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Review Article

# Global overview of *Leishmania* virulence factors, and the role of GP63 in promastigotes

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## Abstract

Protozoa parasites of the genus *Leishmania* have a great ability to avoid damage in the hostile environments they encounter throughout their life cycle within the host's body. Parasites have developed many virulence factors to ensure their persistence and replication within the host, and the first role of these factors is to attenuate the host's defenses against them through innate and adaptive immunity, as evidence indicates that the determinants of parasite virulence are responsible for evading the host's defenses, allowing these organisms to survive on Alive in the host's hostile immune environment. Understanding the molecular details of how these pathogens persist with impunity under extreme conditions is beginning to begin. The fact that *Leishmania* parasites have adapted not only to survive but are likely to reproduce is due to the protection afforded by specialized molecules on the parasite's cell surface. Although recent years have seen clear and significant progress in the research on *Leishmania* in different directions, many issues have yet to be clarified. The surface of all parasites, especially protozoa, usually undergoes pronounced changes during their life cycle. It is of particular interest in the case of protozoan parasites of the genus *Leishmania* whose surface is exposed to different and hostile environments within vertebrate and invertebrate organisms. Because of the importance that the cell surface of pathogenic parasites plays in their interaction with the host for survival, some efforts have been devoted to their characterization. This review aims to give an overview of the main virulence factors that contribute to parasite survival and survival. We have attempted to provide a brief picture of the factors that influence the interaction of the parasite in its host, further highlighting GP63 as a critical virulence factor affecting macrophage physiology as well as the functioning of the immune system.

**Keywords** *Leishmania*, parasite, virulence factors, GP63

## Introduction

Leishmaniasis is a group of parasitic diseases that pose a public health challenge worldwide, and is categorized among the most serious endemic diseases, with a wide range of clinical signs and manifestations (de Souza et al., 2000) Leishmaniasis is a widespread parasitic disease caused by the dimorphic parasitic flagella of the genus *Leishmania*. These obligatory parasites of macrophages are transmitted by multiple species of Phlebotomized sandfly (Pearson and de Queiroz Sousa, 1996), and there are more than 20 species and subspecies of the genus *Leishmania* that infect humans by the bite of sandflies. The sandflies *Lutzomyia* acts as the vector in

the (New World), while the species of *Phlebotomus* transfers the infection in the (Old World). It is a female small sandfly that sucks blood and feeds in caves and burrows in the forest area of the tropical and subtropical regions (Markle and Makhoul, 2004).

Leishmaniasis can appear in many different forms depending on the affected types of leishmaniasis, and the disease can be in the form of cutaneous, mucocutaneous, or visceral leishmaniasis (Abdellahi et al., 2022). Cutaneous leishmaniasis (CL) presents as ulcerated skin lesions, mucocutaneous leishmaniasis (MCL), or Espundia, which affects the mucous membranes of the nose, mouth, and throat

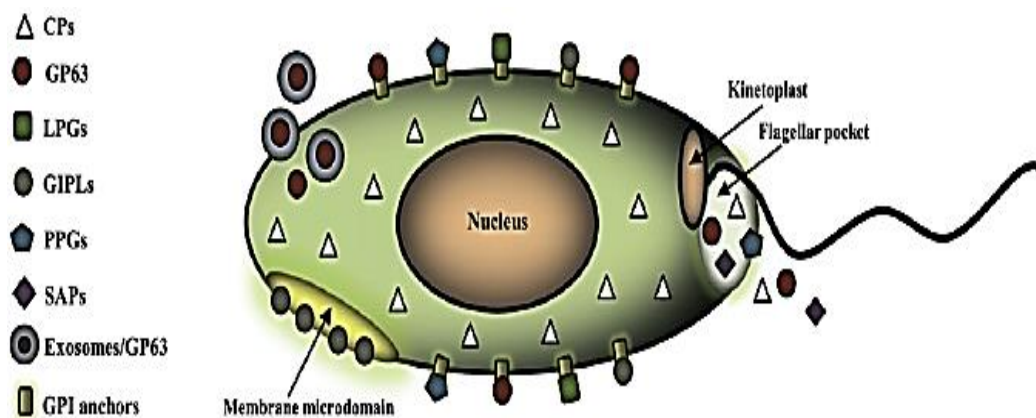
and can lead to partial or complete destruction of the associated membranes, and visceral leishmaniasis (VL) called kala-azar or Black fever, is a potentially fatal systemic disease caused by the parasite *Leishmania donovani* (Pradhan et al., 2022). Leishmaniasis is a parasitic disease caused by blood-feeding leishmaniasis. The disease is widespread and may cause serious health problems in communities throughout the Mediterranean region and the Middle East, including Iraq (Hepburn, 2003).

The surface of all parasites usually undergoes significant changes during their life cycle. This is of great importance, especially in the case of protozoan parasites of the genus *Leishmania* whose surface is exposed to different environments within vertebrate and invertebrate hosts. Because of the importance that the cell surface of pathogenic parasites plays in their interaction with the host, this article is devoted to their characterization (Ilgoutz and McConville, 2001). In this context, several molecules have been shown to be important factors in the virulence of *Leishmania* species. Three major surface molecules, lipophosphoglycans [LPG], glycosylinositol phospholipids [GIPLs], and zinc metalloprotease [gp63], are the most studied (Yao et al., 2003). Leishmanolysin, surface protease (PSP), major surface protease (MSP), or gp63 are designations of the most abundant surface glycoprotein in *Leishmania* spp, which are distributed over the entire surface of the promastigote forms within the invertebrate host, including the flagella (Flaih, 2022). Each *Leishmania* major promastigote in the stationary phase is estimated to have [500,000] copies of gp63, constituting about (1%) of the organism's total protein content

(Bouvier et al., 1995). This protein is synthesized in the invertebrate host's endoplasmic reticulum, where the signal sequence is cleaved post-translationally, a N-linked carbohydrate is added and the C-terminal [approximately (25) amino acid residues] are replaced with a glycosyl phosphatidylinositol (GPI) membrane anchor structure (Borges et al., 2021).

Most of these specialized molecules are members of the phosphoglycan family while others are a family of glycosynositol phospholipids. Together, they share a surprisingly large number of functions for parasites throughout their life cycle and are thus fundamental in causing disease. This review summarizes the biological roles of these glucocorticoids and how they are believed to contribute to the survival of *Leishmania* in a devastating setting (Ilgoutz and McConville, 2001).

Parasites have always shown great creativity and skill when it comes time to infect their host, survive and reproduce, and *Leishmania* symbionts are key in this. Indeed, it is known that *Leishmania* can use various surface proteins, re-identified as potential virulence factors, for example, glycosylinositol phospholipids [GIPLs], lipophosphoglycans [LPG], cysteine protease, [GP63], to frustrate the host macrophage defense system allowing for survival and advancement in the harsh environment (Chang and McGwire, 2002). This global overview aims to summarize some facts about *Leishmania* virulence factors (Fig. 1), and *Leishmania* [GP63] will be discussed in detail as a critical virulence factor affecting macrophage physiology.



**Fig. 1** *Leishmania* virulence factors. Diagram representation of a promastigote stag showing the [GPI-anchored surface molecules GP63], [LPGs], [PPGs] and [GIPLs], which are mostly associated to membrane microdomains. Virulence factors that are not membrane-anchored exist in the intracellular milieu and can be released by the parasites via exosomes [GP63], which are virulence co-factors, or via classical secretion through the flagellar pocket [GP63, PPGs, SAPs and CPs] (Olivier et al., 2012).

## Virulence factors

The protozoan parasites of the genus *Leishmania* have a unique ability to avoid damage in the hostile environments they encounter throughout their life cycle, to survive, and reproduce. Understanding the molecular details of how these pathogens persist with immunity under harsh and challenging conditions is beginning. We note that *Leishmania* parasites have adapted not only to survive but are likely to reproduce due to the protection provided by specialized molecules on the parasite cell surface. The surface of all parasites usually undergoes many changes during their life cycle. This is very important in the case of primary parasites of the genus *Leishmania* whose surface is exposed to different environments within vertebrate and invertebrate hosts [sandfly] (Ilgoutz and McConville, 2001).

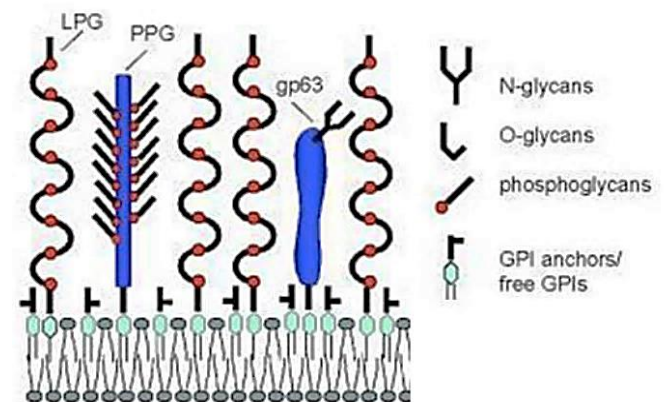
Protozoan parasites are among the most common pathogens worldwide. They cause many diseases such as malaria, leishmaniasis, dysentery, and trypanosomiasis that affect hundreds of millions of people in different countries. Current advances in the study and understanding of the biochemistry and molecular biology of these organisms have focused on certain parasite-specific molecules that are key to the parasite's life cycle or pathogenesis. A special group of enzymes that play multiple and important roles in these processes is parasite-derived proteases. Different types of proteases are frequently expressed at different steps of the parasite's life cycle to contribute to the parasite's reproduction and transformation. The proteases released by the parasite can damage host cells and tissues, contributing to significant host tissue destruction as well as parasite invasion. Detailed studies of these enzymes have led to model systems for studying parasite gene regulation, parasite metabolism, and host-parasite interaction. In some cases lately, it appears that proteases will be used to develop new antiparasitic chemotherapy (J H McKerrow et al., 1993).

The virulence factors of *Leishmania* can be broadly classified into three groups: the first group consists largely of structures and surface proteins, the second group is secretory products, and the third group includes intracellular molecules, which are referred to as "pathogens". In the first and second groups, there are invasive/evasive determinants, which protect not only the parasites themselves but also the infected host cells from premature cellular lysis. These determinants help maintain intracellular infection by growing at a slow rate in the parasitic vacuoles of host macrophages. The second group of immunopathogenic parasites is likely to be related. These are highly conserved visceral proteins, which have been found to contain unique *Leishmania* epitopes that are immunologically active in leishmaniasis. How the intracellular parasite antigens are exposed to the host immune system is accounted for by the cyclic cytolysis of parasites during natural infection (Chang et al., 2003).

In protozoan parasites, proteins play key roles in the invasion of host life cycle shifts, migration across tissue barriers,

degradation of hemoglobin and other blood proteins, immune evasion, and activation of inflammation in the vertebrate host. Parasites have always shown creativity when it comes to infecting their vertebrate and invertebrate hosts, resisting, surviving, and reproducing, and it is clear that the *Leishmania* parasite has a high capacity to live and reproduce. Indeed, it is known that *Leishmania* can use various surface proteins, recognized as potential virulence factors [eg, glycosylinositolphospholipids [GIPLs], lipophosphoglycan [LPG], cysteine protease, [GP63], to frustrate the host macrophage defense system and thus, This allows its survival and development in the host's harsh environment (Chang and McGwire, 2002).

Throughout the life cycle, the surface of the parasite changes. Promastigotes produce, a distinct glycocalyx whose thickness is developmentally regulated, whereas amastigotes lack a discernable cell coat. Molecules that are expressed on, or released from, the surface of *Leishmania* appear to influence parasite survival within the host and the vector (Moody, 1993). The surface of all different parasites undergoes significant changes during their life cycle. This is of particular importance in the case of protozoan parasites of the genus *Leishmania* whose surface is exposed to many different environments within vertebrate and invertebrate hosts. In this context, several molecules have been shown to be important factors in the virulence of various *Leishmania* species. There are three main surface molecules, lipophosphoglycan [LPG], glycosylinositolphospholipids [GIPLs] and zinc metalloprotease gp63, which are the most studied by scientists and researchers. The surface of *Leishmania* spp. is composed of a few dominant components that are present in all species (Fig. 2).



**Fig. 2 Surface coats of *Leishmania* spp. parasites are dominated by [LPG], GPI proteins, and/or no protein-linked GPI glycolipids. Adapted from (McConville et al., 2002)**

### Leishmanolysin (GP63)

The major surface glycoprotein of *Leishmania*, gp63, is especially abundant in the vector stage or promastigotes. It is a zinc protease known as leishmanolysin. The zinc-dependent

metal protease called glycoprotein 63 [GP63] or leishmanolysin, which is naturally present on the surface of the *Leishmania* parasite, was first discovered in the [1980s], where it was genetically and biochemically described as a major surface antigen expressed on the *Leishmania* promastigotes stage of *Leishmania* in various species. It has a wide range of substrates including gelatin, casein, fibrinogen, hemoglobin and albumin. GP63 is present on the amastigote at a greatly reduced level. GP63 is a zinc metalloprotease active in a neutral to alkaline pH range (pH 7–10) (Yao et al., 2003).

gp63 is the major cell surface glycoprotein of *Leishmania* promastigotes with 500,000 copies per cell and accounting for 1 percent of all cellular proteins. In amastigotes gp63 is expressed to a lower level, and the bulk of it is found in the flagellar pocket as opposed to covering the entire surface, as in promastigotes, Leishmanolysin GP63 is abundant in promastigotes stage, but has been shown to be down-regulated in amastigotes stage in sandflies. However, the reduced expression of [GP63] might be remunerated by the absence of [LPG] on the amastigote surface, where GP63 is no longer buried in a sea of LPG and can then play an important role in the capability of amastigotes to modulate the host response despite its lower numbers compared to promastigotes. Given its presence in both forms and stages of the parasite, GP63 is likely to play different roles depending on the parasite stages. In promastigotes of *L. amazonensis* and *L. major*, GP63 was found to cleave (C3b) into (iC3b) and therefore help the parasite to escape by complement-mediated lysis (Medina-Acosta et al., 1989).

GP63 genes are expressed in promastigotes and amastigotes, and their products are involved in the adhesion to and internalization of the parasite by the host macrophages. Furthermore, GP63 is in part responsible for *Leishmania* spp. migrating through the extracellular matrix, avoiding lysis by inactivating components of the complement system, and hydrolyzing intracellular macrophage targets. Its mechanism is used by *Leishmania* to facilitate its survival and propagation within its mammalian host cells. Better knowledge concerning the mechanisms whereby this pathogen can escape the innate immune response may help to develop new anti-*Leishmania* therapy (Contreras et al., 2010).

Leishmanolysin, the *Leishmania* surface metalloproteinase of 63 kDa (GP63) has been described as a parasite virulence factor and is involved in the direct interaction of promastigotes and host macrophage receptors and interaction with the complement. The function of GP63 in a vector is still unclear. The enzyme could participate in the acquisition of nutrients and it could protect promastigotes from degradation by the midgut digestive enzymes. Sand flies midgut proteases appear to reach peak activities about one to three days after. gp63 plays different roles in the host-parasite interactions and has been postulated as a virulence factor. The phenotypic differences could be significantly

improved by the expression of a cloned leishmanolysin gene. These results demonstrate that leishmanolysin is a vital virulence factor in *Leishmania* pathogenesis (Joshi et al., 2002).

The (gp63) has been reported in *Leishmania* spp., which naturally lives in the vector sandflies as extracellular promastigotes, and in the phagolysosome compartment of macrophages as intracellular amastigotes. The role of gp63 for *Leishmania* in the vector is less clear. It has been suggested that gp63 may degrade hemoglobin and other proteins in the blood meals, thereby providing nutrients needed for the growth of promastigotes. In addition, it interacts with the complement system, and may contribute to the ability of the amastigote form of *Leishmania* spp. to survive inside the macrophage (Chaudhuri et al., 1989).

It is well known that *Leishmania* GP63 is a very highly active protease that can rapidly act on a wide range of host cell substrates that are involved in cell signaling pathways and their functional regulation. The effect of GP63 on antimicrobial and anti-inflammatory functions of macrophages is also quite clear on a very large scale, enhancing its pivotal role as an important virulence factor that contributes, at least, to the survival of *Leishmania* during the initial moment of infection, and the presence of GP63, in host macrophages appears to be a strategy used by the parasite to interact and reproduce and survive within its host (Gomez et al., 2009).

Parasites of *Leishmania* genus have developed stylish strategies permitting them to avoid the innate immune response upon their initial interaction with macrophages. Cooperatively, the *Leishmania* metalloprotease GP63 is still just revealing its importance as a critical virulence factor, and future research will be warranted to be pursued to fully appreciate its impact on host cell functions, as a better knowledge of its mode of action could lead to the development of new therapeutic and even new prophylactic to reduce its infectivity and capacity to invade mammalian macrophages (Olivier et al., 2012).

Despite their medical importance, there is little available structural information for the surface antigens of infectious protozoa. Diseases caused by the protozoan parasite *Leishmania* are common in many developing countries. Human infection occurs during the bite of infected sandflies when *Leishmania* promastigote cells from the insect gut enter the bloodstream. Promastigotes in the blood parasitize macrophages, often causing serious disease. Leishmanolysin is the predominant protein surface antigen of promastigotes and is assumed to have a key role during infection. Leishmanolysin is a membrane-bound zinc proteinase. Promastigotes of all *Leishmania* species express an abundant surface glycoprotein leishmanolysin, which is thought to be a ligand involved in the interaction of the parasite with the defensive systems of the host, including components of the complement system and the macrophage surface.



Leishmanolysin is therefore an attractive vaccine candidate. In *L. major*, there are seven gp63 genes and they exhibit stage-specific differences in their expression: five homologous tenderly repeated gp63 genes 1–5 are expressed in promastigotes only, a separated gene 6 is expressed in both promastigotes and amastigotes, while a gene 7 is expressed in stationary phase promastigotes and amastigotes. gp63 is

(Schlagenhauf et al., 1998). abundantly expressed on the surface of the promastigote form, upregulated in infectious metacyclic promastigotes, and has a low but detectable expression level in the intracellular amastigote stage (Al-Mayali and Alyasiri, 2020) see the amino acid sequence gp63 protein of *L. infantum* (Fig. 3).

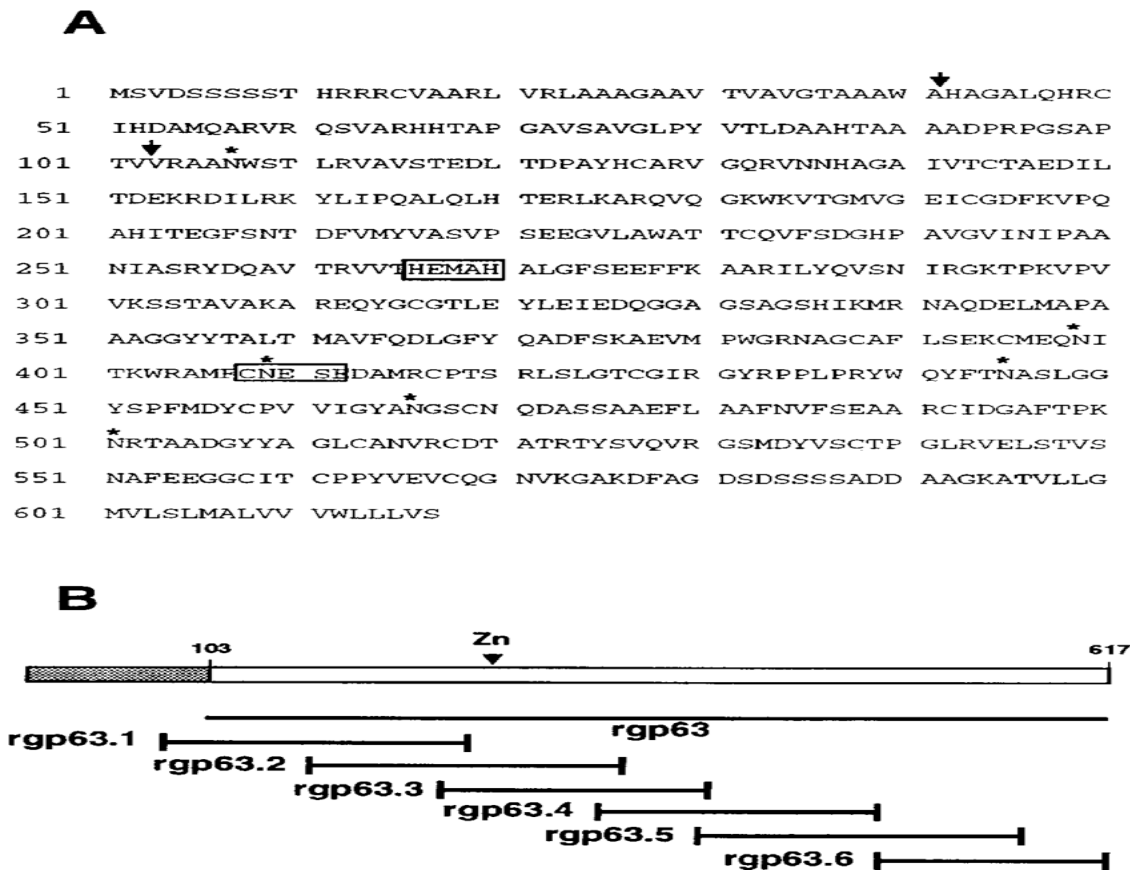


Fig. 3 Predicted amino acid sequence of the complete gp63 protein of *Leishmania infantum* deduced from the corresponding nucleotide sequence (Accession number: EMBL-Y08156). Position 1 corresponds to the initiation methionine. The arrows between Ala 41 and His 42 and between Val 102 and Val 103 designate the cleavage site of the signal peptide, the pro-peptide respectively, to give rise to the mature protein (Button & McMaster, 1988). The Zn<sup>2+</sup> binding domain, His-X-Met-X-His, and the potential catalytic site are boxed. The potential Nglycosylation sites are indicated with an asterisk. (B) Scheme showing the situation of the overlapping fragments 1-6 on the complete *L. infantum* gp63 (Morales et al., 1997)

**Lipophosphoglycan (LPG)**

The fact that *Leishmania* parasites have adapted to not only survive but to proliferate probably is due to the protection conferred by specialized molecules on the parasite's cell surface. One such macromolecule is a novel glycoconjugate called lipophosphoglycan. This heterogeneous, lipid-containing polysaccharide is the major surface molecule of the parasite and has been implicated in a surprisingly great number of functions that may contribute to the parasite's pathogenesis. The structure of LPG from diverse *Leishmania* species has been determined and the organization of its four

domains is best illustrated by the prototypic *L. donovani* LPG in Fig. 4. The four domains of the *L. donovani* LPG are (i) a 1-O-alkyl-2-lyso-phosphatidyl (myo) inositol anchor (ii) a glycan core, (iii) repeating disaccharide phosphate units, and (iv) a small oligosaccharide cap. LPG from all species of *Leishmania* has an identical lipid anchor and glycan core (Turco and Descoteaux, 1992).

Protozoan parasites of the genus *Leishmania* cause several important diseases in humans and undergo a complex life cycle, alternating between a sand fly vector and vertebrate hosts. The parasites have a remarkable capacity to avoid

destruction in which surface molecules are determinants for *Leishmania*, the glycoconjugates are known to play a central role in host–parasite interactions. The major cell surface glycoconjugate of *Leishmania* is the lipophosphoglycan (LPG), implicated in a wide range of functions, both in (vertebrate, invertebrate) hosts. In the invertebrate host, LPG variations are important for *Leishmania* specificity to the

survival. Amongst the many surface molecules of sand fly, where attachment of the parasite to a midgut receptor is a crucial event. In the vertebrate host, the main functions of this virulence factor during the earlier steps of infection include: protecting the parasite from complement-mediated lysis, attachment, and entry into macrophages (de Assis et al., 2012).

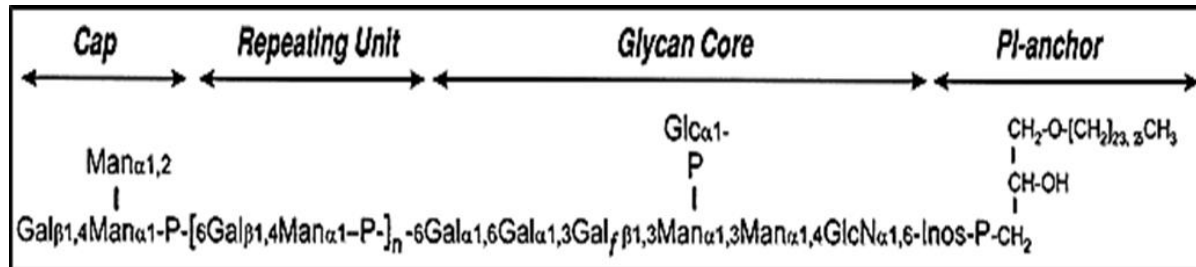


Fig. 4 Structure of LPG from *L. donovani*. Galf, galactofuranose; P, phosphate (Descoteaux and Turco, 1999)

Because [LPG] takes part in different stepladders of the development of *Leishmania* promastigotes, from the insect vector to the initiation of the infection in the mammalian host, that provided us with a valuable understanding of the parasite-host interaction mechanisms highlighting the role of LPG as a main virulence factor for some *Leishmania* species, for example, *L. major* (Olivier et al., 2012).

#### Cysteine Protease (CP)

Cysteine peptidases (CPs) have been characterized as virulence factors in *Leishmania*. Proteinases of *Leishmania* as virulence factors, Proteinases are also important virulence factor candidates as they are enzymes that hydrolyze peptide bonds and thus have the potential to degrade proteins and peptides that participate in a broad range of biological functions, including the infection process. Proteinases occur ubiquitously in biological systems and have functions that range from the digestion of proteins for nutritive purposes to the exquisite control of protein function by hydrolyzing a highly specific peptide bond in a protein substrate (Barrett, 1994).

Cysteine peptidases, also called cysteine protease, are a group of enzymes produced in both phases of *Leishmania* and stored in the megasome, a large lysosome, of amastigotes or the multi-vesicular tubule-lysosome in promastigotes. Although the exact roles of CPs in *Leishmania* pathogenesis are uncertain, it has been demonstrated that *Leishmania* cannot grow within macrophages in the presence of CP inhibitors (Mottram et al., 2004). The global contribution to the study of *Leishmania* genomics will help to understand the mechanisms underlying the aetiology of this parasite which will lead to the generation of vaccine targets. Cysteine proteinases of *Leishmania* are one of the target molecules that have been studied extensively in current years, Cysteine proteinases are enzymes that belong to the papain superfamily. Three classes of CPs have been identified in

*Leishmania*. Type I CP [CPB] is encoded by multicopy genes arranged in tandem arrays and is categorized by the presence of a long (C-terminal) extension [CTE] rich in proline, serine, and/or threonine residues. Type II (CPA) and Type III (CPC) are encoded by a copy gene(one) only. Both native and recombinant forms of the cysteine proteinases are recognized by the immune system of the individuals recovered from cutaneous leishmaniasis. Cysteine proteases (CPs) are present in most all organisms and are related to numerous physiological and pathological conditions. These observations provide evidence of the importance of these molecules in the survival of both promastigote and amastigote forms of these parasites (Rafati et al., 2003).

In 1982, Coombs was the first to an indication that amastigotes of *L. mexicana* contain unusually high cysteine proteinase activity and multiple soluble enzymes with an apparent size range of 16-36 kDa, The amastigote form of the human pathogen *Leishmania mexicana* has high proteinase activity, some 20 times bigger than that in the promastigote form and macrophages and appreciably higher than the activity in other flagellate protozoa form. The major amastigote enzymes are soluble, while those of the promastigote is particulate, and have inhibitor sensitivities characteristic of cysteine proteinases. The very high soluble proteinase activity of *L. mexicana* amastigotes may be a principal factor in the survival and growth of this mammalian phase in its potentially degradative intracellular habitat (Coombs, 1982).

#### Proteophosphoglycan (PPG)

Most leishmaniasis interaction with its vectors at the molecular level remains unidentified. A common feature of infected leishmaniasis sand flies is the presence of a mass of parasites inside a gel-like material. The source of the gel was unknown until relatively recently, when it was proved to arise from the parasite, now termed the promastigote



## Conflict of Interests

The authors declared that no competing interests exist.

## Ethical Issues

In this research, ethical considerations have been fully observed.

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