

Analysis of Medication Rules of Traditional Chinese Medicine for Malaria Treatment Based on Data Mining

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ABSTRACT

Objective To analyze the medication rules of traditional Chinese medicine (TCM) for malaria treatment.

Methods Statistical analysis was conducted on the basic attributes of TCM drugs with regard to property, therapeutic methods, flavor, and meridian tropism. A complex network of TCM drug associations was constructed. Cluster analysis was applied to obtain the core drugs for malaria treatment. The Apriori algorithm was applied to analyze the association rules of these core drugs.

Results A total of 357 herbs were used 3,194 times in 461 prescriptions for malaria treatment. *Radix Glycyrrhizae* (甘草), *Rhizoma Pinelliae* (半夏), *Radix Bupleuri* (柴胡), and *Radix Dichroae* (常山) were the frequently used herbs through supplementing, exterior-releasing, heat-clearing, qi-rectifying, and damp-resolving therapeutic methods. Such herbs had warm, natural, and cold herbal properties; pungent, bitter, and sweet flavors; and spleen, lung, and stomach meridian tropisms. Cluster analysis showed 61 core drugs, including *Radix Glycyrrhizae*, *Rhizoma Pinelliae*, *Radix Bupleuri*, and *Radix Scutellariae* (黄芩). Apriori association rule analysis yielded 12 binomial rules (herb pairs) and 6 trinomial rules (herb combinations). *Radix Bupleuri* plus *Radix Scutellariae* was the core herbal pair for treating malaria. This pair could be combined with *Rhizoma Atractylodis Macrocephalae* (白术) for treating warm or cold malaria, combined with *Pericarpium Citri Reticulatae* (陈皮) or *Radix Dichroae* (地黄) for treating miasmatic malaria, or combined with turtle shells (鳖甲) for treating malaria with splenomegaly.

Conclusions TCM can be used to classify and treat malaria in accordance with the different stages of development. As the core herbal pair, *Radix Bupleuri* and *Radix Scutellariae* can be combined with other drugs to treat malaria with different syndrome types.

Key words: malaria; data mining; complex network; cluster analysis; medication rules

INTRODUCTION

Malaria remains a global public health problem and continues to spread worldwide, posing a serious threat to human health, particularly in African countries^[1]. In 2021, approximately 95% of global malaria cases occurred in Africa, resulting in 602,000 deaths^[2-4]. The use of artemisinin-based combination

therapies (ACTs), as recommended by the World Health Organization, has significantly reduced the incidence rate of malaria^[5]. However, over the past decade, the resistance of *Plasmodium falciparum* to ACTs has emerged in Southeast Asia and Africa^[6, 7], with a poorly known mechanism^[8-10], which highlights the importance of searching for new antimalarial drugs.

Traditional Chinese medicine (TCM) has a long history of treating malaria with different types of syndrome. Many TCM classics have described the origin, syndromes, dialectical treatments, and empirical formulas of malaria, providing rich evidence and data sources for mining malaria treatment regimens and drugs^[11]. Based on the records of artemisinin against malaria in the *Elbow Reserve Emergency Prescription*

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(《肘后备急方》), Tu Youyou (屠呦呦) successfully isolated artemisinin from *Herba Artemisiae Annuae* (青蒿) and saved millions of lives^[12]. In the present study, data mining methods such as statistical analysis, cluster analysis, and association rule analysis were used to summarize the medication patterns of malaria treatment formulas, thereby promoting clinical practice, research, and new drug development.

MATERIALS AND METHODS

Source and selection of prescriptions

The textual prescription provided by the Traditional Chinese Medicines Integrated Database^[13] (<http://www.megabionet.org/tcmid/>) was used as the original data. A self-developed TCM text prescription-structured design and implementation system (National Copyright Administration of the People's Republic of China; soft copy registration number: 2020SR1166428) was applied to decompose and structure the composition of prescriptions. For the main types of malaria, we searched the terms "malaria", "warm malaria", "cold malaria", "miasmatic malaria", "labor malaria", and "malaria with splenomegaly" in the indications of prescriptions. Consequently, 483 prescriptions for malaria treatment were obtained.

Exclusion criteria

The following records were excluded: records of incomplete prescription composition, records that cannot be verified, and records of prescription composition errors.

Data pre-processing

Considering that many TCM drugs have different names caused by the era of data source, region, and medical schools, the data were pre-processed by using the standard names in the *Chinese Pharmacopoeia* (2020 edition) and the *Chinese Materia Medica*.

Data analysis

Statistics of essential attributes of herbs

Essential attributes, such as the frequency of use, property, therapeutic methods, flavor, and meridian tropism of herbs used to treat malaria, were classified and counted.

Complex network of herbs

The composition, property, flavor, and meridian tropism of herbs were correlated using Excel, and the

complex network of the prescriptions was constructed and visualized using Cytoscape.

Cluster analysis

The MCODE plug-in for Cytoscape was used to cluster the complex network of the herbs and to obtain the core drugs for malaria treatment.

Analysis of association rules among drugs

The Apriori algorithm package in the R language was applied to analyze the association rules, with a confidence level of 0.6 and a support frequency set to 40.

RESULTS

Basic characteristics

Essential attributes of herbs

A total of 357 herbs were used 3,194 times in 461 prescriptions for the treatment of malaria, among which the frequently used herbs were *Radix Glycyrrhizae* (甘草), *Rhizoma Pinelliae* (半夏), *Bupleurum chinense* (柴胡), *Pericarpium Citri Reticulatae* (陈皮), and orange *Cortex Magnolia officinalis* (厚朴) (**Table 1**).

The frequently used therapeutic methods of the above mentioned 357 herbs included supplementing, exterior releasing, heat clearing, qi rectifying, and dampness resolving (**Table 2**).

The statistics of the four properties, five flavors, and meridian tropisms of herbs are shown in **Table 3**. Among the five flavors, the number of pungent, bitter, and sweet herbs were the largest. Warm, mild, and cold herbs had the highest frequency with regard to the four properties, whereas spleen, lung, stomach, and liver meridians had the highest frequency of meridian tropism.

Complex network of prescriptions

The complex network of the herbs was established on the basis of the composition of the prescriptions, properties, flavors, and meridian tropism of the drugs (**Fig. 1**).

Cluster analysis

After associating the five malaria syndromes and herbs into the complex network, the MCODE plug-in of Cytoscape was used for cluster analysis (parameter setting: degree cutoff: 2; node density cutoff: 0.1; node score cutoff: 0.2; k-core: 5; and max depth: 100). The clustering results are shown in **Fig. 2**, which is divided into four regions. The depth of the edge is colored to reflect the importance of drug pairs, and the size of the nodes reflects

Table 1. Statistical results of the frequency of herbal use (top 40)

Medicine name	Chinese name	Frequency/times
<i>Radix Glycyrrhizae</i>	Gan cao (甘草)	200
<i>Rhizoma Pinelliae</i>	Ban xia (半夏)	100
<i>Radix Bupleuri</i>	Chai hu (柴胡)	99
<i>Radix Dichroae</i>	Chang shan (常山)	99
<i>Pericarpium Citri Reticulatae</i>	Chen pi (陈皮)	94
<i>Cortex Magnoliae Officinalis</i>	Hou po (厚朴)	77
Poria	Fu ling (茯苓)	69
Ginseng	Ren shen (人参)	67
<i>Fructus Tsaoko</i>	Cao guo (草果)	64
<i>Radix Scutellariae</i>	Huang qin (黄芩)	63
<i>Rhizoma Atractylodis</i>	Cang zhu (苍术)	57
<i>Rhizoma Atractylodis Macrocephalae</i>	Bai zhu (白术)	57
Cinnabaris	Zhu sha (朱砂)	56
<i>Pericarpium Citri Reticulatae Viride</i>	Qing pi (青皮)	55
<i>Semen Arecae</i>	Bing lang (槟榔)	55
<i>Cortex Cinnamomi</i>	Rou gui (肉桂)	51
<i>Rhizoma Anemarrhenae</i>	Zhi mu (知母)	48
<i>Radix Angelicae Sinensis</i>	Dang gui (当归)	47
<i>Fructus Mume</i>	Wu mei (乌梅)	46
Realgar	Xiong huang (雄黄)	41
<i>Rhizoma Chuanxiong</i>	Chuan xiong (川芎)	41
<i>Carapax Trionycis</i>	Bie jia (鳖甲)	37
<i>Cablin Potchouli</i>	Huo xiang (藿香)	36
<i>Radix Aucklandiae</i>	Mu xiang (木香)	36
<i>Radix Et Rhizoma Rhei</i>	Da huang (大黄)	30
<i>Radix Paeoniae Alba</i>	Bai shao (白芍)	30
Moschus	She xiang (麝香)	29
<i>Rhizoma Cimicifugae</i>	Sheng ma (升麻)	29
Dried ginger	Gan jiang (干姜)	28
<i>Folium Perillae</i>	Zi su ye (紫苏叶)	26
<i>Radix Aconiti Lateralis Praeparata</i>	Fu zi (附子)	26
<i>Rhizoma Zingiberis Recens</i>	Sheng jiang (生姜)	26
<i>Fructus Aurantii</i>	Zhi ke (枳壳)	25
<i>Rhizoma Et Radix Notopterygii</i>	Qiang huo (羌活)	25
Arsenic	Pi shuang (砒霜)	24
Chinese date	Da zao (大枣)	24
Arsenlite	Pi shi (砒石)	23
<i>Fructus Crotonis</i>	Ba dou (巴豆)	23
<i>Semen Persicae</i>	Tao ren (桃仁)	22
<i>Bulbus Fritillariae Cirrhosae</i>	Bei mu (贝母)	20

Table 2. Commonly used therapeutic methods of 357 herbs

Therapeutic methods	Chinese term	Number of herbs	Therapeutic methods, n(%)
Supplementing	Bu xu (补虚)	43	572(17.91)
Exterior-releasing	Jie biao (解表)	26	373(11.68)
Heat-clearing	Qing re (清热)	44	296(9.27)
Qi-rectifying	Li qi (理气)	15	271(8.48)
Dampness-resolving	Hua shi (化湿)	9	258(8.08)
Blood-invigorating and stasis-dissolving	Huo xue hua yu (活血化瘀)	29	176(5.51)
Phlegm-dissolving and cough-panting-relieving	Hua tan zhi ke (化痰止咳)	13	171(5.35)
Interior-warming	Wen li (温里)	12	147(4.60)
Urination-promoting and dampness-percolating	Li shui qu shi (利水祛湿)	20	125(3.91)
Emetic	Yong tu (涌吐)	3	114(3.57)
Poison-attacking, insect-killing, and antipruritic	Gong du sha chong zhi yang (攻毒杀虫止痒)	17	106(3.32)
Mind-calming	An shen (安神)	15	86(2.69)
Purgative	Xie xia (泻下)	13	83(2.60)
Detoxifying and muscle-activating	Ba du sheng ji (拔毒生肌)	14	69(2.16)
Digestant	Xiao shi (消食)	10	61(1.91)
Worm-expelling	Qu chong (驱虫)	3	58(1.82)
Astringent	Shou se (收涩)	5	57(1.78)
Wind-dampness-expelling	Qu feng shi (祛风湿)	18	48(1.50)
Resuscitative	Kai qiao (开窍)	5	45(1.41)
Liver-calming and wind-extinguishing	Ping gan xi feng (平肝息风)	13	33(1.03)
Bleeding-stanching	Zhi xue (止血)	9	14(0.44)
Others		21	31(0.97)
Total		357	3194(100)

the number of drugs that has been used. The specific information on the clustering region is shown in **Table 4**.

Based on the degree, weight, closeness centrality, and betweenness centrality of nodes in the clustering results, 61 herbs were selected as the core herbs for malaria treatment (**Table 5**).

Different malaria syndromes are treated with different herbs. The core herbs used for the treatment of cold malaria include *Fructus Mume*, *Rhizoma Chuanxiong*, *Rhizoma Atractylodis*, *Cortex Magnoliae*

Table 3. Statistics of the properties, flavors, and meridian tropisms of 357 herbs in prescriptions for malaria, n (%)

Property	Number of herbs	Flavor	Number of herbs	Meridian tropism	Number of herbs
Warm	100 (34)	Pungent	135 (30)	Liver	116 (21)
Natural	62 (21)	Sweet	114 (25)	Lung	93 (17)
Cold	54 (19)	Bitter	109 (24)	Heart	75 (13)
Slightly cold	25 (9)	Salty	36 (8)	Kidney	67 (12)
Cool	21 (7)	Sour	25 (5)	Stomach	67 (12)
Slightly warm	14 (5)	Light	12 (3)	Spleen	63 (11)
Hot	9 (3)	Slightly bitter	11 (2)	Large intestine	41 (7)
Extremely hot	3 (1)	Astringent	8 (2)	Bladder	24 (4)
Extremely cold	2 (1)	Slightly sweet	5 (1)	Small intestine	8 (1)
Extremely warm	1 (0)			Sanjiao	3 (1)
Total	277		455 (100)		557 (100)

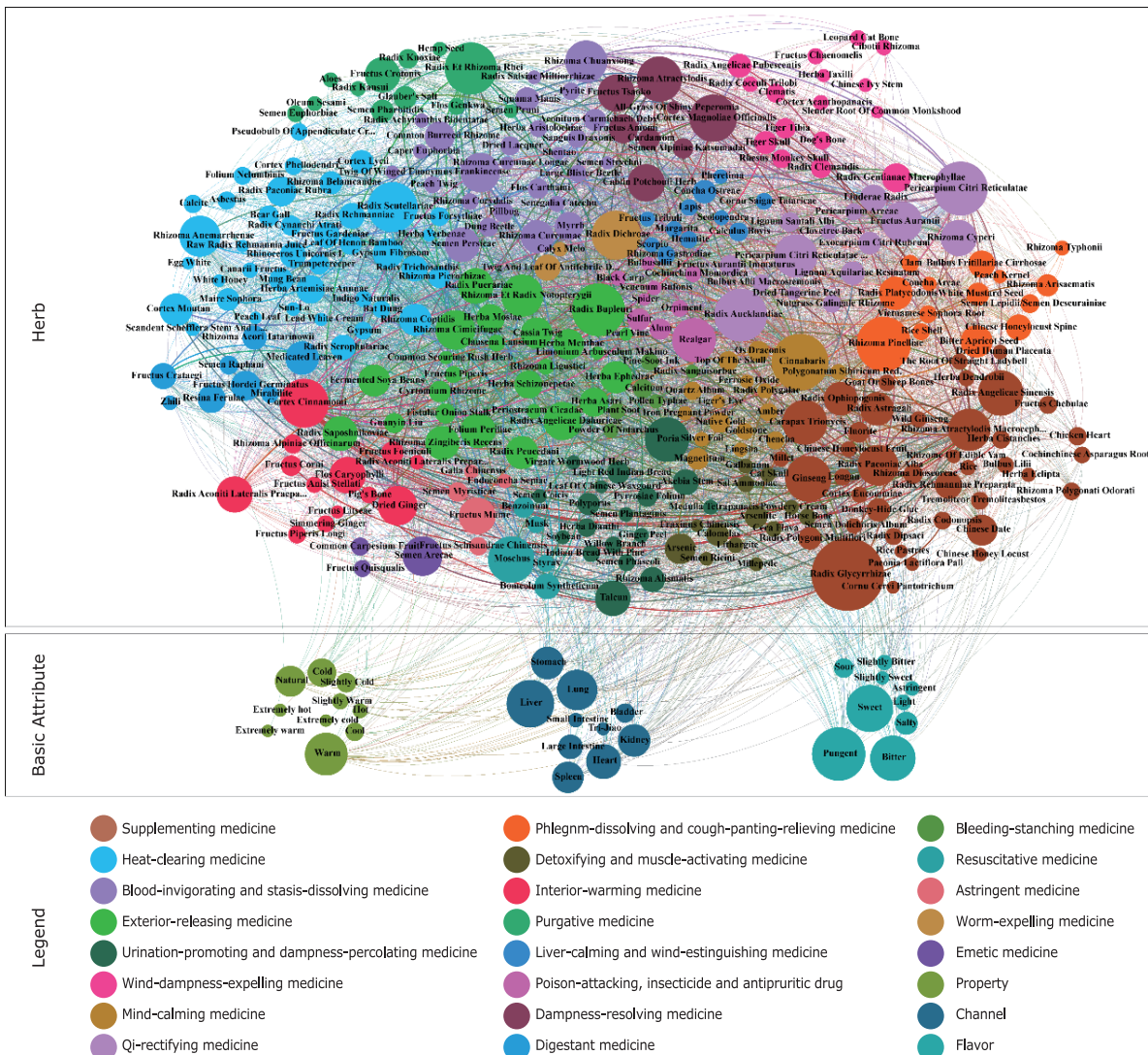


Figure 1 Complex network of herbs of the prescriptions for malaria in TCM. Each node in the herb area represents a herb, and the node size represents the number of drug citations. A larger node indicates more citations. The edge represents the formula's typical citation relationship between the two drugs. A darker color of the side represents more citations, and different colors represent different drug classes. The basic attribute area represents the three essential attributes of herbs: property, flavor, and meridian tropism. The node size represents the number of drugs related to this attribute. A larger node represents more drugs belonging to this attribute. The legend area describes the classes and essential attributes of the herbs.

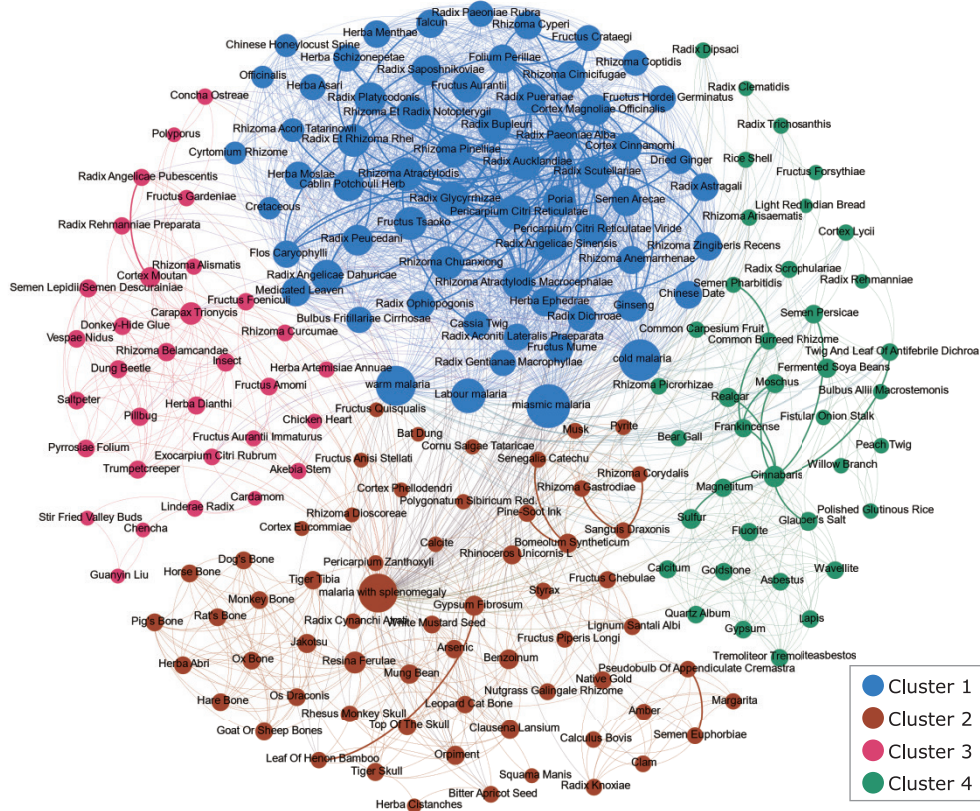


Figure 2. Results of cluster analysis for the complex network of herbs of the prescriptions for malaria in TCM

Table 4. Information of cluster analysis for the complex network of herbs of the prescriptions for malaria in TCM

Cluster	Score (Density*#Nodes)	Nodes	Edges	Seed node
1	45.000	59	1417	Ginseng (人參)
2	9.033	61	277	Resina Ferulae(阿魏)
3	8.581	32	134	Carapax Trionycis(鳖甲)
4	8.579	39	173	Radix Clematidis(威灵仙)

Officialis, Fructus Tsako, Cablin Potchouli herb, Radix Dichroae, and Radix Bupleuri. The core herbs used for the treatment of warm malaria include Fructus Mume, Rhizoma Chuanxiong, Rhizoma Atractylodis, Cortex Magnoliae Officinalis, Fructus Tsako, Radix Dichroae, Radix Bupleuri, Rhizoma Zingiberis Recens, and Rhizoma et Radix Notopterygii. The core herbs used to treat miasmatic malaria include Radix Angelicae Sinensis, Rhizoma Pinelliae, Radix Glycyrrhizae, Radix Bupleuri, Pericarpium Citri Reticulatae, Radix Scutellariae, poria, Rhizoma Atractylodis Macrocephalae, and Radix Aucklandiae. The core herbs used for the treatment of labor malaria include Radix Aucklandiae, Rhizoma Zingiberis Recens, Radix Angelicae Sinensis, Pericarpium Citri Reticulatae Viride, Rhizoma et Radix Notopterygii, Rhizoma Chuanxiong, and Rhizoma Cimicifugae. The

core herbs used for the treatment of malaria with splenomegaly include Flos Caryophylli, Rhizoma Curcumae, medicated leaven, cinnabaris, Carapax Trionycis, and Cortex Moutan. The same herbs can also be used to treat malaria with different syndrome types. The use of core herbs for treating different malaria syndrome types is shown in Fig. 3 (Venn diagram), and the list of herbs is shown in Table 6.

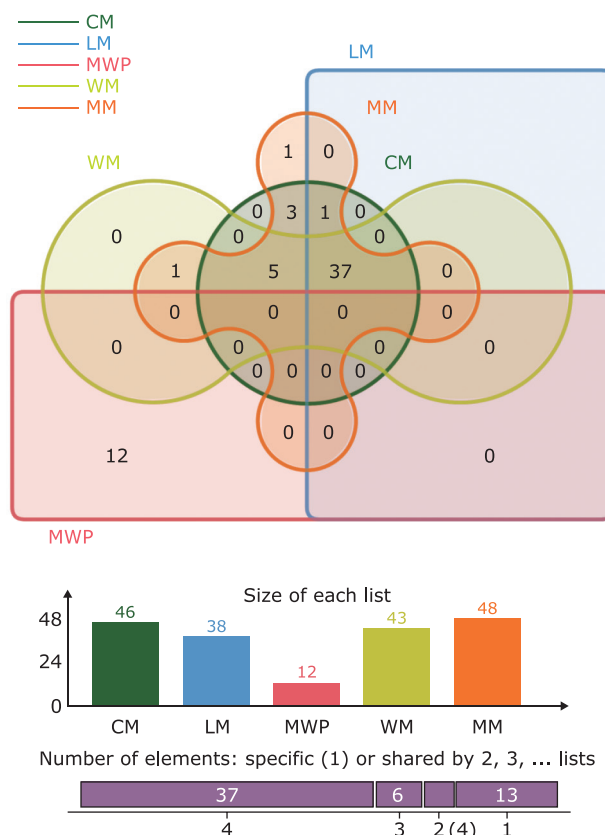
Association rules

The Apriori algorithm was used to analyze the association rules of 61 core herbs, setting the "support" frequency of 40 and a confidence level of 0.6 to obtain core drug combinations, and the distribution of the rules is shown in Fig. 4.

In maintaining high confidence and support, a

Table 5. Core herbs ($n=61$) for the prescriptions for malaria in TCM

ID	Herb name	ID	Herb name
1	<i>Radix Glycyrrhizae</i> (甘草)	32	<i>Radix Angelicae Dahuricae</i> (白芷)
2	<i>Cinnabaris</i> (朱砂)	33	<i>Fructus Mume</i> (乌梅)
3	<i>Rhinoceros Unicornis L</i> (犀角)	34	<i>Cablin Potchouli</i> (藿香)
4	<i>Pericarpium Citri Reticulatae</i> (陈皮)	35	<i>Radix Aconiti Lateralis Praeparata</i> (附子)
5	<i>Rhizoma Pinelliae</i> (半夏)	36	<i>Flos Caryophylli</i> (丁香)
6	<i>Radix Aucklandiae</i> (木香)	37	<i>Rhizoma Cyperi</i> (香附)
7	<i>Radix Bupleuri</i> (柴胡)	38	<i>Radix Puerariae</i> (葛根)
8	<i>Radix Et Rhizoma Rhei</i> (大黄)	39	Talcun
9	<i>Cortex Cinnamomi</i> (肉桂)	40	<i>Rhizoma Zingiberis Recens</i> (生姜)
10	<i>Radix Scutellariae</i> (黄芩)	41	<i>Semen Persicae</i> (桃仁)
11	<i>Radix Dichroae</i> (常山)	42	<i>Radix Ophiopogonis</i> (麦冬)
12	<i>Cortex Magnoliae Officinalis</i> (厚朴)	43	<i>Radix Astragali</i> (黄芪)
13	<i>Radix Angelicae Sinensis</i> (当归)	44	<i>Folium Perillae</i> (紫苏叶)
14	Ginseng (人参)	45	<i>Radix Saposhnikoviae</i> (防风)
15	<i>Rhizoma Atractylodis</i> (苍朮)	46	<i>Medicated Leaven</i> (神曲)
16	<i>Poria</i> (茯苓)	47	<i>Rhizoma Coptidis</i> (黄连)
17	<i>Moschus</i> (麝香)	48	<i>Herba Ephedrae</i> (麻黄)
18	<i>Carapax Trionycis</i> (鳖甲)	49	<i>Rhizoma Curcumae</i> (莪朮)
19	<i>Pericarpium Citri Reticulatae Viride</i> (青皮)	50	Chinese date (大枣)
20	<i>Rhizoma Atractylodis Macrocephalae</i> (白朮)	51	<i>Cortex Moutan</i> (丹皮)
21	<i>Rhizoma Et Radix Notopterygii</i> (羌活)	52	<i>Bitter Apricot seed</i> (杏仁)
22	<i>Rhizoma Chuanxiong</i> (川芎)	53	Fermented soya beans (豉)
23	Realgar (雄黄)	54	<i>Cassia Twig</i> (桂枝)
24	<i>Semen Arecae</i> (槟榔)	55	<i>Gypsum Fibrosum</i> (石膏)
25	<i>Rhizoma Cimicifugae</i> (升麻)	56	<i>Akebia Stem</i> (木桶)
26	<i>Frankincense</i> (乳香)	57	<i>Common Burreed Rhizome</i> (三棱)
27	<i>Rhizoma Anemarrhenae</i> (知母)	58	<i>Herba Artemisiae Annuae</i> (青蒿)
28	<i>Radix Paeoniae Alba</i> (白芍)	59	<i>Linderae Radix</i> (乌药)
29	Dried ginger (干姜)	60	<i>Maire Sophora</i> (黑豆)
30	<i>Fructus Aurantii</i> (枳壳)	61	<i>Bomeolum Syntheticum</i> (冰片)
31	<i>Fructus Tsaoko</i> (草果)		

**Figure 3.** Venn chart of core herbs of the prescriptions for treating different malaria syndromes in TCM

CM: cold malaria; LM: labor malaria; MWP: malaria with splenomegaly; WM: warm malaria; MM: miasmatic malaria

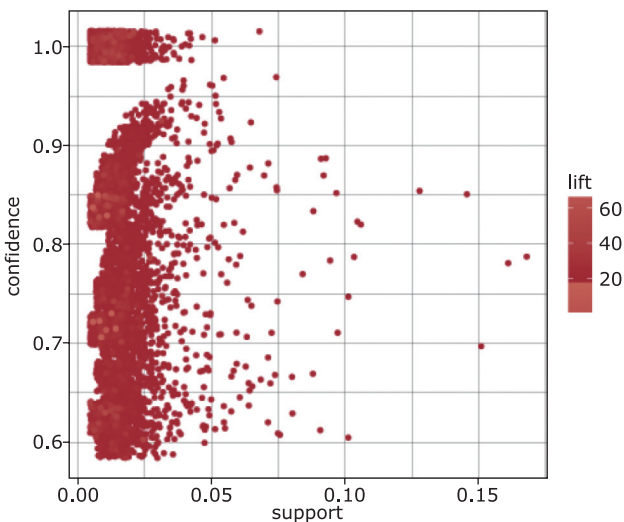
confidence level of 0.7 and a support level of 0.075 were selected to filter the conditions, which yielded 18 rules, including 12 binomial rules (**Table 7**) and six tripartite rules (**Table 8**).

DISCUSSION

In our present analysis, herbs with the highest frequency included *Radix Rhizoma Glycyrrhizae*, *Rhizoma Pinelliae*, *Radix Bupleuri*, *Radix Dichroae*, *Pericarpium citri reticulatae*, *Cortex Magnoliae Officinalis*, *poria*, *ginseng*, *Fructus tsaoko*, and *Radix Scutellariae*. If malaria is in Shaoyang, with the malaria gas stored half in the surface and half in the interior (i.e., inside the skin and outside the stomach), then the wind-heat-dispersing medicines (such as *Radix Bupleuri*) and heat-clearing-and-dampness-drying medicines (such as *Radix scutellariae*), together with *Semen Arecae*, *Magnolia Officinalis*, and *Fructus Tsaoko* are used to reconcile Shaoyang. Warm malaria is hot inside and

Table 6. Core herbs used for treating different malaria syndromes

Intersection	Count	Items
Labour malaria, cold malaria, miasmatic malaria, and warm malaria	37	<i>Fructus Mume</i> (乌梅), <i>Rhizoma Chuanxiong</i> (川芎), <i>Rhizoma Atractylodis</i> (苍术), <i>Cortex Magnoliae Officinalis</i> (厚朴), <i>Fructus Tsaoko</i> (草果), <i>Radix Dichroae</i> (常山), <i>Radix Bupleuri</i> (柴胡), <i>Rhizoma et Radix Notopterygii</i> (羌活), <i>Rhizoma Zingiberis Recens</i> (生姜), <i>Herba Ephedrae</i> (麻黄), <i>Rhizoma Cimicifugae</i> (升麻), <i>Cassia Twig</i> (桂枝), <i>Radix Scutellariae</i> (黄芩), <i>Herba Artemisiae Annuae</i> (青蒿), <i>Cortex Cinnamomi</i> (肉桂), dried ginger (干姜), <i>Radix Aconiti Lateralis Praeparata</i> (附子), <i>Rhizoma Pinelliae</i> (半夏), <i>Radix Platycodonis</i> (桔梗), <i>Bulbus Fritillariae Cirrhosae</i> (贝母), <i>Radix Et Rhizoma Rhei</i> (大黄), <i>Radix Aucklandiae</i> (木香), <i>Pericarpium Citri Reticulatae Viride</i> (青皮), <i>Radix Angelicae Sinensis</i> (当归), ginseng (人参), <i>Radix Glycyrrhizae</i> (甘草), <i>Rhizoma Atractylodis Macrocephalae</i> (白术), <i>Radix Paeoniae Alba</i> (白芍), Chinese date (大枣), <i>Radix Astragali</i> (黄芪), <i>Radix Ophiopogonis</i> (麦冬), <i>Radix Rehmanniae Preparata</i> (熟地黄), poria (茯苓), <i>Radix Gentiana Macrophyllae</i> (秦艽), and <i>Semen Arecae</i> (槟榔)
Cold malaria and miasmatic malaria	3	<i>Cablin Potchouli</i> (藿香), <i>Fructus Amomi</i> (砂仁), and <i>Rhizoma Cyperi</i> (香附)
Cold malaria, miasmatic malaria, and warm malaria	5	<i>Radix Puerariae</i> (葛根), <i>Radix Angelicae Dahuricae</i> (白芷), <i>Folium Perillae</i> (紫苏叶), <i>Radix Saposhnikoviae</i> (防风), and <i>Rhizoma Coptidis</i> (黄连)
Labour malaria, cold malaria, and miasmatic malaria	1	<i>Radix Peucedani</i> (前胡)
Miasmatic malaria and warm malaria	1	<i>Herba Asari</i> (细辛)
Miasmatic malaria	1	<i>Herba Menthae</i> (薄荷)
Malaria with splenomegaly	12	<i>Flos Caryophylli</i> (丁香), <i>Rhizoma Curcumae</i> (莪术), <i>Fructus Foeniculi</i> (小茴香), <i>Medicated Leaven</i> (神曲), <i>Exocarpium Citri Rubrum</i> (橘红), <i>Radix Angelicae Pubescentis</i> (独活), <i>Fructus Aurantii Immaturus</i> (枳实), <i>Cinnabaris</i> (朱砂), <i>Carapax Trionycis</i> (鳖甲), <i>Cortex Moutan</i> (丹皮), <i>Fructus Crataegi</i> (山楂), and <i>Concha Ostreae</i> (牡蛎)

**Figure 4.** Scatter plot for 7,414 association rules of core herb distribution.

The rules are densely distributed in the support range of 0 to 0.05, with low support but high confidence, and these rules are used less frequently.

cold outside, and it is stagnated in Shaoyang. It is typically treated by heat-clearing and detoxicating medicines as well as wind-heat-dispersing medicines such

as *Cinnamomi Modulus*, leaf of Henson bamboo, and *Gypsum fibrosum*. Cold malaria is due to the combination of yang deficiency and malarial pathogen^[14], and it is treated by reconciling the exterior and the interior surfaces and warming the yang^[15] using drugs such as *Bupleurum*, *Cinnamomi Modulus*, *Radix Glycyrrhizae*, dried ginger, *Radix Scutellariae*, *Radix Trichosanthis*, and *Concha Ostreae*. Miasmatic malaria is often caused by the sensation of the toxic gas of mountain mist and damp heat stagnation^[16, 17], and dampness-resolving and qi-rectifying medicines (such as *Fructus Tsaoko*, *Radix Angelicae Dahuricae*, *Folium Perillae*, *Rhizoma Chuanxiong*, and *Pericarpium Citri Reticulatae Viride*) are used to reduce dampness and regulate the spleen and stomach. Labor malaria results in a deficiency of Qi and blood caused by prolonged malaria. In addressing the rule of law for the deficiency of benefit, supplementing medicines (such as *Astragalus Radix*, *Radix Glycyrrhizae*, the twig and leaf of antifebrile dichroa, ginseng, *Fructus mume*, and *Radix angelicae sinensis*) are used to make up for the deficiency of qi and blood^[18, 19]. Blood-activating medicines, such as *Carapax triptychs*, *Algae*, *Knoxia* root, *Rhizoma Curcumae*, and common burreed rhizome, are used to

Table 7. Binomial rules in association rules of core herbs for treating malaria

ID	From	To	Support	Confidence	Lift	Count
1	<i>Radix Scutellariae</i> (黄芩)	<i>Radix Bupleuri</i> (柴胡)	0.11	0.81	3.77	51
2	<i>Cortex Magnoliae Officinalis</i> (厚朴)	<i>Radix Glycyrrhizae</i> (甘草)	0.15	0.86	1.98	67
3	Poria	<i>Radix Glycyrrhizae</i> (甘草)	0.13	0.86	1.97	59
4	<i>Rhizoma Chuanxiong</i> (川芎)	<i>Radix Glycyrrhizae</i> (甘草)	0.08	0.85	1.97	35
5	<i>Rhizoma Atractylodis Macrocephalae</i> (白术)	<i>Radix Glycyrrhizae</i> (甘草)	0.1	0.81	1.86	46
6	<i>Pericarpium Citri Reticulatae</i> (陈皮)	<i>Radix Glycyrrhizae</i> (甘草)	0.16	0.8	1.84	75
7	<i>Radix Scutellariae</i> (黄芩)	<i>Radix Glycyrrhizae</i> (甘草)	0.11	0.79	1.83	50
8	<i>Radix Bupleuri</i> (柴胡)	<i>Radix Glycyrrhizae</i> (甘草)	0.17	0.78	1.79	77
9	<i>Rhizoma Atractylodis</i> (苍术)	<i>Radix Glycyrrhizae</i> (甘草)	0.1	0.77	1.78	44
10	Ginseng (人参)	<i>Radix Glycyrrhizae</i> (甘草)	0.11	0.73	1.69	49
11	<i>Fructus Tsaoko</i> (草果)	<i>Radix Glycyrrhizae</i> (甘草)	0.1	0.72	1.66	46
12	<i>Rhizoma Pinelliae</i> (半夏)	<i>Radix Glycyrrhizae</i> (甘草)	0.15	0.71	1.64	71

Table 8. Tripartite rules in association rules of core herbs for treating malaria

ID	From	To	Support	Confidence	Lift	Count
1	<i>Radix Glycyrrhizae</i> (甘草), <i>Radix Scutellariae</i> (黄芩)	<i>Radix Bupleuri</i> (柴胡)	0.09	0.84	3.91	42
2	<i>Cortex Magnoliae Officinalis</i> (厚朴), <i>Pericarpium Citri Reticulatae</i> (陈皮)	<i>Radix Glycyrrhizae</i> (甘草)	0.09	0.89	2.05	40
3	<i>Cortex Magnoliae Officinalis</i> (厚朴), <i>Rhizoma Pinelliae</i> (半夏)	<i>Radix Glycyrrhizae</i> (甘草)	0.09	0.88	2.02	42
4	<i>Pericarpium Citri Reticulatae</i> (陈皮), <i>Rhizoma Pinelliae</i> (半夏)	<i>Radix Glycyrrhizae</i> (甘草)	0.09	0.87	2.00	40
5	<i>Radix Bupleuri</i> (柴胡), <i>Radix Scutellariae</i> (黄芩)	<i>Radix Glycyrrhizae</i> (甘草)	0.09	0.82	1.90	42
6	<i>Radix Bupleuri</i> (柴胡), <i>Rhizoma Pinelliae</i> (半夏)	<i>Radix Glycyrrhizae</i> (甘草)	0.08	0.76	1.75	38

attack and supplement the rule of law simultaneously. Given its incurability, malaria with splenomegaly is primarily due to abdominal clumping^[20]. Thus, attacking and increasing the rule of law is necessary, which is composed of invigorating blood circulation, eliminating stasis, and dissolving phlegm and panting cough using herbs such as *Carapax Trionycis*, *Knoxia*, *Rhizoma Curcumae*, and common burreed rhizome^[21]. Considering that *Radix dichroae*, *Radix bupleuri*, and *Fructus tsaoko* can prevent malaria, they are used frequently in all kinds of malaria treatment^[11, 22-24].

The statistics on the efficacy of herbs for malaria treatment show that drugs are primarily used as supplementing, exterior-releasing, heat-clearing, qi-rectifying, and dampness-resolving medicines. Qi-supplementing herbs include *Radix Glycyrrhizae*, ginseng, *Rhizoma Atractylodis Macrocephalae*, *Astmgali Radix*, *Jujube*, etc. Blood-supplementing medicines include *Radix Paeoniae Alba* and *Radix Angelicae*. Exterior-releasing medicines include *Radix Bupleuri*, *Rhizoma Cimicifugae*, *Rhizoma Zingiberis Recens*, *Rhizoma et Radix Notopterygii*, etc. Heat-clearing medicines include *Radix scutellariae* and *Rhizoma anemarrhenae*. Qi-rec-

tifying medicines include dried tangerine peel and *Pericarpium Citri Reticulatae Viride*. Dampness-resolving medicines include *Cortex Magnoliae Officinalis*, *Fructus Tsaoko*, and *Rhizoma Atractylodis*.

The statistical results of the four properties, five flavors, and meridian tropism of the herbs used to treat malaria show that the four properties are primarily warm, mild, and cold; the four flavors are primarily pungent, bitter, and sweet, and meridian tropism primarily occurs in the spleen, lung, and stomach. The relationship between medicine flavors and meridian tropism is described as follows: pungent acts on the lung; bitter acts on the heart; sweet acts on the spleen, and all flavors act on the stomach. Among the medicines used to treat malaria, *Rhizoma pinelliae*, dried tangerine peel, *Cortex Magnoliae Officinalis*, *Semen Arecae*, *Pericarpium Citri Reticulatae Viride*, *Rhizoma Atractylodis Macrocephalae*, *Fructus Tsaoko*, *Rhizoma Atractylodis*, *Rhizoma chuanxiong*, *Radix Angelicae Sinensis*, and realgar have a warm property. These medicines are mainly bitter and pungent, and they act on the spleen, lungs, and heart channels. *Semen persicae*, *Radix Platycodonis*, *Rhizoma Cyperi*,

common burreed rhizome, black bean, *Fructus Hordei Germinatus*, myrrh, *Radix Gentianae Macrophyllae*, and other herbs are mainly sweet, and they act on the spleen and stomach channels. *Radix Bupleuri*, *Radix Dichroae*, *Radix Scutellariae*, *Rhizoma Anemarrhenae*, *Kaempfer Dutchmanspipe*, *Carapax Trionycis*, *Rhizoma Cimicifugae*, *Radix et Rhizoma Rhei*, *Bulbus Fritillariae Cirrhosae*, *Herba Artemisiae Annuae*, and other cold herbs taste bitter and pungent, and they act on the liver, lung, stomach, and heart channels.

The cluster analysis show that 61 core herbs can be used for malaria treatment. In addition, 37 herbs can be used for the treatment of cold malaria, warm malaria, miasmatic malaria, and labor malaria, including *Fructus Mume*, *Rhizoma Chuanxiong*, *Rhizoma Atractylodis*, *Cortex Magnoliae Officinalis*, and *Fructus Tsaoko*. Twelve herbs can be used to treat malaria with splenomegaly, including *Flos Caryophylli*, *Rhizoma curcumae*, *Fructus foeniculi*, medicated leaven, and *Exocarpium Citri Rubrum*. A turtle shell is primarily used for treating malaria with splenomegaly, and *Herba Menthae* is used for treating miasmatic malaria.

Association rule analysis showed 12 binomial rules and six tripartite rules for malaria treatment. *Bupleurum* and *Scutellaria* are the core herb pair, combined with other herbs or herb pairs to treat different malaria syndromes. Therefore, *Bupleurum* and *Scutellaria* are the core herb pair for treating malaria. The core herb pair is compatible with *Radix Glycyrrhizae* is the core combination for treating cold malaria, warm malaria, miasmatic malaria, and malaria with splenomegaly. The core herb pair is compatible with dried ginger and cinnamon twigs specializes in cold malaria. The core herb pair is compatible with *Pinellia* specializes in warm malaria. The core herb pair is compatible with *Pinellia* and *Rhizome Atractylodes* specializes in miasmatic malaria. The core herb pair is compatible with turtle shells specializes in malaria with splenomegaly. The core herb pair is compatible with *Rhizoma Chuanxiong* specializes in labor malaria. Furthermore, The core herb pair is compatible with *Rhizome Atractylodes*, *Magnolia Officinalis*, *Radix Glycyrrhizae*, and *Pinellia* is used to treat cold malaria, warm malaria, and miasmatic malaria.

The treatment of malaria with medicines containing *Bupleurum* and *Scutellaria* has been extensively recorded and discussed in ancient Chinese medical texts, such as Zhang Zhongjing (张仲景)'s "Treatise on Typhoid Fever" (《伤寒论》) and Wu Qian's (吴谦) "Record of Deleted and Supplementary Famous Formulas"

(《删补名医方论》) in the Qing Dynasty. In addition, Zhou Liping has studied the combination of *Bupleurum* and *Scutellaria* as well as the characteristics of the formula. Her research shows that *Bupleurum* and *Scutellaria* formulae are widely used to treat malaria^[25]. Furthermore, the medical case of Wang Mengying (王孟英), a famous doctor in the Qing Dynasty, showed that Xiao Chai Hu Tang, which contains the herb pair of *Bupleurum* and *Scutellaria*, was effective in treating and preventing cold malaria in a short period^[26].

After searching the main components and targets of *Bupleurum* and *Scutellaria* in the TCSMP database and malaria targets in OMIM data, 18 common targets of *Bupleurum*, *Scutellaria*, and malaria disease are identified, namely, ADA, ADRB2, ATP2B4, CCL2, CD36, EPO, G6PD, GNAS, ICAM1, IDO1, IFNG, IL10, IL4, LCT, LILRB1, NOS2, TIRAP, and TNF. These common targets in the STRING database are used to construct the PPI network, which can be initially identified as the critical targets of CCL2, EPO, ICAM1, IDO1, IFNG, IL10, IL4, NOS2, and TNF. In addition, *Radix Bupleuri* saponins, the main component of *Radix Bupleuri*, can increase IL-10 and NO levels and decrease TNF- α levels and TGF- β protein expression levels in the serum of animal models of liver fibrosis, and IL-10 and TNF- α are critical targets for malaria^[27]. Furthermore, research has shown that IL-10 has a protective effect on severe malaria^[28]. TNF- α plays a vital role in the pathogenesis of cerebral malaria, which suggests that the local accumulation and activation of macrophages may lead to the predominance of lesions in the central nervous system^[29]. By evaluating the cytokine profiles of patients with different clinical outcomes of *P. interna*, one study showed that IL-4, IL-10, CCL2, and TGF- β might be developed as biomarkers for severe *P. vivax* malaria^[30]. This evidence suggests that *Radix Bupleuri* and *Scutellaria* pairs contain potential targets for treating malaria, and their critical components, mechanisms of action, and indications must be further investigated.

This research has preliminarily revealed the rule of prescription for malaria treatment by using the complex network of drug association, fundamental attribute statistical analysis, cluster analysis, and association rule analysis, which can provide a reference for the research, clinical practice, and new drug development of malaria treatment.

Conflict of interests

None disclosed.

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Author contributions

Guo WL and Jiang HJ contributed to the conception of this manuscript and wrote the draft; Li YR contributed to manuscript revision, data collection, and funding; Yang JL helped with revision. All authors have read and approved the final manuscript.

Data availability statement

The datasets generated and analyzed during the study are publicly available and can be obtained by contacting the corresponding author by E-mail.

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论著

基于数据挖掘的中医治疗疟疾用药规律分析

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摘要

目的 挖掘中医治疗疟疾的用药规律。

方法 从中药的性、味、归经、药效等基本属性方面进行统计分析。在药物关联的基础上, 构建了中药关联复杂网络。通过聚类分析得到治疗疟疾的核心药物。应用 Apriori 算法对核心药物的关联规则进行分析。

结果 357 种草药在 461 首治疗疟疾的处方中共使用 3,194 次。在药材方面, 使用频率最高的依次是甘草、黄连、柴胡、地骨皮等。在药效方面, 使用频率最高的依次是补益、解表、清热、理气和化湿类药等。在药性方面, 使用频率最高的依次是温、平、寒等。在药味方面, 使用频率最高的是辛、苦、甘等。在归经方面, 使用频率最高的依次是脾、肺、胃等。聚类分析得到甘草、半夏、柴胡、常山等核心药物 61 味。应用 Apriori 关联规则分析, 得到 12 条二项规则 (药对) 和 6 条三项规则 (药物组合), 其中柴胡和黄芩是治疗疟疾的核心药对。

结论 柴胡和黄芩是治疗疟疾的核心药对, 该药对与白术组合, 可用于治疗温疟和寒疟; 与陈皮或地黄组合, 可用于治疗瘴疟; 与人参、当归组合, 可用于治疗劳疟; 与鳖甲组合, 可用于治疗疟母。

关键词: 疟疾; 数据挖掘; 复杂网络; 聚类分析; 用药规则。

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