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# Role of Herbal Plants in Prevention and Treatment of Parasitic Diseases

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***Abstract:*** **All over the world infectious diseases are responsible for high morbidity and mortality. Incidences of emerging infectious diseases in human beings have increased within the recent past few years. From times immemorial, herbal medicines have been used for healing purposes. On the other hand, synthetic drugs are dangerous and have numerous side effects leading to loss of human health. At the same time a continuous consumption of synthetic drugs can lead to serious issues like development of drug resistance. As herbal medicines cause very few side effects so these are regaining much popularity. This article reviews role of herbal drugs in treatment of some parasitic diseases like Filariasis, Leishmaniasis, Amoebiasis, Teaniasis, Malaria and Ascariasis.**

***Index Terms*****: Herbal treatment for Malaria, Anti- Filarial herbs, Antimonials.**

## I. INTRODUCTION

Any infectious disease that is caused by a parasite is known as a parasitic disease. Most parasites are smart enough not to kill their host as eventually it would mean a threat to their own survival. At the same time parasitic infections are always accompanied by serious discomfort. Today parasitic diseases pose a humongous problem for entire mankind especially in tropical areas of the world. Parasites are causative agents of Leishmaniasis, Malaria, Lymphatic Filariasis, Schistosomiasis, Onchocerciasis, Amebiasis and Taeniasis. Some of them like Malaria, Leishmaniasis, Chagas disease pose even as deadly threat (Ndjonka *et al* 2013) to the patients. Social management and demographic conditions have a strong impact on distribution of parasitic diseases. The spread of parasitic diseases is also dependent upon population density and behavior, sanitation, sewage management, household types and hygiene. Tropical climates are continuous breeding grounds for mosquitoes and flies. In a tropical country like India conditions such as temperature, humidity and rainfall patterns promote the factors responsible for infectious diseases (Dhara *et al* 2013).

Today a large number of the Indian population is suffering from parasitic zoonotic diseases. Parasitic diseases are usually abundant in rural population and the chances of high occurrence of disease in the rural community are due to lack of awareness and illiteracy among communities (Dikid *et al* 2013).

From ancient times human beings have been dependent on nature and natural products to provide food and drugs for a large proportion of the world's population. Indian subcontinent has a long history for the use of herbal medication in treatment of various ailments. The ancient traditional system of medicines is maintained in India due to easy availability of herbal plants. The use of traditional medicinal plants is widely spread in China, India, Japan, Pakistan, Sri-Lanka and Thailand. China alone accounts for approximately 40% of total herbal medicinal consumption. India too, has a huge bio-diversification in plants and numerous of these have medicinal importance. The vastly diversified habitats and favorable climate in India is highly suitable for medicinal plants. India is known for its ancient herbal medicinal sciences which are based on long safe and continuous consumption of many herbal drugs to maintain good

Fig-1: *Cinchona officinalis* for treatment of Malaria.

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health. These systems include Ayurveda, Yoga, Unani etc. to cure health. Nearly 70% of Indian medicinal plants are found abundantly in the tropical forests of Eastern and Western Ghats, Chota Nagpur plateau, Aravali Vindhya range and Himalayas (Dar *et al* 2017). This review aims to give a compendious account of herbal medicinal plants used for treatment of parasitic diseases which are common in Indian sub-continent.

## II. MEDICINAL HERBS USED FOR TREATMENT OF PROTOZOAN DISEASES

Parasitic protozoan are one of the biggest health issues of present times and these infections are common in both developed and developing countries. Malaria is one of the biggest life-threatening diseases of present times. It is caused by a unicellular sporozoa of Plasmodium species which are transmitted by bites of infected Anopheles mosquitoes. Malaria is more common in tropical and subtropical countries including India. The four malarial species that infect humans are *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Among them, *P. falciparum* and *P. vivax* are more common. In India the predominant species of *Plasmodium* causing malaria is *vivax* (Anuvikar *et al* 2016). In 2017, 219 million new cases and ~435000 deaths were reported due to malaria worldwide. According to World Health Organization report almost 80% of the global malaria burden is borne by 15 countries of sub-Saharan Africa and Indian subcontinent. Five countries including India account for nearly half of all malaria cases. In 2017 nearly 80% of deaths caused by malaria were concentrated in 17 countries in India and African countries (WHO 2018).

Drugs available for malaria like chloroquine, mefloquine, primaquine, pyrimethamine, artemisinin derivatives and various amino alcohols etc. represent to be satisfactory treatment. Nevertheless, the biggest problem with these treatments is the emergence of drug resistant strains of plasmodium species. (Bahekar *et al* 2013). Several researches in this area have suggested that at least some anti-malarial drugs can also cause severe neurological problems, which raises the question for further use of these medications (Grabias *et al* 2016). Due to emergence of multidrug-resistant strains of Plasmodium and numerous side effects of synthetic anti-malarial drugs a need for novel and efficient anti-malarial drug, which would target either vector or parasite, became almost a necessity in recent years. Besides being eco-friendly, herbal drugs could be an appropriate vector control tool also. Since many of the synthetic mosquito killer chemicals are available in the market but they are harmful to the environment and have high cost as well, so finding an environment-friendly treatment could provide a relief from malarial vectors. Herbal drugs can be used as a remedy either alone or in combination. As water is a cheap solvent so it is the most preferred method to prepare herbal remedies. Decoction, concoction, boiling, infusion are some of the predominantly used methods for herbal remedy preparation.

For treatment of malaria apart from pharmacological treatment various herbal plants are being used since ancient time. The first drug to treat malaria came from *Cinchona officinalis* and related *Cinchona* species (Rubiaceae) (Fig-1). Cinchona bark contains various quinoline alkaloids such as quinine which is used to treat various stages of Plasmodium. It has been suggested that extract of *Allium sativum* when prepared in combination with some of the plants such as *Girardinia diversifolia*, *Lepidium sativum*, *Ruta chalepensis*, *Datura stramonium*, *Otostegia integrifolia*, *Ocimum basilicum*, *Ginger officinale* shows great curative effects .It has been found that *Allium sativum* can also be useful in combination with a group of plants such as *Artemisia afra*, *Ruta chalepensis*, *Lepidium sativum*, *Solanum dasyphyllum*, *Withania somnifera*, *Schinus molle* and *Sida schimperi* (Alebie *et al* 2017). Anti-plasmodial activity was observed in herbal extracts of traditional plants from south India. Methanolic extract of *Aegle marmelos*, ethyl acetate leaf extract of *Lantana camara*, *Leucas aspera*, *Mormordica charantia*, *Phyllanthus amarus* and *Piper nigrum* were shown to be effective against plasmodium (Kamraj *et al* 2012). Herbal products obtained from *Aloe schweinfurthii*, *Khaya senegalensis*, *Piliostigma thonningii* and *Cassia siamea* have potent activity against gametocytes of *P. falciparum* (Amoah *et al* 2015). A very potent plant species, *Artemisia annua* can even kill the multidrug-resistant strain of *P. falciparum* (Wink 2012).

Parasitic infections such as Trypanosomiasis, Leishmaniasis, Schistosomiasis, Lymphatic Filariasis and Onchocerciasis are very common in tropical areas (WHO 2018). All of these lead to major health concerns in tropical countries like Africa, South and Central America and the tropical regions of the Asian continent. Leishmaniasis is a protozoan parasitic disease caused by an intracellular parasite belonging to genus Leishmania. The disease is transmitted by the bite of an infected female Phlebotomus sand fly. Leishmaniasis has been classified into 3 types: Visceral Leishmaniasis (VL), Cutaneous Leishmaniasis (CL) and Mucocutaneous Leishmaniasis (ML). Of all these classes of Leishmaniasis, VL is fatal if left untreated (Tiwari *et al* 2017). The disease is mainly associated with low income population in Africa, Asia and Latin America. According to WHO out of 200 countries and territories, 97 countries are endemic for Leishmaniasis. 65 countries are endemic for both VL and CL. In 2016 seven countries Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan have reported more than 90% global VL cases (WHO 2017). Since vaccines are not available for Leishmaniasis so chemotherapy is the only option. Usually, pentavalent antimonials are the primary treatment against different forms of Leishmaniasis.

Antimonials are antimony-containing compounds which act by inhibiting glycolytic pathway or can also act directly on infected macrophages by evoking oxidative stress (Sundar *et al* 2001, Croft *et al* 2003). Antimonials have toxic side effects on liver and heart tissues. Drug Amphotericin B is one such drug

Fig-2: Stem bark of *Holarrhena antidysenteria*

used for Leishmaniasis treatment which targets specific plasma membrane steroids. This drug shows side effects like kidney failure, anaemia, fever and hypokalemia (Dorlo *et al* 2014). Lately, Miltefosine and paromomycin were introduced as effective oral drugs for treatment of VL. Nevertheless, long term therapy with these drugs can lead to drug resistance in parasite. In the case of VL, the immune response that is generated is mainly by the action of molecules like cytokines and lipid mediator Leukotriene B4. These molecules in turn activate phagocytic cells that start producing Nitric Oxide (NO). NO molecule plays a key role in killing of parasites In Leishmaniasis immune reaction is also associated with induction of the Th-1 response and production of interferon IFN-ϒ; very often this inflammatory reaction leads to tissue damage (Ghorbani *et al* 2018).

As VL is associated with immunological response so for its treatment one has to find a potent herbal drug which can target the immune system. In this context once again traditional medicines have proven effective as they can reduce the risk of chronic diseases by acting as antibiotics, antioxidants and immune-modulators. Several studies have described the effect of herbal medicines or their active compounds on immune cells or cytokine production. An *in vitro* study conducted on an axenic culture of *L. donovani* by using leaf extracts of medicinal plants showed an effective reduction in parasite viability. A study used ten different plants namely *Acorus calamus, Alstonia scholaris, Andrographis paniculata, Berberis aristata, Butea monosperma, Eclipta prostrata, Gloriosa superba, Juglans regia, Mesua ferrea, Tinospora cordifolia* for investigating the anti-Leishmania effect of these plants. Three of them named *Acorus calamus, Alstonias cholaris* and *Berberis aristata* showed significant anti-leishmanial activity (Sidana *et al* 2015). Mahanine a carbazole alkaloid isolated from an Indian medicinal plant *Murraya koenigii*, induced apoptosis in *L. donovani* through phosphatidyl serine externalization, DNA fragmentation and cell cycle arrest. Leishmania-infected macrophages exhibit anti-amastigote activity through ROS generation when treated with Mahanine (Roy *et al* 2017). Leaf extract of *Cedrusdeodara* in different organic solvents has also been tested on Leishmania parasites and the extract made in benzene showed strong anti-leishmanial and immunomodulatory effects (Narayan *et al* 2017).

Non-flagellated protozoan parasite *Entamoeba histolytica* causes Amoebiasis, which is an infection of the large intestine. These parasites enter through the mouth and settle in the large intestine. Infection caused by *E. histolytica* could be asymptomatic, but it can lead to the development of severe infections like amoebic colitis and amebic liver abscesses. These parasites live in the large intestine so they are also passed through faeces and contaminate the soil and water supply. These infections frequently occur in the area of poor sanitation or places where human faeces are used as fertilizers. The highest burden of amoebic infection is prevalent in the developing countries of tropics and subtropics where people are not aware about sanitation and personal hygiene (Shirley *et al* 2018). Amebic colitis caused by *E. histolytica* is a leading cause of diarrhea which is approximately killing more than 55000 people each year (Lozano *et al* 2012). Amoebiasis is quite prevalent in developing countries of central and South America, Africa and Asia (Gunther *et al* 2011). The infection is more frequent in travelers who are returning from endemic countries (Cordel *et al* 2013). To assess true prevalence of amoebiasis a cross sectional study has been performed in selected North-Eastern states of India. This study was based on DNA screening techniques followed by PCR assay, which showed presence of *E. histolytica* in 13.7% of the faecal samples (Nath *et al* 2015).

The available drugs for treatment of amoebiasis are Metronidazole and Tinidazole, both these are highly effective but Metronidazole is more effective in clearing parasites (Gonzales *et al* 2009). Nevertheless, numerous side effects associated with amebicidal drugs include nausea, headache, anorexia, peripheral neuropathy and disulfiram-like reaction with alcohol (Rossignol *et al* 2007). Some herbal plants like *Alpinia galanga*, *Barleria lupulina, Boesenbergia pandurata, Piper betle* and *Piper chaba* were shown to produce significant anti-amoebic results and have been classified as active i.e. with IC 50 less than 100µg/ml. Some plants such as *Murraya paniculata* and *Zingiber zerumbet* were classified as moderately active and having slightly higher IC50 in comparison to above mentioned plants (Subhadhirasakul *et al* 2006). Kutajarishta a polyherbal drug was shown to be remarkably effective in treatment of amoebiasis. Kutajarishta is the main ingredient of bark of *Holarrhena antidysenteric* (Fig-2) which is also been prescribed by Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy), India to patients of amoebic dysentery. Kutajarishta is helpful in other disorders like fever, indigestion and malabsorption syndrome (Garg *et al* 2008). A summary of herbal plants having anti-protozoal activities is provided in Table-I.

## III. MEDICINAL HERBS USED FOR TREATMENT OF HELMINTH DISEASES

Additionally, Lymphatic Filariasis (LF) is one of the major global health problems affecting 120 million people in 72 countries. LF is a vector-borne infectious tropical disease caused by nematodes parasitic worms *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. The infection spreads through the bites of mosquitoe species like Culex, Anopheles, Aedes and Mansonia (Lourens *et al* 2019). These parasites enter in a new host as larvae, which swim to the host's lymph nodes in legs and genitals later on the young ones moult and mature into adults. When these worms die, they trigger intense inflammation, blocking the flow of lymph, which accumulates under the skin and causes limbs and groins to swell to gigantic proportions. The Global program to Eliminate Lymphatic Filariasis (GPELF) initiated by WHO aims to stop the spread of infection and alleviate suffering among patients. WHO has recommended drugs such as Diethylcarbamazine (DEC), Albendazole and Ivermectin under the mass drugs administration (MDA) program for LF treatment (Lourens *et al* 2019, WHO). Although these drugs are effective against microfilariae stage but are ineffective in killing adult worms. Besides this, these drugs also show side effects such as mild itching to distress, cough and syncope. In some patients, few kinds of physiological changes such as fever, tachycardia, tachypnoea and hypertension have also been observed (Behera *et al* 2018). Albendazole and Ivermectin are two efficient drugs in removal of microfilariae stage, but side effects associated with them compel for finding newer treatment modalities. Major side effects associated with Ivermectin include fever, myalgia, headache, sore throat, and cough. These symptoms are usually more prevalent in individuals with higher microfilaremic levels. Ivermectin acts via nervous system so manifestations linked with neurotoxicity cannot be ignored (Ménez *et al* 2012). Albendazole in patients undergoing LF treatment may cause abdominal cramps, headache, sore throat and cough frequently (Babu *et al* 2006). It can be reiterated that none of the anti-filarial drugs can act on the adult stage of filarial parasites, which remain unaffected in their hosts for several years.

Howbeit, Anti-filarial activity has been reported in 25 plants of Fabaceae, Asteraceae and Euphorbiaceae families. The study performed on *Setaria digitata* reported macrofilaricidal activity of *Cassia occidentalis*, *Oldenlandia herbacea* and *Sida acuta*. Among them, *O. herbacea* has been shown to be a potential macrofilaricidal agent. This study has been performed by using methanolic extract of *O. herbacea* plant with solution concentration 1, 5 and 10 mg/ml (Bahera *et al* 2018). The anti-filarial activity of *Butea monosperma* had been observed by exploring it against *Setaria cervi* along with antibiotic ciprofloxacin. Ethanolic extract of *Butea monosperma* was shown to have significant anti-filarial effects (Radhika *et al* 2014). *Piper betel* belonging to the Piperaceae family has been reported to have both anti-filarial and anti-leishmanial activity. So for observing the anti-filarial effects, experiments have been conducted on *Brugia malayi* infected BALB/C mice using methanolic leaf extract and its n-hexane, chloroform, n-butanol fractions of female *P. betel* plant ranging between 0.3-500 mg/kg of body weight (Singh *et al* 2009). According to Singh *et al* 2009 the methanolic extract and n-hexane fraction of *P. betel* showed significant effects in the enhancement of humoral and cell-mediated immunity. A remarkable immunomodulatory property was observed with methanolic extract demonstrating mixed type-1 and type-2 cytokine responses. The alkaloid, saponin, and flavonoids present in the roots of the same plant exhibited the anti-filarial activity as well. The herbal root extract of *Vitex negundo* and leaf extract of *Aegle marmelos* at concentration 100ng/ml showed complete loss of motility of *B. malayi* microfilarae after 48 hours of incubation (Sahare *et al* 2008).

Table I. Herbal plants having Anti-protozoal activities

| Plant name | Effective part | Regions of abundance | Target parasite |
|---|---|---|---|
| *Artemisia annua* | Whole Plant | Himalayan region | *P. falciparum* |
| *Cassia siamea* | Leaves | Tropical and subtropical regions of the world | *P. falciparum, P. berghei* |
| *Alstonia scholaris* | Leaves | Southeast Asia countries | Promastigotes form of *L. donovani* |
| *Berberis aristata* | Leaves | Himalayan region | Promastigotes form of *L. donovani* |
| *Butea monosperma* | Flower | Indian Subcontinent and Southeast Asia | Promastigotes form of *L. donovani* |
| *Eclipta prostrata* | Whole plant | Tropical and subtropical continents | Promastigotes form of *L. donovani* |
| *Allium sativum* | Bulbs | Central Asia and India | *E. histolytica* |

A herbal plant with antifilarial activity *Streblus asper* (Siamese rough bush, a traditional medicinal plant) has been studied in both conditions i.e. *in vivo* and *in vitro*. *S. asper* was found to be effective in filarial lymphedema treatment. *S. asper* decoction was named as filacid which was shown to be very efficient as compared to other plants such as *Crataeva nurvala*, *Argyreia nervosa* and *Butea monosperma* (Murthy *et al* 2011). Leaf extracts of *Mallotus phillippensis* and *Senecio nudicaulis* prepared in alcohol and water showed efficacious results in inhibiting the movement of the nerve-muscle preparations of *Setaria cervi*. Aqueous extract preparation of *Mallotus*

Fig-3: Flower and leaves of *Lippianodiflora* for Ascariasis treatment

*phillippensis* and *Senecio nudicaulis* blocks the stimulatory response of acetylcholine on whole worm movement (Singh *et al* 1997).

Taeniasis is an intestinal infection caused by adult tapeworms. Major species causing these infections include *Taenia solium* (pork tapeworm), *T. saginata* (beef tapeworm) and *T. asiatica* (pork tapeworm). Taeniasis/ Cysticercosis is majorly associated with people living in developing countries of Africa, Asia and Latin America (Garcia *et al* 2003). Infection caused by *T. solium* is widely distributed in economically low or middle-income countries, where health awareness is less. Taeniasis infection has been spread in human population through consumption of raw or undercooked or cyst infected pork. *T. saginata* has no major impact on human health while *T. solium* leads to Taeniasis and its severe form i.e. neurocysticercosis (https://www.who.int/news-room/fact-sheets/detail/taeniasis/cysticercosis). *T solium* infection can lead to tissue infection with the larval stage of the pork tapeworm forming cysts in tissue, this condition is known as cysticercosis. Neurocysticercosis is the most severe form of cysticercosis when larval stages of *T. solium* enter into various organs including central nervous system (CNS). Neurocysticercosis (NCC) is associated with epilepsy and a recent review states that 31.5% of epilepsy cases could be due to NCC in endemic settings. The WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) has estimated that around 2.8 million disability-adjusted life-years could be attributed to NCC associated epilepsy (Dixon *et al* 2018). Anti-helminthic drugs such as Praziquantel and Niclosamide are available for the treatment. Although, Praziquantel shows efficient result but on the other hand, it shows serious epileptic seizures or convulsions as well (Pawlowski *et al* 2005).

In a study, it was implicated that treatment with Areca nut extract and Pumpkin seeds might represent a good cure against taeniasis. In China the individual effect of pumpkin seed and areca nut was studied and a positive result in a community of patients with taeniasis was observed. The synergistic effects of these two have shown complete elimination of tapeworm in a mean time of 2 hours (Li *et al* 2012). Later studies showed root oil *Hedychium coronarium (*Zingiberaceae*)* and *H. spicatum (*Zingiberaceae*)* had better effects than synthetic anti-helminthic drugs like piperazine phosphate against tapeworms (Tandon *et al* 2011). Another study reported the case of a 43-year-old Tibetan woman who took the treatment of pumpkin seeds and was cured (Ito *et al* 2013). A toxicological study was performed on rats to assess the toxicity of *Glinus lotoides* which is traditionally used to treat taeniasis/tapeworm infections in Ethopia (Demma *et al* 2007). This study showed that there was no toxicity associated with *Glinus lotoides* extracts and it could be further evaluated for clinical trials.

Helminthic parasite *Ascaris lumbricoides*, a roundworm, causes infection in the small intestine. Ascariasis is a widely distributed infection around the world and ~1 billion people in the world are infected with *Ascaris lumbricoides* causing death of more than 60,000 people annually. It mostly affects populations living in tropical and subtropical countries around the world and it is most common in Sub-Saharan Africa, Latin America, China, and East Asia (Fahim *et al* 2018, Darlington *et al* 2018). Ascariasis infection is most common at places where sanitation is poor and the infection spreads by consuming unhygienic food and water. Infection is also spread in human through accidentally ingesting eggs of *A. lubricoides*, which are found in the soil contaminated with human faeces or on improperly cooked food having soil contamination. Children easily become infected while playing in contaminated soil.

Plant extracts obtained from *Clausena anisata*, *Zanthoxylum zanthoxyloides* and *Punica granatum* were shown to be having potent anti-Ascariasis activities. To observe anti-Ascariasis activity an *in vitro* study was performed on *Ascaris suum*, a swine parasite showing resemblance with *A. lumbricoides* (Williams *et al* 2016). An *in vitro* study was conducted to study the anthelmintic action of *Lippiano diflora*; where in alcoholic extract of *L. diflora* (Fig-3) was used against human *Ascaris lumbricoides* (Senthilkumar *et al* 2018). Extracts prepared from *Clausena anisata, Zanthoxylum zanthoxyloides* and *Punica granatum* exhibited potent anthelminthic activity against *A. suum* at concentrations of 74, 97 and 164 µg/mL, respectively (Williams *et al* 2016).

A sesquiterpene lactone named Santonin isolated from *Artemisia santonica* was effective in expulsion of *A. lumbricoides*. Though, it is also associated with toxic side effects, which could be overcome by synthetic drug derivatives of benzimidazole. Another secondary metabolite isolated from *Chenopodium ambrosioides* called as Ascoridole is known for their anti-ascariasis properties (Romero-Benavides *et al* 2017). Several other herbal plants have been used in control and elimination of intestinal worms like *Ricinus communis*, *Juglans nigra*, *Artemisia vulgaris, Matricaria chamomilla*, *Dryopteris filixmas*, *Syzygium aromaticum (*Bahmani *et al* 2014*).*

## IV. SECONDARY METABOLITES AS ACTIVE CONSTITUENTS

It has been seen that the active constituents of plants having therapeutic properties are mostly products of secondary metabolic pathways such as shikimate, phenyl-propanoid pathway, acetate-mevalonate and glucosinolate pathways to name a few. Earlier secondary metabolites (SM) were considered as waste products of plant metabolism but now it has been well established that SM participate in numerous plant functions. SM secreted by plants can have different functional groups like aldehyde and SH groups, epoxide double bonds with enon configuration and sometimes triple bonds. These specific groups of secondary metabolites bind with either proteins or DNA and modulate their bioactivities (Wink, 2012). SM can act on specific proteins, such as a neuroreceptor, an enzyme, ion channels and cytoskeleton elements thereby modulating the function of these proteins. The biochemical nature of secondary metabolites is very often alkaloid, terpenoids, polysaccharides and peptides. Tarpenes are a class of made up of C-5 isoprene units. Monoterpenes, Sesquiterpenes, Diterpenes etc. are subdivisions of terpenes. As terpenes are lipophilic in nature, so they can easily interact with biomembranes and related proteins. Terpenes control the activity of cells by regulating efflux of ions metabolites and cell leakage. Sesquiterpenes lactones are abundant in plant families such as Asteraceae, Apiaceae, Magnoliaceae etc. Sesquiterpene lactones bind with glutathione through SH group and affect the regulation of reactive oxygen species in cells resulting in depletion of glutathione content in liver (Wink, 2015). Alkaloids are a class of naturally occurring nitrogen containing secondary metabolites and are found widely distributed among plant kingdom. Alkaloids contain one or more basic nitrogen atoms either in ring structure or inside chains. Alkaloids perform various physiological functions in living organism. Primary molecular targets of alkaloids are neuro-receptors. Some alkaloids are mutagenic in nature, and they function by alkylating DNA. Some of them also interfere with enzymes like telomerases, topoisomerases and protein biosynthesis eventually culminating in apoptosis. Cyanogenic glucosides are typical examples of nitrogen containing SM. They are abundantly found in seeds, leaves and roots of plant families like Caprifoliaceae, Euphorbiaceae, Fabaceae, Juncaginaceae, Linaceae. Cyanogenic glycosides are split into sugar and nitrile moiety after they come in contact of β-Glucosides. This split generates HCN, which upon further hydrolysis functions as an inhibitor of mitochondrial respiration.

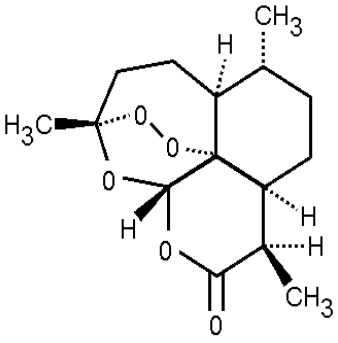


Fig-4: Structure of Artemisinin

## V. MODE OF ACTION OF ARTEMISININ

Artemisinin (ART) is a Chinese herbal drug derived from *Artemisia annua* also known as sweet wormwood plant. Chemically Artemisinin and its derivatives are sesquiterpene lactone trioxanes as a pharmacophore (Fig-4). Trioxanes of ART contain endoperoxide which is responsible for anti-malarial activity. ART is considered as a pro-drug which is activated by binding either with iron ($Fe^{2+}$) or haem group obtained after digestion of hemoglobin by malarial parasites (Cui *et al* 2009). During erythrocytic stage in parasitic lifecycle, it consumes a large amount of hemoglobin which generates free iron and haem post digestion. In infected erythrocytes excess heme is converted to hematin which shows toxic effects to parasite by causing

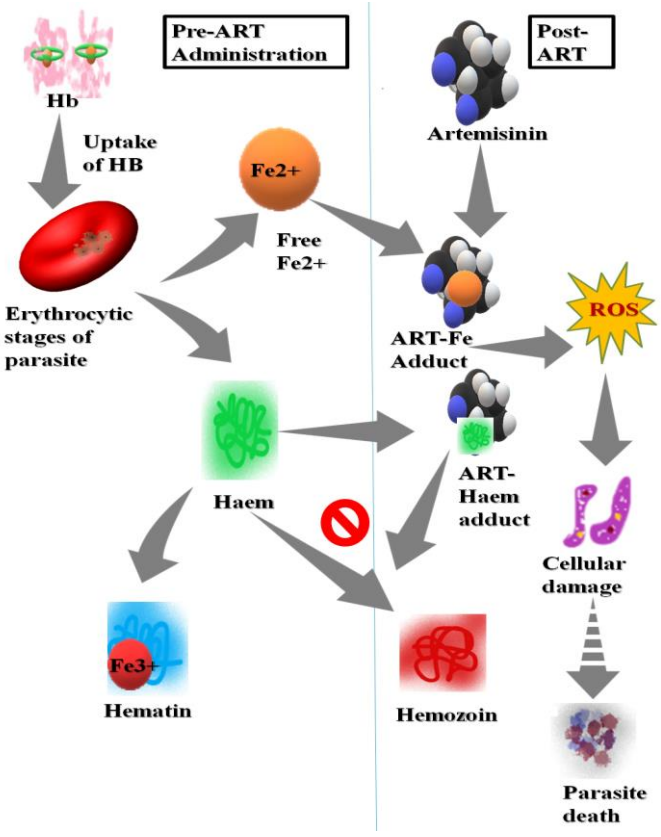


Fig-5: Mode of action of Artemisinin: During erythrocytic stage of parasite, it consumes large amount of Hb and generates free ferrous ions and haem as a digestive product. ART gets activated by binding either with free $Fe^{2+}$ ion or by haem. ART-ferrous or ART-haem adducts interrupt hemozoin formation or they could cause generation of free radicals ultimately leading to death of parasites by causing cellular damage.

oxidative damage. Hence the parasites evolved a self-defense mechanism to overcome this hematin mediated toxicity. Malarial parasites can coverts these haem molecules into hemozoin pigment which is not toxic to the parasites.

Likewise, it has been shown that there is a correlation between binding affinity of ART with heme and anti-malarial properties of ART. ART activation is dependent on heme rich environment, so active hemoglobin is an activator as well as a target for ART. Activated ART inhibits hemozoin formation by alkylating haem (Fig-5). ART generates ROS which further modulates oxidative stress in parasites thereby reducing antioxidant and glutathione (GSH) level in parasite. Reactive oxygen species generated by ART cause cellular damage ultimately leading to the death of the parasite (Wang *et al* 2019).

## CONCLUSION

Since ancient time traditional herbal medicinal plants have been a part of human life. India has a huge plant bio-diversity and is known worldwide for its rich flora of herbal and medicinal plants. Treatment with herbal drugs is easily available and cost effective for developing countries. It is worthwhile to mention here that herbal drugs are the best affordable way to overcome infectious diseases. From the perspective of side effects associated with synthetic drugs, herbal drugs represent a better cure of human diseases. Lately, parasitic diseases have become major health problems especially in developing countries and an indiscriminate use of synthetic drugs has led to development of resistance in parasites. In this article we have attempted to present a review of the medicinal plants used for treatment of parasitic diseases in the Indian sub-continent.

Anti-helminthic plants like *Butea monosperma* and *Piper betel* have great efficacy against helminthic parasites whereas some herbal plants like *Andrographis paniculata* have potent anti-leishmanial effects. Artimisinin, which is derived from *Artimisia annua* is one of the most effective herbal drugs. The active constituent of majority of the medicinal compounds isolated from plants species are known to be secondary metabolites. The exact mechanism underlying the mode of action of herbal compounds is not clearly understood and till date only mechanism that has been proposed is for Artimisinin. Further exploration of the medicinal plants discussed in this review may provide leads to development of new drugs and better approaches for treatment of parasitic diseases.

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