Man is affected with infections caused by various helminthes or worms. These infections pose a major health problem. Multiple infections are common in men. Large populations are affected by serious disease thereby causing ill health, inefficiency, malnutrition. The disease caused by helminthes is known as helminthiasis. Man acquires it by contact, eating infected food, via mosquitoes (filarial worms) soil and water. The worms enter the body in the form of eggs or larvae.

The term worm\(^1\) is applied to an assemblage of organisms with elongated bodies and have more or less creeping habit; it has a precise zoological meaning. The parasitic helminthes fall under four different phyla\(^2\), namely platyhelminthes, acanthocephalla, nematohelminthes and annelida. These phyla occupy an important position in the animal kingdom. In 1947 stoll\(^3\) estimated that around 400 million, helminthes occur in among 2,000 million people. There is enough reason to believe that the number of people with helminth infections has increased considerably.

Helminthes cause mechanical damage by biting intestinal wall and causing hemorrhages (hook worms) tumors, (schistosomes spirata and peforate) and cause peritonitis of walls of digestive tract. Tissue damage and inflammation due to burrowing is caused by lung flukes and guinea worms. Some cause loss of blood, anemia and vitamin deficiency ex. dibothricephalus cause B\(_{12}\) deficiency. Some block
passages and cause obstruction ex. Ascaris, liver flukes and bancroffs filarial and they interfere with the normal flow of lymph, bile etc. some cause eosinophilia, carry pathogenic bacteria allergic reactions (migrating larvae, guinea worms etc.). These allergic reactions give rise to the symptoms of helminth infections. Helminthes cause variety of diseases. Domestic animals also carry the burden of parasitic worms. The infections of helminthes are wide and cause number of diseases in man and animals. The main parasitic worms of india are roundworms, hookworms, threadworms, tapeworms, filarial worms, guineaworms, and flukes which fall under the categories of nematodes, cestodes and trematodes. The brief account of the different types of common helminth diseases and drugs are given below.

1. **Ancyclostomiasis:** It is caused by an intestinal infection in man by two hookworms, *ancyclostoma duodenale* and *necatar americanas*. The disease is found in tropical and subtropical countries. Man acquires infection when the filarial worm larvae penetrate through the skin of hand and feet. They develop in small intestine. Infections results in gastrointestinal disturbances like anemia and nervous disorders.

   **Drug:** Tetrachloroethylene and carbon tetrachloride are effective.

2. **Ascariasis:** It is roundworm infection, caused by *Ascaris lumbricoides*. It lives in small intestine of man, certain apes and pigs. About 16% of the population of country has been affected by
ascariasis. Worms in intestine cause abdominal pains, headache and vomiting.

**Drugs**: piperazine salts are most useful.

3. **Trichuriasis**: it is a whipworm infection caused by *trichuris trichiura*, which occurs in man and pigs. It resides in the large intestine, Infection in human results from the ingestion of ova from facially polluted soil. It was common in worm climate. Loss of appetite and diarrhoea may occur, due to infaction of this worm.

4. **Enterobiasis**: It is commonly called pinworm infection caused by *Enterobius vermicularis*. This kind of infection is most common in children. The worms cause irritation, loss of appetite, sleeplessness and nervousness.

**Drug**: Piperazine is the drug of choice in enterobiasis.

5. **Strongyloidiasis**:

This is most frequently by penetration of the skin by the larva of *strongyloides stercoralis*, commonly called thread worms. These invade the lining of the alimentary canal.

**Drug**: Drugs used are dithiazine.

6. **Trichinosis**: Trichinosis is caused by *Trichinella spiralis*. These occur in small intestine of man, pig, rat and many other mammals. Infection is acquired by eating raw or improperly cooked pork.

**Drug**: Piperazine citrate

7. **Taeniasis**: It is a tapeworm. Infection is caused by the species belonging to the genus Taenia which include mainly *Taenia solium*,


and *T. saginata*. Infection is acquired by eating improperly cooking pork.

**Drug:** Commonly antimalarial drugs are used.

8. **Schistosomiasis:** It is caused by three species of blood flukes. *Schistosoma mansori S Japonicum and S. haematobiuia*. These live in blood streams.

**Drug:** Antimony compounds are used.

9. **Fascioliasis:** It is caused by intestinal fluke *fosciolopsis foelleborni*. It causes erosion of intestinal lining, resulting in bleeding and pain.

**Drug:** Hexylresorcinol is helpful.

10. **Fascioliasis:** It is caused by liver fluke *fasciola hepatica*. It usually inhabits the liver and bile duct of cattle, sheep, rabbit and also other vertebrates. It damages the liver as well as bile duct of the host and causes the diseases called liver rot or fascioliasis.

**Drug:** Hexachloroethane and ccl₄ are effective.

11. **Paragonimiasis:** This disease is caused by lungs fluke *paragonimus westermanel* and result in chest pain and shortness of breath.

**Drug:** Emetine hydrochloride and sulpha drugs are effective.

12. **Filariasis:** It is caused by filarial worms *wucheria bancroft* and *W. malayi*. These worms live in the lymphatic vessels and connective tissues of the body. Infection is acquired through the bites of culex mosquito. This disease disfigure legs and other parts of the body and are enormously enlarged called elephantiasis.
**Drug**: Hetrazan.

In this way these parasitic worms cause so much harm to man and animals.

Therefore methods are being tried to suppress the disease in man and animals for this purpose, the search is on for chemicals which have the properties to remove or kill these pathogenic worms or helminthes. These substances or chemicals are known as anthelmintic agents.

Many compounds show good activity against worm infections, carbontetrachloride, tetrachloro ethylene, hexachloro resorcinol were earlier known anthelmintics. Lamson and his coworkers reported various phenolic anthelmintics. McDonagh and Christopherson reported the properties of antimony compound for curing schistosomiasis. Later piperazine for enterobius and dithiazine for skin fluke (strongyloides) and chloroquine for clonorchis were discovered in 1938. Phenothiazine and hexachloro ethane were reported by Harwood. Later various drugs atabrin for tapeworm antimony and arsenic compounds for filariasis and hetrazan were introduced as anthelmintics.

Earlier number of workers\textsuperscript{10-12} have reported the anthelmintic activities of a large number of plants as well as synthetic compounds and found many of them possess good anthelmintic activities. Recently some compounds like triazolothiadiazines\textsuperscript{13}, quinozolines\textsuperscript{14}, heterocyclic compounds\textsuperscript{15}, and S. substituted phenothiazine\textsuperscript{16} and piperazine have been suggested as good potential anthelmintic agents.
Anthelmintic may act in two ways. The drugs which directly or indirectly kill the worms are called vermicides ex. dichlorophene, hexylresorcinol etc. Those which expel worms from the body of host usually by paralyzing them, are known as vermifuges eg. piperazine santonin, chenopodium oil etc. The chemotherapeutic anthelmintics destroy the parasitic worms or remove them from hosts either by the way of.

1. Direct action on the worm cause paralysis or death.
2. By irritating the tissue of the parasite.
3. Antimetabolic interfering with the metabolism of parasite.

An ideal anthelmintic should have a broad spectrum of action. It should first paralyse the worm and then expel it. It should achieve a high percentage of cure with a single therapeutic dose. It should be free from toxicity to the host and should be cheap. But at present only few anthelmintics drugs meet all requirements of a good anthelmintic agent.

**Classification:**

Anthelmintics may be classified in two different ways.

(a) According to their mode of action

(i) Vermicides are drugs that weaken the worms so that they can no longer attach themselves to the intestinal mucosa and thus can be expelled.

(b) According to their chemical structure:

(i) Chlorinated hydrocarbons ccl₄, tetrachloroethylene etc.
(ii) Phenols and related compounds thymol (oil of thyme) hexylresorcinol.

(iii) Antimonials and arsenicals. Stibophen, tartaremetin.

(iv) Piperazine derivatives - hetrazan, antepar,

(v) Triphenyl methane, cyanide dyes, gentian violet, crystal violet.

(vi) Phenothiazines, certain antimalarials (azacrine) certain xanthones, carbamates,

(vii) Natural products pelletierine, santonin, oil of chenopodium, aspidium and emetin.

**Mode of Action:**

Anthelmintics are the drugs used in the treatment of helminthiasis. They are used to kill or remove the parasitic worms and rid the host of them. An ideal and effective anthelmintic drug, is one that causes minimum toxicity to the mucous membrane of gastrointestinal tract and alimentary tract, if absorbed from it. Drug should be chemically stable, inexpensive and tolerable orally without producing symptoms. Most important is that the drug should reach that portion of the intestine, where the worm infection occurs with minimal degree of absorption. It should be immediately lethal. Anthelmintic causes death or remove the worm by stimulating paralysis or necrosis. This is accomplished by gaining access into the body via cuticle or ingestion and interfering with worms’ metabolism. It should be specific.

Vegetable remedies like malefern Cusso, arecanut (tape worms) and santonin (nematods) are the earliest known anthelmintics. In
1880, a landmark was set when the value of thymol for hook worms was established by some Italian workers, other anthelmintics were oil of chenopodium(1913), CCl₄(1921), tetrachloroethene(1925), hexylresorcinol(1930), replaced oil of chenopodium in ascariasis. McDonagh and christopherson established the value of antimony compound for schistosomiasis, Gentian violet (1927) was replaced by chloroquine for clonorchis piperazine for enterobius and dithiazine for stronglyloides. Phenothiazine (1938) by Harwood and hexachloroethane (1926) for fasciola was discovered. After world war II aterbin (for tape worms), antimony and arsenic compounds and hetrazan (for filariasis) were introduced after world war II. Piperazine salts played vital role as anthelmintics (i.e.) hetrazan is useful against a number of helminthes. Several workers have illustrated the anthelmintic activity of a large number of compounds of synthetic origin.

**Literature survey of some group is given below.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Group</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterocyclic compound</td>
<td>isoxazoles 3-aryl 5-hexamethylisoxazole</td>
<td>Anthelmintic</td>
<td>F.H.G Sen et al.²²</td>
</tr>
<tr>
<td>Heterocyclic compounds</td>
<td>Coumarin</td>
<td>Anthelmintic</td>
<td>Mahmounel et al.²³</td>
</tr>
<tr>
<td>Heterocyclic Compounds</td>
<td>Benzoxazole and Benzothizole</td>
<td>Anthelmintic (Fisemia Foetida)</td>
<td>Probodh Chandar Sharma et al.²⁴</td>
</tr>
<tr>
<td>Heterocyclic Compounds</td>
<td>B-hydroxyketo amides (BKAs)</td>
<td>Haemonchus contorts</td>
<td>Byung. H. Lee et al.²⁵</td>
</tr>
</tbody>
</table>
Evaluation of technique:

In vitro techniques involve lumbricoides, unicara strencephala and some other species of worms. Very few helminthes of man infect the laboratory animals. The condition of alimentary canal of different experimental animals may not be the same. So the screening of anthelmintic activity may be done by exposing the worm to the solution of anthelmintic substances.

In has been reported by Sollman\textsuperscript{26} that all clinical anthelmintics are toxic to earth worms. Trandelberg proved that various species of Ascaris have remarkable anatomical similarities with common earthworms. Furthermore a number of workers\textsuperscript{27} have used earthworms for preliminary in vitro evaluation of anthelmintic activity of new substances. Due to the availability of earth worms and their acceptance as substitute, qualitative in vitro anthelmintic screening of synthesized heterocyclic compounds was done using earth worms by adopting the technique given by watkins\textsuperscript{28}.

Materials and Methods:

4 and 2 percent solutions of thiazolidinone, quinoline, benzoxazole and coumarin were prepared in ethylene glycol. Same concentrations (4\% and 2\%) of standard drug piperazine hydrochloride were also prepared in ethylene glycol.

In the Petridish, 25 ml normal saline solution and 2 ml of test sample solution were poured. Two living earthworms of nearly equal size washed with normal saline solution were transferred into the petridish, same experiment was performed with the standard drug.
The time taken by earthworm to become motionless was noted as paralytic time. The time of death is noted as lethal time. Death of motionless earthworm was ascertained by placing the earthworm in luckworm water, which stimulates movement if the worm is alive. Experiments were carried out in duplicated and average values are shown in the forms of graphs. The blank experiments with only ethyleneglycol showed no activity and the earthworms were active even after 100 hrs.
Fig. 6.1 Anthelmintic activity of synthesized quinoline derivatives
(2 % solution)

![Anthelmintic activity of synthesized quinoline derivatives (2 % solution)](image)

Fig. 6.2 Anthelmintic activity of synthesized quinoline derivatives
(4 % solution)

![Anthelmintic activity of synthesized quinoline derivatives (4 % solution)](image)
Fig. 6.3 Anthelmintic activity of synthesized quinoline derivatives (2 %)

Fig. 6.4 Anthelmintic activity of synthesized quinoline derivatives (4 %)
Fig. 6.5 Anthelmintic activity of synthesized quinoline derivatives (2 %)

Fig. 6.6 Anthelmintic activity of synthesized quinoline derivatives (4 %)
Fig. 6.7 Anthelmintic activity of synthesized thiazolidinone derivatives (2 %)

Fig. 6.8 Anthelmintic activity of synthesized thiazolidinone derivatives (4 %)
Fig. 6.9 Anthelmintic activity of synthesized thiazolidinone derivatives (2 %)

Fig. 6.10 Anthelmintic activity of synthesized thiazolidinone derivatives (4 %)
Fig. 6.11 Anthelmintic activity of synthesized Benzoxazole derivatives (2 %)

![Graph showing time (in minutes) for paralytic and lethal activity of synthesized Benzoxazole derivatives at 2% concentration.]

Fig. 6.12 Anthelmintic activity of synthesized Benzoxazole derivatives (4 %)

![Graph showing time (in minutes) for paralytic and lethal activity of synthesized Benzoxazole derivatives at 4% concentration.]

Chapter-6  Anthelmintic Activity
**Fig. 6.13 Anthelmintic activity of synthesized Benzoxazole derivatives (2%)**

![Bar chart showing the anthelmintic activity of synthesized Benzoxazole derivatives (2%)](chart1.png)

**Fig. 6.14 Anthelmintic activity of synthesized Benzoxazole derivatives (4%)**

![Bar chart showing the anthelmintic activity of synthesized Benzoxazole derivatives (4%)](chart2.png)
Fig. 6.15: Anthelmintic activity of synthesized Chromen-2-one derivatives (2%)

![Bar chart showing paralytic and lethal time for synthesized Chromen-2-one derivatives (2%)](chart1.png)

Fig. 6.16: Anthelmintic activity of synthesized Chromen-2-one derivatives (4%)

![Bar chart showing paralytic and lethal time for synthesized Chromen-2-one derivatives (4%)](chart2.png)
Fig. 6.17 Anthelmintic activity of synthesized Chromen-2-one derivatives (2%)

Fig. 6.18 Anthelmintic activity of synthesized Chromen-2-one derivatives (4%)
**Results and Discussion:**

On comparing the paralytic time and lethal time of synthesized derivatives with standard drug used, it has been observed that thiazolidinone derivatives, substituted with chlorophenyl, 4-hydroxy-3-methoxy, dimethylaminobenzaldehyde, groups have shown significant anthelmentic activity due to the increase of basic moiety.

In case of Benzoxazole derivatives, compounds substituted with p-methoxy and chloro substituted, dimethylamino, trimethyl benzaldehyde groups showed moderate to good anthelmentic activity, while coumarin derivatives have exhibited good anthelmentic activity, if substituted by methylamino, aminophenyl, methoxy, bromo and chloro, substituted aniline and quinoline group chloro, methyl group showed moderate activity.

In the comparison of all four groups derivatives with standard drug. Thiazolidinone group have shown promising anthelmentic activity while benzoxazole, coumarin and quinoline groups have shown moderate to good anthelmentic activity, and some of the chromen-2-one derivatives have shown higher activity than the standard drug.
REFERENCES


