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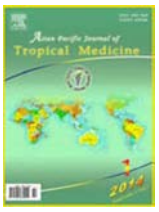

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The most common herbal medicines affecting Sarcomastigophora branches: a review study

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ABSTRACT

Parasitic diseases cause annual mortality of more than 200 thousand people. Currently many drugs are used to treat parasitic diseases; however, they are mostly 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*.

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. However, medicinal plants and herbs having effective bioactive metabolites with pharmacological effects can well represent natural source of cheap drugs and are less harmful. In this review article, the most common and most effective herbal medicines on pathogenic protozoa Sarcomastigophora branches such as *Trypanosoma*, *Leishmania*, *Amoeba*, *Trichomonas* and *Giardia* were reviewed. Protozoa Sarcomastigophora branch is divided into two subcategories: Sarcodina and

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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 hartmany*, *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 anually infected with parasites, from them 450 million ones get severe mobidity[2]. 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 many 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 dumdum 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 antimonates 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 phosphatidylcholine 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[6,17], atherosclerosis[18,19], cardiovascular and Alzheimer deseases 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, so 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 schistosomasis[30]. The amoeba infection is asymptomatic in 80% of cases[31]. Infants who are not breastfeed, 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 furoate, 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 furoate, 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 trypanosomasis 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 Al 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 *Trypanosomya* 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 absorbtion[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[66]. 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 cotaining *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 wemen 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 deseases 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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References

[1] Service MW. *Medical entomology for students*. 1st ed. Cambridge: Chapman & Hall; 1996, p. 95-103.

[2] World Health Organization. *WHO Tech Rep Ser No. 701. Expert committee: the leishmaniasis*. Geneva: World Health Organization; 1984, p. 2-4.

[3] World Health Organization. *WHO Tech Rep Ser No. 793. Expert committee: epidemiological aspects. Control of the leishmaniasis*. Geneva: World Health Organization; 1990, p. 41-46.

[4] Singh RK, Pandey HP, Sundar S. Visceral leishmaniasis (kala azar): challenges ahead. *Indian J Med Res* 2006; **123**: 331-344.

[5] Ouellette M, Drummelsmith J, Papadopoulou B. Leishmaniasis: drugs in the clinic, resistance and new developments. *Drug Resist Update* 2004; **7**: 257-266.

[6] Nasri H, Rafieian-Kopaei M. Protective effects of herbal antioxidants on diabetic kidney disease. *J Res Med Sci* 2014; **19**(1): 82-83.

[7] Nasri H, Rafieian-Kopaei M. Tubular kidney protection by antioxidants. *Iran J Public Health* 2013; **42**(10): 1194-1196.

[8] Baradaran A, Madihi Y, Merrikhi A, Rafieian-Kopaei M, Nematbakhsh M, Asgari A, et al. Nephrotoxicity of hydroalcoholic extract of *Teucrium polium* in Wistar rats. *Pak J Med Sci* 2013; **29**: 329-333.

[9] Amini FG, Rafieian-Kopaei M, Nematbakhsh M, Baradaran A, Nasri H. Ameliorative effects of metformin on renal histologic and biochemical alterations of gentamicin-induced renal toxicity in Wistar rats. *J Res Med Sci* 2012; **17**(7): 621-625.

[10] Karimi A, Moradi MT, Saeedi M, Asghari S, Rafieian-Kopaei M. Antiviral activity of *Quercus persica* L.: high efficacy and low toxicity. *Adv Biomed Res* 2013; **2**: 36.

[11] Bahmani M, Vakili-Saatloo N, Gholami-Ahangaran M, Karamati SA, Banihabib E, Hajigholizadeh G, et al. A comparison study on the anti-leech effects of onion (*Allium cepa* L) and ginger (*Zingiber officinale*) with levamisole and triclabendazole. *J HerbMed Pharmacol* 2013; **2**(1): 1-3.

[12] Sharafati-Chaleshtori R, Sharafati-Chaleshtori F, Rafieian-Kopaei M. Biological characterization of Iranian walnut (*Juglans regia*) leaves. *Turk J Biol* 2011; **35**(5): 635-639.

[13] Bahmani M, Vakili-Saatloo N, Maghsoudi R, Momtaz H, Saki K, Kazemi-Ghoshchi B, et al. A comparative study on the effect of ethanol extract of wild *Scrophularia deserti* and streptomycin on *Brucellla melitensis*. *J HerbMed Pharmacol* 2013; **2**(1): 17-20.

[14] Bahmani M, Rafieian-Kopaei M, Eftekhari Z, Banihabib E, Hajigholizadeh G, Bahmani F, et al. Evaluating the anti-leech effects of methanolic extracts of *Peganum harmala* L. and *Olea europaea* L. on immature worm *Limnatis nilotica*. *Word's Vet J* 2013; **3**(2): 33-37.

[15] Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibrosarcoma tumor growth in BALB/c mice. *J Med Food* 2011; **14**(9): 969-974.

[16] Shirzad H, Kiani M, Shirzad M. Impacts of tomato extract on the mice fibrosarcoma cells. *J HerbMed Pharmacol* 2013; **2**(1): 13-16.

[17] Akbari F, Ansari-Samani R, Karimi A, Mortazaei S, Shahinfard N, Rafieian-Kopaei M. Effect of turnip on glucose and lipid profiles of alloxan-induced diabetic rats. *Iran J Endocrinol Metab* 2013; **14**(5): 492-497.

[18] Asgary S, Kelishadi R, Rafieian-Kopaei M, Najafi S, Najafi M, Sahebkar A. Investigation of the lipid-modifying and antiinflammatory effects of *Cornus mas* L. supplementation on dyslipidemic children and adolescents. *Pediatr Cardiol* 2013; **34**(7): 1729-1735.

[19] Heidarian E, Rafieian-Kopaei M, Ashrafi K. The effect of hydroalcoholic extract of *Allium latifolium* on the liver phosphatidate phosphatase and serum lipid profile in hyperlipidemic rats. *J Babol Univ Med Sci* 2013; **15**(4): 37-46.

[20] Khosravi-Boroujeni H, Mohammadifard N, Sarrafzadegan N, Sajjadi F, Maghroun M, Khosravi A, et al. Potato consumption and cardiovascular disease risk factors among Iranian population. *Int J Food Sci Nutr* 2012; **63**(8): 913-920.

[21] Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Sajjadi F, Maghroun M, Asgari S, et al. White rice consumption and CVD risk factors among Iranian population. *J Health Popul Nutr* 2013; **31**(2): 252-261.

[22] Rabiei Z, Rafieian-Kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. *Neurochem Res* 2014; **39**(2): 353-360.

[23] Rabiei Z, Rafieian-Kopaei M, Mokhtari S, Alibabaei Z, Shahrani M. The effect of pretreatment with different doses of *Lavandula officinalis* ethanolic extract on memory, learning and nociception. *Biomed Aging Pathol* 2013; **4**(1): 71-76.

[24] Nasri H, Shirzad H. Toxicity and safety of medicinal plants. *J HerbMed Plarmacol* 2013; **2**(2): 21-22.

[25] Rafieian-Kopaei M. Medicinal plants and the human needs. *J HerbMed Plarmacol* 2012; **1**(1): 1-2.

[26] Nasri H, Baradaran A, Ardalan MR, Mardani S, Momeni A, Rafieian-Kopaei M. Bright renoprotective properties of metformin: beyond blood glucose regulatory effects. *Iran J Kidney Dis* 2013; **7**(6): 423-428.

[27] Hamano S, Petri Jr WA. Amebiasis. In: Feigin RD, Cheray J, Demmler-Harrison GJ, Kaplan SL, editors. *Feigin and Cherry's textbook of pediatric infectious diseases*. 6th ed. Philadelphia: Saunders; 2009, p. 2841-2849.

[28] WHO/PAHO/UNESCO report. A consultation with experts on amoebiasis. Mexico City, Mexico 28-29 January, 1997. *Epidemiol Bull* 1997; **18**(1): 13-14.

[29] Nazemalhosseini Mojarad E, Rostami Nejad M, Haghighi A. Update of knowledge for best amebiasis management. *Gastroenterol Hepatol Bed Bench* 2008; **1**(1): 45-50.

[30] Entamoeba taxonomy. *Bull World Health Organ* 1997; **75**: 291-294.

[31] John C, Salata RA. Amebiasis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BMD, editors. *Nelson textbook of pediatrics*. 18th ed. Philadelphia: Saunders; 2007, p. 1460-1462.

[32] Haque R, Mondal D, Duggal P, Kabir M, Roy S, Farr BM, et al. *Entamoeba histolytica* infection in children and protection from subsequent amebiasis. *Infect Immun* 2006; **74**(2): 904-909.

[33] Karimi Zarehi AA, Mahmoodzadeh A, Vatani H, Shirbazo S. An epidemiologic study of intestinal amoebiasis in borders villages of Sarakhs. *J Mil Med* 2003; **5**(1): 27-31.

[34] Sayyari AA, Imanzadeh F, Bagheri Yazdi SA, Karami H, Yaghoobi M. Prevalence of intestinal parasitic infections in the Islamic Republic of Iran. *East Mediterr Health J* 2005; **11**(3): 377-383.

[35] Ardalan MR, Nasri H, Rafieian-Kopaei M. Comment on: protective role of recombinant human erythropoietin in kidney and lung injury following renal bilateral ischemia reperfusion in rat model. *Int J Prev Med* 2013; **4**: 1226-1227.

[36] Nasri H, Rafieian-Kopaei M. Medicinal plants and new concerns in statin consumption. *Iranian J Public Health* 2013; **42**(9): 1071-1072.

[37] Tierney LM, McPhee SJ, Papadakis MA. *Current medical diagnosis and treatment*. 38th ed. Stamford: Appleton & Lange; 1999, p. 1356-1361.

[38] Behrman RE, Kliegman RM, Jenson HB. *Nelson textbook of pediatrics*. 16th ed. Philadelphia: Saunders; 2000, p. 1035-1036.

[39] Rahimian G, Sanei MH, Shirzad H, Azadegan-Dehkordi F, Taghikhani A, Salimzadeh L, et al. Virulence factors of *Helicobacter pylori* vacA increase markedly gastric mucosal TGF-β1 mRNA expression in gastritis patients. *Microb Pathog* 2014; **67-68**: 1-7.

[40] Sadeghi M, Khosravi-Boroujeni H, Sarrafzadegan N, Asgary S, Roohafza H, Gharipour M, et al. Cheese consumption in relation to cardiovascular risk factors among Iranian adults- IHHP study. *Nutr Res Pract* 2014; **8**(3): 336-341.

[41] Sharafati-Chaleshtori R, Rafieian-Kopaei M. Screening of antibacterial effect of the *Scrophularia striata* against *E. coli in vitro*. *J HerbMed Pharmacol* 2014; **3**(1): 31-34.

[42] Asgary S, Rafieian-Kopaei M, Shamsi F, Najafi S, Sahebkar A. Biochemical and histopathological study of the anti-hyperglycemic and anti-hyperlipidemic effects of cornelian cherry (*Cornus mas* L.) in alloxan-induced diabetic rats. *J Complement Integr Med* 2014; **11**(2): 63-69.

[43] Madihi Y, Merrikhi A, Setorki M, Baradaran A, Ghobadi S, Shahinfard N, et al. Bioactive components and the effect of hydroalcoholic extract of *Vaccinium myrtillus* on postprandial atherosclerosis risk factors in rabbits. *Pak J Med Sci* 2013; **29**: 384-389.

[44] Hamilton PB, Stevens JR, Gaunt MW, Gidley J, Gibson WC. Trypanosomes are monophyletic: evidence from genes for glyceraldehyde phosphate dehydrogenase and small subunit ribosomal RNA. *Int J Parasitol* 2004; **34**(12): 1393-1404.

[45] Piontkivska H, Hughes AL. Environmental kinetoplastid-like 18S rRNA sequences and phylogenetic relationships among Trypanosomatidae: paraphyly of the genus *Trypanosoma*. *Mol Biochem Parasitol* 2005; **144**(1): 94-99.

[46] Asadi SY, Parsaei P, Karimi M, Ezzati S, Zamiri A, Mohammadizadeh F, et al. Effect of green tea (*Camellia sinensis*) extract on healing process of surgical wounds in rat. *Int J Surg* 2013; **11**(4): 332-337.

[47] Nasri H, Madihi Y, Merrikhi A, Gheissari A, Baradaran A, Kheiri S, et al. Association of proteinuria with various clinical findings and morphologic variables of oxford classification in immunoglobulin A nephropathy patients. *Int J Prev Med* 2013; **4**(5): 546-551.

[48] Karimi M, Parsaei P, Asadi Y, Ezzati S, Boroujeni RK, Zamiri A, et al. Effects of *Camellia sinensis* ethanolic extract on histometric and histopathological healing process of burn wound in rat. *Middle East J Sci Res* 2013; **13**(1): 14-19.

[49] Parsaei P, Karimi M, Asadi SY, Rafieian-Kopaei M. Bioactive components and preventive effect of green tea (*Camellia sinensis*) extract on postlaparotomy intra-abdominal adhesion in rats. *Int J Surg* 2013; doi: 10.1016/j.ijsu.2013.08.014.

[50] Rafieian-Kopaie M, Nasri H , Alizadeh F, Ataebi B, Baradaran A. Immunoglobulin A nephropathy and malaria *Falciparum* infection; a rare association. *Iran J Public Health* 2013; **42**(5): 529-533.

[51] Sewell RDE, Rafieian-Kopaei M. The history and ups and downs of herbal medicine usage. *J HerbMed Pharmacol* 2014; **3**(1): 1-3.

[52] Nasri H, Sahinfard N, Rafieian M, Rafieian S, Shirzad M, Rafieian-Kopaei M. Turmeric: a spice with multifunctional medicinal properties. *J HerbMed Pharmacol* 2014; **3**(1): 5-8.

[53] Rafieian-Kopaei M, Ansari R, Shahinfard N, Namjou A, Rafieian M, Shirzad H. Ameliorative property of *Teucrium polium* on second degree burn. *J HerbMed Pharmacol* 2013; **2**(1): 9-11.

[54] Sepulveda-Boza S, Cassels BK. Plant metabolites active against *Trypanosoma cruzi*. *Planta Med* 1996; **62**: 98-105.

[55] Fournet A, Barrios AA, Munoz V. Leishmanicidal and trypanocidal activities of Bolivian medicinal plants. *J Ethnopharmacol* 1994; **41**: 19-37.

[56] Rojas de Arias A, Ferro E, Inchausti A, Ascurra M, Acosta N, Rodriguez E, et al. Mutagenicity, insecticidal and trypanocidal activity of some Paraguayan Asteraceae. *J Ethnopharmacol* 1995; **45**: 35-41.

[57] Markel EK, Voge M, John DT. *Medical parasitology*. 11th ed. Philadelphia: W.B. Saunders; 2000, p. 63-70.

[58] Topley WWC. *Topley and Willson's microbiology and microbial infections. Vol 5*. 10th ed. New York: Springer; 2001, p. 141-155.

[59] Addiss DG, Juranek DD, Spencer HC. Treatment of children with asymptomatic and nondiarrheal *Giardia* infection. *Pediatr Infect Dis J* 1991; **10**: 843-846.

[60] Adam D. Biology of *Giardia lamblia*. *Clin Microbiol Rev* 2001; **14**: 447-475.

[61] Marquardt WC, Demaree RS, Grieve RB. *Parasitology and vector biology*. 2nd ed. London: Academic Press; 2000, p. 89-98.

[62] Saebi E. *Text book of clinical parasitology, porotozal disease in Iran*. Tehran: Aeeizh; 1998, p. 81-95.

[63] Mirzaei MGR, Azimian M, Moezzi M, Vameghi R, Rafieian-Kopaei M. Effect of lamotrigine on prophylaxis of pediatric classic migraine. *Iran J Child Neurol* 2009; **35**: 35-38.

[64] Akhlaghi M, Shabanian G, Rafieian-Koupaei M, Parvin N, Saadat M, Akhlaghi M. *Citrus aurantium* blossom and preoperative anxiety. *Rev Bras Anestesiol* 2011; **61**(6): 702-712.

[65] Shirzad H, Shahrani M, Rafieian-Kopaei M. Comparison of morphine and tramadol effects on phagocytic activity of mice peritoneal phagocytes *in vivo*. *Int Immunopharmacol* 2009; **9**(7-8): 968-970.

[66] Taghikhani M, Nasri H, Asgari A, Afrough H, Namjoo AR, Ansari-Samani R, et al. The renal toxicity of hydroalcoholic extract of *Stachys lavandulifolia* Vahl in Wistar rats. *Life Sci J* 2012; **9**(4): 3025-3031.

[67] Taghikhani A, Afrough H, Ansari-Samani R, Shahinfard N, Rafieian-Kopaei M. Assessing the toxic effects of hydroalcoholic

extract of *Stachys lavandulifolia* Vahl on rat's liver. *Bratisl Lek Listy* 2014; **115**(3): 121-124.

[68] Lau AH, Lam NP, Piscitelli SC, Wilkes L, Danzinger LH. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. *Clin Pharmacokinet* 1992; **23**: 328-364.

[69] Jokipii L, Jokipii AM. *In vitro* susceptibility of *Giardia lamblia* trophozoites to metronidazole and tinidazole. *J Infect Dis* 1980; **141**: 317-325.

[70] Azadmehr A, Hajiaghaee R, Afshari A, Amirghofran Z, Refieian-Kopaei M, Yousofi-Darani H, et al. Evaluation of *in vivo* immune response activity and *in vitro* anti-cancer effect by *Scrophularia megalantha*. *J Med Plants Res* 2011; **21**: 2365-2368.

[71] Gordts B, Hemelhof W, Asselman C, Butzler JP. *In vitro* susceptibilities of 25 *Giardia lamblia* isolates of human origin to six commonly used antiprotozoal agents. *Antimicrob Agents Chemother* 1985; **28**: 378-380.

[72] Bagheri N, Taghikhani A, Rahimian G, Salimzadeh L, Azadegan Dehkordi F, Zandi F, et al. Association between virulence factors of *helicobacter pylori* and gastric mucosal interleukin-18 mRNA expression in dyspeptic patients. *Microb Pathog* 2013; **65**: 7-13.

[73] Bagheri N, Rahimian G, Salimzadeh L, Azadegan F, Rafieian-Kopaei M, Taghikhani A, et al. Association of the virulence factors of *helicobacter pylori* and gastric mucosal interleukin-17/23 mRNA expression in dyspeptic patients. *EXCLI J* 2013; **12**: 5-14.

[74] Nasri H, Tavakoli M, Ahmadi A, Baradaran A, Nematbakhsh M, Rafieian-Kopaei M. Ameliorative effect of melatonin against contrast media induced renal tubular cell injury. *Pak J Med Sci* 2014; **30**(2): 261-265.

[75] Warren KS, Mahmood AAF. *Tropical and geographical medicine*. New York: McGrawh Hill Inc.; 1989, p. 221-223.

[76] Kengne P, Veas F, Vidal N, Rey JL, Cuny G. *Trichomonas vaginalis*: repeated DNA target for highly sensitive and specific polymerase chain reaction diagnosis. *Cell Mol Biol (Noisy-le-grand)* 1994; **40**: 819-831.

[77] Madico G, Quinn TC, Rompalo A, McKee KT Jr, Gaydos CA. Diagnosis of *Trichomonas vaginalis* infection by PCR using vaginal swab samples. *J Clin Microbiol* 1998; **36**: 3205-3210.

[78] Petrin D, Delgaty K, Bhatt R, Garber G. Clinical and microbiological aspects of *Trichomonas vaginalis*. *Clin Microbiol Rev* 1998; **11**: 300-317.

[79] Riley DE, Roberts MC, Takayama T, Krieger JN. Development of a polymerase chain reaction-based diagnosis of *Trichomonas vaginalis*. *J Clin Microbiol* 1992; **30**: 465-472.

[80] Quinn Krieger J. Trichomoniasis. In: Warren KS, Mahmoud AAF, editors. *Tropical and geographical medicine*. 2nd ed. New York: McGrawh Hill Inc.; 1989, p. 358-365.

[81] Manson-Bahr PEC, Bell DR. *Manson's tropical diseases*. London: Bailliere Tindall; 1989, p. 1154-1155.

[82] World Health Organization. An overview of selected curable sexually transmitted disease. In: *Global program on AIDS*. Geneva: World Health Organization; 2000, p. 2-27.

[83] Schwebke JR, Burgess D. Trichomoniasis. *Clin Microbiol Rev* 2004; **17**(4): 794-803.

[84] Ackers JP. Immunologic aspects of human trichomoniasis. In: Honigberg BM, editor. *Trichomonads parasitic in humans*. New York: Springer-Verlag; 1999, p. 36-52.

[85] Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of *Aloe vera* on gentamicin-induced nephrotoxicity in male Wistar rats. *Clin Ter* 2014; **165**(1): 7-11.

[86] Bahmani M, Eftekhari Z. An ethnoveterinary study of medicinal plants in treatment of diseases and syndromes of herd dog in southern regions of Ilam Province, Iran. *Comp Clin Pathol* 2012; **22**: 403-407.

[87] Bahmani M, Banihabib E, Rafieian-Kopaei M, Gholami-Ahangaran M. Comparison of disinfection activities of nicotine with copper sulphate in water containing *Limnatis nilotica*. *Kafkas Univ Vet Fak Derg* 2014; doi: 10.9775/kvfd.2014.11223.

[88] Bahmani M, Rafieian-Kopaei M, Avijgan M, Hosseini S, Golshahi H, Eftekhari Z. Ethnobotanical studies of medicinal plants used by Kurdish owner's in south range of Ilam province, west of Iran. *Am Eurasian J Agric Environ Sci* 2012; **12**(9): 1128-1133.

[89] Ghasemi Pirbalouti A, Momeni M, Bahmani M. Ethnobotanical study of medicinal plants used by kurd tribe in dehloran and abdanan districts, Ilam province, Iran. *Afr J Tradit Complement Altern Med* 2013; **10**(2): 368-385.

[90] Bahmani M, Rafieian-Kopaei M. Medicinal plants and secondary metabolites for leech control. *Asian Pac J Trop Dis* 2014; **4**(4): 315-316.

[91] Bahmani M, Farkhondeh T, Sadighara P. The anti-parasitic effects of *Nicotina tabacum* on leeches. *Comp Clin Pathol* 2012; **21**(3): 357-359.

[92] Bahmani M, Karamati SA, Banihabib E, Saki K. Comparison of effect of nicotine and levamisole and ivermectin on mortality of leech. *Asian Pac J Trop Dis* 2014; **4**(Suppl 1): S477-S480.

[93] Amirmohammadi M, Khajoenia S, Bahmani M, Rafieian-Kopaei M, Eftekhari Z, Qorbani M. *In vivo* evaluation of antiparasitic effects of *Artemisia abrotanum* and *Salvia officinalis* extracts on *Syphacia obvelata*, *Aspiculoris tetrapetra* and *Hymenolepis nana* parasites. *Asian Pac J Trop Dis* 2014; **4**(Suppl 1): S250-S254.

[94] Bahmani M, Abbasi J, Mohsenzadegan A, Sadeghian S, Gholami-Ahangaran M. *Allium sativum* L.: the anti-ammature leech (*Limnatis nilotica*) activity compared to Niclosomide. *Comp Clin Pathol* 2013; **22**: 165-168.

[95] Bahmani M, Saki K, Gholami-Ahangaran M, Parsaei P, Mohsenzadegan A, Zia-Jahromi N. Evaluating the anti-leech activity of methanolic extract of M*atricaria chamomilla* L. comparing with ivermectin, mebendasole, praziquantel, rafoxanide, febantel and albendasole. *Middle East J Sci Res* 2012; **12**(2): 260-263.

[96] Bahmani M, Rafieian M, Baradaran A, Rafieian S, Rafieian-Kopaei M. Nephrotoxicity and hepatotoxicity evaluation of *Crocus sativus* stigmas in neonates of nursing mice. *J Nephropathol* 2014; **3**(2): 81-85.

[97] Rafieian-Kopaei M, Ghaed-Amini F, Nasri H. Ginger and diabetic nephropathy: a letter to the editor. *J Isfahan Med School* 2014; **32**(273): 86-89.

[98] Nasri H, Rafieian-Kopaei M. Medicinal plants and antioxidants: why they are not always beneficial? *Iran J Public Health* 2014; **43**(2): 255-257.