Man is effected with infections caused by various helminths or worms. These infections pose a major health problem. Multiple infections are common in man. Large populations are affected by serious diseases, there by causing ill health, inefficiency, malnutrition. The disease caused by helminths 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 more or less creeping habitat. It has a precise zoological meaning. The parasitic helminths fall under four different phyla\(^2\) namely platyhelminths, acanthocephala, nematohelminths and annelida. These phyla occupy an important position in the animal kingdom. In 1947 Stoll\(^3\) estimated that around 400 million helminths occur in among some 2,000 million people. There is enough reason to believe that the number of people with helminth infections has increased considerably.

Helminths cause mechanical damage by biting intestinal wall and causing haemorrhages (hook worms), tumors (schistosomes, spirurata 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, anaemia and vitamin deficiency ex. dicrothriocephalus cause B\(_{12}\) deficiency. Some block passages and cause obstruction ex. ascaris, liver flukes and bancrofts filaria 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. Helminths\(^4\) cause a variety of diseases. Domestic animals also carry the burden of parasitic worms. The infections of helminths are wide and cause number of diseases in man and animals.
The main parasitic worms found in India are roundworms, hookworms, thread worms, tapeworms, filarial worms, guinea worms 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 used for them are given below.

1. Ancylostomiasis:

   It is caused by an intestinal infection in man by two hookworms _Ancylostoma duodenale_ and _Necator americanus_. 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 anaemia and nervous disorders.

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

2. Ascariasis:

   It is a roundworm infection caused by _Ascaris lumbricoides_. Infection causes with contaminated food and water. It lives in small intestine of man, certain apes and pigs. About 16% of the population of country is affected by ascariasis. Worms in intestine cause abdominal pains, headache and vomittings.

   **Drug** - 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 faecally polluted soil. It was common in warm climate. Loss of appetite and diarrhoea may occur.
4. Enterobiasis:

It is commonly called pinworm infection caused by Enterobius vermicularis. This kind of infection is most common in children. It's larval forms mature in the ileum. 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 acquired by penetration of the skin by the larva of Strongyloides Stercralis, commonly called thread worms. These invade the lining of the alimentary canal.

**Drugs** - 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 cooked pork.

**Drug** - Commonly antimalarial drugs are used.
8. Schistosomasis:

It is caused by three species of blood flukes, *Schistosoma mansoni*, *S. Japonicum* and *S. haematobium*. These live in blood streams.

**Drug-** Antimony compounds are used.

9. Fasciolopsiasis:

It is caused by intestinal fluke *Fasciolopsis 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 westermani* and results in chest pain and shortness of breath.

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

12. Filariasis:

It is caused by filarial worms *Wuchereria bancrofti* 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 helminths. These substances or chemicals are known as anthelmintic agents.

Many compounds show good activity against worm infections. Carbontetrachloride, tetrachloroethylene, hexachloro resorcinol were earlier known anthelmintics. Lamson and his coworkers reported various phenolic anthelmintics.

McDonagh and Christopherson reported the properties of antimony compounds for curing schistosomiasis. Later piperazine for enterobius and dithiazone 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 possessed good anthelmintic activities. Recently some compounds like, triazolothiadiazines\textsuperscript{13-14}, quinozolines\textsuperscript{15}, heterocyclic compounds\textsuperscript{16} and s-substituted phenothiazine\textsuperscript{17} 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 paralysing them are known as vermilfuges eg. piperazine, santonin, chenopodium oil etc. The chemotherapeutic anthelmintics, destroy the parasitic worms or remove them from hosts either the way of:
1. Direct action on the worm causing 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 a few anthelmintic 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 paralyse or kill parasites.

(ii) Vermifuges 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, tartar emetin.

iv. Piperazine derivatives- hetrazan, antepar.

v. Triphenyl methane cyanine dyes- gentian violet, crystal violet.

vi. Phenothiazines, certain antimalariais (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\textsuperscript{22} 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 infestation occurs with minimal degree of absorption. It should be immediately lethal. Anthelmintic causes death or remove the worm by stimulating paralysis or nacrosis. This is accomplished by gaining access into the body via cutile 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], CCl\textsubscript{4} [1921], tetrachloroethylene [1925], hexylresorcinol [1930], replaced oil of chenopodium in asciasis. McDonagh and christopherson established the value of antimony compounds for schistosomiasis. Gentian violet [1927] was replaced by chloroquine for clonorchis, piperazine for enterobius and dithiazine for strongyloides. Phenothiazine [1938] by Harwood and hexachloroethane [1926] for fasciola were discovered. After world war II, aterbin (for tape worms), antimony and arsenic compounds and hetrazan (for filiasis) were introduced. After world war II, piperazine salts played vital role as anthelmintics (i.e.) hetrazan is useful against a number of helminths. Several workers have illustrated the anthelmintic activity of a large number of compounds of synthetic origin. They are given in table.
## Literature Survey.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Group</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterocyclic</td>
<td>isoxazoles, 3-aryl-5-halomethyl isoxazoles</td>
<td>anthelmintic</td>
<td>H. G. Sen et al.(^{23})</td>
</tr>
<tr>
<td>compounds</td>
<td>isoxazoles, dihydro isoxazole</td>
<td>anthelmintic (pinworm A.tetraptera)</td>
<td>L. Herbort et al.(^{24})</td>
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<tr>
<td></td>
<td>isoxazoles, 3-tolyl thio-4-amino-4,5-dihydroisoxazole</td>
<td>anthelmintic (Syphacia obvelata and Aspiculurus)</td>
<td>Jing Jong et al.(^{25})</td>
</tr>
<tr>
<td></td>
<td>3-oxy-substituted isoxazolines</td>
<td>anthelmintics (endoparasites)</td>
<td>D. Gerald et al.(^{26})</td>
</tr>
<tr>
<td>Heterocyclic</td>
<td>pyrazoles</td>
<td>anthelmintics</td>
<td>H. G. Sen et al.(^{27})</td>
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<tr>
<td>compounds</td>
<td>pyridines</td>
<td>anthelmintic</td>
<td>B. Tullio(^{28})</td>
</tr>
</tbody>
</table>

### Evaluation of technique:

In vitro techniques involve *A. lumbricoides, Unicara strencecephala*, and some other species of worms. Very few helminths 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\(^{29}\) that all clinical anthelmintics are toxic to earthworms. Trandelberg proved that various species of Ascaris have remarkable anatomical similarities with common earthworms. Furthermore a number of workers\(^{30-38}\) 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 synthesised heterocyclic compounds, was done using earth worms by adopting the technique given by Watkins\(^{39}\).
Materials and Methods

4 and 2 percent solutions of pyrazolines, isoxazoles, isoxazolines, imidazolin-5-one and 1,4-dihydropyridines were prepared in ethylene glycol. Same concentrations (4% and 2%) of standard drug piperazine hydrochloride was also prepared in ethylene glycol.

In the petridish, 25ml. normal saline solution and 2ml. 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.

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 luke warm water, which stimulates movement if the worm is alive. Experiments were carried out in duplicate and average values are shown in the form of graphs. The blank experiments with only ethylene glycol showed no activity and the earthworms were active even after 100hrs.
Fig. 2: Anthelmintic Activity of Pyrazolines (Series 2)

**Paralytic/lethal time in minutes**
4% Concentration solutions graph

- Lethal time
- Paralytic time

**Compound Code**
- PS20
- PS19
- PS18
- PS17
- PS16
- PS15
- PS14
- PS13
- PS12
- PS11

**Standard**
- 10

**Paralytic/lethal time in minutes**
2% Concentration solutions graph

- Lethal time
- Paralytic time

**Compound Code**
- PS20
- PS19
- PS18
- PS17
- PS16
- PS15
- PS14
- PS13
- PS12
- PS11
Fig. 3: Anthelmintic Activity of Isoxazoles/Isoxazolines (Series 1)

Paralytic/lethal time in minutes
4% Concentration Solutions Graph

- Lethal time
- Paralytic time

Paralytic/lethal time in minutes
2% Concentration Solutions Graph

- Lethal time
- Paralytic time
Fig. 4: Anthelmintic Activity of Isoxazoles/Isoxazolines (Series 2)

Paralytic/lethal time in minutes
4% Concentration Solutions Graph

Lethal time  Paralytic time

Paralytic/lethal time in minutes
2% Concentration Solutions Graph

Lethal time  Paralytic time
Fig. 5: Anthelmintic Activity of Imidazolin-5-ones

Paralytic/lethal time in minutes
4% Concentration Solutions Graph

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Paralytic time</th>
<th>Lethal time</th>
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<tbody>
<tr>
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<td>23</td>
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<td>PS49</td>
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Paralytic/lethal time in minutes
2% Concentration Solutions Graph

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<tr>
<th>Compound Code</th>
<th>Paralytic time</th>
<th>Lethal time</th>
</tr>
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<tbody>
<tr>
<td>Standard</td>
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<td>18</td>
</tr>
<tr>
<td>PS50</td>
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<tr>
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<td>28</td>
</tr>
<tr>
<td>PS41</td>
<td>18</td>
<td>30</td>
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</tbody>
</table>
Fig. 6: Anthelmintic Activity of 1,4-dihydropyridines

**4% Concentration Solutions Graph**

- **Standard**: 10
- **PS60**: 12
- **PS59**: 14
- **PS58**: 10
- **PS57**: 13
- **PS56**: 8
- **PS55**: 11
- **PS54**: 17
- **PS53**: 8
- **PS52**: 6
- **PS51**: 10

Paralytic/lethal time in minutes

**2% Concentration Solutions Graph**

- **Standard**: 12
- **PS60**: 18
- **PS59**: 17
- **PS58**: 14
- **PS57**: 17
- **PS56**: 13
- **PS55**: 15
- **PS54**: 12
- **PS53**: 9
- **PS52**: 8
- **PS51**: 14

Paralytic/lethal time in minutes

☐ Lethal time  ☐ Paralytic time
Results and Discussion:

On comparing the lethal time of pyrazoline (1st series) with that of standard, it is observed that the methoxy phenyl and chlorophenyl derivatives are more potent. In the second series of pyrazolines the chloro phenyl and 4-hydroxy-3-methoxy phenyl derivatives exhibited more potency. In the two series of isoxazoles & isoxazolines, almost all the derivatives exhibited promising anthelmintic activity. In the imidazolin-5-one series and 1,4-dihydropyridine series maximum number of compounds showed good potency.

SUMMARY

4 and 2 percent solutions of synthesized compounds were prepared in ethylene glycol. Same concentration of standard drug piperazine hydrochloride was also prepared in ethylene glycol. The test sample solutions are poured in to the petridish containing earthworm. The time taken by the earthworm to become motion less was noted as paralytic time. The time of death is noted as lethal time. Experiments were performed in duplicate and average values are noted. Overall the anthelmintic activity of synthesized compounds was good and they may be used as good anthelmintics.
References:


