia saginata* and *Taenia solium*, it has lost its importance in anthelmintic therapy with the introduction of niclozamide [10,63].

1.4.2.35 Various Heterocyclic Compounds

Different heterocyclic compounds are also used for the treatment and management of parasites. In the current topic we are discussing important heterocyclic compounds.

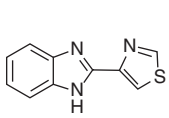
1.4.2.36 Benzimidazole Derivatives

Thiabendazole (4-(1*H*-benzimidazol-2-yl)-1,3-thiazole), mebendazole (methyl *N*-(6-benzoyl-1*H*-benzimidazol-2-yl) carbamate) and albendazole (methyl *N*-(6-propylsulfanyl-1*H*-benzimidazol-2-yl)carbamate) are benzimidazole derivative compounds used in the treatment of infections caused by gastrointestinal helminths. Initially, benzimidazole derivatives were thought to block several enzymes, including helminth fumarate reductase and malate dehydrogenase enzymes. It was later found that benzimidazoles bind to the beta-tubulin structure of the parasite with high affinity and inhibit microtubule polymerization. As a result, the cell structure deteriorates and the parasite dies. It has been observed that benzimidazoles used as anthelmintics selectively bind to the microtubules of the parasite and do not harm the host [10, 64].

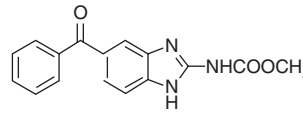
Thiabendazole is first benzimidazole derivative and is relatively non-toxic. It entered treatment in 1961. It acts by inhibiting the parasite's fumarate reductase and malate dehydrogenase enzymes. As a result, the release of acetylcholinesterase is blocked. It is a broad-spectrum compound and is ineffective only against filaria type nematodes [10, 64].

Mebendazole, a benzimidazole derivative, is a safe and broad-spectrum anthelmintic that has been used for many years for nematode infections. Its mechanism of action is that it binds to nematode tubulin and inhibits intestinal microtubule polymerization. Inhibition of microtubule synthesis prevents glucose absorption in the parasite. This mechanism results in the elimination of the parasite from the body. The dissociation rate from the microtubule of the parasite is lower than that of the human microtubule [65].

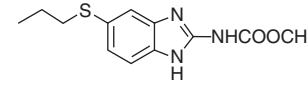
Albendazole, like other benzimidazole derivative anthelmintic compounds, is an oral drug for the treatment of intra- and extraluminal parasitic infections. Although its absorption from the gastrointestinal tract is weak, absorption can be increased with fatty foods. The compound, which is also used in the treatment of hydatid cyst, is also used in *Strongyloides stercoralis* and tapeworm infections [10, 66].



Thiabendazole



Mebendazole

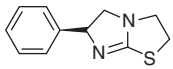


Albendazole

1.4.2.37 Imidazothiazole Derivatives

Imidazothiazoles, which are nicotinic acetylcholine receptor antagonists, are compounds that allow the elimination of the parasite by paralyzing it. The first anthelmintic compound discovered from this group was tetramisole. It has also been used in the treatment of rheumatoid arthritis.

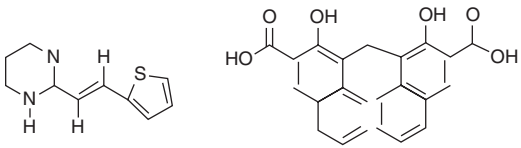
Tetramisole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b][1,3]thiazole) is a compound in raceme form. The L isomer of the compound is levamisole ((6*S*)-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b][1,3]thiazole). The activity of the L isomer is higher than the D isomer, and the L isomer is less toxic. It is a broad spectrum anthelmintic. It has been used successfully in the treatment of ascarid infections. It has also been used in the treatment of rheumatoid arthritis [67–70].



Levamisole

1.4.2.38 Vinylpyrimidines

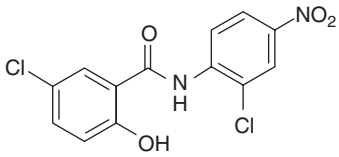
Pyrantel pamoate is a broad spectrum antinematodal anthelmintic compound with a vinyl pyrimidine structure. It causes paralysis by depolarizing at the neuromuscular junction of the nematode. These effects are the opposite of the effects of piperazine and these two anthelmintic drugs should not be used together. It is especially used in pinworm infections such as *Enterobius vermicularis* and *Ascaris lumbricoides*. It has low hepatotoxicity due to poor absorption [71].



Pyrantel pamoate

1.4.2.39 Halogenated Salicylanilide Derivatives

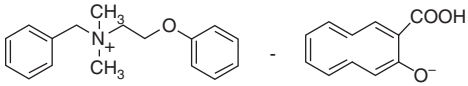
Niclosamide (5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) was the first commercialized compound to act as an anticestode. The mechanism of action of all salicylanilide derivatives and niclosamide is also because they are hydrogen ionophores, displacing their protons across the inner membrane of the mitochondria. Thus, it inhibits ATP production, causing oxidative phosphorylation to be separated from electron transport. This process is observed in isolated mitochondria of the helminth and the host. It is used in parasitic infections caused by taenia species, *Dipylidium caninum* and *Joyeuxiella pasqualei*. It is also used as molluscite [72].



Niclosamide

1.4.2.40 Quaternary Ammonium Compounds

Bephenium hydroxynaphtoate (benzyl-dimethyl-(2-phenoxyethyl)azanium;3-carboxynaphthalen-2-olate) is used in the treatment of infections caused by *Ascaris lumbricoides*, *Ancylostoma duodenale* and *Necator americanus*. Since the salt form is less soluble in water, it is not absorbed from the gastrointestinal tract and passes into the intestine. Nowadays, its use has been superseded due to the introduction of new compounds with better pharmacokinetic properties [10].

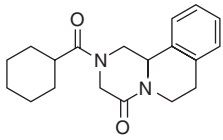


Bephenium hydroxynaphtoate

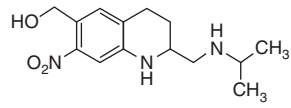
1.4.2.41 Quinoline Derivatives

Praziquantel (2-(cyclohexanecarbonyl)-3,6,7,11*b*-tetrahydro-1*H*-pyrazino[2,1-a] isoquinolin-4-one) is a medicine used to treat infections caused by *Schistosoma* species. Although the exact mechanism of action is not known, it is known to antagonize voltage-gated calcium channels, although it was thought to impair calcium homeostasis in the past. The uncontrolled flow of calcium ions as a result of antagonism of these channels causes uncontrolled muscle contraction and paralysis of the parasite. In addition, experimental studies have shown that myosin regulatory light chains and uptake of adenosine are important in the drug's mechanism of action. The R isomer has been shown to be anthelmintic, therefore, it is the R isomer that is used in therapy [73].

Oxamniquine ([7-nitro-2-[(propan-2-ylamino) methyl]-1,2,3,4-tetrahydroquinolin-6-yl] methanol), the hydroxylated metabolite of 2-aminotetrahydroquinoline, is used in the treatment of infections caused by *Schistosoma mansoni*. It has been superseded by the introduction of praziquantel into treatment. Oxamniquine is a prodrug that is sulfonated by endogenous sulfotransferases in the presence of 3′-phosphoadenosine-5′-phosphosulfate (PAPS). The resulting sulfate ester is unstable and alkylates macromolecules by forming an electrophilic intermediate. Thus, the cellular functions of the parasite are disrupted and this mechanism results in parasite death [74].



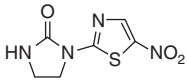
Praziquantel



Oxamniquine

1.4.2.42 Heterocyclic Compounds Bearing Nitro Group

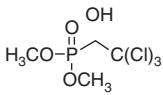
Niridazole (1-(5-nitro-1,3-thiazol-2-yl) imidazolidin-2-one) is used in the treatment of infections caused by the *Schistosoma* species *S. haematobium*, *S. mansoni*, and *S. japonicum*, and *Dracunculus medinensis*. Niridazole shows its effect by binding to the macromolecules of the parasite with the reactive intermediates formed by the nitroreductase. The 5-nitro group is essential for anthelmintic activity [75].



Niridazole

1.4.2.43 Organophosphate Compounds

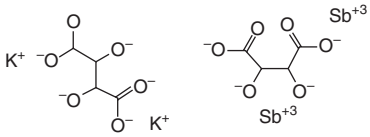
Metrifonate (2,2,2-trichloro-1-dimethoxyphosphorylethanol) is an organophosphorus cholinesterase inhibitor. It has been used to treat human schistosomiasis. It has no place in treatment protocols today due to its low therapeutic efficacy and the fact that it requires repeated doses. It is still used in veterinary medicine. It is being researched for the treatment of Alzheimer's disease [76, 77].



Metrifonate

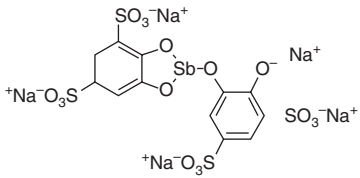
1.4.2.44 Antimony Compounds

One of the oldest known anti-schistosome drugs is antimony potassium tartrate (dipotassium; antimony(3+);2,3-dioxidobutanedioate). This compound is active against *S. mansoni* and *S. haematobium* species. Antimony potassium tartrate shows its effect by paralyzing the parasite. It also prevents the parasite from laying eggs. Due to its high toxicity, side effects and application difficulties, it is not currently used in the treatment of schistosomiasis [77].



Antimony potassium tartrate

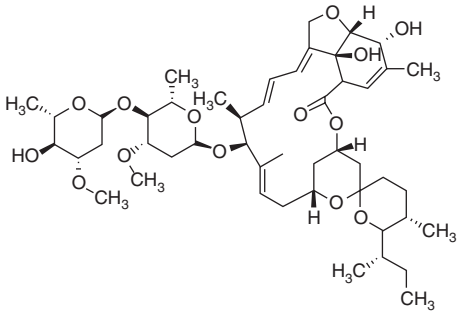
Stibophen (pentasodium;2-(2-oxido-3,5-disulfonatophenoxy)-1,3,2-benzodioxastibole-4,6-disulfonate) shows activity by affecting the phosphofructokinase activity of the parasite. Stibophen has a much higher affinity for parasite enzymes than for host liver enzymes. Despite its high toxicity and especially cardiovascular side effects, it is included in schistosomiasis treatment protocols [78].



Stibophen

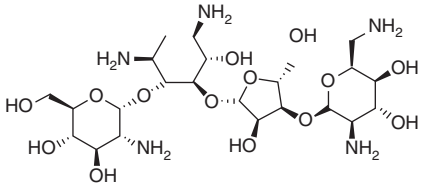
1.4.2.45 Natural Compounds

Discovered in Japan in the 1970s, ivermectin ((1*R*,4*S*,5'*S*,6*R*,6′*R*,8*R*,10*E*,12*S*,13*S*,14*E*,16*E*,20*R*,21*R*,24*S*)-6′-[(2*S*)-butan-2-yl]-21,24-dihydroxy-12-[(2*R*,4*S*,5*S*,6*S*)-5-[(2*S*,4*S*,5*S*,6*S*)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]oxy-4-methoxy-6-methyloxan-2-yl]oxy-5′,11,13,22-tetramethylspiro[3,7,19-trioxatetracyclo[15.6.1.1^{4,8}.0^{20,24}]pentacosa-10,14,16,22-tetraene-6,2′-oxane]-2-one), is a new antiparasitic drug. Ivermectin is a 16-membered macrocyclic lactone derived from its precursor, avermectin, from *Streptomyces avermitilis*. Ivermectin is obtained by saturating the double bond between 22–23 in avermectin. It has a broad spectrum and is effective against gastrointestinal roundworms, lungworms, mites, lice and hornflies. It is used for the oral treatment of various internal nematode infections including onchocerciasis, strongyloidiasis, ascariasis, cutaneous larval migrans, filariasis, gnathostomiasis and trichuriasis, as well as ectoparasitic infections such as lice and scabies. Since it is an effective drug against *Onchocerca volvulus*, it has replaced diethylcarbamazine in the treatment of that parasite. In the treatment of onchocerciasis, a single dose is used orally for six months or once a year. Initially, it was believed that ivermectin blocked neurotransmitters acting on GABA-gated Cl- channels. GABA is considered the primary inhibitory neurotransmitter in the somatic neuromuscular system of nematodes. Later, ivermectin was found to target glutamate-gated Cl-channels. By this mechanism, while ivermectin affects nematodes, it cannot reach the central nervous system where GABA receptors are localized, as it cannot cross the blood–brain barrier and thus does not affect mammals [10,79,80]. In the current COVID-19 pandemic, a large number of drugs for treatment have been tried in the clinic as part of the drug repositioning strategy. One of these drugs is ivermectin. The therapeutic effect on COVID-19 infection is still under investigation. The general opinion is that ivermectin does not reduce either the risk of mortality or the need for mechanical ventilation in severe COVID-19 infection [24, 81–86].



Ivermectin

Paromomycin ((2*S*,3*S*,4*R*,5*R*,6*R*)-5-amino-2-(aminomethyl)-6-[(2*R*,3*S*,4*R*,5*S*)-5-[(1*R*,2*R*,3*S*,5*R*,6*S*)-3,5-diamino-2-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3-amino-4,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-6-hydroxycyclohexyl]oxy-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl]oxyoxane-3,4-diol) is a macrolide antibiotic used in the treatment of giardiasis, amoebaiasis and cryptosporidiosis. It acts by interacting with ribosomal subunits [87].



Paromomycin

1.4.2.46 Drugs Used against Ectoparasites

Ectoparasites are insects that settle on the skin or in the stratum corneum of the skin due to inadequate personal care. They cause dermatitis with itching in the area where they are located. Infections are caused mainly by scabies (*Sarcoptes scabiei*), the common bed bug (*Cimex lectularius*), fleas, and lice, including the body louse (*Pediculus humanis*), pubic louse (*Phthirius pubis*), and head louse (*Pediculus humanus capitis*). Ectoparasite infections are more common in underdeveloped countries. Sulfur preparations were used for the treatment of ectoparasitic infections until modern drugs became available. Then, compounds such as benzyl benzoate and chlorophenotan were synthesized and their insecticidal effects were investigated. Active compounds isolated from *Pyrethrum* led to the synthesis of pyrethrin analogs.

Drugs used against ectoparasites can be classified as:

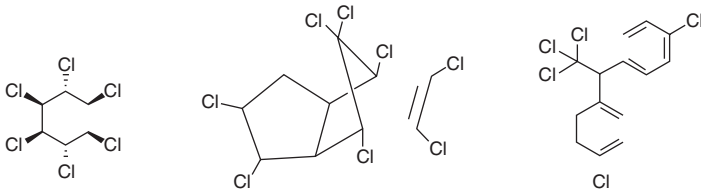
chlorinated hydrocarbons;
pyrethrins and prethyroids;

sulfur compounds; and
other compounds.

1.4.2.47 Chlorinated Hydrocarbons

Having a hexachlorocyclohexane structure, lindane (1,2,3,4,5,6-hexachloro-cyclohexane) is one of the first-generation anthelmintic compounds that inhibits insect and GABA A receptors. Thus, it inhibits the flux of chlorine channels. Lindane is used as a model compound for insecticide activity determination. Shampoo and lotion lindane formulations are used to treat scabies and lice. It is toxic to the central nervous system, reproductive system, cardiovascular system, kidney and liver. It is not a first line therapy drug due to its toxicity [88, 89]. Chlordane (1,3,4,7,8,9,10,10-octachlorotricyclo [5.2.1.$0^{2,6}$]) dec-8-ene, like other chlorinated hydrocarbons, is a highly toxic compound. It is a broad-spectrum insecticide. It disrupts the hormone balance by causing endocrine damage [90, 91].

Clofenotane, which has 1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl) ethyl] benzene structure, has been used in insect control since the 1940s. Due to its widespread use, it has caused significant environmental pollution. Its use is banned in most countries today. It acts by blocking voltage-gated sodium channels [92].

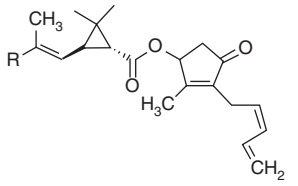


Lindane Chlordane Clofenotane

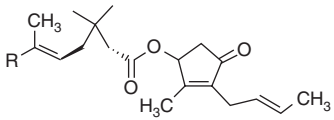
1.4.2.48 Pyrethrins and Prethyroids

Pyretrum is a natural insecticide obtained from the plant *Chrysanthemum cinerariaefolium*. It shows structural similarity with pyrethroid insecticides and pyrethrin I, one of the active components of pyrethrum. Chemically, this group of compounds is called pyrethrins because they are a mixture of esters (pyrethrin I ([(1*S*)-2-methyl-4-oxo-3-[(2*Z*)-penta-2,4-dienyl]cyclopent-2-en-1-yl] (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate)) and II ([(1*S*)-2-methyl-4-oxo-3-[(2*Z*)-penta-2,4-dienyl]cyclopent-2-en-1-yl](1*R*,3*R*)-3-[(*E*)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate) and (cinerin I ([(1*S*)-3-[(*Z*)-but-2-enyl]-2-methyl-4-oxocyclopent-2-en-1-yl] (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate)) and II([(1*S*)-3-[(*Z*)-but-2-enyl]-2-methyl-4-oxocyclopent-2-en-1-yl](1*R*,3*R*)-3-[(*E*)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate)

of *Chrysanthemum cinerariaefolium*, the plant from which they are obtained. Synthetic pyrethroids are more stable than natural pyrethroids. Synthetic derivatives are quite diverse and toxic to the insect species. The high fat solubility of pyrethrins makes them selective in the insect. The first synthetic insecticides in the prethyroid structure were developed in the 1950s. Pyrethroids affect the insect's nervous system by interacting with voltage-gated chloride, calcium and sodium channels. Since the effect of pyrethrins starts quickly and lasts for a short time, it is combined with piperonyl butoxide to create a synergistic effect. In this combination, piperonyl butoxide delays the oxidative inactivation of pyrethrins by inhibiting cytochrome P450 monooxygenases that metabolize pyrethrins in the insect [93–95].

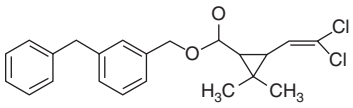


Permethrin I:R = CH_3
Permethrin II:R = $COOCH_3$



Cinerin I:R = CH_3
Cinerin II:R $-COOCH_3$

Permethrin ((3-phenoxyphenyl) methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate) is an FDA-approved compound for the treatment of lice and scabies, as a pet shampoo, to treat wooden furniture, and on the surface of clothing. Since it is a synthetic compound with high stability, it cannot be used together with a synergist. Its insecticidal effect is as much as natural compounds, its toxicity to mammals is low [10, 84, 85, 96–98].



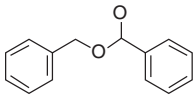
Permethrin

1.4.2.49 Sulfur Compounds

Sulfur is the oldest compound used in the treatment of scabies. It is used in ointment form, its effect is lower than other drugs, and it can be used on the whole body. It has low toxicity [99, 100].

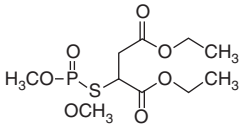
1.4.2.50 Other Compounds

Benzyl benzoate is one of the oldest drugs used as a scabicide. It kills the parasite by acting on its nervous system. It has the advantages of being odorless and not irritating to the skin. Benzyl benzoate is also used in permethrin resistance infections [10, 101, 102].



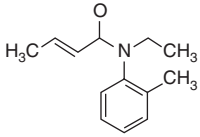
Benzyl benzoate

Malathion (diethyl 2-dimethoxyphosphinothioylsulfanylbutanedioate) is an organophosphate insecticide and shows its effect by converting its active metabolite malaoxone. It irreversibly inhibits acetylcholine esterase. It is safe because it does not show serious systemic adverse reactions in topical use. On topical application, it is converted to inactive rather than active metabolites. It is used in the treatment of head and pubic lice [84].



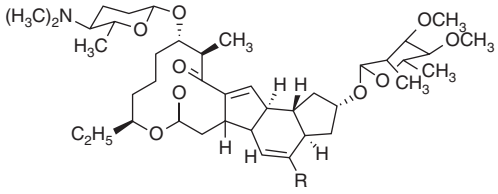
Malathion

Crotamiton ((*E*)-*N*-ethyl-*N*-(2-methylphenyl) but-2-enamide) has been used topically for many years to treat lice and relieve itching caused by lice. It can also be used in pediatric patients due to its low toxicity, but it must be applied multiple times for treatment success [85,103].



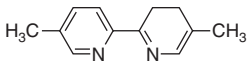
Crotamiton

Spinosad is the chemical compound formed by the fermentation of *Saccharopolyspora spinosa*, a naturally occurring soil actinobacteria. It is a macrolide compound consisting of a mixture of spinosyn A and D. In spinosad, Spinosyn A is the major component and Spinosyn D is the minor component. it is approved by the FDA for the topical treatment of head lice. It acts by excitation in the insect's nervous system and disrupting the function of nicotinic and GABA ion channels [10, 104, 105].



Spinosyn A : R = H
Spinosyn D : R = CH_3

Abametapir is a pediculicide drug with 5-methyl-2-(5-methylpyridin-2-yl) pyridine structure. It shows its effect by chelating with metals such as iron, copper and zinc. These metals are essential for the vital functions of the insect. It is used in cases where other resistant drugs such as permethrin are not successful in treatment [106, 107].



Abametapir

1.5 Conclusions

Parasites are unicellular or multicellular organisms that have the potential to cause disease in the host and have been present throughout the existence of humanity. Chronic illnesses, which lower the quality of life for the host, and even death can result from parasitic infections. In the past, parasite-related infections have been treated with herbal remedies. Later, medications that had active ingredients that were chemically manufactured entered the therapy. Research on parasites is now being forward in two primary directions: medication development and understanding how parasites interact with their hosts to cause disease. As our understanding of parasites and their relationship to disease advances this will enable the development of medications with more logical approaches and to control parasitic infections.

1.5.1 Future Prospects

Chronic diseases and infections are phenomena that threaten human life and cause economic and physical losses all over the world. Comprehensive studies have not been conducted on the development of antiparasitic drugs, and the number of drugs offered for treatment is limited, as is research on existing drugs. Some of the drug research and development studies carried out aim to discover new molecules as drug candidates for the treatment of these diseases. Due to the resistance to the drugs used in the treatment of infections, the difficulties experienced

in getting the drug to some parts of the world and the developing technology, the knowledge gained at the molecular level has increased the development of new drug candidate molecules. Drugs for parasitic infections also have an important place in these studies. In the future, it can be said that there will be important developments in the treatment of parasitic infections and the prevention of diseases caused by parasites. In this context, studies on compounds with optimized pharmacokinetic properties, which are more effective, and whose side effects are minimized, are continuing. In addition, due to the similarity between cancer and parasitic diseases, antiparasitic drugs are thought to be a new starting point in cancer treatment within the scope of drug repositioning strategy. In this context, trials are underway for tumor treatment of some antiparasitic drugs (eg macrolides, benzimidazole derivatives and artemisinin). The drug repositioning strategy, which is a popular approach today, is also used to develop antiparasitic drugs. According to this strategy, compounds with various mechanisms of action, such as kinase inhibitors or antirheumatic drugs, are being tested for their antiparasitic activities in vitro.

References

1 Muhaj, F.F., George, S.J., Nguyen, C.D., and Tyring, S.K. (2022). Antimicrobials and resistance part II: antifungals, antivirals, and antiparasitics. *Journal of the American Academy of Dermatology* 86 (6): 1207–1226.

2 Carnero, P.R., Mateo, P.H., Martin-Garre, S. et al. (2017). Unexpected hosts: imaging parasitic diseases. *Insights into Imaging* 8: 101–125.

3 Elsheikha, H.M. (2014). The future of parasitology: challenges and opportunities. *Frontiers in Veterinary Science* 1: 1–3.

4 Dziduch, K., Greniuk, D., and Wujec, M. (2022). The current directions of searching for antiparasitic drugs. *Molecules* 27 (5): 1534–1558.

5 Kolodziej-Sobocinska, M. (2019). Factors affecting the spread of parasites in populations of wild European terrestrial mammals. *Mammal Research* 64: 301–318.

6 Khater, H.F. (2017). *Natural Remedies in the Fight against Parasites*. IntechOpen.

7 Dimijian, G.G. (2000). Evolving together: the biology of symbiosis, part 1. *Proceedings (Baylor University Medical Center)* 13 (3): 217–226.

8 Solomon, N.U., James, I.M., Alphonsus, N.O.O., and Nkiruka, R.U. (2015). A review of host-parasite relationships. *Annual Research & Review in Biology* 5 (5): 372–384.

9 Hahn, M.A. and Dheilly, N.M. (2016). Experimental models to study the role of microbes in host-parasite interactions. *Frontiers in Microbiology* 7: 1300.

10 Akgün, H., Aytemir, M, Balkan, A. et al. (2021). *Farmasötik ve Medisinal Kimya*. Hacettepe Üniversitesi Yayınları.

11 Allen, J.A. and Sutherland, T.E. (2014). Host protective roles of type 2 immunity: parasite killing and tissue repair, flip sides of the coin. *Seminars in Immunology* 26 (4): 329–340.

12 Hotez, P.J., Brindley, P.J., Bethony, J.M. et al. (2008). Helminth infections: the great neglected tropical diseases. *Journal of Clinical Investigation* 118 (4): 1311–1321.

13 McNair, C.M. (2015). Ectoparasites of medical and veterinary importance: drug resistance and the need for alternative control methods. *Journal of Pharmacy and Pharmacology* 67 (3): 351–363.

14 Wood, C.L. and Johnson, P.T.J. (2015). A world without parasites: exploring the hidden ecology of infection. *Frontiers in Ecology and the Environment* 13 (8): 425–434.

15 Cox, F.E.G. (2002). History of human parasitology. *Clinical Microbiology Reviews* 15 (4): 595–612.

16 Whitehead, B., Christiansen, S., Ostergaard, L., and Nejsum, P. (2022). Helminths and COVID-9 susceptibility, disease progresion, and vaccination efficacy. *Trends in Parasitology* 38 (4): 277–279.

17 Antushevich, H. (2020). Interplays between inflammasomes and viruses, bacteria (pathogenic and probiotic), yeasts and parasites. *Immunology Letters* 228: 1–14.

18 Melo, G.D., Silva, J.E.S., Grano, F.G. et al. (2015). *Leishmania* infection and neuroinflammation: specific chemokine profile and absence of parasites in the brain of naturally-infected dogs. *Journal of Neuroimmun* 289: 21–29.

19 Wink, M. (2012). Medicinal plants: a source of anti-parasitic secondary metabolites. *Molecules* 17 (11): 12771–12791.

20 Faheem, D.S., Johri, S., Abirami, M. et al. (2022). Search for structurally diverse heterocyclic analogs as dual-acting antimalarial and antileishmanial agents: an overview. *European Journal of Medicinal Chemistry Reports* 4: 100031.

21 Parhizgar, A.R. and Tahghighi, A. (2017). Introducing new antimalarial analogues of chloroquine and amodiaquine: a narrative review. *Iranian Journal of Medical Sciences* 42 (2): 115–128.

22 Sullivan, D.J. (2011). Cinchona alkaloids: quinine and quinidine. In: *Treatment and Prevention of Malaria* (eds H.M. Staines and S. Krishna). Springer.

23 Unlu, B., Simsek, R., Kose, S.B.E. et al. (2022). Neurological effects of SARS-CoV-2 and neurotoxicity of antiviral drugs against COVID-19. *Mini-Reviews in Medicinal Chemistry* 22 (2): 213–231.

24 Gluchowska, K., Dzieciatkowski, T., Sedzikowska, A. et al. (2021). The new status of parasitic diseases in the COVID-19 pandemic-risk factors or protective agents? *Journal of Clinical Medicine* 10 (11): 2533–2546.

25 Ashley, E.A., Recht, J., and White, N.J. (2014). Primaquine: the risks and the benefits. *Malaria Journal* 13: 418–424.

26 Chairat, K., Jittamala, P., Hanboonkunupakarn, B. et al. (2018). Enantiospecific pharmacokinetics and drug-drug interactions of primaquine and blood-stage antimalarial drugs. *Journal of Antimicrobial Chemotherapy* 73 (11): 3102–3113.

27 Duparc, S., Chalon, S., Miller, S. et al. (2020). Neurological and psychiatric safety of tafenoquine in plasmodium vivax relapse prevention: a review. *Malaria Journal* 19: 111.

28 White, N.J. (2014). *Manson's Tropical Infectious Diseases,* 23e (eds J. Farrar et al.). Elsevier.

29 Aronson, J.K. (2016). *Meyler's Side Effects of Drugs*, 16e (ed. J.K. Aronson). Elsevier.

30 Enna, S.J. and Bylund, D.B. (2009). *xPharm: The Comprehensive Pharmacology Reference* (eds S.J. Enna and D.B. Bylund). Elsevier.

31 Amusengeri, A., Tata, R.B., and Bishop, O.T. (2020). Understanding the pyrimethamine drug resistance mechanism via combined molecular dynamics and dynamic residue network analysis. *Molecules* 25: 904–927.

32 Chadwick, M., Trewin, H., Gawthrop, F., and Wagstaff, C. (2013). Sesquiterpenoids lactones: benefits to plants and people. *International Journal of Molecular Sciences* 14 (6): 12780–12805.

33 Krishna, S., Bustamante, L., Haynes, R.K., and Staines, H.M. (2008). Artemisinins: their growing importance in medicine. *Trends in Pharmacological Sciences* 29 (10): 520–527.

34 Ho, W.E., Peh, H.Y., Chan, T.K., and Wong, W.S.F. (2014). Artemisinins: pharmacological actions beyond anti-malarial. *Pharmacology&Therapeutics* 142 (1): 126–139.

35 Krishna, S., Uhlemann, A.C., and Haynes, R.K. (2004). Artemisinins: mechanisms of action and potential for resistance. *Drug Resistance Updates* 7 (4–5): 233–244.

36 Baggish, A.L. and Hill, D.R. (2002). Antiparasitic agent atovaquone. *Antimicrob. Agents Chemother.* 46 (5): 1163–1173.

37 Salles, J.M., Moraes, L.A., and Salles, M.C. (2003). Hepatic amoebiasis. *The Brazilian Journal of Infectious Diseases* 7 (2): 96–110.

38 Espinosa-Cantellano, M. and Martinez-Palomo, A. (2000). Pathogenesis of intestinal amoebiasis: from molecules to disease. *Clinical Microbiology Reviews* 13 (2): 318–331.

39 Aloisio, C. and Longhi, M. (2018). Diloxanide furoate binary complexes with -, methyl–, and hydroxypropyl–cyclodextrins: inclusion mode, characterization in solution and in solid state and in vitro dissolution studies. *Pharmaceutical Development and Technology* 23 (7): 723–731.

40 Pippi, B., Reginatto, P., Machado, G.M. et al. (2017). Evaluation of 8-hydroxyquinoline derivatives as hits for antifungal drug design. *Medical Mycology* 55 (7): 763–773.

41 Lee, M.R. (2008). Ipecacuanha: the South American vomiting root. *Journal of the Royal College of Physicians of Edinburgh* 38 (4): 355–360.

42 Jain, S., Chaudhary, P.N., and Gawade, V.B. (2012). Late stages in the biosynthesis of ipecac alkoloids-cephaeline, emetine and psychotrine in Alangium lamarckii Thw. (Alangiaceae). *Scientific World* 10 (10): 24–28.

43 Gupta, R., Sharma, S., Singh, R. et al. (2022). Functionalized nitroimidazole scaffold construction and their pharmaceutical applications: a 1950–2021 comprehensive overview. *Pharmaceuticals* 15: 561.

44 Lee, N., Bertholet, S., Debrabant, A. et al. (2002). Programmed cell death in the unicellular protozoan parasite Leishmania. *Cell Death & Differentiation* 9: 53–64.

45 Haldar, A.K., Sen, P., and Roy, S. (2011). Use of antimony in the treatment of leishmaniasis: current status and future directions. *Molecular Biology International* 2011: 571242.

46 Tunalı, V., Harman, M., Çavuş, İ. et al. (2022). Leishmaniasis'te Miltefosin Etkinliğinin *in vitro* Olarak Araştırılması. *Türkiye Parazitoloji Dergisi* 46 (2): 97–101.

47 Secor, W.E. (2012). Trichomonas vaginalis: treatment questions and challenges. *Expert Review of Anti-Infective Therapy* 10 (2): 107–109.

48 Thomas, J.A., Baker, N., Hutchinson, S. et al. (2018). Insights into antitrypanosomal drug mode-of-action from cytology-based profiling. *PLOS Neglected Tropical Diseases* 12 (11): e.0006980.

49 Alsford, S., Eckert, S., Baker, N. et al. (2012). High-throughtput decoding of antitrypanosomal drug efficacy and resistance. *Nature* 482: 232–236.

50 Falk, N., Berenstein, A.J., Moscatelli, G. et al. (2022). Effectiveness of nifurtimox in the treatment of Chagas disease: a long-term retrospective cohort study in children and adults. *Antimicrobial Chemotherapy* 66 (5): 1–10.

51 Boiani, M., Piacenza, L., Hernandez, P. et al. (2010). Mode of action of nifurtimox and N-oxide-containing heterocycles against Tyrpanosoma cruzi: is oxidative stress involved? *Biochem. Pharmacol* 79 (12): 1736–1745.

52 Wiedemar, N., Hauser, D.A., and Maser, P. (2020). 100 years of suramin. *Antimicrobial Agents and Chemotherapy* 64 (3): e01168–19.

53 Larson, S., Carter, K., and Hovel-Miner, G. (2021). Effects of trypanocidal drugs on DNA synthesis: new insights into melarsoprol growth inhibition. *Parasitology* 148 (10): 1143–1150.

54 De Koning, H.P. (2020). The drugs of sleeping sickness: their mechanisms of action and resistance, and a brief history. *Tropical Medicine and Infectious Disease* 5 (1): 14–36.

55 Torrele, E., Trunz, B.T., Tweats, D. et al. (2010). Fexinidazole-A new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLOS Neglected Tropical Diseases* 4 (12): e923.

56 Franco, J., Marcelo, L.S., and Comini, M.A. (2018). Drugs and drug reistance in African and American trypanosomiasis. *Annual Reports in Medicinal Chemistry* 51: 97–133.

57 Kaiser, M., Bray, M.A., Cal, M. et al. (2011). Antitrypanosomal activity of fexinidazole, a new oral nitroimidazole drug candidate for treatment of sleeping sickness. *Antimicrobial Agents and Chemotherapy* 55 (12): 5602–5608.

58 Rajao, M.A., Furtado, C., Alves, C.L. et al. (2014). Unveiling benznidazole'e mechanism of action through overexpression of DNA repair proteins in *Trypanosoma cruzi*. *Environmental and Molecular Mutagenesis* 55: 309–321.

59 Silva, L.A., Fernandes, M.D., Machado, A.S. et al. (2019). Efficacy of sulfadiazine and pyrimetamine for treatment of experimental toxoplasmosis with strains obtained from human cases of congenital disease in Brazil. *Experimental Parasitology* 202: 7–14.

60 Walson, J.L. and John-Stewart, G. (2007). Treatment of helminth co-infection in individuals with HIV-1: a systematic review of the literature. *PLoS Neglected Tropical Diseases* 1 (3): e102.

61 Gunderson, E.L., Bryant, C., Bulman, C.A. et al. (2022). Pyrvinium pamoate and structural analogs are early macrofilaricide leads. *Pharmaceuticals* 15 (2): 189–205.

62 Howard, B. (2007). Diethylcarbamazine. In: *xPharm: The Comprehensive Pharmacology Reference* (eds S.J. Enna and D.B. Bylund). Elsevier.

63 Agube, A.A., Ajaghaku, D.L., and Uzochukwu, I.C. (2020). In silico and in vitro investigations of antihelmintic activities of selected approved drugs. *Archives of Community Medicine and Public Health* 6 (2): 261–269.

64 Abongwa, M., Martin, R.J., and Robertson, A.P. (2017). A brief review on the mode of action of antinematodal drugs. *Acta Veterinariat (Beogr)* 67 (2): 137–152.

65 Larsen, A.R., Bai, R., Chung, J.H. et al. (2015). Repurposing the antihelmintic mebendazole as a hedgehog inhibitor. *Molecular Cancer Therapeutics* 14 (1): 3–13.

66 Pawluk, S.A., Roels, C.A., Wilby, K.J., and Ensom, M.H.H. (2015). A review of pharmacokinetics drug-drug interactions with the anthelmintic medications albendazole and mebendazole. *Clinical Pharmacokinetics* 54: 371–383.

67 Shankerrao, S., Bodke, Y.D., and Santoshkumar, S. (2017). Synthesis and antimicrobial activity of some imidazothiazole derivatives of benzofuran. *The Arabian Journal of Chemistry* 10 (1): 554–558.

68 Lee, K.C., Ladizinski, B., and Federman, D.G. (2012). Complications associated with use of levamisole-contaminated cocaine: an emerging public health challenge. *Mayo Clinic Proceedings* 87 (6): 581–586.

69 Soudkolaei, A.S., Kalidari, G.A., and Borji, H. (2021). Anthelmentic efficacy of fenbendazole and levamisole in native fowl in northern Iran. *Parasites & Vectors* 14: 104–111.

70 Clarkson, M.J. and Beg, M.K. (1971). Critical tests of levamisole as an anthelmintic in the horse. *Annals of Tropical Medicine & Parasitology* 65 (1): 87–91.

71 Horton, J. (2003). Human gastrointestinal helminth infections: are they now neglected diseases? *Trends in Parasitology* 19 (1): 527–531.

72 Page, S.W. (2008). Antiparasitic drugs. In: *Small Animal Clinical Pharmacology*, 2e (eds J.E. Maddison, S.W. Page and D.B. Church). 198–260.

73 Thomas, C.M. and Timson, D.J. (2020). The mechanism of action of praziquantel: can new drugs exploit similar mechanisms? *Current Medicinal Chemistry* 27 (5): 676–696.

74 Taylor, A.B., Pica-Mattocica, L., Polcaro, C.M. et al. (2015). Structural and functional characterization of the enantiomers of the antischistosomal drug oxamniquine. *PLoS Neglected Tropical Diseases* 9 (10): 1–13.

75 Huang, H., Rigouin, C., and Williams, D.L. (2012). The redox biology of schistosome parasites and applications for drug development. *Current Pharmaceutical Design* 18 (24): 3595–3611.

76 Davis, A. and Bailey, D.R. (1969). Metrifonate in urinary schistosomiasis. *The Bulletin of the World Health Organization* 41: 209–241.

77 Trainor-Moss, S. and Mutapi, F. (2016). Schistosomiasis therapeutics: what's in the pipeline? *Expert Review of Clinical Pharmacology* 9 (2): 157–160.

78 Cours, J.R. and Conceicao, M.J. (2010). Specific schistosomiasis treatment as astrategy for disease control. *Memórias do Instituto Oswaldo Cruz* 105 (4): 598–603.

79 Crump, A. and Ivermectin, O.S. (2011). "Wonder drug" from Japan: the human use perspective. *Proceedings of the Japan Academy Ser B Physical and Biological Sciences* 87 (2): 13–28.

80 Reis, G., Silva, E.A.S.M., Silva, D.C.M. et al. (2022). Effect of early treatment with ivermectin among patients with covid-19. *The New England Journal of Medicine* 386: 1721–1731.

81 Lim, S.C.L., Hor, C.P., Tay, K.H. et al. (2022). Efficacy of ivermectin treatment on disease progression among adults with mild to moderate COVID-19 and comorbidities the I-TECH randomized clinical trial. *JAMA Internal Medicine* 182 (4): 426–435.

82 Marcolino, M.S., Meira, K.C., Guimaraes, N.S. et al. (2022). Systematic review and meta-analysis of ivermectin for treatment of COVID-19: evidence beyond the hype. *BMC Infectious Diseases* 22: 639–663.

83 Okumus, N., Demirturk, N., Cetinkaya, R.A. et al. (2021). Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infectious Diseases* 21 (1): 411–421.

84 Idriss, S. and Levitt, J. (2009). Malathion for head lice and scabies: treatment and safety considerations. *Journal of Drugs in Dermatology* 8 (8): 715–720.

85 Chandler, D.J. and Fuller, L.C. (2019). A review of scabies: an infestation more than skin deep. *Dermatology* 235: 79–90.

86 Wolday, D., Gebrecherkos, T., Arefaine, Z.G. et al. (2021). Effect of co-infection with intestinal parasites on COVID-19 severity: a prospective observational cohort study. *EClinical Medicine* 39: 101054.

87 Chawla, B., Jhingran, A., Panigrahi, A. et al. (2011). Paromomycin affects translation and vesicle-mediated trafficking as revealed by proteomics of paromomycin-susceptible-resistant *Leishmania donovani*. *PLoS One* 6 (10): e26660.

88 Islam, R. and Lynch, J.W. (2012). Mechanism of action of the insecticides, lindane and fipronil on glycine receptor chloride channels. *British Journal of Pharmacology* 165 (8): 2707–2720.

89 Piskac-Collier, A.L. and Smith, M.A. (2009). Lindane-induced generation of reactive oxygen species and depletion of glutathione do not result in necrosis in renal distal tubule cells. *Journal of Toxicology and Environmental Health, Part A* 72 (9): 1160–1167.

90 Pridmore, R.D., Thrush, S.F., Wilcock, R.J. et al. (1991). Effect of the organochlorine pesticide technical chlordane on the population structure of suspension and deposit feeding bivalves. *The Marine Ecology Progress Series* 76: 261–271.

91 Mendes, V., Ribeiro, C., Delgada, I. et al. (2021). The association between environmental exposures to chlordanes, adiposity and diabetes-related features: a systematic review and meta-analysis. *Scientific Reports* 11: 14546.

92 Pietrantoni, I., Rossi, M., Scarselli, M. et al. (2018). Dichlorodiphenyltrichloroethane, an old pesticide with a new mechanism of toxicity. *Current Topics in Pharmacology* 22: 69–76.

93 Tiwari, B., Khaewar, S., and Tiwari, D.N. (2018). Pesticides and rice agriculture. In: *Cyanobacteria* (eds A.K. Mishra, D.N. Tiwari and A.N. Rai), 303–325. Elsevier.

94 Gleave, K., Lissenden, N., Chaplin, M. et al. (2021). Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. *The Cochrane Database of Systematic Reviews* 5 (5): CD012776.

95 Syme, T., Gbegbo, M., Obuobi, D. et al. (2022). Pyrethroid-piperonyl butoxide (PBO) nets reduce the efficacy of indoor residual spraying with pirimiphos-methyl against pyrethroid-resistant malaria vectors. *Scientific Reports* 12: 6857.

96 Sharma, R. and Singal, A. (2011). Topical permethrin and oral ivermectin in the management of scabies: a prospective, randomized, double blind, controlled study. *Indian J Dermatol Venereol Leprol* 77: 581–586.

97 Omotoso, G., Oloyede, O., Lawal, S. et al. (2002). Permethrin exposure affects neurobehavior and cellular characterization in rats' brain. *Environmental Analysis Health and Toxicology* 35 (4): e2020022.

98 Yamada, T., Lake, B.G., and Cohen, S.M. (2022). Evaluation of the human hazard of the liver and lung tumors in mice treated with permethrin based on mode of action. *Critical Reviews in Toxicology* 52 (1): 1–31.

99 Sharquie, K.E., Al-Rawi, J.R., Noaimi, A.A., and Al-Hassany, H.M. (2012). Treatment of scabies using 8% and 10% topical sulfur ointment in different regimens of application. *Journal of Drugs in Dermatology* 11 (3): 357–364.

100 Mila-Kierzenkowska, C., Wozniak, A., Krzyzynska-Malinowska, E. et al. (2017). Comparative efficacy of topical pertmehrin, crotamiton and sulfur ointment in treatment of scabies. 11(3):357-364. *Journal of Arthropod-Borne Diseases* 11 (1): 1–9.

101 Sharma, G., Dhankar, G., Thakur, K. et al. (2016). Benzyl benzoate-loaded microemulsion for topical applications: enhanced dermatokinetic profile and better delivery promises. *AAPS PharmSciTech* 17: 1221–1231.

102 Karthikeyan, K. (2005). Treatment of scabies: newer perspectives. *Postgraduate Medical Journal* 81: 7–11.

103 Choi, D., Ji, Y., Jang, Y. et al. (2020). Crotamiton, an anti-scabies agent, suppresses histamine- and chloroquine-induced itch pathways in sensory neurons and alleviates scratching in mice. *Biomolecules & Therapeutics (Seoul)* 28 (6): 569–575.

104 Seiler, J.C, Keech, R.C., Aker, J.L. et al. (2022). Spinosad at 0.9% in the treatment of scabies: efficacy results from 2 multicenter, randomized, double-blind, vehicle-controlled studies. *Journal of the American Academy of Dermatology* 86 (1): 97–103.

105 Kirst, H.A (2010). The spinosyn family of insecticides: realizing the potential of natural products research. *The Journal of Antibiotics* 63: 101–111.

106 Woods, A.D, Porter, C.L, and Feldman, S.R (2021). Abametapir for the treatment of head lice: a drug review. *Annals of Pharmacotherapy* 56 (3): 352–357.

107 Aditya, S. and Abametapir:, R.A (2021). A novel pediculicide with a unique mechanism. *Journal of Dr. NTR University of Health Sciences* 10 (2): 69–71.