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Review Articles

Herbal Remedies Connected to Malaria like Fever in Iranian Ancient Medicinal Books- Brief Review Article

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Abstract
Malaria is a major international public health problem. Drug-resistant parasites have made treatment and control of malaria more difficult. Therefore, safe, affordable and effective new drugs are urgently needed. Traditional medicine is an important source for new drugs. Determining the ancient medicinal books was the first step of this study for finding malaria or disease that has symptoms like malaria. Then the plants that used to treat "*Ghebbe Khalesseh fever*" were listed. Finally, recent antimalarial researches were explored. About 31 plants were identified. Information from these resources is valuable for the selection of plants for antiplasmodial screening programs.

Introduction

Malaria is a major international public health problem. In 2010, there were about 219 million cases of malaria and an estimated 660000 deaths mostly among young children below 5 years of age living in Africa (1).

Malaria is an acute febrile illness. It is caused by *Plasmodium* parasites. The parasites are transmitted to humans via the bites of infected *Anopheles* mosquitoes, called "malaria vectors". There are four types of human malaria: *Plasmodium falciparum, P. vivax, P. malariae* and *P. ovale. Plasmodium falciparum* and *P. vivax* are the most

common. *Plasmodium falciparum* is the most deadly. The first symptoms – fever, headache, chills and vomiting – may be mild and difficult to recognize as malaria (2).

There are three different forms of malaria:

- Malaria tertiana caused by *P. vivax* and *P. ovale* with recurring fevers every 48h.
- Malaria quartana caused by *P. malariae* and fevers occur every 72h.
- The most dangerous form is malaria tropica "tropical fever" caused by *P. falciparum* and also cause high fevers every 48h or else irregulatory (3).

Drug – resistant parasites and insecticide – resistant mosquito vectors have made treatment and control of malaria more difficult. Therefore safe, affordable, and effective new drugs are urgently needed (4). Throughout history man has searched for remedies to fight against disease and used plants for the treatment of ailments such as malaria. In Africa and probably in many parts of the world, populations use traditional medicines more than modern medicine. This is because traditional medicines are easily accessible to the majority of the populations (5).

The search for natural product derived antimalarials has been ongoing over the past four decades and resulted in notable discoveries, quinine and artemisinin (6,7).

Over 1200 plant species from 160 families are used to treat malaria and fever. On average, a fifth of patients used traditional herbal remedies for malaria in endemic countries. The Research Initiative on Traditional Antimalarial Methods (RITAM) was founded in 1999 with the aim of furthering research on traditional medicines for malaria (8). Nowadays, even the WHO suggests basic procedures for the validation of drugs of plant origin in developing countries (9). Geographical location and climatic condition variety as well as abundance of medicinal herbs species have provided Iran with very high potential for the manufacturing of medicinal herb products.

Malaria had been widely prevalent for a long time in Iran. Avicenna, the Iranian philosopher and physician, (980-1037 A.D.) about 1000 years ago described the clinical features of an intermittent febrile attack with 4-12 hours period of cold, hot and sweating stages which is actually the characters of paroxysm of malaria (10). The term malaria (mal'aria) was probably first used by the Italian physician Francisco Torti (1658 – 1741) in 1740, and literally means "bad air" referring to the swamp vapours, which supposedly caused the disease (11). The term of malaria was thus not used in these books. Among the symptoms of malaria, fever attacks are the most common symptom. According to this symptom, in the ancient medicinal books found a kind of fever that named "*Ghebbe Khalesseh fever*". Symptoms of this fever were very near to malaria. It had four distinct phases like malaria: I. Initial phase with muscle aches and headaches that named "*Malileh*". II. Cold phase with uncontrollable tremors and severe chills. III. Hot phase with very high fever for several hours. IV. Final phase that the body starts to sweat to lower body temperature. Its treatment in traditional medicine included these ways: the first step was bringing down the temperature with cold and moisture foods and medicinal plants. The second step was softening the abdomen with laxatives plants and finally removing the putridity from the body (12).

Traditional medicine dates back more than 3000 years in Iran. This research aimed to identify the important herbal remedies for treatment of the most related disease to malaria used in traditional medicine of Iran.

Materials and Methods

Ancient medicinal books

This research is based on the ancient books of medicine and pharmacy produced from 800s – 1700s A.D. These books were amongst the most important Iranian physicians' authors. The books used in this work are listed in Table 1.

Table 1: Ancient medicinal books used for the research

Name of book	Author	Description	Century of publication (A.D.)
Al-Mansouri	Muhammad ibn Zakariya Razi (Rhazes)	Medical book	9
Hedayat al-Motaallemin fi-Tebb	Ahmad Akhawayni Bukhari	Medical book	10
Qanun fi al-Tebb (Canon in Medicine)	Ibn Sina (Avicenna)	Medical and pharmacy book	11
Zakhireyi Kharazmshahi	Ismaeil Jurjani	Medical book	12
Khulasat al-Tajarub	Bahaaddin Nurbakhsh	Medical book	15
Tebbe Akbari	Hakim Mohammad Akbar Arzani	Medical book	17
Makhzan al-Adwiyyah	Seyyid Mohammad Hossein	Pharmacy book	18

Herbal remedies

As the term of malaria did not exist in the ancient medicinal books, so we searched the term of "fever". The textbooks were in Persian and Arabic, so we investigated keywords such as "Tab" in Persian and "Hommaa" in Arabic books. In these books, fever falls into three categories based on ethiology and period of fever: "*Yomiyyeh fever* (ephemeral fever)" "*Degh fever* (hectic fever)" "*Ofouni fever* (infectious fever)". If the external heat effects on *Arwah* (vital forces of life), yomiyyeh fever (one day fever) occurs and if the external heat effects on *Adha* (Fully-Grown Organs), degh fever (every day fever) occurs. Infectious fever occurs when *Akhlat* (structural components) receive external heat. This kind of fever is periodical like malaria. Physician of traditional medicine said *"Nobeh fever"* to this fever. The infection of phlegm, yellow bile, blood and black bile can cause fever. *"Ghebbe Khaleseh"* is a kind of yellow bile (*safra*) fever that takes 12h and then 36h without any fever. It means the fever recurring every 48h (Like tertian fever). The other symptoms of this fever include initial tremor, body tempreture (40 °C), headache and sweating are similar to malaria (12-17). So the term *"Ghebbe Khalesseh fever"* was nearer to malaria.

In the next step, we searched the plants used to treat *"Ghebbe Khalesseh fever"* (12-18). The Persian, Arabic or other names of plants are matched with scientific names compared with reference books (19-21).

Additionally recent antiplasmodial results of the plants in the world were reviewed.

Results and discussion

In total, 31 species of plants in 21 families were identified used for treating *"Ghebbe Khaleseh"* (Like tertian fever) in ancient medicinal books (Table 2). Plants are listed alphabetically by traditional name. The last column describes which books reported on them.

A further research was done to find recent scientific results relevant to possible antiplasmodial activities of the plants. Plants with reported activity are highlighted in bold in the table. Most remedies in the traditional books were prepared by boiling or soaking in water. Rhazes said "soak *Halile* (*Terminalia chebula*) in hot water for 24 hours, then filter the preparation and add *Taranjebin* (*Alhagi persarum*). Then give it in the morning when the patient has no fever". In a recent study, Pinmai et al. (2010) evaluated the in vitro and in vivo antiplasmodial activity of *Terminalia chebula* in *Plasmodium falciparum* K1 multidrug-resistant strain. It showed in vitro antimalarial activity with IC_{50} 15.41± 0.61(µg/ml).

Table 2: Plants, found in the seven books to treat malaria, are sorted by family, genus and species. Species names given in bold indicate those plants discussed in the text

Traditional name	Scientific name	Common name	The book listing the plant (Reference No.)
Adas	*Fabaceae* *Lens culinaris* = *Lens esulenta*	Adas	Q.(12)
Ajaas or Ejaas	*Rosaceae* *Prunus domestica* or *Prunus divaricata* or *Prunus spinosa*	Aalou	H.(14), Q.(12), Z.(15), A.(17), T.(16), MA.(18)
Baghlat-al-homghaa	*Portulacaceae* *Portulaca oleracea*	Khorfe	Z.(15), A.(17), MA.(18)
Banafsaj	*Violaceae* *Viola odorata*	Banafshe	Q.(12), Z.(15), T.(16), MA.(18)
Bazr-eghatouna or Esparze or Espaghul	*Plantaginaceae* *Plantago psyllium* or *Plantago ovata*	Esfarze	Q.(12), Z.(15), T.(16)
Bettikh-e hindi	*Cucurbitaceae* *Cucumis vulgaris*	Kharbozeh hindi	M.(13), Q.(12), Z.(15), MA.(18)
Ehlilaj-e Kaboli	*Combretaceae* ***Terminalia chebula***	Halile	M.(13), H.(14), Q.(12), MA.(18)
Esfaanaakh	*Amaranthaceae* *Spinacia oleracea*	Esfenaaj or Spenaaj	Z.(15),A.(17)
Hendebaa	*Asteraceae* ***Cichorium intybus***	Kaasni	H.(14), A.(17), MA.(18)
Khasse	*Asteraceae* *Lactuca sativa*	Kahou	A.(17), Q.(12)
Khatmi or Khetmi	*Malvaceae* *Althaea officinalis*	Khatmi	Q.(12), Z.(15)
Kheyaar shanbar or Folus	*Fabaceae* *Cassia fistula*	Kheyaar chanbar	M.(13), H.(14), Q.(12), Z.(15), A.(17), MA.(18)
Kozborah or Kazborah	*Apiaceae* ***Coriandrum sativum***	Geshniz or Keshniz	A.(17)
Lablaab-e kabir or Qassus	*Araliaceae* *Hedera helix*	Lablaab	Q.(12)
Maash	*Fabaceae* *Vigna radiate* = *Phaseolus radiates*	Maash	Z.(15), A.(17), MA.(18)
Onnab	*Rhamnaceae* *Ziziphus jujube* = *Ziziphus vulgaris*	Onnab or Annab	H.(14), Q.(12)
Oroz or Aroz	*Poaceae* *Oryza sativa*	Berenj	A.(17), MA.(18)
Qará or Yaqtin	*Cucurbitaceae* *Cucurbita pepo*	Kadou	M.(13), Q.(12), Z.(15), A.(17), MA.(18)
Qasad	*Cucurbitaceae* *Cucumis sativus*	Kheyaar-e sabz or Kheyaar-e baalang	M.(13), Q.(12), Z.(15), A.(17), T.(16), MA.(18)
Romman or Anaareyn	*Punicaceae* ***Punica granatum***	Anaar-e meykhosh	Q.(12), Z.(15), A.(17), T.(16), MA.(18)
Saghmouneya or Mahhmoude	*Convolvulaceae* *Convolvulus scammonia*	Saghmouneya	M.(13), H.(14), Q.(12), MA.(18)
Sanaa makki	*Fabaceae* *Cassia angustifolia*	Sanaa or Senaa	Q.(12)
Selq	*Chenopodiaceae* *Beta vulgaris*	Choghondar	Q.(12), T.(16)
Sepestaan or Sebestaan	*Boraginaceae* *Cordia myxa*	Sepestaan	Q.(12), Z.(15), MA.(18)
Shaah-e tare or Shaah-e taraj	*Fumariaceae* *Fumaria parviflora*	Shaahtare	Q.(12)
Shir khesht or Shir khoshk	*Rosaceae* *Cotoneaster nummularia*	Shir khesht	Q.(12), Z.(15), A.(17), T.(16), MA.(18)
Sous	*Fabaceae* ***Glycyrrhiza glabra***	Shirin bayaan	Q.(12), MA.(18)
Tabaashir	*Poaceae* *Bambusa arundinaceae*	Tabaashir	A.(17)
Tamarr-e hindi or Khormay-e hindi	*Fabaceae* ***Tamarindus indica***	Tamarr-e hindi	H.(14), Q.(12), Z.(15), A.(17), T.(16), MA.(18)
Taranjabin or Khar shotor	*Papilionaceae* *Alhagi persarum* = *Alhagi camelorum*	Taranjebin	M.(13), H.(14), Q.(12), Z.(15), MA.(18)
Zereshk – e abi	*Berberidaceae* *Berberis integerrima* or *Berberis densiflora*	Zereshk	T.(16)

Al-Mansouri (M), Hedayat al-Motaallemin fi-Tebb (H), Qanun fi al-Tebb (Q), Zakhireh kharazmshahi (Z), Tebbe Akbari (A), Khulasat al-Tajarub (T) and Makhzan al-Adwiyyah (MA)

A standard 4-day suppressive test on *P.berghei* infected mice was used to evaluate the in vivo antiplasmodial activity of the extract at 250 mg/kg/day. The result showed good suppression activity (68.89%) (22).

In "Tebbe Akbari" the author recommended to boil *Kaasni* (*Cichorium intybus*) in water and give to the patient before the onset of fever. Bischoff et al. (2004) studied the effects of *Kaasni* (*Cichorium intybus*) because of its use as antimalarial in Afghanistan that need to be prepared in a special process in the dark. They used the HB3 clone of the Honduras-1 *Plasmodium falciparum* and quantified parasite numbers by GIEMSA stained smears after 48h. At 10 µg/ml and 50 µg/ml the sesquiterpene lactones inhibited the growth of the parasites completely (23).

Avicenna described about soaking fruits of *Tamarr-e hindi* (*Tamarindus indica*) in water and then boiling it. The preparation is then filtered. The extract could be consumed with sugar. The patient should drink it every night. Asase et al. (2005) studies in Ghana showed that instead of leaf decoction, bark decoction can effectively be used to treat malaria (24). Koudouvo et al. (2011) investigated the antimalarial effect of a few plants in Togo folk medicine. Aqueous extract of fruit of *T. indica* has antimalarial activity with IC_{50} 4.786 µg/ml (25).

In "Tebbe Akbari" author said: "Sweet and sour *Anaar* (*Punica granatum*) juice with a little sugar is good for relief of fever". Dell'Agli et al. (2009) evaluated antiplasmodial activity of *Punica granatum* L. fruit rind. The *P. granatum* methanolic extract inhibited parasite growth in vitro with a IC_{50} of 4.5 and 2.8 µg/ml, for D10 and W2 strain, respectively. The activity was found to be associated to the fraction enriched with tannins (IC_{50} 2.9 and 1.5 µg/ml) in which punicalagins, punicalins, ellagic acid and its glycoside could be identified. Both the *P. granatum* methanolic extract and the fraction enriched with tannins did not show any in vivo efficacy in the murine model (26).

Shirin bayaan (*Glycyrrhiza glabra*) in the form of extract was given for treatment of fever. Esmaeili et al. (2009) studied antimalarial effects of methanolic extract of *Glycyrrhiza glabra* (27). The chalcone licochalcone A can be isolated from all *Glycyrrhiza* species in different amounts and has been shown to exhibit good antimalarial activity. In in vivo tests against *P. yoelii* in mice, oral doses of 1000 mg/kg resulted in the complete eradication of the malaria parasite and no toxicity was noted (28). Licochalcone A inhibited in vitro growth of both chloroquine-susceptible (3D7) and chloroquine-resistant (Ddz) strains of Plasmodium falciparum to same extent in [3H] hypoxanthine uptake assay (29).

Ruiz et al. (2011) evaluated the antimalarial potential of traditional remedies used in Peru. The survey took place on six villages and led to the collection of 59 plants. Thirty five hydro-alcoholic extractions were performed on the 21 most cited plants. The extracts were then tested for antiplasmodial activity in vitro on *Plasmodium falciparum* chloroquine resistant strain (FCR-3). *Coriandrum sativum* L. showed antiplasmodial activity with IC_{50}>10 (µg/ml) (30).

The family *Fabaceae* was represented by six species and the family *Cucurbitaceae* was represented by three species. The other families had one or two species each. Two plants of *Fabaceae*, *Glycyrrhiza glabra* and *Tamarindus indica* have showed antiplasmodial effect.

Conclusion

A quick glance at the PubMed database (http://www.ncbi.nlm.nih.gov/) with the keywords: "malaria drug", 13,147; "malaria and immunity", 5,300; while searching "malaria and plants", 769; and "malaria and traditional medicine" only gives 216 references (citations dating back to the mid-1950s) (9). According to table (2), only 20% of plants have recent scientific results against *Plasmodium*. Very little antimalarial research has been done with traditional medicine (especially traditional medicine of Iran), and the vast majority of plants de-

scribed here for their effects on fever have never been studied for antiplasmodial activity. Research on active principles present in these plants should be studied to produce lead compound for treatment of malaria.

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In memoriam: Farzaneh Naghibi passed away on Jan. 2014. She was known for her ability to span a wide range of scientific disciplines. She will be remembered for her scientific integrity in Ethnobotany and Pharmacognosy.

References

1. WHO fact sheet malaria; 2010. Available from: http://www.who.int/mediacentre/factsheets/fs094/en/.
2. Brooks GF, Carroll KC, Butel JS, Morse SA. Parasitology. In: Jawetz, Melnick, & Adelberg's Medical Microbiology 24th ed. New York: McGraw-Hill; 2007. Chapter 46.
3. Adams M, Alther W, Kessler M, Kluge M, Hamburger M. Malaria in the renaissance: Remedies from European herbals from the 16th and 17th century. J Ethnopharmacol. 2011; 133:278-88.
4. WHO-TDR the World Health Organization, Special Programme for Research and Training in Tropical Diseases. April 26th 2006 revision date. Malaria. Available from: http://www.who.int/tdr/diseases/malaria/default.htm/.
5. Willcox M, Bodeker G, Rasoanaivo P. Traditional medicinal plants and malaria. CRC Press: Boca Raton; 2004.
6. Saxena S, Neerja Pant N, Jain DC, Bhakuni RS. Antimalarial agents from plant sources. Current Science. 2003; 85(9):1314-29.
7. White NJ. Qinghaosu (Artemisinin): the price of success. Science. 2008; 320:330-4.
8. Willcox M.L, Bodeker G. Traditional herbal medicines for malaria. Br Med J. 2004; 329:1156-9.
9. Bourdy G, Willcox M.L, Ginsburg H, Rasoanaivo Ph, Graz B, Deharo E. Ethnopharmacology and malaria: New hypothetical leads or old efficient antimalarials? Int J Parasitol. 2008; 38:33-41.
10. Edrissian GhH. Malaria in Iran: Past and Present situation. Iran J Parasitol. 2006; 1(1):1-14.
11. Packard RM. The making of a Tropical Disease. The John Hopkins University Press. Baltimore: Maryland; 2007.
12. Avicenna. Canon in Medicine (in Arabic). 1st ed. *Dar Ihya* al-*Turath al*-Arabi: Beirut; 2005. vol.4.
13. Muhammad ibn Zakariya Razi. Al-Mansouri (in Arabic). 1st ed. Arab League Education, Culture and Science Organization: Kuwait; 1987.
14. Ahmad Akhawayni Bukhari. Hedayat al-Motaallemin fi-Tebb (in Persian). 2nd ed. Mashhad University. Mashhad: Iran; 1992.
15. Ismaeil Jurjani. Zakhireyi Kharazmshahi (in Persian). 1st ed. Tehran: Academy of Medical Sciences. Tehran: Iran; 2001.
16. Bahaaddin Nurbakhsh. Khulasat al-Tajarub (in Persian). 1st ed. Tehran University of Medical Sciences. Tehran: Iran; 2008.
17. Hakim Mohammad Akbar Arzani. Tebbe Akbari (in Persian). 1st ed. Institute of Natural Medicine. Qom: Iran; 2008.
18. Seyyid Mohammad Hossein. Makhzan al-Adwiyyah (in Persian). 1st ed. Tehran University of Medical Sciences. Tehran: Iran; 2011.
19. Amin Gh. Popular medicine plants of Iran. Medical Science Tehran University and Ethic and Medical History Research Centre. Tehran: Iran; 2005.
20. Ghahreman A, Okhovvat AR. Matching the old medicinal plant names with scientific terminology. University of Tehran Press. Tehran: Iran; 2004.
21. Soltani A. Encyclopedia of Traditional Medicine (Dictionary of Medicinal Plants). Iran University of Medical Sciences and Health Services. Tehran: Iran; Vol(s). 1-3.

22. Pinmai K, Hiriote W, Soonthornchareonnon N, Jongsakul K, Sireeratawong S, Tor-Udom S. In vitro and In vivo Antiplasmodial Activity and Cytotoxicity of Water Extracts of *Phyllanthus emblica*, *Terminalia chebula*, and *Terminalia bellerica*. J Med Assoc Thai. 2010; 93(7):120-6.
23. Bischoff TA, Kelley CJ, Karchesy Y, Laurantos M, Nguyen-Dinh P, Arefi AG. Antimalarial activity of lactucin and lactucopicrin: sesquiterpene lactones isolated from *Cichorium intybus* L. J Ethnopharmacol. 2004; 95(2-3):455-7.
24. Asase A. Ethnobotanical study of some Ghanaian anti-malarial plants. J Ethnopharmacol. 2005; 99:273-9.
25. Koudouvo K, Karou SD, IIboudo DP, Kokou K, Essien K, Aklikokou K, de Souza C, Simpore J, Gbeassor M. In vitro antiplasmodial activity of crude extracts from Togolese medicinal plants. Asian Pac J Trop Med. 2011; 4(2); 129-32.
26. Dell'Agli M, V.Galli G, Corbett Y, Taramelli D, Lucantoni L, Habluetzel A, Maschi O, Caruso D, Giavarini F, Romeo S, Bhattacharya D, Bosisio E. Antiplasmodial activity of *Punica granatum* L. fruit rind. J Ethnopharmacol. 2009; 125(2):279-85.
27. Esmaeili S, Naghibi F, Mosaddegh M, Sahranavard S, Ghafari S, Abdullah NR. Screening of antiplasmodial properties traditionally used among some Iranian plants. J Ethnopharmacol. 2009; 121(3):400-4.
28. Sianne S and Fanie RVH. Antimalarial activity of plant metabolites. Nat Prod Rep. 2002; 19:675-92.
29. Rastogi RP and Mehrotra BN. Compendium of Indian Medicinal Plants published by Central Drug Research Institute, Lucknow and National Institute of Sciences Communication and Information Resources. New Delhi: India; 1990-1994; 6: 395-8.
30. Ruiz La, Ruiz Li, Maco M, Cobos M, Gutierrez-Choquevilca A, Roumy V. Plants used by native Amazonian groups from the Nanay River (Peru) for the treatment of malaria. J Ethnopharmacol. 2011; 133(2):917-21.