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A Review on Plant-Based Anthelmintics

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Saurabh Mundada, Vasanti Suvarna*

Department of Pharmaceutical Chemistry and Quality Assurance, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V.L. Mehta Road, Vile Parle (West), Mumbai 400056, Maharashtra, India

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ABSTRACT

About two billion people worldwide are infected with intestinal parasitic worms. In the absence of human intestinal nematode vaccines, infection control is now based on synthetic drugs, however, resistance is becoming a serious issue. Controlling helminth parasites is difficult due to drug resistance, adverse effects, lack of efficacy, and cost-effectiveness for human and veterinary medicine that drive the need for new classes of anthelmintics. As a result, novel anthelmintic drug research and development, particularly those with novel mechanisms of action, are needed. Medicinal herbs, notably anthelmintic therapy, show a lot of potential as a source of successful therapies. Cinnamoyl derivatives, polyphenols, flavonoids, isoflavonoids, etc from plants, have proven anthelmintic properties. Many medical plant-derived medicines, such as artemether, galantamine, tiotropium, etc having proven anthelmintic properties with a novel mechanism of action, are available commercially around the world and have been discussed here.

INTRODUCTION:

Nematodes belong to the class of invertebrate roundworms which generally grow in marine, freshwater, and/or terrestrial environment. Phylum Nematoda of Nematodes comprises a parasite that relies on plants, animals, or human beings. Nematoda members have symmetrical elongated bodies that have an intestinal system and a large body cavity.[1] During the infective stages, parasites rely on their hosts for physiological and metabolic demands. One of the categories of the nematode as an intestinal parasite is an important pathogen for not only animals but also human beings. *Ascaris lumbricoides*, *Trichuris trichiura,* and the two hookworms *Ancylostoma duodenale* and *Necator Americans* are four dominant species of intestinal parasites.[2] Control of helminth parasites is difficult for human and veterinary medicine due to drug resistance, adverse effects, lack of efficacy, and cost-effectiveness, which drives the need for new classes of anthelmintics. Even though there is a huge need for anthelmintics only three new drugs had been approved since the year 2000.[3]

The parasitic infection could be controlled primarily by hygienic practice while secondary is to treat it using medicines. There are now only a few main classes of anthelmintics: Benzimidazoles, imidazothiazoles, tetrahydro pyrimidines, macrocyclic lactones, amino acetonitrile derivatives, salicylanilides, and organophosphates.[4] Various chemical moieties used for the helminthic treatment have several toxic and adverse effects. Drug resistance and the limited availability of drugs is the main cause of uncontrolled intestinal parasite infections. The use of plant-based natural products for the treatment is needed to avoid such life-threatening adverse effects of drug moieties. Cinnamoyl derivatives, polyphenols, flavonoids, isoflavonoids, etc from plants, have proven anthelmintic properties. Since the dawn of civilization, plants have been used in traditional medicine. Their use was mostly passed down orally, based on their efficacy and safety in treating certain ailments, before being documented in herbal literature. The therapeutic effects of medicinal plants are due to biologically active molecules having drug-like characteristics. Medicinal plant drug discovery continues to be a significant source of novel medications and therapeutic leads. Many plant-derived medicines, such as artemether, galantamine, and tiotropium, have been released to the market around the world.[5]

Table 1 mentioned below presents the different classes of the intestinal parasites responsible for the nematode infection in humans and animals.

Table No. 1: Commonly found human intestinal parasites

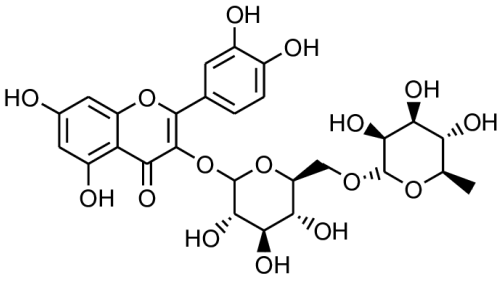
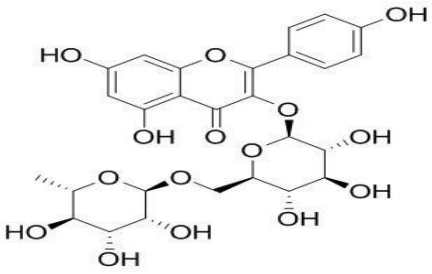
Category	Class	Examples
Protozoa	Rhizopod	*Dientamoeba fragilis*
		Entamoeba Coli
		Entamoeba hartmanni
Helminths	Trematoda (flukes)	*Metagoniusyokogawai*
		Opisthorchis felieus
		Fasciolopsisbuski
		Heterophyesheterophyes
	Cestoda (Tapeworms)	*Taeniarhynchussaginatus*
		Taenia solium
		Diphyllobothrium latum
	Zoomastigophorea (flagellates):	*Giardia intestinalis*
		Chilomastixmesnili
	Ciliata (Ciliates):	*Enterobius vermicularis*
	Nematoda (roundworms):	*Balantidium coli*
		Ascaris lumbricoides
		Ancylostoma duodenale

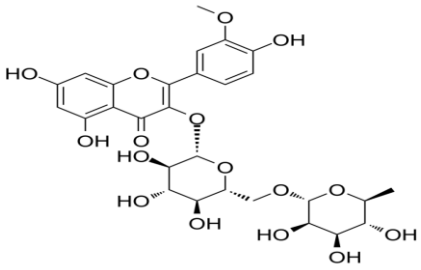
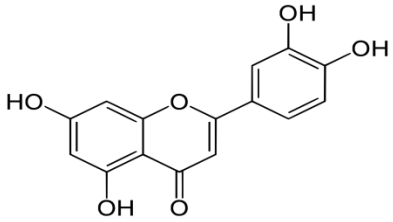
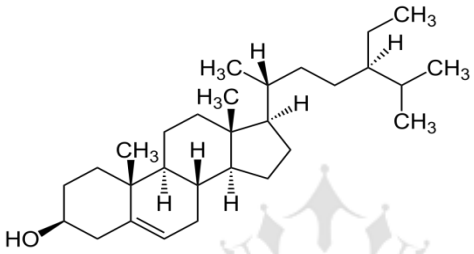
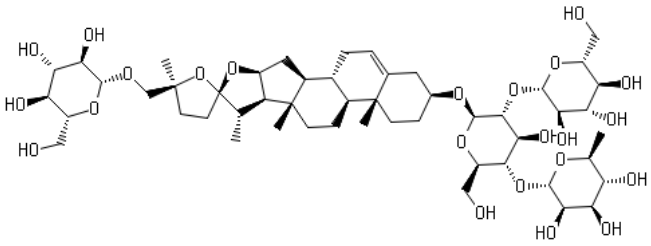
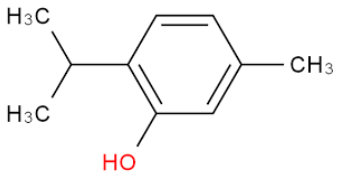
MECHANISM OF ACTION OF ANTHELMINTICS:

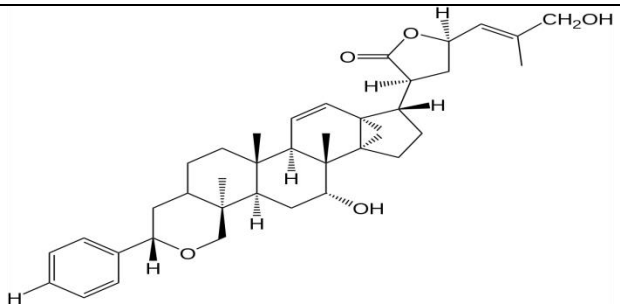
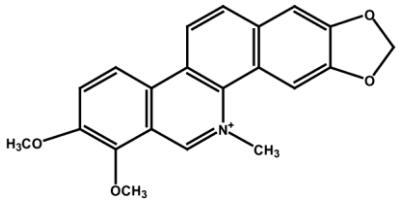
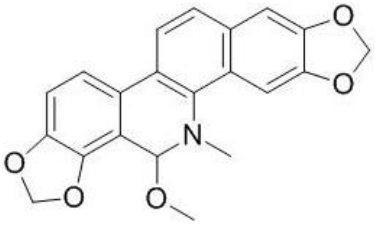
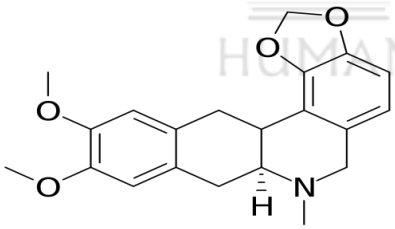
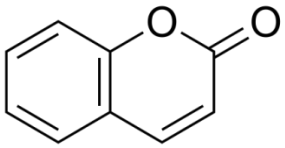
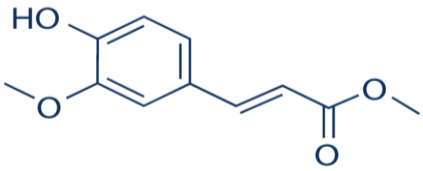
Piperazine acts as a weak GABA (4-aminobutyric acid) analog in Ascaris, causing a loss of body control, and reversible paralysis of body wall muscles. According to the gating mechanism of the ion channel, it is a low-efficacy partial agonist at GABA-gated chloride channels.[6] Benzimidazoles, such as albendazole, have been developed as anthelmintics. Benzimidazoles bind to parasite-tubulin with high affinity and impede microtubule polymerization, causing the cytoskeleton to be disrupted and the worm to die.[7] Tetramisole's pure L-isomer is known as levamisole. It is a nicotinic acetylcholine receptor (nAChR) agonist that causes muscular spasms and spastic paralysis in worms.[8]Amidantel's symmetrical diamidine derivative is tribendimidine. It works against a variety of human parasitic nematodes, including hookworm, Strongyloides, and Ascaris, but not against Trichuris. In a forward genetic screen for tribendimidine-resistant mutants in *Caenorhabditis elegans*, researchers discovered that they were also resistant to L-subtype nAChR agonists, implying

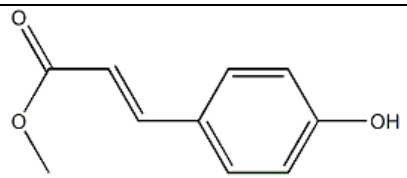
that the L-type nAChR is a shared target for tribendimine and levamisole. Tributandimidine, on the other hand, is not selective for the same receptor subtypes as levamisole and is more selective for the B-subtype of nAChRs in Ascaris suum than the L-subtype, according to a recent study.[9] Streptomyces produces macrocyclic lactones (avermectin, ivermectin, and abamectin). These compounds have broad-spectrum efficacy against nematodes and can cause a powerful and long-lasting paralysis of nematode pharyngeal and body wall muscles. They are glutamate-gated chloride channel selective agonists found only in invertebrates such as worms and insects. GABA and nicotinic receptors expressed in parasitic worm somatic muscle cells are also blocked by avermectins.[10]

Table No. 2: Chemical structures of different natural products active against intestinal nematodes

Class	Compounds
Lipids	Glycerol monostearate 
Phenolics	Rutin 
	Nicotiflorin 
	Narcissin

	
	Luteolin 
Saponin	β-sitosterol 
	Avenacoside A 
Terpenoids	Thymol 
	Dichapetalin

	
Alkaloids	Chelerythrine 
	6-Methoxydihydrosanguinarine 
	Dicentrene 
Coumaric acid	2H-Chromen-2-one 
	Methyl ferulate 
	Methyl coumarate

RESISTANCE AGAINST ANTHELMINTICS:

Benzimidazole based anthelmintics:

Benzimidazole is a bicyclic ring system in which benzene is fused to the 4th and 5th positions of the heterocyclic ring system. In search of anthelmintic activity, certain modifications in the structure of benzimidazole were captured. They target on β-tubulin of the helminth. A broad spectrum molecule against gastrointestinal parasites i.e Thiabendazole was evaluated in 1961.[11] Benzimidazole chemicals have species selectivity and serve as microtubule inhibitors. Tubulin, a microtubule subunit, is a dimeric protein with alpha and beta subunits of around 50 kD each. Both are heterogeneous products of multi-gene families in terms of structure, as well as post-translational modification. Microtubules and tubulin are in a dynamic equilibrium. Several endogenous regulatory proteins and cofactors regulate the ratio of dimeric tubulin to polymeric microtubules. Exogenous chemicals known as microtubule inhibitors can change the equilibrium in vivo and in vitro. Most, but not all, of these inhibitors, work by binding to tubulin to block subunits from self-associating onto developing microtubules, resulting in microtubule blocking at the associating end and microtubule dissociation at the opposite end, resulting in a net loss of microtubule length. This fact implies that inhibitors do not need to bind to all tubulin dimers to prevent polymerization. Simply blocking the microtubules is adequate for them.[12]

Imidazothiazole based anthelmintics:

They target the nicotinic acetylcholine receptor genes of the helminth. These bind to the nicotinic acetylcholine receptors and prevent the binding of the drug on them. The nicotinic acetylcholine receptors are encoded by specific genes (Hco-unc-63a, Hco-unc-29.3, etc.) that are underexpressed.[13]

Macrocyclic lactone based anthelmintics

They attack helminth in two ways. The first works by affecting Glutamate-gated chloride ion channels, whereas the second work by affecting the P-glycoprotein gene. On HEK293 cells,

macrocyclic lactone causes a mutation of the glycine residue, resulting in drug sensitivity loss.

Closantel:

Resistance is linked to resistant helminths' lower closantel intake, the drug's strong binding to albumins in the intestine of helminths, and the drug's enhanced excretion from resistant helminths.

Due to the increased resistance of helminth towards synthetic medicinal drugs, there is a need for some natural, plant-based anthelmintic.

Plant-based anthelmintics

Schistosomiasis is the second most significant tropical infection after malaria affecting the human populations in terms of the number of affected people and the endemic areas. Praziquantel and oxamniquine are the current mainstays of anthelmintic treatment. However, the development of resistant strains of parasites, inactivity against *juvenile Schistosoma*, and inability to prevent re-infection warrants the need for novel natural products against schistosomiasis.

***Artemisia annua*:**

Artemisinin derivative such as methyl ether derivative i.e. artemether having anti-malarial activity also has shown tremendous anti-schistosomal activity. The chemical structure of artemisinin i.e. sesquiterpene lactone bearing a peroxide group. Schistosomal species *Schistosoma japonicum* infested in the host when treated with artemether with varying doses and routes of administration showed a highly significant reduction in worm burden between 55% and 99%. Other artemisinin derivatives such as arteether, artesunate, and very recently, dihydroartemisinin have also shown therapeutic activity against Schistosomal species. Due to its chemical stability and high effectiveness against *Schistosoma japonicum*, artemether was the earlier drug tested for this disease. It showed that it mainly causes morphological alterations on the worm tegument, genital glands, and intestine, and female worms are disproportionately more susceptible than male worms. Artemether did show any adverse effects on the host. Although the mechanism of action by which the effect on the worm is seen is not clearly understood, however, it kills the larval migratory stage of the parasite and hence it precludes the development of egg-laying adult worm pairs thereby preventing the

pathology since these eggs are trapped in intestinal and hepatic tissues causing the schistosomiasis. The morphological alterations in the parasite worm started to appear after 8 hours of drug administration and were observed as swelling of the tegumental ridges later in about 3 to 7 days, the severity of the worm condition peaked and observation included swelling and fusion of tegumental ridges, vesiculation, peeling and erosion Swelling and fusion of tegumental ridges, vesiculation, peeling, and erosion were all found in female worms, with more severe and intensive tegumental damage. Most interestingly, the morphological changes observed started to reverse and the worm recovered partially or completely in 14 to 28 days post-treatment. A possible mechanism of action of the tegumental damage effect could be a decrease in glycogen content by 28-78% post-treatment and is probably related to the decrease in glucose uptake. However, it seems that the effect is more due to the inhibition of the glycolysis process and less due to the decreased incorporation of glucose to form glycogen.[14-18]

***Dryopteris species*:**

An experimental study by Magalhaes and colleagues on Dryopteris species has been also used as a vermifuge, antibacterial and anthelmintic in tapeworm infections. Primary actives present in Dryopteris, which has shown anthelmintic activity along with the antibacterial, and antioxidant activity are phloroglucinol derivatives such as aspidin and flavaspidic acid. Other phloroglucinol derivatives are desaspidin, desaspidinol, and methylene-bis-aspidinol are also tested to have shown anthelmintic activity against adult worm pairs. Worms showed both tegumental alterations and decrease motor activity with aspidin and flavaspidic acid in the concentration ranges from 10 to 100 micromolar, whereas desaspidin and methylene-bis-aspidinol seem to decrease motor activity without causing tegumental alteration. Desaspidinol did not show any anthelmintic activity according to the study. The study also showed that flavaspidic acid with concentrations of 10 and 25 micromolar decreases the production of eggs by worms by 97% and 91.6% respectively whereas, desaspidin at a concentration of 10 micromolar inhibited the egg production by 92.5% as compared to the negative control. 100% inhibition of egg production by worms was seen with aspidin and methylene-bis-desaspidinol at the concentration of 10 to 50 micromolar. It is not clearly understood how these phloroglucinol derivatives exert their schistosomicidal activity but the effects of aspidin and flavaspidic were related to the inhibition of oxidative phosphorylation in heart mitochondria of rats. The production of ATP is dependent on glycolysis and

oxidative phosphorylation. This study warranted the potential use of phloroglucinol derivatives in the treatment of schistosomiasis.[19]

***Momordica balsamina*:**

Triterpenes have also been shown to have schistosomicidal activity as demonstrated by a study performed by Ramalhete *et al.* These five cucurbitane-type triterpenes are isolated from *Momordica balsamina* have schistosomicidal activity against adult Schistosoma worms. Balsaminol F and karavilagenin C are the two actives responsible for the activity at a concentration of 15µM to 30 µM after 24 hrs of incubation. Both compounds significantly reduced the motor activity of the adult worms and significantly decreased egg production. At a concentration ranging from 10µM to 100µM, these compounds separated the worms pairs into adult male and female worms.[20]

***Origanum vulgare*:**

A monoterpene phenol, carvacrol obtained from *Origanum vulgare*, was tested for its schistosomicidal activity in the form of carvacryl acetate. It was demonstrated that carvacryl acetate has antischistosomal activity at 6.25 µg/ml affecting parasite mobility and viability. Significant morphological feature changes were observed on the tegumental surfaces of worms such as some tubercles appearing to be swollen with numerous small blebs emerging from the tegument around the tubercles. At sub-lethal concentrations of 1.25 µg/ml to 6.25 µg/ml, carvacryl acetate seemed to affect the daily egg output of adult worms, signifying that at high concentrations, carvacryl acetate is toxic while at lower doses it could affect with the reproduction machinery of adult worms.[23]

***Curcuma longa*:**

Another potential natural activity of curcumin was tested for its schistosomicidal activity by Magalhaes, Machado *et al.* Curcumin is found in the rhizome *Curcuma longa* commonly known as turmeric, and is also known to possess antibacterial, antioxidant, anti-inflammatory, anti-viral, anti-infectious and anti-carcinogenic activity. The study found that curcumin at 50 and 100 micromolar caused the death of all worms. At 5 and 10 micromolar, curcumin reduced egg production by worms by 50% when compared with the positive control group. Just like desaspidin and methylene-bis-aspidinol, but at a lower concentration of 5 to 20 micromolar, curcumin decreased the motor activity of the worms without tegumental alterations. At 5 to 10 micromolar concentration, curcumin decreased the egg

production by adult worms by 40-50% as compared to the negative control group Roswell Park Memorial Institute (RPMI) 1640 medium (Invitrogen) while also affecting the development of eggs produced by adult worms. Again, the mechanism of action is not clear, however, curcumin exerts its *in vitro* schistosomicidal activity by targeting the ubiquitin-proteasome pathway. Curcumin acts as an inhibitor of 20S proteasome proteolysis and cellular deubiquitinating. In turn reducing the number of schistosomula, the worm burden, and eventually decreases the number of eggs produced by *Schistosoma mansoni* in experimental mice. Hence it seems curcumin acts by inhibiting the ubiquitin-proteasome pathway, however, research studies are in progress to determine the schistosomicidal activity of curcumin.[24-28]

***Oldenlandia affinis*:**

Cyclotides such as kalata B1 and kalata B2 are peptides extracted from the plant *Oldenlandia affinis*, are shown to be effective against nematodes, and hence were tested for schistosomicidal activity. At a concentration range of 500-1000 µg/ml, kalata B1 and kalata B2 killed *Schistosoma japonicum* and *Schistosoma mansoni* adults within 5 minutes. Kalata B showed higher antischistosomes activity than kalata B1 and either of them was more effective in killing male worms than female worms. Both acted by lysing the tegument of adult worms. An observation was that after drug exposure, strong coiling of worms occurred due to distortion of longitudinal and radial muscle fibers.[29]

***Phyllomedusa species*:**

Antimicrobial peptide such as Dermaseptin 01 (DS 01), which is found in the skin secretion of frogs of the genus *Phyllomedusa* has also been tested for their activity against Schistosomes. At a concentration of 100µg/ml, DS 01 reduced the motor activity of worms and caused the death of all the worms within 48 hrs. 100% reduction in egg output was observed at a sub-lethal dose of 75µg/ml. The anti-schistosomes activity of DS 01 was found to be concentration-dependent in the range of 50-200µg/ml. Morphological alterations of tegument were significantly observed after worms were exposed to DS 0117.[30,31]

Citrus fruits:

Another potent schistosomicidal natural product, hesperidin at a higher concentration of 200mg/ml, is shown to be highly active against adult worms in *in-vitro* conditions. The mechanism of action for hesperidin is still to be determined, however, a study shows that it

acts both by inhibiting lipase activity at a concentration of 32 and 132mg/ml, and by inhibiting tyrosinase diphenolase activity at a concentration of 16 mM. Hesperidin also decreased tissue egg burden by 58.6%, mainly due to a decrease in the number of possible worm pairs. In *in-vivo* conditions, hesperidin at a concentration of 600 mg/kg body weight reduced adult worm burden, both male and female worms by 50 and 45.2% respectively. Two reasons attributed to this effect, one being a direct schistosomicidal effect and secondly, it may induce a strong immune response against *Schistosoma mansoni*. This humoral immune response is seen by the augmentation of IgG antibodies against soluble worm antigen protein and soluble egg antigen. The levels of IgG seen with hesperidin-treated mice are similar to levels of IgG observed with praziquantel-treated mice. These antibodies affect worm viability by interacting with membrane-surface proteins such as glucose transporter, and enzymes like amino acid permease and other enzymes necessary for the generation of ATP and energy. This eventually leads to the death of the adult worm. There is a need for further investigation of the mechanism of anti-schistosomicidal activity in *in-vivo* conditions as the activity seemed to be moderate and involved immune response against *Schistosoma mansoni*.[33,34]

***Chinchona officinalis*:**

The antimalarial natural drug, Mefloquine, amino alcohol, broadly used for the treatment of malaria and prophylaxis, has also shown certain anti-schistosomal potential according to a study performed by Jennifer Keiser, *et al.* for the treatment of schistosomiasis mostly in areas where malaria and schistosomiasis co-exist. Single-dose oral administration of 400 mg/kg mefloquine into mice infected with *Schistosoma mansoni* and *Schistosoma japonicum*, resulted in significant complete juvenile and adult worm burden reduction. This is a major advantage related to mefloquine over the use of praziquantel in treating this infection since the latter only shows an effect on adult worms and does not kill juvenile worms. Just as with any other mentioned natural products here, the mechanism through which mefloquine acts is not clear, however, it seems to play a role in hemoglobin digestion. Interestingly, female *Schistosoma mansoni* were more affected by mefloquine than male *Schistosoma mansoni* at the concentration of 100 – 400 mg/kg. Although well tolerated by adults and children, mefloquine has shown certain adverse events to the gastrointestinal and central nervous system such as diarrhea, nausea, vomiting, dizziness, pruritus, rash, headache, and abdominal pain. In another research study done by Shu-hua Xiao and colleagues, the minimal effective concentration of mefloquine was 10 µg/mL, at which mefloquine induced changes in worm motor activity, elongation of the body of the worm, focal swelling, and death of the worm

after 24 hours of administration of the drug. At the concentration of 5 µg/mL of mefloquine, no effect was observed whereas, at higher concentrations of 20 and 30 µg/mL, similar effects were observed but at a fast rate resulting in the death of 50% of worms in 4 hours after mefloquine administration.[36-37]

***Piper species*:**

Several species of Piper have been showing promising results as an anti-parasitic compound against *Schistosoma mansoni*. In a study by V. S. Carrara and colleagues, dichloromethane (DCM) and aqueous extract of roots, leaves, and stem of Piper species such as *Piperaduncum*, *Piperamalago*, *Piper arboretum*, etc were tested for anti-schistosomicidal activity against *Schistosoma mansoni*. Dichloromethane extract of Piper species leaves was more active than aqueous fractions of stems of Piper species such as *Piper nigrum* and *Piper Chaba*. On chromatography of DCM extract of *Piperamalago* leaves, a piperamide named N-[7-(30,40-methylenedioxyphenyl)-2(Z),4(Z)-heptadienoyl] pyrrolidine (Piperamide 1) appeared as a major compound showing anti-schistosomicidal activity at a concentration of 100 mg/ml, killing all parasites and separate all pair of adults.[38] Other major active compounds inducing anti-schistosomicidal activity are still a subject of research in progress. As observed with mefloquine, male and female adult worms differed in their sensitivity to the effects of piperamide 1. Another piperamide, namely Piplartine isolated from *Piper tuberculatum* showed a significant effect on motor activity of adult *Schistosoma mansoni*. At a lower dose of 25–50mM, Piperamide 1 induced early loss of spontaneous movement and later complete immobilization of both male and female worms. The mechanism of action through which piperamide and piperine are unclear, however, there seems to be a direct effect on the muscles of the worm by these piperamides. Further biological and toxicological studies are warranted to elucidate the mechanism of action of these agents.[39]

***Sanguinaria species*:**

Plumbagin and sanguinarine are other two plant-derived compounds (secondary plant metabolites) obtained from *Sanguinaria species* which have shown anti-schistosomicidal activity at a concentration of 10 micromolar and are found to be more efficacious than mefloquine and curcumin, with 100% mortality rate in 45 hrs post-administration. The morphology of worms treated with plumbagin and sanguinarine differs significantly. After death, plumbagin-treated worms become withered, whereas sanguinarine-treated worms do not. This suggests that plumbagin promotes muscle contraction, which affects muscle

function.[40] Similarly, hydroalcoholic extract of *Psidium guajava* (PgHA), a tanniferous plant, showed anthelmintic activity at a concentration of 534µg mL-1. Increased total proteins, intracellular H_2O_2, and lipid peroxidation products, as well as increased antioxidant activity of enzymes such as glutathione S-transferase and superoxide dismutase, all contributed to the antiparasitic mechanism. Thus, the PgHA showed antiparasitic activity *in vitro.*[45]

***Ozoroa insignis*:**

The ethnobotanical plant *Ozoroa insignis* Del has long been used in traditional medicine to treat schistosomiasis and hookworm diseases. *Schistosoma mansoni*, *Strongyloides ratti*, and other bacteria were examined with three isolated compounds: 6-[8(Z)-pentadecenyl] anacardic acid, 6-[10(Z)-heptadecenyl] anacardic acid, and 3-[7(Z)-pentadecenyl] phenol. All three compounds examined had good activity against *Schistosoma mansoni*, with compound 1 having the best activity against juvenile schistosomula, with 50% activity at 1M. Pharmacodynamics and pharmacokinetics studies are unknown for these compounds are needed to be done for a better understanding of the role of these agents as anthelmintics.[46]

***Pilocarpus microphyllus*:**

Another alkaloid-rich plant, *Pilocarpus microphyllus* ex Wardlaw (Rutaceae), popularly known as jaborandi was researched by Jefferson A. Rocha and colleagues for the anthelmintic activity of these alkaloids against *Schistosoma mansoni*. Alkaloids extracted from pilocarpus plant include pilocarpine, pilosine, isopilosine, epiisopilosine, epiisopiloturine, and macaubine among others. Epiisopiloturine (EPI) has shown potent activity against *Schistosoma mansoni*. After 96 hours of incubation, the efficacy of *in vitro* EPIIS treatment on *Schistosoma mansoni* revealed 100 percent death of adult worms at a dosage of 3.125 µg/mL. It has been reported that the anthelmintic activity of epiisopilosine (EPIIS) is 100 times greater than EPI against *Schistosoma mansoni* decreased motor activity and alteration in the tegument were the effects observed in the treated worm.[47]

***Zanthoxylum naranjillo*:**

In a chemical investigation of ethyl acetate extract fraction of *Zanthoxylum naranjillo* (Rutaceae) leaves, which contains actives such as protocatechuic acid (1), gallic acid (2), p-hydroxybenzoic acid (3), and 5-O-caffeoylshikimic acid (4) were tested against schistosomes. Results obtained demonstrated that these four compounds caused a significant decrease in daily egg production by 29.8%, 13.5%, 28.4%, and 17.7% respectively. Compounds 1 and 3

showed better inhibitory properties than compounds 2 and 4 and were also able to separate adult worm pairs into male and female worms.[48]

***Baccharis trimera*:**

In *in vitro* assay of essential oil of *Baccharis trimera* tested for its schistosomicidal activity, it was found that 100% mortality was observed after 30 hrs at a concentration of 130µg/ml. Male worms were more susceptible to the essential oil and it also showed a significant decrease in worm motility. Morphological changes observed after exposure to essential oil included peeling on the tegument surface and destruction of tubercles and spines resulting in smooth areas on the body surface of worms.[49]

***Cucurbita pepo*:**

Pumpkin i.e *Cucurbita pepo* seed oil (PSO) was tested against schistosomes and was found to be significantly active against juvenile and schistosomula. At a concentration of 100µL/mL, PSO showed 100% mortality after 48 and 72 hrs exposure. Adult *Schistosoma mansoni* motility was remarkably affected by rising concentrations of PSO. At lower concentrations of 20 and 40µL/mL, significant morphological changes did not appear after 24 hrs, however, bodily changes such as stretched head end, slight elongation, and focal swelling of the worm body were observed when worms were exposed to PSO after 72 hrs.[50]

Few Brazilian cerrado species such as *Miconia langsdorffii* (Melastomataceae), *Roupala Montana* (Proteaceae), *Struthanthus syringifolius* (Loranthaceae), and *Schefflera vinosa* (Araliaceae) have not yet been described for their schistosomicidal activity. The organic extracts of these species were tested *in vitro* for their activity against adult Schistosoma worms. Major active constituents found in the extracts included triterpenes such as betulin, oleanolic acid, ursolic acid, and flavonoids such as quercetin 3-O-β-D-rhamnoside, quercetin 3-O-β-D-glucoside, quercetin 3-O-β-D-glucopyranosyl-(1-2)-α-L-rhamnopyranoside and isorhamnetin 3-O-β-D-glucopyranosyl-(1-2)-α-L-rhamnopyranoside. Results obtained from the experiments suggested that betulin caused the death of 25% of worms after 120 hrs at a concentration of 100µM, and 25% and 50% after 24hrs and 120hrs at a concentration of 200µM. Flavanoid quercetin 3-O-β-D-rhamnoside caused the death of 25% of worms at 100µM, while other flavonoids such as flavonoids quercetin 3-O-β-D-glucoside and quercetin 3-O-β-D-rhamnoside caused a significant decrease in motor activity of worms.[51]

Table No. 3: Plant-based anthelmintics

Plant (Biological name)	Compound class	Actives	Concentration	Activity	Reference
Artemisia annua L. (Asteraceae)	Sesquiterpene lactone	Artesunate	~100–780 micro molar	Antischistosomal (against immature worms)	14-17
		Artemether	~335–1000 micromolar	Antischistosomal (against immature worms)	14,15
		Artemisinin	N.A	Antischistosomal (against immature worms)	14-16,18
Dryopteris genus (Dryopteridaceae)	Phloroglucinol/ phenol	Aspidin	10 micromolar	*In vitro* against adult worms	19
Momordica balsamina L. (Cucurbitaceae)	Triterpene	Balsaminol F	~15 micromolar	*In vitro* against adult worms	20
Schefflera vinosa (Cham. &Schltdl.) Frodin (Araliaceae)	Triterpene	Betulin	100 micromolar	*In vitro* against adult worms	21
Viguiera (Asteraceae)	Sesquiterpene lactone	Budlein-A	12.5 micromolar	*In vitro* against adult worms	22
Origanum	Monoterpene	Derived	~30	*In vitro* against	23

vulgare		from carvacrol (Carvacryl acetate)	micromolar	adult worms	
Curcuma longa L. (Zingiberaceae)	Polyphenol	Curcumin	50 micromolar	*In vitro* and *in vivo* against adult worms	24-28
Oldenlandia affinis (R&S) DC. (Rubiaceae)	Peptide	Kalata B1	18 micromolar	*In vitro* against adult worms	29
		Kalata B2	~1 micromolar	*In vitro* against adult worms and In vivo against immature and adult worms	29
The frog of the genus Phyllomedusa (Hylidae)	Peptide	Dermaseptin 01	~15 micromolar	*In vivo* against immature and adult worms	30,31
Pilocarpus microphyllus Stapf ex (Rutaceae)	Alkaloid imidazole	Epiisopilotu rine	>500 micromolar	*In vitro* against immature and adult worms	32
Citrus fruits	Flavanone glycoside	Hesperidin	165 micromolar	*In vitro* against adult worms and in vitro and in vivo against the immature and adult worms.	33,34
Styrax pohlii Pohl (Styracaceae)	Flavonoid	Kaempferol	100 micromolar	*In vitro* against adult worms	35
Cinchona	Aminoalcohol	Mefloquine	~15–30	*In vitro* and *in*	36,37

officinalis	/ quinolines		micromolar	*vivo* against immature and adult worms	
Essential oils found in *Zingiber officinale*, *Jasminum officinale*, *Cymbopogon citratus*, Stapf.	Sesquiterpene	Nerolidol	~30 micromolar	In vitro against adult worms	38
Piper amalago L. (Piperaceae)	Alkaloid amide	Piperamide 1	100 micromolar	*In vitro* against adult worms	39
Sanguinaria spp. (Papaveraceae)	Benzophenanthridine alkaloid	Sanguinarine	10 micromolar	*In vitro* against adult worms	40
Solanum lycocarpum A. St. Hil. (Solanaceae)	Steroidal alkaloids (glycoalkaloids)	Solamargine	32 micromolar	*In vitro* against adult worms	41
Roupala Montana Aubl. (Proteaceae)	Flavonoid	Quercetin 3-O-β-d-glucoside	N.A	*In vitro* against adult worm	42
Schefflera vinosa (Cham. &Schltdl.) Frodin (Araliaceae)	Flavonoid	Quercetin 3-O-β-d-rhamnoside	100 micromolar	*In vitro* against adult worms	42
Spondias mombin L	Chlorins	Phaeophorbide-a	200 µM	Against Haemonchuspla cei (Nematodes)	43
*Psidium guajava (*L.)	Tannins	PgHA (*Psidium*	1500 mg/ml	Gastrointestinal nematode of	44

		guajava hydroalcoholic extract)		sheep	
Ozoroa insignis Del.	Anacardic acids	6-[8(Z)-pentadecenyl] anacardic acid, 6-[10(Z)-heptadecenyl] anacardic acid	51.9 µM – 93.4 µM	schistosomiasis, tapeworm, and hookworm (e.g Schistosoma mansoni)	45
Pilocarpus Microphyllus	Imidazole alkaloid	Epiisopilosine	1.5625 -25 µg/mL	*Schistosoma mansoni*	46
Pelargonium endlicherianum FENZL	Condensed tannins	MeOH extract	400 and 800 µg/ml	Gastrointestinal nematode (Haemonchuscontortus).	47

CONCLUSION:

From this brief analysis, it is clear that various anthelmintic compounds have been identified from medicinal plants in the last few years, the majority of which are traditionally used to treat intestinal worms. The majority of these compounds were proven to be effective *in vitro,* but just a few were tested *in vivo*. Additional proof will be required if these compounds are to be developed further in the preclinical stage. We believe that this review will inspire fundamental scientists to investigate the mechanisms of more anthelmintic compounds. Traditional medicine expertise has become sufficiently appealing for pharmaceutical or biotech businesses, which will very certainly be required to develop them further into novel anthelmintic medications.

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