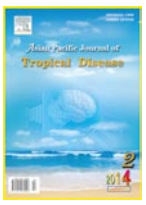
Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Document heading doi: 10.1016/S2222-1808(14)60686-1

Herbal and chemical drugs effective on malaria

Seyed Ahmad Karamati[1], Hassan Hassanzadazar[2], Mahmoud Bahmani[3*], Mahmoud Rafieian-Kopaei[4]

[1]*Department of Parasitology and Mycology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2]*Deputy for Food and Drug, Urmia University of Medical Sciences, Urmia, Iran*

[3]*Razi Herbal Medicine Research Center, Lorestan University of Medical Sciences, Khorram Abad, Iran*

[4]*Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran*

Dear editor,

Malaria is still one of the most contagious diseases of the world in the 21st century that is endemic in 106 countries. A total of 265 million people were suffering from this disease in 2010, and 345 thousand of them lost their lives. Malaria is caused by protozoa of the genus of *Plasmodium* and Apicomplexa phylum in human and animals. Biological transmission of parasite is done by the infected female *Anopheles* bite. Mechanical transmission (diffusion) is possible through blood transfusion or infected needles among drugs addicts[1].

Malaria still remains one of the world's major health problems. It has become one of the most important infectious diseases; qua 300 to 500 million cases suffered by malaria and 1.5-2.5 million people were dead of this disease annually[2].

Fever is diagnosed in most cases of malaria in endemic areas. The most common symptoms include fever, chills and sweats, splenomegaly, pallor, nausea, vomiting, weakness and malaise. Severe disease with typical symptoms is common in children and peoples of non-endemic areas[3].

Malaria caused by *Plasmodium falciparum* can be severe and fatal witch if untreated, the death rate is high. Malaria can cause multiple organ involvement including brain and kidneys[4].

Nowadays one of the challenges in malaria control strategy is drug resistance of malaria parasites[5].

Because of different reasons, using of medicinal products with plant origin has been extended such as fewer side effects, improving in patient acceptance due to traditional use and recommendation, lower cost and also more consistency with normal physiological function of the human body[6-9]. Nowadays, the study of antiparasitic herbs becomes more widespread because the positive effects of these herbs have been proven effective[10-16].

Anti-malarial drugs belong to groups of aminoquinoline, quinine and related compounds, anti-folate compounds, antibiotics, halofantrine, atovaquone, pyronaridine and lumefantrine. Chloroquine is the most famous compound of these groups. This compound affects four types of the blood stages of human *Plasmodium*. *Plasmodium falciparum* resistance to this compound was reported in 1959 and gradually expanded to world other areas[17].

Primaquine as one of the aminoquinoline drugs is considered as the only drug available to eliminate liver forms of *Plasmodium vivax*. Before drug administration to prevent hemolysis, detailed knowledge of the situation of blood glucose 6-phosphate dehydrogenase is essential[17].

Quinine and its isomer quinidine are used as last resort to treat disease especially malignant form. Chloroquine as quinine derivative has been used as a first choice until recently. *Plasmodium* resistance to these drugs reduced its application. Amodiaquine and mefloquine are other quinine derivatives[18].

It can be pointed out that in these groups there are dihydropteroate reductase inhibitor compounds such as sulfonamides (dapsone sulfalen, sulfamethoxazole and sulfadiazine) and dihydrofolate reductase inhibitor compounds (proguanil, pyrimethamine and trimethoprim). These compounds can cause inhibition of biosynthesis of folate. Each of these compounds can be used alone. It should be used in combination of two drugs because of the incidence of drug resistance and incidence of their synergistic effects[18].

Nowadays compounds such as sulfalen/pyrimethamine (metakelfin) and sulfamethoxazole-trimethoprim (cotrimoxazole) and sulfadoxine/pyrimethamine (fansidar) are

*Corresponding author: Dr. Mahmoud Bahmani, Razi Herbal Medicine Research Center, Lorestan University of Medical Sciences, Khorram Abad, Iran.
Tel: 0989186157084
E-mail: mahmood.bahmani@gmail.com

Article history:
Received 8 Apr 2014
Received in revised form 22 Apr 2014
Accepted 15 Jul 2014
Available online 20 Aug 2014

commercially available in the marketplace. New combination of anti-folate compounds is in clinical study; this drug is a combination of dapsone and chlorproguanil that commercially is called Lapdap with highly effective synergism[18].

Tetracycline and its derivatives such as doxycycline have antimalarial effects that are used as treatment and prevention agents. To improve the efficacy of quinine, tetracycline is prescribed with quinine[18]. Halofantrine, atovaquone, pyronaridine and lumefantrine are considered as new antimalarial compounds[18].

Quinine is the first anti-malarial drug that was obtained from cinchona bark. Chloroquine was produced in 1940 and is widely used as an antimalarial agent. This drug in combination with ferriprotoporphyrin IX acts as treatment for malaria and ultimately prevents the polymerization of toxic metabolites to haemozoin crystal. Mefloquine is an anti-malarial combination of which mechanism of action is like chloroquine. Primaquine is used to eradicate *Plasmodium vivax* and *Plasmodium ovale* liver hypnozoites after treatment with chloroquine which has a mechanism of action similar to chloroquine. It also used to simplify and multiply falciparum malaria treatment. Combination of atovaquone/proguanil is given to treatment of simple form of falciparum malaria[18].

Artemisinin is an antimalarial compound extracted from the *Artemisia annua* plant which two thousand years ago in China had been used as an antipyretic drug.

Application of this drug in the past decade for treatment of falciparum and vivax malaria has had very hopeful results that eliminates parasite from blood circulation more rapid than chloroquine[19].

Artemisinin and its derivatives are used for treatment of simple and chronic form of falciparum malaria. Other common derivatives of artemisinin are artemether, artesunate and artether[20]. Artemisinin has a sesquiterpene lactone structure obtained from the Chinese medicinal herb *Artemisia annua*[21].

Artemisia annua is used in traditional Chinese medicine as a treatment for colds and fever, which are grown in many countries including India. Drug group of artemisinin has features such as rapid declining of fever, rapid clearance of parasites in the blood, and no significant side-effects. Endoperoxide end presence in artemisinin is essential for its activity. When malaria parasites infect red blood cells, hemoglobin consumed and iron-porphyrin (heme) is released. The heme group makes reducing activity of artemisinin and producing of iron-oxo compound with high capacity. The iron-oxo species targets a sequence of reactions producing reactive oxygen radicals. These reactive radicals kill malaria parasites. Further deep investigation of relationship between structure and activity of artemisinin is still an active area for research[22]. Artemisinin drugs have short half-life (1-4 h). They can reduce the parasite biomass by 95% in each recommended dose. The malaria parasites are mostly killed in sexual stages. The remained parasites are eliminated by the host immune system. Unfortunately counterfeit medicines are very common and this can lead to the development of resistance to artemisinin[23]. Nowadays resistance and toxicity are the main problems in drug use[24,25].

World Health Organization recommended a combination of artemisinin derivatives to overcome resistance to routine single drug prescriptions[26], such as:

(1) artemether

(2) artesunate-amodiaqine

(3) artesunate-sulphdoxine-pyremethamine

(4) artesunate-mefloquine

(5) amodiquine-sulphdoxine-pyremethamine.

Conventional antimalarial drugs are rapidly losing their effectiveness, due to enhanced resistance to malaria parasites. As a result, there is a great demand for the development of new anti-malaria drugs[27].

Long time ago, herbs were the only weapon to fight against malaria parasite. Therefore researchers have strong belief that plants may be able to offer as alternative medicines and compounds which are safe and effective to treatment of malaria. Recent attempts resulted in isolating and identifying a number of anti-malarial metabolites with plants structural features.

Regarding to importance and occurrence resistance to malaria drugs, extensive research to identify medicinal plants against malaria on the world, isolation and identification of anti-protozoa plant metabolites, further studies to produce new herbal medicines against the most important infectious disease of the world are essential.

Medicinal plants are more consistent with normal physiological function of the human body and recent studies have been shown that they are reliable sources not only for treatment of malaria parasites, but also for other hard curable diseases such as atherosclerosis, diabetes, cancer and gastrointestinal diseases and preparation of an effective drug with low toxicity from medicinal plants is not accessible[28-39].

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] World Health Organization. World malaria report 2011. Geneva: World Health Organization; 2011. [Online] Available from: http://www.who.int/malaria/world_malaria_report_2011/en/ [Accessed on 25th May, 2013]

[2] Beljaev AE. The malaria situation in the WHO eastern Mediterranean region. *Med Parazitol* 2000; **2**: 12-15.

[3] Saebi A, Ranjbar M, Raeisi A, Nabavi M, Salehi M, Jamshidi M, et al. Malaria treatment guide in the Islamic Republic of Iran, ministry of health and medical education: Center for Diseases Control. Tehran: Center for Sound Publishing; 2006: 11-18.

[4] Harrison TB, Thorn GW, Wintrobe MM, Adams RD, Bennett Jr IL, Braunwald E, et al. *Harrison's principles of internal medicine*. 6th ed. New York: McGraw-Hill; 1970.

[5] Favere EM, Barnish G, Yamokgul P, Rooney W. Sensitivity *in vitro* of *Plasmodium falciparum* to three currently used antimalaria drugs on the western border of Thailand. *Trans R Soc Trop Med Hyg* 1999; **93**: 180-184.

[6] 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 Path* 2012; **22**(3): 403-407.

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

[8] 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.

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

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

[11] Bahmani M, Karamati SA, Banihabib EK, 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.

[12] Bahmani M, Banihabib EK. Comparative assessment of the anti-*Annelida* (*Limnatis nilotica*) activity of nicotine with niclosamide. *Global Vet* 2013; **10**(2): 153-157.

[13] Bahmani M, Avijgan M, Hosseini SR, Bahmani E, Mehrzadi S. Traditional application of medicinal plants in southern area of Ilam province for treatment diseases and clinical syndromes in small ruminants. *J Herb Drugs* 2011; **1**(2): 51-59.

[14] 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.

[15] Eftekhari Z, Bahmani M, Mohsenzadegan A, Gholami-Ahangaran M, Abbasi J, Alighazi N. Evaluating the anti-leech (*Limnatis nilotica*) activity of methanolic extract of *Allium sativum* L. compared with levamisole and metronidazole. *Comp Clin Pathol* 2012; **21**: 1219-1222.

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

[17] Shanks GD, Edstein MD. Modern malaria chemoprophylaxis. *Drugs* 2005; **65**(15): 2091-2110.

[18] 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 *Brucella melitensis*. *J Herb Med Pharmacol* 2013; **2**(1): 17-20.

[19] Hamedi Y, Safa O, Zare S, Tan-Ariya P, Kojima S, Looarreesuwan S. Therapeutic efficacy of artesunate in *Plasmodium vivax* malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2004; **35**(3): 570-574.

[20] Rosenthal PJ. Antimalarial drug discovery: old and new approaches. *J Exp Biol* 2003; **206**(Pt 21): 3735-3744.

[21] Woerdenbag HJ, Lugt CB, Pras N. *Artemisia annua* L.: a source of novel antimalarial drugs. *Pharm Weekbl Sci* 1990; **12**(5): 169-181.

[22] Avery MA, Gao F, Chong WK, Mehrotra S, Milhous WK. Structure-activity relationships of the antimalarial agent artemisinin. 1. Synthesis and comparative molecular field analysis of C-9 analogs of artemisinin and 10-deoxoartemisinin. *J Med Chem* 1993; **36**(26): 4264-4275.

[23] Saxena S, Pant N, Jain DC, Bhakuni RS. Antimalarial agents from plant sources. *Curr Sci* 2003; **85**(9): 1314-1329.

[24] Rafieian-Kopaei M. Medicinal plants and the human needs. *J Herb Med Pharmacol* 2012; **1**(1): 1-2.

[25] Nasri H, Shirzad H. Toxicity and safety of medicinal plants. *J Herb Med Pharmacol* 2013; **2**(2): 21-22.

[26] Jonville MC, Kodja H, Humeau L, Fournel J, De Mol P, Cao M, et al. Screening of medicinal plants from reunion island for antimalarial and cytotoxic activity. *J Ethnopharmacol* 2008; **120**(3): 382-386.

[27] do Ce´u de Madureira M, Paula Martins A, Gomes M, Paiva J, Proenca da Cunha A, do Rosario V. Antimalarial activity of medicinal plants used in traditional medicine in S. Tome and principe islands. *J Ethnopharmacol* 2002; **81**(1): 23-29.

[28] 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.

[29] 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.

[30] Setorki M, Rafieian M, Heidarian E, Ghatreh K, Shahinfard N, Ansari R, et al. Effect of *Rhus coriaria* consumption with high cholesterol food on some atherosclerosis risk factors in rabbit. *J Babol Univ Med Sci* 2012; **14**(3): 38-45.

[31] Kazemi S, Asgary S, Moshtaghian J, Rafieian M, Adelnia A, Shamsi F. Liver-protective effects of hydroalcoholic extract of *Allium hirtifolium boiss*. in rats with alloxan-induced diabetes mellitus. *ARYA Atheroscler* 2010; **6**(1): 11-15.

[32] Shamsi F, Asgari S, Rafieian M, Kazemi S, Adelnia A. Effects of *Cornus mas* L. on blood glucose, insulin and histopathology of pancreas in alloxan-induced diabetic rats. *J Isfahan Med School* 2011; **29**(147): 929-938.

[33] Behradmanesh M, Ahmadi M, Rafieian-kopaei M. Effect of glycogol on blood glucose level of patients with type II diabetes. *Iran J Endocrin Metabol* 2012; **14**(2): 163-168.

[34] 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.

[35] Azadmehr A, Hajiaghaee R, Afshari A, Amirghofran Z, Refieian-Kopaei M, Yousofi H, et al. Evaluation of *in vivo* immune response activity and *in vitro* anti-cancer effect by *Scrophularia megalantha*. *J Med Plants Res* 2011; **5**(11): 2365-2368.

[36] 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.

[37] Rafieian-Kopaei M, Hosseini-asl K. Effects of *Ocimum basilicum* on functional dyspepsia: a double-blind placebo-controlled study. *Iran J Med Sci* 2005; **30**(3): 134-137.

[38] Shahrani M, Rafieian M, Shirzad H, Hashemzadeh M, Yousefi H, Khadivi R, et al. Effect of *Allium sativum* L. extract on acid and pepsin secretion in basal condition and stimulated with vag stimulate in rat. *J Med Plants* 2007; **6**(24): 28-37.

[39] Sedighi M, Rafieian-kopaei M, Noori-Ahmadabadi M. *Kelussia odoratissima* Mozaffarian inhibits ileum contractions through voltage dependent and beta adrenergic receptors. *Life Sci J* 2012; **9**(4): 1033-1038.