Polysaccharides and their vanadium complexes: New therapeutic perspectives by their ability of modulating macrophages

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Received: March 21, 2015
Published online: April 13, 2015

Certain polysaccharides and their derivatives have been used in different applications including in medicine. As biological response modifiers, activities as immunomodulator, antitumor and antileishmanial are researched. Leishmaniasis is a very epidemiologically important disease and the World Health Organization (WHO) classifies it as a neglected disease. In mammal hosts, the Leishmania parasites live inside mononuclear phagocytes, which impair the action of drugs. The pentavalent antimonials sodium stibogluconate and meglumine antimoniate make up the primary treatment for leishmaniasis, which is associated with serious side effects and resistance to antimony. Since the survival of Leishmania parasites in the host cells is associated with the immune system modulation, compounds able to activate these cells to produce cytotoxic mediators could have great potential of promoting leishmanicidal effects. Therefore, immunomodulation is considered a promising strategy to cure leishmaniasis with fewer side effects. The polysaccharides that activate macrophages for proinflammatory activity have been studied aiming at leishmanicidal effect. When complexed with vanadium, galactomannans, arabinogalactans, and xyloglucans, polysaccharides had greater leishmanicidal effects and were more effective than the antimonials currently used in leishmaniasis treatment.


Polysaccharides of various sources have been the target of study for applications in technological, food, and pharmaceutical industries and medicine [1, 2]. In addition to the studies with native polymers, different types of chemically modified polysaccharides, including the complexation with metals aiming at different applications, has been investigated [3]. The complexation of carbohydrate biopolymers with different metals is facilitated mainly due to the presence of hydroxyl groups in these polymers and, in some instances, the presence of charged groups such as carboxyl or sulfate [4-8]. Vanadium exhibits several important biological effects [9, 10] and has been suggested to be an excellent target for antiparasitic purposes, including antileishmanial action [11-14].

Plant polysaccharides have received great interest in medicine mainly due to their availability, low cost, and low toxicity [15]. Many of these biopolymers are biological response modifiers, in particular able to modulate macrophages to produce immunomodulatory mediators like cytokines and nitrogen and oxygen radicals such as nitric oxide (NO) and superoxide anion, respectively. These mediators are involved in activities such as antitumoral [15, 16], antimicrobial, and antileishmanial [11, 13, 18, 19]. The action of polysaccharides on macrophages occurs by the interaction of these polymers with specific receptors on the cell surface. In addition to complement receptor 3 (CR3), scavenger receptor (SR), dectin-1, manose, fucose, β-glucans, Toll-like receptors
(TLRs) are the main membrane receptors in macrophages that interact with polysaccharides isolated from various sources\cite{15,20}. It has been demonstrated that the polysaccharide recognition by certain receptors depends on structural aspects such as molecular mass, degree of branching, presence of charge, solubility, and conformation\cite{20}. Thus, many studies about the structure-activity relationship of polysaccharides have been performed\cite{20-23}.

Through some of these receptors, the macrophages internalize many pathogens by the phagocytosis process, and, in certain circumstances, become their host cells, such as *Leishmania*\cite{24}. Once internalized in macrophages of the mammal hosts, the *Leishmania* parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and included in the parasites can develop leishmaniasis, a disease with great epidemiological importance and 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GALMAN-A:VO$_{2^+}$/VO$_{3^+}$ (25 µg/ml) exhibited ~60% antileishmanial effect against the amastigote form [13]. These data show that GALMAN-A is three times more potent and its oxovanadium complex is 12 times more potent than Glucantime (300 µg/ml), the main drug used to treat leishmaniasis.

Recently, we investigated the production of antileishmania mediators by macrophages and leishmanicidal activity by polysaccharides whose immunomodulatory action had already been confirmed. Arabinogalactan (ARAGAL) obtained from Anadenanthera colubrina trunk exudate [42], xyloglucan (XGJ) isolated from cotyledon seeds from Hymenaea courbaril [43], and galactomannan (GM POLY) obtained from the Ramalina celastri lichen [44] were investigated. Earlier, the polysaccharides had been complexed with oxovanadium (IV/V) and the amount of vanadium in the complexes was determined so the complexes’ 50% inhibitory concentration (IC$_{50}$) could be calculated [14]. In this study, ARAGAL, GM POLY, and XGJ, as well as their oxovanadium (IV/V) complexes (ARAGAL:VO, GM POLY:VO, and XG J:VO) activated macrophage production of IL-1β and IL-6, but the oxovanadium complexes were much more potent than uncomplexed polymers because they increased the levels of these mediators by over 500%. In addition to the NO and proinflammatory mediators involved in the leishmanicidal effect, the complexes promoted expressive generation of one or more proinflammatory mediators, that could culminate in an effective leishmanicidal effect.

Concerning the leishmanicidal effect evaluated in macrophages infected with Leishmania (L.) amazonensis, the polysaccharides and their oxovanadium complexes were more effective than Glucantime (300 µg/ml), which was used as positive control. ARAGAL and ARAGAL:VO (both 10 µg/ml), GM POLY and GM POLY:VO (25 µg/ml and 10 µg/ml), and X G J and XG J:VO (25 µg/ml and 10 µg/ml) promoted leishmanicidal effect against amastigote forms at around 60-70%, Glucantime was also effective at ~60%, but at about 10-12 times higher concentrations. The IC$_{50}$ values of the complexes and their vanadium contents were determined. XG J:VO showed the lowest IC$_{50}$ value (6.2 mg/ml; 0.07 mg/ml of vanadium), which was 6.5 mg/ml (0.21 mg/ml of vanadium) for ARAGAL:VO and 7.3 mg/ml (0.06 mg/ml of vanadium) for GM POLY:VO [14].

In view of what has been described, we can make some relevant considerations concerning the future application of polysaccharides and their complexes with vanadium in leishmaniasis treatment. The onset of leishmaniasis and its evolution to healing or non-healing depends on whether the host’s immune system triggers types Th1 or Th2 response by T-help (Th) cells [45, 46]. When Th2 response is favored, which is sustained by mediators like interleukins (IL-4, IL-10, IL-13) and the gamma interferon (IFN-γ): IL-10 ratio, the macrophages undergo downregulation and the Leishmania amastigotes replicate and proliferate, thus increasing the susceptibility to disease development. On the other hand, if Th1 response is favored, which triggers a proinflammatory response with the production of proinflammatory mediators like nitric oxide, superoxide anion, IL-1β, IL-6, and IL-12, and tumor necrosis factor alpha (TNF-α), the macrophages are upregulated and kill the parasites [28, 47]. It has been reported that clonal T cells are capable of high production of IFN-γ and low production of IL-10, which interrupts Th2 response and promotes significant leishmanicidal effect [46]. Based on these immunological responses, it is a fact that, if macrophages can be activated by molecules from exogenous sources (e.g., polysaccharides) to trigger the production of proinflammatory mediators, that could culminate in an effective leishmanicidal effect.

In our studies, both polysaccharides and their vanadium complexes promoted expressive generation of one or more proinflammatory mediators involved in the leishmanicidal effects. Although the action mechanism of these compounds is not yet understood, the leishmanicidal activity of over 50% at concentrations up to 12 times below that of the antimonials currently used in leishmaniasis chemotherapy suggests that native polysaccharides and their vanadium complexes can be investigated for future application in leishmaniasis treatment.

The physicochemical properties such as the high viscosity of aqueous solutions, the ability to form gels under specific conditions, increase in viscoelastic properties, and emulsion stability shown by polysaccharides as mannan, galactomannan, and xyloglucans [49-51] enable the formulation of creams or gels that could be used in combination with chemotherapy for cutaneous leishmaniasis. This treatment alternative has been reported for some compounds with known leishmanicidal activity [39, 52].

Considering the potential of polysaccharides and their complexes to upregulate macrophages for proinflammatory effects, their topical use would be a strategy with great potential to achieve healing in cutaneous leishmaniasis. Even if they are not used alone, their use in combination with currently used drugs could reach 100% of the effect and decrease side effects and time of treatment. Further studies focusing on the mechanism of action and an experimental model to characterize the in vivo leishmanicidal effect of polysaccharides and their vanadium complexes are being scheduled.

**Acknowledgments**

The authors are thankful to the Brazilian research funding agencies CNPq, CAPES, and Fundação Araucária.
References


