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PHYTOCHEMICALS AS CURE OF WORM INFECTIONS IN TRADITIONAL MEDICINE SYSTEMS

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ABSTRACT

Helminthic infections continue to be the major health hazard to the people, especially those living in tropical developing countries. Although these infections do not cause significant morbidity and mortality when compared with many other parasitic infections, they do cause substantial, but often less measurable effects. For example, infections with gastrointestinal helminths often lead to malabsorbtion, diarrhoea, anaemia and other states of poor health, particularly in infants and school-age children. Though there are several synthetic anthelmintics available at the present time against these parasites, the fact remains that a large proportion of the world's population still does not have access to, or cannot afford to pay for modern medicines, particularly in remote rural areas in poor countries. Besides, the continued usage of current anthelmintic drugs is also posing a major problem of drug resistance in several parasite species. There is thus an urgent need for newer and inexpensive drugs that are able to act for longer periods before resistance sets in. In this context, traditional medicines, based largely on medicinal plants, offer a major and accessible source of health care to people living in developing countries.

For much of our past history, forages, plant parts or extracts have been used to combat worm infections, and in many parts of the world natural products are still in use as herbal remedies. In recent years, there has been a rapid increase in new reports of the antiparasitic activity of natural products, both from scientific studies and from studies into the traditional uses of these products for treating diseases. Thus, plant/herbal based medicines are gaining a lot of attention and forming an integral part of the primary health care system the world over. Reports from around the world include an exhaustive list of plants that have been found to possess significant activity against helminth parasites. In several of such studies based on traditional use information, the crude extract of the plant has been tested for its putative anthelmintic properties, while in others the active ingredients responsible for the activity have also been identified and characterized to establish their mode of action.

North-east India is known for its vast resources of medicinal plants. There is a strong tradition of using plant-based medicines in alternate system of medicine that is widely practiced among the native societies of the region and continues to thrive based on oral and emperical traditions. However, in respect of many phytochemicals, their medicinal potential and efficacy- as vermicidal or vermifugal- has been scientifically validated.

This paper reviews the present state of knowledge regarding the use of some traditional medicinal plants in curing worm infections in different regions of the world, with particular reference to north-east India.

Keywords: Anthelmintic plants, Traditional medicine, Phytochemicals, Intestinal helminths, Northeast India.

INTRODUCTION

Helminthic infections continue to be major health hazard of people, especially those living in tropical developing countries. Current estimates suggest that over half of the world population is infected with intestinal helminths, such as *Ascaris*, hookworms, *Trichuris*, *Enterobius*, *Strongyloides*, and tapeworms, and that most of these infected people live in remote rural areas in the developing countries[1,2]. Although helminthic infections do not cause significant morbidity and mortality when compared with many other parasitic infections, they do cause substantial, but often less measurable effects. For example, infections with gastrointestinal helminths often lead into malaborbtion, diarrhoea, anaemia and other states of poor health, particularly in infants and school-age children[3,4]. In a similar manner, helminthic diseases also pose a major health hazard to millions of livestock and cause significant economic losses in domestic and farm animals. Though there are several synthetic anthelmintics available at the present time against these parasites, the fact remains that a large proportion of the world's population still do not have access to, or cannot afford to pay for modern medicines, particularly in remote rural areas in poor countries[5]. Besides, the continued usage of current anthelmintic drugs is also posing a major problem of drug resistance in several parasite species[6,7]. There is thus an urgent need for newer and inexpensive drugs that are able to act for longer periods before resistance sets in. In this context, traditional medicines, based largely on medicinal plants, offer a major and accessible source of health care to people living in developing countries[5].

For much of our past history, forages, plant parts or extracts have been used to combat worm infections, and in many parts of the world natural products are still in use as herbal remedies[8,5]. In recent years, there has been a rapid increase in new reports of the antiparasitic activity of natural products, both from scientific studies and from studies into the traditional uses of these products for treating diseases[9-11]. Thus, plant/herbal based medicines have become indispensable and are forming an integral part of the primary health care system the world over. Reports from around the world include an exhaustive list of medicinal plants that have been found to possess significant activity against helminth parasites[9,11,12]. In several of such studies based on traditional use information, the crude extracts of herbal plants have been tested for their putative anthelmintic properties, while in others the active ingredients responsible for the activity have also been identified and characterized to establish their mode of action. In context of India, which is endowed with vast resources of medicinal plants, there is a strong tradition of using plant-based medicines in alternate system of medicine among native societies[9,12]. The focus of this paper is to provide an overview of a large number of traditional medicinal plants that are used for curing intestinal helmintic infections in different regions of the world, with particular reference to north-east India.

In recent times, plant/herbal based medicines have become indispensable and are forming an integral part of the primary health care system in many nations, including India[5]. Elsewhere in the world, case studies reveal that owing to complexities and cost of controlling the helminth diseases, treatment from plant sources has been an alternative approach in several societies[13]. In a tactical approach to control the intestinal helminths, the World Health Organization in its Tropical Diseases Control Programme has also provided a special emphasis on the use of traditional medicines to combat the menace of parasitic diseases globally[14]. Based on experiences of current usages of anthelmintic plants in veterinary medicine it has been opined that these plants may offer a traditional alternative to manufactured anthelmintics that is both sustainable and environmentally acceptable. Such plants could have a more important role in the future control of helminth infections in the tropics[15].

The origin of many effective drugs is found in the traditional treatment practices and in view of this several workers have undertaken studies pertaining to testing of a large number of traditionally used medicinal plants for their proclaimed anthelmintic efficacy[15-22]. Although until recently the majority of the evidence on the anthelmintic activity of folklore medicinal plants was anecdotal and lacked scientific validity, there is currently an increasing number of experimental studies that aim to verify and quantify such plant activity. There are indeed a large number of plants whose anthelmintic activity has been demonstrated under controlled experimentation. However, contrary to traditional expectation, there are also a great number of plants with purported antiparasitic properties, which have not been reproduced under experimental conditions.

Anthelmintic Efficacy of Plant-based Products

In India, the history of medicinal uses of plants dates back to 3500-1800 B.C. wherein the Rig-Veda mentions a number of plants with different healing practices. However, a vast majority of knowledge on the subject has also been inherited through folklore that persists in several societies[12]. With respect to use of anthelmintic plants, a perusal of literature reveals that in the beginning quite a few studies on anthelmintic activity of traditional anthelmintic plants, their oils or extracts frequently employed earthworm, *Pheritima posthuma* as a test worm[23-38]. The essential oil of *Piper betle* (Piperaceae) has revealed anthelmintic effect on earthworms *in vitro*[24]. Anthelmintic studies of the essential oils of *Cymbopogon nardus* (Graminaceae), *C. citratus* (Graminaceae) and *Zanthoxylum alatum* (Rutaceae) have revealed that the oil of *C. nardus* has very good effect against earthworms, while the oils of *C. citratus* and *Z. alatum* have moderate activity[25]. Merely on the basis of some morphological similarity of parasitic roundworms with earthworm, the workers in their studies very often advocated that substances which kill and/or are toxic to earthworms may also bring the similar actions in parasitic worms and thus may result in their withdrawal from the host. It may be mentioned here that an easy availability of earthworm might prompted early workers to use them as a suitable test agent but it may be mentioned here that except a morphological similarity, the

earthworm do not share any anatomical or physiological resemblance to common roundworms.

In later years, however, helminth parasites from all three major groups were utilized as experimental models to evaluate the efficacy of plants as anthelmintic. The test parasites which have more frequently been used to evaluate the anthelmintic efficacy of plants are the ones which are readily available from locally slaughtered domestic animals and include parasitic species such as, *Ascaris suum*, *Ascaridia galli*, *Setaria*, *Haemonchus contortus*, *Trichinella spiralis*, *Taenia spp.*, *Hymenolepis diminuta*, *Raillietina echinobothrida*, *Fasicola hepatica*, *Fasciolopsis buski*, *Gasthrothylax cruminifer*, and *Paramphistomum spp*. for *in vitro* studies, while anthelmintic activity of some plants has been tested *in vivo* in sheep/goats infected with *Haemonchus* or mixed species of gastrointestinal nematodes or experimental models such as *Hymenolepis diminuta* infections in albino rats and some monogeneans, *Dactylogyrus intermedius* (Monogenea) in goldfish fish have also been employed[9,11,39-42].

With regard to plant parts, it emerges that different parts of plant such as roots, tubers, stems, leaves, flowers, fruits and seeds or the plant as a whole have been used to evaluate the anthelmintic efficacy. However, in general, the leaves of medicinal plants have been put for anthelmintic investigation rather more frequently. In a similar manner, aqueous or alcoholic extracts, decoctions, essential oils and dried powders of plant parts have constituted as the common the test materials. In few cases, the phytochemical examination of concerned plants has also been made and the active principle has been isolated and tested for putative anthelmintic activity. In all these studies, comparisons of plants' efficacy has been made with one or other synthetic anthelmintic drug namely, praziquantel, albendazole, piperazine citrate, etc[8-11].

In vitro Anthelmintic Efficacy of Plant-based Products

The indigenous system of medicine reports a number of medicinal plants that have been investigated *in vitro* for their anthelmintic activity from different regions of the world[8-10]. Kalesaraj and Kurup[43] reported alkaloid hydrochlorides extracted from seeds of *Butea frondosa* to be 100% lethal to earthworms within 24 h thus indicating their anthelmintic activity. Garg and Atal[44] observed anthelmintic activity of Calotropain (proteolytic enzyme isolated from the latex of *Calotropis procera*) and Bromelain (an enzyme obtained as a by-product from pineapple industry) against *Oesophagostomum columbianum* and *Bunostomum trigonocephalum* of sheep origin. The aqueous extracts of *Chebulic myrobalans*, *Belleric myrobalans* and *Emblic myrobalans*, separately and as a mixture in equal parts (called locally as triphala) were each found to possess good anthelmintic activity. However, triphala was found to possess a greater activity indicating a synergistic action of the three constituents combined[45]. The aqueous and alcoholic extracts of *Ananas sativus* (Bromeliaceaea), *Embellia ribes*, *Macuna prurita* (Leguminosae) and *Melia azedarach* have been found to bear significant activity against *Taenia canina* and

Paramphistomum cervi; *M. prurita*, in particular, has been found to be more effective against trematodes[46]. The anthelmintic property of the aqueous extract of the seeds of *Carica papaya* (Carbicaeceae) against *Ascaris lumbricoides* and *Ascaridia galli* has been also well been established[47]. The aqueous, etheral and alcoholic extracts of *Cucurbita mexicana* (Cucurbitaceae) seeds have exhibited significant anthelmintic activity against *Moniezia expansa*, *Fasciolopsis buski*, *Ascaris lumbricoides* and *Hymenolepis diminuta*. In this study the aqueous extract was found to possess the most significant efficacy as compared to alcoholic and etheral extracts[48]. Dubey and Gupta[49] reported the anthelmintic efficacy of the root bark of *Alangium larmarckii* (Alangiaceaea) against the hookworms of dogs and poultry ascarids. Similarly, Chattopadhyaya and Khare[50] reported that anacardic acid isolated from the oil of nuts of *Semecarpus anacardium* (Anacardiaceae) and its sodium salt possess good anthelmintic efficacy. The anticestodal activity of essential oil from *Piper betle* has been found to be superior to that of piperazine phosphate, and the activity against hookworms has been reported greater than that of hexylresorcinol[51]. Extracts of *Cucurbita pepo* (Cucurbitaceaea), *Calotropis gigantea* (Asclepiadaceae), *Juglans regia* (Juglandaceae), *Momordica charantia* (Cucurbitaceae), *Musa paradisaca* (Musaceae) and *Scindapsus offcinalis* (Araceae) have been found to show profound anthelmintic activity on *Haemonchus contortus* of goat origin[52]. Likewise, alcoholic extracts of stem of *Helleborus niger* (Ranunculaceae), rhizomes of *Zingiber offcinale* (Zingiberaceae), seeds of *Carum copticum* (Umbelliferae), *Agati gratifola* (Leguminosae) and *Mangifera indica* (Anacardiaceae) have shown appreciable anthelmintic activity against human *Ascaris lumbricoides*[53]. Kalesaraj[54] also reported that rhizomes of *Zingiber zerumbet* (Zingiberaceae) bear significant anthelmintic activity against human *A. lumbricoides*, whereas the alcoholic extract of the bark of *Albizzia lebbek* (Leguminosae), the bulb of *Allium sativum* (Litiaceae), rhizomes of *Alpinia calcarata* (Zingiberaceae), rind of *Citrus acida* (Rutaceae) rind of *Citrus aromatica* (Rutaceae), rind of *Citrus medica* (Rutaceae), rhizomes of *Cucuruma aromatica* (Zingiberaceae), rind of *Punica granatum* show moderate level of anthelmintic activity. Dixit and Varma[26] in their study reported that the oils of the rhizomes of *Hedychium coronarium* (Zingiberaceae) and *H. spicatum* (Zingiberaceae) possess better anthelmintic activity than piperazine phosphate against earthworms and tapeworms. *Caraca papaya*, *Sapindus trifoliatum* (Sapindaceae), *Butea frondosa* and *Momordica charantia* has been found to possess good *in vitro* anthelmintic activity against *Ascaridia galli* worms[55]. Palasonin, an active principle of *Butea monosperma* (Leguminosae), has also been established to possess good anthelmintic activity against *A. lumbricoides*, using *an vitro* assay[56]. Girgune *et al.*[28] reported that essential oils of *Boswellia serrata* (Burreaceae) and *Cinnamomum tamala* (Lauraceae) possess better *in vitro* anti-tapeworm activity than piperazine citrate. The essential oils of *Gardenia lucida* (Rubiaceae), *Cyperus rotendus* (Cyperaceae), *Inula racemosa* (Compositae), *Psitacia integrrima* (Anacardiaceae), *Litsea chinensis* (Lauraceae) and *Randia dumetorum* (Rubiaceae) seeds have been reported to possess good anthelmintic activity against tapeworms and earthworms[30-31]. Agarwal *et al.*[29] reported that essential oils of *Nigella sativa* exhibit

considerable anthelmintic activity against tapeworms, hookworms and nodular worms with the activity being comparable with that of hexylresorcinol against hookworms and nodular worms. Similarly, essential oils from leaves and flowers of *Ageratum conyzoides* (Compositae), *Cyathocline lyrata* (Poaceae) and *Lantana camara* (Verbeuaceae) have also been found to possess profound anthelmintic activity against tapeworms and hookworms[57-59]. The anthelmintic activity of *Zanthoxylum alatum* (Rutacae) has been found to be comparable to that drug against roundworms[32], while the essential oil from the fruits of *Z. limonella* has been reported to bear better anthelmintic efficacy than that of piperazine phosphate[60]. In an assay of inhibition of transformation of eggs to filariform larvae of *H. contortus*, Prakash *et al.*[62] established the dose-dependent anthelmintic activity of the alcoholic extract of *Punica granatum*. Kaushik *et al.*[62] evaluated extracts of 11 plants which proved lethal to *Ascaridia galli in vitro*, including those from *Amomum aromaticum* (Zingiberaceae) root and rhizome, *Ammora wallichii* stem, *Anthocephalus indicus* (Rubiaceae) stem and bark, *Calamintha umberosa* (Labiatae) plant, *Dalbergia latifolia* (Leguminosae) stem and bark, *Datura quercifolia* (Solanaceae) fruit, *Datura metal* (Solanaceae) plant, *Ficus religiosa* (Urticaceae) stem and bark, *Sentia myrtina* plant, and *Sumplocos crataegoides* (Sumplocos) leaves. The essential oils of several plants namely, *Callistemon viminalis* (Myrtaceae), *Anacardium occidentale* (Anacardiaceae), *Buddlea asiatica* (Loganiaceae), *Chloroxylon swientenia* (Rutaceae) and oleo-gum resin of *Commiphora mukul* (Buberaceae) have been reported to possess profound anthelmintic activity against tape and hookworms and their efficacy was also noted to be comparable to that of piperazine phosphate and hexylresorcinol[33-35,63]. In other studies the essential oils of *Artemisia pallens* (Compositae), *Eupatorium triplinerve* (Compositae), *Artabotrys odoratissimus* (Annonanceae), *Capillipedium foetidum* (Poaceae) and the grass of *Cymbopogon martini* (Poaceae) have been reported to possess strong anthelmintic activity against *T. solium* and *A. lumbricoides*[64-66].

Several other workers have undertaken studies pertaining to testing of a large number of traditionally used medicinal plants for their proclaimed anthelmintic efficacy[15-20,67,68]. An *in vitro* study on fruit extract of Indian mulberry revealed highest anthelmintic activity against *H. contortus*[69]. Sangwan and Sangwan[70] reported the presence of anthelmintic efficacy in *Melia azedarach*. Purified condensed tannins from *Danish legumes* were reported to kill nematode larvae *in vitro*[71]. The essential oil of *Ocimum sanctum* and eugenol, tested *in vitro*, showed potent anthelmintic activity in the *Caenorhabditis elegans* model[72]. Different solvent fractions of *Berlina grandiflora* and its major triterpenoid, betulinic acid showed anthelmintic activity against *C. elegans*[73]. Mølgaard[74] reported a number of Zimbabwean plants, *Acacia karroo*, *Cassia singueana*, *Ozoroa insignis*, *Vernonia amygdalina*, *Ximenia caffra* etc. to bear significant anthelmintic properties against *H. diminuta*, a tapeworm of zoonotic importance. Young pine apple fruit juice and the whole extract of coleus leaves and croton twigs showed *in vitro* anthelmintic activity against *H. nana* and *Aspiculuris tetraptera*[75]. The crude extracts of *Artemisia santonica*, *Albizzia lebbek* and *Inula helenium* showed promising anthelmintic efficacy against *A. lumbricoides*[76]. Singh and Nagaichi[77] evaluated the antiparasitic effects of ethyl alchohol

extract of *Ocimum sanctum* against *A. galli in vitro*. Dash *et al.*[78] tested *in vitro* anthelmintic activity of *Evolvulus alsinoides* extract against earthworm, *P. posthuma* and reported it to be better than piperazine citrate. The essential oil of *Ocimum gratissimum*, a tropical plant well known for its ethnoveterinary use, showed strong anthelmintic activity *in vitro* against *H. contortus*[79]. Ethanolic extract of *Evolvulus alsinoides* (Convolvulaceae) was observed to show more anthelmintic action as compared to piperrazine citrate[78].

Plants such as, *Adhatoda vasica*, *Nicotiana tabacum* and *Spigelia anthelmia* were reported to possess considerable anthelmintic activity against *H. contortus*[80-82]. The anthelmintic activity of ethanolic extract of *Melia azedarach* Linn. (Meliaceae) was found to be better against *T. solium* than that of piperazine phosphate[83]. The crude aqueous and methanol extracts of *Artemisia brevifolia* exhibited profound activity against *H. contortus in vitro*[84]. The woody plants, *Rubus fructicosus*, *Quercus robur* and *Corylus* showed remarkable anthelmintic activity when tested on 3rd-stage larvae (L_3) and adult worms of *Teladorsagia circumcincta*, *H. contortus* and *Trichostrongylus colubriformis*[85]. Hounzangbe-Adote *et al.*[86] reported the anthelmintic activity of *Zanthoxylum zanthoxyloides*, *Morinda lucida* and Newbouldia leaf extracts and *Carica papaya* seed extracts collected in Western Africa against different stages of *H. contortus*. In another study, *Z. zanthoxyloides*, *M. lucida*, *N. laevis* and *C. papaya* extracts induced a dose-dependent inhibition of egg hatching of *T. colubriformis*. These plant extracts also showed their effects against the infective larvae of *T. colubriformis*. In contrast, for adult worms, the effects were statistically significant only for *N. laevis* and *C. papaya*[87]. Fajimi and Taiwo[21] reported that *Nauclea latifola* possesses high anthelmintic efficacy against strongyle nematodes of small ruminants. Based on the results of ethnomedical survey in Northern Cote d'Ivoire, Koné *et al.*[88] made a pilot study on 79 plant species for their anthelmintic efficacy using *H. contortus* as the test parasite and found *Sclerocarya birrea*, *Lannea kerstingii*, *Aframomum alboviolaceum*, *Pericopsis laxiflora*, *Pseudocedrela kotschyi*, *Securidaca longepedunculata*, *Alchornea cordifolia*, *Anthostema senegalense*, *Ficus vallis-choudae*, *Ampelocissus grantiil*, *Vitellaria paradoxa* and *Hibiscus asper* to possess either significant larvicidal or ovicidal activity. *Cardiospermum halicacabum* extract when tested *in vitro* for its efficacy against L_3 of *Strongyloides stercoralis* showed reduction in the viability of larvae[89]. In a study by Hördegen *et al.*[90], Bromelain, the enzyme complex of the stem of *Ananas comosus* (Bromeliaceae), the ethanolic extracts of seeds of *Azadirachta indica* (Meliaceae), *Caesalpinia crista* (Caesalpiniaceae) and *Vernonia anthelmintica* (Asteraceae), and the ethanolic extracts of the whole plant of *Fumaria parviflora* (Papaveraceae) and of the fruit of *Embelia ribes* (Myrsinaceae) showed anthelmintic efficacy (up to 93%), relative to pyrantel tartrate against infective larvae of *H. contortus*. The methanol extracts of *Mentha piperita* and *Lantana camara* (leaves, stems and roots) exhibited considerable anthelmintic activity against *P. posthuma*[91]. The anthelmintic activity of the drupe extracts of *Melia azedarach* growing in Argentina was tested against tapeworms, hookworms, nodular worms and earthworms, and was reported to be better than the standards piperazine

phosphate and hexylresorcinol against tapeworms and hookworms, respectively[92]. *In vitro* anthelmintic activities of crude aqueous and hydro-alcoholic extracts of the seeds of *Croton macrostachyus* and *Ekebergia capensis* showed significant activity on the egg and adult of *H. contortus*[93]. *Trachyspermum ammi* seeds used locally in Pakistan as anthelmintic for worm control in sheep were evaluated for their ovicidal activity against *H. contortus* eggs and were reported to possess some anthelmintic properties[94]. The anthelmintic activity of *Croton zehntneri* and *Lippia sidoides* essential oils and their major constituents, anethole and thymol were determined by *in vitro* assays with the eggs and larvae of *H. contortus*[95]. The essential oils and their constituents prevented more than 98% of the *H. contortus* eggs from hatching at a concentration of 1.25 mg/ml and inhibited more than 90% of *H. contortus* larval development at a concentration of 10 mg/ml. Eguale *et al.*[96] reported that hydro-alcoholic extract of *Hedera helix* possesses better *in vitro* anthelmintic activity against adult *H. contortus* compared to aqueous extract. Yet in another study by Eguale *et al.*[97], it was reported that the hydro-alcoholic extract of the seeds of *Coriandrum sativum* showed better *in vitro* activity against adult *H. contortus* than the aqueous one. Nirmal *et al.*[98] reported that the ethyl acetate and petroleum ether extracts of *Pongamia glabra* seeds exhibit significant anthelmintic activity when tested against Indian adult earthworm, *P. posthuma*. Cysteine proteinases from papaya, pineapple and fig were reported to be substantially effective against three rodent gastrointestinal nematodes, *Heligmosomoides polygyrus*, *Trichuris muris* and *Protospirura muricola*[99]. López-Aroche[100] evaluated the anthelmintic activity of twenty plants from Mexico and found *Bursera copallifera*, *B. grandifolia*, *Lippia graveolens*, *Passiflora mexicana*, *Prosopis laevigata*, *Randia echinocarpa* and *Urtica dioica* to have anthelmintic properties against *H. contortus* unsheathed third stage infective larvae. Khadatkar *et al.101* reported noteworthy anthelmintic activity in *Clitoria tematea* extract against *P. posthuma*.

In recent years, Kataki[102] reported the anthelmintic activity of ethanolic extract of *Anana comosus* L. tender leaves using adult Indian earth worms. Similarly, the anthelmintic activity of *Eucalyptus staigeriana* essential oil has been well established using egg hatching test and the inhibition of larval development of *H. contortus*. Its *in vivo* anthelmintic effects were also noticed through fecal egg count reduction test in goats[103]. Marie-Magdeleine *et al.*[104] investigated the anthelmintic effects of aqueous, methanolic and dichloromethane extracts on four developmental stages of *H. contortus* using egg hatching assay, larval development, L_3 migration inhibition assay and adult worm motility assay and observed that the methanolic extract of plant leaves possesses significant efficacy against larval development. Several Cameroonian and Ghanian medicinal plants have been studied for their potential anthelmintic activity using *Onchocerca ochengi* and *C. elegans* as test parasites. Among the extracts used in this study, ethanolic extracts of *Anogeissus leiocarpus*, *Khaya senegalensis*, *Euphorbia hirta* and aqueous extracts from *Annona senegalensis* and *Parquetina nigrescens* have been observed to possess significant anthelmintic efficacy[105]. Anantha *et al.*[106] reported that ethanolic extract of *Aerva lanata* seeds and leaves bear better anticestodal activity than that of albendazole.

In a comparative study of anthelmintic activity of three plants, *Amaranthus spinosus*, *Amaranthus caudatus* and *Amaranthus viridis* L. (Amaranthaceae), used traditionally as vermicides, Ashok Kumar *et al.*[107] noticed a potent anthelmintic activity in these plants when compared to piperazine. *Smilax myosotiflora* extract, at 5 mg/ml of concentration, was reported to show a 100% mortality of third-stage *H. contort*us larvae of goats origin[108]. Aremu *et al.*[109] investigated the efficacy of ten South African medicinal plants against *C. elegans* and found that organic solvent extracts from *Cyathea dregei* (roots and leaves), *Felicia erigeroides* (leaves and stems), *Hypoxis colchicifolia* (leaves) and *Senna petersiana* (leaves) exhibit noteworthy anthelmintic activity. Marie-Magdeleine *et al.* [110] studied the *in vitro* effects of *Tabernaemontana citrifolia* fruit, leaf and root aqueous, methanolic and dichloromethane extracts using egg hatch assay, larval development assay, L_3 migration inhibition assay, and adult worm motility assay of *H. contortus*. Significant effects were observed for the different parts of *T. citrifolia* but with differences depending on the parasitic stage; the root gave the best result on egg hatching assay. Ethanolic and aqueous leaf extracts of *Pithecellobium dulce* were studied for their anthelmintic activity against *P. posthuma* and it was observed that the aqueous extract is more potent than the alcoholic extract even though both the extracts are endowed with significant anthelmintic property which was comparable with that of piperazine citrate[111]. Gunaselvi *et al.*[112] reported a very high degree of anthelmintic activity in the methanolic and aqueous extracts of fruits of *Solanum xanthocarpum* (Solanaceae). In another study, the chloroform methanol and crude tannin extracts of *Leucas indica* (L) showed very good activity. Paralysis and death time of crude tannins, isolated from methanol extract, were very close to standard drug Albendazole[113]. Wabo Pone *et al.*[114] recorded the nematicidal activity of extracts of *Canthium mannii* bark, used by traditional healers in Cameroon to cure intestinal helminthiasis, on different life-cycle stages of *Heligmosomoides polygyrus* (Nematoda, Heligmosomatidae). Sunilson *et al.*[115] studied the anthelmintic activity of various doses of aqueous extract of *Pongamia pinnata* Linn leaves against earthworms and found that there was no final recovery of worms treated with aqueous extract of plant. *Musa paradisiaca* leaves, used locally for worm control in sheep, were found to possess significant anthelmintic activity based on egg hatch test on nematode ova of sheep origin. On the basis of their study authors advocated further large scale pharmacological and toxological studies for their safer use in veterinary medicine[116]. The effects of condensed tannins extracted from five species of plants (*Lotus pedunculatus*, *Lotus corniculatus*, *Dorycnium pentaphyllum*, *Dorycnium rectum* and *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 cycles of nematodes[117]. The effects of acetone leaf extract and fractions of *Combretum molle* were investigated for potential anthelmintic efficacy using an egg hatch and larval development and viability assay against *H. contortus* of sheep origin. The efficacy of extracts was established as anthelmintic on the basis of inhibition of egg hatching and development of the larvae in a concentration-dependent manner[118]. Pawar *et al.*[119] reported the anthelmintic activity of ethanol and water extract

of whole plant *Gloriosa superba* Linn. (Liliaceae) using *Pheretima posthuma* as test worms. The anthelmintic properties of some tannin-rich Mediterranean plants namely, *Pistacia lentiscus*, *Quercus coccifera*, *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[120].

In many studies, the helminth parasites' tegument/cuticle has been ascertained as one of the principal target site for mode of action of synthetic and/or natural anthelmintic products[121-122]. It is in this background that several workers while investigating the putative anthelmintic efficacy of plants have also extended their studies to investigate the mode of action of plants with the help of scanning electron microscopy (SEM). The fresh-tuber extract of *Flemingia vestita* which was reported to bring about paralysis of *A. suum* under *in vitro* conditions showed wrinkles and cracks on lips and body cuticle following treatment with plant extract[123]. Vacuolization and pit formation was also recorded in *Artyfechinostomum sufrartyfex* and *F. buski* when treated *in vitro* with root tuber peel extract of *F. vestita*[124] (Roy and Tandon, 1996). In another study by Tandon *et al.*[125], exposure of *R. echinobothrida* to genistein, an active principle of *F. vestita*, caused spontaneous loss of movement of cestode parasite followed by structural alteration in its tegumental architecture. The isoflavones of *F. vestita* has been shown to alter carbohydrate metabolism and the activity of nitric oxide synthase leading to change in the concentration of cGMP in *R. echinobothrida* at paralytic time[126-127]. Roy and Tandon[19] reported *in vitro* anthelmintic activity as well as marked surface tegumental alternations in *F. buski* when treated with extract of *Alpinia nigra*. The extract-treated flukes manifested deformed body contours, particularly at the anterior sucker, with a shrunken and wrinkled surface tegument. The ventral papillae which have a distinct size and shape also showed deformity accompanied by deep scar formation at the base of each papilla. Roy[128] in another study on the morphology of *Orthocoelium dinniki* after treatment with *Spilanthes oleracea* extract revealed contraction and deformation of general tegumental surface and suckers with total disorganization and elongation of sensory papillae in the oral aperture region of parasite. *In vitro* treatment of *R. echinobothrida* to the extract of *Stephania glabra*, a folk lore anthelmintic plant in Meghalaya, showed pronounced disruption of its body tegument[129].

In vivo Activity of Traditional Anthelmintic Plants

A perusal of the literature reveals that a great variety of animal models and methods have also been commonly used to test the anthelmintic properties of plants that are used traditionally as vermicides. The anthelmintic efficacy of 'Diospyrol' from *Diospyros mollis*, a shrub known popularly as Ma-Klua in Thailand, has been reported using the hookworm, *Necator americanus* infections maintained in golden hamsters[130]. While, Maki and Yanagisawa[131] employed *Hymenolepis nana* - mice model to evaluate the anthelmintic effects of alcoholic extract from same plant. Ibrahim *et al.*[132] studied 18 plants traditionally used for the treatment of animal and human helminthiasis in Nigeria for

anthelmintic activity using the *Nippostrongylus* - rat model. The anthelmintic efficacies of *A. anthelmintica* and *A. lebbek* extracts were established following their screening in *H. diminuta* - rat model[133-134]. *Zingiber officinale* extract tested against experimentally induced *Setaria cervi* infections in rats showed significant antifilarial activity[135]. A high efficacy of *papaya latex* against experimental *Heligmosomoides polygyrus* infections has been reported by Satrija *et al.*[136] (1995). Ghosh *et al.*[137] reported the cestocidal efficacy of *Acacia auriculiformis* in *H. diminuta* - rat model. Bogh *et al.*[138] reported the anthelmintic efficacy of extracts of *Embelia schimperi* against *Echinostoma caproni*, *H. polygyrus* and *H. microstoma* in mice and also against *H. diminuta* in rats. The stem bark extract of *Berlinia grandiflora* has been reported to possess anthelmintic efficacy based on its testing against *N. brasiliensis* infections in albino rats[139]. The anthelmintic efficacy of *Leucana leucocephala* infusion has been ascertained using experimental *H. nana* infections in mice[140]. Githori *et al.*[141-142] evaluated the anthelmintic properties of *Albizia anthelmintica* extracts against *H. polygrus* infections in mice. The anthelmintic properties of Vimang, an aqueous extract of *Mangifera indica* family stem bark and mangiferin, the major polyphenol present in Vimang, were investigated in the experimentally induced *T. spiralis* infections in mice[143]. Bany *et al.*[144] reported the effect of Alchinal, a complex preparation of three substances - *Echinacea purpurea* extract, *Allium sativum* extract and cocoa, on the development of *T. spiralis* in mice. Quinolines that exhibited good activity *in vitro* have been studied *in vivo* on *T. spiralis* in mice model[145].

The anticestodal properties of few other plants namely, *Gladiolus gandavensis*, *Trifolium repens*, *Strobilanthes discolor* and *Butea minor* have been well ascertained using experimentally induced *H. diminuta* in albino rats[146,40-42]. Sukul *et al.*[147] reported the antelmintic potentials of plant-based homeopathic drugs such as Santonium 30 and podophyllum mother tincture against the muscle phase of *T. spiralis* in mice. Kozan *et al.*[148] reported the anthelmintic activity of some plants used in Turkish folk medicine in *Syphacia obvelata* and *Aspiculuris tetraptera* - mice models. The anthelmintic efficacy of plant cysteine proteinases of *Carica papaya* have been reported in mice infected with adult *Trichuris muris*, a rodent gastrointestinal nematode[149]. In another study, Stepek *et al.*[99] reported the anthelmintic effects of cysteine proteinases of *C. papaya* against *Protospirura muricola* in rodent model.

In vivo trials have also been carried out in domestic animals such as sheep, goats and cattle etc. for the evaluation of anthelmintic activity of various medicinal plants and/or their active principles. The efficacy of test substances in such studies has generally been adjudged on the basis of expulsion of worms from hosts[150-155] or reduction in the number of eggs per gram of feces (EPG) passed by the infected hosts following treatment with substances of plant origin[156]. The fruit rind powder of *Punica granatum* tested for its efficacy against gastrointestinal nematodes of sheep showed a remarkable decrease of 85% in the EPG counts in the treated groups. In a separate experiment the same fruit rind powder also showed considerable reduction in EPG in sheep naturally infected with mixed cestode species[157]. The glycosides and alkaloids of *P. granatum* have also shown

good anticestodal efficacy in goats[158]. Akhtar and Riffat[159] reported the anthelmintic activity of *Melia azedarach* against gastrointestinal nematodes of goats. *M. azedarach* was also reported to be capable of reducing the EPG in *A. galli* infected chickens[160]. Based on reduction in EPG, the whole plant powder of *Fumaria parviflora*, its water and ethanol extracts were also observed to be possessing significant anthelmintic efficacy against *Trichostrongylus*, *Haemonchus* and *Trichuris* infections in sheep[161]. In a similar manner, *Saussurea lappa* roots powder, its water and methanol extracts have also been found to possess anthelmintic effects in mixed infections of nematodes in sheep[162]. The efficacy of glycosides extracted from the roots of *S. lappa* was noted to be even better than aqueous or methanol extracts in sheep and buffalo-calves infected with mixed species of nematodes[163]. The powder of *C. crista* seeds and its water and methanol extracts have been reported to be possessing prominent anthelmintic effects against *Neoascaris vitulorum* infections in buffalo calves, *H. contortus* infections in sheep and *A. galli* infections in chickens[164-165]. Many more studies have been made in this direction which establishes the anthelmintic effects of plants such as, *Psoralea coylifolia*, *Peganum harmala*, *Morus alba* and *Lagenaria siceraria* through their testing in sheep infected either with nematode or cestode infections[166-169].

Taenil, a combination of Male fern (*Filix mass*), *M. phillipinensis*, Barbrung, Senna, Ajwain and Sounf @ 6 g/12 kg has been reported to be effective in expelling *Taenia* species and *Dipylidium caninum* in 56.7% of dogs treated[170]. Taenil @ 2 g/bird in feed was also found 100% effective in removing tapeworms of poultry within 1 week after treatment[171]. Various essential oils and eugenol isolated from *Ocimum sanctum* Linn. (Lamiaceae) have shown potent anthelmintic activity against *C. elegans*[72]. Martinez-Ortiz-de-Montellano *et al.*[172] studied the effect of a tropical tannin-rich plant, *Lysiloma latisiliquum* on adult populations of *H. contortus* in sheep and opined that a short-term consumption of *L. latisiliquum* can modulate directly the biology of adult *H. contortus* affecting the worm size and female fecundity. The anthelmintic effects of *Matricaria chamomilla* L. were established in experimental *Ostertagia ostertagi* experimental infection in lambs[173]. The anthelmintic activity of trillin and gracillin, the two bioactive compounds of *Dioscorea zingiberensis* C. H. Wright was investigated against *Dactylogyrus intermedius* (Monogenea) in goldfish under *in vivo* conditions. The study revealed that both trillin and gracillin are effective against *D. intermedius*, and the gracillin exhibits more interesting perspectives for the development of a candidate antiparasitic agent[174].

The methanol extract of rhizomes of *Paris polyphylla* and its two steroidal saponins compounds, dioscin and polyphyllin D were established to possess a promising *in vivo* anthelmintic activity against *Dactylogyrus intermedius*[175]. The anthelmintic study of five alkaloids (sanguinarine, cryptopine, â-allocryptopine, protopine and 6-methoxyl-dihydro-chelerythrine) from *Macleaya microcarpa* (Maxim) Fedde against *Dactylogyrus intermedius* in *Carassius auratus* provided an evidence that the plant extract, as well as the isolated compounds, especially sanguinarine, might be the potential plant-based medicines for the treatment of *D. intermedius* infection[174]. The orange oil emulsion has

been observed to show considerable anthelmintic activity against *H. contortus* maintained in gerbils (*Meriones unguiculatus*) and also in the natural ovine host[176]. The anthelmintic activity of *Balanites aegyptiaca* fruits has been reported using *T. spiralis* mouse model. In this study, oral administration 1,000 mg/kg b.wt. dose of extract for five successive days led to a marked reduction of migrating and encysted larval rate by 81.7% and 61.7%, respectively, in the muscular tissue[177].

Anthelmintic Activity of Plants/active Principles from Northeast India

The north east region of India is endowed with vast potentials of medicinal plants. The native tribes of the region have a good tradition of using several plants in their own traditional medicine system. A number of studies have been made in the recent past to identify and scientifically validate the efficacy of several of such plants which are frequently used as popular anthelmintics among natives of the region. *Flemingia vestita* Benth. (Fabaceae) is considered to be a lesser-known tuberous crop of north-east India. The fleshy tubers of the plant along with the peel are consumed by natives of Meghalaya and other north-eastern states 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 it credentials as an anthelmintic. Yadav and Tandon[123] reported its *in vitro* efficacy activity against *A. suum*. Its crude extract was also found to be quite effective against *Artyfechinostomum sufrartyfex* and *Fasciolopsis buski*. Vacuolization and pit formation was also recorded in these parasites when treated *in vitro* with its root-tuber peel extract[124]. In another study the exposure of *R. echinobothrida* to its active principle, genistein caused spontaneous loss of movement of cestode parasite followed by structural alteration in its tegumental architecture[125]. Genistein was found to alter the activity of some glycolytic enzymes and nitric oxide synthase of *R. echinobothrida*[126,178,127]. Roy and Tandon[179] 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 mode of action of plant. Crude extracts of *Alpinia nigra* was reported to possess significant flukicidal activity against *Fasciolopsis buski*[19]. The leaf extract of *Spilanthes oleracea*, a traditional anthelmintic plant of Meghalaya, was reported to possess significant activity against *Orthocoelium dinniki*[128]. It was reported to bring about surface alterations in worm's tegument. Temjenmongla and Yadav[180] studied the *in vitro* anticestodal efficacy of nine plants that are used in the indigenous system of medicine by Naga tribes in north-east India to cure intestinal-helminth parasitic 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 colebrookianum*, *Lasia spinosa* and *Centella asiatica* possess a moderate efficacy and *Curcuma longa*, *Cinnamomum cassia*, *Gynura angulosa*, *Lasia spinosa* (stem) and *Aloe vera* show a negligible degree of *in vitro*

anticestodal activity. Yadav and Tangpu[181] 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 *Hymenolepis diminuta*. The stem bark extract of *Acacia oxyphylla*, a traditional anthelmintic plant of Mizo tribes, have been demonstrated to exhibit profound anthelmintic effects on fowl cestode, *R. echinobothrida*[182]. The ethanolic extract from the root bark of *Millettia pachycarpa*, traditionally used as a remedy for gastrointestinal infections among the Mizo tribes of north-east India, was tested *in vitro* against *R. echinobothrida* and reported to be possessing significant anthelmintic property. Scar formation in the tegument surface of worm and alternation of several carbohydrate metabolism related enzymes were suggested as mode of action of plant crude extract[183]. Lalchhandama *et al.*[184] observed that *Milletia pachycarpa* brings out its anthelmintic activity by causing scar formation in worm's tegument surface and by altering several carbohydrate metabolism related enzymes in the extract treated worm. Dasgupta and Roy[185] reported the anthelmintic activity of *Acacia 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 be possessing *in vitro* efficacy against *F. buski*, *A. suum* and *R. echinobothrida* from domestic fowl. The alcoholic extract treated parasites revealed complete inactivation and flaccid paralysis that was followed by death at varying periods of time. The SEM observations revealed conspicuous deformity of the surface architecture in all the parasites exposed to the test plant extract[186].

Besides *in vitro* studies, lot of traditional anthelmintic plants of north-eastern region of India has also been studied for their putative anthelmintic activity employing various animal models. 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.*[40], 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 praziquantel. Tangpu *et al.*[187] studied the anticestodal efficacy of *Strobilanthes discolor* T. Anders (Acanthaceae), an ethnomedicanal plant of Naga tribes of north-east India, using *H. diminuta* -rat experimental model. On the basis of its effects on eggs per gram of feces (EPG) counts and percentage worm recovery rates, the authors concluded that extract bears remarkable anthelmintic activity against larval cestodes. While its efficacy was observed to be almost comparable with that of a standard drug, Praziquantel in adult cestode infections. Temjenmongla *et al.*[188] 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. The anticestodal efficacy of *Lasia spinosa* (L.) Thwaites (Araceae) leaves have also been well established

in experimentally induced *H. diminuta* infections in albino rats, where their extract have been recorded to reduce the faecal egg counts of treated animals by 83.2%[189]. Yadav and Temjenmongla[190] 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*. The 1600 mg/kg dose of 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 *Hymenolepiasis* in albino rats. Its leaf extract was observed to show better anthelmintic efficacy when compared with 5 mg/kg single dose of praziquantel[191]. The *Zanthoxylum rhetsa* DC (Rutaceae) leaf extract when tested in *H. diminuta*-rat animal model showed a high degree of efficacy against larval stage and a moderate level of efficacy against immature and adult stages of tapeworm[192].

CONCLUSION

For much of our past history, forages, plant parts or extracts have been used to combat worm infections, and in many parts of the world natural products are still in use as herbal remedies. In the recent years, there is an increasing awareness of the potential of natural products, which may lead to the development of much-needed new antiparasitic drugs. While many of the traditionally used anthelmintic plants have been evaluated for their putative anthelmintic activity, several other such plants still need to be documented and their efficacy is yet to be established under controlled experimentation. The use of untested traditional medicines will no doubt continue, there is need to distinguish between the efficacious and safe products and the ineffective and/or unsafe products to promote their use for the improvement of the health of people in developing countries. Since the active constituents of many of these products are poorly known, there is also a strong need to focus future studies on phytochemical examination of these efficacious plants. Further, the possible mode of actions of these products needs to be well established, so as to also exploit them from commercial point of view.

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