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Review

Alkaloids: Future prospective to combat leishmaniasis

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ABSTRACT

Leishmaniasis, a vector-borne parasitic disease resulting from infection of macrophages by obligate intracellular parasites of genus *Leishmania*, has been considered a major tropical disease by the World Health Organization. Generic pentavalent antimonials have been the mainstay for therapy in the endemic regions because of its efficacy and cost effectiveness. However, the growing incidence of resistance for the pentavalent antimony complex in endemic and non-endemic regions has seriously hampered their use in these regions. The second line drugs such as amphotericin B, paromomycin and miltefosine are the other alternatives, but they merely fulfill the desired requirements of a safe drug. The recent researches focused on plants have shown a wise way to get a true and potentially rich source of drug candidates against leishmaniasis, where alkaloids have been found more effective. The present review initially highlights the current status of leishmaniasis, synergy of the disease with HIV, therapeutic options available and in later sections summarizes all alkaloids, which have shown significant antileishmanial activities.

Contents

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1. Introduction

Leishmaniasis, a neglected tropical parasitic disease resulting from infection of macrophages by obligate intracellular parasites of genus *Leishmania*, has been considered as a major health problem worldwide, especially in developing nations [1]. Leishmaniasis is prevalent in 88 countries throughout the world (72 are developing countries) and affects more than 12 million people with more than 90% of VL patients located in India, Sudan, Brazil and Bangladesh [2].

Leishmania sp. appears as a heterexenous protozoan that essentially requires two different hosts to complete its biological cycle: (a) an invertebrate insect vector, generally females of *Phlebotomus* (in the Old World) or *Luztomiya* (in the New World) sandfly mosquito and (b) a definitive host, human, dog or even a wild vertebrate [3]. Infections can vary from simple cutaneous leishmaniasis (CL) to mucocutaneous (MCL) and visceral leishmaniasis (VL), which is fatal if left untreated. The annual global burden of VL (visceral leishmaniasis) is about 500,000. Out of these 90% cases occur in India, Nepal, Bangladesh and Brazil [3]. In India, about 100,000 cases of VL are estimated to occur annually and epidemiology of VL is changing due to widespread migration of population and HIV/VL co-infections. *Leishmania*-HIV co-infection is regarded as an "emerging" infectious disease, for in certain countries up to 70% of adult cases of leishmaniasis are related to HIV infection-AIDS. To date, the greatest prevalence of *Leishmania*-HIV co-infection has been in the Mediterranean basin [4]. Among more than 2000 cases notified to the WHO, 90 % of them belong to Spain, Italy, France and Portugal. The epidemiological data for Southern Europe indicates that HIV infection is a risk factor associated with VL [5].

The symptoms of leishmaniasis are skin sores that erupt weeks to months after the person affected is bitten by sand flies. Other clinical symptoms are characterized by prolonged and irregular fever often associated with rigor and chills, splenomegaly, lymphadenopathy, hepatomegaly, pancytopenia, progressive anemia, weight loss and hypergammaglobulinemia (mainly IgG from polyclonal B cell activation) with hypoalbunemia. It is always fatal if left untreated [6].

There are several practical aspects to consider when trying to explain the difficulties that are typically associated with natural products research: (i) compound availability is very low (low yield, one-sample-one-source problem and related resource issues), (ii) relative structural complexity is very high and includes the occurrence of multiple stereoisomers, (iii) follow-up studies are mostly lacking, since most efforts (e.g. in academic environments) are not part of focused drug development programs and simply lack the opportunity for e.g. synthetic follow-up of promising leads; (iv) the isolated active principles rarely exhibit potent activity themselves, but require follow-up improvement in order to be attractive.

The review is aimed to cover truly interdisciplinary nature of the scientific challenges that are associated with the early steps of the antileishmania drug discovery process and highlights significant and constant research on leishmanicidal alkaloids from the mid-1980 to late 2008. Furthermore, we have focused on the SAR based activity and mechanisms of action for promising alkaloids for development of novel chemotherapeutics. In order to highlight any possible structure–activity relationships, the review is organized according to chemical structural class.

2. *Leishmania* taxonomy

Taxonomic classification [30] of genera *Leishmania* may be summarized from Fig. 1.

3. Morphology of *Leishmania* parasites

Leishmania parasites exist in two forms that are morphologically and biochemically different. The insect form, called a promastigote, is a motile parasite, closely resembling a hemoflagellate. A promastigote displays one flagellum attached to a mitochondrial-like organelle, called a kinetoplast that contains very repetitive chains of ring DNA called kinetoplast DNA [2]. Promastigotes have a spindle-shaped body and are 10 to 15 pm in length, measuring 1.5 to 3.5 µm at their widest part. The monoflagellated amastigotes are spherical in shape, with approximately 2 to 3 pm in diameter [7,8].

Infection starts when a sand fly takes a blood meal from an infected host (e.g., canines, marsupials, edentates, and rodents). Small amounts of blood, lymph and macrophages infected with *Leishmania* amastigotes are ingested. Once ingested, the amastigotes migrate to the midgut of the sand fly, where they transform into the promastigotes by means of binary fission. After a period of four to five days, promastigotes move forward to the oesophagus and the salivary glands of the insect. Infected sand fly during the second blood meal regurgitates the infectious promastigotes from its pharynx into the bloodstream of the host vertebrates. Once inside the bloodstream of reservoirs for the disease, promastigotes are phagocytosed by the mononuclear phagocytic cells of the host. After phagocytosis, transformation to dividing amastigotes occurs within 24 h. The *Leishmania* are able to resist the microbiocidal action of the acid hydrolases release form the lysozymes and so survive and multiply inside the macrophages. Eventually, the host cells lyse, releasing the free parasites which spread to new cells and tissues of different organs (especially the spleen, liver and bone marrow) causing lesions and tissue destruction [2,9].

4. Chemotherapy of leishmaniasis

Most of the drugs used in the treatment of leishmaniasis have one or more limitations like unaffordable cost, difficulty in administration, toxicity or more importantly the development of resistance in the parasite. The development of resistance is most alarming against the antimonial compounds and poses a major impediment in successful therapy of the disease. There