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Traditional Herbal Treatment for Plasmodium Falciparum: A Systematic Review on Traditional Plants to Treat Malaria in Iran

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Abstract--

Background and Objective: *Malaria is a vector-borne disease of global importance, with the vast majority of its life-threatening cases caused by infection with Plasmodium falciparum parasites. A marked decrease in malaria-related deaths worldwide has been attributed to the administration of effective antimalarial against Plasmodium falciparum. Considering the great potential of Iran in terms of plant biodiversity, rich traditional knowledge and practice, and malaria endemicity in the southeast of Iran. The present systematic review attempted to explore, synthesize and compile medicinal research findings on antimalarial plants in Iran.*

Material and Method: *The searches were conducted by three independent researchers to find the relevant studies published from January 1999 until the end of December 2018. We searched for published literature in the English language in MEDLINE via PubMed, EMBASETM via Ovid, The Cochrane Library, and Trip database. The keywords used in the search strategy were malaria, Plasmodium falciparum, herbal medicine, traditional medicine, antimalaria treatment, anti-parasitic herbs.*

Results: *Detailed findings from five studies identified a total of Forty-one different plant species used in traditional malaria treatments throughout Iran. Khouzestan province represents the most antimalarial species, followed by Golestan. Arial parts and flowers were the most frequently used plant parts. Six plants, including Citrullus colocynthis, Buxushyrcana, physalis alkekengi, Glycyrrhiza glarba, Glycyrrhiza glabra, and Ferula oopoda showed more antiplasmodial activity that others with IC50 values ranging from 2.01to 26.6μg/ml against K1(Chloroquine-resistant) or 3D7 (Chloroquine-sensitive).*

Conclusion: *The investigated medicinal plants gathered in this article as a systematic review could be a key to identify the compounds with antimalarial effects.*

Key words--*Herbal treatment, Malaria, Plasmodium Falciparum, Plant biodiversity.*

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I. INTRODUCTION

Malaria is the most severe parasitic disease and one of the oldest recorded diseases in the world (1, 2). Malaria is the vast majority of its life-threatening cases caused by infection with Plasmodium falciparum parasites (3). It affects 219 million people per year worldwide (4). It is one of the world's leading health problems, causing about 435,000 deaths in 2017, the vast majority of deaths (99.7%) were due to Plasmodium falciparum malaria (5).

Malaria has now spread across a wide area around the equator, some regions of the Americas, Africa, and a large part of Asia. The importance of malaria in the World Economy and Health has led to important scientific projects that are considered to Evaluate and recognize the therapeutic solutions for this disease (6-9)

In recent years, the emergence of drug-resistant Plasmodium species has exacerbated the health and economic impact of malaria. In particular, P. falciparum (the most pathogenic human parasite) has developed resistance to virtually all currently available antimalarial drug (10). History shows that plants have been a pivital source of medicines against malaria with two of the primary drugs used in malaria treatment, quinine and, more recently artemisinin, both having derived from traditional medicine and plants (11, 12). Artemisinin derivatives are now recommended by the World Health Organization worldwide. In combination with other drugs, such as lumefantrine, amodiaquine, mefloquine, sulphadoxine-pyrimethamine (SP), as the first-line treatment of malaria. This fact has encouraged the continuing search for new natural product-derived antimalarial drugs. There are several plants to treat malaria in endemic countries, also several studies have been conducted to evaluate the inhibitory effects of the plant extracts on P.falciparum (13-17).Traditional medicines are a potential supply source of new drugs against malaria and other infectious diseases (11). Using the medicinal products with plant origin has been extended due to fewer side effects, improving in patient acceptance, lower cost, and also more consistent with the normal physiological function of the human body (12). Despite the intensive efforts to control malaria, the disease continues to be one of the most significant health problems in the southeastern part of the country. Resistance to chloroquine for P. falciparum has been reported since 1983 in Iran.

Proper documentation of traditional medicine and plants used in the prophylaxis and treatment of malaria constitutes a critical task not only in preserving precious indigenous knowledge and biodiversity but also in enhancing community access to and stakes in the improvement of malaria control interventions. It is also crucial for stimulating future research on the safety and efficacy of medicinal plants and identification of chemical entities that could be developed into new standardized phytomedicines (18-30). Moreover, available research evidence on indigenous antimalarial plants is highly Scattered, which underscores the serious need for systematic compilation and synthesis. Considering the enormous potential of Iran in terms of plant biodiversity, rich traditional knowledge and practice, and malaria endemicity in the southeast of Iran, the present systematic review attempted to explore, synthesize and compile medicinal research findings on antimalarial plants in Iran.

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II. MATERIAL AND METHOD

Search methods for eligible studies

Three independent researchers of the research team developed a strategy to search for articles to be included in the systematic review. Between 13th April and 18th June 2019 six medical databases, including Medline, Scopus, Excerpta Medica Database (EMBASE), Ovid, Trip database, and the Cochrane library, were used to search for potentially eligible publications. For literature published in Persian, we searched national databases (Magiran and SID). Supplemental sources included Boolean operators that helped to conduct more efficient searches from these databases. Also, search engines such as Google and Google Scholar were also used to identify all potentially eligible publications. Another search was performed between 7th February and 5th November 2019.

Eligibility criteria

The inclusion criteria we used to select articles are as follows: 1) Published medicinal surveys reporting on anti-Plasmodium falciparum plants conducted in Iran without time limitation; 2) Original retrospective and prospective blinded studies investigating the medicinal research findings on anti-Plasmodium falciparum plants in Iran; and 3) Published peer-reviewed and research articles between January 1999 and December 2018 and, written in English or Persian.

Exclusion criteria

The following types of research data were excluded from analysis: 1) Data from review articles, conference papers, preprints, historical documents or experimental studies; 2) Data from published and unpublished medicinal surveys lacking information on anyone of the following: study areas/localities, informant's involvement, scientific plant names, and not reporting information about antimalarial medicinal plants.

Search strategy

Three persons reviewed titles and abstracts of retrieved studies from medical database of interest. The full texts of each study were retrieved, analyzed, and the screened studies were included in the review. The special search strategies were created using the Health Sciences Librarian website with specialization in systematic review searches using the Medical Subject Headings (MeSH) phrases and open phrases in accordance with the PRESS standards. After finalizing the MEDLINE strategy, the results were compared to search the other databases. Similarly, PROSPERO was searched to find recent or ongoing systematic reviews. The key search terms, including malaria, *Plasmodium falciparum*, herbal medicine, traditional medicine, antimalaria treatment, and anti-parasitic herbs. Corresponding authors of relevant documents were asked to provide full texts when not free or inaccessible and when it was not possible, i.e., non-reply or negative reply from corresponding authors, these full texts were purchased. In addition, the reference list of relevant documents was also examined to increase the chances of finding eligible papers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to depict the entire stepwise process of the screening strategy.

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Data extraction and risk of bias evaluation

The data were extracted for evaluating the characteristics of the participants and independently keyed in an Excel spreadsheet (Microsoft Office 2016, USA) by a person to ensure internal quality control of the database. The index test included characteristics, including specialized equipment, reference standard (executor of the tests, and the interval between tests). The information related to medicinal research findings on antimalarial plants in Iran was also extracted. The first reader extracted the data. The second and third readers confirmed the data, and he would have completed them if they were incomplete.

III. RESULTS

Study Selection

A total of 985 articles were extracted through our preliminary searches in different databases. Of the 465 non-redundant studies identified by analyzing the titles and abstracts, 432 studies were ruled out due to irrelevant titles. Of the existing 33 studies, 5 studies met the inclusion criteria, and of the 28 excluded studies, 18 did not have the full text, 5 were review articles, 2 were the letter to editor, and 3 did not meet the minimum inclusion criteria (Fig. 1).

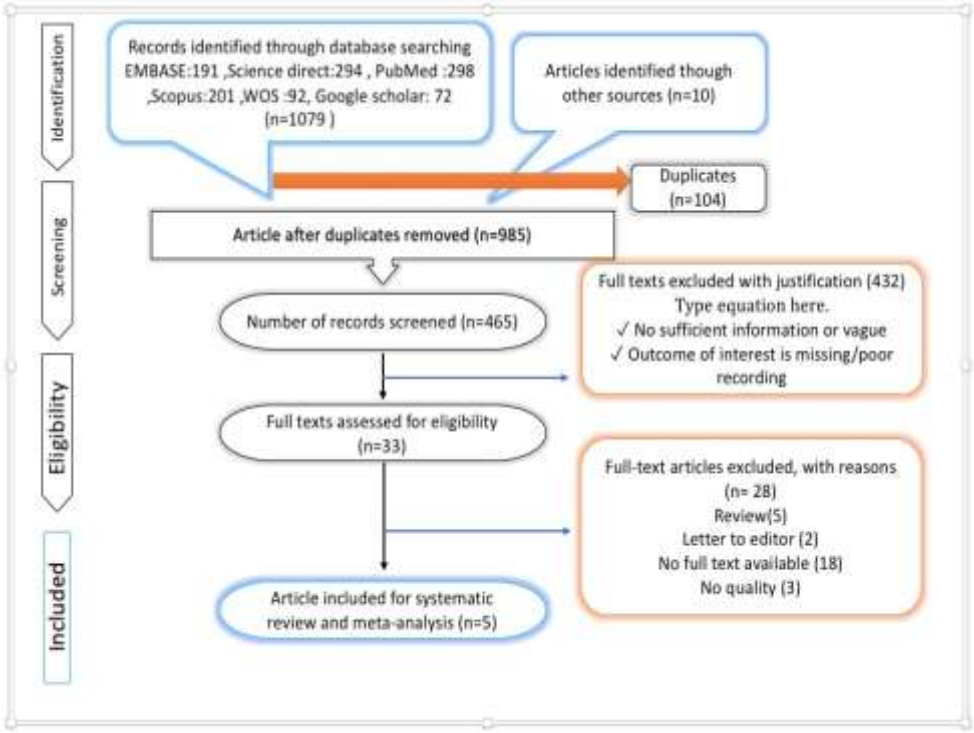

Fig 1. PRISMA flow diagram

Research Specifications

Forty-one different plant species used in traditional malaria treatments throughout Iran were studied. A total of 5 studies reporting the anaimalarial species of 10 provinces meeting the inclusion criteria were reviewed. Of these 5 studies, three studies conducted in Tehran, Ahvaz and Zanjan. All of the studies were in vitro. Two of the studies were performed on the methanolic extracts of medicinal plants and the other three were done on the Ethanolic extracts (Table 1).

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Table 1. Included studies characteristics

ID	Author	Publication year	Province	Invitro/ Inivitro	Number of plant study	Extracted of
1	Esmaeili	2008	Tehran	Invitro	32	Methanol extracted
2	Ramazani	2010	Tehran	Invitro	10	Ethanol extracted
3	Ramazani	2010	Tehran	Invitro	5	Ethanol extractet
4	Sangian	2013	Zanjan	Invitro	10	Ethanol extracted
5	Hadaddad	2017	Ahvaz	Invitro	10	Methanol extracted

Anti‐ malarial medicinal plants in Iran

A total of 5 studies identified a total of Forty-one different plant species used in traditional malaria treatments throughout Iran. Table 1 summarizes the overall study characteristics. Table 2 summarizes the detail of traditional herbal medicine used for the treatment of malaria in Iran.

Fig 2. Geographic distribution of antimalarial plants in Iran

Geographic distribution of antimalarial plants

The geographic distribution of antimalarial plants is likely to be predicated on local trends concerning disease risk, floral diversity, and cultural diversity, including traditional medicinal practices. Khouzestan province represents the most antimalarial species, followed by Golestan (table 2).

Diversity of antimalarial plants

The antimalarial plant species identified in different region of Iran belonged to seventeen different plant families cited plant families included: Lamiaceae(16-18),Moraceae (16, 17), Solanaceae (16-18), Fabaceae (16, 17), Malvaceae (12, 18), Apiaceae (16), Asteraceae (16), Buxaceae (16), Cucurbitaceae (18), Salicaceae (18), Compositae (12, 18), Verbenaceae (18), Portulacaceae (18), Arteemisia (19), Boranginaceae (12),

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Papilionaceae (12), Plantaginaceae (12), Myrtaceae (12) Frequent citation of particular plant species or families could indicate potentially higher bioactive antimalarial content. Such evidence is pertinent for prioritizing future pharmacological research agendas. (table2)

Plant parts used and condition of preparations

The majority of antimalarial herbal remedies were prepared from a single plant part, while some were prepared from a combination of two or more plant parts. Arial parts and flowers were the most frequently used plant parts (table2).

In vitro antiplasmodial activity

In the studies included, the anti-plasmodial activity of the extracts was determined against the chloroquine-resistant (K1) and chloroquine sensitive(3D7) strains of Plasmodium falciparum that were continuously cultured according to the methods described by Trager et al (20). Among these Forty-one plants, six plants showed better antiplasmodial activity: Citrullus colocynthis (cucurbitaceae), Buxus hyrcana (Buxaceae), physalis alkekengi (Solanceae), Glycyrrhiza glarba (Papilionaceae), Glycyrrhiza glabra(Fabaceae) and Ferula oopoda (Apiaceae) with IC50 values ranging from 2.01to 26.6**µ**g/ml against K1 or 3D7. (table 2)

Table 2. Medicinal plant families, species, locality, parts used, Date of collection, other medicinal values and Antiplasmodial activity *(Plasmodium falciparum*) of plants used for the treatment of malaria in Iran

Family	Scientific name	Locality(pro vince)	PU	Date of collection	Other medicinal values	Antiplasmodial activity *Plasmodium falciparum*, IC50 (µg/ml)		Reference
						Extracts IC50 3D7 (µg / ml)	Extracts IC50 K1 (µg / ml)	
Lamiaceae	*Otostegiapersica* (Burm.) Boiss .	SistanvaBaluchestan	Fr, L	June 2008	Malaria, rheumatism	>64	31.1	16
	*Perovskiaabrotanoides*Karel.	Golestan	AP	June 2008	Leshmaniasis, dermal disorders	>64	37.3	16
	Eremostachyslaciniata	N/A	R	July 2010	Malaria	>200	N/A	18
	*Otostegiamichauxii*Briq.	Fars	AP	June 2008	Malaria	>64	44.6	16
	Teucriumpolium	Tehran	AP	July 2014	Fever, infection, inflammation	>200	>200	19
	Marrubiumvulgare L	Mazandaran	B	N/a	Fever, bronchitis, vermifuge	>64	>64	16
	*Scutellariamulticaulis*Boiss. *subsp.multicaulis*	KohkilouiehBuierahmad	AP	N/A	Antimicrobial	>64	>64	16
	Lavandulaangustifolia	Tehran	FL	August 2014	Fever, infection, inflammation	173.26	>200	19

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Solanaceae	*Solanumalatum*	Khouzestan	N/A	October, 2007	Headache, infection, wound healing, dysentery	>200	>200	17
	Solanumsurattense	SistanvaBaluchestan	N/A	March, 2005	Antipyretic, inflammation	N/A	50	17
	Solanumnigrum	Guilan	Fr	September 2014	Fever, infection, inflammation	18.67	10.29	19
	Physalis alkekengi	Guilan	L,Fr	August 2014	Fever, infection, inflammation	13.08	11.31	19
Moraceae	*Ficuscarica*L. var. genuinaBoiss.	Tehran	AP	N/A	Hepatic tonic, malaria	>64	>54	16
	Ficusbengalensis	Khouzestan	N/A	May, 2007	Wound healing, sedative, antirheumatism, inflammation	>200	>200	17
	Ficuscarica	Khouzestan	N/A	May, 2007	Ascites, Anemia, inflamation	>200	>200	17
	Morus alba	Khouzestan	N/A	May, 2007	Antipyretic, diuretic, laxative	>200	>200	17
Fabacea e	*Coluteapersica*Boiss.	Mazandaran	AP	N/A	Antimicrobial	>64	>64	16
	*Glycyrrhizaglabra*L.	Gilan	AP	N/A	Gastric ulcers, hepatic disorders, malaria	>64	17.5	16
	Prosopisjuliflora	Khouzestan	N/A	October, 2007	Fever, inflammation	N/A	14.78	17
	Acacia farnesiana	Khouzestan	N/A	May, 2007	wound healing, analgesic	>200	>200	17
Malvaceae	Althea officinalis	N/A	Fl	june 2010	Malaria	62.77	N/A	18
	Gossypiumherbacum	Golestan	L	July 2014	Fever, infection, inflammation	146.56	159.36	19
Apiaceae	*Asftrodaucusorientalis*(L.) Drude.	Tehran	AP	N/A	Antimicrobial	42.6	46.1	16
	Ferula oopoda (Boiss and Bushe) Boiss.	Golestan	R	N/A	Cough, Migraine	24.9	26.6	16
Asteraceae	*Centaureabrugueriana* DC	Khorasan-e Shomali	AP	N/A	Antimicrobial	36.9	>64	16
	Centaureagolestanica (Akhani and Wagenitz.)	Golestan	AP	N/A	Antimicrobial	31.6	35.6	16
	*Matricariachamomilla*L.	Tehran	AP	N/A	Dermal wound, inflammation, malaria	>64	>64	16
Buxaceae	*Buxushyrcana*Pojark.	Gilan	AP	N/A	Rheumatism, malaria	7.7	4.7	16

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Cucurbitaceae	*Citrullus colocynthis*	Khouzestan	Fr	July 2014	Fever, infection, inflammation	2.01	6.9	19
Salicaceae	*Salix alba*	Alborz	L	July 2014	Fever, infection, inflammation	164.49	>200	19
Compositae	*Achilleamillefolium*	Golestan	fl	May 2014	Fever, infection, inflammation	34.36	142.36	19
	Anthemisnobilis	N/A	fl	June 2012	Malaria	>200	N/A	18
	Arctiumlappa	N/A	R	June 2010	Malaria	107.25	N/A	18
Verbenaceae	*Verbena officinalis*	Khozestan	Fl	June 2014	Fever, infection, inflammation	>200	>200	19
Portulacaceae	*Portulacaoleracea*	Tehran	AP	August 2014	Fever, infection, inflammation	136.57	172.39	19
Labiatae	Melissaofficinalis	N/A	AP	June 2010	Malaria	>200	N/A	18
	Stachyslavandulifolia	N/A	Fl	June 2010	Malaria	156.49	N/A	18
Boraginaceae	Boragoofficinalis	N/A	Fl	May 2012	Malaria	62.77	N/A	18
Papilionaceae	Glycyrrhizaglabra	N/A	R	June 2012	Malaria	13.56	N/A	18
Plantaginace	Plantago major	N/A	S	May 2012	Malaria	40.00	N/A	18
Myrtaceae	Myrtuscommunis	N/A	AP	May 2012	Malaria	42.18	N/A	18

PU= Part Used (L=Leaf, S=Stem, R=Root, , AP= Arial Part, Fr=Fruit, B:Bark, , S=Seed, Fl=Flower),N/A=not applicable

The resistance index is expressed as the ratio of the IC50 for strain K1 (Chloroquine resistant) to the IC50 for strain 3D7 Chloroquine-sensitive).

IV. DISCUSSION

This systematic review focused on studies having evaluated the antiplasmodial activity of plants in Iran. The findings of the present study showed that there are important medicinal plants against malaria in Iran that have the potential to inhibit malaria and are useful in removing Plasmodium falciparum infections. The results of this study are in line with those of other researchers around the world about the importance and understanding of antimalarial medicinal plant compounds (31-35).

Besides, the findings of our review study showed a high diversity of medicinal plants. This antimalarial plant species identified in different region of Iran belonged to Seventeen different plant families Cited plant families. Also, a large number of species have been observed in other studies in Africa and the United States (36, 37).

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The antimalarial activity of herbal plants is due to the presence of a number of metabolically active compounds (37). These compounds include alkaloids (naphthyl isoquinolines, bisbenzyl isoquinolines, protoberberines and aporphines, indoles, manzamines, and miscellaneous alkaloids) terpenes (sesquiterpenes, triterpenes, diterpenes, and miscellaneous terpenes) quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones and coumarines, and miscellaneous antimalarials from nature (38-44).

The solvent of extraction largely determines the concentrations of the active metabolites in the extract. For example, methanolic extracts of the herbal plants are more active in vitro than water extracts, probably due to the presence of higher amounts of more active lipophilic compounds. The levels of activity of the antimalarial plant extracts depend on the concentration of the active antimalarial secondary metabolites. For example, gedunin, a very active compound against Plasmodium present in leaves of A. indica showed an IC50 of 0.02 μg/ml against P. falciparum, but its concentration in the plant is very low and thus moderate activity of its extract (32, 45, 46).

The manner and conditions of the use of antimalarial medicinal plants are essential. Effective constituents of medicinal plants are reduced under inappropriate conditions, and proper use of medicinal herbs is vital for disease recovery.

Most commonly, the herbal medicines are prepared as water extracts in the form of decoction and infusion or as steam baths. The dose of the extract given is dependent on the age of the patient and the "strength" of the herbal medicine, although occasionally the weight of the patient. The quantity of extract given ranges from 100 to 500 ml, 100 to 250 ml, and 1 to 3 tea or tablespoons for adults, older children, and young children below five years of age, respectively, between 1 and 3 times a day for about a week or until when the patient has recovered .The extracts are mostly prepared from single herbal plants or from the combination of two herbal plants, for example, a decoction of Tamarindus indica and Mangifera indica is common. Medicine for malaria treatment from a herb such as B. pilosa can be made by squeezing a handful of its freshly picked leaves and drinking 1–3 teaspoons of the extract a day. Occasionally, malaria herbal medicines can be obtained by preparing different plant parts in combination; for example, an infusion can be made from fresh leaves and pounded fresh roots of V. amygdalina (32, 46-50).

Now, the important problem with malaria is the mutations in the back of the head that cause the resistance of some Plasmodium falciparum strains to many drugs, including artemisinin (50-53). Genetic studies have shown that Plasmodium falciparum isolated from the Amazon forest possesses mutant drug resistance genes that affect treatment (54).

In this studies, the antiplasmodial activity of the extracts was determined against the chloroquine-resistant and chloroquine-sensitive strains of Plasmodium falciparum. Six plants including: Citrullus colocynthis, Buxushyrcana, physalis alkekengi, Glycyrrhiza glarba, Glycyrrhiza glabra and Ferula oopoda showed more antiplasmodial activity with IC50 values ranging from 2.01to 26.6μg/ml against K1 or 3D7. Similar studies have investigated the antiplasmodial activity of medicinal plants and obtained similar results (55-62).

The suggestion of this study is to introduce a new drug for the control of malaria using medical and herbal sciences and combine the different herbal species in Iran and other parts of the world. Further studies and

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in vivo studies on the efficacy of these herbal remedies in the in vivo environment are needed to determine the effective concentration of these herbal remedies on clinical strains, their side effects, and their optimal performance. Evaluation to finally introduce these strains as a new anti-Plasmodium drug after completion.

V. CONCLUSION

It provides an overview of the antiplasmodial potential of medicinal Iran plants and highlights their usefulness as promising sources for new antimalarial drugs. The investigated medicinal plants gathered in this article as a systematic review could be a key to identify the compounds with antimalarial effects; therefore, if their compounds are examined, they might help to develop new and more efficient drugs.

It is hoped that such research can be used effectively in different parts of society to achieve better and healthier results and that the results of theoretical and laboratory studies will be applied to the world of medicine and industry.

Declaration of interest

The authors report no conflicts of interest.

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