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Review Article

To Study Anthelmintic Activity of Herbal Drug

Indra Mohan Kumar*, Sana Nusrat Praween

A and E College of Pharmacy Samastipur, Bihar.

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ABSTRACT

Anthelmintic drugs are used to treat helminthiasis, a condition brought on by parasitic worms known as helminths. These worms can infect both people and animals, resulting in a variety of illnesses and health problems. In order to assess the effectiveness of various medicinal plants as anthelmintics, researchers investigated alternatives to conventional medicine and performed studies. In these investigations, several screening techniques and strategies have been used to identify the potential anthelmintic activity of plant species. These plants' extracts include bioactive substances that may disrupt the systems and metabolism of the parasites, resulting in their anthelmintic activity. According to the research so far, traditional medicinal herbs have the potential to produce entirely new, powerful anthelmintic chemicals. In order to replace currently available synthetic medications, which frequently have drawbacks and undesirable side effects, researchers are actively exploring such herbal remedies. Helminths or Parasitic worms of humans may cause chronic and sometimes deadly diseases, considered as neglected tropical diseases (NTDs) that infect around two billion people worldwide. Plants have been used as anthelmintics from ancient times. This review is a compilation of plants as source of anthelmintic drug. All information presented in this review article regarding the anthelmintic activities of plants from 2005 and has been acquired by approaching various electronic databases, including Scopus, Google scholar, Web of science and PubMed. Literature was surveyed for anthelmintic activity of plants which showed that secondary metabolites of plants like terpenes, glycosides, saponins, flavonoids, tannins and alkaloids were having anthelmintic activity. Since this review is a compilation of anthelmintic activity of plants from the year 2005, it will definitely be a fruitful study for researchers working in this field.

INTRODUCTION

Parasitic worms or helminths cause chronic and sometimes deadly diseases that have a major socio-economic impact worldwide.[1] In humans, the disease caused by the parasitic worms is about

***Corresponding Author:** Indra Mohan Kumar
Address: *A and E College of Pharmacy Samastipur, Bihar.*
Email ✉: indramohan7277@gmail.com

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14 million globally, also called neglected tropical diseases (NTDs).[2] In agricultural animals, diseases caused by parasites led to losses of about billions of dollars per year throughout the world.[3,4] Gastrointestinal nematodes (GI), such as hookworms, whipworms, and roundworms affected under 15 years most.[5] Approximately more than 10% of the population is infected by GI nematodes worldwide.[6] As of now, no vaccines are available in the market, so, control of helminths lies on the some of effective drugs, called anthelmintics, but their inadequate use causes serious drug resistance problems worldwide, so, urgent need is there for isolating, identifying new anthelmintic drugs,[7] for humans, its lies on chemotherapy.[8] Parasitic nematodes in human are two types : intestinal nematodes and tissue or blood nematodes.[9] Intestinal nematodes includes - Ancylostoma duodenale, Trichuris trichiura, Ascaris lumbricoides, Enterobius vermicularis, and Strongyloides stercoralis, etc.[10] Helminths lives in the GI tract of their hosts, and feed off living hosts, taking nutrients from host and causing infection/diseases and normally more prone to children, soil-transmitted schistosomiasis and helminthiasis are the most significant helminthiases, responsible for neglected tropical disesses.[11,12] It also causes indirect disease burden through the immune system impairment, leads to malaria, tuberculosis, or human immunodeficiency virus/acquired immunodeficiency syndrome.[13] Adult parasites survive for a long time in their human host and feeds directly from the blood of their hosts, thus helminths cause iron-deficiency anemia.[14] Chronic helminth infections are characterized by a Type II helper T cells type response.[15,⇓,⇓,⇓-20] Helminthiasis also known as worm infestation is one of the most prevalent parasitic infestations both in developed and developing countries affecting around 1/3rd of the world's population. As per WHO, around 1.5 billion people are infested with soil-transmitted helminths (STH) worldwide [21]. India has the highest burden of STH among all the countries contributing to one-fourth of total global cases which is prevalent among children of age group 1-14 y [22]. Overall prevalence of STH in India ranges from 13% to 66% [23]. Parasites causing infections can be broadly classified into tapeworms, flukes, and roundworms. Helminths cause infection by faeco-oral route or by direct entry through the skin of the host and then lodging in the intestine [24]. Intestinal worms cause decreased absorption, blood loss, intestinal or lymphatic obstruction and secretion of toxins which leads to health hazards like undernourishment, anaemia, eosinophilia and pneumonia [25]. In extreme cases of intestinal infestation, the mass and volume of the worms may cause tear of the muscular layer leading to peritonitis, volvulus and gangrene of the intestine [26]. A large number of anthelmintic drugs (AHDs) are now available in the market which include benzimidazole class like albendazole and mebendazole, macrocyclic lactones like ivermectin or pyrazinoisoquinoline derivative like praziquantel [27, 28]. The current anthelmintic therapies exert their action by incapacitating the parasite by causing damage and paralysis of the worm so that the immune system can eliminate it, or by altering its metabolic processes. But the metabolic requirements of these parasites vary greatly from one species to another and because of that drugs that are highly effective against one type of worm may be ineffective or less effective against others [29]. But the emergence of resistance to the currently available AHDs is a major concern and newer anthelmintics with a novel mode of action has become necessary [30]. Herbal drugs in recent years have become popular and also gained importance due to their safety, efficacy and cost effectiveness in treating various

diseases. Centella asiatica Linn. known as 'Gotu Kola' in Hindi, 'Thanakuni' in Bengali, 'Peruk' in Manipuri, 'Indian Pennywort' in English is a medicinal plant that has been in use since prehistoric times in folk medicine for the treatment of a wide range of diseases. The herb is used for the treatment of wound healing, various skin conditions such as leprosy, varicose ulcers, eczema, psoriasis. It is also used in diarrhoea, liver diseases, fever, amenorrhoea, diseases of the female genitourinary tract. The plant also has analgesic, anticonvulsant, antidiabetic, antispasmodic, antiulcer, anxiolytic and nootropic actions [31-33]. Centella asiatica Linn. contains phytochemical constituents like tannins such as phlobatannins, saponins, flavonoids, terpenoids, alkaloids and cardiac glycosides etc [34]. As such, considering its use in gastro-intestinal ailments by locals, the present study was aimed at the evaluation of in vitro anthelmintic effect of ethanolic extract of leaves of Centella asiatica Linn. (EECA) on Indian earthworms (Pheretima posthuma). MATERIALS AND METHODS Collection of plant materials The present study was conducted in the Department of Pharmacology, Regional Institute of Medical Sciences, Imphal, Manipur. The plant Centella asiatica Linn. was collected from Lamphel local market, Imphal, Manipur and was authenticated by the Department of Botany, D. M. College, Imphal having Acc. No. DMH 09.15. Preparation of plant extract The leaves of the plant Centella asiatica Linn. were shade dried and powdered using a mixer grinder. Powdered dry plant material (50 gm) was extracted with 100 ml ethanol for 24 h and thus ethanolic extract was obtained using soxhlet apparatus manufactured by Jain Scientific Glass Works, Ambala Cantt, Haryana, India. The extract was filtered and concentrated under vacuum-sounding apparatus for 30 min and then stored at 4 °C [35-36].

The percentage yield was 21 % and the extract thus obtained was used for the anthelmintic study. Worm collection and authentication The study was done on adult Indian earthworm Pheretima posthuma because of its similar anatomical and physiological features to Ascaris lumbricoides [37, 38]. There are various drugs to be studied in anthelmintic activity but in this paper we have listed some 20 drugs such as Punica granatum, Carica papaya, Trachyspermum ammi, Azadirachta indica, Ziziphus mauritiana, Cissus quadrangularis etc.. Information about formulation of some plants indigenous (Indian plants), their anthelmintic action and evaluation have been reviewed.

1. HERBS USED AS ANTHELMINTIC:

2.1 Punica granatum:

Figure: 1 Punica Granatum

Punica granatum (Pomegranate) the divine fruit which originated in Iran and then propagated to northern parts of the Himalayas,India which belongs to the family Punicaceae. It is mainly cultivated in arid environments. The principle components of the pomegranate are lignins, punic acid, oleic, linoleic, stearic acid, palmitic, tocopherols, sex steroids, sterols, gallic, ellagic acid, crude fibers, protein, minerals, vitamins, hydroxycinnamic acids sugars, triacylglycerols, polyphenols, and alkaloids. The peel of this fruit shows anthelmintic action hence Pomegranate peel ethanolic extract (PPEE), the

extraction was done for three days at room temperature and with sporadic shaking, each 500 g chopped plant material was immersed in 2.5 liters of 90% ethanol in a dark area, then was filtered thrice using Whatman filter paper. The combined filtrate was evaporated at 50°C and lower pressure in a vacuum rotary evaporator to obtain the crude ethanolic extract [39]. Both in vivo and in vitro investigations were conducted on Schistosoma mansoni (S.mansoni) and the anthelmintic effect of Pomegranate (PPEE) against Schistosoma mansoni was evaluated. Punica granatum fruit rind(peel) powder demonstrated impressive efficacy by 85% reduction in gastrointestinal nematodes in sheep. In another study where the sheeps were naturally infected with mixed cestode species showed a significant decrease in ECG when exposed to the same fruit rind powder. The alkaloids and glycosides of P. granatum have demonstrated strong anticestodal activity in goats as well [40]. It can also be used for treatment or prevention of a number of risk factors, such as oxidative stress, hyperglycemia, high blood pressure and high cholesterol levels.

2.2 Carica papaya Linn:

Figure: 2 Carica papaya Linn

Carica papaya plant Originated in tropical America, it was introduced in India during the 16th century. It belongs to the family Caricaceae. The young leaves of Carica papaya contains several flavonoids such as kaempferol and myricetin, phenolic compounds such as chlorogenic acid, caffeic acid, ferulic acid and benzyl glucosinolate, alkaloids such as carpaine, pseudocarpaine dehydrocarpaine I and II as well as cyanogenic compounds that are found in the leaves [41]. The aqueous extract of Carica papaya seeds (Caricaceae) was assessed for their anthelmintic properties against nematodes Ascaris lumbricoides and Ascardia galli (roundworm). Inhibition of parasitic worms along with eosinophils destroyed their structural proteins [42]. The high efficacy of Carica papaya has also been well-established in Heligmosomoides polygyrus (Nematospiroides dubius) infections in experiments are prevented by papaya latex as reported by Satria et al. The isothiocyanate benzyl was obtained from Carica papaya seed and applied as an anthelmintic treatment for Caenorhabditis elegans. The extract demonstrated that they inhibit the infectious larvae of T. Colubriformis. Carica papaya contains cysteine proteinases which show anthelmintic properties. It is also known that this substance has healing properties such as reducing inflammation, lowering blood sugar levels, preventing fertility, supporting liver health and promoting wound healing. Additionally, studies have shown that it may also have benefits for controlling blood pressure and fighting tumours.

2.3 Azadirachta indica:

Figure : 3 Azadirachta indica

Azadirachta indica (neem) is indigenous to sections of Southern-east Asia and the Indian subcontinent. It belongs to the family Meliaceae. It contains phytoconstituents such as isoprenoids, which include limonoids, azadirone, diterpenoids, triterpenoids, gedunin, non-isoprenoids like sulphurous compounds, amino acids, polysaccharides, flavonoids, glycosides, coumarins and tannins. Aqueous extract of neem demonstrated a dose-dependent anthelmintic activity with larger potency against roundworms even at the lowest concentration (10 mg/ml) [43]. Various investigation on this plant had demonstrated for their efficacy against a wide range of parasites including helminths protozoa and ectoparasites like Triatoma infestans, H.contortus, Rhipicephalus microplus and Trichomonas vaginalis [44]. Azadirachta indica is toxic to organisms such as Trypanosma, Salmonella and Plasmodium species. It acts against L.acuminata as well as Fasciola gigantica larvae. By using azadirachtin at a concentration of 1?rived from seeds of Azadirachta indica showed an inhibition of 68.3% against the Haemonchus contortus larval hatching. Neem leaves have various uses such as treating skin conditions, malaria, fever, diabetes and heartburn . In addition, the leaves can be used as a diuretic, for headaches and heartburn.

2.4 Ziziphus mauritiana:

Figure 4 - Ziziphus mauritiana

Ziziphus mauritiana (Indian Jujube) is a prickly evergreen shrub that can grow upto 15 meters tall and belongs to the family Rhamnaceae. It consists of ziziphin N, O, P, and Q, polysaccharides, peptides, alkaloids, cyclopeptides, flavonoids, dodeca acetyl prodelphinidin B3, fatty acids and saponins. The ova (eggs) of the nematodes were used for knowing the in vitro ovicidal effects and the egg hatch test by using methanolic extract and aqueous extract of Ziziphus mauritiana. According to the findings, Ziziphus mauritiana exhibited anthelmintic activity with the lethal concentration values 0.1773 and 0.6778 of the aqueous and methanolic extracts respectively. According to results aqueous extract has higher anthelmintic activity than that of methanolic extract [45]. Ziziphus mauritiana is used as anthelmintics, antipyretics and has also been reported for its uses in managing conditions such as nausea, diuretic, scabies, biliousness, heartburn, asthma, stomatitis and typhoid fever.

2.5 Cissus quadrangularis:

Figure: 5 Cissus quadrangularis

Cissus quadrangularis is the perennial plant species which is indigenous to Arabian Peninsula, tropical Asia and a large portion of Africa and belongs to the family of Vitaceae. It consists of ?-sitosterol, ?-amyrone, ?-amyrin and flavonoids, the stem of Cissus quadrangularis consists of two asymmetric tetracyclic triterpenoids and two steroidal principles. There is evidence that the tannins may have anthelmintic effects. To assess

the in vitro anthelmintic activity on earthworm Pheretima posthuma (Annelida), the alcoholic and aqueous extract of plant Cissus quadrangularis root was done. Cissus quadrangularis stems were washed with tap water, dried, and then ground into a powder. Following that, n-hexane, dichloromethane, ethyl acetate, and methanol were used to extract the powder (246.8 g). After filtering the solutions and eliminating the solvents in a vacuum, the resulting crude extracts were 7.68 g (3.11%, w/w), 4.73 g (1.92%, w/w), 2.71 g (1.09%, w/w), and 14.14 g (5.73%, w/w) of hexane, dichloromethane, ethyl acetate, and methanol, respectively. Dimethyl sulfoxide (DMSO) was used to dissolve the dried powder of ethyl acetate extract, which was then run through a 0.22 ~M sterile filter. According to studies Schinus molle and Cissus quadrangularis are used in Ethiopia to treat helminthic infections. C.quadrangularis is said to be used in cattle to treat leech infestation, helminthiasis and infestation by ticks and lice [46].

2.6 Curcuma longa:

Figure: 6 Curcuma longa

Curcuma longa Linn is a perennial plant grown in southern parts of Asia, belonging to the family Zingiberaceae. It contains Curcuminoids which make up 3-6% of the polyphenolic compounds in the turmeric rhizome also known as bisdemethoxycurcumin or curcumin demethoxycurcumin [47]. The phytoconstituents were extracted using a Soxhlet apparatus, a 70% ethanolic extract of each plant's rhizomes was obtained from the crude extract. To identify the different active ingredients qualitative testing was done. In a Petri dish the earthworms were sorted into regular groups (Piperazine 20 mg/ml), test groups (10 mg/ml or 20 mg/ml or 50 mg/ml) and control groups (normal saline). The extract demonstrated vermifuge activity and measured paralysis and death times were noted and the effect of the vermicidal activity was observed with respect to change in concentration. Pheretima posthuma (Earthworms) were categorized into test groups, standard groups and control groups of piperazine. The paralysis time of the crude extracts at concentration of 20 mg/ml, 50mg/ml and control group were evaluated. The Curcuma longa ethanolic extract showed both vermicidal and vermifuge activity [48]. Additionally Curcuma longa shows anti-inflammatory, antispasmodic, anti-carcinogenic, anti-parasitic and gastrointestinal effects.

2.7 Zingiber officinale :

Figure : 7 Zingiber officinale

The plant Zingiber officinale (ginger) is rhizomatous, the plants have perennial flowers, it belongs to the family Zingiberaceae. Ginger has many active compounds which include volatile oils between 1 and 3% of its weight, while others are non-volatile. These three sesquiterpenes (30–70%) bisabolene, zingiberene, and zingiberol are the main active components of ginger oil. Shogaols and gingerols are two phenolic compounds and major active chemical constituents in ginger [49]. The ethanolic extract

of zingiber was evaluated and in vitro anthelmintic activity was determined at the concentration of 50 mg/ml where earthworms were used for observing paralysis and death time. The combined extract of pomegranate (Punica granatum) peel and ginger (Zingiber officinale) bulb were evaluated using in vitro experiments that had antiparasitic properties against Dactylogyrus species. Different dosages of pomegranate peel (50,100,250 and 500 mg/ml) and ginger (10,50,100 and 250 mg/ml) were given to parasites for a predetermined amount of time. The in-vitro cumulative mortality values reached 100?ter the ginger was subjected to 250 mg/ml for 9 minutes, 100 mg/ml, and 50 mg/ml for 5 minutes. After being exposed to 10 mg/ml of ginger for nine minutes the cumulative death rate was 58%, Dactylogyrus species showed resistance to ginger bulb and pomegranate peel solutions based on the concentration of the solution and the length of exposure to some extent [50]. Ginger has been shown to be effective in treating heartburn, nausea and vomiting, analgesic, anti-inflammatory and antipyretic properties . It is effective against Trypanosoma brucei, Giardia lamblia, and Toxoplasma gondii species.

2.8 Ficus indica:

Ficus indica or Ficus benghalensis is indigenous to the Indian Subcontinent and is also referred to as the indian banyan tree. It belongs to the family Moraceae. The plant mainly contains flavonoids, tannins, saponins, alkaloids and terpenoids. The therapeutic action and ecological interactions are facilitated by these constituents. The aqueous extract of Ficus benghalensis roots were done by decoction method and the obtained crude extract underwent qualitative tests to determine the presence of active ingredients. Pheretima posthuma (Indian EarthWorms) were classified into standard categories after being examined using the petri dish method. The root extracts of Ficus benghalensis exhibited strong anthelmintic activity over time and demonstrated vermifuge and vermicidal activity. It works well for diabetes, rheumatism, diarrhoea, dysentery, piles, dental problems and skin sores. It also serves as an immune booster [51].

2.9 Achyranthes aspera:

Latjeera Chichira also known as Achyranthes aspera belonging to the family Amaranthaceae. The plant Achyranthes aspera has a high phytochemical content and saponins A and B in their seeds. D-Glucuronic acid was found to be saponin A, and ?-D galactopyranosyl ester of D Glucuronic acid was shown to be saponin B. Oleanolic acid glycosides are found in Achyranthes aspera seeds. Aqueous extract of stem samples were taken at concentrations of 2.5, 5, 10, 20 mg/ml were prepared for the initial assessment of anthelmintic activity [52]. Antiparasitic activity of A.aspera was done using ethyl acetate extracts which showed good activity against the internal parasite Paramphistomum cervi in sheep and the larvae of the cattle Rhipicephalus sanguineus (brown dog tick) and Boophilus (Rhipicephalus microplus). Some of its important uses include hepatoprotective, anti-allergic, laxative, diuretic, purgative, and antiperiodic effects. This herb has historically been used to treat rheumatism, dropsy, cough, pneumonia, diarrhea, dysentery, ulcers, piles, scabies, snake bites and other skin conditions [53].

2.10 Allium sativum:

The Allium sativum (Garlic) is a species of bulbous member of the Amaryllidaceae family. Garlic constitutes various bioactive substances such as allicin, diallyl trisulfide, diallyl disulfide, diallyl sulfide, ajoene and S-allyl-cysteine. The Soxhlet apparatus was used for obtaining

methanolic extract of Allium sativum and on investigation it showed anthelmintic property . Red stomach worms or Haemonchus contortus were grouped into the test, standard and control groups & the crude extracts were used to measure the motility into control groups (normal saline), they showed survival as well as efficacy rise with longer exposure times. Allium sativum functions as an antibacterial agent, nematicide, pesticide and preservative and also shows activity against cancer, hypertension, common cold and red mite [54].

2.10 Cucurbita pepo:

Cucurbita pepo is a warm season annual vegetable vine which is native to South America belonging to the Cucurbitaceae family. The major chemical constituents of the Cucurbita pepo are minerals (like potassium, magnesium and zinc), fiber, proteins, lipids, carbs, vitamins such as A, C and E along with carotenoids and flavonoids, presence of other bioactive substances like cucurbitacins is responsible for their wide pharmacological activity. The fruit of Cucurbita pepo was coarsely pulverized and defatted at 60–80°C using petroleum ether. Hydoalcohol was then extracted using a Soxhlet apparatus and left for approximately 72 hours at 40°C.Following that, Whatman No. 1 filter paper (Whatman Ltd., England) was used to filter the sediment. A rotary vacuum evaporator (Buchan R-V120, Switzerland) was used to further concentrate the fruit extract at 40°C while it was under vacuum. For the next study, the obtained crude extract was weighed. An increase in exposure time showed a significant increase in anthelmintic activity. Even the alcoholic and aqueous extract of seeds of Cucurbita pepo showed potent action against other organisms like Fasciolopsis buski, Hymenolepis diminuta, Moniezia expansa and Ascaris lumbricoides. The most notable component was discovered using aqueous extract, harmless in contrast to ethereal and alcoholic extracts. The ethanol and water extract of Cucurbita pepo seeds exhibited a high degree of anthelmintic effectiveness in mice against Aspiculuris tetraptera. Other uses are lower blood sugar level, worm-borne parasitic infection [55].

2.11 Thespesia lampas:

Figure: 8 Thespesia lampas

Thespesia lampas also known as “Hibiscus lampas” is a tall undershrub that grows in the uphill slopes belonging to the family Malvaceae. The presence of active constituents in Thespesia lampas stem was demonstrated which includes 9-tetradecenal, dodecanoic acid, n-hexadecanoic acid and tetradecanoic acid also shows the presence of quercetin and ?-sitosterol. Samples of roots were cleaned, then allowed to air dry at room temperature (RT). After that, a grinder was used to turn the samples into a fine powder. Afterwards, 150 ml of 80% methanol (v/v) and 150 ml of 95% chloroform were used to macerate 15 g of powdered materials. The extract was then dried at 40?C in a water bath, filtered using Whatman® Grade 1 filter paper, and kept at 4°C until needed again. The crude extract of Thespesia lampas displayed good vermicidal & vermifuge activity. The time for mortality and paralysis decreased along with increase in the concentration. Fruits and roots of Thespesia lampas are useful against syphilis and gonorrhea, while leaves are effective

against ringworms, inflammation and other skin related disorders [56].

3. Helminthiasis Disease

Any macroparasitic disease affecting both humans and other animals and characterized by the presence of parasitic worms called helminths in a specific body region is referred to as helminthiasis.[57] Today, helminth parasites make up the most prevalent infectious diseases, affecting around one-third of the global population. and causing a wide range of painful diseases and syndromes. Helminths are also common in cattle and result in significant losses to agriculture. Helminths create long-lasting, chronic infections in both human and animal hosts, along with considerable levels of host immune response downregulation. The goal of eradicating helminth illnesses is still far off due to an absence of effective vaccines, constrained pharmaceutical efficacy, evolving drug resistance, and rapid reintroduction in situations where the spread cannot be stopped.[58]. Multicellular worms called helminths are classified into three taxonomic groups: cestode tapeworms, nematode roundworms, and trematode flukes. [59]. They frequently reside in the gastrointestinal tracts of their hosts, but they can also enter other organs and result in physiological harm there.[57] These parasites have remarkably varied life histories, including direct faecal-oral transmission, growth via free-living stages, and reliance on invertebrate vectors. Similar to parasites, helminths can enter the body by a number of different routes, including contact with the skin (schistosomes and hookworms), bites from mosquitoes (filarial worms), and, most commonly, the digestive tract.[59]. It may be wise to check for infection in other family members when one person is found to be infected. Patients should be reminded to practice good personal cleanliness and to take precautions while preparing food, but they should also be reassured that most helminths do not typically spread easily within the home.[60] Clinical signs of helminthiasis include the following four fundamental symptoms: One may simply proactively avoid the disease if we are aware of the parasitic worms' locations and the mode of transmission. Spread the word and educate people about the importance of food culture. Clean your food well before eating it and drinking it. This is especially important in residential regions where people have a practice of eating raw, rare, and utilizing blood soup.[61] There is usually a rise in awareness but not always an alteration in behaviour when individuals are educated about the illness and encouraged to take preventive measures.[62] Educational materials (posters, brochures, broadcasting, and video footage messages) are among the traditional ways to spread health-related messages, but techniques used in the private sector are currently being encouraged for their potential value in creating and disseminating health-related messages.[63,64] Frequent medication therapy is the primary method of infection control in regions with high rates of infection transmission, little resources for disease prevention, and inadequate funding for sanitary facilities. Alternative methods of administering drug treatment in society at large include: universal treatment, which provides care to everyone in the community regardless of age, sex, infection status, or other social characteristics; targeted treatment, which provides care to population groups based on age, sex, or other social characteristics regardless of infection status; and particular treatment, which administers care at each person's level.[65]

4. Classes of synthetic anthelmintic drugs

Anthelmintics are a diverse group of medications that are grouped into classes based on similarities in their chemical structure and modes of action.

4.1 Benzimidazole

Thiabendazole is a broad-spectrum anthelmintic that was first identified in 1961. The literature on benzimidazole compounds is broad and demonstrates a variety of biological effects. The capacity of benzimidazoles to selectively bind with tubulin factor and compromise the cytoskeleton accounts for their effectiveness as anthelmintics.[66] Through this, the chemical basis of benzimidazole molecule resistance in parasitic nematodes has been discovered. Haemonchus contortus, a worm, exhibited resistance to the benzimidazole molecule, which is linked to the drug's presence of particular alleles of tubulin .[67]

4.2 Ivermectin

It is an effective medication, and its discovery sparked the creation of ivermectin analogues such as moxidectin, milbemycin oxime, doramectin, selamectin, abamectin, and eprinomectin. Pharyngeal and body wall muscles are paralyzed by ivermectin.[68]

4.3 Emodepside

Cyclodepsipeptide molecule and semi-synthetic derivative emodepside. a substance produced by fermenting Mycelia sterilia, a fungus. Recently, its anthelmintic properties and discoveries were found.[69]

4.4 Piperazine

It is the most well-liked and frequently applied medication for the treatment of parasitic illness. Piperazine was first used as an anthelmintic in the 1950s, and it is currently an active ingredient in several over-thecounter medications and treatments for pediatric thread worm infections.[65]

4.5 Levamisole

Pyrantel and Morantel These anti-helminthics are nicotinic receptor agonists that result in spastic muscular paralysis and sustained activation of the excitatory nicotinic acetylcholine (nACh) receptors on muscle.[70]

4.6 Paraherquamide

Penicillium paraherquei and Penicillium roqueforti, which produce the drugs paraherquamide and marcfortine A, respectively, are both members of the oxindole alkaloid family.[71] Parasitic nematodes undergo flaccid paralysis when exposed to paraherquamide or its derivative, deoxyparaherquamide.[70]

4.7 Nitazoxanide

The pyruvate ferredoxin oxidoreductase inhibitor nitazoxanide is effective against a variety of intestinal protozoa and helminths. Because putative targets for this substance include anaerobic electron transport enzymes, its mode of action in nematodes has not been determined.[72] Nitazoxanide stops population growth after seven days in culture by 33%. Mebendazole and albendazole, in contrast, significantly slowed the growth (by over 90%). As a result, as compared to other anthelmintic medications, this compound's effectiveness is rather modest. [73] Since there are currently no vaccinations in the market, controlling helminths must instead rely on some effective medications, known as anthelmintics. However, because these drugs are frequently misused, major drug resistance issues arise throughout the world, necessitating the urgent need to isolate and find novel anthelmintic

drugs.[74] An ideal anthelmintic agent would be one that has a broad scope of action, provides a significant number of cures with a single therapeutic dose, is not harmful to the host, and is reasonably priced. None of the synthetic drugs on the market satisfies this criterion. There is evidence that even the most widely used medications, can cause digestive issues, giddiness, and nausea.[75] Tolerance of the infections to the current therapies and their expensive price justifies the need to search for fresher anthelmintic compounds. Due to the fact that many effective medications have their roots in traditional medical procedures, various researchers have conducted studies to assess the purported anthelmintic efficiency of folkloric medicinal plants.[76] In order to find novel potential anthelmintic molecules and to determine their potential mechanism(s) of action, researchers have evaluated the effectiveness of plant species through a variety of screening procedures and approaches. These efforts have been reviewed further.

5. Methods for Studying Anthelmintic Activity

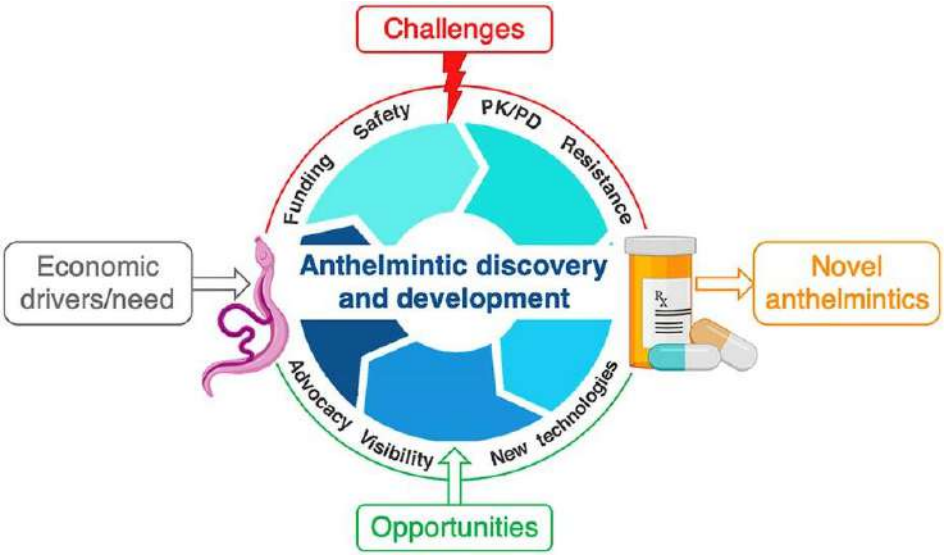

Figure : 9 Anthelmintic Discovery and Development

5.1. Most in vitro studies on the anthelmintic properties of plants, their oils, or their extracts have been conducted based on their toxicities to earthworms. The majority of compounds that are poisonous to earthworms cause an initial irritability or agitation, which causes the worm to die. Anthelmintics possibly sometimes eject the parasite due to this effect if their concentration does not increase enough to kill the worm.

5.2. Hookworms, H. contortus, tapeworms, and/or A. lumbricoides have also been utilized by certain researchers to assess the in vitro anthelmintic activity of various plant materials..[77]

5.3. To assess the effectiveness of plant items against the eggs of Haemonchus contortus or other trichostrongylids, a modified egg hatch assay is frequently utilized.

5.4. A modified version on the larval development assay (LDA) or larval motility assays, which are frequently used to test a parasite's resistance to anthelmintics, have been employed by some other researchers doing in vitro studies.[78]

5.5. In one of the anthelmintic activity investigation, worms from houseflies that mimic parasitic pinworms found in humans were

produced under laboratory settings, revealing a novel technology. Using housefly worms and earthworms, researchers examined the anthelmintic effects of several medications.[79]

5.6. The effectiveness of several plant materials as anthelmintics has additionally been tested in vivo. The criteria for this kind of activities included the evacuation of worms from their hosts or a decrease in the quantity of eggs per gram of faeces (EPG) that the hosts with the infection passed when compared to animals that had been given commercial anthelmintics. As an example, oral feeding of Indonesian papaya (Carica papaya) decreased parasite burden up to 100% within seven days after treatment for pigs who were infected with Ascaris suum. Similar to this, various other plant extracts discovered with anthelmintic qualities were examined for their effectiveness against gastrointestinal nematodes in experimentally infected sheep.[78]

6. Plants studied for anthelmintic activity

6.1 Adhatoda vasica (Family- Acanthaceae)

Crude aqueous extracts (CAE) as well as crude methanol extracts (CME) of A. vesica had an anthelmintic impact on live Haemonchus contortus, as shown by the mortality of the test subjects, according to in vitro tests. Sheep already infected with a variety of gastrointestinal nematodes were given A. vesica roots as crude powder (CP), CAE, and CME for in vivo experiments. Despite having anthelmintic efficacy against nematodes, it was discovered that A. vesica roots did not compare to Levamisole.[80]

6.2 Aerva lanata Linn Juss (Family- Amaranthaceae)

According to the findings, both the methanolic and aqueous extract of Aerva lanata's aerial parts exhibit anthelmintic activity when compared to the common medication. Each crude extract demonstrated anthelmintic action in a dose-dependent manner at concentrations of 25, 50, and 100 mg/ml. Aerva lanata aerial parts extraction in methanol at a dosage of 100 mg/ml caused paralysis in 7.5 minutes and death in 11.16 minutes, whereas aqueous extract against Pheritima postuma exhibited paralysis in 13.83 minutes and death in 18 minutes. Piperazine citrate, the standard of reference, demonstrated identical results at 14.16 and 31.83 minutes, respectively. Given the paralysis's shortest duration (P) and death (D) with 100 mg/ml concentration. The reference medication, piperazine citrate, demonstrated the same at 14.16 and 31.83 minutes, respectively. The traditional utilization of Aerva lanata's aerial parts as an anthelmintic has been verified, since the extracts have demonstrated action against Pheritima postuma.[81]

6.3Annona squamosa (Family- Annonaceae)

A. squamosa has therapeutic qualities. Internal roots are used to treat spinal disorders. Bark has a reputation for being a potent astringent. Fruits are regarded as good tonics in Ayurveda; they enrich the blood, are employed as expectorants, promote muscular strength, are cooling, lessen burning sensations and the tendency toward biliousness, are sedative to the heart, and alleviate vomiting. According to the study's findings, Annona squamosa Linn extracts of leaves had significantly higher anthelminthic activity than the standard the standard.[82]

6.4 Azadirachta indica (Family- Meliaceae)

In this work, neem (Azadirachta indica) extracts from the leaves were tested in the laboratory with Fasciola spp. with albendazole, a commonly used dewormer, and nutritional broth, which served as

a negative control. A comparison with the average recorded mean, the investigation identified the extract quantity which generated the highest effectiveness.[83]

6.5 Butea monosperma (Lam.) (Family- Fabaceae)

The seeds have been shown to have anthelmintic activity and to be effective against ascarids. One investigation discovered that the isolated seed ingredient palasonin, a lactone (C16 H22O6), had considerable anthelmintic properties. [76] Palasonin appears to have an impact on the parasite's system for generating energy because it hindered glucose uptake and reduced the amount of glycogen in the presence of glucose. Additionally, lactic acid levels considerably increased, indicating ATP generation was being inhibited. The findings suggested that palasonin may exert its effects via impairing energy metabolism or by changing the parasite's motor activity.[84]

6.6 Buchholzia coriaceae (Family- Capparidacea)

The anthelmintic abilities of Buchholzia coriaceae were genuine. With all of the worms utilized in the study, the extracts demonstrated concentration-related anthelmintic activity, with 100 mg/ml providing the shortest time for paralysis (P) and death (D). The findings revealed that for all of the worm kinds studied, the plant leaves had greater activity than the plant stems.[85]

6.7 Calotropis procera (Family-Apocynaceae)

Through in vitro and in vivo investigations, the anthelmintic activity of Calotropis (C.) procera florals in contrast to levamisole was assessed.Calotropis procera floral crude aqueous and crude methanolic extracts both showed time-dependent anthelmintic efficacy in vitro against Haemonchus contortus.[86]

6.8 Cassia tora L. (Family- Fabaceae)

According to research, the most effective C. tora extract is the ethyl acetate fraction since it kills worms faster and paralyzes them more quickly than the methanolic extract. Both extracts demonstrated anthelmintic properties that were concentration dependent. The extracts showed efficacy against the worms utilized in the study, supporting the traditional assertion that C. tora leaf is an anthelmintic.[87]

6.9 Coriandrum sativum (Family- Umbellifers)

The aqueous and hydro-alcoholic extracts of Coriandrum sativum (Apiaceae) seeds were tested for their in vitro anthelmintic properties. Additionally, the in vivo anthelmintic activity of Coriandrum sativum's aqueous extract in sheep sick with Haemonchus contortus was examined. At a concentration of less than 0.5 mg/ml, Coriandrum sativum's two extract varieties fully prevented eggs from hatching. The ED50 of Coriandrum sativum's aqueous extract was 0.12 mg/ml, whereas that of its hydro-alcoholic extract was 0.18 mg/ml. Among aqueous and hydro-alcoholic extracts, there were no statistically noteworthy change ($p > 0.05$). In vitro tests against adult parasites indicated that the hydro-alcoholic extract was more efficient than the aqueous one.[88]

6.10 Cucurbita maxima Duch. (Family- Cucurbitaceae)

The plant's seeds have a reputation in the Ayurvedic medical system as an anthelmintic, particularly against tape worms. Evaluated in vivo and in vitro using extracts of the seeds. Aqueous, alcoholic, and ether extracts in the in vitro trials

were in decreasing order of extract potency. According to the kymographic tests, the seed extracts work by causing a reduction in motility, which results in momentary paralysis.[89]

6.11 Capparis decidua Edgew. (Family-Capparidaceae)

It is a tiny, glabrous shrub that can be found in most of India. In the ancient medical system, root bark has been shown to be effective for treating helminthes infections, rheumatoid arthritis, cough, and asthma. The Pheretima posthuma (Annelida) has been employed as the test animal using the ethanolic extract of root bark of C. decidua Edgew because of its physical and physiological similarity to the roundworm parasite. When the extract utilized in the study was concentrated to a greater concentration of 100 mg/ml, the activity was discovered to be dose-dependent and similar with piperazine citrate (10 mg/ml). [90]

6.12 Carica papaya Linn. (Family-Caricaceae)

Due to its morphological and physiological similarity to human intestinal round worm parasites, the anthelmintic activity of the adult Indian earthworm Pheretima posthuma was assessed.[91]

In a different investigation, benzyl isothiocyanate, which was extracted from C. papaya Linn. seed extract, was identified as the main anthelmintic agent after being viability tested using Caenorhabditis worms.[92]

6.13 Erythrina indica Lam (Family-Papilionaceae)

At concentrations of 50 mg/ml and 100 mg/ml, ethanol, chloroform, and ethyl acetate extracts of Erythrina indica leaves demonstrated considerable anthelmintic action against Pheritima poshthuma. By attaching to free protein in the host animal's gastrointestinal system or glycoprotein on the parasite's cuticle, tannins exerted anthelmintic action. By decoupling oxidative phosphorylation, phenolic substances (tannins are poly phenolic compounds) reduce the ability of helminth parasites to produce energy. A phytochemical examination of the leaves of the Erythrina indica plant identified tannins as one of the components. Erythrina indica's anthelmintic properties may result from one or both of the aforementioned mechanisms.[93]

6.14 Eucalyptus globulus (Family Myrtaceae)

In accordance to the observations of the study by D. J. Taur, V. B. Kulkarni, and R. Y. Patil, albendazole took 5.82 0.46 and 6.54 0.429 minutes to paralyze and kill P. posthuma, while eucalyptus oil at an amount of 0.15 ml/ml takes 4.598 1.151 and 6.57 1.374 minutes to do the same. Therefore, the current study comes to the conclusion that E. globulus oil has anthelmintic potential since it contains phytoconstituents including borneol, linalool, cineol, geranyl acetate, anethol, and saffrol.[94]

6.15 Evolvulus alsinoides Linn. (Family-Convolvulaceae)

As an effective aphrodisiac, anthelmintic, and brain stimulant, it is frequently used in Ayurveda. An ethanolbased extract of the whole plant was examined to validate its anthelmintic effect utilizing the adult Indian earthworms Pheretima posthuma as an experiment animal. The extract immobilized the worms at all dose levels that were tested before killing them. At a higher dosage of 100mg/ml, the ethanolic extract was found to be more effective than the reference control Piperazine citrate.[95]

6.16 Gynandropsis gynandra (Family-Capparidacea)

For many years, plants from this family have been utilized in traditional African ethnomedicine, and different genera of plants have been documented for the treatment of various illnesses. The G. gynandra leaf methanol extract was highly toxic to earthworms. When compared to the reference medicine, which caused paralysis to last for 2 minutes and an 8-minute duration to death, respectively.[85]

6.17 Hugonia mystax (Family- Linaceae)

Hugonia mystax leaves were dried for two weeks in the shade. Dried leaves were ground into a coarse powder, sieved (#40), and kept at room temperature in an airtight container. Then, dried powder was successively extracted with petroleum ether, chloroform, and ethanol utilizing soxhlation extraction. In this bioassay, anthelmintic activity of all prototypes were evaluated at doses of 25, 50, and 100 mg/ml. Hugonia mystax aerial parts' long-standing reputation as an anthelmintic was validated by the action of the extracts over Pheretima posthuma.[96]

6.18 Juglans regia L. (Juglandaceae)

It was found that all of the Juglans regia extracts responded favourably to a specific level of anthelmintic activity. In comparison to the standard, acetone extract of plant material shows noticeable activity at all dilutions. The least effective of the four extracts is ethanol extract. More concentrated extracts have higher rates of death and paralysis. It indicates that compared to lower dosages, paralysis and death occur less frequently at greater concentrations. The crude extracts' phytochemical screening revealed the presence of flavonoids and polyphenolic compounds.[97] The tannins known as chemically polyphenolic substances have anthelmintic action.[98]

6.19 Melia azedarach Linn.(Family-Meliaceae)

This species of tree, which is native to Persia, India, and China, has been used for centuries as a therapeutic and insect repellent herb all throughout the planet. Using piperazine phosphate as the reference both the tapeworm Taenia solium (Cestoda) & an earthworm called Pheretima posthuma (Annelida).Both the tested tapeworm and the earthworm were resistant to the extract. Furthermore, its efficacy against the tapeworm Taenia solium was superior compared to the use of piperazine phosphate.[99]

6.20 Mussaenda frondose (Family- Rubiaceae)

The anthelmintic activity was carried out as per the method of Ajaiyeoba et al. This study has shown that the Mussaenda frondosa plant contains a large number of secondary metabolites (phytocostituents). The ability of the plant extract to combat and demonstrates how Mussaenda frondosa may be used to create novel, very effective anthelmintics.[100]

6.21 Murraya koenigii (Family- Rutaceae)

Using various doses (12.5, 25, 50 mg/ml) for aqueous and methanolic extracts, which demonstrate to be dose-dependent, the in vitro investigation indicated anthelmintic impacts of M. koenigii against Haemonchus contortus as obvious due to its paralytic condition and/or mortality at eight-hour post treatment. Egg hatching was found to be only mildly inhibited by M. koenigii aqueous and methanolic extracts. M. koenigii shown strong anthelmintic activity, it can be said.[101]

6.22 Neolamarckia cadamba (Family-Rubiaceae)

In accordance to the research, the extract caused the earthworms to die as well as be paralyzed. The greatest concentration of the methanolic extract

demonstrated substantial anthelmintic activity since it caused paralysis and death more quickly than the medication albendazole did. It is possible that the terpenoids and phenolic chemicals in N. cadamba's fruit extract are what give it its anthelmintic properties. [102]

6.23 Nyctanthes arbor-tristis (Family- Oleaceae)

The chloroform-methanol extract included flavonoids, whereas the methanolic portion revealed an inclusion of both tannins and flavonoids. The water-based extracts of Nyctanthes arbor-tristis consisted of steroid plus carbohydrate content. The biological components of Nyctanthes arbor-tristis have significant anthelmintic action, making them a potential replacement for routinely prescribed and expensive anthelmintic medications for the deworming of grazing animals.[103]

6.24 Punica granatum Linn. (Family- Punicaceae)

It is grown all over India and is known locally as Anar. In the indigenous system of medicine, the plant's root and stem bark are employed as astringents and anthelmintics. Its stem bark's alcoholic extract was tested for its purported anthelmintic properties. It was discovered that the action was dose-dependent and prevented Haemonchus contortus eggs from developing into filariform larvae.[104]

6.25 Psidium guajava (Family- Myrtaceae)

The testing of phytochemicals took place in accordance with accepted procedures. Minor adjustments were made to the Ajaiyeoba EO et al. procedure for the anthelmintic assay. Different extract concentrations were investigated in order to ascertain the experiment's worms' paralysis and death times. It was discovered that Psidium guajava leaf ethanol extract has strong anthelmintic activity at elevated concentrations (100 mg/ml). As a standard reference, albendazole in the same concentration as the extract was employed, and saline water served as the control. The results of the current studies support the ethno-medical assertion that this herb has anthelmintic properties. It can be included into medicine formulations and utilized in an alternate source for herbal anthelmintics.[105]

6.26 Spigelia anthelmia Linn (Family- Loganiaceae)

Spigelia anthelmia Linn (Loganiaceae) is frequently used by locals in South Western Nigeria to get rid of worms. In South Western Nigeria, the Yoruba people refer to the plant as "Aparan," (apa- kill, araworm), and "ewearan."[106] Spigelia anthelmia's aqueous component had a respectable level of anthelmintic effectiveness. The extract's estimated median effective dose (ED50) was 21 mg/kg body weight. According to the therapeutic index found in this investigation, the extract is rather safe even at greater doses. This investigation verified Spigelia anthelmia Linn's anthelmintic properties. Additionally, rat exposed to the extract have considerable anthelmintic activity towards Nippostrongylus braziliensis.[107] Preliminary phytochemical analysis of the leaves and stem of Spermacoce articularis L.f. revealed the presence of tannins, flavonoids, carbs, the saponins steroids, and triterpenoids. The methanolic extracts of the leaves, stems, and roots demonstrated anthelmintic activity in a dosage-dependent manner; as the extracts' dose was raised, a progressive increase in anthelmintic activity was noticed. At maximal dosages of 100 mg/ml, all Spermacoce articularis L.f. extracts demonstrated considerable anthelmintic action in addition to paralysis. The results of this study have demonstrated the

presence of anthelmintic activity in methanolic extracts of Spermacoce articularis L.f. leaves, stems, and roots at doses of 12.5, 25, 50, and 100 mg/ml.[108]

6.27 Trachyspermum ammi Linn. (Family-Apiaceae)

The ajowan seeds are used as diuretics, analgesics, anthelmintics, and asthma medications. The herb's seed extract was evaluated for its anthelmintic effect on sheep in one study, and it produced n oteworthy outcomes.[109]

Using the egg hatch test (EHT) on Haemonchus contortus eggs , the ovicidal effectiveness of the crudeaqueous and methanolic extracts from T. ammi Linn. seeds were assess ed as well.The LC50 values forthese compounds were found to be 0.1698 and 0.1828 mg/ml, respectively. [110]

6.28 Trifolium repens Linn. (Family-Fabaceae)

In Indian Naga tribal folk medicine, it is a deworming treatment. The anticestodal effectiveness of T. repens Linn. was evaluated utilizing testing Hymenolepis diminuta infections in albino rats. At doses of 200 and 500 mg/kg, the herb's aerial shoot extract reduced H. diminuta's mean fecal egg counts by 47.72 and 54.59% and its worm rate of recovery by 60 and 40%, respectively. The advised cestocidal drug, praziquantal, lowered the average fecal egg number by 65.90% & the worm rate of recovery by 26.67%.[111]

6.29 Trigonella foenum-graecum (Family-Leguminoceae)

Trigonella foenum-graecum, a plant that is commonly referred to as fenugreek, is a member of the Leguminoceae family. The results of anthelmintic activity on the earthworm Phertima prosthuma demonstrate that various concentrations of both aqueous and alcoholic extracts caused the paralysis and death of earthworms when opposed to albendazole as a reference medicine at the exact same concentration. When compared to the identical concentration of standard drug, an alcoholic extract at a concentration of 60 mg/ml took somewhat longer to paralyze and slightly less time to kill earthworms.[112]

6.30 Zingiber officinale (Family-Zingiberaceae)

Ginger (Zingiber officinale) is among the most often utilized plants whose anthelmintic abilities have been studied. In order to demonstrate the anthelmintic effects of Z. officinale rhizome on diverse parasite species, certain in vitro experiments as well as in vivo investigations have been conducted. In comparison to Mebendazole, this study shown that adding 25g/kg of ginger powder to pig feed is far better at lowering the overall parasite load of gastrointestinal nematodes.[113]

7. Causative Worms of Soil Transmitted Helminthiasis

Soil-transmitted helminthiasis (STH) is a group of parasitic infections of the intestine caused by nematode worms usually transmitted by soil. STH is the most prevalent of neglected tropical diseases and is responsible for significant morbidity and, indirectly, mortality in poor developing countries. STH contributes to general weakness, malnutrition, iron-deficiency anemia, and impaired physical and intellectual development in school-age children.[114] the three main causative worms of soil-transmitted helmenthiasis of public health importance are:

7.1. Whipworm

The human whipworm (Trichuris trichiura or Trichocephalus trichiuris), is the third most common roundworm found in humans. The name "whipworm" refers to the shape of the worm; the worms look like whips with wider "handles" at the posterior end. There is an estimated 800 million people infected worldwide. It is also highly prevalent in children. Coinfection of whipworm with Giardia, Entamoeba histolytica, Ascaris lumbricoides, and hookworm is common. Symptoms range from asymptomatic through vague digestive tract distress for light infestations to emaciation with dry skin and diarrhea (usually mucoid and/or bloody) for heavy infestations. In children, heavy infections could lead to growth retardation.Whipworm infestation is detectable by stool examination, which can detect eggs and charcot-leyden crystals. The Kato-Katz is the technique of choice for diagnosis and quantification of infection with T. trichiura. Adult worms may be seen in a prolapsed rectal mucosa. [115]

7.2. Hookworm

Human hookworm infection is a soil-transmitted helminthiasis infection caused by nematode parasites Necator americanus, Ancylostoma duodenale or both. Mild infections with hookworm cause mild diarrhea and abdominal pain. More severe infections with hookworm can create serious health problems for newborns, children, pregnant women, and persons who are malnourished. Hookworm infection is the leading cause of anemia and protein malnutrition in developing nations, afflicting an estimated 740 million people. Hookworm infection may be associated with dermatitis, eosinophilia, pulmonary infiltrates, pneumonitis, Satkar et al. / SGVU Journal of Pharmaceutical Research & Education, 2018, 3(2), 330-337 332 and urticarial rash. Gastrointestinal symptoms would include mild abdominal pain, nausea, vomiting, and anorexia. Iron-deficiency anemia due to blood loss is often associated with hookworm.[116]

7.3. Round worm (Ascaris)

Ascariasis, one of the most common human helmentic infections, is caused by the intestinal parasite Ascaris lumbricoides (A. lumbricoides [large roundworm], affecting an estimated one billion persons at any one time worldwide. It affects 50 percent of populations in tropical and subtropical areas. Globally, Ascariasis causes an estimated 20,000 deaths per year. The clinical effects include a wide range of manifestations. Most potential and common complications comprise pneumonitis due to passage of worms in the lungs, with pulmonary eosinophilia (Loeffler's syndrome); intestinal obstruction by mass of worms; biliary obstruction and pancreatic obstruction by worms. Infection with A. lumbricoides may contribute substantially to child morbidity when associated with malnutrition, pneumonia, enteric diseases and vitamin A deficiency. Ascariasis adversley affects children's growth and development.[117]

8. Drug Used as Anthelmintic

Following drugs are used as a anthelmintic which have various mechanism of action Albendazole A broad spectrum oral anthelmintic Albendazole is a drug of choice and its mechanism of action is through inhibitory microtubule synthesis in nematodes, thus irreversibly impairing glucose uptake. As a result intestinal parasites are immobilized. Mebendazole It is broad spectrum anthelmintic which selective and irreversibly block glucose uptake by adult intestinal – dwelling nematodes and cestodes and their tissue- dwelling larve. Inhibition of glucose uptake appears to lead to endogenous depletion of glycogen stored within the parasite. The lack of glycogen result in a

decreased formation of adenosine triphosphate, required for survival and reproduction of the helminth. As Mebendazole acts by affecting the entire energy metabolism, it is used as a standard drug for anthelmintic activity.[117]

8.1 Niclosamide

Niclosamide was the drug of choice for tapeworm infections and which is inversely damage proximal segment separating worms from the intestinal wall and thus expelling them out of the host body. (Rang and Dale2003).

8.2 Piperazine

Piperazine can be used to treat infection with the common round worm and the thread worm. It reversibly inhibits neuromuscular transmission in the worm, probably by acting like GABA, on GABA-gated chloride Channels in nematode muscle. As a result paralysed worm are expelled alive.

8.3 Praziquantel

It is broad spectrum anthelmintic drug, which acts by altering calcium homeostasis in parasite cells causing contraction of the musculature and eventually result in paralysis and death of the worm.

8.4 Diethyl carbamazine

A piperazine derivative, it is active in filarial infections. It has been suggested that it modifies the parasite so that it becomes suspectible to the host's normal immune response. It may also interfare with the parraite's arachidnate metabolism.

8.5 Pyrantel Pamoate

A derivative of tetrahydropyrimidine that act by depolarizing the helminth neuromuscular junction, causing spasm and paralysis. It also has some anticholinesterase activity.

8.6 Levamisole

A drug effective in common round worm infection, acts by stimulating and subsequentely blocking the neuromuscular junctions. This paralyzing the worms to be expelled out.

8.7 Ivermectin

A semisynthetic agent, obtained from an actinomycyte, is thought to paralyse the worm by opening chloride channels and increasing chloride conductance.

8.8 Oxamniquine

Active against schistosoma mansoni, it affects both mature and immature form of parasite. It's mechanism of action may involve interaction in the DNA and its selective action may be related to the ability of the parasite to concentrate the drug.

8.9 Metriphonate

It's action is thought to be due to an inhibitory effect on cholinesterases in the helminth causing paralysis.

8.10 Thiabendazole

It is benzimidazole poly anthelmintic, which covered practically all species of nematodes i.e round worm, hook worm, pin worm, Trichuris Strongyloides and trichinella spiralis. It inhibit development of eggs of worm and kills larve.

9. Herbal drug Used as Anthelmintic

Helminthes infections are the most common infection in man affecting the large proportions of

the world population. The synthetic anthelmintic drugs are having too much adverse effect and toxicity and many of them are not recommended for young children and pregnant ladies. In the treatment of parasitic disease, the anthelmintic drugs are used indiscriminately. Recently the use of anthelmintic produces toxicity in human beings hence the development and discovery of new substance which acting as anthelmintic are being derived through plants. Various plants were used in venereal diseases to promote healing of wounds, swelling, abscesses, rheumatism and treating pain in lower extremities, skin diseases, leucorrhoea, dysentery, and fever.[118]

Table – 1 - Herbal drug Used as Anthelmintic

S. No	Name of Plants	Family	Part used	Effective against
1	Allium sativum [119]	Lillaceae	Bulb	Round-worms
2	Annona senegalensis [120]	Annonaceae	Leaf, bark, root	Nippostrongyllus braziliensis
3	Acacia albida [121]	Fabaceae	Seeds	Sheep, goat
4	Adhatoda versica [122]	Acanthaceae	Roots	GI nematodes
5	Ageratum conyzoides [123]	Asterceae	Leaves, Flowers	Tape-worms
6	Alangium lamarckii [124]	Alangiaceae	Roots and bark	Hook-worms, ascarids
7	Albizia anthelmintica [125]	Fabaceae	Bark	Anthelmintic
8	Azadirachta indica [126]	Meliaceae	Cake and leaves	Anthelmintic
9	Bixa Orellana [127]	Bixaceae	Seeds	Ascaridia galli, Ascaris suum
10	Butea frondosa [128]	Fabaceae	Seeds	Ascaridia galli
11	Calliandra calothyrsus [129]	Fabaceae	Legume	Haemonchuscontortus, Trichostrongylus, Strongyloides papillosus
12	Capillipedium foetidum [130]	Poaceae	Oil, grass	Pheretima posthuma
13	Carum copticum [131]	Umbelliferae	Seeds	Ascaris lumbricoides;
14	Chenopodium album [132]	Chenopodiaceae	Leaves	Nematodes
15	Commiphora [133]	Burseraceae	Oleo-gum resin	Tape-worms, hookworms
16	Cucurbita moschata [134]	Cucurbitaceae	Seeds	Cestodes
17	Cyathocline lyrata [135]	Asteraceae	Essential oil	Tape-worms, hookworms
18	Datura quercifolia [136]	Solanaceae	Fruit	Ascaridia galli
19	Diospyros scabra [137]	Ebenaceae	Seeds	Fasciolosis, lungworms
20	Dodonea viscose [138]	Sapindaceae	Leaves	Intestinal-worms
21	Embelia ribes [139]	Myrsinaceae	Seeds	Tape-worms
22	Eupatorium Triplinerve [140]	Asteraceae	Flowers	Ascaris lumbricoides and Taenia solium
23	Gardenia lucida [141]	Rubiaceae	Essential oil	Tape-worms, earthworms

24	Hagenia abyssainicia [142]	Rosaceae	Fruit	Round-worms
25	Helleborus niger [143]	Ranunculaceae	Stem	Ascaris lumbricoides
26	Hyoscyamus niger [144]	Solanaceae	Seeds	Nematode
27	Lagenaria siceraria [145]	Cucurbitaceae	Seeds	Cestodes, moniezia
28	Lantana trifolia [146]	Verbenaceae	Fruit	Fasciolosis, lungworms
29	Lawsonia inermis [147]	Lythraceae	Leaves	Fasciolosis
30	Mitragyna stipulosa [148]	Rubiaceae	Roots	Guinea-worm
31	Moringa olelfera [149]	Moringaceae	Seeds	Ascaris suum
32	Randia dumetorum [150]	Rubiaceae	Seeds	Earth-worms, tapeworms
33	Swertia chirata [151]	Gentianaceae	Whole plant	Ascaridia galli
34	Trichilia emetic [152]	Meliaceae	Bark	Fasciolosis, lungworms
35	Uvaria hookeri [153]	Annonaceae	Root, bark	Heamonchus contortus
36	Vernonia amygdalina [154]	Asterac	Stem, bark	Haemonchus contortus

10. Anthelmintic resistance

Anthelmintic resistance occurs when a heritable genetic change occurs in the parasite's DNA, rendering it insensitive to a previously effective anthelmintic drug. This is a particularly serious problem in helminth parasites of small ruminant farm animals.[155] There are many factors that contribute to anthelmintic resistance, such as frequent, mass anthelmintic treatment, underdosing, treating repeatedly with only one anthelmintic, and resistance being transmitted during transfer of animals.[155] Anthelmintic resistance in parasites is widespread; drug resistance exists in all livestock hosts and to all anthelmintic drug classes.[156] This is a major threat to the sustainability of modern ruminant livestock production, resulting in reduced productivity, compromised animal health and welfare,[155] and increased greenhouse gas emissions through increased parasitism and farm inputs.[157] A database of published and unpublished European AR research on gastrointestinal nematodes was collated in 2020. A total of 197 publications were available for analysis, representing 535 studies in 22 countries and spanning the period 1980–2020. Results in sheep and goats since 2010 reveal an average prevalence of resistance to benzimidazoles of 86%, moxidectin 52%, and levamisole 48%. All major gastrointestinal nematode genera survived treatment in various studies. In cattle, prevalence of anthelminthic resistance varied between anthelmintic classes from 0–100% (benzimidazoles and macrocyclic lactones), 0–17% (levamisole) and 0–73% (moxidectin), and both Cooperia and Ostertagia survived treatment.[157] However, resistance is not seen as often in the parasitic helminths that affect cattle, compared to sheep. Reasons for this include the fact that cattle receive anthelminthic drugs less frequently than sheep, and the different nature of their faecal pats that could leave different numbers of resistant infective larvae on the pasture.[158] Unlike sheep, cattle can develop sufficient immunoprotection against such parasites.[159] Both in vitro (egg hatch assay, larval development test, larval motility test, polymerase chain reaction and in vivo methods (fecal egg count reduction test) can be used to detect anthelmintic resistance. [160] Treatment with an antihelminthic drug kills worms whose phenotype renders them susceptible to the drug, but resistant parasites survive and pass on their "resistance" genes. Resistant varieties accumulate, and treatment failure finally occurs.[161] The ways

in which anthelmintics are used have contributed to a major anthelmintic resistance issue worldwide. From the 1950s to the 1980s, new classes of effective and inexpensive anthelmintics were made available every decade, leading to excessive use throughout agriculture and disincentivizing alternative anti-nematodal strategies.[156] Developing new anthelmintics is time-consuming and expensive therefore, it is important to use the ones that currently exist in a way that will minimize or prevent the development of anthelmintic resistance.[11] Some of these methods are ensuring animals are not being underdosed, rotating the anthelmintics that are being used, and rotation of grazing land to reduce the parasite population.[162] Other methods include using a combination of multiple different anthelmintics, and the use of refugia based strategies. Refugia refers to the portion of the parasite population not being exposed to anthelmintics. This population is therefore not undergoing selection for resistance. Use of refugia helps to slow down the speed of evolution of resistance to anthelmintic drugs.[163] Due to the problem of anthelmintic resistance, research into alternatives is continuing, including in the field of rational drug design.[164]

11. DISCUSSIONS

The Helminths infection induce severe morbidity by affecting population in autochthonous region with chief economic and social consequences. The numerous studies documented the extracts of natural products exhibited anthelmintic activity[165-166]. Hence for the present study earthworm Pheritima posthuma were selected as a model for the anthelmintic activity. The biological activities of the medicinal plant are due to the presence of secondary metabolites. The production of novel therapeutic drugs from plants are based on the reconnoitered of the phytoconstituents. The secondary metabolites demonstrated various health benefits like antidiabetic, anticancer, anthelmintic, antibacterial, CNS depressant, etc. The flavonoids and polyphenol have strong antioxidants, which scavenged the free radicals and inhibitors of lipid peroxidation. Hence flavonoids and polyphenol have chief role for the therapeutic efficacy of medicinal plants, and researchers are more focused to explore their biological activities.[167].The findings of phytochemical studies demonstrate the presence of flavonoids, tannins and polyphenol compounds along with other chemical constituents. Swargiary et al. presented the similar studies on different medicinal plants exhibiting the presence of similar kind of phytoconstituents.[168] Zhou et al found higher quantity of flavonoid and polyphenol in Cyclocarya paliurus leaves and expressed its maximum antioxidant capacity. It suggested that the presence of large quantity of flavonoid and polyphenol might be interconnected with greater antioxidant property of the plant.[168] The findings of antioxidant activity of Cassia tora, Portulaca oleracea, Alternanthera sessilis, Ipomoea aquatica, Basella alba, Digera muricata, Leucas cephalotes and Solanum nigrum indicates that with higher phenolic and flavonoid contents could be a significant source of natural antioxidants.[170] The crude saponins of Achillea wilhelmsii and Teucrium stocksianum demonstrated significant anthelmintic activity by inducing mortality of earthworms[171] Further, it was reported a prominent anthelmintic activity against gastrointestinal nematodes from donkey[172] and goats[173] for Medicago sativa saponin mixtures. Pratap et al. reported that presence of alkaloids, phenols and tannins in methanol extract of Mimosa pudica responsible for significant anthelmintic activity.[174]. The medicinal plant having secondary metabolites like alkaloids, polyphenol, flavonoids, tannins and saponins

reported significant anthelmintic activity in previous studies.[175,176] The outcomes of the phytochemical studies revealed the presence of alkaloids, polyphenol, flavonoids, tannins and saponins as a chief components in Justicia adhatoda, Vernonia amygdalina, Mikania micrantha and Momordica charantia which support that these plants might be produce anthelmintic activity. The researchers are giving more attention toward the medicinal plant for the development of anthelmintic drug because it give new bioactive compounds with no or little side effects and easily accessible to the peoples of developing countries. Moreover, the medicinal plants have the best compatibility with human physiology than allopathic medicines. The anthelmintic activity of decoction of Justicia adhatoda, Vernonia amygdalina, Mikania micrantha and Momordica charantia were evaluated by perceiving the time required to paralysis and death of each worm. The standard drug Albendazole showed anthelmintic activity due to inhibitory action on microtubular function of earthworm.[177]. The decoction of Justicia adhatoda, Vernonia amygdalina, Mikania micrantha and Momordica charantia displayed paralysis and death of the earthworm. The findings of studies suggest that the Justicia adhatoda, Vernonia amygdalina, Mikania micrantha and Momordica charantia retain prominent anthelmintic activity. The presence of alkaloids, polyphenol, flavonoids, tannins and saponins in plants may be responsible for the anthelmintic activity. The alkaloids induce paralysis in earthworm by its inhibitory action on the central nervous system. Consequently, tannins and polyphenol selectively bind to free proteins present in the gastrointestinal tract of host parasite or glycoprotein on the cuticle of the parasite and thereby cause deaths cause mortality[178-180] In addition, these chemical constituents meddle with the energy generation by uncoupling the oxidative phosphorylation which meddle with the glycoprotein of cell surface prompts parasite demise[180]. The prepared herbal formulation has prominent anthelmintic activity, but for safety purpose of formulation, toxicological studies will conduct in future.

12. CONCLUSIONS

A number of plants/extracts are reported to have anthelmintic activity. Most of the studies reported *in vitro* activity and only a few studies report *in vivo* activity. So, more research is needed to investigate the molecular mechanism of action of the reported anthelmintic plants/extracts as well as there is a need to either modify existing anthelmintic agents or explore new molecular targets to get next generation anthelmintic agents.

Future perspectives

Now a days novel anthelmintic targets like lysine deacetylases, lysine deacetylases, KDAC inhibitors, kinase inhibitors are explored. Modification of chemical structure and combination of known anthelmintics is also one of the ways to combat this challenge. Drug repurposing is also an emerging trend in anthelmintic drug discovery *e.g.* trichlorfon, a broad-spectrum organophosphorus insecticide has recently proved as anthelmintic agent.

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