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Authored by:

Trini Suryowati, Forman Erwin Siagianv and Lusia Sri Sunarti

Published in:
2022 - Volume 32 [Issue 2]
Date of Publication: 28-Jun-22
Certificate validation link: https://journalmrji.com/index.php/MRJI/article/view/30373

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Review Article

Biochemical Properties Of Parasite Virulence Factor: Lesson Learned From Leishmania

ABSTRACT

Leishmania, a parasitic protozoan, is a single-celled organism of the genus trypanosomes that are responsible for the disease leishmaniasis. Transmission ~~occured~~ occurred by sandflies of the genus *Phlebotomus* in the Old World, and of the genus *Lutzomyia* in the New World. Globally, at least 93 sandfly species are proven or probable vectors. Their primary hosts are vertebrates.~~;~~ Leishmania commonly infects hyraxes, canids, rodents, and humans. Leishmaniasis encompasses diverse clinical syndromes, including cutaneous, mucosal, and potentially life-threatening visceral forms. Three widely known virulence factors ~~belongs~~ belong to the genus *Leishmania* ~~include~~ including the active compound named proteophosphoglycan (PPG), GP63 metalloprotease, and lipophosphoglycan (LPG). ~~these substance~~This substance established on the surface of the parasite. The aim of this review article is to make an insight ~~of~~ into the biochemical characteristics of *Leishmania* spp. virulence factors, the armamentarium that ~~predispose~~ predisposes their pathogenesis, its invasion, and virulence to the mammalian host.

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Keywords: protozoan, Trypanosomes, proteophosphoglycan, GP63 metalloprotease and lipophosphoglycan, leishmaniasis

1. INTRODUCTION

Parasites are organisms that live on or within their hosts. As intelligent organisms, parasitic agents ~~have the ability to~~can evade the host's immune system [1,2]. Their goal is to ensure its existence is permanently sustainable in the host's body. Although at the same time, parasitic organisms must obtain optimal nutrition from their host in order to stay alive [3]. Its continual sensing ~~accomodation~~ accommodation and adapt to environmental ~~shift~~ shifts is condemnatory for all organisms to carry on homeostasis and eventually ~~its~~ it's for survival [4].

Every ~~parasites~~ parasite actually experience sophisticated life cycles; this process ~~consist~~ consists of a broad array of cellular distinction stages in probably different host compartments [5]. The potency of transmission might also ~~occurs~~ occur across multiple hosts [6]. As any parasites primarily depend on ~~its~~ their host assets, it is crystal clear they have evolved the most efficient mechanisms to sense alterations and modify ~~itself~~ themselves to any resources which ~~is~~ are available; in a wide range of conditions in their environments. Virulence strategies are also modified and adjusted by parasites to invade its host and ~~it~~ they must be suitable for different ~~kind~~ kinds and ~~type~~ types of tissue. ~~Parasite~~ The parasite also must be able to enhance its clonal replication and escalate, as well as

other ~~action~~ actions for immunomodulation or ~~immuno~~immune-evasion of their host immune responses.

Here we provide an insight ~~of~~ into the biochemical properties of parasite virulence factor with a focus on *Leishmania* spp.; properties that facilitate their disease formation including their virulence and invasion ~~to~~ of the mammalian host.

2. *LEISHMANIA* SPP., LEISHMANIASIS AND ITS~~-~~ GLOBAL EPIDEMIOLOGY

Leishmania (/liːʃˈmeɪniə/) is a genus of parasitic ~~organisme~~ organism ~~belongs~~ belonging to the *Trypanosomes.* This organism ~~causing~~ causes leishmaniasis, a parasitic disease that is commonly found in parts of the tropics, subtropics, and southern Europe. Based on the occasion or time of ~~occurence~~occurrence, the vector ~~divide~~ divided into two: the sandflies from the genus *Phlebotomus* in the Old World, and on the other hand, of the genus *Lutzomyia* in the New World. So far, not less than 93 species of sandfly are Entomologically ~~evince~~evinced or have the status as potential or probable vectors, globally. This protozoan parasite ~~actually has~~has a vertebrate organism as its primary host. *Leishmania* is repeatedly found to infect rodents, canids, hyraxes, and ~~even~~ even humans [7,8]. Leishmaniasis encompasses diverse clinical syndromes, including cutaneous, mucosal, and potentially life-threatening visceral forms [9,10].

Leishmaniasis is endemic in ~~the~~ a vast area across the globe from the tropics, subtropics, and southern Europe [9-11]. It is estimated more than one billion individuals are at threat of leishmaniasis with an annual incidence of more than two million cases throughout the tropical and subtropical region (in number might reach to 100 countries) [11]. Recent literature revealed a significant increase elevation ~~regarding~~ in imported leishmaniasis cases in developed, non-endemic countries, *e.g.*, Italy, and this took place in conjunction with improvement in mass and rapid transportation ~~intercontinentally~~intercontinental, massive international tourism, asylum seekers/immigrants from endemic countries, and even multinational based military operations in endemic areas [13,14]

Area ~~where Leishmaniasis acquired~~, where Leishmaniasis acquired, is already suspected; South America is the main source area of cutaneous leishmaniasis, and escapade tourists on long-term ~~vacation~~ vacations in highly-endemic forested areas are at certain peril1[5,16]. On contrary, international tourists are in danger ~~while~~ when they travel to certain the Mediterranean or middle east destinations where there is an emerging risk of unfortunate acquisition of visceral leishmaniasis [17,18].

Leishmaniasis should be appraised in vulnerable individuals suffer from well-matched clinical syndrome along with a recent history of ~~travelling~~ traveling to and staying in an endemic area, even if this occurred several months or years ago; this become an important key factor in making a correct diagnosis [11,14,16] Appropriate counseling should be provided to adventure travelers, military personnel, researchers, and other groups of travelers likely to be exposed to sandflies in endemic areas [20].

Overall, leishmaniasis in humans is created by approximately 20 genus that belongs to the *Leishmania* spp. classified in the sub-genera *Leishmania* and *Viannia* [20-22]. Epidemiologically, it is possible that in certain ~~condition~~ conditions there might be more than one species of *Leishmania* spp. found in the same geographic area [20]. The effort of making correct identification of the species often has clinical relevance, such as implications regarding whether and which initial medication is urgently indicated and whether and how to closely asses ~~for~~ the consequence of potential sequelae regarding the infection (*e.g.*, the condition of mucosal leishmaniasis, which is ordinarily created by the New World species

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belongs to the group of the *Viannia* subgenus, particularly, but must kept in mind that it is not barely, by the genus *Leishmania* [*Viannia*] *braziliensis* in certain restricted terresterial areas) [21,22].

Approximately, 350 million ~~individual~~ individuals globally are at hazard of infecting leishmaniasis and an estimated 1.6 million new cases actually occur, annually [7,22]. The disease primarily infects impoverished individuals ~~lining~~ living in a low socio-economy level of countries in Africa, Latin America and Asia, and this condition is often linked with underlying ~~condition~~ conditions such as malnutrition, refugees that made fast migration across borders, countries, and even continents, unfortunate poverty-stricken housing conditions, limited assets due to the inability of the authorities and frail personal immune system [23].

The ability of the immune system to fight infectious diseases must also be related to the virulence factors of the pathogenic agent. The following section will discuss some of the virulence factors of the *Leishmania*; especially the biochemical aspect.

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3. VIRULENCE FACTORS

Virulence is described as an internal ~~properties~~ property of an organism that enabled them to infect their host, a substance pinned internally and can cause ~~a~~ disease in a vulnerable host. Virulence factors are the molecules that assist the organism colonize its host at the cellular level. These factors are either secretory, ~~membrane associated~~membrane-associated or cytosolic in nature. In terms of bacteria, the cytosolic factors facilitate the bacterium to undergo quick adaptive-metabolic, ~~physiological~~physiological, and morphological shifts [24].

Three widely known virulence factors ~~belongs~~ belong to the genus *Leishmania* ~~include~~ including the active compound named proteophosphoglycan (PPG), GP63 metalloprotease and lipophosphoglycan (LPG). These ~~substance~~ substances established on the surface of the parasite [25-27]

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Leishmania spp. Actually induce autophagy in a variety of cell types, eventhough that published results regarding the effects of autophagic modulation on Leishmania survival inside their host's cella are contradictory. Upon infecting the innate immune cells, namely the macrophage, *Leishmania* parasite soon launch into an organelle named parasitophorous vacuole. It soon begins to control and 'hijack' the cell, with the inner vacuole ~~actually acting~~acting as a safeguard against the host cell's immunity [28] *Leishmania* then take over the macrophage's membrane fusion machinery, ~~didacting~~ didactic them to work according to its will, to export their important virulence factors out of the vacuole [29]. The protozoan parasite *Leishmania*, is particularly adept at shifting the macrophage to become a suitable and hospitable host cell for their existence inside their host, so that the host's cellular immune system failed to recognize them [30]

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As the parasite transfers its virulence factors to the other side of the vacuole's membrane, it was necessary to learn the compartment used to contain these factors [31]. The virulence factors actually were found in a cell organelle called the endoplasmic reticulum (ER) and this step was pivotal in the ~~lay out~~layout of virulence factors within the inhabited cell.

3.1. BIOCHEMICAL PROPERTIES AND CHALLENGES ~~ON~~ TO THEIR GENOMES DATA

The biochemistry and cell biology of *Leishmania* spp. ~~is~~ are similar to that of other kinetoplastids. They share the same main morphological features, including a single flagellum ~~which~~ that has an invagination, the flagellar pocket, at its base, a kinetoplast, which is found in the single mitochondrion, and a ~~subpelicular~~subpellicular array of microtubules, which make up the main part of the cytoskeleton.

The result of genomes sequencing regarding three major species of *Leishmania* spp (*L. braziliensis, L. infantum, L. major*) has ~~succesfully~~ successfully apportioned the initial diagrams of the metabolism pathway ~~belongs~~ belonging to these protozoans [32]. Another systems approach was used to initiate another metabolism network for the *L. major Friedlin* strain and in continuation with that is to make forecasts in conjunction with possible essential genes and pathway usefulness. However, > 65% of the protein-encoding sequences in the parasite *Leishmania* genome cannot yet be allocated any single ~~functi on~~function based on homology searches, and therefore it is likely that *in silico* models must be ~~continously~~ continuously upgraded and improved as recent metabolic pathways are recognized, just like the approach conducted by Bora and Jha that developed an *in silico* metabolic pathway analysis identifying target against Leishmaniasis – a kind of kinetic modeling approach which can be a breakthrough in problem alleviation approaches [33,34]

Leishmania genomic database in the majority is available in the GeneDB genome resource, the effort first confirmed by scientists from the Sanger Institute, and then soon made available via the Eukaryotic Pathogens Database Resource (EuPathDB) [35,36]. GeneDB was in the beginning aimed to keep all genomic data regarding *T. brucei, L. major*, and *S. pombe*, and was later ~~broaden~~ broadened to comprise carefully collected curated data regarding a vast number of different organisms, including fungi, bacteria, and protozoa [37]. GeneDB authorizes the act of gene searching-finding, protein feature predictions, and any other form of searches against tailored and or protein domain/~~families~~family's databases [37,38]. It provides several functional instruments for inquiring about genomic features needed, including (1) BLAST searches, (2) plain text searches, (3) regular expressions enabled motif searches, and (4) AmiGO browsing of genes [39]. Unfortunately, although GeneDB is a crucial ~~assets~~ asset for the Leishmania investigation group, this genome resource does not incorporate all recent globally available genomic data into biochemical networks, or in other words, it is not automatically connected.

~~Other~~ Another famous database that can be mentioned is the Kyoto Encyclopedia of Genes and Genomes (KEGG) ~~that~~ which combines three ~~kind~~ kinds of data: (1) chemical, (2) genomic, and also (3) functionality information for a wide array of species [40] ~~Eventhough~~ Even though this top-down method easily help the incorporation of all accessible data/information and only need visual exploration of pathways regarding dissimilar organisms, but unfortunately the lack of organism-species specialization frequently means that, for more doubtful organisms, that the specific information need is not easily approachable, and in some conditions, not even incorporated.

An interesting dissimilar ~~accesion~~ accession provided by the BioCyc project, which method is constructed regarding the ontology evolved in order to express certain biological tasks based on the combination of cellular and molecular grade [41] On contrary to the incorporated ~~accesion~~ accession provided by the KEGG database, the BioCyc databases are highly dispersed. The BioCyc comprises of MetaCyc (an extensive reference database regarding metabolism pathways) and a set of organism-specific databases which delineate starting from genes to gene products to metabolites and continued to their relationships and the incorporation into metabolism pathways. MetaCyc ~~accomodates~~ accommodates preliminary elucidated metabolism pathways from a wide diversity of species. Actually, many

organism-specific BioCyc databases are still under ~~continously~~ continuously agile buildout and ~~continous~~ continuous curation [41].

With the advancement of biomolecular science, there is almost no scientific limit in studying and studying something. getting deeper and more detailed, each comes with advantages and disadvantages. Time has always been the catalyst for many of these advances; scientists from far apart places can continue to contribute so that scientific progress can continue to be accelerated.

Next, we will discuss the biochemical aspects of several parasite-related compounds that ~~are considered to be~~are virulence factors. In the case of *Leishmania* spp., the list of its virulence factors ~~are~~ is as follow~~:~~ (1) lipophosphoglycan (LPG), (2) glicoinositolphospholipids (GIPLs), (3) proteophosphoglycan (PPG) and (4) the 11 kDa kinetoplastid membrane protein (KMP-11). ~~Eventhough~~ Even though the precise impact of these *Leishmania* biologic properties on the clinical manifestations observed in mammalian hosts is not yet revealed clearly, and there is confirmation that these components are able to facilitate and even modify the Leishmania-host immune cells relationship.

3.2. LIPOPHOSPHOGLYCAN (LPG)

Leishmania parasite owns ~~a~~ an LPG, a class of molecules that is made up of two parts; a lipid part and a (also called glycan) part, that surround ~~over~~ the outer part of the cell wall [25,42]. Immunologically, *Leishmania*'s LPG ~~have~~ has the ability to TLR-2, a specific ~~signalling~~ signaling receptor elaborated in precipitating an initial activation of the immune response, *e.g*, the innate immune cells, in mammals [43].

The exact formation and composition of LPG content are ~~actually very~~very dynamic and ~~oscillates~~ oscillate over time, depending on two things namely (1) the species involved and (2) its lifecycle phase [42,44]. Regarding its content, the amount and composition of ~~the polysaccharide~~the polysaccharide glycan in the LPG is exceptionally fluctuating and contrasting. The amount and variants of lLPG are ~~actually exploitable~~exploitable in terms of making them as a biochemical marker. Distinct lifecycle stages of the parasite *Leishmania* might produce different LPG. Furthermore, Lectins, a set of proteins ~~which~~ that attach to several different categories of glycans, are repeatedly used to perceive and sense these LPG variants, *e.g*., peanut agglutinin specifically ~~attachs~~ attaches to a particular LPG located on the facet of the infective form of *L. major* [46].

Lipophosphoglycan is ~~actually empowered~~empowered strongly by the parasite primarily to maintain its survival inside ~~their~~ its host [46]. The exact techniques ~~that~~ used by the parasite apply is not clearly revealed~~;~~ , but this property ~~being~~ is the midpoint around modifying the immune response of their primary host. Considering this is very critical to the disease formation, due to the fact that (1) the *Leishmania* parasites live inside the host's cellular innate immune cell named macrophages and (2) it really ~~need~~ needs to avert the inhabited macrophages from processing them further and ends with killing them.47 Lipophosphoglycan also has a duty in (1) facilitating resistance and preventing activation of the complement system armamentarium, (2) inhibiting ~~host's~~ host's oxidative burst response, and also (3) initiating an adequate inflammation and (4) preventing the natural killer T cells realizing that the host's macrophage is already infected with the Leishmania parasite [25,48]. There may be an association between the immune cell's response to Leishmania and the exact cell stage/subset being evaluated, with differentiated macrophages being more permissive to infection in vitro than the monocytes.

In order to keep away from destruction and killing by the immune cells and also to facilitate its thrive, the *Leishmania* actually ~~'disguise'~~ 'disguises' itself inside its host's immune cells [46,48]. This safe location actually facilitates them to circumvent the work of the humoral immune feedback because in this situation, the pathogen ~~is keep~~is kept safe inside an intact cell that belongs to ~~their~~ its ~~host's~~ hosts and actually not in blood vessels where open blood flow is likely to increase its contact with the immune cells. Furthermore, it may avert the immune cells from destroying the host's own tissue through the mechanism of non-danger surface signals which unfortunately for the host ~~dettered~~ deterred the process of apoptosis [49] The primary cell types that the parasite Leishmania actually ~~attack~~ attacks and then infiltrates are a subset of phagocytotic cells, *e.g.*, neutrophils and macrophages, ~~and~~ and this is what determines the fate of the chronicity of this infection [50].

Regularly, a phagocytotic cell, *e.g.*~~, macrophage~~, macrophage, will internalize and further kill a pathogen covered within an enclosed endosome and in order to do so, they then pervade this endosome with certain enzymes which will digest the pathogen [25,46-48]. However, in the case of *Leishmania*, these enzymes of ~~macrophage~~ macrophages have no effect ~~to~~ on the parasite. This ~~allowing~~ allows internalized *Leishmania* even to undergo multiplication, fastly and enormously [51]. This almost ~~unstopable~~unstoppable growth of parasites eventually submerges the host's macrophage and ~~other type~~another type of the host's immune cell available, and even ~~making~~ makes the infected host's cell ~~to~~ die [51,52].

The protozoan parasites of *L. major* may change the regular pattern of the first immune defense from eating-inflammation-killing and turn it upside down to eating-with no inflammation production- further no killing~~; and~~, and all of this took place inside of their host phagocyte. Unfortunately, this smart parasite ~~corrupt~~ corrupts its ~~defence~~ defense properties for ~~their~~ its own welfare [27,28,52]. They use the mechanism of immune evasion by using phagocytosing ~~cell~~ cells named the polymorphonuclear neutrophil granulocytes (PMNs) carefully as their hidden vehicle, where they proliferate silently and undetected from the immune system and then enter the long-lived macrophages, unnoticed by the immune armamentarium to create a "*dormant*" infection [47,50].

According to van Zandbergen et al [52] that cited Sunderkotter et al which experimentally infecting mice with 1–2 × 10^6 ~~*Leishmania*, The~~*Leishmania*, The first phagocytic cells that infiltrate the site of experimental infection are the bunch of neutrophilic granulocytes (polymorphonuclear neutrophil granulocytes (PMN), and immediately act in accordance with the coming of a stream of macrophages (MF) in approximately in the following 48 hours. The PMN cells have the 'built-in' ability to internalize *Leishmania* promastigotes [28,51]. Unfortunately, within the PMN, ~~these parasite~~this parasite can manipulate its actual primary function, make them 'toothless' and hijack the PMN antiparasite properties for their own survival [5,53]. ~~Eventhough~~Even though, during this intracellular 'staycation' the parasites failed to multiplicate, ~~an interesting phenomena~~interesting phenomenon whose answers are still hidden and need to be explored further. Perhaps as far as we know, these cells might solely be available as the ~~parasite~~ parasite's temporary shelter within the first hours or even days after infection is established [54].

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The PMN cell ~~actually only~~only have a very short life span and soon will undergo spontaneous apoptosis within the duration of 6–12 hours. According to van Zandbergen *et al*, [52] that infection with Leishmania actually slows down what supposed to ~~be happen~~happen soon, named the apoptotic cell death program of PMN; this retardation can even delay it until up to 40+ ~~hour~~ hours and, therefore, promotes longevity of the parasite. However, after 42 hours, even most ~~of~~ infected PMN soon encounter apoptosis. ~~An interesting~~Interesting phenomen~~a~~on that need further exploration is the fact that the time point at which infected PMN ~~undergo~~ undergoes apoptotic process, ~~it~~ coincides with the

peak migration of the parasite into the infected tissue. Thus, *in situ*, the parasites would encounter apoptotic PMN harboring intracellular parasites rather than free extracellular Leishmania promastigotes [46,52]

A key factor in elongating infection is by way of the reticence of the adaptive immune cells [48-50]. This took place primarily during the intracellular ~~inhabition~~ inhibition phases, when amastigotes search for newly prone uninfected macrophages and then infecting them [44,51,52]. By ~~underwent~~ undergoing this process, the parasite actually are less prone to immune reactions. Almost all types of phagocytes are attacked [46]. For example, mincle has been described to be selected by the parasite *L. major*. Interaction between mincle and a protein liberated by the infecting parasite results in actual weakened immune response in dendritic cells.

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Lipophosphoglycan, biochemically, is a macrophage ligand ~~which~~ that function immediately elaborated in the early steps of the ~~occuring~~ occurring infection [55]. ~~An interesting assays~~Interesting assays conducted with a mutant type of *L. major* which lacking in the gene lpg1 (lpg1-) ~~actually revealed~~revealed that this type ~~of mutant~~of mutant organism are lessened for virulence when ongoing infection of murine macrophages, eventhough phenotypically there is no considerable changes [56]. These parasites ~~actually do~~do not harbor any LPG, but still accommodated normal levels of related GPI-anchored proteins ~~and also~~and glycoconjugates ~~enzyme~~ enzymes [57].

The lpg1- promastigotes are extremely prone to the activated complement system ~~and also~~and to the oxidative end-products of the host cells [25,57]. In addition to that condition, they failed to prevent phagolysosome fusion [42]. It has also been reported that L. major LPG2 null mutants (lpg2-) cannot live inside sandflies or in mammalian host cells. This type of ~~organisms~~ organism were even more revised than the lpg1- mutants strain and ~~be~~ was short of all type of phosphoglycans enzyme, including LPG and proteophosphoglycans. Leishmania LPG has been shown to diminish the nuclear translocation of NF-κB in monocytes, ~~bring~~ bringing about a subsequent decline in the assembly of IL-12. It can also affect the host's early immune reaction by modifying dendritic cells via the inhibition of antigen presentation and boosting an early response of IL-4 [56].

3.3. GLICOINOSITOLPHOSPHOLIPIDS (GIPLs)

Glicoinositolphospholipids (GIPLs) ~~facilitates~~ facilitate the survival of *L.major* inside macrophages by way of suppressing the enzyme nitric oxide ~~synthase~~ synthase and also protein kinase C. ~~Schneider~~ Schneider et al.,[58] revealed the relation between the rate of macrophage infection by *L. braziliensis* and the GILP-containing detergent-resistant membrane domains of this parasite [58].

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In both parasite developmental stages, the amount of the enzyme glycoinositol phospholipids (GIPLs) is actually expressed at a near-constant amount [59]. The construction of the enzyme GIPLs from amastigotes obtained from the tissue ~~have~~ has been determined by ~~hplc~~ HPLC analysis of the deaminated and reduced glyc an head classes, and also by profiling the chemical and enzymic sequencing. The deduced structures appear to form a complete biosynthetic series, ranging from Man alpha 1-4GlcN-phosphatidylinositol (PI) to Gal alpha 1-3Galf beta 1-3Man alpha 1-3Man alpha 1-4GlcN-PI (GIPL-2). A small proportion of GIPL-2 was further extended by addition of a Gal residue in either alpha 1-6 or beta 1-3 linkage. From gc-ms analysis and mild base treatment, all the GIPLs were shown to contain either alkylacylglycerol or lyso-alkylglycerol lipid moieties, where the alkyl chains were predominantly C18:0, with lower levels of C20:0, C22:0 and C24:0. The parasite *L.*

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major amastigotes also contained at least two PI-specific phospholipase C-resistant glycolipids which are absent from promastigotes [60].

These neutral glycolipids were defiant to both mild acid and or mild base hydrolysis, contained terminal beta-Gal residues, and were restrained during immense purification of amastigotes from cell membranes of the host. It is likely that these glycolipids actually are glycosphingolipids ~~earn~~ earned from the mammalian host. There have been studies comparing the GIPL profile of *L. major* amastigotes, *L. major* promastigotes and *L. donovani* amastigotes [58].

3.4. PROTEOPHOSPHOGLYCANS (PPG)

~~Other~~ Another biochemical substance that also ~~behave~~ behaves as the parasite's virulence factors is called Proteophosphoglycans.61 It is a highly glycosylated ~~polypeptides~~ polypeptide with O-glycosylations; a structure indistinguishable ~~to~~ from those found in the LPG and also in acid phosphatase [62]. Proteophosphoglycans are a growing family of highly glycosylated proteins ~~belongs~~ belonging to *Leishmania* with many atypical and ~~some~~ idiosyncratic architectural features [61-63]. The obscure protein-glycan linkage in proteophosphoglycans - phosphoglycosylation of Ser by lipophosphoglycan-like structures– actually ~~appear~~ appears as a prime configuration of protein glycosylation in this parasite organism [62].

The main role of membrane PPGs actually is only partially revealed, but some experts postulated that its ~~long chain~~long-chain configuration that ~~enclosess~~ encloses the surface of the parasite's plasma membrane might take part partially in its binding to the macrophage receptors [25]. The ~~emmision~~ emission of modified PPG by parasites when they colonized the macrophages seems to contribute to the maintenance of the parasitophorous vacuole [31]. Furthermore, the PPG ~~is also have~~also has ~~has~~ has the ability to trigger the complement via the ~~route~~ route of mannose-binding protein.

During the course of infection, Leishmania parasites are transmitted to ~~its~~ their vertebrate hosts by the aid of female sand flies from the genus of Phlebotomine as they obtain blood from its host by puncturing deep into the dermis's upper capillaries with their spiked mouthparts [7-9]. In the sand fly midgut, secreted specific proteophosphoglycans from Leishmania actually form a biological plug known as the promastigote secretory gel (PSG), which blocks the gut and facilitates the regurgitation of infective parasites [64]. In a study using an animal model, PSG injected to BALB/c mouse skin lead to the differential expression of 7900+ copy of transcripts, and ~~those transcript~~those transcripts transiently up-regulated during the initial six hours post-wound and become more augmented for potently exacerbated cutaneous infection, and in turn will ~~improved~~ improve the probability of developing a patent cutaneous lesion, parasite growth and the evolution of the lesion [65].

3.5. 11 KDA KINETOPLASTID MEMBRANE PROTEIN (KMP-11)

KMP-11 is a hydrophobic protein that has been described to be associated ~~to~~ with LPG which ~~show~~ shows strong immunoregulatory properties [66]. Kinetoplastid Membrane Protein -11 is present in both promastigotes and ~~also~~ also amastigotes. The protein KMP-11 was associated with the membrane composition, which to some amount available at the cellular facet, flagellar pocket, and also in the intracellular vesicles. The amount of its surface

expression is actually higher in amastigotes than in promastigotes and the ~~concnetration~~ concentration escalates during the stage of metacyclogenesis [67].

The rising expression of the protein KMP-11 in metacyclic promastigotes, and especially in the stage amastigotes, designates a role for this molecule in the close interaction of the ~~parasite~~ parasite with its mammalian host. The presence of this molecule in amastigotes is consistent with the previously demonstrated immunoprotective capacity of vaccine prototypes based on the KMP-11-coding gene and the presence of humoral and cellular immune responses to KMP-11 in Leishmania-infected humans and animals [67,68].

This protein is already recognized through its immunoregulatory properties and ~~ahve~~ has the ability to induce the expression of IL-10 in cells ~~from~~ of patients to suffer from cutaneous and mucocutaneous leishmaniasis; ~~unfrotunately~~unfortunately, the mechanism through which this effect occurs remains unrevealed [66-68].

3.6. PROTEINASES

Proteinases are also ~~a~~ crucial virulence properties that ~~belongs~~ belong to *Leishmania*. It can be grouped according to their catalytic domains, as serine-, threonine-, aspartyl-, metallo- and cysteine-proteinases . Among these, only the aspartyl-, metallo- and cysteine-proteinase classes have been extensively studied in *Leishmania*.[56].

Proteinases are also considered as a crucial virulence factor of *Leishmania*, because as enzymes and through direct contact, it has the ability to hydrolyze any peptide bonds. This enzyme ~~have~~ has the potency to destroy any proteins and peptides that might engage in a wide ~~scale~~ scale of biological purposes, including the making and establishing an infection [69]. The enzyme Proteinases actually occur pervasively in all living biological systems [70]. It is rich in functions, e.g., in ~~human~~humans, varying from the digestion of proteins in order to achieve nutritive motives to the magnificent control of general protein role, *e.g.,* by hydrolyzing ~~a~~ an extremely particular peptide bond in a certain protein surfactant [69,70].

Parasite proteinases ~~widely known~~are widely known being elaborated in the (1) Pathogenesis, (2) Invasion- migration of the parasite through host tissues, (3) Degradation of ~~immune related~~immune-related proteins, (4) Immune evasion, and (5) Activation of inflammation [71,72]. Among protozoan parasites, the enzyme proteinases play a crucial part in several ~~acitivites~~activities, including (1) Transition of the parasite's life cycle, (2) Invasion of hosts, (3) Migration through tissue barriers, (4) Degradation of hemoglobin and other blood proteins, (5) Immune evasion, and (6) Activation of inflammation in the mammalian host [71-73].

Analysis of the ~~genom~~ genome carried out with different species of Leishmania that have been sequenced revealed that the amount of proteinase genes is maintained constantly among the various species [73]. Nonetheless, its heterogeneity is very diverse, *e.g.*, the result of the genomic survey on multiple databanks unveil that *L. braziliensis* alone has at least forty-four cysteine proteinases, twenty-three serine proteinases, and ninety-seven metalloproteinase [74] Therefore, due to the wide range of action of *Leishmania* proteinases while the parasite is inside the mammalian host, it is equitable to seek for the relation between proteinase enzymatic activity and the clinical manifestation of leishmaniasis.

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Review Article

Biochemical Properties Of Parasite Virulence Factor: Lesson Learned From Leishmania

ABSTRACT

Leishmania, a parasitic protozoan, a single-celled organism of the genus trypanosomes that are responsible for the disease leishmaniasis. Transmission occured by sandflies of the genus Phlebotomus in the Old World, and of the genus Lutzomyia in the New World. Globally, at least 93 sandfly species are proven or probable vectors. Their primary hosts are vertebrates; Leishmania commonly infects hyraxes, canids, rodents, and humans. Leishmaniasis encompasses diverse clinical syndromes, including cutaneous, mucosal, and potentially life-threatening visceral forms. Three widely known virulence factors belongs to the genus Leishmania include the active compound named proteophosphoglycan (PPG), GP63 metalloprotease and lipophosphoglycan (LPG). these substance established on the surface of the parasite. The aim of this review article is to make an insight of the biochemical characteristics of Leishmania spp virulence factors, the armamentarium that predispose their pathogenesis, its invasion and virulence to the mammalian host.

Keywords: protozoan, Trypanosomes, proteophosphoglycan, GP63 metalloprotease and lipophosphoglycan, leishmaniasis

1. INTRODUCTION

Parasites are organisms that live on or within their hosts. As intelligent organisms, parasitic agents have the ability to evade the host's immune system [1,2]. Their goal is to ensure its existence is permanently sustainable in the host's body. Although at the same time, parasitic organisms must obtain optimal nutrition from their host in order to stay alive [3]. Its continual sensing accomodation and adapt to environmental shift is condemnatory for all organisms to carry on homeostasis and eventually its for survival [4].

Every parasites actually experience sophisticated life cycles; this process consist of a broad array of cellular distinction stages in probably different host compartments [5]. The potency of transmission might also occurs across multiple hosts [6]. As any parasites primarily depend on its host assets, it is crystal clear they have evolved the most efficient mechanisms to sense alterations and modify itself to any resources which is available; in a wide range of conditions in their environments. Virulence strategies also modified and adjusted by parasites to invade its host and it must be suitable for different kind and type of tissue. Parasite also must be able to enhance its clonal replication and escalate, as well as other action for immunomodulation or immunoevasion of their host immune responses.

Here we provide an insight of the biochemical properties of parasite virulence factor with focus on *Leishmania* spp.; properties that facilitate their disease formation including their virulence and invasion to the mammalian host.

2. LEISHMANIA SPP., LEISHMANIASIS AND ITS GLOBAL EPIDEMIOLOGY

Leishmania (/liːʃˈmeɪniə/) is a genus of parasitic organisme belongs to the *Trypanosomes.* This organism causing leishmaniasis, a parasitic disease that is commonly found in parts of the tropics, subtropics, and southern Europe. Based on the occasion or time of occurence, the vector divide into two: the sandflies from the genus *Phlebotomus* in the Old World, and on the other hand, of the genus *Lutzomyia* in the New World. So far, not less than 93 species of sandfly are Entomologically evince or have the status as potential or probable vectors, globally. This protozoan parasite actually has a vertebrate organism as its primary host. *Leishmania* repeatedly found to infect rodents, canids, hyraxes, and even humans [7,8]. Leishmaniasis encompasses diverse clinical syndromes, including cutaneous, mucosal, and potentially life-threatening visceral forms [9,10].

Leishmaniasis is endemic in the vast area across the globe from the tropics, subtropics, and southern Europe [9-11]. It is estimated more than one billion individuals are at threat of leishmaniasis with an annual incidence of more than two million cases throughout tropical and subtropical region (in number might reach to 100 countries) [11]. Recent literature revealed significant increase elevation regarding imported leishmaniasis cases in developed, non-endemic countries, *e.g.*, Italy, and this took place in conjunction with improvement in mass and rapid transportation intercontinentally, massive international tourism, asylum seekers/immigrants from endemic countries and even multinational based military operations in endemic areas [13,14]

Area where Leishmaniasis acquired is already suspected; South America is the main source area of cutaneous leishmaniasis, and escapade tourists on long-term vacation in highly-endemic forested areas are at certain peril1[5,16]. On contrary, international tourists are in danger while they travel to certain Mediterranean or middle east destinations where there is emerging risk of unfortunate acquisition of visceral leishmaniasis [17,18].

Leishmaniasis should be appraised in vulnerable individuals suffer from well-matched clinical syndrome along with a recent history of travelling to and staying in an endemic area, even if this occurred several months or years ago; this become important key factor in making correct diagnosis [11,14,16] Appropriate counseling should be provided to adventure travelers, military personnel, researchers, and other groups of travelers likely to be exposed to sandflies in endemic areas [20].

Overall, leishmaniasis in humans is created by approximately 20 genus that belongs to the Leishmania spp. classified in the sub-genera *Leishmania* and *Viannia* [20-22]. Epidemiologically, it is possible that in certain condition there might be more than one species of *Leishmania* spp. found in the same geographic area [20]. The effort of making correct identification of the species often has clinical relevance, such as implications regarding whether and which initial medication is urgently indicated and whether and how to closely asses for the consequence of potential sequelae regarding the infection (*e.g.*, the condition of mucosal leishmaniasis, which is ordinarily created by the New World species belongs to the group of the *Viannia* subgenus, particularly, but must kept in mind that it is not barely, by the genus *Leishmania* [*Viannia*] *braziliensis* in certain restricted terresterial areas) [21,22].

Approximately, 350 million individual globally are at hazard of infecting leishmaniasis and an estimated 1.6 million new cases actually occur, annually [7,22]. The disease primarily infects impoverished individuals lining in low socio-economy level of countries in Africa, Latin America and Asia, and this condition is often linked with underlying condition such as malnutrition, refugees that made fast migration across borders, countries and even continents, unfortunate poverty-stricken housing conditions, limited assets due to the inability of the authorities and frail personal immune system [23].

The ability of the immune system to fight infectious diseases must also be related to the virulence factors of the pathogenic agent. The following section will discuss some of the virulence factors of the Leishmania; especially the biochemical aspect.

3. VIRULENCE FACTORS

Virulence is described as an internal properties of an organism that enabled them to infect their host, a substance pinned internally and can cause a disease in vulnerable host. Virulence factors are the molecules that assist the organism colonize its host at the cellular level. These factors are either secretory, membrane associated or cytosolic in nature. In terms of bacteria, the cytosolic factors facilitate the bacterium to undergo quick adaptive-metabolic, physiological and morphological shifts [24].

Three widely known virulence factors belongs to the genus Leishmania include the active compound named proteophosphoglycan (PPG), GP63 metalloprotease and lipophosphoglycan (LPG). These substance established on the surface of the parasite [25-27]

Leishmania spp. Actually induce autophagy in a variety of cell types, eventhough that published results regarding the effects of autophagic modulation on Leishmania survival inside their host's cella are contradictory. Upon infecting the innate immune cells, namely the macrophage, Leishmania parasite soon launch into an organelle named parasitophorous vacuole. It soon begins to control and 'hijack' the cell, with the inner vacuole actually acting as a safeguard against the host cell's immunity [28] *Leishmania* then take over the macrophage's membrane fusion machinery, didacting them to work according to its will, to export their important virulence factors out of the vacuole [29]. The protozoan parasite Leishmania, is particularly adept at shifting the macrophage to become a suitable and hospitable host cell for their existence inside their host, so that the host's cellular immune system failed to recognize them [30]

As the parasite transfers its virulence factors to the other side of the vacuole's membrane, it was necessary to learn the compartment used to contain these factors [31]. The virulence factors actually were found in a cell organelle called the endoplasmic reticulum (ER) and this step was pivotal in the lay out of virulence factors within the inhabited cell.

3.1. BIOCHEMICAL PROPERTIES AND CHALLENGES ON THEIR GENOMES DATA

The biochemistry and cell biology of *Leishmania* spp. is similar to that of other kinetoplastids. They share the same main morphological features, including a single flagellum which has an invagination, the flagellar pocket, at its base, a kinetoplast, which is found in the single mitochondrion, and a subpelicular array of microtubules, which make up the main part of the cytoskeleton.

The result of genomes sequencing regarding three major species of *Leishmania* spp (*L. braziliensis, L. infantum, L. major*) has succesfully apportioned the initial diagrams of the metabolism pathway belongs to these protozoans [32]. Another systems approach was used to initiate another metabolism network for the *L. major Friedlin* strain and in continuation with that is to make forecasts in conjunction with possible essential genes and pathway usefulness. However, > 65% of the protein-encoding sequences in the parasite *Leishmania* genome cannot yet be allocated any single functi on based on homology searches, and therefore it is likely that *in silico* models must be continously upgraded and improved as recent metabolic pathways are recognized, just like the approach conducted by Bora and Jha that developed an *in silico* metabolic pathway analysis identifying target against Leishmaniasis – a kind of kinetic modeling approach which can be a breakthrough in problem alleviation approaches [33,34]

Leishmania genomic database in majority is available in the GeneDB genome resource, the effort first confirmed by scientists from the Sanger Institute, and then soon made available via the Eukaryotic Pathogens Database Resource (EuPathDB) [35,36]. GeneDB was in the beginning aimed to keep all genomic data regarding *T. brucei, L. major*, and *S. pombe*, and was later broaden to comprise carefully collected curated data regarding a vast number of different organisms, including fungi, bacteria, and protozoa [37]. GeneDB authorizes the act of gene searching-finding, protein feature predictions, and any other form of searches against tailored and or protein domain/families databases [37,38]. It provides several functional instruments for inquiring genomic features needed, including (1) BLAST searches, (2) plain text searches, (3) regular expressions enabled motif searches, and (4) AmiGO browsing of genes [39]. Unfortunately, although GeneDB is a crucial assets for the Leishmania investigation group, this genome resource does not incorporate all recent globally available genomic data into biochemical networks, or in other words it is not automatically connected.

Other famous database that can be mentioned is the Kyoto Encyclopedia of Genes and Genomes (KEGG) that combines three kind of data: (1) chemical, (2) genomic, and also (3) functionality information for a wide array of species [40] Eventhough this top-down method easily help the incorporation of all accessible data/information and only need visual exploration of pathways regarding dissimilar organisms, but unfortunately the lack of organism-species specialization frequently means that, for more doubtful organisms, that the specific information need is not easily approachable, and in some conditions, not even incorporated.

An interesting dissimilar accesion provided by the BioCyc project, which method is constructed regarding the ontology evolved in order to express certain biological tasks based on the combination of cellular and molecular grade [41] On contrary to the incorporated accesion provided by the KEGG database, the BioCyc databases are highly dispersed. The BioCyc comprises of MetaCyc (an extensive reference database regarding metabolism pathways) and a set of organism-specific databases which delineate starting from genes to gene products to metabolites and continued to their relationships and the incorporation into metabolism pathways. MetaCyc accomodates preliminary elucidated metabolism pathways from a wide diversity of species. Actually, many organism-specific BioCyc databases are still under continously agile buildout and continous curation [41].

With the advancement of biomolecular science, there is almost no scientific limit in studying and studying something. getting deeper and more detailed, each comes with advantages and disadvantages. Time has always been the catalyst for many of these advances; scientists from far apart places can continue to contribute so that scientific progress can continue to be accelerated.

Next, we will discuss the biochemical aspects of several parasite-related compounds that are considered to be virulence factors. In case of *Leishmania* spp., the list of its virulence factors are as follow: (1) lipophosphoglycan (LPG), (2) glicoinositolphospholipids (GIPLs), (3) proteophosphoglycan (PPG) and (4) the 11 kDa kinetoplastid membrane protein (KMP-11). Eventhough the precise impact of these *Leishmania* biologic properties on the clinical manifestations observed in mammalian hosts is not yet revealed clearly, and there is confirmation that these components able to facilitate and even modify the Leishmania-host immune cells relationship.

3.2. LIPOPHOSPHOGLYCAN (LPG)

Leishmania parasite owns a LPG, a class of molecules that made up of two parts; a lipid part and a (also called glycan) part, that surround over the outer part of the cell wall [25,42]. Immunologically, *Leishmania*'s LPG have the ability to TLR-2, a specific signalling receptor elaborated in precipitating an initial activation of the immune response, *e.g*, the innate immune cells, in mammals [43].

The exact formation and composition of LPG content actually very dynamic and oscillates over time, depending on two things namely (1) the species involved and (2) its lifecycle phase [42,44]. Regarding its content, the amount and composition of the polysaccharide glycan in the LPG is exceptionally fluctuating and contrasting. The amount and variants of lLPG are actually exploitable in terms making them as a biochemical marker. Distinct lifecycle stages of the parasite *Leishmania* might produce different LPG. Furthermore, Lectins, a set of proteins which attach to several different categories of glycans, are repeatedly used to perceive and sense these LPG variants, *e.g*., peanut agglutinin specifically attachs to a particular LPG located on the facet of the infective form of *L. major* [46].

Lipophosphoglycan is actually empowered strongly by the parasite primarily to maintain its survival inside their host [46]. The exact techniques that used by the parasite apply is not clearly revealed; but this property being the midpoint around modifying the immune response of their primary host. Considering this is very critical to the disease formation, due to the fact that (1) the *Leishmania* parasites live inside the host's cellular innate immune cell named macrophages and (2) it really need to avert the inhabited macrophages from processing them further and ends with killing them.47 Lipophosphoglycan also has a duty in (1) facilitating resistance and preventing activation of the complement system armamentarium, (2) inhibiting host's oxidative burst response, and also (3) initiating an adequate inflammation and (4) preventing the natural killer T cells realizing that the host's macrophage is already infected with the Leishmania parasite [25,48]. There may be an association between the immune cell's response to Leishmania and the exact cell stage/subset being evaluated, with differentiated macrophages being more permissive to infection in vitro than the monocytes.

In order to keep away from destruction and killing by the immune cells and also to facilitate its thrive, the *Leishmania* actually 'disguise' itself inside its host's immune cells [46,48]. This safe location actually facilitates them to circumvent the work of the humoral immune feedback because in this situation, the pathogen is keep safe inside an intact cell that belongs to their host's and actually not in blood vessels where open blood flow is likely to increase its contact with the immune cells. Furthermore, it may avert the immune cells from destroying the host's own tissue through the mechanism of non-danger surface signals which unfortunately for the host dettered the process of apoptosis [49] The primary cell types that the parasite Leishmania actually attack and then infiltrates are subset of phagocytotic

cells, *e.g*., neutrophils and macrophages, and this is what determines the fate of the chronicity of this infection [50].

Regularly, a phagocytotic cell, *e.g*., macrophage, will internalize and further kill a pathogen covered within an enclosed endosome and in order to do so, they then pervade this endosome with certain enzymes which will digest the pathogen [25,46-48]. However, in the case of *Leishmania*, these enzymes of macrophage have no effect to the parasite. This allowing internalized *Leishmania* even to undergo multiplication, fastly and enormously [51]. This almost unstopable growth of parasites eventually submerges the host's macrophage and other type of the host's immune cell available, and even making the infected host's cell to die [51,52].

The protozoan parasites of *L. major* may change the regular pattern of the first immune defense from eating-inflammation-killing and turn it upside down to eating-with no inflammation production- further no killing; and all of this took place inside of their host phagocyte. Unfortunately, this smart parasite corrupt its defence properties for their own welfare [27,28,52]. They use the mechanism of immune evasion by using phagocytosing cell named the polymorphonuclear neutrophil granulocytes (PMNs) carefully as their hidden vehicle, where they proliferate silently and undetected from the immune system and then enter the long-lived macrophages, unnoticed by the immune armamentarium to create a "*dormant*" infection [47,50].

According to van Zandbergen *et al* [52] that cited Sunderkotter *et al* which experimentally infecting mice with 1–2 × 10^6 *Leishmania*, The first phagocytic cells that infiltrate the site of experimental infection are the bunch of neutrophilic granulocytes (polymorphonuclear neutrophil granulocytes (PMN), and immediately act in accordance with the coming of a stream of macrophages (MF) in approximately in the following 48 hours. The PMN cells have the 'built-in' ability to internalize *Leishmania* promastigotes [28,51]. Unfortunately, within the PMN, these parasite can manipulate its actual primary function, make them 'toothless' and hijack the PMN antiparasite properties for their own survival [5,53]. Eventhough, during this intracellular 'staycation' the parasites failed to multiplicate, an interesting phenomena whose answers are still hidden and need to be explored further. Perhaps as far as we know, these cells might solely available as the parasite temporary shelter within the first hours or even days after infection established [54].

The PMN cell actually only have a very short life span and soon will undergo spontaneous apoptosis within the duration of 6–12 hours. According to van Zandbergen *et al*, [52] that infection with Leishmania actually slows down what supposed to be happen soon, named the apoptotic cell death program of PMN; this retardation can even delay it until up to 40+ hour and, therefore, promotes longevity of the parasite. However, after 42 hours, even most of infected PMN soon encounter apoptosis. An interesting phenomena that need further exploration is the fact that the time point at which infected PMN undergo apoptotic process, it coincides with the peak migration of the parasite into the infected tissue. Thus, *in situ*, the parasites would encounter apoptotic PMN harboring intracellular parasites rather than free extracellular Leishmania promastigotes [46,52]

A key factor in elongating infection is by way of the reticence of the adaptive immune cells [48-50]. This took place primarily during the intracellular inhabition phases, when amastigotes search for newly prone uninfected macrophages and then infecting them [44,51,52]. By underwent this process, the parasite actually are less prone to immune reactions. Almost all types of phagocytes are attacked [46]. For example, mincle has been described to be selected by the parasite *L. major*. Interaction between mincle and a protein

liberated by the infecting parasite results in actual weakened immune response in dendritic cells.

Lipophosphoglycan, biochemically, is a macrophage ligand which function immediately elaborated in the early steps of the occuring infection [55]. An interesting assays conducted with a mutant type of *L. major* which lacking in the gene lpg1 (lpg1-) actually revealed that this type of mutant organism are lessened for virulence when ongoing infection of murine macrophages, eventhough phenotypically there is no considerable changes [56]. These parasites actually do not harbor any LPG, but still accommodated normal levels of related GPI-anchored proteins and also glycoconjugates enzyme [57].

The lpg1- promastigotes are extremely prone to the activated complement system and also to the oxidative end-products of the host cells [25,57]. In addition to that condition, they failed to prevent phagolysosome fusion [42]. It has also been reported that L. major LPG2 null mutants (lpg2-) cannot live inside sandflies or in mammalian host cells. This type of organisms were even more revised than the lpg1- mutants strain and be short of all type of phosphoglycans enzyme, including LPG and proteophosphoglycans. Leishmania LPG has been shown to diminish the nuclear translocation of NF-κB in monocytes, bring about a subsequent decline in the assembly of IL-12. It can also affect the host's early immune reaction by modifying dendritic cells via the inhibition of antigen presentation and boosting an early response of IL-4 [56].

3.3. GLICOINOSITOLPHOSPHOLIPIDS (GIPLs)

Glicoinositolphospholipids (GIPLs) facilitates the survival of *L.major* inside macrophages by way of suppressing the enzyme nitric oxide synthase and also protein kinase C. Schneider *et al*.,[58] revealed the relation between the rate of macrophage infection by *L. braziliensis* and the GILP-containing detergent-resistant membrane domains of this parasite [58].

In both parasite developmental stages, the amount of the enzyme glycoinositol phospholipids (GIPLs) actually expressed at near-constant amount [59]. The construction of the enzyme GIPLs from amastigotes obtained from the tissue have been determined by hplc analysis of the deaminated and reduced glyc an head classes, and also by profiling the chemical and enzymic sequencing. The deduced structures appear to form a complete biosynthetic series, ranging from Man alpha 1-4GlcN-phosphatidylinositol (PI) to Gal alpha 1-3Galf beta 1-3Man alpha 1-3Man alpha 1-4GlcN-PI (GIPL-2). A small proportion of GIPL-2 was further extended by addition of a Gal residue in either alpha 1-6 or beta 1-3 linkage. From gc-ms analysis and mild base treatment, all the GIPLs were shown to contain either alkylacylglycerol or lyso-alkylglycerol lipid moieties, where the alkyl chains were predominantly C18:0, with lower levels of C20:0, C22:0 and C24:0. The parasite *L. major* amastigotes also contained at least two PI-specific phospholipase C-resistant glycolipids which are absent from promastigotes [60].

These neutral glycolipids were defiant to both mild acid and or mild base hydrolysis, contained terminal beta-Gal residues and were restrained during immense purification of amastigotes from cell membranes of the host. It is likely that these glycolipids actually are glycosphingolipids earn from the mammalian host. There have been studies comparing the GIPL profile of *L. major* amastigotes, *L. major* promastigotes and *L. donovani* amastigotes [58].

3.4. PROTEOPHOSPHOGLYCANS (PPG)

Other biochemical substance that also behave as the parasite's virulence factors is called Proteophosphoglycans.61 It is a highly glycosylated polypeptides with O-glycosylations; a structure indistinguishable to those found in the LPG and also in acid phosphatase [62]. Proteophosphoglycans are a growing family of highly glycosylated proteins belongs to *Leishmania* with many atypical and some idiosyncratic architectural features [61-63]. The obscure protein-glycan linkage in proteophosphoglycans - phosphoglycosylation of Ser by lipophosphoglycan-like structures– actually appear as a prime configuration of protein glycosylation in this parasite organism [62].

The main role of membrane PPGs actually is only partially revealed, but some experts postulated that its long chain configuration that enclosess the surface of parasite's plasma membrane might take part partially in its binding to the macrophage receptors [25]. The emmision of modified PPG by parasites when they colonized the macrophages seems to contribute to the maintenance of the parasitophorous vacuole [31]. Furthermore, the PPG is also have the ability to trigger the complement via the route of mannose-binding protein.

During the course of infection, Leishmania parasites are transmitted to its vertebrate hosts by the aid of female sand flies from the genus of Phlebotomine as they obtain blood from its host by puncturing deep into the dermis's upper capillaries with their spiked mouthparts [7-9]. In the sand fly midgut, secreted specific proteophosphoglycans from Leishmania actually form a biological plug known as the promastigote secretory gel (PSG), which blocks the gut and facilitates the regurgitation of infective parasites [64]. In a study using animal model, PSG injected to BALB/c mouse skin lead to the differential expression of 7900+ copy of transcripts and those transcript transiently up-regulated during the initial six hours post-wound and become more augmented for potently exacerbated cutaneous infection, and in turn will improved the probability of developing a patent cutaneous lesion, parasite growth and the evolution of the lesion [65].

3.5. 11 KDA KINETOPLASTID MEMBRANE PROTEIN (KMP-11)

KMP-11 is a hydrophobic protein that has been described to be associated to LPG which show strong immunoregulatory properties [66]. Kinetoplastid Membrane Protein -11 is present in both promastigotes and also amastigotes. The protein KMP-11 was associated with the membrane composition, which to some amount available at the cellular facet, flagellar pocket and also in the intracellular vesicles. The amount of its surface expression is actually higher in amastigotes than in promastigotes and the concnetration escalates during the stage of metacyclogenesis [67].

The rising expression of the protein KMP-11 in metacyclic promastigotes, and especially in the stage amastigotes, designates a role for this molecule in the close interaction of the parasite with its mammalian host. The presence of this molecule in amastigotes is consistent with the previously demonstrated immunoprotective capacity of vaccine prototypes based on the KMP-11-coding gene and the presence of humoral and cellular immune responses to KMP-11 in Leishmania-infected humans and animals [67,68].

This protein already recognized through its immunoregulatory properties and ahve the ability to induce the expression of IL-10 in cells from patients suffer from cutaneous and mucocutaneous leishmaniasis; unfrotunately, the mechanism through which this effect occurs remains unrevealed [66-68].

3.6. PROTEINASES

Proteinases also a crucial virulence properties that belongs to Leishmania. It can be grouped according to their catalytic domains, as serine-, threonine-, aspartyl-, metallo- and cysteine-proteinases . Among these, only the aspartyl-, metallo- and cysteine-proteinase classes have been extensively studied in *Leishmania*.[56].

Proteinases also considered as a crucial virulence factor of *Leishmania*, because as enzymes and through direct contact, it has the ability to hydrolyze any peptide bonds. This enzyme have the potency to destroy any proteins and peptides that might engage in a wide scale of biological purposes, including the making and establishing an infection [69]. The enzyme Proteinases actually occur pervasively in all living biological systems [70]. It is rich in functions, e.g., in human, varying from the digestion of proteins in order to achieve nutritive motives to the magnificent control of general protein role, *e.g.,* by hydrolyzing a extremely particular peptide bond in a certain protein surfactant [69,70].

Parasite proteinases widely known being elaborated in the (1) Pathogenesis, (2) Invasion-migration of the parasite through host tissues, (3) Degradation of immune related proteins, (4) Immune evasion and (5) Activation of inflammation [71,72]. Among protozoan parasites, the enzyme proteinases play crucial part in several acitivites, including (1) Transition of the parasite's life cycle, (2) Invasion of hosts, (3) Migration through tissue barriers, (4) Degradation of hemoglobin and other blood proteins, (5) Immune evasion, and (6) Activation of inflammation in the mammalian host [71-73].

Analysis of the genom carried out with different species of Leishmania that have been sequenced revealed that the amount of proteinase genes is maintained constantly among the various species [73]. Nonetheless, its heterogeneity is very diverse, *e.g.*, the result of genomic survey on multiple databanks unveil that *L. braziliensis* alone has at least forty-four cysteine proteinases, twenty-three serine proteinases and ninety-seven metalloproteinase [74] Therefore, due to the wide range of action of *Leishmania* proteinases while the parasite is inside the mammalian host, it is equitable to seek for the relation between proteinase enzymatic activity and the clinical manifestation of leishmaniasis.

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Review Form 1.6

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PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments	**- The summary should be rewritten and the most important findings should be mentioned in the article** **- The researcher should clarify the Parasite Virulence.** **- It is necessary to include results for biochemical characteristics of Leishmania spp virulence factors.** **What is the application required in the article? It should be written?** **add references to the introduction:** **- Leishmania parasites cause human tegumentary and visceral infections that are commonly referred to as leishmaniasis. Despite the high incidence and prevalence of cases, leishmaniasis has been a neglected disease because it mainly affects developing countries. .** **[1] Silva-Almeida, M., Pereira, B.A.S., Ribeiro-Guimarães, M.L. et al. Proteinases as virulence factors in Leishmania spp. infection in mammals. Parasites Vectors 5, 160 (2012).** **[2] Akraa, M., Hasan, A. S., & Kadhim, M. J. H. (2020). Spectroscopy Characterization of Ethylene Vinyl Acetate Degradation by Different Kinds of Accelerated Aging. Baghdad Science Journal, 17(3), 0795-0795.** **[3] Habeeb, S. A., Hasan, A. S., Ţălu, Ş., & Jawad, A. J. (2021). Enhancing the Properties of Styrene-Butadiene Rubber by Adding Borax Particles of Different Sizes. Iran. J. Chem. Chem. Eng. Research Article Vol, 40(5).** **[4]Hasan, A. S., Mohammed, F. Q., & Takz, M. M. (2020). Design and Synthesis of Graphene Oxide-Based Glass Substrate and Its Antimicrobial Activity Against MDR Bacterial Pathogens. Journal of Mechanical Engineering Research and Developments.** **- The shape and form of protozoan parasites are inextricably linked to their pathogenicity. The evolutionary pressure associated with establishing and maintaining an infection and transmission to vector or host has shaped parasite morphology. However, there is not a 'one size fits all' morphological solution to these different pressures, and parasites exhibit a range of different morphologies, reflecting the diversity of their complex life cycles. In this review, we will focus on the shape and form of Leishmania spp., a group of very successful protozoan parasites that cause a range of diseases from self-healing cutaneous leishmaniasis to visceral leishmaniasis, which is fatal if left untreated.** **.** **[4]Sunter, J., & Gull, K. (2017). Shape, form, function and Leishmania pathogenicity: from textbook descriptions to biological understanding. Open biology, 7(9), 170165..** **[5]Kadhim MH, Hasan AS, Akraa MA, Layla AY. Preparation and optimization of heterojunction donor (DLC)–acceptor (SI) as a solar cell by DFT and PLD. Journal of Ovonic Research Vol. 2021 May;17(3):273-81. .** **[6] Mohammed, F. Q., Edan, M. S., Hasan, A. S., & Haider, A. J. (2021). Synthesis and Theoretical Concepts of Boron Nitride Nanowires Grown on Nitrides Stainless Steel Surface by Hybrid Gas Phase Process. In Key Engineering Materials (Vol. 886, pp. 97-107). Trans Tech Publications Ltd.**	

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Thank you for your mail and attachments. We hereby acknowledge the receipt of the revised paper and duly filled review forms. The paper is under final evaluation now and we'll let you know the final decision very soon.

Thank you for your interest in this journal.

Please be safe during this COVID-19 pandemic situation. We wish best of health for you and your family members.
With Best Regards
Ms. Ruma Bag

Journal editorial office
Reg. Offices:
India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India, Tel: +91 8617752708 | +91 9163821242, WhatsApp: +91 8617752708
UK: Third Floor, 207 Regent Street, London, W1B 3HH, UK, Fax: +44 20-3031-1429
EMP-003-RM

On Sun, 26 Jun 2022 at 22:52, Forman Erwin Siagian <forman.siagian@uki.ac.id> wrote:

> dear Ms Ruma Bag
> Here is the correction that we conduct based on the reviewer suggestion.
> hopefully that it can meet the high standards of the journal.
> we are waiting patiently for your further instrcution.
> with ebstr egrads

Erwin

From: Forman Erwin Siagian <forman.siagian@uki.ac.id>
Sent: Monday, June 27, 2022 12:17 AM
To: Accounts Dept. ME30 <editor.30@sciencedomain.org>
Subject: Re: Minor review comments for manuscript number:2022/MRJI/88967

Dear Ms Ruma Bag,
thank you very mcuh for your update.
we conduct the revision, asap.
Hopefully that it can meet up with the high standards of the journal.
we are waiting patiently for your further instrcuton.
with bestr egards,
Erwin

From: Accounts Dept. ME30 <editor.30@sciencedomain.org>
Sent: Saturday, June 25, 2022 5:35 PM
To: Forman Erwin Siagian <forman.siagian@uki.ac.id>
Subject: Minor review comments for manuscript number:2022/MRJI/88967

Dear Dr. Forman Erwin Siagian,

We are contacting from **Microbiology Research Journal International** regarding Manuscript Number. 2022/MRJI/88967

Title of the Manuscript**: Biochemical Properties Of Parasite Virulence Factor: Lesson Learned From Leishmania**

All review comments (…02.. nos.) are attached with this email.
Please do the correction as per the review comments in the following file
File name: Ms_MRJI_88967

Deadline:
Authors are requested to send revised paper as soon as possible (within 2-3 days) to accelerate the pre-publication formalities. If we receive the revised version within this deadline, the paper can be published in the current issue of the journal within 7 days. If extra time is required, kindly inform us.

Revised paper:
1. Comments of all the reviewers should be addressed during revision. Authors are requested to submit the revised paper with all the corrections highlighted in yellow color (for example. abc…….efg).
2. Authors should write their feedback in the review form in the space provided for 'author's comment' and send back the filled forms to us along with the revised paper.
3. **Please send us the revised version along with feedback via E-mail attachment in reply mail.**

You are hereby requested to kindly acknowledge the receipt of this mail.

Please be safe during this COVID-19 pandemic situation. We wish best of health for you and your family members.

NB: This email is sent from three email ids (sciencedomain.org/Yahoo/Gmail) to avoid delivery failure

With Best Regards
Ms. Ruma Bag

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Reg. Offices:
India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India, Tele: +91 8617752708 | +91 9163821242, WhatsApp: +91 8617752708,
UK: Third Floor, 207 Regent Street, London, W1B 3HH, UK, Fax: +44 20-3031-1429

EMP-003-AR

Fwd: Fw: Post publication support for your published paper

Trini Suryowati <trinisuryowati11@gmail.com>
Rab 19/07/2023 22.12
Kepada:Edi Wibowo <edi.wibowo@uki.ac.id>

---------- Forwarded message ---------
Dari: **Forman Erwin Siagian** <forman.siagian@uki.ac.id>
Date: Sab, 15 Jul 2023 pukul 20.59
Subject: Fw: Post publication support for your published paper
To: Trini Suryowati <trini.suryowati@uki.ac.id>
Cc: trinisuryowati11@gmail.com <trinisuryowati11@gmail.com>, trinisuryowati@gmail.com <trinisuryowati@gmail.com>

From: Editor SDI <publication.6@sciencedomain.biz>
Sent: Tuesday, June 28, 2022 8:10 PM
To: Forman Erwin Siagian <forman.siagian@uki.ac.id>
Subject: Post publication support for your published paper

Subject: Post publication support for your published paper: 2022/MRJI/88967

Dear Dr. Forman Erwin Siagianv,

Congratulations for publishing your new paper. This mail is regarding post-publication management of your published papers. It is proven by different researches that citations of any paper depend not only on the quality of published paper but also on the “Post-publication management”. Recent investigations suggest when researchers explain and share their work, it can increase downloads of the full text by 23% (See here: https://goo.gl/gLTTTs).

Therefore, as part of our post-publication support we strongly suggest you to use the following services to boost your citations

1. Share your paper in researchgate (https://www.researchgate.net/signup.SignUp.html)
2. Share your paper in https://www.growkudos.com/register

As post-publication support, we'll be submitting your paper to different indexing organizations. With the technical help of Google, authors can see real-time data of different interesting Article Metrics like Article download, Article access, etc. See example 1, example 2, example 3, etc.

Thank you for your interest in this Journal.

Please be safe during this COVID-19 pandemic situation. We wish best of health for you and your family members.

With Best Regards

Ms. Ruma Bag

Journal editorial office

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India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India, Tel: +91 8617752708 | +91 9163821242, WhatsApp: +91 8617752708

UK: Third Floor, 207 Regent Street, London, W1B 3HH, UK, Fax: +44 20-3031-1429

EMP-014-SS

Fwd: Fw: Final Decision for Manuscript Number : 2022/MRJI/88967

Trini Suryowati <trinisuryowati11@gmail.com>
Rab 19/07/2023 22.13
Kepada:Edi Wibowo <edi.wibowo@uki.ac.id>

---------- Forwarded message ---------
Dari: **Forman Erwin Siagian** <forman.siagian@uki.ac.id>
Date: Sab, 15 Jul 2023 pukul 21.00
Subject: Fw: Final Decision for Manuscript Number : 2022/MRJI/88967
To: Trini Suryowati <trini.suryowati@uki.ac.id>
Cc: trinisuryowati11@gmail.com <trinisuryowati11@gmail.com>, trinisuryowati@gmail.com <trinisuryowati@gmail.com>

From: sdi.6@sciencedomain.info <sdi.6@sciencedomain.info> on behalf of Managing Editor <sdi.6@sciencedomain.info>
Sent: Tuesday, June 28, 2022 4:48 PM
To: Forman Erwin Siagian <forman.siagian@uki.ac.id>; Trini Suryowati <trini.suryowati@uki.ac.id>
Subject: Final Decision for Manuscript Number : 2022/MRJI/88967

Dear Dr. Forman Erwin Siagian,

We are delighted to inform you that the Editor of this journal accepted your following paper for publication.

Manuscript number: 2022/MRJI/88967

Title: “Biochemical Properties Of Parasite Virulence Factor: Lesson Learned From Leishmania”

Journal name:Microbiology Research Journal International

Kindly note, soon we will proceed for proof reading and publication of the paper.

Thank you for submitting your paper to SDI journal.

Please be safe during this COVID-19 pandemic situation. We wish best of health for you and your family members.

This mail has been sent from following 3 emails to avoid email failure delivery:

1. sdi.6@sciencedomain.org

2. sdi.6@sciencedomain.info
3. sdi.6@sciencedomain.in

With Best Regards
Ms. Ruma Bag
SCIENCEDOMAIN *international*
www.sciencedomain.org

Journal editorial office
Reg. Offices:
India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India, Tel: +91 8617752708 | +91 9163821242, WhatsApp: +91 8617752708

EMP-007-OL

Fwd: Fw: Acceptance letter for your manuscript number : 2022/MRJI/88967

Trini Suryowati <trinisuryowati11@gmail.com>
Rab 19/07/2023 22.08
Kepada:Edi Wibowo <edi.wibowo@uki.ac.id>

1 lampiran (188 KB)
Acceptance_Letter5.jpg;

---------- Forwarded message ---------
Dari: **Forman Erwin Siagian** <forman.siagian@uki.ac.id>
Date: Sab, 15 Jul 2023 pukul 20.58
Subject: Fw: Acceptance letter for your manuscript number : 2022/MRJI/88967
To: Trini Suryowati <trini.suryowati@uki.ac.id>
Cc: trinisuryowati11@gmail.com <trinisuryowati11@gmail.com>, trinisuryowati@gmail.com <trinisuryowati@gmail.com>

From: Editor SDI -01 <editor.sdi01@sciencedomain.biz>
Sent: Wednesday, June 29, 2022 6:41 PM
To: Forman Erwin Siagian <forman.siagian@uki.ac.id>; Trini Suryowati <trini.suryowati@uki.ac.id>
Subject: Acceptance letter for your manuscript number : 2022/MRJI/88967

Dear Colleague,

Please find attached herewith the acceptance letter for your manuscript number.2022/MRJI/88967.

With Best Regards

Ms. Ruma Bag

Journal editorial office

Reg. Offices:

India: Guest House Road, Street no - 1/6, Hooghly, West Bengal, India, Tel: +91 8617752708 | +91 9163821242, WhatsApp: +91 8617752708

EMP-007-DD

SD Publisher Group
Publisher of peer reviewed international journals, books and monographs

F. No. SDI/ MRJI/22/13883
Dated 28th Jun 2022

Subject: Final decision of review process for (Manuscript Number. 2022/MRJI/88967) submitted in Microbiology Research Journal International

Dear Colleague,

We are pleased to inform that peer review process and editorial review process have been completed for your following manuscript

Manuscript Number: 2022/MRJI/88967

Title: Biochemical Properties Of Parasite Virulence Factor: Lesson Learned From Leishmania

Author(s): Trini Suryowati, Forman Erwin Siagian, Lusia Sri Sunarti

We are ready with the final decision. We are happy to inform you that your manuscript is officially accepted for publication in Microbiology Research Journal International

Once your manuscript is moved to publishing, our production editor will keep you informed of your article's progress in the production process. You will also receive a galley proof of your manuscript for final review. We're excited to move forward with your submission. Please feel free to email me with any questions.

Thank you for submitting your paper.

Thanking you.

Dr. M. Basu
Chief Managing Editor