Review Paper

Antileishmanial activity of *Annona* species (Annonaceae)

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Abstract
Annona species are widely used in traditional medicine against leishmaniasis. In vitro studies have confirmed their antileishmanial activity. Objective: review the antileishmanial activity of *Annona* species. Results: This article provides a review *Annona* species activity against leishmaniasis, in which it suggests that extracts of *A. mucosa* were active against promastigotes and amastigotes of *L. amazonensis*. Moreover, extracts of *A. crassiflora* were active only against promastigotes of *L. donovani*, whereas the extract, alkaloid fraction and liriodenine of *A. foetida* were active against promastigotes of *L. braziliensis* and *L. guyanensis.* Liriodenine was also very active against *L. amazonensis.* Furthermore, extracts and fractions from stems of *A. muricata* were active against *Leishmania* sp. This activity may be related to the presence of acetogenins, since fractionation contributed to increase activity. The fractionation of *A. purpurea* extract contributed to antileishmanial activity, and resulted in a fraction with high selectivity. Such activity may be related to alkaloids or acetogenins. Conclusions: In this review article it is suggested that *Annona* species are promising as leishmanicide and this activity may be related to acetogenins and alkaloids.

Keywords *Annona* · Leishmaniasis · Alkaloid and acetogenin

1 Introduction

Leishmaniasis is caused by parasites belonging to the Trypanosomatidae family and *Leishmania* genus. There are three main forms of leishmaniasis—visceral, cutaneous and mucocutaneous [1]. Most cases of cutaneous leishmaniasis occur in Afghanistan, Algeria, Brazil, Colombia, Islamic Republic of Iran, Pakistan, Peru, Saudi Arabia and Syrian Arab Republic [1].

Leishmaniasis treatment is performed with pentavalent antimonials (sodium stibogluconate and meglumine antimoniate), amphotericin B and pentamidine. However, the use of these agents is questionable due to the variability in their efficacy among *Leishmania* species, high cost, need for parenteral administration, and high toxicity [2, 3]. The search for alternative therapies is very important, and medicinal plants are a source of bioactive molecules [4].

Annona species are used in traditional medicine to treat leishmaniasis. In vitro, antileishmanial studies of extracts validated the popular use [5–7]. Some studies about antileishmanial activity of *Annona* attribute its activity to alkaloids [8, 9] and acetogenins [10].

Several alkaloids were active against *Leishmania*, among these are coronaridine (Fig. 1a), 18-methoxycoronaridine (Fig. 1b) [11], O-methylarmepavine (Fig. 1c) [10], liriodenine (Fig. 1d) [12]. Moreover, acetogenins annonacinone (Fig. 1e) and corossolone (Fig. 1f) were also promising as leishmanicide [10].

Previous studies on species of the genus *Annona* present biological investigations on promastigote and amastigote forms of *Leishmania*, for example, from seeds of *A.*

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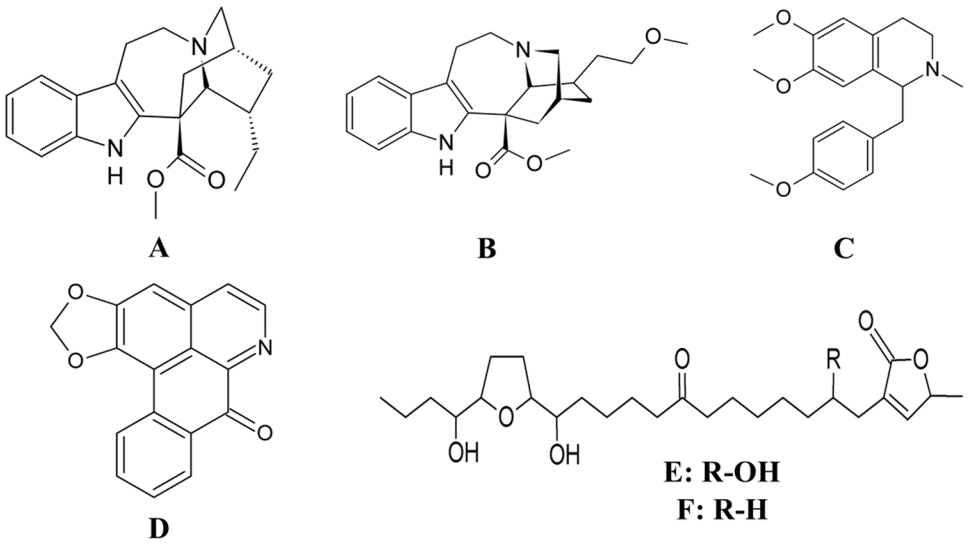

Fig. 1 Compounds isolated from species of *Annona*. Legend: (**a**) Coronaridine, (**b**) 18-Methoxycoronaridine, (**c**) O-methylarmepavine, (**d**) Liriodenine, (**e**) Corossolone, (**f**) Annonacinone

squamosa a trihydroxylated acetogenin with two tetrahydrofuran rings and α, β-unsaturated lactonic ring of 37 carbon atoms endowed with antihelmintic and antiprotozoal properties was isolated. This substance showed leishmanicidal action against promastigotes and amastigotes of *L. chagasi* [10]. The volatile oil of *A. foetida* was active against promastigotes of four different species of *Leishmania*, having been more active in *L. guyanensis* (IC_{50}: 4.1 µg/mL) [9].

The alkaloids fraction from leaves of *A. coriacea* revealed activity against promastigotes of *L. chagasi*, with an IC_{50} of 41.6 µg/mL. In amastigote forms, they caused death to 27.2% of the parasites, at a concentration of 20 µg/mL [8]. The alkaloid fraction of *A. foetida*, showed activity against the promastigotes of *L. braziliensis* and *L. guyanensis* [12].

In this context, to validate the popular use on leishmaniasis, the analysis of several studies of *Annona* species was performed, focused on their antileishmanial activity.

2 Materials and methods

A survey was performed with the selection of scientific articles available at CAPES, PUBMED and GOOGLE SCHOLAR DATABASE; the year of publication was not limited. The search was carried out in January 2020 and only articles in Portuguese, English and Spanish, which presented leishmanicidal activity (inhibitory concentration 50%—IC_{50}) were considered. The following exclusion criteria were adopted: articles in other languages, those that did not address the proposed theme, in duplicate, and articles that could not be accessed in full.

For the search, descriptors related to the theme were used in an associated way: *Leishmania* and *Annona*. The preliminary result included 1796 papers for screening (CAPES = 21, PUBMED = 15 and GOOGLE SCHOLAR DATABASE = 1760), using as criterion articles with titles that fit the theme, summary compatible with this study proposal, and the exclusion of duplicate occurrences. Four articles from CAPES and twelve from PUBMED were eliminated due to duplication. Regarding GOOGLE SCHOLAR DATABASE, most of the eliminated articles had inappropriate title or duplication (1757). When the title and abstract were analyzed, 14 papers were included. Figure 2 shows the screening identification procedure included for analysis.

Two reviewers selected, independently, studies based on their title and abstract, those considered potentially relevant were obtained for complete analysis. Any discrepancies were solved by consensus and a third reviewer was consulted to ensure compliance with the inclusion criteria. At the end, 13 articles were selected for discussion and inclusion in this analysis (Fig. 2).

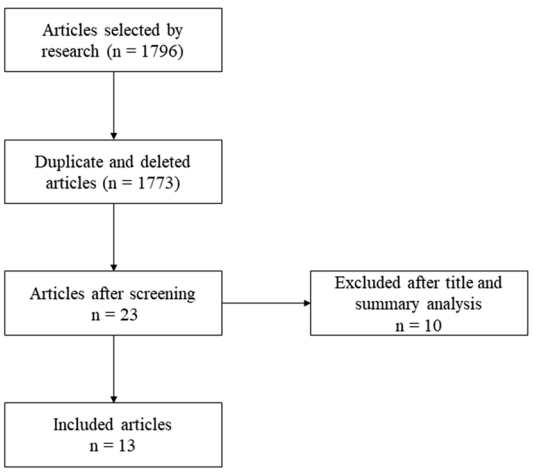

Fig. 2 Flowchart of article eligibility

Regarding data analysis, it was done in two stages: in the first, a table with the following data was used: plant material, type of extract, fractions and isolated substances, IC_{50} and the cytotoxic concentration (CC_{50}). The results are summarized in tables and anti-*Leishmania* activity was assessed using the following criteria: $IC_{50} \leq 100$ µg/mL active, IC_{50} between 101 and 200 µg/mL moderately active and $IC_{50} \geq 200$ µg/mL inactive [13]. Cytotoxicity results were assessed by the following criteria: $CC_{50} \leq 100$ µg/mL cytotoxic, CC_{50} between 101 and 500 µg/mL moderately cytotoxic, and $CC_{50} \geq 500$ µg/mL non-cytotoxic [13].

3 Results

In order to identify whether *Annona* extracts presented antileishmanial activity, an extensive literature review was done, and the results are highlighted in Table 1. Studies about antileishmanial activity for these species are scarce, with only their anti-promastigote activity being evaluated (Table 1).

The ethanol extracts obtained from root barks, stem barks, and stem wood *of A. crassiflora* were active against promastigotes of *L. donovani* (IC_{50}: 3.7 ± 0.3 µg/mL, 12.4 ± 0.3 µg/mL, and 8.3 ± 0.8 µg/mL, respectively; Table 1) [14]. The total alkaloids obtained from the ethanol extract of *A. crassiflora* leaves were active against *L. chagasi* (IC_{50}: 24.9 ± 0.8; Table 1) [8]. The essential oil of *A. foetida* was active against promastigotes of *L. guyanensis* (IC_{50}: 4.1 ± 0.1 µg/mL), *L. braziliensis* (IC_{50}: 9.9 ± 1.2 µg/mL), *L. amazonensis* (IC_{50}: 16.2 ± 1.9 µg/mL), and *L. chagasi* (IC_{50}: 27.2 ± 6.2 µg/mL), however, it was cytotoxic in peritoneal macrophages BALB/c (PMBC; CC_{50}: 5.67; Table 1) [9]. The hexane extract from of *A. foetida* was active against promastigotes of *L. guyanensis* (IC_{50}: 42.7 ± 5.4 µg/mL). The dichloromethane extract was active against promastigotes of *L. guyanensis* (IC_{50}: 2.7 ± 0.4 µg/mL) and *L. amazonensis* (IC_{50}: 23.0 ± 0.6 µg/mL). The dichloromethane extract fractionation yielded the alkaloid fraction. However, this fraction showed lower activity against promastigotes of *L. guyanensis* (IC_{50}: 10.3 ± 0.9 µg/mL) and *L. amazonensis* (IC_{50}: 18.3 ± 2.5 µg/mL). Nevertheless, the methanol extract of *A. foetida* was active against *L. guyanensis* (IC_{50}: 23.6 ± 3.1 µg/mL) and *L. amazonensis* (IC_{50}: 40.4 ± 3.2 µg/mL), and fractionation contributed to the activity (*L. guyanensis* IC_{50}: 9.1 ± 0.8 µg/mL and *L. amazonensis* IC_{50}: 24.3 ± 1.9 µg/mL; Table 1) [12].

The antileishmanial activity of alkaloids and acetogenins isolated from *A. foetida* were evaluated. The alkaloid liriodenine was more promising against *L. guyanensis* (IC_{50}: 21,0.5 ± 0.4 µg/mL and 55.92 ± 3.55 µg/mL) [9, 15] and PH8- *L. amazonensis* (IC_{50}: 1.43 ± 0.58 µg/mL). Liriodenine showed high toxicity for BALB/c mice peritoneal macrophages (CC_{50}: 19.11 ± 1.06 µg/mL) and low selectivity in *L. guyanensis* (SI: 0.34; Table 1) [15].

Different extracts obtained from *Annona mucosa* were tested on *L. donovani*, *L. amazonensis*, and *L. braziliensis*. Most of the extracts showed activity against promastigotes of *L. amazonensis* (PH8, IC_{50}: 9.3–46.5 µg/mL), although it was not observed significant reduction in the rate of macrophages infection by amastigotes (30%). When cytotoxicity and anti-promastigote activity are related, a low selectivity index is observed (SI: 0.9–6; Table 1) [15].

From *Annona mucosa,* the alkaloids oxoaporphine, atherospermidina and liriodenine were isolated. Liriodenine was active against promastigotes of *L. amazonensis* (IC_{50}: 1.43 ± 0.58 µg/mL) and amastigotes forms of *L. amazonensis* [15]. High selectivity was observed (SI: 13.36), especially for liriodenine (SI: 13.37; Table 1).

The anti-promastigote activity of *A. muricata* was extensively evaluated, yielding inactive (hexane and methanol extracts from pericarp: $IC_{50} > 1000$ µg/mL), moderately active (hexane and methanol extracts from leaves: $IC_{50} > 100$ µg/mL), and active extracts (hexane and methanol extracts from stem and ethyl acetate extracts from pericarp, leaves, and stem: $IC_{50} \leq 100$ µg/mL). Fractionation of *A. muricata* extracts led to the isolation of acetogenins, which were more active than the extracts against promastigotes (Table 1) [10, 16].

Scoparone, corossolone, and annonacinone isolated from *A. muricata* were active against promastigotes of *L. donovanni*, *L. mexicana*, and *L. major* [10, 16]. Annonacinone displayed the major activity against those three *Leishmania* species (IC_{50}: 6.72–8.00 µg/mL) [16]. Annonacinone (IC_{50}: 37.6 µg/mL) and corossolone (IC_{50}: 25.9 µg/mL) showed less activity against promastigotes of *L. chagasi*. These substances were also tested against amastigotes of *L. chagasi*, being annonacinone (IC_{50}: 13.5 µg/mL) more active than corossolone (IC_{50}: 28.7 µg/mL). Annonacinone also presented higher selectivity (CC_{50}: 59.5 µg/mL; SI: 4.4) than corossolone (CC_{50}: 54 µg/mL; SI: 1.9; Table 1) [10].

Scoparone presented lower activity than others acetogenins against promastigotes of *L. donovanni* (IC_{50}: 27.51 ± 0.97 µg/mL), but presented activity similar to the others compounds against *L. mexicana* (IC_{50}: 9.11 ± 0.25 µg/mL) and *L. major* (IC_{50}: 14.37 ± 0.98 µg/mL; Table 1) [16].

The alkaloid O-methylarmepavine and the acetogenin C_{37} trihydroxy adjacent bistetrahydrofuran were isolated from *A. squamosa*. Both O-methylarmepavine and trihydroxy adjacent bistetrahydrofuran showed similar inhibitory effects against promastigotes (IC_{50}: 23.3 and 26.4 µg/mL) and amastigotes of *L. chagasi* (IC_{50}: 25.4 and 25.3 µg/mL). However, this acetogenins showed higher cytotoxicity in RAW 264.7 cells (CC_{50}: 43.5 µg/mL) than the alkaloid (CC_{50}: 79.7 µg/mL; Table 1) [16].

Table 1 Antileishmanial activity of *Annona* species

Samples	Antileishmanial activity (IC_{50} µg/mL ± SD)		*Leishmania* species and cell	Cytotoxicity (CC_{50} µg/mL)	Activity classification	Selectivity index (SI)	References
	Promastigote	Amastigote					
			Annona crassiflora				
EE SB	12.4 ± 0.3	ND	*L. donovani*	ND	Active	ND	Mesquita et al. (2005)
EE SW	8.3 ± 0.8	ND	*L. donovani*	ND	Active	ND	Mesquita et al. (2005)
EE RB	3.7 ± 0.3	ND	*L. donovani*	ND	Active	ND	Mesquita et al. (2005)
EE RW	8.7 ± 0.6	ND	*L. donovani*	ND	Active	ND	Mesquita et al. (2005)
Total alkaloids of leaves	24.9 ± 0.8	ND	*L. chagasi*	ND	Active	ND	Tempone et al. (2005)
			Annona foetida				
HE bark	> 160 42.7 ± 5.4	ND	*L. braziliensis* *L. guyanensis*	ND	Moderate or inactive Active	ND	Costa et al. (2006)
DCE bark	23.0 ± 0.6 2.7 ± 0.4	ND	*L. braziliensis* *L. guyanensis*	ND	Active Active	ND	Costa et al. (2006)
Alkaloide fraction (DCE)	18.3 ± 2.5 10.3 ± 0.9	ND	*L. braziliensis* *L. guyanensis*	ND	Active Active	ND	Costa et al. (2006)
ME bark	40.4 ± 3.2 23.6 ± 3.1	ND	*L. braziliensis* *L. guyanensis*	ND	Active Active	ND	Costa et al. (2006)
Alkaloid fraction (ME)	24.3 ± 1.9 9.1 ± 0.8	ND	*L. braziliensis* *L. guyanensis*	ND	Active Active	ND	Costa et al. (2006)
Alkaloid N-hydroxyannomontine	252.7 ± 2.2 437.5 ± 2.5	ND	*L. braziliensis* *L. guyanensis*	ND	Inactive Inactive	ND	Costa et al. (2006)
Alkaloid O-methylmoschatolin	320.8 ± 3.1 103.7 ± 3.4	ND	*L. braziliensis* *L. guyanensis*	ND	Inactive Moderate active	ND	Costa et al. (2006)
Alkaloid liriodenine	58.5 ± 1.8 21.5 ± 0.4	ND	*L. braziliensis* *L. guyanensis*	ND	Active Active	ND	Costa et al. (2006)
Alkaloid annomontine	34.8 ± 1.5 > 613.0	ND	*L. braziliensis* *L. guyanensis*	ND	Active Inactive	ND	Costa et al. (2006)
Essential Oil	16.2 ± 1.9	ND	*L. amazonensis*		Active	0.35	Costa et al. (2009)
	9.9 ± 1.2	ND	*L. braziliensis*		Active	0.57	
	27.2 ± 6.2	ND	*L. chagasi*		Active	0.20	
	4.1 ± 0.1	ND	*L. guyanensis*		Active	1.38	
			PMBC	5.67	Cytotoxic		
			Annona mucosa				
HE of leaves	24.24 ± 1.51	ND	PH8		Active	2.58	Lima et al. (2012)
	65.27 ± 1.20		M2903		Active	0.95	
			PMBC	62.63 ± 4.10	Cytotoxic		
HE of seeds	44.22 ± 5.64	ND	PH8		Active	5.93	Lima et al. (2012)
	170.15 ± 1.46		M2903		Moderate active	1.54	
			PMBC	262.33 ± 5.81	Moderate cytotoxicity		
DCE of leaves	9.32 ± 0.56	ND	PH8		Active	2.58	Lima et al. (2012)
	27.42 ± 5.42		M2903		Active	0.87	
			PMBC	24.07 ± 0.72	Cytotoxic		

Table 1 (continued)

Samples	Antileishmanial activity (IC_{50} µg/mL ± SD)		*Leishmania* species and cell	Cytotoxicity (CC_{50} µg/mL)	Activity classification	Selectivity index (SI)	References
	Promastigote	Amastigote					
ME of leaves	28.32 ± 1.15	ND	PH8		Active	1.03	Lima et al. (2012)
	44.74 ± 5.89		M2903		Active	0.65	
			PMBC	29.41 ± 0.89	Cytotoxic		
ME of seeds	46.54 ± 4.95	ND	PH8		Active	2.98	Lima et al. (2012)
	133.17 ± 5.41		M2903		Moderate active	1.04	
			PMBC	139.0 ± 3.13	Moderate cytotoxicity		
Alkaloid liriodenine	1.43 ± 0.58 55.92 ± 3.55	ND	PH8		Active	13.36	Lima et al. (2012)
			M2903		Active	0.34	
			PMBC	19.11 ± 1.06	Cytotoxic		
			Annona muricata				
HE of leaves	100.0	ND	PH8	ND	Active	ND	Osorio et al. (2007)
	> 100.0		M2903		Moderate or inactive		
	> 100.0		PP75		Moderate or inactive		
HE of stem	98.6	ND	PH8	ND	Active	ND	Osorio et al. (2007)
	76.3		M2903		Active		
	83.1		PP75		Active		
EAE of leaves	25.0	ND	PH8		Active	0.312	Osorio et al. (2007)
	25.0		M2903		Active	0.312	
	25.0		PP75		Active	0.312	
			PMBC	7.8 ± 0.3	Cytotoxic		
EAE of stem	63.2	ND	PH8	ND	Active	ND	Osorio et al. (2007)
	63.2		M2903		Active		
	63.2		PP75		Active		
ME of leaves	> 100.0	ND	PH8	NDND	Moderate or inactive	ND	Osorio et al. (2007)
	> 100.0		M2903		Moderate or inactive		
	> 100.0		PP75		Moderate or inactive		
ME of stem	98.6	ND	PH8	ND	Active	ND	Osorio et al. (2007)
	98.6		M2903		Active		
	98.6		PP75		Active		
Acetogenin corossolone	25.9	28.7	*Leishmania chagasi*		Active	2.08	Villa-Nova et al. (2011)
			RAW 264.7	54.0	Cytotoxic		
Acetogenin annonacinone	37.6	13.5	*Leishmania chagasi*	59.5	Active	1.58	Villa-Nova et al. (2011)
			RAW 264.7		Cytotoxic		
Acetogenin scoparone	27.51 ± 0.97	ND	*L. donovani*	ND	Active	ND	Villa-Nova et al. (2013)
	9.11 ± 0.25		*L. mexicana*		Active		
	14.37 ± 0.98		*L. major*		Active		

Table 1 (continued)

Samples	Antileishmanial activity (IC_{50} µg/mL ± SD)		*Leishmania* species and cell	Cytotoxicity (CC_{50} µg/mL)	Activity classification	Selectivity index (SI)	References
	Promastigote	Amastigote					
Acetogenin corossolone	18.73 ± 0.82	ND	*L. donovani*	ND	Active	ND	Villa-Nova et al. (2013)
	18.64 ± 0.79		*L. mexicana*		Active		
	16.14 ± 1.13		*L. major*		Active		
Acetogenin annonacinone	7.66 ± 0.77	ND	*L. donovani*		Active	ND	Villa-Nova et al. (2013)
	8.00 ± 1		*L. mexicana*		Active		
	6.72 ± 0.37		*L. major*		Active		
			Annona squamosa				
Alkaloid O-methyl-armepavine	23.3	25.4	*L. chagasi*		Active	3.42	Villa-Nova et al. (2011)
			RAW 264.7	79.7	Cytotoxic		
Acetogenin	26.4	25.3	*L. chagasi*	43.5	Active	1.64	Villa-Nova et al. (2011)
C_{37} trihydroxy adjacent bistetrahydrofuran			RAW 264.7		Cytotoxic		
			Annona glabra				
HAE of leaves	37.8 ± 0.1	ND	*L. amazonensis*	ND	Active		García et al. (2012)
			Annona senegalensis				
EE of leaves	10.8	ND	*L. donovani*	273.49	Active	25.32	Ohashi et al. (2018)
			JURKAT		Moderate cytotoxicity		
EE of stem cutting	27.8	ND	*L. donovani*	127.95	Active	4.60	Ohashi et al. (2018)
			JURKAT		Moderate cytotoxicity		
			Annona purpurea				
ME of bark	113.24 ± 1.2	ND	*L. donovani*		Moderate active	0.0008	Camacho et al. (2003)
			KB	0.0098	Cytotoxic		
H_2O of bark	289 ± 3.70	ND	*L. donovani*		Inactive	ND	Camacho et al. (2003)
			KB	> 500	Non cytotoxic		
ME of seed	28.57 ± 1.78	ND	*L. donovani*	7.81 ± 1.45	Active	0.27	Camacho et al. (2003)
			KB		Cytotoxic		
H_2O of seed	179.9 ± 4.1	ND	*L. donovani*	96.7 ± 3.9	Moderate active	0.53	Camacho et al. (2003)
			KB		Cytotoxic		
E_2 fraction of HAE leaves	0.961	ND	*L. panamensis*	124.02	Active	129.05	Cárdenas et al. (2005)
			U937		Moderate cytotoxicity		
			Annona cornifolia				
Extract	175	ND	*L. amazonensis*		Moderate active	0.196	De Toledo et al. (2011)
			VERO	34.33	Cytotoxic		

HAE: hydroalcoholic extract; HE: Hexane extract; EAE: ethyl acetate extract; ME: methanol extract; CE: chloroform extract; DCE: Dichloromethane extract; SB: stem bark; SW: stem wood; RB: root bark; KB: Human nasopharyngeal KB cells; RAW 264.7: Murine macrophage cells; PMBC: Peritoneal macrophage BALB-C; U937: Human monocytic cell lineage; PH8: *Leishmania amazonensis*; PP75: *Leishmania donovani*; M2903: *Leishmania braziliensis*; ND: Not determined. JURKAT: human acute T-cell leukemia cells

The hydroalcoholic leaf extract of *A. glabra* was active against *L. amazonensis* promastigotes (IC_{50}: 37.8 ± 0.1 µg/mL) [17]. The extracts obtained from the leaves and branches of *A. senegalensis* also showed activity against another strain of Leishmania (*L. donovani*; IC_{50} 10.8 µg/mL and 27.8 µg/mL respectively) [18]. However, the two samples were moderately cytotoxic for human T-cell of acute leukemia (JURKAT; CC_{50}: 273.49 µg/mL and 127.95 µg/mL respectively) [18] and the leaf extract showed best selectivity index (SI: 25.3; Table 1).

The methanol and aqueous extracts from *A. purpurea* bark and seed were evaluated against *L. donovani* promastigotes. The methanol extract from the seed showed better activity (IC_{50}: 28.57 ± 1.78 µg/mL) but was cytotoxic in nasopharyngeal cells. (KB; CC_{50}: 7.81 ± 1.45; IS: 0.27). However, the aqueous seed extract presented the best selectivity index (IC_{50}: 179.9 ± 4.1 µg/mL; CC_{50}: 96.7 ± 3.9 µg/mL; SI: 0.53; Table 1) [19]. The fraction E2 obtained from the hydroalcoholic leaf extract of *A. purpurea* was active against *L. panamensis* (IC_{50}: 0.961) and moderately cytotoxic in human monocyte cells, presenting a high selectivity index (U937; CC_{50}: 124.02 µg/mL; SI: 129.05; Table 1) [20].

The extract from *A. cornifolia* was moderately active in *L. amazonensis* (IC_{50}: 175 µg/mL) and cytotoxic in African green monkey kidney cells (VERO; CC_{50}: 34.33 µg/mL; SI: 0.196; Table 1) [21]. Other extracts from branches and leaves of *A. muricata* were active against promastigotes of *L. amazonensis, L. braziliensis* and *L. donovani* (Table 1) [22].

The ethyl acetate extracts from both the branch and the leaves showed better results in the 3 *Leishmania* species (branch: IC_{50}: 63.2 µg/mL; leaves: 25 µg/mL; Table 1) [22].

4 Discussion

Different species belonging to the *Annona* genus have popular use for leishmaniasis or wounds treatment [7, 10, 12]. However, there is the following question: this activity is related to the presence of acetogenins, or their alkaloids, or it is related to the synergism between these metabolites.

Previous study demonstrated annomontine alkaloid was the most active against *L. amazonensis* [12]. Alkaloids can interfere with tubulin polymerization or stabilize the DNA topoisomerase complex [23]. The biological activity of liriodenine can be attributed to the intercalation between neighboring base pairs of the DNA double helix [24, 25].

The oxo function induces cytotoxicity on precursor incorporation into DNA [25, 26]. Indeed, acetogenins binds to complex I of the mitochondrial electron transport chain [27, 28]. In addition, it inhibits ubiquinone-bound NADH oxidase [29–31]. Due to the differences in mechanisms of action, it is believed that there may be synergy to leishmanicide activity.

In the present review, although acetogenins were very active against promastigotes of different species of *Leishmania*, with an IC_{50} of less than 30 µg/mL [10, 16] corosolone and annonacinona were still active against the amastigote form [10]. In contrast, structural changes seem to interfere in the antileishmanial activity of alkaloids and this activity may be more pronounced depending on the parasite species [10, 12, 15].

If only antiparasitic activity is considered, this may suggest that acetogenins are more promising than alkaloids as leishmanicide. However, you must consider the toxicological aspects and the selectivity index (SI).

Unfortunately, most of the acetogenins isolated from *Annona* lack cytotoxicity studies, and preliminary results suggest that corossolone (SI = 2.08) and annonacinone (SI = 1.58) have a selectivity index of less than 10 [10]. However, additional genotoxicity, mutagenicity and in vivo studies need to be carried out to determine the safety of its use as a leishmanicide.

Another issue that needs to be analyzed is whether the fractionation contributes to antileishmanial activity. In the case of *A. muricata*, fractionation contributed significantly to biological activity, it also seems to contribute to selectivity [7, 22].

Nevertheless, for *A. crassiflora*, some extracts showed better antileishmanial potential than isolated substances [8, 14]. For *A. foetida*, alkaloid fractions appear to be promising for leishmaniasis treatment (Table 1) [12].

The fractionation of *A. purpurea* extract contributed to antileishmanial activity and high selectivity index, with the E2 fraction being a strong candidate for anti-leishmania drug, since this showed better anti-leishmania activity (IC_{50}: 0.961 µg/mL), moderate cytotoxicity, resulting in a selectivity index > 10 among the extracts, fractions and isolated substances evaluated from *Annona* species (IS: 129.05) [20].

5 Conclusion

Annona species are promising for the treatment of leishmaniasis, bearing in mind the importance of extract fractionation and alkaloids or acetogenins isolation, since many alkaloids and acetogenins have antiparasitic activity, which can be important tools against parasites drug resistant.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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