Applicability of plant-based products in the treatment of *Trypanosoma cruzi* and *Trypanosoma brucei* infections: a systematic review of preclinical *in vivo* evidence

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SUMMARY

Chagas disease and sleeping sickness are neglected tropical diseases closely related to poverty, for which the development of plant-derived treatments has not been a promising prospect. Thus, we systematicaly review the preclinical *in vivo* evidence on the applicability of plant-based products in the treatment of *Trypanosoma cruzi* and *Trypanosoma brucei* infections. Characteristics such as disease models, treatments, toxicological safety and methodological bias were analysed. We recovered 66 full text articles from 16 countries investigating 91 plant species. The disease models and treatments were highly variable. Most studies used native ($n = 36$, 54·54%) or exotic ($n = 30$, 45·46%) plants with ethnodirected indication ($n = 45$, 68·18%) for trypanosomiasis treatment. Complete phytochemical screening and toxicity assays were reported in only 15 (22·73%) and 32 (48·49%) studies, respectively. The currently available preclinical evidence is at high risk of bias. The absence of or incomplete characterization of animal models, treatment protocols, and phytochemical/toxicity analyses impaired the internal validity of the individual studies. Contradictory results of a same plant species compromise the external validity of the evidence, making it difficult determine the effectiveness, safety and biotechnological potential of plant-derived products in the development of new anti-infective agents to treat *T. cruzi* and *T. brucei* infections.

Key words: Experimental therapeutics, human trypanosomiasis, neglected diseases, parasitic diseases, parasitology.

INTRODUCTION

American and African trypanosomiasis constitute the two main human systemic trypanosomiases, which are neglected tropical diseases worldwide (Kennedy, 2013; Bern, 2015). American trypanosomiasis or Chagas disease is caused by the intracellular parasite *Trypanosoma cruzi*, which is mainly transmitted through contact with the feces of hematophagous Triatomine insects. About 6 to 7 million people are estimated to be infected worldwide, mostly in Latin America (WHO, 2016*a*). Owing to population migration from Central and South American endemic countries, Chagas disease has also become a health problem in non-endemic areas, especially the USA and European countries, in which non-vectorial transmission routes related to blood and organ donation predominate (Bern, 2015). In North America, this disease accounts for over 300 000 reported cases, while in Europe about 108 000 cases are estimated (Andrade *et al*. 2014). Chagas disease is characterized as the most common cause of non-ischaemic cardiomyopathy in South America (Bocchi, 2013), leading to the death of many patients every year, mainly due to dilated cardiomyopathy, congestive heart failure, dysrhythmias and thromboembolic events occurring in approximately 30% of infected individuals (Marin-Neto *et al*. 2007; Bern, 2015). There is no effective vaccine for Chagas disease, and although drugs such as nifurtimox and benznidazole are effective in acute infections (about 60% cure), these drugs exhibit high toxicity and do not guarantee a cure (about 10–20%) in chronic infections (Cançado, 1999, 2002).

African trypanosomiasis or sleeping sickness is caused by the extracellular protozoa *Trypanosoma brucei gambiense* as well as *Trypanosoma brucei rhodesiense* in 36 sub-Saharan Africa countries (Giordani *et al*. 2016; WHO, 2016*b*). Although the tsetse fly (genus *Glossina*) is responsible for the transmission of both parasite species, *T. brucei gambiense* accounts for more than 98% of reported cases (Kennedy, 2013; Sudarshi and Brown, 2015). About 20 000 cases/year and 65 million people are at risk of infection (WHO, 2016*b*). Due to infection of the central nervous system, neurological disorders (i.e. changes in

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