



World Journal of Current Medical and Pharmaceutical Research

Content available at www.wjcmpr.com

ISSN: 2582-0222



A REVIEW OF *LEISHMANIA* GENOME, HOSTS, VIRULENCE FACTORS, PATHOGENESIS AND TREATMENT

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Article History	Abstract
Received on: 16-01-2024 Revised on: 06-02-2024 Accepted on: 12-03-2024	The study aims in this review to study the <i>Leishmania</i> genus parasite that causes Leishmaniasis, in its clinical forms Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (ML) and Visceral Leishmaniasis (VL). When studying the parasite's genetic composition of the genome of the nucleus and the genome of the kinetoplast, which constitutes 10-20% of the total DNA, it was found that despite the difference in pathogenicity between the types of the parasite <i>L.</i> , the genetic material is similar and maintains the genetic content. CL is a self-healing disease, but prompt treatment is important to avoid unattractive scarring and parasite spread. Of all the drugs of choice, Pentostam and Glucantime are the first line of treatment for all types of leishmaniasis, but there are serious attempts to discover new therapies.
	Keywords: Leishmaniasis, Genomic of <i>Leishmania</i> , Pathogenesis, Treatment.

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DOI: <https://doi.org/10.37022/wjcmpr.v6i1.315>

Introduction

L. genus belongs to the order of Kinetoplastida belonging to the family Trypanosomatidae. The parasite of *L.* has two forms during its life cycle represented by the promastigote form which is in the infection stage and is seen in female sand fly belonging to the genus *Phlebotomus* (vector host) in the Old World and to the genus *Lutzomyia* In the New World, the amastigote form is found in humans and the reservoir host. Leishmaniasis has three clinical forms: Cutaneous Leishmaniasis, Mucocutaneous Leishmaniasis, and Visceral Leishmaniasis [1, 2], and this disease is spread in tropical and subtropical regions, about 12 million infected people in 98 countries of these diseases, with 350 million people at risk incidence worldwide [3].

It was considered an endemic disease in Iraq, both rural and urban, where one of its types was known in the past as Baghdad boil [4].

CL appears in two types, the first: Zoonotic Cutaneous Leishmaniasis (ZCL) when the parasite is transmitted from a group of animals to humans, and is caused by the *L.* major

parasite. It appears in rural areas and causes a sore wet sore, and CL. Anthroponotic Cutaneous Leishmaniasis (ACL) When transmitted from person to person, the parasite is caused by *L.* tropica and is the most common form in urban areas. This species causes a dry sore [5]. In Iraq, both types of CL, dry and wet, appear [6].

Morphology of parasite

The genus *L.* passes in two forms, one of which is an amastigote that grows and multiplies inside the macrophages of the vertebral storage host, and the other form is a promastigote that lives in the intestine of the female sand fly [7].

1- Amastigote

The amastigote stage is also called the Leishmanial form, and it has a round to oval shape devoid of flagella, and its size ranges between 3-5 microns. This stage possesses a single nucleus located near the center of the parasite, in addition to containing an ovoid or rod-shaped kinetoplast from which the axoneme extends. The amastigote stage grows and proliferates obligately in the vertebral host inside phagocytes [8].

2- Promastigote anterior

The promastigote anterior is also called leptomonas. The parasite takes an elongated spindle-shaped form at this stage, and its size ranges between 14-20 microns. It has an anterior flagellum that moves through it, which is approximately the length of the body, while the kinetoplast is approximately 2 microns from the anterior end. The promastigote stage grows and multiplies extracellularly in the intestine of the sand fly insect, in addition to the possibility of observing it when

cultured in culture media. The promastigote stage is considered the infected stage.

The glycosomes appear as small sacs containing a dense substance that appear in the form of sheets and are spread in huge numbers in the promastigote stage. This reflects the high glycolysis efficiency in the promastigote stage compared to the amastigote stage, and the mitochondria are more efficient and developed in the promastigote stage. Therefore Its life is aerobic and it cannot live without oxygen. When its level drops below 0.4%, it will suffer from a loss of movement, a decrease in protein synthesis, a decrease in the size of the parasite, followed by cell death [9]. Figure 1 below.

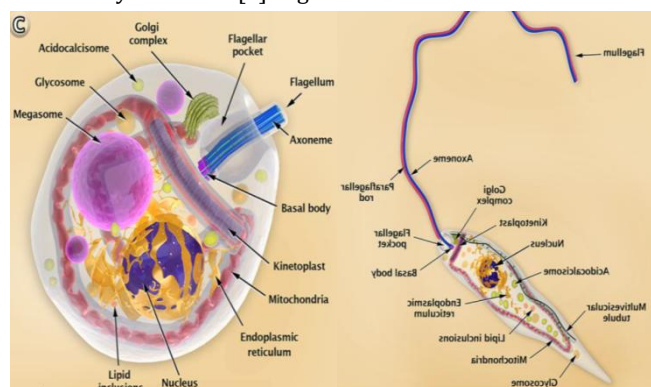


Fig. (1): Structural organization of the two phases of *L.* by transmission electron microscopy.[10]

Genome of Leishmania

1- Nuclear Genome

The genome of the different *L.* parasite species is organized in the nucleus, which is attached to chromosomes and kinetoplasts DNA. The size of the *L.* genome varies, ranging from 29 Mb for the parasite *L. amazonensis* to 33 Mb for *L. major*, *L. infantum* and *L. braziliensis*[11]. It is distributed on different numbers of chromosomes, for example, 34 chromosomes in the parasite *L. amazonensis* and *L. Mexicana*, 35 chromosomes in the parasite *L. brasiliensis*, and 36 chromosomes in the parasite *L. major*, *L. donovani*, and *L. infantum*[12].

The *L. major* genome also contains 911 RNA genes, 39 pseudo-genes and 8272 proteins-encoding genes. The content of G+C nitrogenous bases in the genome is 59.7% [13]. *L.* genes are arranged in repetitive rows with one or more copies distributed in the genome [14].

Sequencing analyzes showed a density of one gene per 3.5 kbp. Previous studies confirmed that 30% of the genome consists of repeated elements, about half of which are telomeric/subtelomeric repeats and the remainder is dispersed transposons, repeated genes, and simple repeat sequences. Other simple repeated sequences.

Genes encoding proteins do not contain introns, and thus it is easy to diagnose these genes in the DNA genome [15]. However, polymorphism is present in the nucleic acid sequences. As the difference in DNA sequences based on specific patterns between the main links or linkages of the *L.* parasite ranges between 13%-25%. This level of divergence was based on a comparison between the genomes of *L. major* and *L. infantum* [16].

Several studies suggested that the number of *L.* chromosomes is mainly diploid with some chromosomes showing aneuploidy

[17]. Despite the difference in pathogenicity between *L.* species, the genetic material is similar and preserves the genetic content. The genome of *L.* parasite species is characterized by high gene density, long rows of polycistronic gene clusters, and a complete absence of introns [18].

2- Kinetoplast DNA genome

The DNA of the kinetoplast constitutes 10-20% of the total DNA and consists of a circular DNA network and is divided into two categories, which are the homogenous maxicircles with a molecular size ranging from (20 kb) and the number of copies ranging from (25-50) and small circles not The heterogeneous minicircles with a molecular size of (0.8 kb) and a number of copies of 104 [2], the maxicircle has a similar function to mitochondria despite its role of editing uracil residues into reporter RNA nucleotides (mRNA) [19].

As for the minicircles, they encode for editing the cytochrome oxidase subunit III mRNA [20]. Kinetoplasts DNA is mainly used for the diagnosis and detection of small quantities or low numbers of *L.* parasite in samples or biological materials because it contains a high percentage of repetitive character and abundant amounts of minicircles. The high degree of sequence heterogeneity in the kinase DNA makes it useful for molecular classification studies [21].

The cytochrome b gene is considered one of the important genetic indicators used in the molecular diagnosis of *L.* species [22]. It is a membrane protein located in the mitochondrial genome of different *L.* species. It consists of approximately 400 amino acids and is characterized by stability. The electron transport chain in the mitochondrial respiratory chain is considered one of the most functional genes of genetics studies because of its sequence variation [23].

Vector host

The sand fly is a small, blood-sucking insect that hosts Leishmaniasis. It belongs to the order Diptera, family Phlebotomidae, under the family Phlebotominae. All sand flies that transmit leishmaniasis belong to the genus *Phlebotomus*, and there are more than 600 species of this genus. The family of Phlebotomidae, includes five genera: *Phlebotomus* and *Sergentomyia* (in Old World countries) and *Lutzomyia*, *Brumptomyia*, and *Warilea* (in New World countries). The genus *Phlebotomus* is the main vector of leishmaniasis in the tropics and subtropics (Old World). The genus *Lutzomyia*, which is spread only in the American continent, is the main vector of leishmaniasis in the countries of the modern world [24]. There are about 30 different species of the genus *Lutzomyia*, *Phlebotomus*, which differ in the basis of their transmission to the different genera of the *L.* parasite. It can transmit at least 20 different types of *L.* parasites.

In the diagnosis of the sand fly in the period 1786-1925 AD, it was relied on the external appearance, as it was adopted as taxonomic characteristics, including the number and spread of hairs on the male reproductive organs (genitalia), the size, color, and spread of hairs and scales on the body, wing veining, the length of the tentacles, and the measurement of the head and abdomen in females, and after describing each from the buccal cavity, pharynx, cibarial teeth, and Spermatheca[25]. The length of the adult insect is 1.5-3 mm, with a yellowish color, with clear black eyes. Its body contains dense hair, especially in the area of the wings and legs. Its wings are oval in

shape and erect above the body when the insect stands still (Figure 2), and it reproduces and grows on organic waste. Such as feces, animal manure, rodent burrows, and leftover leaves [26].

The female sand fly feeds on blood and has great medical and veterinary importance, because it is able to transmit the causes of several important diseases in Iraq and other countries of the world such as protozoa, viruses and bacteria to animals and humans [27], and its painful sting can cause dermatitis that affects on the skin and general health of its host [28].



Fig. (2): The vector host is a female sand fly [29]

The Reservoir Hosts

The storage hosts differ for patients with CL, as humans are considered storage hosts in the Middle East, Asia and Africa as well as wild rodents, wolves, foxes and gerbils [30]. Adler and Theodor (1930) isolated the parasite CL from a dog. Bulk in the city of Baghdad, and this isolate was injected into rats, and it produced skin ulcers, which are no different from the ulcers caused by the stings of the vector sand fly [31].

As for humans, the storage host remains in the event that the original host is not available. Dogs, gerbils, wild animals, and rodents are the storage hosts for ZCL caused by the parasite *L. major* that forms the wet sore [32]. Small rodents, such as rats, are of the type *Rattusrattus*, mice *Musmusculus*, as well as *Crocidurasuaveolens* are rodents that store the disease [33], and for this reason El-Adhami (1976) indicated that the black rat of *Rattusrattus* was infected with the CL parasite in Adhamiya district in Baghdad province [34].

In Iran, the storage host is two other rodent species, *Rhombomysopimus* and *Merioneslipycus*. In Egypt, the storehouse was the black rat (*Rattusruttus*) and the Norwegian rat (*R. norvogenicus*) [35]. In Sudan, the parasite was discovered in rodents of the species *Arvicanthisniloticus* [36].

In Spain and China, dogs are the main reservoir of the parasite [37], as well as in Britain, dogs are also the main reservoir of the parasite [38]. The same is the case in Portugal, where dogs are considered the first accused of storing the *L. parasite*. In an epidemiological study, 3614 dogs were collected, during which antibodies to *L.* were found in 6.9 % of them [39].

Life cycle of Leishmania

L. parasites live in two successive hosts: the invertebrate host, the female sand fly, which plays the role of the final host for *L. parasites*, in which the promastigote stage lives, and the vertebral host (mammals) that plays the role of the intermediate host, in which the amastigote stage lives, as the evolution cycle generally revolves between Three hosts are the human being, the vector insect, and the storehouse of the

parasite, as the female sand fly is the vital carrier of the disease, and all flies that carry the parasite belong either to the genus *Phlebotomus* in the countries of the Old World or to the genus *Lutzomyia* in the countries of the New World [40].

The life cycle begins when the female sand fly stings the infected vertebral host to take its bloody meal, as it takes the parasites along with the blood, which have a circular shape amastigote [41], to begin the first step, which is the transformation of the Amastigote stage into a promastigote stage, which divides at an early stage and is called Then the Procyclicpromastigote is in the back of the fly's intestine, and after three days of feeding the insect have passed, the promastigote stage moves towards the front part of the mid-gut, and on the fourth and fifth day after feeding, an increase in the number of promastigote stages is observed in the midgut of the female sand fly. Then, it settles in the oral parts of the vector insect, adopting a slender fusiform shape characterized by its rapid movement, called Metacyclicpromastigote, and represents the infective stage that causes injury to the vertebral host [42]. A healthy person is infected by the sting of a female sand fly carrying the infective stage of the *L. parasite* while feeding, as it injects these infectious roles that are swallowed by the macrophages of the reticuloendothelial system, and this process takes 4-5 hours [43]. Within these cells, the promastigoteforms turn into rounded shapes amastigote, which begin to multiply and spread within these macrophages, which leads to their explosion due to the large number of parasites inside them, releasing the parasites they contain, which in turn are devoured by other neighboring macrophages, that these infected macrophages It can remain latent in the skin and cause cutaneous disease, or reach through the reticuloendothelial system to various organs of the body such as the liver, spleen, and bone marrow, where the parasite settles and multiplies, causing VL[44]. When the uninfected vector insect feeds on the blood of the infected person, the macrophages will be digested and the parasites will be released that settle in the mid-gut of the vector insect, transforming into the Procyclic form, which multiplies and migrates to the mouth of the vector insect, transforming into the Metacyclic form, and then the insect is ready to be injected. Infective roles when feeding on the blood of a healthy vertebrate host and so continue to repeat the life cycle again [45].

Virulence factors for Cutaneous Leishmania

Virulence factors play an important role in the spread of Leishmaniasis by eluding the immune system and enabling the parasite to invade the host and cause infection, causing damage to the host and being targeted by immune responses. For vaccine production, the most important identified virulence factors are lipophosphoglycan (LPG), proteophosphoglycan (PPG), cysteine protease, Acid Phosphatase Enzymes, GP63 [46].

1. Lipophosphoglycan (LPG)

They are chemical compounds present on the outer surface of the *L. parasite* that facilitate the process of entering the parasite into the macrophages, which occurs when the promastigote form is in contact with the cell membrane, as it binds and interacts with the receptors of the phagocytic cells, and then enters the process of phagocytosis into the phagocytic

cells [47], These compounds work to keep the parasite alive and develop within the host and protect it from oxidants (O₂, H₂O₂) and work on its adhesion to the macrophage and also considered as a mitigating factor for host responses by inhibiting the signaling pathways of phagocytic cells responsible for the destruction of intracellular pathogens of the amastigote stage [48].

2. Proteophosphoglycan

It is a substance of a gelatinous nature in which the *L. parasites* are embedded, and this substance helps to close the lumen of the insect's foregut and the tidal valve, which causes the release and vomiting of the metacyclicpromastigote when the host is stung by the female insect while it is obtaining a meal [49].

3. Cysteine protease

It is one of the proteolytic enzymes produced by the genus *L.* It is related to virulence by degrading host tissues, degrading peptide bonds and degrading host proteins and plays critical roles in the pathogenesis of other parasitic infections [50].

4. Acid Phosphatase Enzymes (APEs).

It is one of the degrading enzymes in CL and is present in many microorganisms and is also known as (EC3.1.3.2). The Golgi apparatus is the main source of these enzymes and is also present in the endoplasmic reticulum, flagellum receptors and the surfaces of outer membranes [51].

Acid phosphatase enzymes have an important role in stopping the production of oxidants products by phagocytic cells, in addition to their role in protecting the parasite in unfavorable environmental conditions [52].

5. Glycoprotein (GP63)

It is a glycoprotein present on the surface of the *L. parasite*. It inhibits lysosomal enzymes inside phagocytic cells through the presence of receptors associated with the phagocytic process. It also has a role in the process of adhesion of the amastigote stage to the host before infection occurs [53].

Pathogenesis

The skin lesion appears as inflammatory papules that develop into nodules and crusts in the center of the lesion. The lesions are usually painless and heal on their own after several months, leaving permanent disfiguring scars [54].

CL caused by *L. tropica* and *L. major* cannot be distinguished on clinical grounds as they both erupt in the same way, lesion size ranges from a few millimeters to 4 centimeters or more, and the number of lesions is indicative of the type of CL. *L. major* usually presents as multiple lesions of more than 3 mm, and it has been shown that primary infestations in *L. major* are 30% more frequent, while that of *L. tropica* is 19%. The preferred sites for *L. major* are the cheeks, arms and legs which represent more than 70% of the cases, while the preferred sites for *L. tropica* are the cheeks which constitute more than 50% [55].

The promastigote stage is transmitted to the host in mammals by the sting of an infected female sandfly during a blood meal. Neutrophils are the first cells to be recruited to the site of the sting and take up the flagella by phagocytosis [56]. The researcher, Ritter et al., (2009) stated that neutrophils are among the most important cells for early defense against infections, and when they are in an active state, they obligately kill the pathogen entering the body of a person infected with

leishmaniasis[57]. However, when the parasite evades killing, neutrophils can play the role of host cells for the parasite, as they silently transfer the *L. parasite* inside the human body to the phagocytes, as they work to infect the macrophage after escaping from the neutrophils [58]. After the parasites have been taken up by macrophages, either by phagocytosis of free parasites or infected neutrophils [59] will involve three distinct macrophage/leishmania interactions which represent stages: parasite attachment, internalization and parasite vacuole formation [60].

Macrophages represent the main host cell for *L. parasites*, as the temperature of the phagocyte increases and the pH decreases, which stimulates the promastigote to differentiate into amastigote and can infect other phagocytes [61].

There are several factors on which the extent of the disease depends, including the humoral and cellular immune response of the host as well as the pathogenicity of human species [62]. Children in endemic areas are at greater risk than adults, malnutrition also contributes to the development of this disease, and incomplete treatment prepares for recurrence of leishmaniasis [63].

Cutaneous leishmaniasis

CL is a worldwide public health problem and a social problem in many developing countries. It can affect the skin and mucous membranes, and is caused by different species of *Leishmania* that are widespread in the Old and New Worlds [64].

CL is called the Oriental sore, Baghdad boil, or Delhi ulcer [65]. This species is caused by parasites *L. major*, *L. tropica*, *L. mexicana*, *L. amazonensis*, *L. guyanensis*, and *L. panamensis*. CL produces large numbers of Skin ulcers, up to 200 ulcers in some cases on the exposed parts of the body, caused by *L. major* or *L. Mexicana*, and it is possible to recover within 3 months of infection. As for those caused by *L. tropica*, it takes 10 months to heal, while infection with *L. braziliensis* long-term infection [66].

The disease begins with a lesion at the site of entry of the infection in exposed areas of the skin such as the face, arms and extremities, as the lesion initially appears in the form of a small nodule with a red color, which enlarges in size, taking the form of a papule or an ulcerated vesicle, after which it bursts, generating a pus, and may heal self within several months but bacterial infection may complicate the healing process leaving a brown flat scar [67].

In Iraq, CL is a common and widespread skin disease, especially in the southern and central regions of the country [68]. As it is one of the endemic diseases in Iraq, both species *L. major* and *L. tropica* have been reported to be present in various parts of Iraq, especially in Baghdad [69].

Clinical features of cutaneous leishmaniasis

CL parasites cause several clinical forms that can be distinguished depending on the behavior, pattern and extent of the disease, the most important of which are:

1. Dry type

It is also called the urban type, and this type usually spreads in urban areas in the countries of the Mediterranean basin, the Middle East, India and Pakistan, caused by *L. tropica*, as this type causes a dry ulcer of small size and single or multiple, painless ulcers and its shape is not fixed, and it ranges between Its incubation period ranges from approximately 2 to 8 months,

and its color changes from red to bluish red, and its dimensions range from (2-4) cm [70].

2. Wet type

It is also called the rural type. This type forms moist skin lesions that often ulcerate at an early age. It is caused by the parasite *L. major*. It is the most widespread and usually affects rural areas. The parasite is transmitted to humans through the vector host represented by female sandflies or reservoir hosts such as dogs or rodents. The incubation period for the parasite ranges from 1-3 weeks, after which it heals spontaneously within two months to a year, leaving low colored scars [71].

3. Recidivans leishmaniasis

It is called Lupoid Leishmaniasis. Lesions resulting from this disease are destructive and corrosive to tissues. It is of little spread and is usually chronic. Infection with it leads to complete disfigurement and is resistant to treatment. It may be misdiagnosed as leprosy, and it is difficult to treat. The original blister appears non-ulcer. The new ulcers formed around the old lesion that appear on the face and trunk are clinically similar to leprosy, and require careful diagnosis to distinguish it from various other infections that include lupus vulgaris, fungal infections, and leprosy [72].

It cannot heal spontaneously, as it is an unusual result of the Oriental sore, and a relapse may occur after taking the treatment, due to a deficiency in the immune response caused by the disease with the *L. tropica* parasite, especially in the absence of parasites in the lesion, and this type may cause of leishmaniasis due to infection with the parasite *L. major* [62].

4. Diffuse cutaneous leishmaniasis

This type is clinically characterized by the appearance of original, non-ulcerating scars, and new scars formed that appear on the face and need an accurate diagnosis to distinguish it from other different skin infections that include common lupus as well as fungal infections. This parasite may attack the cartilage and soft areas of the body such as the nose and ear. It is accompanied by severe pain and is called white leprosy [73].

Immunity and immune response against leishmaniasis infection

Clinical and experimental evidence indicates that the parasite, the vector, and host-specific factors all influence the incidence and progression of *L.* infection. Host's protective immune responses [74].

The promastigote forms of the *L.* parasite, after being injected by a female sand fly into the human body, confront the first line of defense of autoimmunity represented by the complement system and phagocytes [75]. Immediate immunity plays an important role in defense against parasitic infections, as it does not Affected by prior exposure to parasites and includes physical and chemical barriers such as skin, mucous membranes and epithelial tissue lining internal organs such as respiratory and urinary tracts and intestines as well as dendritic cells, macrophage cells, natural killer cells and granulocytes such as neutrophils and eosinophils [76].

When the promastigote penetrates the host's own immune defenses, it is engulfed by macrophages. The phagocytosis process takes (4-8) hours. However, in many cases, the parasite is resistant to protein degradation and degradation within the cell, and the parasite resides in mammals within

phagocytic cells such as macrophages and neutrophils, for example [77]. And that the *L.* parasite effectively avoids the humoral immunity by continuing to live inside the phagocytic cells, and the parasite can be described as sometimes escaping, or sometimes manipulating the acquired immune system, and then avoiding digestion [78].

This immunity is of two types: the humoral immune response and the cellular immune response [79]. The immune response to the *L.* parasite is carried out through cellular immunity mediated by CD4+ T helper lymphocytes, which can be divided according to the cellular kinetics they secrete into two types of T-helper lymphocytes, the first type, Th1, and T-helper lymphocytes, the second type, Th2. The host body's resistance to *L.* parasite depends on the cellular immunity of the first type Th1 helper lymphocytes, while its ability to infection depends on the secretions of the second type Th2 helper lymphocytes. T cells play a very important role in the immune response, as Th1 type 1 T cells secrete both interleukin-2 (IL-2) interleukin-2 and interferon gamma (INF- γ), while Th2 helper T cells secrete (IL). - 4) interleukin-4, (IL-5), (IL-6), (IL-10), (IL-12) [80].

IFN- γ plays a critical role in activating macrophages to produce the enzyme responsible for the production of nitric oxide (NO) to kill the intracellular stages of the flagella [81]. Cellular immune responses in leishmaniasis have been studied extensively in mouse models of different strains, and have been Studies have shown that resistance against CL infection is associated with higher levels of IFN- γ and lower levels of interleukin-4 (IL-4), as it has been proven that injecting IFN- γ directly into the skin lesion leads to its diminishment [82].

Recently, a positive association was observed between ulcer size at the time of first evaluation and INF levels, supporting the use of INF inhibitors in combination with standard therapy to improve healing time in CL patients with severe lesions [83]. Interleukin-10 (IL-10) is also produced by patients with CL and is responsible for downregulated inflammatory responses mainly those induced by INF- γ [84]. IL-10 is produced by a variety of cells, including macrophages, regulatory cells (T-reg), Th1 cells, and CD8+ cells. Studies indicate low production of (INF- γ) and increased production of IL-10 in patients with less than 60 days of age when compared with those infected with more than 60 days of CL, and that low production of (INF- γ) and increased production of IL-10 occur in more than 50% of infected people at the onset of infection with the parasite [75].

Human infection with CL is characterized by the appearance of low levels of leishmaniasis antibodies in the blood serum of infected persons, while high levels of leishmaniasis antibodies are produced in the case of VL. Studies have revealed a high level of immunoglobulins (IgG, IgM, and IgE) in the case of *L.* infection [85], which indicates that the parasite stimulates the immune response by activating B cells. In addition, natural killer cells appear to be Responsible for identifying the disease and removing the parasite from the area of infection for acute CL, the importance of killer cells by stimulating the production of INF- γ and depleting natural killer cells in the first days of infection leads to a significant decrease in the production of INF- γ and an increase in parasite numbers [82].

Treatment

CL is a self-healing disease, and prompt treatment is still important to avoid unattractive scars and parasite spread. Currently, there is no single ideal treatment for CL[86]. There are many chemical compounds used in the treatment of leishmaniasis, the results of which vary depending on the type of parasite causing the disease, the duration of the disease, the number, size and location of the lesion, and the presence of secondary infection [87].

Pentavalent antimony, which includes sodium stibogluconate (Pentostam) and meglumine (Glucantime), is the first-line drug of choice for the treatment of all types of leishmaniasis[88]. Pentostam has been used since the 1940s and cannot be administered by oral route, and it can be given either by intramuscular injection or intravenously, and it is believed that it works by inhibiting the synthesis of ATP[89] and that these drugs have side effects such as muscle pain, arthritis, leukopenia, pancreatitis, and arrhythmia. The heart and that prolonging the duration of treatment can cause the drug to accumulate in the tissues of the body, especially in the liver and spleen, and long periods of treatment may lead to the emergence of parasite resistance to treatment [90].

Pentostam is the treatment of choice for patients with leishmaniasis, despite its toxic effects, which made researchers search for other forms of therapeutic drugs that are less toxic than pentostam[91]. In 1956, Amphotericine B was discovered, which is an antifungal drug and used as a second line treatment for leishmaniasis. Amphotericin B is preferred because it presents a lighter toxicity profile, in addition to a higher spectrum of action and potential, which results in greater reliability of use [90].

Paromomycin or Aminosidine is a broad-spectrum antibiotic, active against L. and some protozoa and Enterobacteriaceae. Paromomycin has fewer side effects than amphotericin B and is not photosensitive [92]. Another interesting group is Alkyl phosphocholines (Alkyl-PC) which were originally developed as an anti-cancer drug [93]. Miltefosine, one of the group of Alkyl-PCs, has already been used against VL (caused by *L.donovani*) [94].

Funding

Self Funding

Acknowledgement

For all the worlds to research

Conflict of Interest

No Conflict of Interest

Inform Consent and Ethical Statement

Not Required

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