Journal of Ayurvedic and Herbal Medicine 2021; 7(4): 265-275

Review Article

ISSN: 2454-5023
J. Ayu. Herb. Med.
2021; 7(4): 265-275
Received: 12-08-2021
Accepted: 13-11-2021

www.ayurvedjournal.com
DOI: 10.31254/jahm.2021.7410

Anthelmintic lead compounds and their targets for drug development

Sonia Singla[1], Satvinder Kaur[2]

[1] Assistant Professor, G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana, Punjab, India
[2] Professor and Principal, G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana, Punjab, India

ABSTRACT

Helminthiasis is a major health issue worldwide. Over 200 million peoples and 600 million school age children are manifested by these parasites. It is a wide spread neglected tropical decease of developing countries and affect majorly poor peoples. The helminthic parasites weaken the immune system and increase susceptibility to HIV/AIDS, pneumonia, tuberculosis, malaria. Trematode (flukes), cestode (tapeworm) and nematodes (round worm) are the members of helminth infection. *Ascaris lumbricoides, Nector americanus, Ancyclostoma duodenale* and *Trichuris trichuria* are are the parasites which spread infection without any vector and cause serious complications in lungs and CNS. Schistosoma species (trematodes or flukes) are mainly transmitted by contaminated fresh water. Cestodes (*Taenia solium, Taenia saginata*) transmit infection through contaminated and uncooked red meat and cyst in different tissue. Cyst in CNS results in pathological changes called neurocysticercosis. Nature is a big store house of remedies for ailments of mankind. Due to toxic effects of synthetic drugs, there's a great need to invent new bio-active constituents and plants can complete this need effectually.

Keywords: Helminthiasis, Anthelmintic drugs, Synthetic lead compounds, Secondary metabolites.

INTRODUCTION

Helminthiasis is a major health issue in both human and animals from ancient time. All kinds of helminth infections affect every second person in the world. Many efforts have been put to control parasitic infections with a level of usefulness and security over predecessors. Beside human complications it also causes significant economic losses [1]. Major cause of these infections is poor sanitation, malnutrition, lack of knowledge; practice about hygiene and overcrowded population [2]. The mode of transmission for helminthiasis is human and animals, acting as primary and secondary host. Insects act as the vector for the host, contaminated soil, water and food. It is a wide spread neglected tropical decease of developing countries and affect majorly poor peoples. Over 200 million peoples and 600 million school age children are manifested by these parasites [3]. The helminthic parasites weaken the immune system and increase susceptibility to HIV/AIDS, pneumonia, tuberculosis, malaria [4]. Trematode (flukes), cestode (tapeworm) and nematodes (round worm) are the members of helminth infection. *Ascaris lumbricoides, Nector americanus, Ancyclostoma duodenale and Trichuris trichuria*are are the parasites which spread infection without any vector and cause serious complications in lungs and CNS. Schistosoma species (trematodes or flukes) are mainly transmitted by contaminated fresh water. Cestodes (*Taenia solium, Taenia saginata*) transmit infection through contaminated and uncooked red meat and cyst in different tissue. Cyst in CNS results in pathological changes called neurocysticercosis [5, 6]. Anthelmintics also termed as vermifuge or vermicides, are the drugs which expel parasites from host through killing and stunning mechanism. If these drugs kill effectively the parasites, also cause side effects. Now a day's resistance against chemotherapeutics by nematodes has also become a major issue of discussion [7]. Like praziquantel, it's not as effective a decade ago. Mebendazole, pyrantel also not much effective against the hookworms. Multi resistance strains nematodes also decrease the use of vermifuges [8]. Additionaly these drugs too costly to use in developing countries. Common anthelmintic with high range of availability and low cost are praziquantel, mebendazole, albendazole.

Nature is a big store house of remedies for ailments of mankind. Due to toxic effects of synthetic drugs, there's a great need to invent new bio-active constituents and plants can complete this need effectually. Anthelmintic derived from plants have very little or no toxicity, wide area of spectrum and are more environmentally compassionate [9]. Secondary metabolites isolated from plants by different isolation and purification techniques play major role as alternative to synthetic drugs. Now a day's herbal medicine capture huge market due to low cost and there easy availability in developing and poor countries. Due to meager medical and economical support it's become big task for pharmaceutical companies to market

***Corresponding author:**
Dr. Sonia Singla
Assistant Professor, G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana, Punjab, India
Email: Soniaasingla786@gmail.com

new botanicals including anthelmintics. Helminthiasis is a problem of low economic status countries which have little or no money to control these infections. There's a great need to develop new molecules against helminth parasites because of resistance against presently used drugs. Plants can effectively help in ridding all these difficulties [10].

Prevalence of helminthiasis

According to world health organization more than 2 billion people are suffering worldwide from these parasitic infections. Infections due to nematode are most widespread like trichinosis caused by *Trichurus trichuria*, Ascariasis caused by *Ascaris lumbricoides*, hookworm infection caused by *Ancylostoma duodenale*, *Nectator americans*and thread or pinworm infection caused by *Enterobius vermicularis.* The infection which occurs in intestine, is migrated to larvae in various tissue and skin [11, 12, 13, 14]. More than 250 million people suffering from disease intestinal Shistosomiasis tropically and subtropically. Infection spread in Africa, East Asia and South America with symptoms granuloma formation, fibrosis, spleen enlargement, dermatitis, liver infection caused by *Schisto somamansoni*, *Schisto somajaponicum* belongs to phylum Trematoda much more than any other counteries [15]. More than 150 million people suffer from lymphatic filariasis in Asia, America and tropical Africa triggered by *Wucheria bancrofti*, *Mansonella* species, *Brugia* species resulting infection in lymphatic system with enlargement of lymph nodes [16]. Around 80 million people suffer from urogenital schistosomiasis in Africa spread by *S. haematobium* causing infection in urinary bladder, haematuria. Pork and beef tapeworm infection occurring worldwide cause infection in intestins and cyst in brain spread by *Taenia* species like *T. solium*, *T. asiatica*, *T. saginata* [17, 18]. Thirty to fifty millions suffer from trichinosis and strongyloidiais caused by *Trichurus trichiura* and *Strongyloidesstercoralis* respectively in tropic, subtropic regions with symptoms of fever, oedema, invasion in muscle tissue, myalgia and intestinal infection and anaemia respectively [18, 19]. Ten to twenty millions suffer from opisthorchiasis, liver flukes in east Asia and east Europe with symptoms of infection in gall bladder and liver caused by *Opisthorchis felineus*, *O. viverrini*; Clonorchiasis caused by *O. sinesis* is prevalent in Japan and China with carcinoma, fibrosis, infection in liver; while paragon miasis occur in America, East Asia, Tropics of America with common symptoms of infection in lungs, brain and internal organs caused by *Paragoniumus westermani*, *P.mexicanus*. Diphyllo bothriasis is spreaded by *Diphyllo bothriumlatum* (fish tapeworm) and other cestodes cause infection in intestine with Vitamin B12 deficiency worldwide [18, 20]. 20-30 million people suffer from dwarf tapeworm infection caused by *Vampirolepis nana* respectively worldwide; Loiasis and Onchocerciasis (blindness) by *loaloa* and *onchocerca volvulus* cause female worm migration through eye and skin, nodules under eyes and skin in central Africa and tropical Africa, respectively [21, 22].

Some of the helminthic infections are not very common (around 2 million people only) like Fasciolopsiasis (*Fasciola hepatica*, *F.gigantica*) belong to phylum trematoda occurr worldwide cause infection in liver; dog tapeworm (*Dipylidium caninum*) and hydatidosis, echinococcosis (*Echinococcus granulosus, Echinococcus multilocularis*) ocurring worldwide cause intestinal infection [18]. Dracunculiasis (*Dracunculusmedinesis*) is also an infection of skin prevalent in Asia and Africa effecting 3 million people [23].

Anthelmintics are the drugs that are effective against the complications due to intrusion of parasites like hookworm, roundworm, tapeworm etc. Mechanism of action of these drugs differ by their biochemical features. Each one has different groups and sites for binding with parasite to kill and expel them from the body. Evaluation of anthelmintics is done by checking their efficacy against parasites and human. Complete data and knowledge is advantageous for further study like resistance, dosage, side effects etc. It also gives us inkling to overwhelmed resistance happening in worms against chemotherapeutics.

Anthelmintic were firstly developed for veterinary practices. With time through alterations these gained market for human uses. Resistance and narrow spectrum of available synthetic drugs are the major two motives to invent new drugs or molecules from plant origin.

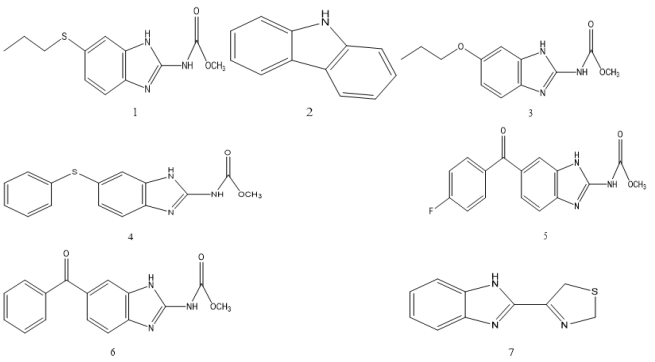
In 1950's first anthelmintic drug piprazine citrate appeared in market with drawbacks like use for long duration constantly and very narrow spectrum. It was effective against *Ascaris* and *Enterobius* species. It was followed by praziquanel effective against shistosomiasis; pyrantel and levimasole effective against hook worms [24].

Chemotherapy for helminthiasis

Anthelmintics have affinity to attach specific target site in parasites due to variation in basic molecular structure. It is to classify anthelmintics on the basis of their basic chemical structures like benzmidazoles, ivermectins, piprazine, pyrazinoisoquinoline, tetrahydropyrimidines and imidathiazoles, phenoxyalkanes, chlorinated sulfonamides, organophosphates, salicylanilides, halogenated phenols and bisphenols.

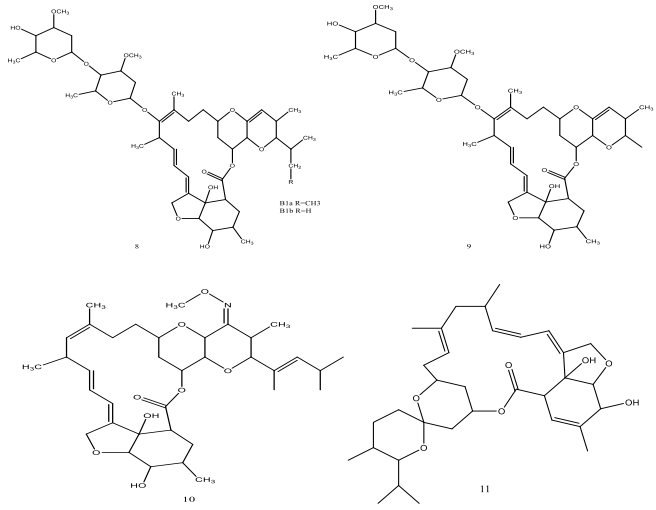
Benzmidazoles

These are microtubule disturbing agents. Drugs belongs to this class are Albendazole (1), Carbazole (2), Oxibendazole (3), Febendazole (4), Flubendazole (5), Mebendazole (6), Thiabendazole (7), Netobimin. Thiabendazole is the first broad spectrum anthelmintic introduced in 1961 [25]. This class of drugs is highly effective against cestodes and nematodes [26]. These drugs having high affinity to attach with b-subunit of helminth microtubule in pseudo-irreversible way and ossify the microtule, disturb microtubules formation and cause stoppage of cell division in parasite ultimately lead to its death. Albendazole (broad spectrum) inhibit glucose uptake by depletion of glycogen storage and reduce ATP storage [27]. Beside all these mechanisms albendazole also up regulae the pro-apoptotic protein expression and down regulate the anti-apoptotic protein expression causing DNA fragmentation in bovine filarial perasie (Setariacervi) [28]. Albendazole and mebendazole effective against Ascaris lumbricoides, Ancylo stomaduodenale; metronidazole is effective against Dracuncula medinensis; albendazole is also effective against Trichinella spiralis [49]. Side effects caused by this class of drugs are fever, rashes, epigastric pain, dizziness, vomiting, headache, urticaria, oedema [29]. In some cases, it retards the growth of children, cause increase in serum aminotransferase activity, jaundice, chemical cholestasis. Mebendazole can cause occipital seizures and teratogenic effect. It is recommended not to be use in pregnancy and by children less than 2-year-old [30].



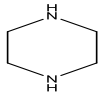
Ivermectin

These are semi-synthetic macrocyclic lactones. Comprising members of this class are Abamectin (8), Doramectin (9), Moxidectin (10), Milbemycin D (11) act by targeting on glutamated chloride channel (glucls) type a-subunit and cause plasma membrane hyperpolarization leading to paralysis of muscle and death of parasite. It also stops feeding to parasites by blocking pharyngeal pumping act as anti-feedant. These are effective against nematodes and majorly used in onchocerciasis in human. Ivermectin is highly effective against *Oncocerca volvulus*, *Oncocerca loaloa* [31, 32, 33, 34]. Side effects related to ivermectin derivtives are CNS toxicity, ataxia, mydriasis.In infected person drug toxicity results due to mazzoti like reaction to dying microfilariae. Even death can occur at high dosage [35, 36].



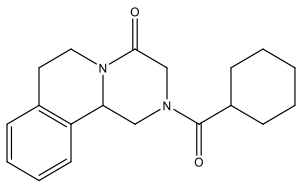
Piprazine

Mostly used as citrate salt and effective against intestinal threadworm infections (enterobius or vermicularis, oxyuris) and roundworm (*Ascaris lumbricoides*). It inhibits neuromuscular transmission reversibly by acting as GABA agonist on receptor present on somatic muscles in nematodes and cause opening of GABA gated chloride channel, which increase permeability to chloride and relaxation take place, which ultimately cause peralysis of parasite. No any major side effect is reported due to piprazine citrate. Prolong use of piprazine (12) in children can cause neurotoxicity [37]. Diethyl carbamazineis also a piprazine derivative used as citrate salt effective against filarial infection caused by *Wucheraria bancrofti*, *Brugia malayi*, *Dirofilaria immitis*. It acts by altering arachidonic acid and cyclooxygenase metabolic pathwayof filarial lead to vasoconstriction and amplified endothelial adhesion which cause immobilization of parasite. It also modifies the surface layer of microfilariae and expose them to immunological cell mediated lysis. Effect of diethyl carbamazine mediated by triggering of platelets with filarial excretory antigen (FEA). Killing mechanism of parasite is free radical mediated [38]. Side effects related to this drug are intense itching with enlargement and tenderness of lymph nodes mostly occuring in patient suffering from onchocerciasia after few hours of first dose administration. Other side effects include headache, limbitis, atrophy of retinal pigment epithelium, punctate keratitis [39, 40].



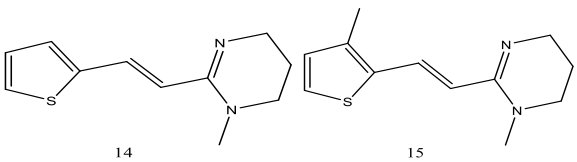
Pyrazinoisoquinoline

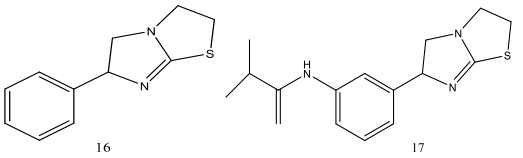
Praziquantel (13) a broad spectrum anthelmintic related to this category effective against cestode infection and schistosomiasis. When parasite is exposed to this drug it induces calcium flux and increases calcium level across membrane and sarcoplasmic reticulum. Increase calcium level leads to muscle contraction due to electrical coupling of membrane and muscle cells causing peralysis of muscle and death of the parasite. It is majorly effective against *schistosoma* and *tenia* species like *S. hematobium, S. mansoni, S. japonicum, T. solium, T. saginata* and *Diphyllobothrium latum* and *Hymenolepsis nana* [41, 42]. Side effects related to this class are fever, pruritis, urticaria, arthralgia, neurocysticercosis, meningismus, seizures, mental changes and cerebrospinal fluid pleocytosis [43].



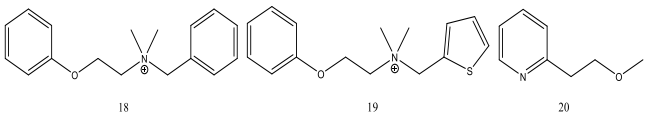
Tetrahydropyrimidines and Imidathiazoles

Pyrantel (14), Morantel (15) belong to class of tetrahydropyrimidines, Levamisole (16), Butamisole (17), Bephenium (18), Thenium (19), Methyridine (20) belong to class imidathiazoles. They act as nicotinic (acetylcholine) agonist bind to specific target site nicotinic acetylcholine receptor present on somatic muscle of nematodes causing depolarization and paralysis in whole body of the parasite. Both of these classes are majorly used in veterinary practices in sheep (gastrointestinal nematodes), horse, dogs, cats, pigs, cattle. These agents affective against *Trichurisvulpis, Ascarislumbricoides, Ancylostoma caninum.* Side effects related to these drugs are mild like gastric disturbance, headache and rashes. These drugs are not being used by pregnant ladies and children under 2 years of age due to their teratogenic effect [44].





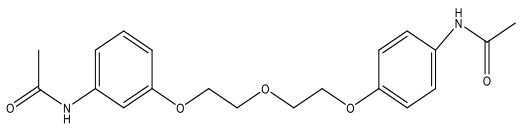
16 17



18 19 20

Phenoxyalkanes

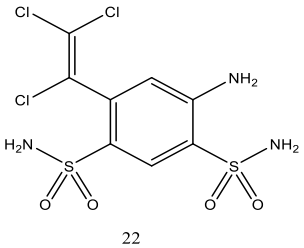
Diamphenethide (21) is a derivative of phenoxyalkane class, highly active against the youngest of immature liver fluke *Fasciola hepatica* present in the liver parenchyma but less effective against *Fasciolain* in bile. It is active against all flukes but adequate results are obtained when acts on mature ones in host liver. Diamphenethide gets deacetylated and produce two active metabolites monoamine and diamine which elevate melate concentration in fasciola, interfere with glucose metabolism because malate is intermediate product of glucose metabolism. This leads to melate accumulation in parasite and prohibit utilization of glucose causing death in parasite [45, 46].



21

Chlorinated sulfonamides

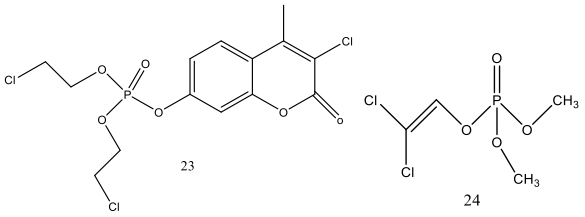
Drug Clorsulon (22) is related to this category. It is structurlysimiler with 1,3-diphosphoglycerate so inhibit phosphoglycerate kinase and phosphoglyceromutase of *Fasciolahepatica*, *Fasciolagigantica*, *Fascioloides magna* (liver flukes). Due to inhibition of these enzymes it stops glucose metabolic Emden-Meyerhoffpathway. This results in utilization of glucose not taking place. Which cause death of parasite [47]. Side effects related to this drug are dry skin, cough, itching of skin, abdominal pain, sore throat, fatigue, transient eosinophilia, nausea, arthralgia, irritation in eye.



22

Organophosphates

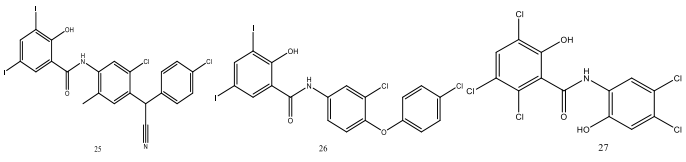
Anthelmintic drugs Haloxon (23), Dichlorvos (DDVP) (24) are derivative of organophosphates. They act by inhibiting the enzyme acetylcholinesterase, which is involved in the termination process of impulse transmission through rapid hydrolysis of the acetylcholine neurotransmitter in the peripheral and central nervous systems. The inactivation of enzyme leads to acetylcholine accumulation and hyper stimulation of muscarinic nicotinic and muscarinic receptors and neurotransmission are disrupted. Major side effects caused by organophosphates are chest discomfort, shortness of breath, coughing, wheezing, bloody or running nose. Other side effects are diarrheas, abdominal cramps, fatigue, in-coordination, respiratory muscle paralysis, pupil dilation or constriction, confusion, dizziness, vomiting, loss of reflexes and sweating [48, 49].



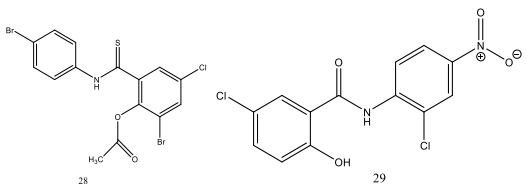
23 24

Salicylanilides

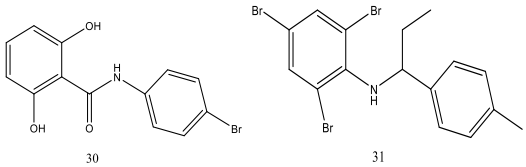
These are veteranary anthelmintics mainly these are used in pets, sheep, horses and cattle. Closantel (25), Rafoxanide (26), Oxyclozanide (27), Brotianide (Bromoxanide) (28), Niclosamide (29), Resorantel (30), Tribromosalane (31) are the drugs related to this category. The drug niclosamidecan be used in human. These are thousand times more potent than dinitrophenols and act as proton ionophores also called oxidative phosphorylaseuncoupler. It contains detachable proton with high lipid solubility, so easily absorbed through phospholipid membrane of cell and also shuttle into inner mitochondrial membrane. ATP production is coupled with gradient developed by proton across inner membrane of mitochondria. Oxidative phosphorylation takes place when electron from NADH/FADH conveyed with the help of protein complexes on the inner membrane and proton pumped out of mitochondrial matrix produce transmembrane electric potential. Proton back into matrix with the help of enzyme complex and ATP formed. Salicylanilides reduce proton gradient in inner membrane and uncouple oxidative phosphorylation. Due to high affinity to bind with plasma these agents have long half-life (14 days). Salicylanilides not only act on mitochondrial membrane also act on tegument membrane of parasites. Major side effects in animals are blindness, mydriasis and opthalmo scopicpapilloedema. While others are diarrhea, dyspnea, muscle tremor, tachpnoea, clonic spasm, peddling movement of forlimbs in cat. [50]



25 26 27



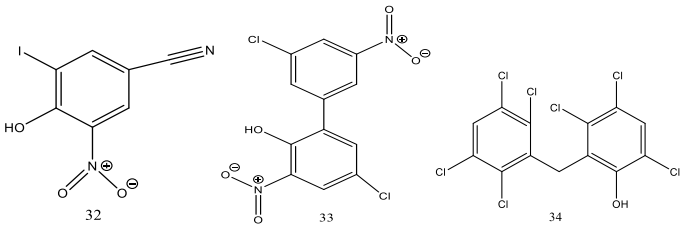
28 29



30 31

Halogenated phenols and bisphenols

Nitroxynil (32), Niclofolan (33), Hexachlorophene (34), Dibromosalan are the drugs considered under this category. These agents also contain a detachable proton so act like as salicylanilides in mitochondrial membrane. Both salicylanilides and halogenated phenols selectively effective against gastrointestinal roundworms (*Bunostomumspp, Haemonchusspp, Oesophagostomumspp, Strongyloidesspp, Trichostrongylusspp*, liver flukes (*Fasciola hepatica*) and tapeworm (*Taenisspp, Moniezaspp*). Not any major side effect reported from this class. Common side effects are difficulty with breathing, fever, headache, nausea, swelling, vomiting and irritation in or around the mouth [51].



Resistance against synthetic drugs

It is a serious threat linked with improper and extensive use of anthelmintics with other factors. The chemotherapeutic agent that was previously effective against particular parasite but now lose its effectiveness and sensitivity against the same called resistance. Now days it's a major issue in pharma field due to serious economic loss and time. Resistance development is greater in case of intestinal filarial parasites as compared to systemic worms due to short life cycle and high desity in GI tract [52, 53]. There are lots of mechanisms involved in the development of resistance against a particular class of drug or drug like due to deficiency of enzyme sulfotranferase, important enzyme to activate drug oxamniquine used for schistosomiasis and hook worm infection [54, 55]. In case of infection from *Oesophago stomum* species resistance developed against benzmindazole and macrocyclic lactone because of polymorphism, alteration in the structure of b-subunit of tubulin and overexpression of drug efflux that is increased and mediated by p-glycoprotein or alteration in subunit of glu cl channel respectively [56, 57, 58, 59]. Same phenomena of alteration for resistance also occurs against benzmidazole and macrocyclic lactones in cattle, sheep, horse and goat, infection caused by Trichostrongylids, Fasciolaand Small Strongyles [60, 61, 62, 63].

Secondary plant metabolites having Anthelmintic Properties

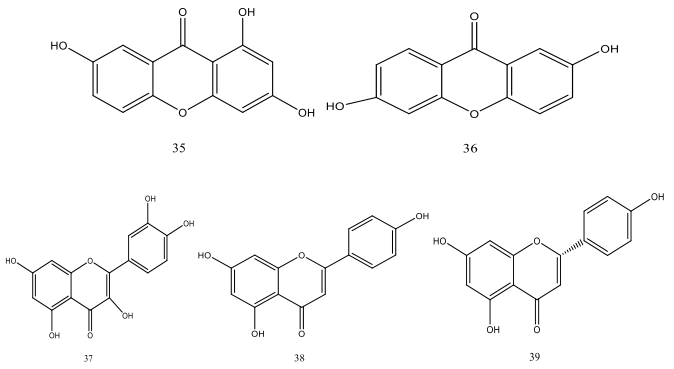
Plants are easily available and low cost source to cure infections. They have always been used as additional and conventional treatment for helminthiasis. Anthelmintic activity of plants is due to presence of secondary metabolite. Traditionally extract of plant part is used in different doses and concentration in different region. Due to broad area of spectrum of secondary metabiolitespresent in plants resistance development is not so easy. Various secondary metabolites like phenolics, flavonoids, tannins, chalcone, coumarins, polyphenolic amides, polyphenolic acids, terpenoids are reported to have anthelmintic activity. Plants also serve as treasured source for development of new leads.

Phenolics

Phenolics contains phenolic moiety are widely distributed among the plants and help to eradicate too many deceases. Up to twenty thousand secondary metabolites are present in nature. Soluble phenolics like flavonoids, tannins are simple phenol which easily absorbed through gastro intestinal tract and give their effect to reach in blood. Insoluble phenols (phenolic acids, condensed tannins, polysaccharides) not easily absorbed and digested in GI tract. Polyphenols obtained from vegetables, grains, tea, coffee, fruits, chocolate are the examples [64, 65].

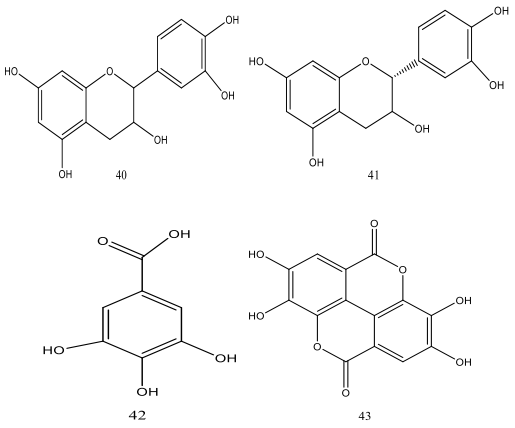
Flavonoids

Structurally these are C6-C3-C6 having two rings A and B. Majorly found in conjugation with sulfate, methyl, lipids, amines, organic acids, carboxylic acids, monosaccarides and disaccharides. Theses inhibit specific enzymes; stimulate some hormones, neurotransmitters and scavange free radicals. Flavonoids can be classified into flavones, flavonones, flavonols, isoflavones, flavononols, neoflavonoids, proanthocynidins and chalcones. Most common flavonoids having anthelmintic activity are flavonesand flavonols. Isoflavones that are effective against parasites are gentisein (35), daidzein (36) obtained from soyabean with glycetein and biochanin A. Flavonols catechins and epicatechins also called proanthocynidins, because it produces anthocynidins. Mainly obtained from cocoa beans, tea, berries, grapes. Anthocynidin impart colour to fruit flower and vegetables [66, 67, 68]. Flavonols glycosylated with rutisonyl are rictiflorin, rutin, narcissin obtained from sainfoin. Delphinidin, cynidin, pelergonidin are the examples of anthocynidines. Under the class flavones luteolin, naringenin is more active than hesperidine after that rutin, naringin and chrysininin order of activity. Flavone quercetin (37) and apigenin (38) obtained from *Artemesia campestris*. Unglycosylated flavonoids are naringenin (39) and apigenin are reported to active against helminthiasis. Flavonoids have antioxidant activity hence they stimulate defense mechanism through detoxifying process and increase host immunity against parasitic infections. Flavonoids decrease glycogen synthase enzyme activity and dcrease glycogen level leading to starvation. These also inhibit tegumental enzyme activity and cause peralysis of worms. Flavonoids are reported to elevate NOS (nitric oxide synthase) activity which results increase production of cGMP and decrease Calcium efflux resulting in rapid muscle contraction. Flavonoids also modulate enzymatic activity in hexose monophosphate system [69].



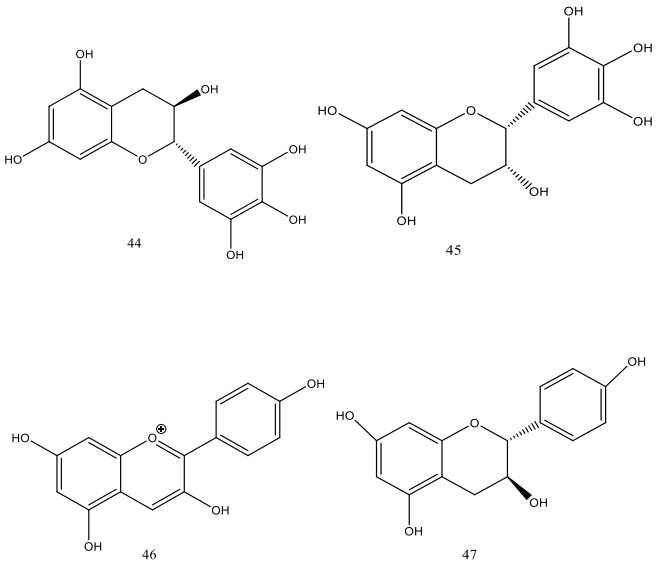
Tannins

These are majorly found in fruits, nuts, roots, leaves and classified into two types condensed [epicatechin (40) and catechin (41)] and hydrolysable tannins [gallic acid (42) and ellagic acid (43)]. They have molecular weight upto 20,000 get absorbed through GI tract by converting to single unit gallic acid and reach to blood. Phlobotannin is one of the tannin that is found in brown saw seed but not edible for human use. Tannins (hydrolysable and condensed) form H-bonding due to hydroxyl group on tannin with protein on membrane and block exchange with environment cause asphyxia or cellular toxicity due to accumulation of metabolic products. In case tannin ingested by parasites it causes precipitation of proteins in buccal cavity cause obstruction in mouth and also block sensory neurons, larvae cannot recognize their environment lead to prevent further starvation and death. Tannins also interfere with neuromuscular co-ordination and lead to peralysis. In case tannin pass buckle cavity reaches to intestine there it interacts with yolk protein present in intestine and prevent reproduction of worm. It also interacts with protein that trigger egg hatch or bind with larvae and egg by forming coat around egg shell. Also tannins are antioxidants stimulate defense mechanism through detoxifying mechanism and increase host immunity [70].



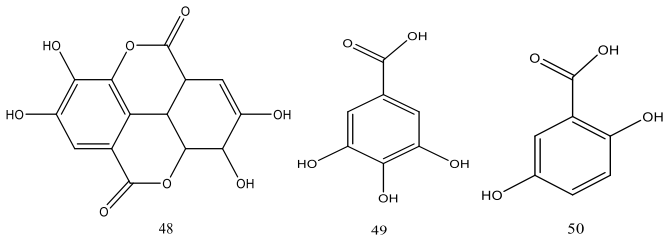
Condensed tannins

These are polyphenols (proanthocynidins), having molecular weight 500-20,000 kDa. These are oligomers of monomeric unit flavan-3-ol. Examples are catechin (41), epicatechin (40). Have high affinity for proteins and polysaccharides. Cause reduction in food intake, growth inhibition and interfere with morphology and proteolytic activity of microbes [71, 72]. Prodelphinidin polymer contains gallocatechin (44) or epigallocatechin (45) obtained from forage legumes. Propelarogonidins (46) from senna, afzelechin (47), catechin (41) are other examples of tannins effective against parasites. High content of condensed tannins always give high anthelmintic activity. High molecular weight tannins (polymeric form) is always less effective than low molecular weight (oligomeric form) perhaps due to less solubilty in membrane polysaccharides. Procynidin B_1, Procynidin B_7 (oligomeric procynidine dimer), Arecatanin B1 (oligomeric procynidinetrimer) are some examples of oligomeric condensed tannins.



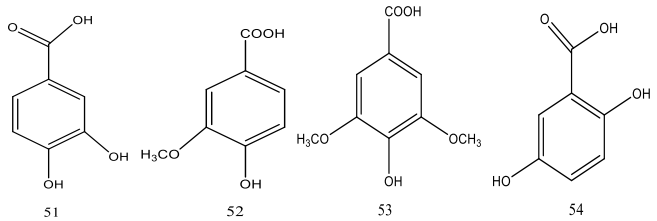
Hydrolysable tannins

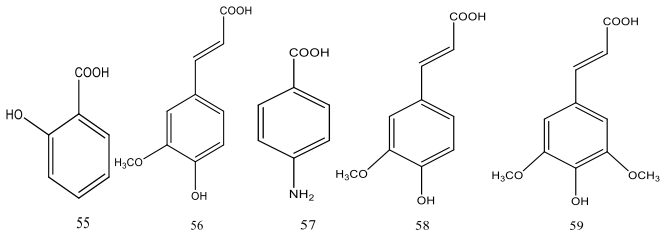
In these tannins carbohydrate glucose part is esterified with hydroxybenzoic acid, gallic acid and its dimer ellagic acid (berry fruit), hydroxyl diphenicacid and nonahydroxytriphenic acid main structural unit of hydrolysable tannins. Ellagic acid (48) stronger anthelmintic than gallic acid (49) and gentisic acid (50) perhaps due to high affinity for protein binding. Tetrameric, pentameric, hexameric derivatives rugosin E and D, agrimonin, gemin A, sanguiin H6, lambertianin C, salicarinin A moderately effective due to low permeability through cell membrane. Isoterchebulin obtained from terminalismacroptera. In case of ellagi tannins anthelmintic activity is due to urolithinsformed in human gut by microbial flora [70].



Phenolic acids

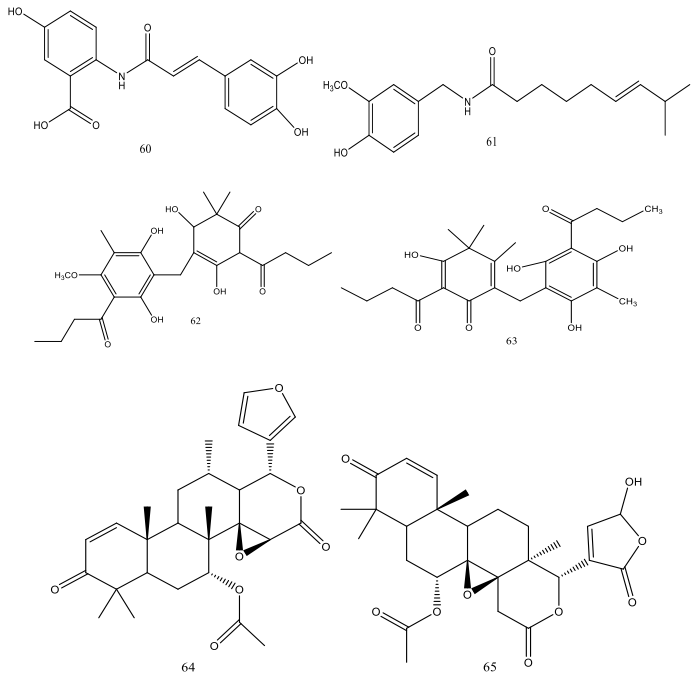
these are major components of daily diet of human and animals. Phenolic acids classified into two type's benzoic acid derivatives other is cinnamic acid derivatives. Examples of phenolic acids are protocatechuic acid (51), vanillic acid (52), syringic acid (53), gentisic acid (54), salicylic acid (55), gallic acid (48), ferulic acid (56), p-hydroxybenzoic acid (57), caffeic acid (58), sinapic acid (59).





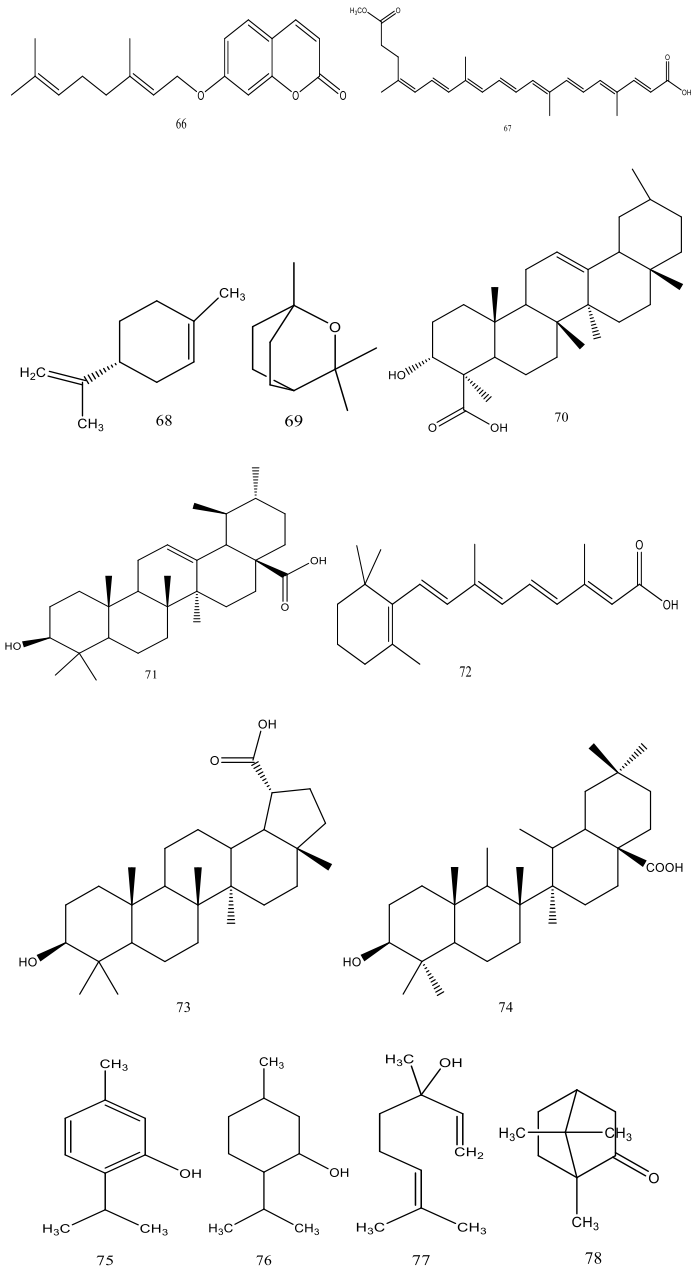
Phenolic amide

Chemically these are organic substance containing nitrogen atom. These are present in plants in low concentration. Avenanthramides (60) found in oats and capsaicinoids (61) from chilli peepers are the examples of phenolic amides. Piplaritine obtained from *Piper tuberculatum* cause tegumental destruction and inhibition of neurotransmission pathway including blebbing, granularity and shorter body length [73]. Aspidin (62), flavaspidic acid (63), methylene bisaspidinol, disaspidine are phloroglucinols (trihydroxybenzene derivatives) cause alteration in tegument and decrease motor activity [74]. Gedunin (64), photogedunin (65) obtained from fruit from Andaman also phenolic amides reported to have anthelmintic activity.



Terpenoids

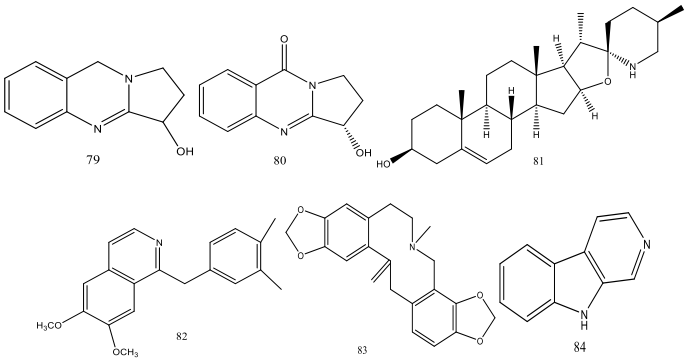
These are volatile, colourless substance. Majorly liquid at room temperature and lighter than water, give smell to fruit and flower. Abietic acid (tricyclic diterpene carboxylic acid), Auraptene (66) occurs in citrus fruits. Bixin (67) obtained from pericarp of seeds *Bixaorellana*. D-limonene (68), 1,8-cineole (69), boswellic acid (70), betulinic acid, β-sitosterol, ursolic acid (71) are the terpenoids have anthelmintic activity. Monoterpenecarnone, d-limonene; diterpene retinol, retinoic acid (72); triterpenebetulinic acid, lupeol (73), oleanolic acid (74), ursolic acid; tetraterpeneα-carotene, β-carotene, lutein, lycopene has protoscolicidal activity with characterstic morphological alteration in parasites. Thymol (75), menthol (76), quercetin, linalool (77), (+)-limonene, camphor (78), geraniol, α-terpinolen, citral, anethole, thymol, coumarins, 3-glucuronide, eugenol, 1,8 cineole, thymoquinine, anethole, estragole [75, 76]. Terpenesgeraniol, carvacrol, thymol, cymene, alphapinene, betapinene, citronellal, farnesol, Sabinene, eucalyptol, neralidol, spathulenol, β-caryophylene, α-thujene, α-pinene, 4-terpineol, β-pinene, ascaridol, menthol, low molecular weight terpenoidcinnamyl alcohol, eugenol, safrole reported to effective against parasites. Hydrophobicity of terpenesenable them to pass through cell wall and cytoplasmic membrane, disrupt the structure of different layers of polysaccharides, fatty acid, phospholipids rendering them permeable. This cause change in fluidity, permeability of membrane, results in leakage of radical, cytochrome C, calcium ion and proteins cause cellular damage [77] and also cause protoscolicidal affect. Act on tegument of protoscoleces, causes morphological changes like contraction of soma regions, formation of belbs on tegument, rosteller disorganization, loss of hooks, destruction of tubercles, spines and suckers of adult worm, destruction of microtriches required for nutrient absorption [78].



Alkaloids

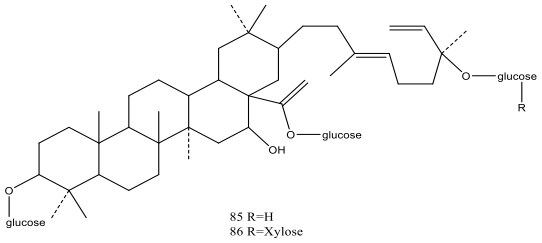
Vascinine (79) (Justicia adhatoda), vascinone (80) from Adhatoda vasaka [79], salsodine (81), solakhasanin, solamargine, khasinin from

Solanum species have been reported to have larvicidal and ovicidal activity [80]. Isoquinoline alkaloid, sallocryptopine, dehydrocryptopine, dehydrocorydaline, papaverine (82) inhibit larval motility. Alkaloids Protopine (83), d-corydaline, l-stylopne, β-carboline (84) also effective against helminthiasis [81, 82].



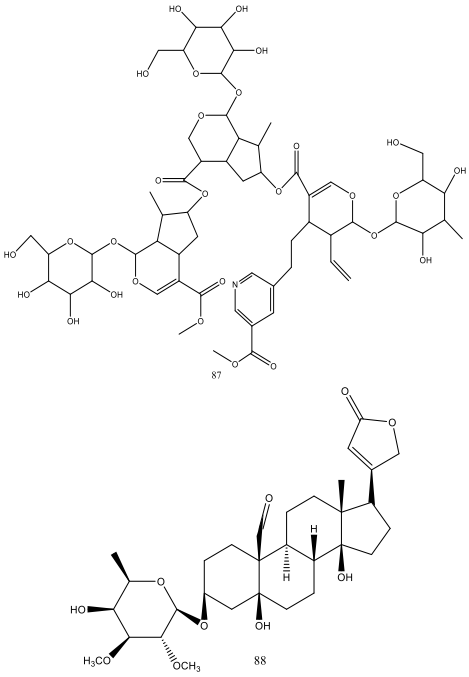
Saponins

Chemically these are glycosides composed of lipid soluble aglycon moiety with water soluble sugar molecule. Saponins enhance cell membrane lipid peroxidation due to formation of free radical, induce membrane damage. These also decrease motility of worms, induce tissue damage in subtegumental and somatic layer muscle causing disorganization of tegument morphology and deformation of microtriches, irreversible destruction of general topography of body. Terpenoid saponin acaciaside A (85) and B (86) [83] possess anthelmintic property. Sapogenin (non-glycolic portion of saponin), hecogenin act by intercalation in cell membrane by their hydrophobic fraction, causing formation of pores in tegument of helminth by acting on L1 stage of larvae.



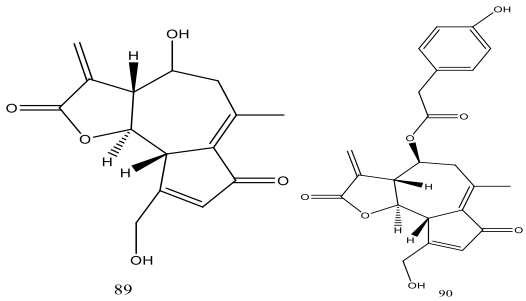
Glycosides

In these compounds sugar is bound to a non-carbohydrate moiety. Many plants store inactive glycosides which activated by enzyme hydrolysis. Cardiac glycosides asperosides (87) and strebloside (88) [84] change the morphology of parasite and cause molting of larvae. Glycosides disturb the integrity of cell membrane as they are required for distribution, metabolism, excretion and absorption of toxic material. So when they act on membrane they disturb the barriers on membrane and membrane damage occurs.



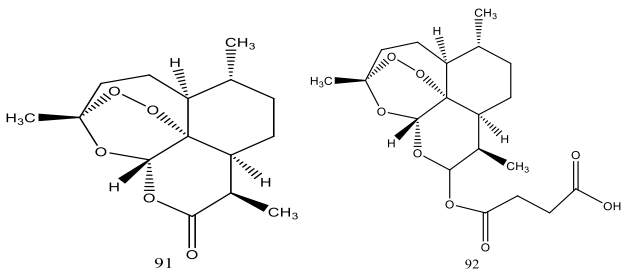
Sesquiterepene lactones

Lactucin (89), lactupicrin (90), 8-deoxylactucin, hydroxyl coumarin chicorin obtained from chicory act on L3 stage of larvae [85].



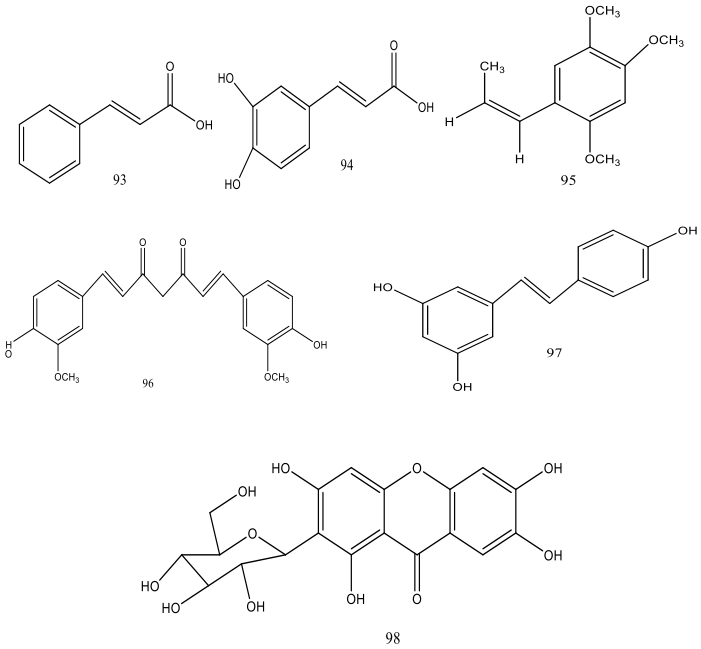
Endoperoxide Sesquiterpene Lactones

Artimisinin (91) and their derivatives artemether, artesunate (92), dihydroartemisinin have high anthelmintic activity [86]. They cause swelling of tegumental ridges, blebbing and repturing of belbs, leading to erosion and lesion, distruption of tegument, inhibit glutathione S-tranferase and superoxide dismutase (anti-oxidant enzyme in parasite cause detoxification).



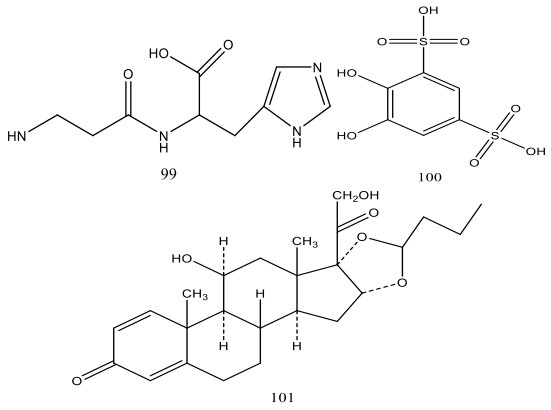
Phenylpropanoids

These are cinnamic acid derivatives such as cinnamic acid (93), hydroxylcinnamic acid, caffeic acid (94), cinnamic acid esters from *Kaempferia galanga.* β-Asarone (95) (trans form) more effective than α-asarone (cis form) is obtained from *Acorus gramineus*. Cinnamic aldehydes, curcuminoides like curcumin (96) (turmeric), demethoxycurcumin, bisdemethoxy curcumin cause alteration in tegument, Lignans (flax, seasome), stilbenes like resveratrol (97) (red wine, grapes), mangiferin (98) (glucosylated tetra hydroxyl xanthone) from Mangifera indica have been investigated for anthelmintic activity [87].



Enzymes

There are certain other compounds in plants present that also active against parasites enzymes like papain (99), chymopapain (100), caricain, glycyl endopeptidase from papaya possess potent anthelmintic activity [88]. Anahain, fruit or stem bromelain (101), comosain in fruit and stem of pineapple, cysteine proteinases from pineapple rowen [89], ficain from American fig [90] also effective against helminthes.



CONCLUSION

The anthelmintic activity is due to presence of these lead molecules present in compounds. But there's need to explore further on these plant extracts and synthetic drugs to get precise mode of action in details for delineation of their therapeutic efficacy, so that new drug molecules come in market painstaking as a principal of forthcoming that might avert helminthiasis and its associated health matters. It would be worthwhile to take these compounds as prototypes to synthesize their congeners that edible to use for human n veterinary both.

Acknowledgement

Authors are thankful to Prof. Satwinder Kaur, Principal, G.H.G.K.C.P. Ludhiana for his valuable guidance. This work was supported by I.K. Gujral Punjab Technical University, Jalandhar and G.H.G. Khalsa College of Pharmacy, Ludhiana.

Conflict of Interest

None declared.

Financial support

Nil.

REFERENCES

1. World Health Organization (2002), "Eliminating soil-transmitted helminthiases as a public health problem in children: progress report 2001-2010 and strategic plan 2011-2020," from web site http://www.who.int/about/licensing/copyright_form/en/index.html accessed on 03/11/2018.
2. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. "Helminth infections: the great neglected tropical diseases," J. Clin. Invest., 2008; 118:1311-1321.
3. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. Lancet, 2009; 373:1570-1575.
4. Gloeckner C, Garner AL, Mersha F, Oksov Y, Tricoche N, Eubanks LM, *et al*. "Repositioning of an existing drug for the neglected tropical disease Onchocerciasis," PNAS, 2010; 107:3424-3429.
5. Waller P. "Sustainable helminth control of ruminants in developing Countries," Vet. Parasitol., 1997; 71:195-207.
6. Chiejina SN. *The epidemiology of helminth infections of domesticated animals in the tropics with emphasis on fascioliasis and parasitic gastroenteritis*, In: Chowdhury, N., Tada, I. (Eds.), Perspectives on Helminthology, Science Publishers Inc., 2001; pp. 41-87.
7. Kaplan RM. "Drug resistance in nematodes of veterinary importance: a status report," Trends Parasitol., 2004; 20:477-481.
8. Chandrawathani P, Waller PJ, Adnan M, Hoglund J. Evolution of high-level, multiple anthelmintic resistance on a sheep farm in Malaysia," Trop. Anim. Health Prod., 2003; 35:17-25.
9. Hammond JA, Fielding D, Bishop SC. "Prospects for plant anthelmintics in tropical veterinary medicine," Vet. Res. Commun., 1997; 21:213-228.
10. Cioli D. "Praziquantel: is there real resistance and are there alternatives," Curr. Opin. Infect. Dis., 2000; 13:659-663.
11. Centers for Disease Control and Prevention (CDC). "Parasites-Trichuriasis,", 2013. http://www.cdc.gov/parasites/whipworm/epi.html, accessed on 10/01/2018.
12. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. "Hookworm infection," N. Engl. J. Med., 2004; 351:799-807.
13. Grencis R, Cooper E. "Enterobius, Trichuris, Capillaria, and hookworm Gastroenterol," Clin. North. Am., 1996; 25:579-596.

14. Desilva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L. “Soil-transmitted helminth infections: updating the global picture,” Trends Parasitol., 2003; 19:547-551.
15. World Health Organization (WHO). “Schistosomiasis Factsheet,” 2014. http://www.who.int/mediacentre/factsheets/fs115/en/ accessed on 13/11/18.
16. World Health Organization (WHO), (2014), “Lymphatic filariasis Factsheet,” http://www.who.int/mediacentre/factsheets/fs102/en/ accessed on 13/11/18.
17. Centers for Disease Control and Prevention (CDC), (2013), “Parasites-Fascioliasis (Fasciola Infection),” http://www.cdc.gov/parasites/fasciola/epi.html accessed on 13/11/18.
18. Wink M. “Medicinal plants: a source of anti-parasitic secondary metabolites,” Molecules, 2012; 17:12771-12791.
19. Centers for Disease Control and Prevention (CDC), (2014), “Parasites-Strongyloides,” http://www.cdc.gov/parasites/strongyloides/epi.html accessed on 13/11/18.
20. Qian MB, Chen YD, Liang S, Yang GJ, Zhou XN. “The global epidemiology of clonorchiasis and its relation with cholangiocarcinoma,” Infect. Dis. Poverty, 2012; pp. 1-4.
21. Centers for Disease Control and Prevention (CDC), (2015), “Parasites-Loiasis,” http://www.cdc.gov/parasites/loiasis/epi.html, accessed on 13/01/19.
22. Centers for Disease Control and Prevention (CDC), (2013), “Parasites-Onchocerciasis,” http://www.cdc.gov/parasites/onchocerciasis/epi.html, accessed on 13/01/19.
23. Centers for Disease Control and Prevention (CDC), (2014), “Parasites-Dracunculiasis,” http://www.cdc.gov/parasites/guineaworm/epi.html, accessed on 13/01/19.
24. Reynoldson JA, Behnke JM, Pallant LJ, Macnish MG, Gilbert F, Giles S, *et al*. “Failure of pyrantel in treatment of human hookworm infections (*Ancylostoma duodenale*) in the Kimberley region of north west Australia,” Acta Trop., 1997; 68:301-312.
25. Brown HD, Matzuk AR, Ilves IR, Peterson LH, Harris SA, Sarett LH, *et al*. “Antiparasitic drugs-IV. 2-(40-Thiazolyl)- benzimidazole, a new anthelmintic,” J. Am. Chem. Soc., 1961; 83:1764-1765.
26. Borgers M, De Nollin S. “Ultrastructural changes in *Ascaris suum* intestine after mebendazole treatment *in vivo*,” J. Parasitol. 1975; 61:110-122.
27. Chambers E, Ryan LA, Hoey EM, Trudgett A, McFerran NV, Fairweather I, *et al*. “Liver fluke β-tubulin isotype 2 binds albendazole and is thus a probable target of this drug,” Parasitol. Res., 2010; 107:1257-1264.
28. Nayak A, Gayen P, Saini P, Maitra S, Sinha Babu SP. “Albendazole induces apoptosis in adults and microfilariae of *Setaria cervi*,” Exp. Parasitol., 2011; 128:236-242.
29. Horton J, Witt C, Ottesen EA. “An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis,” Parasitology, 2000; 121:147-60.
30. Bagheri H, Simiand E, Montastruc JL, Magnaval JF. “Adverse drug reactions of anthelmintics,” Ann. Pharmacother, 2004; 38:383–388.
31. Sangster NC, Gill J. “Pharmacology of anthelmintic resistance,” Parasitol. Today, 1999; 15:141-146.
32. Kotze AC. “Effects of macrocyclic lactones on ingestion in susceptible and resistant *Haemonchus contortus* larvae,” J. Parasitol., 1998; 84:631-635.
33. Xu M, Molento MB, Blackhall W, Ribeiro P, Beech R, Prichard R. “Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog,” Mol. Biochem. Parasitol., 1998; 91:327-335.
34. Le Jambre LF, Gill JH, Lenane IJ, Baker P. “Inheritance of avermectin resistance in *Haemonchus contortus*,” Int. J. Parasitol., 2000; 30:105-111.
35. Campbell WC. “Ivermectin: an antiperasitic agent,” Med. Res. Rev., 1993; 13:61–79.
36. Campbell WC, Benz GW. “Ivermectin: a reviw of efficacy and safety” J. Vet. Pharmacol. Ther., 1984; 7:01–16.
37. Martin RJ, Robertson AP, Bjorn H. “Target sites of anthelmintics,” Parasitol., 1997; 114:S111-S124.
38. Cesbron JY, Capron A, Vargaftig BB, Lagarde M. “Platelets mediate the action of diethylcarbamazine on microfilariae,” Nature, 2011; 325:533-6.
39. Dominguez A, Taylor HR, Greene BM, Ruvalcaba AM. “Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis,” The Lancet, 1, pp.139-43.
40. Rivas AR, Greene BM, Taylor HR, Vázquez AD. “Chemotherapy of onchocerciasis: a controlled comparison of mebendazole, levamisole, and diethylcarbamazine,” The Lancet, 2009; 2:485-90.
41. Prichard RK, Bachmann R, Hutchinson GW, KoĖhler P. “The effect of praziquantel on calcium in *Hymenolepis diminuta*,” Mol. Biochem. Parasitol., 1982; 5:297-308.
42. Redman CA, Robertson A, Fallon PG, Modha J, Kusel JR, Doenhoff MJ, Martin RJ. “Praziquantel: an urgent and exciting challenge,” Parasitol. Today, 1996; 12:14-19.
43. Elwasila T, Homeida M. “Is praziquantel therapy safe during pregnancy?,” Trans R Soc Trop Med Hyg., 2004; 98(9):540-3.
44. Evans AM, Martin RJ. “Activation and cooperative multi ion block of single nicotinic- acetylcholine channel currents of Ascaris muscle by the tetrahydropyrimidine anthelmintic, morantel.,” Br. J. Pharmacol., 1996; 118:127-140.
45. Coles GC. “The inactivity of diamphenethide against liver fluke in certain species of mammals,” Res Vet Sci., 1976; 20(1):110-1.
46. Edwards SR, Campbell AJ, Sheers M, Moore RJ, Montague PE. “Studies of the effect of diamphenethide and oxyclozanide on the metabolism of Fasciola hepatica,” Mol Biochem Parasitol., 1981; 2(5-6):323-38.
47. Fetterer RH, Rew RS, Gasbarre LC, Ostlind DA. “Prophylactic efficacy of clorsulon against Fasciola hepatica in calves and sheep,” Veterinary Parasitology, 1985; 18(1):21-27.
48. Martin RJ, Robertson AP, Bjorn H. “Target sites of anthelmintics,” Parasitology., 1997; 114:111-24.
49. https://www.pesticides.news/2017-12-03-dichlorvos-toxicity-side-effects-diseases-and-environmental-impacts.html, accessed 21/12/2018.
50. Swan GE. “The pharmacology of halogenated salicylanilides and their anthelmintic use in animals,” Afr. vet. Ass., 1999; 70(2):61–70.
51. Bossche V, Den H. “How anthelmintics help us to understand helminthes,” Parasitol., 1985; 90:675-685.
52. Demeler J, Van Zeveren AMJ, Kleinschmidt N, Vercruysse J, Hoglund J, Koopmann R, *et al*. “Monitoring the efficacy of ivermectin and albendazole against gastro intestinal nematodes of cattle in Northern Europe,” Vet. Parasitol., 2009; 160:109-115.
53. Gasbarre LC, Smith LL, Lichtenfels JR, Pilitt PA. “The identification of cattle nematode parasites resistant to multiple classes of anthelmintics in a commercial cattle population in the US,” Vet. Parasitol., 2009; 166:281-285.
54. Cioli D. “Praziquantel: is there real resistance and are there alternatives,” Curr. Opin. Infect. Dis., 2000; 13:659-663.
55. Liang YS, Coles GC, Doenhoff MJ. “Detection of praziquantel resistance in schistosomes,” Trop. Med. Int. Health, 2000; 5:72.
56. Evans AM, Martin RJ. “Activation and cooperative multi ion block of single nicotinic- acetylcholine channel currents of Ascaris muscle by the tetrahydropyrimidine anthelmintic morantel,” Br. J. Pharmacol., 1996; 118:127-140.
57. Xu M, Molento MB, Blackhall W, Ribeiro P, Beech R, Prichard R. “Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog,” Mol. Biochem. Parasitol., 1998; 91:327-335.
58. Roos MH, Kwa MSG, Grant WN. “New genetic and practical implications of selection for anthelmintic resistance in parasitic nematodes,” Parasitol. Today, 1995; 11:148-50.
59. Martin RJ, Robertson AP. “Electrophysiological investigation of anthelmintic resistance,” Parasitol., 2000; 120:87-S94.
60. Xu M, Molento MB, Blackhall W, Ribeiro P, Beech R, Prichard R. “Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog,” Mol. Biochem. Parasitol., 1998; 91:327-335.
61. Le Jambre LF, Gill JH, Lenane IJ, Baker P. “Inheritance of avermectin resistance in Haemonchus contortus,” Int. J. Parasitol., 2000; 30:105-111.

62. Martin RJ, Robertson AP. “Electrophysiological investigation of anthelmintic resistance,” Parasitol., 2000; 120:87-S94.
63. Kotze AC. “Effects of macrocyclic lactones on ingestion in susceptible and resistant Haemonchus contortus larvae,” J. Parasitol., 1998; 84:631-635.
64. Scalbert A, Williamson G. “Dietary intake and bioavailability of polyphenols,” J. Nutr., 2000; 130:20735-2085S.
65. Moreno CS. “Compuestos polifenólicos: estructuray classificación: presencia en alimentos y consumo: biodisponibilidad y metabolism,” Alimentaria, 2002; 329:19-28.
66. Bravo L. “Polyphenols: chemistry, dietary sources, metabolism and nutritional significance,” Nutr. Rev., 1998; 56(11):317-333.
67. Jovanovic SV, Steenken S, Tosic M, Marjanovic B, Simic MG. “Flavonoids as antioxidants,” J. Am. Chem. Soc., 1994; 116(11):4846-4851.
68. Karakaya S. “Bioavailability of phenolic compounds,” Crit. Rev. Food Sci. Nutr., 2004; 44(6):453-464.
69. Pal P, Tandon V. “Anthelmintic efficacy of flemingia vestita (fabaceae): Genistein-induced alterations in the esterase activity in the cestode raillietina echinobothrida,” Journal of Biosciences, 1998; 23(1):25–31.
70. Spiegler V, Hensel A, Liebau E. “Medicinal plant extracts and plant derived polyphenols with anthelmintic activity against intestinal nematodes,” Nat. Prod. Rep., 2017; 34:627.
71. Min BR, Hart SP. “Tannins for suppression of internal parasites,” J. Anim. Sci., 2011; 81(2):102-109.
72. Waghorn GC, Mc Nabb WC. “Consequences of plant phenolic compounds for productivity and health of ruminants,” Proc. Nutr. Soc., 2003; 62(2):383-92.
73. De Moraes J, Nascimento C, Lopes POMV, Nakano E, Yamaguchi LF, Kato MJ, *et al*. “Schistosoma mansoni: in vitro schistosomicidal activity of piplartine,” Exp. Parasitol., 2011; 127:357-364.
74. Socolsky C, Borkosky SA, Asakawa Y, Bardon A. “Molluscididal phloroglucinols from the fern Elaphoglossum piloselloides,” J. Nat. Prod., 2009; 72:787–790.
75. Carvalhoa CO, Chagas ACS, Cotinguiba F, Furlan M, Brito LG, Chaves FCM, *et al*. “The anthelmintic effect of plant extracts on Haemonchus contortus and Strongyloides venezuelensis,” Vet. Parasitol., 2012; 183:260–268.
76. Eguale T, Tilahun G, Debella A, Feleke A, Makonnen E. “In vitro and in vivo anthelmintic activity of crude extracts of Coriandrum sativum against Haemonchus contortus,” J. Ethnopharmacol., 2007a; 110:428–433.
77. Turina AV, Nolan MV, Zygadlo JA. “Natural terpens: self-assebly and membrane partitioning,” Biophys Chem., 2006; 122:101–113.
78. Elissondo MC, Albani CM, Gende L, Eguaras M, Denegri G. “Efficacy of thymol against Echinococcus granulosus protoscoleces,” Parasitol. Int., 2008; 57:185–190.
79. Tangpu VT, Temjenmongla K, Yadav AK. “Anticestodal activity of Trifolium repens extracts,” Pharmaceut. Biol., 2004; 42:656-658.
80. Weissenberg M. “Isolation of solasodine and other steroidal alkaloids and sapogenins by direct hydrolysis-extraction of Solanum plants or glycosides therefrom,” Phytochemistry, 2001; 58:501-508.
81. Cao CH, Liu Y, Lehmann M. “Fork head controls the timing and tissue selectivity of steroid-induced developmental cell death,” JCB, 2007; 176:843-852.
82. Satou T, Horiuchi A, Akao N, Koike K, Fujita K, Nikaido T. “Toxocara canis: search for a potential drug amongst b-carboline alkaloids in vitro and mouse studies,” Exp Parasitol., 2005; 110:134–139.
83. Ghosh M, Sinha Babu SP, Sukul NC, Mahato SB. “Antifilarial effect of two triterpenoid saponins isolated from Acacia auriculiformis,” Indian J. Exp. Biol., 1993; 31:604–606.
84. Chatterjee RK, Fatma N, Murthy PK, Sinha P, Kulshrestha DK, Dhawan BN. “Macrofilaricidal activity of the stembark of Streblus asper and its major active constituents,” Drug Dev. Res., 1992; 26:67–78.
85. Foster JG, Clapham WM, Belesky DP, Labreveux M, Hall MH, Sanderson MA. “Influence of cultivation site on sesquiterpene lactone composition of forage chicory (*Cichorium intybus* L.),” J. Agric Food Chem., 2006; 54:1772–1778.
86. Olliaro PL, Haynes RK, Meunier B, Yuthavong Y. “Possible modes of action of the artemisinin-type compounds,” Trends Parasitol., 2001; 17:297-300.
87. Braguine CG, Bertanha CS, Goncalves UO, Magalhaes LG, Rodrigues V, Gimenez VMM, *et al*. “Schistosomicidal evaluation of flavonoids from two species of Styrax against Schistosoma mansoni adult worms,” Pharmaceut. Biol., 2012; 50:925–929.
88. Satrija F, Nansen P, Bjorn H, Murtini S, He S. “Effect of papaya latex against Ascaris suum in naturally infected pigs,” J. Helminthol, 1994; 68:343–346.
89. Rowan AD, Buttle DJ, Barrett AJ. “The cysteine proteinases of the pineapple plant” Biochem J., 1990; 266:869–875.
90. Hansson A, Veliz G, Naquira C, Amren M, Arroyo M, Arevalo G. “ Preclinical and clinical studies with latex from Ficus glabrata HBK, a traditional intestinal anthelminthic in the Amazonian area.,” J. Ethnopharamacol., 1986; 17:105–138.
91. Jha KK, Khosa RL. “Achyranthes aspera-An important medicinal plant,’’ Nat. Prod. Plant Resour., 2011; 1 (1):1-14.
92. Banerjee J. “Phytochemical constituents and pharmacological uses of medicinal plant Achyranthes Aspera,” World Journal of Pharmaceutical Research, 2014; 4(1):470-489.
93. Raji R. “Achyranthes aspera- Medicinal Plant: A Review,” International Journal of Pharma and Bio Sciences, 2013; 4(1):719-724.
94. Gupta RK. *Medicinal & Aromatic Plants*, CBS Publishers & Distributors, 2010; pp. 190.
95. Bhattaraj NK. “Folk use of plants in veterinary medicine in Central Nepal,” Fitoterapia, 1992; 63(6):497-506.
96. Singh VK, Ali ZA, Zaidi STH. “Ethnomedicinal uses of plants from Gonda district forests of Uttar Pradesh, India,” Fitoterapia, 1996; 67(2):129-139.
97. Gupta RK. *Medicinal & Aromatic Plants*, CBS Publishers & Distributors, 2010; pp. 190.
98. Rameshwar RD. Indian Perfumer, 2007; 51(1):33-34.
99. Goyal AK, Middha SK, Usha T, Chatterjee S, Bothra AK, Nagaveni MB, *et al*. “Bamboo-infoline: A database for North Bengal bamboo's,” Bioinformation, 2010; 5(4):184-185.
100. Koshy CK. “Bambusa vulgaris blooms: a leap towards extinction,” Curr. Sci., 1997; 72(9):622-624.
101. Ghana GY, Coffie C, Antwi-Boasiako NA. “Darkwa Phytochemical constituents of the leaves of three bamboo (Poaceae) species,” Journal of Pharmacognosy and Phytochemistry, 2014; 2(6):34-38.

HOW TO CITE THIS ARTICLE
Singla S, Kaur S. Anthelmintic lead compounds and their targets for drug development. J Ayu Herb Med 2021;7(4):265-275. DOI: 10.31254/jahm.2021.7410