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Sanguinarine as an Antiparasitic against Helminths and Protozoa with Importance in Human and Veterinary Medicine: A Systematic Review

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Abstract

There is a constant search for new pharmacological alternatives, mainly of plant origin, for the treatment and control of parasites that compromise the health of humans and animals of economic importance. In this context, Sanguinarine (SA) stands out, an alkaloid with multiple pharmacological and biological properties, including antiparasitic properties. We sought to compile articles that explored plant extracts containing SA and/or SA isolated against helminths and/or protozoa with importance in human and veterinary medicine. This is a systematic review of the literature whose original articles were searched in electronic databases using the cross between health science descriptors and free terms between February and August 2023. Fifteen articles were found that report antiparasitic activity, *in vitro* and *in vivo*, against different species, such as *Trichinella Spiralis*, *Dactylogyrus intermedius*, *Toxocara canis*, trophozoites of *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*, *Leishmania* sp and *Schistosoma mansoni*. Furthermore, SA showed activity in lesions caused by parasites. The studies highlight the promising antiparasitic activity of SA against different species and genera of parasites with importance in human and veterinary medicine and we highlight the importance of continuing these studies that may include SA in the limited range of antiparasitic drugs.

Keywords: Human parasitology; Parasitology veterinary; Antiparasitic; Helminths; Protozoa.

1. Introduction

There is a constant search for new drugs for the treatment and control of parasitic infections that compromise human health and other animals with importance in veterinary medicine and the economy. However, the research and development of new drugs is a process with a high financial and time investment, which involves basic and applied research *in* vitro and *in vivo* screening and studies on toxicological safety and clinical studies (Andrade, Kümmerle and Guido, 2018). Furthermore, the sales price is not attractive for the pharmaceutical industry, especially for antiparasitics.

Worldwide, parasitic infections are responsible for serious human and veterinary public health problems. In the human population, they are endemic or epidemic infections prevalent in developing countries in Latin America, Africa and Asia. Due to population migration and climate change, these infections can affect populations in developed countries, such as North America and Europe (Pushpakom et al., 2029; Santos et al., 2020). They are infections that mainly affect populations with low political voice and economic visibilit and with little investment in research for new drugs, classifying these infections as Neglected et Diseases (Curico al., 2022; Dziduch, Greniuk and Wujec, 2022).

Parasitic infections of importance in veterinary medicine directly affect animal productivity, highlighting that in 2022 alone, approximately 500 million large ruminants were infected by some type of helminth, resulting in losses of more than US$ 3 billion worldwide (Dziduch, Greniuk and Wujec, 2022). In addition, studies have already reported the resistance of gastrointestinal nematodes and protozoa that live in the gills of fish to important classes of antiparasitics such as avermectins, milbemycins, benzimidazoles, and imidazothiazoles (Cezar et al., 2011), causing economic and in animal health problems (Zhang et al., 2013; Wang et al., 2010). In addition to the emergence of resistant strains of protozoa and helminths to conventional antiparasitics, producers and consumers are increasingly concerned about the presence of synthetic chemical residues in the meat and milk of animals for human consumption and the health of pets. This scenario encourages the search for new antiparasitic alternatives based on products of plant origin (Cezar et al., 2011; Caselani, 2014).

Compounds of plant origin are promising candidates for antiparasitic drugs due to their phytochemical variety that confers broad pharmacological and biological activity, in addition to low cost, low or absence of toxicity and cytotoxicity, and acceptable side effects when compared to compounds of synthetic origin (Fu, Guan and Wang, et al., 2018; Adinortey, Galyuon and Asamoah, 2018; Huang et al., 2020). Among the compounds from plant metabolism, alkaloids stand out, a general class of essential organic compounds belonging to the group of cyclic amines due to the presence of a heterocyclic ring in their molecular structure (Kishimoto et al., 2016; Bhambhani, Kondhare and Giri, 2021). In addition, they are known for their numerous pharmacological and biological properties and are extracted from seeds, roots, stems, flowers, leaves, and fruits, especially from the families ranunculaceae, papaveraceae, fangke, solanaceae, apocynaceae, rutaceae, leguminosae, and polygonaceae, as well as can also be extracted from fungi and bacteria (Heinrich, Mah, Amirkia et al., 2021; Singh and Sharma, 2018). The alkaloid Sanguinarine (SA), [13-methyl-(1,3)benzodioxol(5,6-c)-1,3-dioxolane(4,5-I)phenanthridinium], is a quaternary benzophenanthridine (QBAs) isolated from Sanguinaria canadensis, Poppy fumaria, Bocconia frutescens, Chelidonium majus and Macleya chordata with a wide variety of biological and pharmacological effects (Fu, Guan, Wang, 2018; Wu, 2020). The present study sought, through a systematic review of the literature, to compile original articles that explore the antiparasitic activity in the control and treatment of infections caused by helminths and/or protozoa with importance in human and veterinary medicine of plant extracts containing the SA among their metabolites or SA is isolated.

2. Methodology

The methodological procedures of this systematic literature review article are descriptive and qualitative in nature. A systematic review is a study method that aims to collect information selectively, with rigorous analysis and a critical and succinct look, in the search for demonstrating evidence on a specific question. Furthermore, it is characterized by a comprehensive, transparent and replicable methodology, in addition to being considered a more rational and less biased scientific investigation as a means of evidencing scientific data (Donato; Donato, 2019). The methodological path was through the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Metaanalyses), which consists of a checklist of items and the creation of a four-step flow diagram, whose purpose is to guide researchers in reporting their systematic reviews and meta-analyses (Galvão; Pansani; Harrad, 2015). Systematic literature review was carried out from February and August 2023. Original articles were searched from the following electronic databases: MEDLINE (International Literature in Health Sciences), SciELO (Electronic Library Online), LILACS (Latin American and Caribbean Literature on Health Sciences), and PubMed (National Library of Medicine). The research was carried out using the crossing between Health Sciences Descriptors (DeCS) and Free Terms (TL) in English, Spanish and Portuguese, to know: sanguinarine (TL), plant extract (DeCS), human parasitology (TL), parasitology veterinary (TL), antiparasitic(s) (DeCS), helminths (DeCS) and protozoa (DeCS), applying the Boolean operators AND/OR.

As inclusion criteria, we selected original articles that studied *in vitro* and *in vivo* antiparasitic activity of plant extracts with SA among its metabolites and isolated SA. Theses, dissertations and incomplete articles were excluded. There was no limitation for the year of publication. The first step was to the literature of the title and abstract of the articles to select those that met the objectives of the study and to exclude duplicate articles. For the composition of the final sample, all articles were selected independently by three researchers, all with experience in systematic review, natural products and human and veterinary parasitology.

Possible disagreements between researchers were discussed among the research group to determine the inclusion or exclusion of the article in question. The synthesis of the final data was carried out in a descriptive way and recorded in a summary table and the main results of the selected original articles were analyzed and discussed to construct the presentation of this review. Furthermore, to facilitate reader understanding and subsequent discussion with other articles, the results are presented in groups of parasites according to similar taxonomic.

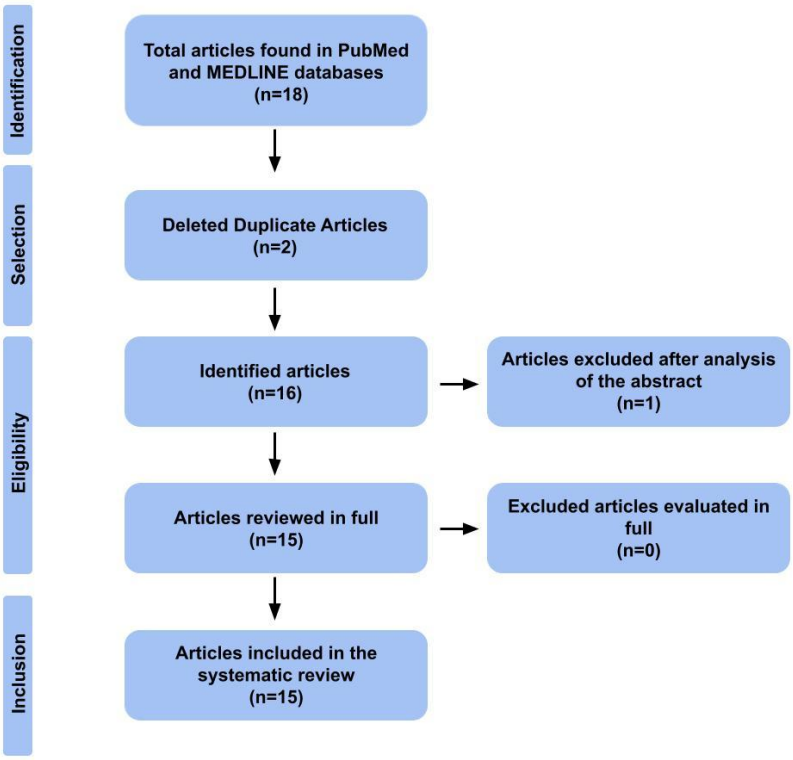
3. Results and discussion

3.1 Literature search and records general data

A total of 18 articles were recovered from databases, of these 2 were excluded due to being duplicates and 1 after accurate abstract reading. After full-text reading, 15 studies remained for final data extraction and systematic analysis (13 articles from Pubmed, 2 articles from MEDLINE and no articles were found in LILACS and SciELO) (Fig. 1). The data of the final included studies are given in Table 1. Through the search it was possible to compile articles that were published from 2001 to 2020, against different species of the protozoa and helminth, such as *Trypanosoma brucei, T. congolense, Dactylogyrus intermedius, Toxocara canis, Plasmodium* sp., *Ichthyophthirius multifiliis, Haemonchus contortus, Fasciola hepática, Teladorsagia circumcinta, Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis, Leishmania* sp., *Schistosoma mansoni and Trichinella Spiralis*. For better understanding, the presentation of results and their discussion will be displayed in topics grouped according to taxonomy of protozoa and helminths.

Botanical species synthesize a variety of important secondary metabolites, including SA, used as a source of protection against pests and parasites. Different solvents are used to obtain crude extracts and are also used for the fractionation and isolation of secondary metabolites according to their polarities (Hoste et al., 2006; Santos et al., 2020; Bhambhani, Kondhare and Giri, 2021; Chuo et al., 2022). In the crude extract, different phytochemical components are present, since proteins, fatty acids, polysaccharides, saponins, alkaloids, tannins, flavonoids, and terpenes. It is known that extracts and isolated molecules can present different biological activities. Thus, in addition to the phytochemical characterization, it is necessary to understand whether the biological activity is derived from the association between the different components or whether it is due to isolated fractions or molecules (Alvarez-Mercado et al., 2015). In this context, given the side effects of conventional antiparasitics and the resistance and/or tolerance of parasite strains, in recent years many studies have explored plant extracts, mainly those used in traditional medicine (Carvalho et al., 2012; Paula et al., 2019; Sachdeva et al., 2020).

Figure 1: Flowchart of the study selection process



Source: Own Authorship

Table 1: Summary table of articles reporting the activity of plant extracts containing Sanguinarine (SA) among its metabolites and/or isolated SA against parasites with importance in human and veterinary medicine.

Authors, year	**Title**	**Purpose**	**Test**	**Main results**
Mersch johann et al, 2001.	*In vitro* effect of alkaloids on bloodstream forms of *Trypanosoma brucei* and *t. congolense*	Evaluate the effect of alkaloids on the protozoan *Trypanosoma brucei* and *T. congolense*	*in vitro*	• SA showed trypanocidal activity against *Trypanosoma brucei* with an ED_{50} (50% effective dose) of 1.9 μM, activity similar to that of anti-trypanosome drugs, but showed no action against *T. congolense.* • SA showed cytotoxicity against human HL60 cells (ED_{50} values of 1.4 μM).
Satou et al, 2002.	Inhibitory Effect of Isoquinoline Alkaloids on Movement of Second-Stage Larvae of *Toxocara canis*	Screen isoquinoline alkaloids for nematicidal activity against *Toxocara canis* larvae.	*in vitro*	• SA showed particularly strong nematicidal activity RM:5863 mmol/l (Relative Mobility). • SA showed high cytotoxicity in human HL60 cells (ED_{50} values of 0.560 mmol/l).
Calzada; Yépez-Mulia b; Aguilar, 2006.	*In vitro* susceptibility of *Entamoeba histolytica* and *Giardia lamblia* to plants used in Mexican traditional medicine for the treatment of gastrointestinal disorders	Evaluate the methanol extract of 26 plants used in traditional Mexican medicine for antiprotozoal activity against trophozoites of *Entamoeba histolytica* and *Giardia lamblia.*	*in vitro*	• *Bocconia frutescens* extract showed moderate activity against both microorganisms: *Entamoeba histolytica* (ED_{50} of 96.4 -g/ml) and *Giardia lamblia* (ED_{50} of 79.32 **μ**g/ml).

Calzada; Yépez-Mulia b; Tapia-Contreras, 2007.	Effect of Mexican medicinal plant used to treat trichomoniasis on *Trichomonas vaginalis* trophozoites	To evaluate the crude methanolic extract of 22 Mexican medicinal plants with antitrichomonal activity against trophozoites of *Trichomonas vaginalis*	*in vitro*	• *Bocconia frutescens* extract showed moderate antitrichomonal activity with an ED_{50} of 30.9 **µ**g/ml.
Rosenkran; Wink, 2008.	Alkaloids Induce Programmed Cell Death in Bloodstream Forms of Trypanosomes (*Trypanosoma b. brucei*)	Analyzed the potential of 55 alkaloids for inducing programmed cell death in *Trypanosoma brucei* by measuring DNA fragmentation and changes in mitochondrial membrane potential.	*in vitro*	• SA showed trypanocidal activities against *T. brucei* with ED_{50} of 1.9 µM. • SA induces programmed cell death (ED_{50}: 4.8 µM) in *T. brucei* and disturbance of membrane fluidity and DNA intercalation. • SA showed cytotoxicity (ED_{50}: 1.4 µM) on human leukemia cells (Jurkat APO-S, HL60).
Yao et al, 2010.	Effect of sanguinarine from the leaves of *Macleaya cordata* against *Ichthyophthirius multifiliis* in grass carp (*Ctenopharyngodon idella*)	Perform bioactivity-guided isolation applied to the ethanolic extract of *Macleaya cordata* leaves to provide active compounds with antiparasitic efficacy against *Ichthyophthirius multifiliis*.	*in vitro* *in vivo*	• SA, *in vitro*, generated severe lesions in the structure of trophozoites of *I.multifiliis* after 4h of treatment. With ED_{50} of 0.437 mgl^{-1} and ED^{90} of 0.853 mgl^{-1}. • SA, *in vivo*, leading to a significant dose-dependent decrease of *I.multifiliis* in the gills.
Wang et al, 2010.	*In vivo* anthelmintic activity of five alkaloids from *Macleaya microcarpa* (Maxim) Fedde against *Dactylogyrus intermedius* in *Carassius auratus*	Perform fractionation guided by monitored bioassay to investigate the anthelmintic activity of *Macleaya microcarpa* against *Dactylogyrus intermedius*.	*in vivo*	• Pure presents anthelmintic efficacy of 100% at a concentration of 0.7 mgl^{-1} and ED_{50} of 0.37 mgl^{-1}. • SA in the ethanol extract showed ED_{50} of 121.70 mgl^{-1}

Chinchilla-Carmona et al, 2012.	*In vitro* antimalarial activity of extracts of some plants from a biological reserve in Costa Rica	Evaluate fresh and dry extracts of roots, bark, leaves, flowers, and fruits of 25 plants from a biological reserve in Costa Rica to investigate the presence of substances with antimalarial activity.	*in vitro*	• ED_{50} of the dry extract of flowers, unripe fruit, mature fruit and young leaves of *B. frutescens* were 16.9, 5.5, 8.8 and 17.2 **µ**g/mL, respectively. • ED_{50} of fresh extract of bark, flowers, unripe fruit, mature fruit, young leaves, mature leaves, and root of *B. frutescens* were 5.9, 2.8, 2.4, 4.6, 15.2, 2.2, and 2.6 **µ**g/mL, respectively.
Zhang et al., 2013.	Effects of praziquantel and sanguinarine on expression of immune genes and susceptibility to *Aeromonas hydrophila* in goldfish (*Carassius auratus*) infected with *Dactylogyrus intermedius*	The changes of expression of selected immune genes (CCL-1, CXCL-8, IL-1β-1, IL-1β-2, TNFα-1, TNFα-2 and TGF-β) in gill, kidney and spleen following bath administration of these antiparasitic	*In vivo*	• SA up-regulated to varying degrees of CXCL-8, IL-1β-1, IL-1β-2, TNFα-1 and TNFα-2 in gill, kidney and spleen. • SA decreased the CCL-1 expression in gill while increased it in kidney and spleen. • SA decreases susceptibility to *A. hydrophila.*
Zhang; Coutas, 2013.	Identification of plumbagin and sanguinarine as effective chemotherapeutic agents for treatment of schistosomiasis	To describe schistosomicidal activities in plumbagin and sanguinarine and integumentary changes observed in worms after treatment.	*in vitro*	• All worms were killed by SA in 6h at a concentration of 50 µM. • SA significantly damaged the integument of the worm. It resulted in severe erosion and disintegration of the integumentary surface between the tubercles.
Acharya; Hildreth; Reese, 2014.	*In vitro* screening of forty medicinal plant extracts from the United States Northern Great Plains for anthelmintic activity against *Haemonchus contortus*	To use the *Haemonchus contortus* egg hatching assay (EHA) and larval migration assay (LMA) to evaluate the nematicidal activity of methanol extracts from 40 plants from the Great Plains of the northern United States.	*in vitro.*	• *Sanguinaria canadensis* root extract diluted in DMSO inhibited 98.5% of EHA. • *Sanguinaria canadensis* root extract diluted in MOPS buffer inhibited 96.5% of EHA.
Chi	Actividad contra *Leishmania* sp.	Research and characterize active	*in vitro*	• Fresh extract of the bark, flowers, immature fruit, mature fruit, young leaves,

nchilla-Carmona et al, 2014.	(Kinetoplastida: Trypanosomatidae) de plantas en una Reserva Biológica de Costa Rica	chemical components in Costa Rican plants with potential activity against *Leishmania* sp.		and root *B. frutescens* presented ED_{50} of 9.7, 56.9, 7.5, 6.3, 30.3 and 6.5 **µ**g/mL, respectively. ● Dry extract of the bark, flowers, immature fruit, mature fruit, mature leaves, young leaves, and root *B. frutescens* presented ED_{50} of 2.8, 38.1, 12.5, 6.4, 66.7, 10.8, and 3.5 **µ**g/mL, respectively.
Alvarez-Mercado et al, 2015.	*In vitro* antihelmintic effect of fifteen tropical plant extracts on excysted flukes of *Fasciola hepatica*	To evaluate the anthelmintic effect of the extract of fifteen plants from Veracruz - Mexico against *Fasciola hepatica.*	*in vitro*	● *B. frutescens* extract was 100% effective at a dose of 125 mg/L.
Esteban-Balleteros et al, 2019	*In vitro* anthelmintic activity and safety of different plant species against the ovine gastrointestinal nematode *Teladorsagia circumcincta*	Evaluate anthelmintic activity through egg hatching assay (EHA), as well as the safety of aqueous and methanolic extracts obtained from 9 plants using gastrointestinal nematodes (GINs).	*in vitro*	● Model GIN was the parasite *Teladorsagia circumcinta.* ● Aqueous and methanolic extract of *Chelidonium majus* induced a 100% reduction in egg hatching at a concentration of 50 mg/ml.
Huang et al, 2020.	Sanguinarine has anthelmintic activity against the enteral and parenteral phases of *Trichinella* infection in experimentally infected mice	To analyze the lethal effect of sanguinarine against adult worms, newborn larvae, and muscle larvae (*in vitro*) and pre-adult stages, migratory larvae, and encysted larvae (*in vivo*) of *Trichinella spiralis*. In addition, they investigated the number of goblet cells and serum	*in vivo* *in vitro*	● Antiparasitic effect of SA *in vitro*: ○ Lethal effect on muscle larvae was dose-dependent, with a high mortality rate in 24h at concentrations of 16 to 30 mg/L of SA. ○ Lethal effect on newborn larvae was dose-dependent, with a 100% mortality rate at a concentration of 3 mg/L in 24. ○ Strong lethal effect on adult worms at a concentration of 15 mg/L. ● Antiparasitic effect of SA *in vivo*: ○ The pre-adult worm rate was reduced by 37.2% and 36.9% at doses of 70

		levels of reactive oxygen species (ROS).		and 80 mg/kg, respectively. ○ The rate of migratory larvae was reduced by 26.4% and 47.5% at doses of 80 and 100 mg/kg. ○ The rate of encysted larvae was reduced by 31.7% and 42.3% at doses of 150 and 200 mg/kg, respectively. ● SA severely damaged the cuticle of the adult worm. The adult male showed a collapse in the leaflet and reproductive pores. ● SA significantly reduces inflammatory cells and pathological changes at the intestinal level. ● ROS levels were significantly higher in mice that received SA.

Source: Own Authorshi

3.2 Protozoa

3.2.1 Filo Sarcomastigoporae

Entamoeba histolytica, *Giardia lamblia* and *Trichomonas vaginalis*

Bocconia frutescens stands out for presenting different biological and pharmacological activities attributed to its secondary metabolites, including SA. Among protozoa, the methanolic extract of leaves of *B. frutescens* showed moderate activity *in vitro* against *E. histolytica* and *G. lamblia* with ED_{50} of 96.4 μg/ml and 79.32 μg/ml, respectively (Calzada et al., 2006). The methanolic extract of *B. frutescens* leaves also demonstrated action against *T. vaginalis*, with ED_{50} of 30.9 μg/ml (Calzada et al., 2007). In both studies, the authors report that the action against these protozoa is attributed to the SA alkaloid through its toxicity and genotoxicity, as reported by Ansari et al. (2006). Furthermore, other alkaloids, isolated from plant species, showed activity on the viability and infectivity of *E. histolytica*, *Giardia lamblia* and *T. vaginalis* trophozoites (Mehriardestani et al., 2017; Díaz-Godínez et al., 2020; Al-Jaber et al., 2021; Villegas-Gómez et al., 2021; Carrero et al., 2023).

3.2.2 Family Trypanosomatidae

Genus Trypanosoma and Leishmania

Currently, there is a limited arsenal of drugs used in the control and treatment of trypanosomiasis and leishmaniasis, which have high production costs, are difficult to acquire and distribute to health centers in endemic locations and have high toxicity and serious side effects, factors that contribute to low adherence to complete treatment of those infected and the imminent maintenance and spread of these parasitic infections. Furthermore, studies have already reported the emergence of strains that are resistant and/or tolerant to recommended drugs. In this context, the World Health Organization (WHO) encourages and recommends research into new alternatives for the control and treatment of these parasites.

Merschjohann et al. (2001) and Rosenkranz and Wink (2008) explored the effect of alkaloids, including SA, on *Trypanosoma* sp. SA exhibited trypanocidal activities on *T. brucei* with ED_{50} values (dose that produces an effect in 50%) of 1.9 μM, activity similar to that of conventional antitrypanosomal applied in clinical medicine, but showed no action against *T. congolense* (Rosenkranz and Wink; 2008). In the studies by Rosenkranz and Wink (2008), 55 alkaloids were evaluated against *T. brucei* through the potential of inducing programmed cell death (PCD), deoxyribonucleic acid (DNA) fragmentation, and changes in mitochondrial membrane potential. In this study, SA caused disruption of membrane fluidity and DNA intercalation, in addition to inducing PCD (ED_{50} 4.8 μM) and was cytotoxic (ED_{50} 1.9 μM) against *T. brucei*. In both studies, the authors highlighted that SA inhibited the growth and development of blood forms of *T. brucei* and point out that alkaloids, especially SA, are important chemical prototypes for researching new antitrypanosomal. Recent studies highlight alkaloids as candidates for new drugs against *T. cruzi*, etiological agent of American trypanosomiasis known as Chagas disease. In this screening, the alkaloids demonstrated promising results with an effective trypanocidal effect at low concentrations, in addition to low toxicity and cytotoxicity and being as effective as the conventional drug (Musikant et al., 2019; Martinez-Peinado et al., 2020; Martinez-Peinado et al., 2022).

Chinchilla-Carmona et al., (2014) evaluated the activity against *Leishmania* sp. from the hydroalcoholic extract of different parts of *B. frutescens*, where the fresh extract of flowers and young leaves showed greater activity with ED_{50} of 56.9 and 30.3 μg/mL, respectively. While the dry extract of flowers and mature leaves showed higher activity with ED_{50} of 38.1 and 66.7, μg/mL, respectively. In contrast, Jansen (2011) explored the crude extract of *B. frutescens* seeds against *L. tarentolae* reaching an ED_{50} of 2.61 μg/mL. The fractionation identified four benzophenanthridine compounds with leishmanicidal activity with ED_{50} values between 10 - 20 μg/mL. Recently, seropositivity for *L. tarentolae*, species isolated from reptiles, was reported in endemic areas for leishmaniasis through molecular diagnosis in humans and dogs, highlighting interest in interactions between these animals and reptile hosts in maintaining of leishmaniasis (Mendoza-Roldan et al., 2022).

The genus *Leishmania* presents widespread species of protozoa that infect a variety of hosts through sandfly bites, causing an infection called leishmaniasis. This parasite is endemic to the Mediterranean basin, South America and Central and Southwest Asia, being the most widespread Leishmania species. In humans, leishmaniasis can affect the mouth mucosa, local or disseminated cutaneous and visceral. In dogs, especially domestic, they can be infected by several species of *Leishmania*, which also primarily cause visceral leishmaniasis, but can also cause cutaneous or mucosal forms. Canine leishmaniasis is a multisystemic disease that affects dogs, the main reservoir of *L. infantum*. Given the high prevalence and incidence of leishmaniasis in humans and dogs, several research groups are looking for pharmaceutical alternatives for the control, treatment and prevention of leishmaniasis and studies highlight the leishmanicidal properties of alkaloids (Paula et al., 2019; Lorenzo et al., 2020; Socorro et al., 2022; Naik et al., 2022).

3.2.3 Genus *Plasmodium*

Although some studies report plant extracts containing alkaloids or isolated alkaloids as antimalarials against different evolutionary phases of *Plasmodium* sp (Szabó et al., 2021; Amelia et al., 2021; Oluyori et al., 2022), in our research we found only one study that explored different types of *B. frutescens* extracts that presented SA as a constituent. Chinchila-Carmona et al, (2012) was the only one that had SA as a constituent in its chemical composition. In this study, hydroalcoholic extract of different parts of *B. frutescens* showed activity against the protozoan *P. bergheiso*, while the dry extract of flowers and young leaves showed greater activity with ED_{50} of 16.9 and 17.2 μg/mL, respectively. The fresh extract of young leaves showed the highest activity with an ED_{50} of 15.2 μg/mL.

3.2.4 Order Hymenostomatida

Ichthyophthirius multifiliis

The ciliate *I. multifiliis* is one of the most pathogenic protozoa in fish kept in captivity. In aquaculture, SA from the leaves of *Macleaya cordata* showed *in vitro* e *in vivo* promising antiparasitic against load of *I. multifiliis* on the gills of *Ctenopharyngodon idella* (grass carp) (Yao et al., 2010). SA isolated from *M. chordata* leaves caused 90% mortality in *I. multifiliis* trophozoites at a concentration of 9.0 mg l^{-1}, in addition to causing effect on the trophozoite stages. It led to severe alterations in the parasite's structure after 4 h treatment. All of the parasites in treatment group were severely damaged; the outer cell membrane of *I. multifiliis* was destroyed, macronucleus was invisible, the cilia could not be recognized, and the cytoplasm of the trophozoites was characterized by vacuoles. *In vivo*, the treatment with SA lead to a significant dose-dependent decrease in the number of *I.multifiliis* on the gills compared to the controls. When the concentrations of SA were 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9 mgl−1, the numbers of parasites on the gills were reduced by 16.1%, 17.3%, 32.9%, 53.9%, 75.3%, 82.3%, 89.4% and 96.8%, respectively (Yao et al., 2010). A substantial reduction of the parasite burden, as shown in this study, led to the recovery of the fish and paved the way for the development of protective host immunity and could be seen as a alternative for aquaculture and the environment than the use of some chemicals.

I. multifiliis is a holotrichous protozoan that invades the gills and skin surfaces of freshwater fish causing the disease ichthyophthiriosis, commonly referred to as ich or white spot. It is one of the most common and serious parasitic diseases of freshwater fish in aquaculture, and can cause morbidity and high mortality in most species of freshwater fish worldwide and can result in heavy economic losses for aquaculture, by reducing the breathing capacity and promoting secondary bacterial or viral infections (Abu-Elala et al., 2021). Obligate parasite mature embedded in the epithelium where they form visible white spots (trophozoites). The mature trophozoite leaves the fish and falls to the bottom or attaches to vegetation, where a cyst forms in which 250 to 1,000 infective units, called trophozoites, are produced Abu-Elala et al., 2021. However, all compounds do not have widespread use because of its lower efficacy and problems associated with human handling. SA promote animal growth by increasing feed intake and decreasing aminoacid degradation from decarboxylation. As reported by Rawling et al. (2009) low levels (25-100 mgkg−1) of Sangrovit® (The main component is sanguinarine) had a positive effect on tilapia growth performance with no apparent effects towards carcass composition, hepatic function, or health status. The food supplement Sangrovit® (Phytobiotics, Eltville, Germany), produced from the extract of *S. canadensis*, *C. majus,* or *M. cordata*, has SA as its main constituent. When produced from *M. cordata* extract (3.5% of its composition) it contains at least 1.5% of SA, the alkaloid responsible for its pharmacological effects. This supplement is indicated for body weight gain through its effect on improving palatability caused by increased food intake, results reported in piglets (Kantas et al., 2015), poultry (Lee et al., 2015), fish (Rawling et al., 2009), and sheep (Estrada-Ângulo et al., 2016). Furthermore, it does not caused hematological and biochemical changes in calves (Matulka et al., 2022).

3.3 Helminths

3.3.1 *Nematodes*

Haemonchus contortus, Teladorsagia circumcinta, Trichinella spiralis, Toxocara canis

Acharya, Hildreth; Reese (2014) evaluated *in vitro* the methanolic extract of the root of *S. canadensis* against *H. contortus*, which was able to reduce egg hatching by more than 95% at a concentration of 50 mg/mL but had no effect on larval migration. A similar result was observed with the aqueous and methanolic extract of *C. majus* against *T. circumcinta*, which resulted in 100% inhibition of egg hatching at a concentration of 50 mg/ml (Esteban-Ballesteros et al., 2019). *H. contortus* (barber's pole worm) and *T. circumcincta* (brown stomach worm), are the most economically important pathogenic nematodes infecting small ruminants (sheep and goats) worldwide. These blood-feeding strongylid nematodes where they infect the fourth stomach (abomasum) reducing animal production and causing anemia, edema, and associated complications often leading to death (Palevich et al., 2020).

Trichinellosis, also called trichinosis, is caused by consuming undercooked or raw meat (usually pork). Trichinella spiralis species is the common cause of human disease, but other mammals like wild carnivores and horses can be reservoirs of infection. It can cause symptoms varying from generalized fever, abdominal pain, diarrhea, nausea, vomiting, myalgia to more severe like myocarditis and encephalitis (Rawla and Sharma, 2023). Huang et al. (2020) reported the action of SA against different evolutionary stages of *T. spiralis*. *In vitro* SA on newborn larvae, muscle larvae, and adult worms caused 100% mortality at concentrations of 3, 30, and 15 mg/L, respectively. Furthermore, exposure to SA caused profound tegumentary alterations with emphasis on necrosis, the leaflet cross-patch device collapsed and the reproductive pores and mastoids were covered.

While in mice treated with 70 mg/kg against adult worms, 100 mg/kg against migratory larvae, and 200 mg/kg against encysted larvae, SA caused a reduction of 37.2%, 47.5%, and 42.3% in worm load, respectively. Furthermore, the mice showed increased levels of Reactive Oxygen Species (ROS) and histopathological improvement of intestinal tissue through reduced inflammation and increased goblet cells. Indeed, in addition to SA being absorbed and eliminated rapidly (24h) (Wu et al., 2020). SA is reported to increase small intestinal villi and crypts (Huang et al., 2020). The authors believe that the action of SA on *T. spiralis* is attributed to the production of ROS since the increase in ROS has also been reported in studies with planaria (Balestrini et al., 2017; Pirotte and Stevens, 2015).

Few anthelmintics are effective against nematodes in diseases caused by the migration of larvae into human tissues, infections that are generally very difficult to cure. Satou et al. (2002) evaluated *in vitro* the effect of isoquinoline alkaloids, including SA, against second-stage larvae of *T. canis*. In this study, SA was obtained from the hydrolysis of 6-methyl dihydro extracted from *M. cordata* leaves. The results show that SA caused reduction in relative mobility in 50% of the larvae at of 58 ± 3 μmol/l, a similar result to pyrantel pamoate (46 ± 3 μmol/l), drugs of choice with action only against adult worms. These results demonstrate the difficulty in identifying an effective remedy for larva migrans.

3.3.2 *Platyhelminthes*

Dactylogyrus intermedius, Fasciola hepática, Schistosoma mansoni

During the search for new antiparasitics compounds, Wang et al. (2010) performed *in vivo* bioassays with the *Macleaya microcarpa* extract to isolate active compounds and subsequent anthelmintic evaluation against *D. intermedius* in *Carassius auratus* (Goldfish). *D. intermedius* can cause inflammation of the gills and increased mucus secretion and respiration, resulting in serious damage to the host, such as reduced growth performance, loss of appetite and high mortality and economic losses. Among the compounds, SA reduced 100% of parasites in the gills at a concentration of 0.7 mgl^{-1}, making it the most effective compound in the study. The authors believe that the antiparasitic action of SA against *D. intermedius* is associated with its ability to break DNA strands, a fundamental characteristic in the antitumor action of SA by inducing apoptosis. Zhang et al. (2013) also studied the action of SA on *D. intermedius*, however, sought to analyze the expression of genes related to the immune system associated with the use of antiparasitic drugs in aquaculture, in which SA modulated the expression of several immune genes of CCL-1, CXCL-8, IL-1β-1, IL-1β-2, TNFγ-1, TNFγ-2 and TGF-γ in the gills, kidneys, and spleen of *C. auratus*. SA decreased the CCL-1 expression in gill while increased it in kidney and spleen. Overall, the results indicate that SA modulates the immune related genes in goldfish and these may, to some extent, affect their ability to resist bacterial pathogens. Penciková et al. (2012) report that SA showed action on the expression of pro-inflammatory cytokines CCL-2, IL-6, and IL-1 in the human monocytic leukemia cell line, cytokines responsible for the recruitment, activation, and migration of monocytes (CCL- 2), induction of protein synthesis in the acute phase (IL-6), and macrophage recruitment (IL-1).

F. hepatica is a worldwide distributed parasite that can be found in the liver and bile ducts, where it produces eggs that are excreted in feces, which can contaminate water or vegetables and infect and affect cattle, sheep, goats, pigs, horses, rabbits and also humans. Production animals can present with myalgia, nausea, anorexia and diarrhea. Early complications can be seen with high parasite load and include ascites, hemobilia, subcapsular hematomas, and severe parenchymal hepatic necrosis. In the chronic course, there may be epigastric and right upper quadrant pain, nausea, vomiting, diarrhea, hepatomegaly, jaundice and growth retardation. Fasciolosis is responsible for major losses in the quality of life of production animals and economic losses in livestock farming due to the decrease in milk and meat production, low reproductive efficiency and cause of mortality and high cost of controlling this parasitic disease. Furthermore, serious accidental human infections can cause serious health problems resulting from obstruction of the bile and hepatic ducts, resulting in jaundice, pancreatitis, inflammation and fibrosis of the bile and hepatic ducts, ascites, and cirrhosis (Ngcamphalala, Malatji, Mukaratirwa, 2022; Bahmaninejad et al., 2019; Good and Scherbak, 2023). Alvarez-Mercado et al. (2015) explored *B. frutescens* against *Fasciola hepatica*. In this study, the extract, obtained by successive extraction in hexane, ethyl acetate, and methanol,

achieved 100% efficacy at a concentration of 125 mg/L. Furthermore, when subjected to phytochemical analysis, the extract revealed strong positivity for alkaloid SA.

Zhang and Coultas (2013) reported *in vitro* action of SA against adult worms of *S. mansoni*, with a mortality of 100% in 6 h of incubation at concentrations of 30 and 50 μM, in addition to causing erosion and disintegration of the integument. The mechanism of action of SA on *S. mansoni* has not yet been fully elucidated. Still, it is known that SA *in vivo* and *in vitro* studies has a similar mechanism of action to Praziquantel, a drug recommended by the WHO for the treatment and control of schistosomiasis. SA acts on Na+/K+-ATPase, a transmembrane protein with the function of maintaining the resting potentials and regulating the transport of extracellular sodium and intracellular potassium and calcium, in addition to regulating the synthesis of reactive oxygen species in mammalian cells (Singh and Sharma, 2018; Balestrini et al., 2017). Ca^{2+} ion is essential for muscle contraction, since there is deregulation of Na+/K+-ATPase mediated by SA, there is an influx of Ca^{2+} into cells and consequently, muscle contraction in *S. mansoni* when exposed to AS (Mendonça-Silva et al., 2006; Aragon et al., 2009).

Schistosomiasis is an important neglected tropical disease associated with severe and irreversible liver damage and high mortality in hundreds of millions of people around the world. There are four species responsible for intestinal schistosomiasis, namely: *S. mansoni*; *S. japonicum*, *S. mekongi* and *S. intercalatum*; and *S. haematobium* causes urinary schistosomiasis. They are endemic species in regions of Africa, Asia, the Middle East and South America, with greater prevalence in poor rural areas and an accelerated increase in cases in urban áreas (Jenkins-Holick and Kaul, 2013; Silva et al., 2021.

4. Conclusion

Finally, studies demonstrate that SA has a wide variety of biological and pharmacological applications, and it is not surprising that it also has antiparasitic activity against helminths and prtorozoans. Given these properties, SA is a molecule that has the potential to continue research on the parasite species presented here as well as other species. In particular, we highlight the need for studies in in vivo experimental models, since most studies were carried out in vitro. Furthermore, new approaches are needed in therapeutic protocols, use of pharmaceutical formulations and elucidation of the mechanism of action of SA on biological targets in parasites. This can certainly contribute to the future development of a new medicine for the treatment, control and prevention of parasites with importance in human and veterinary medicine.

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