The most common herbal medicines affecting Sarcomastigophora branches: a review study

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1. Introduction

Over 450 million people are infected each year due to complications of parasitic diseases. Indicators show that parasitic diseases cause annual mortality of more than 200 thousand people. Currently many drugs used to treat parasitic diseases are expensive, toxic, with side effects and drug resistance. Medicinal plants have been shown to represent natural source of cheap drugs with low toxicity. In this review article, the most common and most effective herbal medicines on pathogenic protozoan Sarcomastigophora branches such as *Trypanosoma*, *Leishmania*, *Amoeba*, *Trichomonas* and *Giardia* were reviewed. The recently published papers about different drugs as well as herbal medicines as alternative for synthetic drugs were searched using scientific sites such as Medline, PubMed and Google Scholar. The used terms included: Medicinal plants, herbal medicine, protozoa, *Trypanosoma*, Sarcomastigophora branches, *Leishmania*, *Amoeba*, *Trichomonas* or *Giardia*.

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Mastigophora. Sarcodina (amoeba) comprise a large group of protozoa, most of their lives are free-living; some are parasitic and some are both parasitic and free-living. Some amoeba can be pathogenic to man, and some live as a commensal in humans and are harmless to humans. Several species of amoeba have been identified as human parasites such as Entamoeba histolytica (E. histolytica), Entamoeba dispar, Entamoeba moshkovskii, Entamoeba hartmanni, Entamoeba coli, Entamoeba gingivalis, Endolimax nana and Iodamoeba butschli. Flagellates are protozoa which are classified under the category of Mastigophora. Some flagellates are free-living and some are parasitic in vertebrates and invertebrates and may impose severe complications. Almost all vertebrates serve as hosts of intestinal flagellates. The parasitic flagellates in blood and tissue of humans and other mammals can belong to Trypanosomatida and genus of Leishmania and Trypanosoma[1]. According to the World Health Organization (WHO), 3.5 billion people are annually infected with parasites, from them 450 million ones get severe complications. More than 200 thousand deaths annually due to parasitic infection have been reported[3]. In this review, we tried to introduce the common herbal medicines and chemicals affecting pathogenic protozoa category including Sarcomastigophora, Trypanosoma, Leishmania, Amoeba, Trichomonas and Giardia.

2. Anti–sarcomastigophora branches (Trypanosoma, Leishmania, Amoeba, Trichomonas and Giardia)

2.1. Leishmania and leishmaniasis

Leishmania is a genus of trypanosomatid protozoa and is the parasite responsible for the disease leishmaniasis. It is spread through sandflies of the genus Phlebotomus in the old world, and of the genus Lutzomyia in the new world. At least 93 sandfly species are proven or probable Leishmania vectors worldwide. Their primary hosts are vertebrates; Leishmania commonly infects hyraxes, canids, rodents, and humans. Leishmaniasis or leishmaniosis is a disease caused by protozoan parasites of the genus Leishmania and spread by the bite of certain types of sandflies. The disease can present in three main ways as: cutaneous leishmaniasis, mucocutaneous leishmaniasis and visceral leishmaniasis[1], WHO has listed leishmaniasis in rows of six major parasitic diseases in tropical areas of the world. These diseases, including zoonotic disease are endemic in 88 countries and exist in four continents. After malaria leishmaniasis is considered as the most important tropical disease. About 12 million people are currently infected in some 98 countries. It is estimated that 350 million people live in areas with the risk of disease. It has been shown that 60 patients die from 500 cases of visceral leishmaniasis. More than 90% cases of visceral leishmaniasis are in Bangladesh, Brazil, India, Nepal, Sudan and more than 90% of cutaneous leishmaniasis are in Iran, Nepal, Syria, Saudi Arabia, Afghanistan and Peru[2]. Cutaneous leishmaniasis is one of the most common diseases among humans and animals in parts of the world that is caused by several species of Leishmania and is considered as a public health problem in more than 88 countries[3].

Visceral leishmaniasis, also known as kala–azar, black fever and dum-dum fever, is the most severe form of leishmaniasis. Leishmaniasis is the second–largest parasitic killer in the world (after malaria), responsible for an estimated 500,000 infections each year worldwide. The parasite migrates to the internal organs such as liver, spleen (hence ‘visceral’), and bone marrow, and, if left untreated, will always result in the death of the host. Signs and symptoms include fever, weight loss, mucosal ulcers, fatigue, anemia, and substantial swelling of the liver and spleen. Of particular concern, according to the WHO, is the emerging problem of HIV/visceral leishmaniasis co-infection[4].

2.2. Chemical and herbal anti–leishmaniasis drugs

The traditional treatment of leishmaniasis is with pentavalent antimonials such as sodium stibogluconate and meglumine antimoniate. Resistance is now common in India, and rates of resistance have been shown to be as high as 60% in parts of Bihar, India. These medications are antimonials but, long–term injections to 28 d for the variable efficacy against visceral leishmaniasis, skin appearance, and resistance against it, limit their consumption. Other medications used to treat leishmaniasis include pentamidine, miltefosine, amphotericin B and so on. Amphotericin B is a pollin antibiotic for the treatment of antibiotic resistance. This drug has a good effect on Leishmania donovani (L. donovani) (visceral leishmaniasis), but the limitations are its toxicity and other restrictions that require slow intravenous infusion over four hours. Use of pentamidine is common because its toxicity is low. The most important achievement of effective oral treatment for visceral leishmaniasis is treatment with miltefosine which is chemically a derivative of alkylphosphocholine compounds that originally developed as an anticancer drug in the late 1980s[5]. After reveal of its antileishmaniasis effect, the drug became the first (and still the only prescribed) oral drug in the treatment of leishmaniasis[6]. The mechanism of treatment of leishmaniasis with miltefosine is that the drug impairs metabolism of alkyl–linked phospholipid and glycolipid and glycoprotein biosynthesis[7]. Studies have shown that miltefosine cause cell death in all forms of leishmaniasis. Baradaran et al. suggested against L. donovani by treatment with a combination of several techniques that include propidium iodide staining and DNA fragmentation assay[8]. In another study, Amini et al.
studied the effect of miltefosine on L. donovani (LD-As20) which became arsenate-resistant promastigotes[9]. Their studies have shown that miltefosine induces programmed cell death in LD-As20 in a time-dependent manner by cell shrinkage; serine and phosphatidylycholine data transfer is determined by DNA fragmentation. Miltefosine treatment leads to loss of mitochondrial membrane potential and release of cytochrome C with subsequent activation of cellular proteases. So this study showed the death of L. donovani, resistant to arsenate, by miltefosine. Because in recent years miltefosine is used in clinical trials as an anti-Leishmania therapy, to better understand the mechanisms regulating cell death for the design of new therapeutic strategies against Leishmania. Today, several factors such as drug toxicity, method of administration, cost of drug and drug resistance in Leishmania spp. have caused some limitations to treat leishmaniasis. Hence, the preparation of new effective drugs with low side effects and toxicity, and affordable price is needed. The traditional medicinal plants have been shown to be effective and inexpensive, and are currently used for the treatment of various infectious diseases such as viral[10], bacterial and parasitic infections complications[11-14], as well as non-infectious diseases such as cancer[15,16], diabetes[8,17], atherosclerosis[18,19], cardiovascular and Alzheimer diseases and complications[20-23]. In comparison to synthetic drugs, the herbal medicines usually have less toxic or side effects[24,25].

Nasri and his colleagues focused on natural products with activity against Leishmania[26]. Compounds isolated from plants and microorganisms have suitable chemical groups such as alkaloids, flavonoids, terpenes, steroids, lactones, quinine and lignans which have positive effects on the parasites. More recent studies have emphasized on the evaluation of medicinal plants used for the discovery of safe and effective drugs[25].

2.3. Amoeba and amoebiasis

Amoebiasis or amebiasis, refer to infection caused by the amoeba E. histolytica. Invasion of the intestinal lining causes amoebic dysentery or amoebic colitis[24]. It is estimated that about 50 million infected with E. histolytica and around 40 000 to 100 000 deaths occur annually worldwide, it is considered as one of the most important human pathogenic protozoa[27-29]. Amoebiasis can cause more than 100 thousand deaths per year, which is regarded as a fatal parasitic disease after malaria and schistosomiasis[30]. The amoeba infection is asymptomatic in 80% of cases[31]. Infants who are not breastfed, pregnant women, children with poor nutrition, nursing and mental retardation as well as people with immunodeficiency conditions are high risk groups of amoeba E. histolytica infection[32]. E. histolytica invades the colon, but in some cases beyond the intestine and the liver, lung and brain which can show signs of severe and fatal condition[33,34].

2.4. Chemical and herbal anti-amoebiasis drugs

Development of anti-amoebiasis new drugs and vaccines is still in its early stages and the dream seems far away. Future development of resistance to drugs may seriously affect the amoebiasis control[35,36]. Metronidazole the drug of choice and other compounds derived from nitroimidazole like tinidazole, secnidazole and ornidazole are equally effective. Diloxanide furatoate, diiodohydroxyquinoline, paromomycin, emetine and chloroquine as well as alternative medicines are used. Metronidazole, tinidazole and other 5–Nitromidazole that kill the trophozoite with changes in organelles of amoeba protoplasm, are ineffective in treating the cyst. Plant–antiparasitic possessing chloroalkyl may act by inhibiting DNA synthesis. Dehydroemetine, emetine and metronidazole affect on amoeba in intestinal lumen wall but not in the intestinal lumen.

Diloxanide furatoate, iodoquinol and paromomycin affect on amoeba in the intestinal lumen. Tetracycline inhibits bacterial growth in the intestinal wall and lumen. Effect of metronidazole on the intestinal wall and the lumen of the affected individual has a 50% failure rate because it needs to strengthen its action to a luminal amebiasis[37,38]. Prevention is essential and includes hand washing, proper food handling and boiling water which are questionable to 55 °C. Investigations on the effects of various plants in Africa have shown that ingestion of fresh papaya seeds can help prevent amoebiasis. Two tablespoons of fresh papaya seeds twice a week may help reduce the incidence[39-42]. Review of plant species assessed in vitro for antibacterial activity against Plasmodium or amoebiasis has also been published[9]. Chemically control of worms with advanced management is an important control strategy around the world. Increased resistance to the drug is a serious problem leading to the search for medicinal plants with antimicrobial activity[43]. Several herbs from traditional medicines are used as alternative for control of intestinal worms. Some common plants are used by different cultures for the control and elimination of intestinal worms include: castor, black walnut, wormwood, Artemisia vulgaris, cloves, chamomile and herbal black seed, and Dryopteris filix-mas L. Although these plants have anthelmintic effects, they should not be used without correct dosage for humans, because they are toxic and dangerous[24].

2.5. Trypanosoma and trypanosomiasis

Trypanosoma is a genus of kinetoplastids and class Kinetoplastida which is a monophyletic group of unicellular parasitic flagellate protozoa. The name is derived from the Greek trypano (borer) and soma (body) because of their corkscrew-like motion. All trypanosomes are
heteroxenous requiring more than one obligatory host to complete life cycle and most are transmitted via a vector. The majority of species are transmitted by blood-feeding invertebrates, but there are different mechanisms among the varying species. In an invertebrate host they are generally found in the intestine, but normally occupy the bloodstream or an intracellular environment in the mammalian host. Trypanosomes infect a variety of hosts and cause various diseases, including the fatal human diseases, sleeping sickness, caused by Trypanosoma brucei, and Chagas disease, caused by Trypanosoma cruzi. The mitochondrial genome of the Trypanosoma, as well as of other kinetoplastids known as the kinetoplast, is made up of a highly complex series of catenated circles and minicircles and requires a cohort of proteins for organisation during cell division[44,45].

2.6. Chemical and herbal anti-trypanosomiasis drugs

The drugs currently used to treat sleep sickness, include suramin, pentamidine, melarsoprol, eflornithine, and nifurtimox[46]. Suramin was introduced in the early 1920s as the drug of choice for treating early phase of infection with Trypanosoma brucei rhodesiense[47]. A drug from Bayer in 1916 by Oscar Drsl and Richard Cote was created[48], which was under investigation for the treatment of prostate cancer. Suramin is used for the treatment of human African trypanosomiasis in first stage of infection when parasites are largely found in the blood, but when the parasites invade the central nervous system it is ineffective due to the inability of suramin in crossing the blood–brain barrier and blood–cerebrospinal fluid barrier to achieve adequate levels of concentration in the tissue target[49]. However, there is evidence that suramin can reach certain parts of the central nervous system. So that the cerebral cortex of mice infected with Trypanosoma brucei rhodesiense was successfully treated[12].

By receptor–mediated endocytosis, suramin is thought to be an anti-parasite drug which acts slowly, possibly because low density lipoprotein endocytosis of host is connected. In addition, El AI Di receptors are expressed at the blood brain barrier and it is believed to be involved in the transit of low density lipoprotein to the brain[49]. Suramin co–administration with drugs that are active against the parasite in the central nervous system, such as melarsoprol, eflornithine and nifurtimox show signs of improvement in the rate of treatment[49].

Pentamidine was first introduced in 1949. This medication is only used as a second–degree drug and its usage is contraindicated during the treatment with suramin[47]. Melarsoprol was introduced in 1949 for the treatment of sleep disorders in its last stages, but caused serious side effects such as reactive encephalopathy in 5% to 10% of cases. It also causes vomiting, abdominal pain and peripheral neuropathy. Melarsoprol can reduce trypanothione reductase and inhibit trypanothione level[50]. Eflornithine is drug of choice for the treatment of late stage of sleeping sickness caused by Trypanosoma brucei gambiense but it is not recommended against Trypanosoma brucei rhodesiense. It inhibits the biosynthesis of polyamines by eflornithine; range of downstream biochemical effects that would cause trypanocidal activity was affected[51].

Nifurtimox has been recorded as another drug to treat sleeping sickness. Nifurtimox often has side effects, and only 50% of patients are able to complete a full course of their treatment, but the treatment of late stage of sleeping sickness in which eflornithine and melarsoprol are used is usually ineffective[52]. Drugs used to treat Americans sleep disorders are nifurtimox and benzimidazole[53]. Because many drugs now available to treat African sleeping sickness are toxic, researchers around the world try to discover new molecules which are safe and cost–effective from the medicinal herbs. Until mid 1995, Spoloda–Bouza and Cassels examined plant metabolites active against Trypanosoma cruzi[54]. Fournet et al. in 1994, collected 43 plants from Bolivia with trypanocidal activities[55]. In another study, Rojas de Arias et al. studied the plants with moderate to high activity in vitro and in vivo against Trypanosoma species (sleeping sickness)[56].

2.7. Giardia and giardiasis

Giardiasis (popularly known as beaver fever) is a zoonotic parasitic disease caused by the flagellate protozoan Giardia lamblia (also sometimes called Giardia intestinalis and Giardia duodenalis). The Giardia organism inhabits the digestive tract of a wide variety of domestic and wild animal species, as well as humans and and compete with the host in food absorption[57–61]. Infection with this parasite has been reported in all parts of the world and the infection rate is 1% to 25%[62]. It is the most common pathogenic parasitic infection in humans worldwide. In 2013, there were about 280 million people worldwide with symptomatic giardiasis.

2.8. Chemical and herbal anti-giardiasis drugs

Treatment is not always necessary as the infection usually resolves on its own. However, if the illness is acute or symptoms persist and medications are needed to treat it, medications such as metronidazole, tinidazole, secnidazole or ornidazole are used[63]. The mechanism of killing of Giardia by metronidazole has been studied more fully. Metronidazole has an anaerobic metabolic pathways in Giardia[63]. The drug enters the trophozoite and destruct its growth[22]. The drug is activated by reducing the nitro group[64]. Slope agrees with the intracellular transport of metronidazole and is spread by the reduction reaction. Metronidazole reduction as a terminal electron acceptor binds covalently to DNA macromolecules[65]. This leads to DNA damage, the loss of helical structure, impaired template
function and strand breakage and subsequent death of trophozoite appears. In addition to this work, metronidazole inhibits the respiration of trophozoite[15].

Metronidazole reduction activities may also lead to toxic radicals that react with cellular components[22]. Within the cyst and trophozoite, nitroimidazole may be less affected, probably due to poor penetration of the drug through the cyst wall[86]. Resistance to metronidazole was tested in vitro. The activity of parasite pyruvate reduction is related to the reduction of nitroimidazole ferredoxin; oxidoreductase is required for activity[67]. Metronidazole is rapidly and completely absorbed after oral administration and penetrates the body’s tissues and saliva, breast milk, semen and vaginal secretions seep. The drug is metabolized primarily in the liver and is excreted through the urine[68]. In 1980, a laboratory experiment was conducted to determine the drug sensitivity of the nitroimidazole. In 1980 by microscopic evaluation of morphology and motility of Giardia lamblia, it was shown that metronidazole and tinidazole are effective[69]. Subsequently, the morphology, growth inhibition, thymidine incorporation, lethal concentration, vital dye exclusion, inhibition of adherence, drug metabolism and response assessment to measure the effect of many therapeutic agents in vitro were evaluated[70]. However, as many studies have shown, there is no standard laboratory conditions to compare the results and laboratory findings with clinical situations. The nitromidazole, tinidazole and metronidazole consistently have been shown to possess the best activity in vitro[71–73]. This disease is treated well with nutritional and herbal therapy intervention. The intervention is done by adding a probiotic containing Lactobacillus such as fructooligosaccharides, dietary fiber, wheat germ, etc. Reduced dairy products containing lactose may help to control giardiasis. Herbs that can help to control giardiasis include garlic and pepper[74]. Pippali rasayana Ayurveda product, may also help in controlling giardiasis. Some flavonoids and tannins found in plants like marjoram, psidium guajava, mangifera indica and plantain are used to control diarrhea.

2.9. Trichomonas or trichomoniasis

Trichomonas vaginalis (T. vaginalis) is a protozoan flagella found in the human genitourinary system that will be replaced by the protozoan trophozoite forms and just multiply by longitudinal binary division[75]. The protozoan is transmitted through sexual contact, so that in all cases, it is the most common sexually transmitted disease in the world. T. vaginalis cause nearly 180 million new infections each year. This parasite is one of the most common causes of non–viral sexually transmitted disease[76–78]. At least six million women and their partners each year in the United States are infected with T. vaginalis for sexually transmitted diseases. Vaginitis and cervicitis in women and urethritis in both sexes may be caused by this parasite. These parasites can cause prostatitis in men as well. The incubation period of the disease is 4 to 28 d. Vulva and vagina itchy and vaginal discharge are usually acute and happen during menstruation or shortly after it[79–81]. As stated, in 90% of women infected with the protozoa in the cervical region, damage is caused by infection with a virus that can cause cancer[82–84].

2.10. Chemical and herbal anti–trichomoniasis

The effect of standard chemotherapy consisting of 5–nitroimidazole like that of metronidazole and tinidazole. Because some strains are resistant to drugs of Trichomonas, new drugs are needed. Natural products like alternative alkaloids (berberine), dibenzofuran, anthraquinones and polyacetylenes, saponins and diterpenoid have been tested[85]. Nowadays, experimental researches on parasitic diseases have increased, which are necessary because parasitic diseases and treatment with natural remedies are very important[86–96].

In this study, we tried to collect information about herbal remedies affecting normal and pathogenic protozoa category Sarcomastigophora and these information can be recommended because of the ideal natural resources for the clinical research work on other parasitic diseases.

3. Discussion and conclusion

In this review study, we identified and presented valuable source of medicinal herbs which are used as natural medicinal products for prevention and treatment of pathogenic protozoan Sarcomastigophora branches (Trypanosoma, Leishmania, Amoeba, Trichomonas and Giardia). These herbs usually have various effects and are used for different diseases in addition to parasitic infections. The mechanism actions of these plants against the complications of these diseases are not clear and should be established. Most of plants properties have been attributed to their antioxidant activities[6,9,74,85,97,98], which is mostly due to the presence of phenolic components[22,40,42]. These phenolic compounds usually have antimicrobial activity[90,93]; however, other components of the plants should be involved in the activities of these plants, too.

Conflict of interest statement

We declare that we have no conflict of interest.

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