

A Study on Leishmaniasis: Causes of Skin Ulcers and Treatment Using Medicinal Plants

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ABSTRACT

Cutaneous leishmaniasis is a parasitic disease transmitted by sand fly bites. It is endemic in Iraq and some neighbouring countries. There are two types of cutaneous leishmaniasis in Iraq that cause infection; L. major and L. tropica. Studies have shown that the incidence of the disease appears in the period between November and February. In his book Summary of Experiences, Al-Razi (1500) was the first one to refer to the presence of the disease in Iraq. He identifies it as a common disease in Baghdad, hence the name Baghdad boil (Pringle, 1957).

Introduction

Previous studies have shown that cases of leishmaniasis are increasing globally, mainly due to environmental changes. Urban slums and unsuitable household garbage collection, in addition to population migration, may also increase the risk of infection. Frequently, disease rates have increased as a result of poverty and malnutrition (Aryan and Akbari, 2016). The skin disease occurs as single ulcerative or nodular lesions on or around the site of insect exposure. The ulcers usually occur on exposed areas of the body, such as the face, forearms and legs, and develop over weeks to months. Nodular lesions of variable sizes often spread to different places, away from the site of insect exposure (McGwire and Satoskar, 2014).

The development of the lesions usually enlarges and stops afterwards, leaving a painless ulcer with a well-defined raised streak. The main problem of this disease is that it results a persistent scar of 0.5-10 cm in diameter after healing (Masmoudi et al 2013).

Vectors

Out of eight hundred species of sandflies, ninety-eight are suspected to be vectors of human leishmaniasis. Females sand flies need blood in order to receive the proteins required for egg formation (Sharma, 2008). A range of creatures, including mammals, birds and reptiles mostly feed around dawn and dusk (Sharma and Singh, 2008). Leishmania cannot develop in a lot of the

sand fly species. Specific vectors that only allow for the development of one species of *Leishmania* and permissive vectors, allow for the growth of other species (Bikova et al., 2005).

There are other ways of transmission of the parasite, such as congenital transmission in most cases of infection that may occur during the exchange of the mother's blood when the fetus passes through the birth canal. Because of the shift in cellular immunity to humoral immunity, pregnant women become more susceptible to developing leishmaniasis (Meinecke et al., 1999).

Direct contact can also be transmitted if an infected person's skin is injured or scratched, and transmission can occur when infected sand flies are crushed by the skin or mucous membranes (Aldifaeii, 2014). Mainly from animal patterns, person-to-person transmission shows that there is some evidences mirror that this mode of spread in VL patients is theoretically possible. This can be done through interaction with contaminated fluids (nasal and oral secretions, tonsil and pharyngeal mucus and urine) (Singh, 2006).

Disease Transmission

The female Phlebotomized sandflies that carry the leishmaniasis parasite, attack victims and pass over the disease because they need blood to deposit their eggs. Leishmaniasis epidemiological features rely on the traits of the parasite and sand fly species, the regional environmental traits of the transmission locations, the degree of human population exposure to parasites in the past and present, and human behavior. It has been discovered that there are about seventy species of animals including humans that serve as a natural reservoir for *Leishmania* parasites (White, 2009).

Epidemiology in Iraq

Cases of cutaneous leishmaniasis were identified in Iraq and the first confirmed case was in Baghdad in 1911 by Winion who recorded six cases of the disease (Abdulghani and Hussein, 2008). It was extremely prevalent in Iraq, specifically in Baghdad and the surrounding areas. Examples are the infection rate in Karkh, Adhamiya, Sinak and Deir Khan in 1929 which was a 100%, while the infections were in Al-Rashid camp and the surrounding areas (Hussain and Iman, 2017).

In Iraq, the disease is endemic and there has been a rise in the number of cases during the last decade. For instance, more than three thousand cases were recorded in 2004 (Ala'din, 2004). Cases of kala-azar have been reported from all regions in Iraq (Bissat and Shanat, 2015). The majority were from the southern regions (adjacent to Iran), fewer in the centre and a few cases from the northern regions. The disease usually affects children; more than 90% of cases are under the age of five and more than 80% are from rural areas. The World Health Organization (WHO) states that in 2019, the highest cases recorded are during the months of December, January, February and March (Salam et al., 2014).

Males are more likely to be infected with the disease than females. In comparison to females, males are more likely to work or sleep in open areas with less body protection. The natural case of males being outside their homes for a longer period causes the insect's activity to be more outside than at home (Arroub et al., 2010). Gender differences occur as a distinct age pattern in some parasitic diseases such as CL. Its occurrence shows major male dominance in childhood, which decreases with age (Guerra and Abad, 2013). Therefore, gender bias tends to worsen in life stages, as levels of sex hormones increase.

Cutaneous leishmaniasis was found in rural areas on the borders of Iran and Iraq. Specifically in Mehran, samples were isolated from these areas, and it was found that 100% was caused by *L. major*. Research on rodents regarding *Leishmania* carriers revealed a variety of transmission cycles. Epidemiological skin diseases caused by *L. major* occur near colonies of gerbil rodents in Asia and include the Khuzestan region on the border between Iraq and Iran (Vazirianzadeh et al.,

2013). That is why the emergence of a high percentage of *L. major* is located on the border of Iran.

The Sheikh Saad and Al-hay region are regarded as rural locations, and several elements including the existence of reservoir animals like rats and dogs, play a significant role in the prevalence and development of CL in these places.

Main Risk Factors

The incidence and presence of cutaneous leishmaniasis in rural settings are influenced by a variety of variables. These include the following:

- The presence of animals that are a reservoir of this disease, especially rodents and dogs.
- The presence of swamps provides a suitable environment for the disease to spread. It leads to the growth of the insect during its life cycle, as it decomposes in the larval stage of the worms to the soil material and animal faeces to feed. This is provided by the soil surrounding the swamps.
- Some houses are built of mud, especially those in villages where rural and agricultural areas attract and harbour many types of insects and make people more susceptible to insect bites. These include sandfly vectors of cutaneous leishmaniasis.
- Long-distance travel and increased human mobility may help leishmaniasis spread to regions where it has not previously been prevalent. This explains why so many people who visited Iran later had the illness in metropolitan areas. Expansions of leishmaniasis are frequently correlated with migration to infection hotspots. For instance, during the Iran-Iraq war, several cases of cutaneous leishmaniasis were observed among soldiers stationed in active foci of infection (Maraghit Al, 2007). These differences can also be explained by some researchers who recorded the infection in the city centre, since it was for years after the 2003 war. Also, it was due to the lack of security stability that led to the failure of the pesticide spraying teams operating in all places which caused its spread. Of the insect vectors in urban areas, the Iraqi Ministry of Agriculture also used annually campaigns for up to several months, a campaign of spraying insecticides on homes and orchards. Yet, this technique disappeared after 2003, and increased the spread of the pest or sandflies that carry the infection (Walden, 2012).

Leishmania Tropica: Evocative Evidences

1. Cutaneous leishmaniasis affects both sexes, but males are more susceptible than females, especially in age groups (twenty years and less).
2. The majority of the studied cases showed affected upper limbs that were bitten by sandflies (vectors).
3. Multiple ulcers are larger than a single ulcer.
4. Rural areas showed a higher incidence of cutaneous leishmaniasis than urban areas.
5. The causative agent of cutaneous leishmaniasis in the region: *L. tropica* and *L. major* are the dominant types (Mukherjee, 2019).

Disease Prevention

Leishmaniasis transmission takes place in a complex biological system that includes human and animal reservoirs, parasite organisms and the sandfly vector. It necessitates the adoption of a number of intervention measures for prevention and management. The main prevention strategies are listed below.

- Disease transmission is halted, disability and death are avoided, and effective and quick case care is used. This lessens the spread of illness and aids in keeping an eye on its impact. Despite being challenging to utilize, there are presently high, powerful and secure medications available to treat leishmaniasis, particularly visceral leishmaniasis. The accessibility of these drugs has greatly improved thanks to the price system negotiated by the WHO and the drug donation program through the same organization.
- By lowering the population of sandflies, vector control aids in slowing or stopping the spread of this illness. Spraying insecticides, using nets coated with pesticide, managing the environment, and using personal protection are all examples of control strategies.
- In epidemics and other circumstances with high mortality rates, effective disease surveillance is crucial for prompt intervention.
- Host animal reservoir management is challenging and necessitates adaptation to the local environment.
- Insecticide spraying campaign on homes and orchards leads to the reduction of pest or sandflies by transmitting infection.

Diagnosis and Treatment

Clinical symptoms, parasitological testing, or serological tests are used to diagnose visceral leishmaniasis (such as rapid diagnostic tests). Serological assays are only partially useful in leishmaniasis of the skin and internal organs. Confirmation of the diagnosis is possible when clinical traits are paired with parasitological testing.

The kind of leishmaniasis, concomitant diseases, parasite species and geographic locations are only a few of the variables that affect treatment. Leishmaniasis is a treatable and curable condition that calls for a capable immune system because treatments cannot completely get rid of the parasite from the body. This increases the danger of relapse if immunosuppression takes place. All patients with a diagnosis of visceral leishmaniasis need rapid and thorough care. In the WHO Technical Report Series No. 949, “Combating Leishmaniasis,” specific information is offered on the various types of the disease’s treatment, according to geography.

Treatment of Leishmania Parasite: Metabolites of Medicinal Plants

The science of medicinal plants in its modern sense is making great progress in various parts of the world. Also, the interest in the study of medicinal plants and their uses in treating various diseases are increasing. The plants contain an extreme high number of medicinally active ingredients that reflect the great therapeutic potential of these plants. It is known that some plant drugs have a greater curative capacity than those manufactured drugs in the treatment of some diseases. Plant medicines contain nutrients and vitamins as well as active ingredients (Majed and Ali-Shtayeb, 2008).

Consequently, the field of ethnopharmacology has recently emerged. It is a new field that is concerned with evaluating medicinal plants used in traditional medicine. Ethnopharmacology also studies these plants using advanced means for the pharmaceutical industry, taking into account all scientific data. This includes biological, chemical, social and economic data, so that it can be used in the medical field.

Most historians have illuminated that human nations over the ages used plants in a way ahead of their time. For example, quinine extracted from the bark of the *Cinchona pitayensis* plant was used to treat symptoms of malaria before identifying the cause of the disease. This can be seen in the case of the Indian snakeroot plant *Rauwolfia serpentine* as a sedative and lowering arterial pressure, and the Virgin's finger plant (*Digitalis spp.*) that treats heart diseases (Yahya, 2003). In the mid nineteenth century, plants and their derivatives made up at least 80% of manufactured

medicinal drugs such as Aspirin, Atropine, Artemisinin, Colchicine, Digoxin, Ephedrine, Morphine, Quinine, Vincristine and Vinblastine. The WHO indicated that about three-quarters of the world's population depends on medicinal recipes with roots in traditional medicine. It is striking in the list of the aforementioned drugs that anti-cancer drugs such as Vincristine and Vinblastine give another dimension to medicinal plants in the treatment of the most challenging disease at present, which is cancer.

The process of carcinogenesis must be preceded by a single mutation or mutations in cells that develop into cancerous tumours. Studies have proven the importance of plants and their active components as anti-mutagenic or carcinogenic substances or both. These can prevent mutation or interfere with the repair process of mutated DNA and mechanisms that prevent the fixation of the mutation and thus reduce the possibility of cell carcinogenesis. Within the plan of the Department of Life Sciences at the College of Science (University of Baghdad), light was shed on the local plants of popular medicinal use and the role of the raw extracts of these plants in treating diseases. Studies have indicated the therapeutic importance of the plant or its active substances as an anti-inflammatory, anti-bacterial, anti-fungal, anti-viral, anti-parasite and anti-carcinogenic.

Studies were directed towards the possibility of using extracts of some medicinal plants and herbs in treating many diseases that humans suffer from. Extracts of seeds and stems of different medicinal plants have been used to resist different types of bacteria, viruses, parasites, fungi, worms and insects. In 2001, a study was conducted by Chan Bacab and Rodriguez-Pena to know the effect of alkaloids separated from wormwood *annua artemisia* in inhibiting activities of *Leishmania* spp.

In the same year, Herwing and Wolfgang conducted a study to test the effect of a group of medicinal plants growing in Guatemala on the growth of parasites *Leishmania* spp., *falciparum*, *P* and *Trypanosoma cruzi*. The study found that the plants which had the most effect on the growth of these parasites were *Neurolaena lobata* and *Wigandia urens*. The results presented that the extracts used for the plants of horsetail *arvense Equisetum* and *Urtica piluifera* had an inhibitory effect on *Leishmania tropica*. The study also reflected that these extracts affected the number and time of generation, as high concentrations led to a reduction in the number of generations (Bilqis et al. 2007).

Furthermore, the aqueous extract of *Cimbopogon citratus* has a marked inhibitory effect on the growth of the anterior flagella of visceral and tropical leishmaniasis. Likewise, the effect of alcoholic extract of *Pimpinella anisum*, *Plantago major* and nettle *piluifera Urtica* on many nematodes that parasitize the plant was presented. This indicates the possibility of these extracts containing effective compounds that may be used as reasonable models for designing anti-leishmania drugs, such as flavonoids, alkaloids, phenols, resins, terpenoids, sterols and other secondary metabolites. One of the most important secondary products used in the pharmaceutical field, especially the production of materials used in the treatment of cancer, is Vinblastine, Vincristine, Taxol, and the drugs used in the treatment of heart disease (Al-Jeborri, 2002).

Digoxin has raised awareness of flavonoids and phenols in recent years, and as a consequence, comprehensive studies in biology and medicine have demonstrated their anti-cancer, anti-allergic, anti-viral, anti-bacterial, anti-parasitic and other effects.

Anti-Inflammatory Effect of Flavonoids and Phenols

In plants, the formation or synthesis of these secondary compounds is in equilibrium with the primary metabolites. It is linked to essential enzymes for conversion from one pathway to another. The activity of these enzymes determines the rates of secondary metabolite synthesis.

The metabolism of arachidonic acid under the influence of the enzymes lipooxygenases and cyclooxygenases leads to the production of prostaglandins and leukotrienes that are responsible

for the manifestations of inflammation. In his book *Modification of Palatal Function*, Landolfi and his team show that some flavonoids can alter the pathway of arachidonic acid inside the platelets. It is proven that myricètine and quercetine in high concentrations inhibit both cyclooxygenase and lipoxygenase. At low concentrations however, they inhibit lipooxygénase enzyme, whereas both chrysin and apigin inhibit the activity of cyclooxygenase (Landolfi et al., 1984).

Antioxidant Activity

The plant Polyphenos has an antioxidant and free radical scavenging property. The leaves of the plant show their ability to protect cells from oxidative damage. This characteristic of the plant is attributed to its therapeutic potential for many diseases. The flavonoids that are isolated from the alcoholic extract of the plant have an anti-oxidant property, as it has been proven (Gálvez et al., 2005) that they scavenge free radicals such as DPPH radicals and inhibit lipid peroxidation.

Among the flavonoid compounds is Luteolin, which plays a major role in increasing the effectiveness of the responsible oxidation enzymes called Superoxide dismutase and Catalase. By removing free ionic radicals that cause oxidation of cell membrane lipids, proteins and nucleic acids induce cytotoxicity and DNA abnormalities (Leung et al., 2006).

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