Terpenoid Derivatives as Potential Trypanocidal Agents

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Abstract
In this review we refer to a promising family of molecules in the fight against Chagas disease. Terpene derivatives are abundant in the plant Kingdom and in the last years many compounds have shown important biological activities. Diterpenes and sesquiterpene lactones have shown in vitro and in vivo trypanocidal activity and they emerge as potential antichagasic drugs. These molecules may act on these parasites by multiple mechanisms, as it has been reported. Moreover, given the chemical structure of these compounds it is feasible to modify these molecules by chemical substitution in order to optimize their action against parasites.

Keywords: Chagas disease; Trypanosoma cruzi; Mammalian cells; Trypanocidal activity

Chagas Disease
Chagas disease or American trypanosomiasis is a disease caused by the kinetoplastid protozoan Trypanosoma cruzi. This parasitic disease affects millions of people in Latin America and is still expanding worldwide due to migration phenomena. Chagas is one of the most devastating diseases caused by parasites of the Trypanosomatidae family. Trypanosoma cruzi is transmitted through the bite of triatomine haematophage insects such as Triatoma infestans. However, congenital and transfusion (iatrogenic) transmission are also relevant in the transmission cycle, since they are responsible for the expansion of this disease in non-endemic areas [1]. After an acute phase and subsequent state of latency, the disease commonly progresses to a chronic phase, with clinical manifestations in various organs. The chronic manifestations of the disease are sometimes life-threatening [2-4]. Although advances have been made in the field of molecular biology and pathophysiology of Chagas disease, the search for an effective treatment has yet been unsuccessful due to several reasons: a) the existence of a wide variety of strains, with different virulence and drug resistance profile, b) the fact that the acute phase is often asymptomatic, c) the difficulty to find a drug with suitable selectivity for the parasite, and d) most funds are intended for the development of diagnostic tests and prevention.

For decades, the search for drugs to treat Chagas disease has been a constant challenge. Nowadays, the treatments of Chagas’ disease entail the election between either one of two nitroheterocyclic compounds, that is, benznidazole or nifurtimox [5-7]. Both drugs are effective when administered at the onset of the acute phase. Conversely, their effectiveness is limited during the chronic stage, there are regional degrees of effectiveness due to drug resistance; and they present severe side effects that lead to the immediate interruption of treatment in a high percentage of the patients. Most of the knowledge that currently exists about the biology of the parasite and the identification of potential molecular targets, together with the wide range of natural molecules, mainly in the plant kingdom, has encouraged researchers to continue the intense search for new drugs against T. cruzi [8-10]. The main vulnerability of parasites is related to the high sensitivity to oxidative stress due to the rudimentary defense system they have [11,12]. Natural compounds are an attractive source of new drugs, because they can be subjected to synthetic modifications to optimize their bioactivity. Thus, families of natural compounds have been tested as potential trypanocidal agents in in vitro and in vivo assays [13,14]. Although many compounds that have been tested have shown strong trypanocidal activity in vitro, few of them have been tested in clinical trials for the treatment of Chagas disease [15,16]. More recently, terpenes and sesquiterpene lactones obtained from the plant leaves have shown high toxicity on the different stages of parasites and with low toxicity on mammalian cells [17,18]. Terpene derivatives are very abundant in nature, therefore, they are an attractive compounds family to be assayed for biological activity. Over the past ten years, hundreds of new terpene-derived molecules exhibiting trypanocidal activity have been described [19-27] and some of them have already been tested against T. cruzi both in vitro and in vivo [28,29]. Interestingly, some of these molecules are feasible to modify chemically in order to optimize their action on parasites. For example, an increase of lipophilicity by chemical modifications has proved to be an adequate strategy for improving the trypanocidal activity of diterpenes (Figure 1) [23,30,31].

Other terpenoid derivatives such as sesquiterpene lactones are known to have a wide spectrum of biological activities, mostly mediated through α,β-unsaturated carbonyl groups [32,33]. Many sesquiterpene lactones with high activity against T. cruzi have been isolated from the aerial parts of plants [34-36]. The mechanism of action of some sesquiterpene lactones is currently under study. In some cases, it has been reported that these compounds can generate free radicals within trypanosomes [37,38]. Accordingly, ultrastructural studies have demonstrated that most of these compounds may affect mitochondrial function [39,40]. It is known that de α-methylene-y-lactone of sesquiterpene lactones is responsible for most of the biological

Figure 1: Structures of Abietane (1), and three derivatives (2-4). R1: COCH3, R2: Si (CH3)3, and R3: CH2-CH=CH2 (30).

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properties of these compounds [41]. Some authors have suggested that the cytotoxicity of these compounds is mediated by an interaction of the α-methylene with sulphydryl groups of enzymes that are crucial for parasite life survival [42]. It is also possible that these compounds may affect calcium metabolism, given their similarity to thapsigargin, a potent inhibitor of this ion (Figure 2). The latter hypothesis has not yet been tested.

All these studies along with others that have been carried out since the 50s [43,44] have contributed to the understanding of the life cycle of parasites [45] and to clarify some molecular targets that could be used for the development of drugs against T. cruzi.

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