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Review Article

HERBAL APPROACHES FOR MALARIA:A REVIEW

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ABSTRACT

Malaria is caused by Plasmodium *parasites. Malaria is one of the most important tropical infectious diseases. The incidence of malaria worldwide is estimated to be 300–500 million clinical cases each year with a mortality of between one and three million people worldwide annually. Malaria control efforts need to identify associated factors and to integrate these efforts with the information, education and communication campaigns and behavior change communication campaigns that are targeting the community of this region. The increasing levels of malaria parasite drug resistance, the herbal knowledge of indigenous communities for malaria treatment can play an important role in identification of any new antimalarial plants that is yet to be discovered.*

Key Word*-Traditonal knowledge of medicine, Transmission, Diagnostic test, Anti-malarial Plant*

INTRODUCTION

The WHO estimates that in 2015 there were 214 million new cases of malaria resulting in 438,000 deaths. There are about 10,000 malaria cases per year in Western Europe, and 1300–1500 in the United States. Malaria is a life-threatening blood disease caused by parasites transmitted to humans through the bite of the ***Anopheles*** mosquito.[1][2] Once an infected mosquito bites a human and transmits the parasites, those parasites multiply in the host's liver before infecting and destroying red blood cells. There are more than 100 types of Plasmodium parasites, which can infect a variety of species. Scientists have identified five types that specifically infect humans, they are: P. falciparum - located worldwide in tropical and suburban areas, but predominately in Africa. An estimated 1 million people are killed by this strain every year.

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The strain can multiply rapidly and can adhere to blood vessel walls in the brain, causing rapid onset of severe malaria including cerebral malaria.P. vivax - located in Latin America, Africa, and Asia, it is arguably the most widespread due to the high population of Asia.[3] This strain has a dormant liver stage that can activate and invade the blood after months or years, causing many patients to relapse.P. ovale - located mainly in West Africa, it is biologically and morphologically very similar to P. vivax. However, unlike P. vivax, this strain can affect individuals who are negative with the Duffy blood group, which is the case for many residents of sub-Saharan Africa. This explains the greater prevalence of P. ovale (rather than P. vivax) in most of Africa.

P. malariae - located worldwide and the only human malaria parasite to have a three-day cycle. If left untreated, P. malariae can cause a long-lasting, chronic infection that can last a lifetime and which may cause the nephrotic syndrome.P. knowlesi - located in Southeast Asia and associated with macaques (a type of monkey). This strain has a 24 hour cycle and

can, therefore, multiply rapidly once a patient is infected, causing an uncomplicated case to become serious very quickly. Fatal cases of infection with this strain have been reported.[6]

LIFE CYCLE OF PLASMODIUM-

Malaria parasite infects and develops both in human as well as in female *Anopheles* mosquito.[8][11][20]

Life cycle of malaria can be divided in two stages:

- Asexual Stage: Human Liver Stage and Human Blood Cell Stage
- Sexual Stage: Occurs in female *Anopheles* mosquito.

Asexual Stage

Human Liver Stage

Malaria infection or life cycle begins when a female *Anopheles* mosquito bites a human and suck his blood, in that process mosquito injects the saliva containing sporozoites into the human body.

These injected sporozoites travel quickly to the liver where they multiply in the liver cells and develop into merozoites. These merozoites are then released in the form vesicles (known as schizonts) which travel to the lungs where they burst into the capillaries, spreading merozites into blood for its development in Human Blood Cell Stage/ Erythrocytic stage. However, in *P. vivax* and *P. ovale*, a dormant stage of malarial parasite known as hypnozoites persists in the liver cells which can cause relapse, weeks or years later after the treatment, by invading into the erythrocytes.[11]

Human Blood Cell Stage

The merozoites, when they enter into circulatory system, invade red blood cells where they grow and multiply asexually until the erythrocyte or red blood cell burst resulting in increase in the number of merozoites to attack other red blood cells. Thus, repetition of this cycle, of breaking free of merozoites and attacking fresh red blood cells, causes fever and other clinical manifestations.

During maturation in the red blood cell, the parasite insert its phospholipid and proteins in the red blood cell membrane which causes host‟s hemoglobin to enter into parasite‟s food vacuole where it is digested providing source of amino acids. The free haem which is obtained after digestion of haemoglobin is toxic to the parasite; hence, the parasite renders it inactive by polymerizing it into haemozoin which is catalyzed by enzyme haem polymerase.

Some of the merozoites which enter erythrocytes undergo multiplication to form gametocytes, two forms -male (microgametocytes) and female (macrogametocytes). These gametes so formed are then taken up by the female *Anopheles* mosquito in her blood sucking or blood meal event.[11]

Sexual Stage

This sporogonic stage occurs in female *Anopheles* mosquito where parasite develops sexually. The microgametes penetrate into macrogametes forming zygotes in the mosquito‟s stomach; this zygote later become elongated and motile forming ookinetes which invade through the mosquito‟s midgut wall and develops into oocysts. The oocysts so formed, matures and develop thousands of sporozoites inside itself which eventually, ruptures, releasing sporozoites in the mosquito‟s body. These sporozoites then travel to the salivary glands of mosquito which on injection or during blood meal event begins the new malarial cycle by infecting the human host.[21]

SIGN AND SYMPTOM

The classic symptom of malaria is paroxysm—a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating, occurring every two days (tertian fever) in P. vivax and P. ovale infections, and every three days (quartan fever) for P. malariae. P. falciparum infection can cause recurrent fever every 36–48 hours, or a less pronounced and almost continuous fever.[13][18]

- Sensation of cold, shivering
- Fever, headaches, and vomiting (seizures sometimes occur in young children)
- Sweats followed by a return to normal temperature, with tiredness.
- Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction. This form has the capacity to be fatal if left untreated. As a general overview, symptoms of severe malaria include:
- Fever and chills
- Impaired consciousness
- Prostration (adopting a prone or prayer position)
- Multiple convulsions
- Deep breathing and respiratory distress
- Abnormal bleeding and signs of anemia
- Clinical jaundice and evidence of vital organ dysfunction.

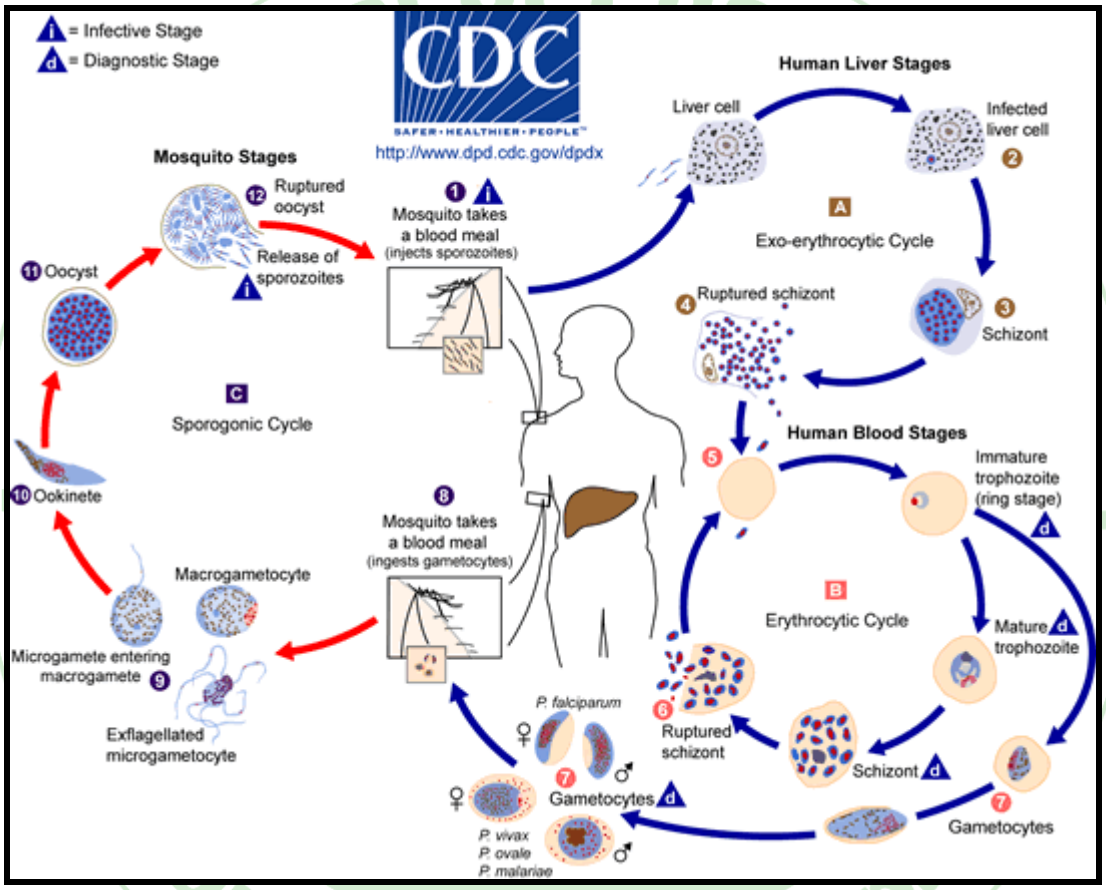

Fig 1: Life Cycle of Plasmodium

TRANSMISSION

The female anopheles mosquito is the vector for human malaria. Some 60 species of this mosquito have been identified as vectors for malaria, and their distribution varies from country.

Mother to the growing fetus **(Congenital malaria)**[16]

Transfer of parasitized red cells from infected mother to the child either transplacentally or during labor can lead to in malaria in the newborn, called as congenital malaria. Congenital malaria seems to be rarely reported and has always been considered to be more frequent in the nonimmune population than in the endemic areas. In recent years, however, higher prevalence of congenital malaria ranging from 8% to 33% has been reported from both malaria-endemic and nonendemic areas, including the United States, Europe, India, etc.

Transfusion Malaria

Malaria can be transmitted by transfusion of blood from infected donors. First reported in 1911, transfusion malaria is one of the most common transfusion-transmitted infections today. The risk of acquiring transfusion malaria is very low (1 case per 4 million) in nonendemic countries such as the United States, whereas in the endemic countries, it is much higher (>50 cases per million donor units).

Needle stick injury

Cases of malaria transmission through needle-stick injuries, accidentally among health care professionals (some even fatal) or due to needle sharing among drug addicts, have also been reported.

DIAGNOSIS

CLINICAL DIAGNOSIS OF MALARIA

This method is least expensive and most widely practiced. Clinical diagnosis is based on the patients' signs and symptoms, and on physical findings at examination. The earliest symptoms of malaria are very nonspecific and variable, and include fever, headache, weakness, myalgia, chills, dizziness, abdominal pain, diarrhea, nausea, vomiting, anorexia, and pruritus.[15][18][25] .

LABORATORY DIAGNOSIS OF MALARIA

Rapid and effective malaria diagnosis not only alleviates suffering, but also decreases community transmission. In the laboratory, malaria is diagnosed using different techniques, e.g. conventional microscopic diagnosis by staining thin and thick peripheral blood smears , other concentration techniques, e.g. quantitative buffy coat (QBC) method , rapid diagnostic tests e.g., OptiMAL, ICT , Para- HIT-f , ParaScreen , SD Bioline , Paracheck, and molecular diagnostic methods, such as polymerase chain reaction (PCR).

Microscopic diagnosis using stained thin and thick peripheral blood smears (PBS)

Malaria is conventionally diagnosed by microscopic examination of stained blood films using Giemsa, Wright's, or Field'stains Malaria is diagnosed microscopically by staining thick and thin blood films on a glass slide, to visualize malaria parasites.[24] Briefly, the patient's finger is cleaned with 70% ethyl alcohol, allowed to dry and then the side of fingertip is picked with a sharp sterile lancet and two drops of blood are placed on a glass slide. To prepare a thick blood film, a blood spot is stirred in a circular motion with the corner of the slide, taking care not make the preparation too thick, and allowed to dry without fixative. After drying, the spot is stained with diluted Giemsa (1 : 20, vol/vol) for 20 min, and washed by placing the film in buffered water for 3 min. The slide is allowed to airdry in a vertical position and examination using a light micro scope. As they are unfixed, the red cells lyse when a water-based stain is applied. A thin blood film is prepared by immediately placing the smooth edge of a spreader slide in a drop of blood,adjusting the angle between slide and spreader to 45 and then smearing the blood with a swift and steady sweep along the surface.The film is then allowed to air-dry and is fixed with absolute methanol. After drying, the sample is stained with diluted Giemsa (1 : 20, vol/vol) for 20 min and washed by briefly dipping the slide in and out of a jar of buffered water (excessive washing will decolorize the film). The slide is then allowed to air-dry in a vertical position and examined under a light microscope.[9]

Figure 2: The blood film is the gold standard for malaria diagnosis *QBC technique*

This method involves staining parasite deoxyribonucleic acid (DNA) in micro-hematocrit tubes with fluorescent dyes. Finger-prick blood is collected in a hematocrit tube containing acridine orange and anticoagulant. The tube is centrifuged at 12,000 g for 5 min and immediately examined using an epi-fluorescent microscope. Parasite nuclei fluoresces bright green, while cytoplasm appears yellow-orange.[15]QBC technique is simple, reliable, and user-friendly, it requires specialized instrumentation, is more costly than conventional light microscopy, and is poor at determining species and numbers of parasites.

Rapid diagnostic tests (RDTs)

RDTs are all based on the same principle and detect malaria antigen in blood flowing along a membrane containing specific anti-malaria antibodies. Detection in patient samples of malaria parasite antigens such as histidine rich protein II (HRP-II) or plasmodium lactate dehydrogenase (pLDH) can be performed by rapid, point-of-care tests based on immunochromatographic methods.[21]

Serological tests

Diagnosis of malaria using serological methods is usually based on the detection of antibodies against asexual blood stage malaria parasites. Immunofluorescence antibody testing (IFA) has been a reliable serologic test for malaria. The first serological test used for the detection of malaria antibodies was the immunofluorescence assay, often abbreviated to IFA. This method uses specific antigen or crude antigen prepared one slide, coated and kept at -30^0 C until use, and quantifies both IgG and IgM antibodies in patient serum samples. Serological tests provide retrospective confirmation of malaria infection or a history of infection, and are useful in epidemiology surveys and the screening of blood collected for blood banks. Nevertheless, the utility of serological methods for the diagnosis of acute malaria infection is limited owing to the delay in antibodies development, lack of species confirmation and the need for a fluorescence (UV) microscope.[18]

MOLECULAR DIAGNOSTIC METHODS

Recent developments in molecular biological technologies, e.g. PCR, loop-mediated isothermal amplification (LAMP), microarray, mass spectrometry (MS), and flow cytometric (FCM) assay techniques, have permitted extensive characterization of the malaria parasite and are generating new strategies for malaria diagnosis.[19]

PCR Technique

The polymerase chain reaction (PCR) allows the specific amplification of a selected region of the malarial genome (8). PCR-based techniques are a recent development in the molecular diagnosis of malaria, and have proven to be one of the most specific and sensitive diagnostic methods, PCR can detect as few as 1-5 parasites/µl of blood (≤ 0.0001% of infected red blood cells) compared with around 50-100 parasites/µl of blood by microscopy or RDT. Moreover, PCR can help detect drug-resistant parasites, mixed infections.

LAMP Technique

The LAMP technique is claimed to be a simple and inexpensive molecular malaria-diagnostic test that detects the conserved 18S ribosome RNA gene of *P. falciparum.* These observations suggest that LAMP is more reliable and useful for routine screening for malaria parasites in regions where vector-borne diseases, such as malaria, are endemic.

FCM Assay

Automated blood cell counters (ACC)

An ACC is a practical tool for malaria diagnosis, with 3 reported approaches. The first used a Cell-Dyn ▪ 3500 apparatus to detect malaria pigment (hemozoin) in monocytes, and showed a sensitivity of 95% and specificity of 88%, compared with the gold-standard blood smear. The second method also used a Cell-Dyn ▪ 3500, and analyzed depolarized laser light (DLL) to detect malaria infection. The third technique used a Beckman Coulter ACC to detect increases in activated monocytes by volume, conductivity, and scatter (VCS), with 98% sensitivity and 94% specificity.[17]

PREVENTION

Mosquito control

Further information: Mosquito control

Man spraying kerosene oil in standing water, Panama Canal Zone1912.Vector control refers to methods used to decrease malaria by reducing the levels of transmission by mosquitoes. For individual protection, the most effective insect repellents are based on DEET or picaridin. Insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) have been shown to be highly effective in preventing malaria among children in areas where malaria is common. Prompt treatment of confirmed cases with artemisinin-based combination therapies (ACTs) may also reduce transmission. Walls where indoor residual spraying of DDT has been applied. The mosquitoes remain on the wall until they fall down dead on the floor.[6]

Flow cytometry has reportedly been used for malaria diagnosis. Briefly, the principle of this technique is based on detection of hemozoin, which is produced when the intra-erythrocytic malaria parasites digest host hemoglobin and crystallize the released toxic heme into hemozoin in the acidic food vacuole. Hemozoin within phagocytotes can be detected by depolarization of laser light, as cells pass through a flow-cytometer channel.

A mosquito net in use. Mosquito nets help keep mosquitoes away from people and reduce infection rates and transmission of malaria. Nets are not a perfect barrier and are often treated with an insecticide designed to kill the mosquito before it has time to find a way past the net.

TREATMENT

The World Health Organization (WHO) defines herbal medicines to include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations thereof .There are 1200 plant specie.

Since many modern drugs such as quinine and artemisinin originate from plants, it is essential that other medicinal plants which have folklore reputation for anti-malarial properties are investigated, in order to establish their safety and efficacy, and to determine their potential as sources of new anti-malarial drugs.[25][26][27][28][29]

CONCLUSION-

Malaria is a worldwide disease. The latest malaria control guidelines issued by the World Health Organization. The resistance of P. falciparum to chloroquine is now a major health problem in INDIA. Main aim of this article is to control, prevention of malaria. Herbal material is used because side effect is lower than allopathic medicine. Nowadays, herbal medicine is used in world wide. This will have an obvious economic advantage for the local populations, as the developed medicinal plant products will be the cheapest therapeutic alternative for malaria.

Table 1: List of Anti-malarial plants reported from northeast India.

S.N.	Name of Plant	Family	Part Used	Methodology
1	*Acacia famesiana*	Mimosaceae	Bark	Decoction
2	*Acorus calamu*	Araceae	Rhizome	If taken with qunine, stop remittent fever.
3	*Adhatoda Zeylanica Madicus*	Acanthaceae	Leaf	The leaves are boiled and the water is used for bathing and the leaf paste is applied on the whole body as an effective cure for chronic malaria.
4	*Alseonia scholaris*	Apocynaceae	Bark	Bark infusion is given once a day.
5	*Andrographis paniculata wall*	Acanthaceae	Leaf	Crushed raw leaves are taken orally for two days twice with half glass of milk.
6	*Artemisia nilagirica*	Asteraceae	Leaf	Decoction of leaves is given.
7	*Asplenium adiantoides*	Aspleniaceae	Plant	Decoction
8	*Aster amellus*	Asteraceae	Root	Decoction
9	*Berberis aristata*	Berberidaceae	Root	The root bark is used as tonic.
10	*Betula alnoides*	Betulaceae	Bark	Decoction
11	*Brucea javanica*	Simaroubaceae	Fruit	Decoction
12	*Carica papaya*	Caricaceae	Leaf	Decoction
13	*Cinnamonum bejolghota*	Lauraecae	Bark and leaf	Bark ,leaves are boiled with the leaves of anacolosa crassips.the water is used for bathing the steam inhalaed and the water taken internally.
14	*Cissampelos pareira*	Menispermaceae	Root	Juice is used.
15	*Citrus medica*	Rutaceae	Fruit	Juice is used.
16	*Citrus sinensis*	Rutaceae	Leaf	Decoction
17	*Clausena excavate*	Rutaceae	Leaf	Juice is rubbed to alleviate muscular pain.
18	*Clerodendron infortunatum gaertn*	Verbenaceae	Root and leaf	Decoction
19	*Clerodendrum colebrookoianum walp*	Verbenaceae	Leaf	Decoction
20	*Clerodendrum serratum moon*	Verbenaceae	Root	Decoction
21	*Coptis teeta*	rananculaceae	Root, rhizome	It is administered orally at a dose of 150 g thrice a day.
22	*Crotolaria occulta*	Fabaceae	Plant	Plant juice taken with warm water.

23	*Croton tiglium*	Euphorbiaceae	Leaf or flower	Plant powder is consumed with a glass of water twice a day till cured.
24	*Croton caudatus*	Euphorbiaceae	Root	Decoction
25	*Cynoglossum glochidion*	Boraginaceae	Root	Root powder and mix with water 10 gm is taken twice daily.
26	*Dichroaf ebrifanga lour*	Saxifragaceae	Root and leaf	Root and leaf tops are used in malaria fever. Therapeutic activity is due to quinazoline derivatives.
27	*Elsholtzia blanda benth*	Lamiaceae	Leaf	It is a mosquito repellent.
28	*Gomphostemma parviflora*	Lamiaceae	Leaf	Decoction
29	*Halenia elliptica*	Gentianaceae	Plant	Taken orally in malaria fever.
30	*Hedyotis scandens*	Rubiaceae	Root and leaf	Infusion of the root and leaf is taken as an effective remedy.
31	*Helianthus annus*	Asteraceae	Leaf and flower	Decoction
32	*Hononoia riparia*	Euphorbiaceae	Wood	Wood infusion is given.
33	*Hybrangea macrophylla*	Sexifraceae	Leaf ,root	More potent then qunine.
34	*Impatiens angustifolia*	Balsaminaceae	Leaf	Leaf paste is given.
35	*Lanltana camara*	Verbenaceae	Plant	Decoction
36	*Magnolia grandiflora*	Magnoliaceae	Bark	Decoction
37	*Melodinus monogynus*	Apocynaceae	Leaf,wood and root	Used as an antimalarial drug.
38	*Mesona wallichina*	Lamiaceae	Root	Boiled extract is given.
39	*Nasturtium officinale*	Brassicaceae	Plant	Decoction
40	*Ocmum sanctum*	Lamiaceae	Root	Decoction
41	*Ocmum tenuiflorun*	Lamiaceae	Root	Decoction
42	*Passiflora mepalensis*	Pasifloraceae	Root	Decoction
43	*Picrasma jayanica*	Simaroubaceae	Bark	The inner bark is very bitter like cinchona. An infusion of the inner coat of bark is taken.
44	*Piper mullesua*	Piperaceae	Leaf and root	Dried plant is consumed during malaria and cough.
45	*Polygala persicariaefolea*	Polygalaceae	Plant	Decoction
46	*Randia fasciculate*	Rosaceae	Leaf	Leaf mixed with piper nigrum and boiled juice extract is given.
47	*Rubus ellipticus*	Rosaceae	Leaf	Leaf mixed with piper nigrum and boiled juice extract is given.

48	*Satyrium nepalanse*	Orchidaceae	Tuber	Consumed as tonic.
50	*Sida rhombifolia*	Malvaceae	Root	Decoction
51	*Solamum vairum*	Solanaceae	Root	Decoction
52	*Solanum torvum*	Solanaceae	Fruit	Burnt fruits are consumed.
53	*Stephania japonica*	Mernispermaceae	Tuber	Sun dried tuber powder is administred orally with boiled water twice a day for more than four days till malaria is cured.
54	*Strobilanthes auritulatus*	Acanthaceae	Leaf	Powdered leaf rubbed on the body during thee cold stage of intermittent fever.
55	*Swertia dilatata*	Gentiaceae	Root	Powdered root is administered.
56	*Swertia nerbosa*	Gentiaceae	Plant	Decoction
57	*Taraxacum officinalis*	Asteraceae	Plant	Powder is used.
58	*Thalictrum foliolosum*	Ranucuklaceae	Rhizome and root	Extract is bitter tonic.
59	*Vandellia sessiliflora*	Scrophulariaceae	Plant	Decoction
60	*Vitex peduncularis*	Verbenaceae	Bark,leaf and stem	The bark is crused and boiled. The steam vapour is inhaled by a patient suffering from malarial fever,infusion of leaves or of root bark or young stem bark is usefull.
61	*Picrorhiza kurooa*	Scrophulariaceae	Root	Root powder in water in given.
62	*Xanthium strumarium*	Asteraceae	Leaf	Decoction
63	*Zanthoxylum hamiltonianum*	Rutaceae	Root and bark	Decoction

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