CHAPTER – 2
REVIEW OF LITERATURE
Helminths, meaning “worms” in Greek have plagued humans since before the era of our earliest recorded history. The eggs of intestinal helminths can be found in the mummified feces of humans dating back thousands of years, and we can recognize many of the characteristic clinical features of helminth infections from the ancient writings of Hippocrates, Egyptian medical papyri, and the Bible (Cox 2002; Hotez et al. 2006; Hotez 2009). Today, helminth infection is one the major cause of concern especially for those living in tropical and subtropical countries where world’s poorest of the poor’s people live, who are left furthest behind by the socio-economic development causing wide spread occurrence of undernourishment, anaemia, eosinophilia and pneumonia (Bundy 1994). Helminths are also recognised as a serious and major threat to the livestock production (Githiori et al. 2004) leading to high economic losses to both the small- and large-scale farming communities where extensive grazing is practised (Waller 2006; Sissay et al. 2007). The favourable conditions in tropical and sub-tropical countries for the development of worm eggs to infective larvae exist leading to the loss of livestock production (Satrija et al. 2001). The high prevalence of the helminth infections may also be closely related to the poor socio-economic conditions, sub-standard housings, lack of access to safe water and hygiene by the rural dwellers, impoverished health care services as well as less attention in national and international health agendas (Montresor et al. 1998; Albonico et al. 1999; WHO 2010). Today, it is estimated that approximately one-third of the world’s population are infected by at least one or more helminth parasites and threatens the lives of millions more (Hotez et al. 2007; Hotez 2008, 2009).

Helminthic infections, though compared with many other parasitic diseases, do not cause significant morbidity and mortality; they do cause substantial, but often less measurable effects. They have pronounced impact on nutrition, growth, physical fitness, anaemia in infants, school-age children and adults (Horton 2003). As many as over 342 species of helminth parasites are found to be associated with human beings and more than 90 sp. are found to be inhabitant of gastro-intestinal tract of animals causing different diseases (Crompton 1999). Epidemiological studies have shown that the most common helminthiases that imposes heavy burden on poor people are those caused by helminths like soil-transmitted nematodes (ascariasis,
trichuriasis, hookworm, strongyloides), filarial nematodes (lymphatic filariasis, loiasis), and fluke parasites (schistosomiasis, food borne-trematodiasis) followed by tapeworms causing cysticercosis and hydatidiasis (Hotez et al. 2008). In terms of its prevalence and distribution, all the infections were found to be endemic mainly in tropical and sub-tropical countries where billions of people are estimated to be infected by nematodes (more than 1 billion), flukes (more than 250 million) and tapeworms (0.4 million) (Hotez et al. 2008; Alum et al. 2010).

At present most common strategy adopted to eradicate helminthic infection therefore, include the use of well-tolerated broad spectrum commercial anthelmintic drugs like mebendazole (MBZ), albendazole (ALB), pyrantel pamoate (PRT), levamisole (LEV) and PZQ. The mode of action of many of these drugs is by interfering with target sites that are either unique to the parasite or differs in their structural features from those of the homologous counterpart present in the host (Martin 1997; Albonico et al. 1999; Kohler 2001; WHO 2010). Despite the effectiveness of various broad spectrum anthelmintic drugs, one of the major challenges of the therapeutic intervention for controlling helminthiasis is the emergence of drug resistance capacity in helminth parasites (Prichard et al. 2007). After the initial report of development of resistance by Haemonchus contortus of sheep against thiabendazole (TBZ), several reports followed, revealing rapid and widespread prevalence of resistance against other commercial drugs (Waller 1997; Kaplan 2004). Anthelmintic resistance is therefore becoming one of the major economic and public health problems in several animal industries and human beings, respectively. Apart from its negative and undesired effects, limited availability to the rural areas further restricted the effective control of helminthiases (Martin et al. 1997; Waller 1997; Satrija et al. 2001; Suleiman et al. 2005), causing new threat to human society. It has been seen that human helminth control programmes mostly rely on the use of PZQ as the main anthelmintic drug. However, there are increasing evidences which suggest that PZQ may become useless in near future because of the resistance developed by many helminth parasites in different endemic regions of tropical countries (Fallon et al. 1995; Guisse et al. 1997). Recently failures of PZQ, oxamniquine and pyrantel in the treatment of schistosome and hookworm infections have also been observed in some geographical areas (Reynoldson et al. 1997).

Similar growing concerns have been shown for other therapeutic drugs such as MEB and pyrantel, which were extensively used for controlling the hookworm
infections. Molecular studies by radioligand-binding experiments revealed a reduction in the abundance of high-affinity BZ-binding sites in BZ-resistant worms compared with susceptible worms (Sangster et al. 1985; Lacey and Prichard 1986). In a similar way, BZ, triclabendazole (TCBZ) and closantel have been shown lower efficacy when treated against *Fasciola hepatica* (Overend and Bowen 1995). The evidence of TCBZ resistance has also been found in *F. hepatica* infected sheep and cattle (Moll et al. 2000). Because of the resistance developed by most of the helminth parasites against anthelmintic drugs which is now a global phenomenon (Jackson and Coop 2000) and limited availability of commercial drugs in rural areas, scientists are now looking for newer and inexpensive drugs based on traditionally used medicinal plants as an alternative remedies (Roy and Tandon 1996, 1999; Mali and Mehta 2008; Dasgupta et al. 2010; Tandon et al. 1997, 2011).

Contribution of plants to fight against various diseases dates back several centuries; and has been documented by the ancient Chinese, Indian and North African Civilisations (Taylor et al. 2001). Today, it has become a topic of global importance, making an impact on both world health and international trade. The plant kingdom is known to provide a rich source of botanicals which has been used as anthelmintic, antibacterial as well as insecticides throughout the world which are cheap, easily available to poor, sustainable and environmentally ostensible (Fabricant and Farnsworth 2001; Stepek 2007). This is particularly true in developing countries, where herbal medicine has a long and uninterrupted history of use in healthcare systems (Akerlele 1988). A number of plants having potential to cure worm infections have been identified and their medical potential established by many workers. Globally, an estimate of about 2.5 lakh higher plant species is believed to be present (Cronquist 1981, 1988; Govaert 2001). However, out of this only about 15% have been evaluated phytochemically and about 6% have been screened for its biological activity (Verpoorte 2000). It has been estimated that about 80% of the world’s population, especially of developing countries, rely predominantly on indigenous practice of plants and plant extracts for control and treatment of various diseases affecting both human beings as well as other animals (Akerlele 1988; Shen et al. 2010). In Africa, up to 80% of the population uses traditional medicine (TM) to meet their daily health care needs. According to world health organization (WHO 2003) more than 60% children with high fever, resulting from malaria uses herbal medicines as the first line of treatment in Ghana, Mali, Nigeria and Zambia.
industrialized countries, adaptations of TM often termed as complementary or alternative medicine, also play an important role in the health care system of 20% population (WHO 2003). In Asia and Latin America, peoples continue to use TM as a result of historical circumstances and cultural beliefs. Similarly, in China, TM accounts for around 30-50% of all the health care delivered (WHO 2002). Due to its easy accessibility, low cost of preparation, and absence of undesirable side-effects, the traditional medicine is increasingly solicited throughout the globe in the treatment of various infectious diseases (Jabbar et al. 2005) and is the only affordable source of health care - especially for the world’s poorest patients.

Several workers have undertaken studies pertaining to testing of a large number of traditionally used medicinal plants for their proclaimed anthelmintic efficacy which is a welcome approach towards developing modern anthelmintic drugs (Hammond et al. 1997; Athanasiadou et al. 2007; Manolaraki et al. 2010). Reports from around the world include an exhaustive list of medicinal plants that have been found to possess significant activity against helminth parasites (Akhtar et al. 2000; Tagboto and Townson 2001; Athanasiadou et al. 2007). The aqueous crude extract of three medicinal plants namely Chebulic myrobalans, Belleric myrobalans and Emblic myrobalans when tested were found to possess remarkable anthelmintic activity (Gaind et al. 1964). The in vitro studies on the aqueous and alcoholic extracts of Ananas sativus, Embelia ribes, Macuna prurita and Melia azedarach revealed that the plants possess significant anthelmintic activity against Taenia canina and Paramphistomum cervi (Neogi et al. 1964). Dhar et al. (1965) confirmed the presence of anthelmintic activity of Carica papaya seeds against two nematodes, Ascaris lumbricoides and Ascaridia galli. Efficacy of Butea frondosa, Vernonia anthelmintica and C. papaya against oxyurids in mice were studied by Mehta and Parashar (1966). The aqueous, ethereal and alcoholic extracts of Cucurbita mexicana seeds exhibited good anthelmintic activity against various helminth parasites such as Moniezia expansa, F. buski, A. lumbricoides and Hymenolepis diminuta (Shrivastava and Singh 1967). Anthelmintic potency of Carum copticum seeds has also been observed against A. lumbricoides (Krantz and Carr 1967). The root bark of Alangium larmorckii has exhibited good efficacy against the hookworms of dogs and poultry ascarids (Dubey and Gupta 1968). Similarly, anacardic acid and its sodium salt isolated from Semecarpus anacardium have been found to be potent anthelmintic agents when treated against cestodes (Chattopadhyaya and Khare 1969). Alcoholic
extract of *Helleborus niger*, rhizomes of *Zingiber officinale*, seeds of *Carum copticum*, *Agati gratifolia*, *Alpinia calcarata*, *Citrus medica* and *Mangifera indica* when treated against human *A. lumbricoides*, showed appreciable anthelminthic property (Kalesaraj 1974, 1975). *Ascardia galli* when exposed to the extracts of *Carica papaya*, *Sapindus trifoliatus*, *Butea frondosa* and *Momordica charantia*, an appreciable anthelminthic activity were noted by Lal et al. (1976). In Kenya, people of Marakwet district reportedly used five main traditional medicinal plants namely *Dryopteris inaequalis*, *Albizia anthelmintica*, *A. gummifera*, *Olea africana* and *Myrsine africana* against intestinal helminthic infections (Lindsay 1978). The essential oils of *Boswellia serrata* and *Cinnamomum tamala* were also found to have anthelminthic efficacy against earthworms and tapeworms (Girgune et al. 1978). Chakraborty et al. (1979) tested the anthelminthic properties of the alcoholic extracts of *Tribulus terrestris* and reported the expulsion of *A. galli* worms from experimentally infected poultry in a dose-dependent manner. Similarly, a large number of plants such as *Ageratum conyzoides*, *Cyathocline lyrata*, *Cyperus rotendus* and *Embelia ribes* were reported to have anthelminthic activity against various helminth parasites (Girgune et al. 1979; Sharma et al. 1979; Qureshi and Sabir 1979). In Nigeria, Nwude and Ibrahim (1980) studied 92 species of plants based on knowledge of traditional veterinary practice, with 15 reported to be used against general worm infestation and three against *Fasciolopsis* in cattle. Likewise, the essential oils from leaves and flowers of *Ageratum conyzoides* (Compositae) and *Lantana camara* (Verbeuaceae) have also been found to possess profound anthelminthic activity against tapeworms and hookworms (Sharma et al. 1979; Avadhoot et al. 1980).

The preliminary investigations on the anthelminthic properties of stem of *Ammora wallichii*, *Picis religiosa*, whole plant of *Calamintha*, *Sentia myrtina*, roots and rhizomes of *Amomum aromaticum*, stem bark of *Anthocephalus* and fruits of *Datura quercifolia*, *Datura metal* were shown to have good anthelminthic activity against *Ascardia galli* (Kaushik et al. 1981). Similarly, Adewunmi and Akubue (1981) studied the anthelminthic activity of aqueous extract of *Calliandra portoricensis* (Jacq) Benth. The essential oil from *Zanthoxylum alatum* has been found better anthelminthic activity compared to piperazine phosphate against earthworms and roundworms (Mehta et al. 1981). Similar kind of preliminary studies on the bark of same plant showed the anthelminthic activity against *A. lumbricoides*,...
F. buski and Hymenolepis nana (Singh et al. 1982). The active component santonin derived from shoot extract of Artemisia herba-alba were found effective against H. contortus of goat (Idris et al. 1982). The whole plant of Artemisia maritima has been found to be effective against Neoascaris swientenia of buffalo (Akhtar et al. 1982). Buddlea asiatica and Chloroylon swientenia has also been studied by Dengre (1982) to investigate its anthelmintic properties against tapeworms and hookworms. The use of Azadirachta indica has been seen throughout the tropics against various ailments including helminth parasites (Deka et al. 1983). Similarly, the in vitro activity of alcoholic extracts of Myrsine africana fruits was reported against the cestode T. solium, and the nematodes Bunostomum trigonocephalum and Oesophagostomum columbianum (Kakrani and Kalyani 1983). Ibrahim et al (1984) investigated 18 plants in Nigeria, which were identified to have anthelmintic effects; although no target animal host species was indicated. The phytochemical isolated from Melia azedarach seeds namely anthraquinone and glycosides were found to have good anthelmintic efficacy against gastro-intestinal nematodes of goat (Akhtar and Riffat 1984, 1985). The essential oils from Commiphora mukul have been found effective against tapeworms and hookworms (Kakrani and Kalyani 1984). Moreover, the extracts of Quisqualis indica, Caesalpina crista, Agrimonia eupatori, Artemisia maritima were also found to possess good anthelmintic property against a large number of helminth parasites such as Ascaris suum, H. contortus, Neoascaris vitulorum, Toxocara vitulorum and A. galli (Akhtar et al. 1985; Farnsworth et al. 1985). Cucurbita moschata, Heracleum sosnoskyi, Peganum harmala, Morus alba and Agrimophol, an active component of Agrimonia pilosa has been investigated for its anthelmintic activity against various tapeworms (Akhtar and Riffat 1986; Gadzhiev and Eminove 1986; Riffat et al. 1986; Xiao and Lin 1986). The whole plant extract of Artemisia maritima found to have potential of expulsing Neoascaris vitulorum from buffalo calves (Sherif et al. 1987). Similarly, seeds of Lagenaria siceraria were found effective against Moniezia and Avitelina species of sheep (Akhtar and Riffat 1987). Datta and Sukul (1987) observed antifilarial effect of Zingiber officinale on Dirofilaria irritis. Seeds of Semecarpus anacardium, Melia azedarach, Hyoscyamus niger, Lagenaria siceraria and aerial parts of Adhatoda vesica, Euphorbia prostrate, Fumaria parviflor and leaves of Cinnamommmum tamala were studied for its anthelmintic activity against various cestodes and nematodes (Akhtar 1988). Similarly, glycosides of Punica granatum fruit and Saussurea lappa
were found to have cestocidal and nematocidal activity, respectively (Akhtar and Aslam 1988; Akhtar and Makhdoom 1988). Likewise, the essential oil from the fruits of *Zanthoxylum limonella* (Rutaceae) revealed to be active against tapeworms and hookworms better than piperazine phosphate (Kalyani et al. 1989). In another study, glycosides at 200 mg/kg extracted from *Caesalpinia crista* seeds and Morantel tartrate at 10 mg/kg caused 94 ± 8 and 100% reductions of *H. contortus* eggs per gram (EPG) of feces in sheep (Akhtar and Aslam 1989). Bhagerwal (1989) reported the expulsion of tapeworms of poultry within 1 week after treatment with Taenil at a concentration of 2.0 g/kg body weight. Reports of nematocidal property of *Vernonia anthelmintica* seed (kali zeeri) and *Embellia ribes* fruit (babrung) was evaluated in goats by Javed and Akhtar (1990). A comparative study carried out with essential oils from *Artabotrys odoratissimus* (leaves), *Capillipedium foetidum* (inflorescence), *Cymbopogon martini* (grass) and the reference drug piperazine showed better anthelmintic activity against *Taenia solium* and *A. lumbricoides* by the essential oil compared to piperazine (Siddiqui and Garg 1990). The opaque, white latex and its active component, ficin of *Ficus insipida*, were also revealed to have anthelmintic property (Phillips 1990).

The oil extracts of *Artemesia scoparia*, *Artemisia pallens* and *Limnophila conferta* were found to exhibit strong anthelmintic activity when treated against *T. solium* and *A. lumbricoides* (Nakhare and Garg 1991; Reddy et al. 1991). Reduction in the EPG count were seen in tapeworm of sheep when the aqueous and methanol seed extract of *Nigella sativa* along with a commercial drug, niclosamide were treated against it (Akhtar and Javed 1991). Good therapeutic anthelmintic efficacy of *Punica granatum* and *Cucurbita maxima* (Cucurbitaceae; tarbuz) were observed against clinical cases of nematodiasis in cattle (Pradhan et al. 1992). Similar kind of anthelmintic property was observed with EPG reduction of more than 95%, when Beetal goats infected with gastrointestinal cestodes were treated with *Mallotus philippinensis* fruit powder extract (Akhtar and Ahmed 1992). In a preliminary study the crude whole tuber extract of *Flemingia vestita* was reported to be effective against *A. suum* (Yadav et a. 1992). Anthelmintic property has also been observed in flower extract of *Eupatorium triplinerve* against *A. lumbricoides* and *T. solium* (Garg and Nakhare 1993). Root extract of *Matteuccia orientalis* revealed to have trematocidal properties when exposed to *Fasciola* species of cattle (Shiramizu et al. 1993). Root bark extract of two medicinal plants namely *Uvaria hookeri* and *U.
were also reported to possess anthelmintic property (Padmaja et al. 1993). Literature reveals that concoctions made from the bark, fruits, leaves and roots of *Myrsine africana* L. have been widely used as anthelmintics in humans and livestock (Kokwaro 1993). The fruits of *Rapanea melanophloeos* were reported to be used as an anthelmintic in livestock (Gachathi, 1993). Similarly, Sharma (1993) confirmed the anthelmintic property of whole plant of *Artemisia maritima*. Seed powder of *C. crista* and its water and methanol extracts were also reported to have anthelmintic property when exposed against *A. galli* (Javed et al. 1994). Likewise, nematocidal property of *C. papaya* latex and *Fumaria parviflora* whole plant was established when treated against *Haemonchus sp.*, *Trichuris sp.*, *Albizia anthelmintica*, *A. coriavera*, *Artemisia maritima*, *A. absinthium* and *A. annua* (Kailani et al. 1995; Satrija et al. 1995; Hammond et al. 1997; Bara et al. 1999; Shuhua et al. 2000).

The anthelmintic efficacy could also been seen in a number of plant such as *Calliandra portoricensis*, *Calotropis procera*, *Ficus religiosa*, *Spigelia anemia*, *Vernonia amygdalina* and *Annona senegalensis* (A1-Qarawi et al. 2001; Alawa et al. 2002; Assis et al. 2003; Iqbal et al. 2005). The essential oil of *Ocimum sanctum* and eugenol, tested in vitro, showed potent anthelmintic activity in the *Caenorhabditis elegans* model (Asha et al. 2001). Different solvent fractions of *Berlina grandiflora* and its major triterpenoid, betulinic acid showed good anthelmintic activity against *C. elegans* (Enwerem et al. 2001). Molgaard et al. (2001) reported a number of Zimbabwean plants viz. *Acacia karroo*, *Cassia singueana*, *Ozoroa insignis*, *Vernonia amygdalina*, *Ximenia caffra* etc. to bear significant anthelmintic properties against *H. diminuta*, a tapeworm of zoonotic importance. Compared to the commercial anthelmintic piperrazine citrate, the ethanolic extract of *Evolvulus alsinoides* (Convolvulaceae) showed better anthelmintic efficacy in vitro (Dash et al. 2002). Plants such as, *Adhatoda vasica* and *Spigelia anemia* were reported to possess considerable anthelmintic activity against *H. contortus* (Lateef et al. 2003; Assis et al. 2003). Ademola et al. (2004) demonstrated both in vivo and in vitro anthelmintic activity of *Khaya senegalensis*, a plant well known for its ethno-veterinary use, has been demonstrated anthelmintic activity both in vitro and in vivo. Diehl et al. (2004) tested as many as 86 samples from leaves, bark and/or roots from 60 plant species for their anthelmintic properties out of which 22 plant extracts were found to cause mortality of *H. contortus* larvae. The roots, leaves and flowers extracts of *Calliandra portoricensis* and *Calotropis procera* revealed to be anthelmintic when treated
against *Toxocara canis* and *H. contortus* of dog and sheep, respectively (Iqbal et al. 2005). Similarly, Hounzangbe-Adote et al. (2005) reported the anthelmintic potential of *Zanthoxylum zanthoxyloides*, *Morinda lucida* (leaf extracts) and *C. papaya* (seed extracts) collected from Western Africa, against different stages of *H. contortus*. Iqbal et al. (2006) established anthelmintic property of *Butea monosperma* and *Zingiber officinale* against various helminth parasites. Ethanolic extracts of seeds of *Azadirachta indica* (Meliaceae), *Caesalpinia crista* (Caesalpiniaceae), *Vernonia anthelmintica* (Asteraceae), whole plant of *Fumaria parviflora* (Papaveraceae) and of the fruit of *Embellia ribes* (Myrsinaceae) showed anthelmintic efficacy when compared with pyrantel tartrate against infective larvae of *H. contortus* (Hordegena et al. 2006). The leaves of *Strobilanthes discolour* were studied by Tangpu et al. (2006) to confirm the anticestoidal activity against *H. diminuta*. Similarly, stem bark of *Acacia oxyphylla* and root peel of *Millettia pachycarpa* showed anthelmintic efficacy against cestode parasite *R. echinobothrida* (Roy et al. 2007, 2008). The root-tuber peel of *F. vestita* (Fabaceae) and a concoction of rhizome pulp of *Stephania glabra* with aerial roots of *Trichosanthes multiloba* has also been shown to have more or less similar kind of anthelmintic efficacy against *Ancylostoma ceylanicum* (Lyndem et al. 2008). Anticestodal activity has also been observed in *Adhatoda vasica* extracts against *H. diminuta* infections in rats by Yadav and Tangpu (2008). Some of the important pharmacological and anthelmintic studies of plants against various helminthic parasites were reviewed by Mali and Mehta (2008). Various concentrations of *Thespesia lampas* (Cav.) root extracts ranging from 10-50 mg/ml of distilled water when treated against adult earthworms (*Pheretima posthuma*), roundworm (*A. galli*) and tapeworms (*Raillietina spiralis*) found to exhibit significant anthelmintic activity at a concentration of 50 mg/ml of PBS (Kosalge and Fursule 2009). Roy and Swargiary (2009) showed alteration of several tegumental enzymes of *F. buski* when treated with crude shoot extract of *A. nigra*. The root peel extract of *Potentilla fulgens* showed remarkable anthelmintic activity against *G. crumenifer* and *Raillietina echinobothrida in vitro* (Roy et al. 2010). Motility, mortality and scanning electron microscopic observations have revealed the anthelmintic activity of *Lysimachia ramosa* against *F. buski*, *A. suum* and *R. echinobothrida* (Challam et al. 2010). The effects of condensed tannins extracted from five species of plants (*Lotus pedunculatus, Lotus corniculatus, Dorycnium pentaphyllum, Dorycnium rectumand, Rumex obtusifolius*) were investigated using
egg hatching and larval development bioassays against *Ostertagia circumcincta* and it was concluded that condensed tannins from these plants are able to disrupt the life cycle of nematodes (Molan and Faraj 2010). The anthelmintic properties of some tannin-rich Mediterranean plants namely, *Pistacia lentiscus*, *Quercus cocciifera*, *Ceratonia siliqua*, *Onobrychis viciifolia* and *Medicago sativa* were established both in *in vivo* and *in vitro*, latter by using larval migration assay against *H. contortus* and *Trichostrongylus colubriformis* larvae (Manolaraki et al. 2010). The anticestoidal activity of the *A. oxyphylla* was studied by Dasgupta and Roy (2010) against *R. echinobothrida*. Recently, Kone et al. (2012) evaluated the anthelmintic activity of the ethanolic extracts from 50 medicinal plants *in vitro* against trematodes (*Echinostoma caproni*, *S. mansoni*) and nematodes (*Ancylostoma ceylanicum*, *Heligmosomoides bakeri*, *Trichurus muris*), and all extracts tested were found to be active against at least one helminth species. Recent studies by Suleiman et al. (2013) revealed the anthelmintic activity of the stem-bark of *Combretum molle* R. Br. x. G. Don (Combretaceae) against *H. contortus*. Ethanolic and water extracts of *Vernonia amygdalina* and *Secamone africana* were found to have potential anthelmintic efficacy against *A. suum* (Nalule et al. 2013). Similarly, Mini et al. (2013) evaluated the *in vitro* anthelmintic property of aqueous and ethanol extract of *Aristolochia indica* against *H. contortus*. In a similar kind of study, Ahmed et al. (2013) evaluated and established the anthelmintic efficacy of five plants viz, *Ananas comosus*, *Aloe ferox*, *Allium sativum*, *Lespedeza cuneata* and *Warburgia salutaris*.

Parasites generally have complex life cycles comprising multiple host species as well as free living stages. Review of literatures revealed that helminth parasites have completely different mode of life cycle compared to free living organisms to enable them to adapt inside the hosts by changing its metabolic pathways (Kita et al. 2010). It is known that early stages of helminth parasites mainly miracidia and cercariae predominantly depends on aerobic respiration, producing CO$_2$ as the main metabolic by-products (Tielens et al. 1992). However, at maturity, the energy production shifts to anaerobic ones with lactic acid as the end product of glycolytic pathway instead of pyruvic acid (Bueding 1950; Von Brand 1979). Chemotherapeutic attack on the energy generating systems of helminth parasites is one of the more rational and promising approaches to combat helminthiasis and other parasitic diseases, since energy (ATP) is one of the few components that parasites cannot directly obtain from the host. Special attention has, of course, been directed
towards enzymes that are absent in the host or work differently between the host and parasites (Marr et al. 2002).

A large number of commercially available anthelmintic drugs were found to interfere with the metabolic pathways of helminth parasites. Effects of PZQ, LEV, MBZ, fenbendazole (FBZ) and ALB on activity of different enzymes like LDH, HK and PEPCK were well documented. *Cotugnia digonopora*, a fowl cyclophyllidean cestode, was found to possess most of the enzymes, associated with the glycolytic sequence and phosphoenolpyruvate (PEP) branch point, in the cytosol fraction. Anthelmintic agents inhibit hexokinase (HK), phosphofructokinase (PFK), glucose-6-phosphate dehydrogenase (G6PDH), malate dehydrogenase (MDH), fumarate reductase (FR), and malic enzyme (ME) (Pampori and Srivastava 1987). The effect of oxyxlozanide, hexachlorophene, nitroxynil, rafoxanide and diamphenethide on MDH activity of homogenates of *Fasciola gigantica*, *F. buski* and *Paramphistomum explanatum* was investigated by Probert et al. (1981) which showed no such appreciable reduction in enzyme activity in *F. gigantica* and *P. explanatum* but oxyxlozanide and hexachlorophene causes inhibition in *F. buski*. The inhibition of phosphoenolpyruvate carboxykinase (PEPCK) by cambendazole in *Moniezia expansa* has been ascribed to diversion of metabolic activity towards lactate production (Rahman and Bryant 1977). Pampori et al. (1984) showed that the commercial drugs like niclosamidc, PZQ and MBZ strongly inhibit the uptake of glucose by *C. digonopora*. Likewise in *C. digonopora*, a strongly inhibited MDH forces the parasite to channelize the metabolism of PEP through pyruvate kinase (PK) and lactate dehydrogenase (LDH) leading to increased production of lactate. Inhibitory activities of four BZs like ALB, parbendazole, MBZ and TBZ were studied on purified MDH from *A. suum*, *F. hepatica* and *Moniezia expansa*, where the highest percentage inhibitions were exhibited by mebendazole (Tejada et al. 1986). In a similar kind of study Sharma et al. (1987) observed inhibition of LDH, MDH, aldolase, acid and alkaline phosphomonoesterase as well as cholinesterase in *A. galli* and *Heterakis gallinae* when exposed to anthelmintics like LEV and ALB. The activities of important glycolytic enzymes PFK, HK, G6PDH, PEPCK and MDH of *C. digonopora* was significantly inhibited by MBZ, niclosamide and PZQ (Pampori and Srivastava 1987). Sanchez-Moreno et al. (1989) showed that activity of MDH was inhibited by a series of BZ and pyrimidine-derived compounds both in host and parasite; however, the extent of reduction was different. Banu et al. (1992)
screened the anthelmintic efficacy of the leaf-and flower-extract of several plants against mitochondrial MDH and mME of *Setaria digitata* and revealed inhibition of activities of both the enzymes by all the plant extracts. Similarly, MBZ, FBZ and ABZ have also significantly inhibited the activity of LDH (Veerakumari and Munuswamy 2000). The crude extract of various plants and their active component(s) were shown to induce flaccid paralysis and alteration in the various glycolytic and tegumental enzymes of helminths (Roy and Swargiary 2009; Roy et al. 2010). Das et al. (2004) revealed stimulatory effects the crude root peel extract of *F. vestita* and its active principle genistein by increasing activities of HK, PFK, PEPCK and LDH in cestode parasite *R. echinobothrida*.

Similarly, a large number of commercial drugs and extracts of plants were found to inhibit the activities of enzymes that are mainly associated with the tegumental regions of the helminth parasite. The presence of several vital enzymes viz., acid phosphatase (AcPase), alkaline phosphatase (AlkPase), adenosine triphosphatase (ATPase), 5′-nucleotidase (5′-Nu) and acetylcholinesterase (AchE) has been reported in the body tegument, and the various organs/tissues of many flat worms (Kwak and Kim 1996; Pal and Tandon 1998; Kar and Tandon 2004; Lalchhandama et al. 2008). All these enzymes which are involved in various metabolic processes are also believed to be involved in absorption and/or digestion in the parasite (Roy 1982; Poljakova-Krustena et al. 1983). *In vitro* investigation of the aqueous extract of *Butea monosperma*, *Embelia ribes* and *Rottleria tinctoria* showed reduction in the enzyme activities of both AcPase and AlkPase in *P. cervi* (Chopra et al. 1991). Many commercial anthelmintics like parbendazole, piperazine adipate, phenothiazine, diethazine, diethylcarbamazine, centperzine, tetramisole and LEV alter the metabolism and disrupt mitochondrial energy formation resulting in decrease in ATP levels (Agarwal et al. 1990; Aggarwal et al. 1992; Vinaud et al. 2009). Activities of many of these enzymes are reported to be altered by extract of traditionally used medicinal plants like *F. vestita*, *A. oxyphylla*, *Millettia pachycarpa*, *A. nigra* and *P. fulgens* (Tandon and Das 2007; Lalchhandama et al. 2007, 2008; Roy and Swargiary 2009; Roy et al. 2010).

Helminth parasites have an external body covering (tegument in cestodes and cuticle in nematode) which protects the helminth parasites from adverse conditions within the host and helps in many other functions such as uptake of nutrients, excretion of certain metabolites, control of motility and osmoregulation.
etc. Therefore, it attracts great attention from scientific community to know and study its structure and function and exploit it as chemotherapeutic target. Microscopy has a long and distinguished history in the study of helminth parasites and has made outstanding contribution to the understanding of how these complex animals organise their lives and relate to their hosts (Halton 2004). Most notable among these is their body surface as the primary site of molecular interaction with the host. Consequently, it has been seen that it is one of the most essential chemotherapeutic drug targets in helminth parasites. A large number of studies have shown that the commercial anthelminthic drug acts on surface tegument of the helminth parasites thereby altering the surface topography (Modha et al. 1990; Liang et al. 2002; Mohamed et al. 2006). In vitro and in vivo studies in F. hepatica have shown extensive swelling and blebbing of the tegument on both dorsal and ventral surfaces, although the dorsal anterior region was more severely affected than either the posterior dorsal region or entire ventral surface on exposure to anthelmintic nitroxynil (McKinstry et al. 2003). Extensive blebbing in the tegumental surface of F. hepatica was observed on incubation of the parasite in genistein (Toner et al. 2008). Similarly, recent studies have revealed the flukicidal activity of A. nigra against F. buski with severe morphological and ultrastructural alterations on exposure to the plant extract treatment (Roy et al. 2008). Adult F. hepatica when incubated in vitro in the synthetic peroxide, OZ78 showed flukicidal activity with disruption to the external surface of the fluke. Significant disruption was observed to the tegument and subtegumental tissues with severe swelling of the basal infolds in the tegumental syncytium, formation of autophagic vacuoles and reduction in the synthesis of tegumental secretory bodies was recorded (Halferty et al. 2009). Ultrastructural observations on tegumental surface of R. echinobothrida showed significant alterations in the tegumental ultrastructure, when the parasites were exposed to root-peel extract of Millettia pachycarpa and stem bark of A. oxyphylla (Dasgupta and Roy 2010).

India is a country of rich traditional folklore healthcare system which is deeply related to the places where rural and tribal communities are rooted. Use of plant as a source of medicine has been inherited and is an important component of the health care system in India. An estimated 65% of rural Indians use Ayurveda medicine system and medicinal plants to meet their primary health care needs (WHO 2002; Pattanaik and Reddy 2008). With three major biodiversity hotspots of the
world (Himalayan, Western Ghats and Indo-Burm), this part of world have a vast repository of flora and fauna. According to Ali et al. (2008), India is bestowed with over 45,000 species of plant which constitute about 7% of the world’s total flora. Geographically, though it covers only 2% of the Earth’s surface, it is the richest country of the whole world as far the genetic resources and medicinal plant is concerned. 11% of the total known plants have been known to have medicinal properties. The north east region of India is endowed with vast potentials of medicinal plants. The native tribes of this region have a rich tradition of using several plants in their own traditional medicine system. A number of studies have been made in the recent past to identify several such plants and validate scientifically which are frequently used as popular anthelmintics among natives of the region. *F. vestita* (Fabaceae) is considered to be a lesser-known tuberous crop of Northeast India. The fleshy tubers of the plant along with the peel are consumed by natives of Meghalaya to cure intestinal-worm infections. During past two decades, a number of studies have been made on its root-tuber extract and/or active principle, genistein to establish its’ credentials as an anthelmintic. Its crude extract was found to be quite effective against *Artyfechinostomum sufrartyfex* and *F. buski*. Vacuolization and pit formation was also recorded in these parasites when treated in vitro with its root tuber peel extracts (Roy and Tandon 1996). In another study the exposure of *R. echinobothrida* to its active principle, genistein caused spontaneous loss of movement in cestode parasite followed by structural alteration in its tegumental architecture (Tandon et al. 1997). Genistein is found to alter the activity of some glycolytic enzymes and nitric oxide synthase of *R. echinobothrida* (Tandon et al. 2004; Tandon and Das 2007; Das et al. 2009). Roy and Tandon (1997) investigated the trematocidal activity of *Cannabis sativa* (Canabinaceae), a traditional anthelmintic plant of Meghalaya, against *F. buski*. The crude extract of plant was reported to possess better trematocidal activity than Oxyclozanide. The deformation of parasite’s oral sucker and its sensory papilla, as revealed by scanning electron microscopic observations, was postulated to be the possible site of action of the plant. Crude extracts of *A. nigra* was reported to possess significant flukicidal activity against *F. buski* (Roy and Tandon 1999). The leaf extract of *Spilanthes oleracea*, a traditional anthelmintic plant of Meghalaya, was reported to possess significant activity against *Orthocoelium dinniki* (Roy 2000). It was reported to bring about surface alterations in worm’s tegument. Temjenmongla and Yadav (2005) studied in vitro anticestodal
activity of nine plants that are used in the indigenous system of medicine by Naga tribes in Northeast India to cure intestinal-helminth infections using *R. echinobothrida*, as a model test parasite. The authors found that the leaves of *Psidium guajava*, *Houttuynia cordata* and stalk of *Lasia spinosa* possess a profound anticestodal efficacy, whereas the leaves of *Clerodendrum colebrookiaum*, *Lasia spinosa* and *Centella asiatica* possess a moderate efficacy and *Curcuma longa*, *Cinnamomum cassia*, *Gynura angulosa*, *Lasia spinosa* (stem) and *Aloevera* show a negligible degree of *in vitro* anticestodal activity. Yadav and Tangpu (2006) studied the anthelmintic activity of a few selected plants used in the traditional medicine system of Naga tribes in Manipur and reported that plants namely, *Strobilanthes discolor* (leaf), *Adhatoda vasica* (leaf), *Butea minor* (seeds), *Solanum myriacanthum* (fruits), *Trifolium repens* (shoots) and *Zanthoxylum rhetsa* (leaf) possess moderate to high degree of *in vitro* anthelmintic activity against adult *H. diminuta*. The anticestodal efficacy of *Trifolium repens* L. (Fabaceae), a folk-lore medicinal plant of Naga tribes of Nagaland state, was also established by Tangpu et al. (2004), using experimentally induced *H. diminuta* infections in albino rats. In this study, the aerial shoot extract of the plant significantly reduced the mean EPG and worm recovery rate in the treated animals when compared to PZQ. On the basis of its effects on EPG counts and percentage of worm recovery rates, the authors concluded that the plant extract bears remarkable anthelmintic activity against larval cestodes. Temjenmongla et al. (2006) investigated the anticestodal efficacy of *Psidium guajava* L. (Myrtaceae), a folk lore medicinal plant of Naga tribes, and found that treatment with its leaf extract results into host clearance of parasites in *H. diminuta*-albino rat experimental model. Yadav and Temjenmongla (2006) reported the anthelmintic activity of *Gynura angulosa* DC. (Asteraceae), a folk lore anthelmintic plant of native tribes in Northeast India, using *Trichinella spiralis* mouse model. The study revealed that its leaf extract possesses significant efficacy against adults, migrating and encysted larvae of *T. spiralis*. 1600 mg/kg dose of the extract resulted into about 73% reduction in the muscle encysted larvae. Likewise, *Adhatoda vasica* Nees (Acanthaceae), another traditionally used anthelmintic plant of Naga tribes, has also been reported to bear profound anthelmintic efficacy against experimental *Hymenolepis* infection in albino rats. Its leaf extract was observed to show better anthelmintic efficacy when compared with 5 mg/kg single dose of PZQ (Yadav and Tangpu 2008). The ethanolic extract from the root bark of *Milletia pachycarpa*,
traditionally used as a remedy for gastrointestinal infections among the Mizo tribes of Northeast India, was tested *in vitro* against *R. echinobothrida* and reported to possess significant anthelmintic property. Scar formation in the tegumental surface of cestode and alternation of several carbohydrate metabolism related enzymes were suggested as possible mode of action of plant crude extract (Lalchhandama et al. 2008). Lalchhandama et al. (2008) observed that *Milletia pachycarpa* brings out its anthelmintic activity by causing scar formation in worm’s tegumental surface and by altering several carbohydrate metabolism related enzymes in the extract treated worm. Besides *in vitro* studies, lot of traditional anthelmintic plants of NE region of India has also been studied for their putative anthelmintic activity employing various animal models. Leaf extract of *Zanthoxylum rhetsa* DC (Rutaceae) when tested in *H. diminuta*-rat model showed a high degree of efficacy against larval stage and a moderate level of efficacy against immature and adult stages of the tapeworm (Yadav and Tangpu 2009). Dasgupta and Roy (2010) reported the anthelmintic activity of *A. oxyphylla* (Leguminosae), used traditionally by the natives of Mizoram against intestinal worm infections. It was observed that the extract brings out its anthelmintic actions against fowl cestode, *R. echinobothrida* by altering the structural and functional integrity of its tegument. *Lysimachia ramosa* Wall (Primulaceae) was recorded to possess *in vitro* efficacy against *F. buski, A. suum* and *R. echinobothrida*. The alcoholic extract treated parasites revealed complete inactivation and flaccid paralysis that was followed by death at varying periods of time. The scanning electron microscopic (SEM) observations revealed conspicuous deformity in the surface architecture of all the parasites exposed to the test plant extract (Challam et al. 2010). The stem bark extract of *A. oxyphylla*, a traditional anthelmintic plant of Mizo tribes, have been demonstrated to exhibit profound anthelmintic effects on fowl cestode, *R. echinobothrida* (Dasgupta et al. 2010). Similarly, Roy et al. (2010) established the anthelmintic efficacy of *Potentilla fulgens* against *R. echinobothrida* and *Gastrothylax crumenifer*. Ethanolic root peel extracts of *P. fulgens* were also found to cause surface topographical changes as well as ultrastructural changes in *R. echinobothrida* when the parasites were exposed to it (Roy et al. 2012). Similarly, Challam et al. (2012) revealed the anthelmintic activity of the ethanolic crude extract of *Carex baccans* against *R. echinobothrida*. A traditionally used medicinal plant of Northeast India, *Clerodendrum colebrookianum* was found to show anthelmintic efficacy when leaf extract was assessed through
monitoring the eggs per gram of faeces counts and worm (H. diminuta) recovery rates from experimentally induced Wistar rats (Yadav and Temjenmongla 2012). Adult cyclophyllidean cestode, R. echinobothrida when exposed to the crude ethanolic extracts of A. oxyphylla and Securinega virosa, showed reduced activities in AcPase, AlkPase and ATPase and alterations in the level of amino acids and trace elements of the parasites (Dasgupta et al. 2013). Similarly, the ethanolic crude extract of S. virosa and its active compound virosecurinine were found to cause surface topographical as well as ultrastructural changes in R. echinobothrida when treated in vitro (Dasgupta et al. 2013). Recently, Singh et al. (2013) revealed the anthelmintic property of Spilanthes acmella Murr. against Gastrothylax crumenifer.