1.0 INTRODUCTION

Human interest in medicinal plants covers the entire spectrum of wonder, aesthetic joy, scientific curiosity, therapeutic use, ecological concerns and industrial exploitation. About 80% of the world population cannot afford the products of the allopathic pharmaceutical industry and has to rely upon the traditional medicines that are mainly derived from plant materials. During the long tradition from instinctive behavior to more rational action there was a conscious realization that certain roots, leaves, barks, fruits, and other plant materials and exudates have some traditional action. Many herbal drugs were used by different civilization and many of them are still used. Rig-Veda (2000 B.C.) mentions 67 herbal drugs, Ayurveda (2000 B.C.) contains 81 and Tarzana Veda (1600-1000 B.C.) includes 290 medicinal plants. Charka Samita (900 B.C.) is the first recorded treatise of Ayurvedic which describes 341 plants and plant products for use in medicine. About 395 medicinal plants are described in Sushruta Samhita (600 B.C.). The Bhava Prakash compiled by Bhava Mishra of Maghadha (1550 A.D.) describes 470 medicinal plants. About 1000 Ayurvedic remedies are used at present, prepared from more than 750 plants.

The utility of plants as therapeutic agents in traditional medicinal system is still prevalent study. For example, the Middle Eastern civilization developed Greco-Arabic system of medicine (Unani System) which is practiced in the Indian sub-continent. Similarly, the Chinese race developed the Chinese system of medicine largely based on its unique system of theories including the concept of the yen and theory of influence imparted from nature. Indians contributed the Ayurveda and Siddha systems of medicine. All these systems procure more than 80% of their medicaments from plants. The system of indigenous medicines has been working under various restrains and constrains. Until recently, the practicing physician himself for the use of his
patients prepares these medicines in the absence of any scientific method of identification and standardization. It is abundantly clear that the preference to drugs, perfumes, cosmetics, flavours and food colors obtained from plant sources has been increased day by day. For example, one of the important plant products is Artemism which is obtained from flowering tops of the Chinese plant Quinghao (*Artemisia annua*). Preliminary clinical trials of a derivative of Artemism have shown that it is effective against strains of plasmodium falciparum, where antimalarials have failed to cure the disease. It is very much useful for treating cerebral malaria (Hussain, A., 1993).

In most developing countries where coverage by health services is limited, it is to traditional practitioner or to the folk medicine practitioner that majority of population turn when sick. The treatment they receive largely based on medicinal plants. Early in this century, the greater part of medicinal therapy in the industrialized countries was dependent on medicinal plants, but with the growth of the pharmaceutical industries, there use was felt out of favour. Even though, 41% of all prescriptions dispensed during 1973 from community pharmacies in the United States of America contained plant extracts as active principles (Fornsworth, N.R., 1984). Now the pendulum is bringing back and the value of the medicinal plants is receiving distinguished global attention. Due to the widespread reports on toxicity and health hazards associated with indiscriminate use of synthetic drugs and antibiotics accompanied by rising cost of organic chemicals and reagents, the basic thinking and attitude of the modern society has been changing since last 15 years.

India is the third richest country after Russia and Brazil in terms of plant wealth but still we import a large number of active principles, essential oils and tanning
materials of plant origin from foreign countries. This is due to the lack of comprehensive information regarding ecological distribution and availability of the plants in nature and at the same time there is no proper coordination between R&D organizations. Majority of plants are left unexposed in the forests and in some cases, a large number of banned species are extracted. This unplanned investigation has resulted in the extinction of many species.

The medicinal value of the crude drug depends on the presence of active chemical constituents and other concentration varies due to ecological, genetic and seasonal condition. Therefore, it is thought to conduct phytochemical investigation of some traditional drugs. A large number of economic plants can be used by various pharmaceutical concerns, data on their availability and biological activities are already published.

Today we understand that plants represents an immense repository of biochemical including pharmaceuticals, flavours and novel bioactive substances, which often serve as chemical models of templates for the design and synthesis of New Drug Entities. Medicinal plants play an important role in the health care of developing countries. Currently 70% of the world population use herbal medicine and World Health Organization (WHO) also encourages and promotes the use of herbal remedies as they are not only safe and easily available at low cost but are also time tested. (Hussain, A., et al., 1993)
1.1 INDIAN SCENARIO OF HERBAL DRUGS

Nature has endowed India with a unique gift of as many as 15,000 plant varieties. India accounts for two thirds of the flowering plants of the world, of which about 2500 are reported to possess medicinal and curative quantities (Rajan, T.P.S., 1994). In India, there are about 6,780 pharmacies in the Indian system of medicine. The export potential of herbal drugs has been estimated to be around Rs 2840 million per annum for India and Rs 16,000 million per annum for China (Handa, S.S., 1993).

The top most research institutions in India have been showing much interest in the scientific research on herbal drugs. For example, the Indian Council of Medical Research (ICMR) has evolved a new strategy for research on plant-based drugs since 1986.

1.2 ANTHELMINTICS

An “ideal” anthelmintic should have a broad spectrum of activity against mature and immature parasites (including hypobiotic larvae). It should also posses a wide margin of safety and be compatible with other compounds, not require long withholding periods because of residue(s) and be economical.

Many highly effective and selective anthelmintics are available, but such compounds must be used correctly and judiciously to obtain a favourable clinical response and to minimize resistance. It is impossible to list all claims and precautions regarding all anthelmintics, the label should be always being read before using any drug. Additional information is found under relevant disease headings.

Modern drugs have a wide margin of safety, considerable activity against immature or larval stage of parasites and a broad spectrum of activity. nonetheless the usefulness of any anthelmintic is limited by the inherent efficacy of the drug itself, its mechanism of action its pharmacokinetic properties, features relating to the host animal (e.g., operation of the esophageal groove reflex) or features relating to the
parasite (e.g. its location in the body, its degree of hypobiotic larvae) be easy to administer to a large number of animals, have a wide margin of safety and compatible with other compounds, not require long withholding periods because of residues and be economical.

Anthelmintics must be selectively toxic to the parasite. This is usually achieved either by inhibiting metabolic process vital or are absent in the host, or by inherent pharmacokinetic properties of the compound that cause the parasite to be exposed to higher concentrations of the anthelmintic than the host cells. While the physiologic mode of action of anthelmintic is not fully understood, the sites of action and biochemical mechanism of many of them are known. Parasitic helminthiasis must maintain an appropriate feeding site, nematodes, and trematodes must actively ingest and move food through their digestive tract to maintain an appropriate energy state. This reproductive process requires proper neuromuscular coordination. Parasites must also maintain homeostasis in the face of host immune reactions. The pharmacologic basis of the treatment for helminthes generally involves interference with the integrity of parasite cells, neuromuscular coordination or protective mechanisms against host immunity, which lead to starvation, paralysis and expulsion of the parasite.

1.3 CHEMOTHERAPY OF HELMINTHIASIS

Anthelmintics are drugs that either act locally to expel worms from the GIT or act systemically to eradicate adult helminthes that invade organs and tissues.

For a clinical trial of a potential anthelmintic agent a well established anthelmintic drug with a similar spectrum should always be incorporated in the experimental design so as to the new drug can be gauged by counting the ova or eggs present in the stools. Patients suffering form multiple parasitic infestations are ideal for investigating a new anthelmintic drug claimed to have a broad spectrum of action.
An ideal anthelmintic should

1. have a broad spectrum of action.
2. achieve a high percentage of cures with in single dose.
3. should not require additional purgative.
4. should not get absorbed.
5. should be free from toxic effect.
6. palatable and cheap.

Absorption

After administration, anthelmintics are usually absorbed into the bloodstream and transported to different parts of the body, including the liver, where they are metabolized and eventually excreted in the feces and urine. With some anthelmintics (e.g., Probenzimidazoles), antiparasitic activity lies not with the original compound but with its metabolites. The speed with which an anthelmintic is metabolized and excreted determines the length of the withdrawal time. This speed can vary among species and can be affected by the route of administration and the dose.

Metabolism

While many GI parasites reside in the lumen or close to the mucosa, others live at other sites, e.g., liver and lungs. For action against these, absorption of drug from the GI tract, injection site or skin is essential. Intestinal parasites come in contact not only with the unabsorbed drug passing through the GI tract but also with the absorbed fraction in the blood as they feed on the intestinal mucosa and with any that is recycled into the gut. This is an important aspect of efficacy of many of the benzimidazoles.

Metabolism of an anthelmintic may alter activity. For example, albendazole is rapidly oxidized to its sulfoxide, this oxidation is reversible. The sulfoxide may be
irreversibly oxidized to its sulfone, which is inactive. Similarly, fenbendazole and oxfendazole (fenbendazole sulfoxide) are exchangeable, but the oxidation product fenbendazole sulfone is inactive and is not reduced back to the sulfoxide or thiometabolites. In the case of fasciolicides (such as diamfenetide) metabolism within the GI tract may be important for full efficacy. Because human bacteria metabolize and destroy the activity of nitroxynil, it must be injected. The more usual site of metabolism is the liver, in which oxidation and cleavage reactions commonly occur. Thiabendazole is rapidly metabolized in the liver to hydroxythiabendazole, with the sulfate and glucuronide conjugates of this metabolite being more soluble in water than the parent drug and rapidly excreted by the kidneys. Frequently, active metabolites are desecrated back into the GI tract. Many of the more modern benzimidazoles and their metabolites reenter the GI tract by passive diffusion. The biliary route may also be important in recycling benzimidazoles such as albendazole to the GI tract. However, desecration via the liver and bile is especially important for drugs active against adult *Fasciola* species. Many fasciolicides, such as the salicylanilides and the substituted phenols, appear to bind strongly to plasma proteins. The fasciolicidal effects of salicylanilides (such as rafoxanide) in sheep were found to depend on persistence of the drug in plasma, which influences their transport throughout the body and the rate of elimination from the host. Associated with persistence, however, is the need for longer withholding periods? Oxyclozanide also is bound to plasma protein and then metabolized in the liver to the anthelmintically active glucuronide and excreted in high concentration in the bile duct where it encounters the mature flukes. Immature flukes in the liver parenchyma ingest mainly liver cells, which contain little anthelmintic, plasma-protein binding limits entry of the drug into the tissue cells. As the flukes grow and migrate through the liver, they cause extensive haemorrhage and come into contact with anthelmintic bound to plasma protein. When they reach the bile ducts, they are the main excretion channels for the active metabolites of the
fasciolicides and, thus, are exposed to toxic concentrations. This may explain why mature flukes are more vulnerable to most fasciolicides than immature ones. The higher concentrations of fasciolicides and their metabolites in faeces than in urine suggest that the bile ducts are their main excretory pathways.

Diamfenetide is metabolized in the gut and largely in the liver, to an active metabolite that can enter the hepatic cells and exert its antiparasitic effect against very young stages of the fluke. The low plasma-protein binding of diamfenetide, coupled with the rapid excretion of its active metabolite, necessitates only a short withdrawal time.

**Route of administration**

Route of administration influences persistence in the body and thus efficacy. In ruminants, administration directly into the abomasums, via the esophageal groove, may increase the rate of excretion in the faeces, which may reduce efficacy. Operation of the luminal bypass acts to reduce the efficacy of certain benzimidazole anthelmintics. (For example, immediate arrival of oxfendazole in the abomasums after dosing reduces its efficacy from 91% to 45% against thiabendazole-resistant strains of *Haemonchus contortus*). The rumen acts as a drug reservoir from which plasma concentrations can be sustained for long periods; it also slows the passage of unabsorbed drug through the GI tract. In general, the benzimidazoles are most effective if deposited directly into the rumen, less so if injected into the abomasums.

The absorption of levamizole is not affected by the route of administration because it is highly soluble and is unaffected by luminal bypass.

In a number of situations, animals deliberately or inadvertently are given less than the recommended dose. The result is likely to be lowered efficacy.

Anthelmintics can be administered in various ways. In general, drench, paste, injectable, and pour-on preparations allow a greater degree of control over the amount
of anthelmintic administered than in-feed or medicated block preparations. Whichever method of administration is selected, the manufacturer’s instructions should be read with particular regard to the following:

1) The spectrum of activity.

2) The class of animal for which the product is recommended and any limitations of its use that may be advised.

3) The dose rate and any increase in dosage that may be recommended to deal with different developmental stages or different species or types of worm.

4) The withholding period (in food-producing animals).

**Sustained release formulations**

The solubility of a compound (and nature of the solvent) largely governs the route of administration. Insoluble anthelmintics usually must be given orally in the form of suspensions, pastes or granules or by intraluminal injection. The more soluble compounds may be given orally as a solution, topically as a “pour-on” (organophosphates, levamizole, macrocyclic lactones) or as an injectable solution (nitroxynil, rafoxanide, levamizole). Particle size has a significant effect on efficacy or toxicity of insoluble agents administered orally. In general, small particle size increases the rate & extent of dissolution in and absorption from the GI tract and may increase the efficacy of a compound.

**Injectable Preparations**

Certain soluble anthelmintics (notably levamizole, diethylcarbamazine, netobimin) or anthelmintics that may be formulated to “behave” like an aqueous solution (e.g. ivermectin, moxidectin and nitroxynil) are available as injectable preparations. With some anthelmintics, the formulation or route of administration may alter efficacy, spectrum, or both. In some situations, notably with cattle and pigs,
injectable formulations have an added advantage of ease of administration. Local reactions at the injection site may occasionally be noticed but generally are of little consequence, provided the site is not an area from which prime cuts of meat are taken.

**Topical Preparations**

Currently available pour-on preparations include levamizole, ivermectin and moxidectin. They are licensed only for use in cattle. In these preparations, the drug is contained within a liquid or vehicle that is thoroughly absorbed through the skin after application.

**In Feed Preparations**

Many of the benzimidazoles are available for mass medication in the feed. In feed preparations, allow limited control over the amount of anthelmintic that individual animals consume, unless they are fed separately or in small-supervised groups. Therefore, some animals may receive more or less than the recommended dose.

**Resistance**

The development by nematodes of resistance to various chemical groups of anthelmintics is recognized as a major problem. Until recently, resistance to anthelmintics in nematodes had been slow to develop in under fed conditions (as compared to antibiotic resistance in bacteria). However, resistance is becoming widespread because relatively few chemically dissimilar groups of anthelmintics have been introduced over the past decades.

Continued application of a highly effective anthelmintic selectively removes most susceptible genotypes, with the resultant progeny of succeeding generations being composed of resistant strains. Resistance to an anthelmintic is expressed by passage of increased numbers of parasite eggs, higher establishment rates of adults in
the host, and greater numbers of larvae on the pasture after treatment than would occur if the parasites were susceptible to the drug. Resistance of *Haemonchus* is becoming a global problem. Resistance of *Trichostrongylus* and *Ostertagia* in sheep and goats is also becoming common in all parts of the world where small ruminants are treated frequently. Resistance of small strongyles in horses is also a problem in many areas. Resistance to benzimidazoles and levamizole has been reported in nematodes of swine. Although resistance to benzimidazoles, levamizole and recently to macrocyclic lactones have all been reported for nematodes of cattle, resistance is less of a problem in cattle than in sheep, goats and horses.

Detection of significant levels of resistance seems to require 9-10 generations of helminthes exposed to the same class of anthelmintic. However, evidence suggests that genes for resistance are already present, at a low frequency, when anthelmintics are introduced. Selection for resistance simply requires the preferential killing of the susceptible parasites and survival of the parasites with the resistance genes. Anthelmintics of different chemical groupings or of differing modes of action should be used in alternate years to prolong their worthwhile therapeutic existence. Care should be taken to use the anthelmintic no more often than is needed to control the parasites; emphasis should be placed on husbandry methods to minimize exposure to the helminthes.

Cross-resistance is frequently seen between members of the benzimidazole group because of their similar mechanism of action. Control of benzimidazole-resistant parasites by levamizole can be expected because of its different mode of action. Although there is no cross-resistance between levamizole and benzimidazole, this does not mean that worms resistant to both kind of drugs will not evolve if both type of anthelmintics are used frequently. Nematodes resistant to levamizole are cross-resistant to moxidectin due to the similarities of their mechanisms of action.
In summary, emphasis should be placed on management practices designed to reduce exposure to parasites and to minimize the frequency of anthelmintic use. The development of an anthelmintic resistance problem may be delayed by using chemicals with different modes of action. The current recommendation to delay the onset of resistance when it is not already apparent is for a slow rotation of the different chemical groups. Because, with important exceptions, such as *Haemonchus contortus*, there are usually one or two generations of parasites per year in temperate zones, anthelmintics from different groups probably should be rotated annually between dosing seasons. In the control of parasites, there is no doubt that economic benefit is best obtained by planned treatment of a whole flock or herd and considering the biology of the parasite(s). Results should be good if correct control measures are directed against the parasitic phase in the body of the host at the appropriate time and that attention is given to the free-living, nonparasitic stages in the environment.

**Withholding period**

Most anthelmintics have withholding periods if milk or meat from treated animals is intended for human consumption, it is important to observe the specific requirements for each. Modern benzimidazoles are retained in the body for longer periods than earlier ones and have correspondingly longer withholding periods. Thiabendazole is absorbed and excreted most quickly; fenbendazole, oxfendazole and albendazole are absorbed and excreted over a longer period, which necessitates withholding periods of 8-14 days before slaughtering for meat, and 3-5 days before milking for human consumption. Other members of the group have withholding periods between these extremes.

A similar relationship between the rate of metabolism and activity against immature parasites also exists with certain fasciolicides. Closantel, rafoxanide, nitroxynil, and brotianide bind more strongly to blood proteins than does
oxyclozanide, and therefore remain in the blood for longer periods. While this greater persistence is associated with greater activity against immature liver flukes, the withholding period is also longer (21-30 days before slaughter for closantel, rafoxanide, nitroxynil, and brotianide, compared with 14 days for oxyclozanide).

Levamizole and morantel are rapidly excreted; thus, withholding periods for meat are short and there is only a short withholding period for milk. Ivermectin and doramectin are excreted in milk and are not recommended when milk is intended for human consumption, commensurate with their long period of activity, they have significant withholding periods before slaughter (e.g., 35 days), which vary with the formulations.

Safety

Most modern anthelmintics have wide safety margins, i.e., the dose that can be given to an animal before adverse effects are induced is much higher than the dose recommended for use. For all benzimidazoles, the safety index (SI) is wide. It is not so wide for levamizole (SI = 6) nor for most of the chemicals active against liver flukes (SI = 3-6). In addition, if for any reason the dose rate of an anthelmintic is increased, the safety margin is correspondingly decreased (e.g., if the dose rate is doubled, the SI is halved).

Drug therapy of Tapeworm

This infestation is transmitted by ingestion of infected beef or pork.

Choice of drug: niclosamide, albendazole, praziquantel, mebendazole.

Drug therapy of Roundworm

This infestation is caused by ascariasis and enterobiasis in human beings.

Choice of drug: piperazine, pyrantel palmoate, levamizole, albendazole.
**Drug therapy of Hookworm**

A duodenal infestation is extremely common in tropical countries and cause iron deficiency anemia. This infestation exists along with ascariasis. Choice of drug: albendazole, pyrantel palmoate, mebendazole.

**Drug therapy of Pinworm**

*E. vermicularis* is a common parasite found in the caecum and the vermiform appendix. This infestation is more common in children. The female worm deposits eggs on the perennial skin leading to intense itching and scratching spreads the itching and autoinfection.

Choice of drug: piperazine, albendazole, mebendazole.

**Drug therapy of Strongyloides**

The adult female of Strongyloides lives in the mucosal epithelium of the duodenum and jejunum. The infective larvae invade the human host by penetrating the skin, travel through the vein to the lungs, and penetrate into intestinal wall to reach circulation. It causes epigastric pain and diarrhoea.

Choice of drug: thiabendazole, ivermectin.

**Drug therapy of Trichuriasis (Whip Worm)**

Trichuriasis caused by *Trichuriasis trichura* is common in warm and humid climates. It is encountered with ringworm and hookworms and it may lodge in the appendix penetrate the bowel wall and cause peritonitis.

Choice of drug: mebendazole.

**Drug therapy of Schistosomiasis**

Schistosomiasis (Bilharziasis) is caused by blood flukes (schistosomes) that parasites the venous channels of the definitive hosts. The three common species are
**S. hemotobium, S. mansoni, S. japonicum** and which causes cercarial dermatitis & katayama fever (illness).

Choice of drug: praziquantel, oxamniquine, metrifonate.

**Drug therapy of Flukes**

The liver, lung and intestinal flukes are treated by using praziquantel and it may cause mild gastrointestinal symptoms.

**Drug therapy of Filirasis**

Filarial infections are caused by parasitic tissue dwelling filarial nematodes, which are transmitted by biting insects (mosquitoes-W.Bancrofti, B. Malayi, blackfly-O. volvulus, biting flies-Loa loa).

Choice of drug: diethylcarbamazine, ivermectin.

**Drug therapy of Guinea worm**

**Dracunculus medinensis** infestation is transmitted by drinking water containing infected cycops (water flea). The adult female usually remains in subcutaneous tissue and come out through a small ulcer, usually on the foot. There is no specific drug remedy for guinea worm at present, and many indigenous preparations are claimed to be useful in helping easy expulsion of the worm by gradual pulling.

Choice of drug: metronidazole, mebendazole.