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ANTIVENOM POTENTIAL OF THE GENUS JATROPHA L. (EUPHORBIACEAE): A SYSTEMATIC REVIEW OF PRECLINICAL EVIDENCE ON NATURAL INHIBITORS OF ANIMAL VENOMS

POTENCIAL ANTIVENENO DO GÊNERO JATROPHA L. (EUPHORBIACEAE): UMA REVISÃO SISTEMÁTICA DAS EVIDÊNCIAS PRÉ-CLÍNICAS SOBRE INIBIDORES NATURAIS DE VENENOS ANIMAIS

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ABSTRACT

Envenomation by venomous animals remains an important public health problem in tropical regions, especially among rural and socially vulnerable populations. Medicinal plants have traditionally been used as complementary resources to manage bites and stings. Species of the genus *Jatropha* L. (Euphorbiaceae), popularly known in Brazil as "pinhão", are used in folk medicine for inflammation, pain, wound healing, and symptoms associated with envenomation. This systematic review synthesized the preclinical evidence on the antivenom potential of Jatropha species, emphasizing ethnopharmacological relevance, Brazilian studies, and experimental models involving animal venoms. Studies on the antivenom activity of *Jatropha*-derived products were retrieved from PubMed, Embase, ScienceDirect, Web of Science, and CAPES Periodicals, without date restrictions, following the PICO(S) framework. Eligible studies included preclinical investigations using extracts, fractions, latex, powders, or formulations obtained from Jatropha species. Exclusively in silico studies were excluded. From 541 records, 13 studies were included, covering six Jatropha species. The evidence indicates growing interest in validating *Jatropha* as a source of natural venom inhibitors. *Jatropha*-derived products inhibited major venom enzymes, including proteases, phospholipases A_2, and hyaluronidases, mainly in snake and scorpion venom models. They also attenuated venom-induced inflammation, nociception, edema, hemorrhage, myotoxicity, dermonecrosis, fibrinolysis, and defibrinogenation. Preclinical evidence supports Jatropha species as promising sources of bioactive compounds capable of reducing venom-induced toxic effects. These findings reinforce the value of ethnomedicinal knowledge and bioprospecting in the search for new anti-venom candidates. However, clinical translation remains limited by the lack

of phytochemical standardization, mechanistic and toxicological characterization, and translational validation.
Keywords: Jatropha; Folk Medicine; Animal Envenomation; Antivenom; Venom Inhibitors; Ethnopharmacology.

RESUMO

O envenenamento por animais peçonhentos permanece como um importante problema de saúde pública em regiões tropicais, especialmente entre populações rurais e socialmente vulneráveis. Plantas medicinais têm sido tradicionalmente utilizadas como recursos complementares no manejo de mordidas e picadas. Espécies do gênero *Jatropha* L. (Euphorbiaceae), popularmente conhecidas no Brasil como "pinhão", são empregadas na medicina popular para inflamação, dor, cicatrização de feridas e sintomas associados ao envenenamento. Esta revisão sistemática sintetizou as evidências pré-clínicas sobre o potencial antiveneno de espécies de *Jatropha*, com ênfase na relevância etnofarmacológica, nos estudos brasileiros e nos modelos experimentais envolvendo venenos animais. Estudos sobre a atividade antiveneno de produtos derivados de *Jatropha* foram recuperados nas bases PubMed, Embase, ScienceDirect, Web of Science e Periódicos CAPES, sem restrição de data, seguindo a estratégia PICO(S). Os estudos elegíveis incluíram investigações pré-clínicas utilizando extratos, frações, látex, pós ou formulações obtidos de espécies de *Jatropha*. Estudos exclusivamente *in silico* foram excluídos. A partir de 541 registros, 13 estudos foram incluídos, abrangendo seis espécies de *Jatropha*. As evidências indicam crescente interesse na validação de *Jatropha* como fonte de inibidores naturais de venenos. Produtos derivados de *Jatropha* inibiram importantes enzimas de venenos, incluindo proteases, fosfolipases A_2 e hialuronidases, principalmente em modelos com venenos de serpentes e escorpiões. Também

atenuaram inflamação, nocicepção, edema, hemorragia, miotoxicidade, dermonecrose, fibrinólise e desfibrinogenação induzidas por venenos. As evidências pré-clínicas sustentam as espécies de *Jatropha* como fontes promissoras de compostos bioativos capazes de reduzir os efeitos tóxicos induzidos por venenos. Esses achados reforçam o valor do conhecimento etnomedicinal e da bioprospecção na busca por novos candidatos antiveneno. No entanto, a translação clínica ainda é limitada pela ausência de padronização fitoquímica, caracterização mecanística e toxicológica, além de validação translacional.
Palavras-chave: Jatropha; Medicina Popular; Envenenamento por Animais Peçonhentos; Antiveneno; Inibidores de Venenos; Etnofarmacologia.

1. INTRODUCTION

Envenomation caused by animal stings and bites is a frequent public health problem, particularly in developing countries, where it disproportionately affects socioeconomically vulnerable populations and is recognized among the main neglected tropical diseases (WHO, 2007). These events result from exposure to venoms or toxins delivered through the bites or stings of clinically important animals, including snakes, spiders, scorpions, bees, ants, certain fish species, and cnidarians. They are associated with high morbidity and mortality, often leading to severe health complications and long-term sequelae (Jenkins et al., 2021). Snakebite envenoming alone is estimated to affect between 1.2 and 5.5 million people annually, causing more than 125,000 deaths (Afroz et al., 2024). Scorpion stings also represent a major concern, with more than 1.2 million cases and over 3,000 deaths reported annually, with relevance in pediatric populations (Vasconez-Gonzalez et al., 2025). Other accidents, such as spider bites and lonomism caused by the urticating bristles of caterpillars of the genus *Lonomia*, are also of concern, especially in biodiverse countries such as Brazil (Favalesso et al., 2021).

In Brazil, envenomation by venomous animals represents a substantial public health issue, with a high number of cases reported annually, predominantly affecting vulnerable populations in rural and peri-urban settings (Menon et al., 2025; Pucca et al., 2025). This scenario reflects the broader characteristics that justify the classification of these accidents as neglected tropical diseases: they mainly affect marginalized communities with limited access to healthcare, are frequently underreported due to weak surveillance systems, and impose a considerable burden on public health resources (WHO, 2023). Furthermore, Brazil's extensive territory, ecological heterogeneity, and socioeconomic inequalities contribute to marked regional disparities in incidence rates, reinforcing the need for region-specific prevention and control strategies (Chippaux, 2015). Consequently, morbidity and mortality rates, as well as temporary or permanent sequelae associated with these accidents, remain high and continue to place a substantial burden on healthcare systems.

Antivenom therapy is currently the main treatment for envenomation caused by venomous animals. It consists of administering antivenom serum produced from the plasma of animals such as horses or sheep, which generate antibodies capable of neutralizing venom toxins and thereby reducing physiological damage and the risk of mortality (Gutiérrez; R. Casewell; Laustsen, 2024). However, this therapeutic approach has important limitations, mainly associated with the biochemical complexity and variability of animal venoms. Venom composition can vary according to geographic region, sex, life stage, feeding habits, and ecological factors, which may affect antivenom specificity and efficacy (Borges et al., 2020; Casewell et al., 2020; Mehdi Ait Laaradia et al., 2025). In addition, the high cost of production and the uneven distribution of anti-venom supplies, particularly in rural and peri-urban areas where the number of recorded cases may not reflect the true incidence, further restrict access to treatment (Patikorn et al., 2020; Potet et al., 2021; Isaacson et al., 2023). These challenges, together with adverse reactions such as hypersensitivity and anaphylaxis, have encouraged growing interest in alternative and complementary therapeutic approaches, including the use of medicinal plants.

The use of medicinal plants has been an integral component of therapeutic practices across diverse cultures since the earliest human societies, including Indigenous peoples (WHO, 2023). This practice is based on the use of plant species because of their bioactive compounds and pharmacological properties, which are employed for the relief or treatment of various illnesses (Hussain and Kingsley, 2024). In contemporary times, the use of medicinal plants remains widespread, particularly among lower-income populations. Traditional, Complementary, and Integrative Medicines (TCIMs) are recognized by the World Health Organization (WHO) and encompass healthcare practices derived from the knowledge, skills, and experiences of different cultures. These practices are used for health promotion, disease prevention, and recovery, considering the individual across multiple dimensions. TCIMs are adopted globally, and products of natural origin play a prominent role within these therapeutic approaches (WHO, 2020).

In this context, several plant genera have been investigated in scientific literature for their potential to mitigate injuries related to neglected tropical diseases, including those resulting from envenomation by venomous animals such as snakes, spiders, and scorpions. Families such as Asteraceae, Apocynaceae, Araceae, Fabaceae, Euphorbiaceae, Lamiaceae, Malvaceae, Rubiaceae, and Zingiberaceae are reported among those containing genera frequently cited for this purpose, including *Abrus*, *Acorus*, *Argemone*, *Aristolochia*, *Barringtonia*, *Bouvardia*, *Citrus*, *Curcuma*, *Dalbergia*, *Hemidesmus*, *Jatropha*, and *Mimosa* (Konrath et al., 2022; Liaqat et al., 2022; Carrera-Fernández et al., 2023; Nath and Mukherjee, 2023). These plants are traditionally used to manage envenomation, with remedies commonly prepared as topical pastes, poultices, decoctions, or oral preparations. They are described as containing bioactive compounds capable of inhibiting venom toxins and are currently being investigated as potential sources of complementary therapies to neutralize venom-induced effects, including tissue damage and lethality (Kumar et al., 2025).

The genus *Jatropha* L., whose name derives from the Greek terms *iatros* meaning “physician” and *trophē* meaning “food” or “nourishment”, was originally described from the Americas but is now widely distributed across African and Asian countries. It is primarily adapted to arid and dry climates (Krishnamurthy et al., 2012a). The genus holds significant ethnopharmacological value, as documented in diverse cultural traditions (Sabandar et al., 2013). Several species have been described in the literature as possessing diverse pharmacological properties, including purgative, anti-allergic, wound-healing, and anti-inflammatory activities (Cavalcante et al., 2020). Preparations made from leaves, bark, roots, seeds, and latex are traditionally used to treat inflammation, wounds, skin ulcers, and infections, mainly due to healing and antimicrobial properties attributed to metabolites such as diterpenes, flavonoids, and tannins (Abdelgadir and Van Staden, 2013; Anani et al., 2016; Hernandez-Hernandez et al., 2017). In rural communities, these species are also used for gastrointestinal disorders, such as diarrhea and intestinal worms, as well as for pain relief and fever (Albuquerque et al., 2007).

Furthermore, some *Jatropha* species have long been used by rural communities as folk remedies for snake and scorpion stings. In Brazil, for example, leaves or latex are prepared as decoctions or applied topically to lessen venom-induced effects (Saraiva et al., 2015; Ferreira et al., 2020). This ethnobotanical background has stimulated pharmacological investigations aimed at correlating traditional reports with experimentally observed biological activities. Such findings suggest that bioactive compounds present in these plants may mitigate venom-induced toxic effects in traditional contexts of immediate care prior to conventional treatment.

Therefore, this study aimed to review *Jatropha* species reported in the literature, with emphasis on species occurring in the Brazilian flora that exhibit antivenom activity. The review highlights their main biological properties, experimental evidence, current limitations, and challenges associated with the continuity and translational advancement of these investigations. Ultimately, this work seeks to provide a scientific basis to support the ethnopharmacological validation of traditional practices and to guide future research on the potential development of new therapeutic agents derived from this genus.

2. METHODOLOGY

This systematic review was designed to identify and synthesize preclinical evidence on the antivenom potential of plant-derived materials obtained from species belonging to the genus *Jatropha* L. The review was conducted in accordance with the PRISMA guidelines, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (Rethlefsen et al., 2021).

2.1. Research Question And Search Strategy

The guiding question of this review was: What biological and pharmacological activities have been reported for *Jatropha* species as antivenom agents in non-clinical studies? The PICO(S) strategy, comprising Population, Intervention, Comparison, Outcome, and Study Design, was used to structure the review question and eligibility criteria (Menthey et al., 2014). The criteria were defined as follows: P — animals subjected to experimental envenomation by animal venoms; I — treatment with extracts or plant-derived materials obtained from different parts of *Jatropha* species; C — untreated or venom-only control groups; O — reduction or inhibition of venom-induced toxic effects; and S — *in vitro* and *in vivo* experimental studies.

Relevant articles were searched in five databases: PubMed, Embase, ScienceDirect, Web of Science, and CAPES Periodicals. The search was conducted without language restrictions and covered the full range of publication years available in each database. The search terms were selected according to the central scope of the review, aiming to retrieve studies related to the antivenom activity of species belonging to the genus *Jatropha* before the application of inclusion and exclusion criteria. General accessible terms were used across all databases, and MeSH terms were additionally applied in

PubMed when appropriate. The general search strategy included the following combination: Jatropha AND (Venom OR Antivenom OR Envenomation OR Medicinal antivenom OR Plant antivenom). The final set of references retrieved from each database was obtained by intersecting the PICO-based search results. The resulting libraries from the five databases were then imported into Rayyan for screening and selection (Ouzzani et al., 2016).

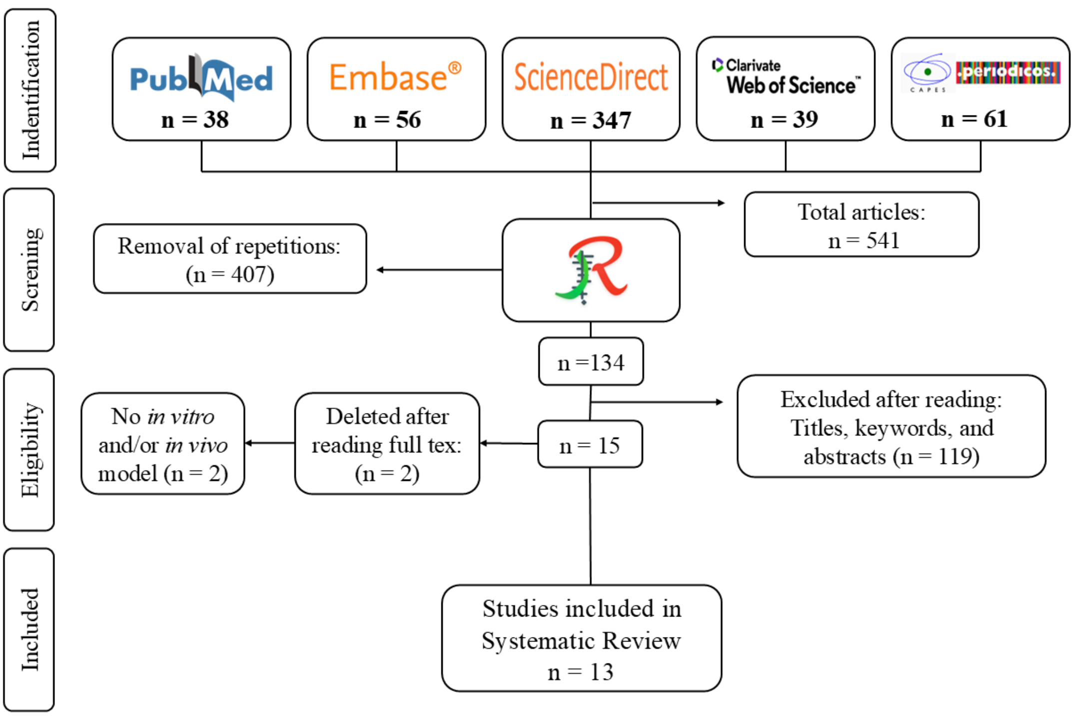
2.2. Eligibility Criteria And Study Screening

Eligible studies included original preclinical investigations evaluating the antivenom potential of plant-derived materials obtained from *Jatropha* species. Studies were included when they assessed the ability of extracts, latex, fractions, powders, formulations, or isolated preparations to inhibit or attenuate toxic effects induced by animal venoms in *in vitro*, *ex vivo*, or *in vivo* models.

Studies were considered eligible when they met the following criteria: investigation of at least one *Jatropha* species; use of animal venom or venom-derived toxic activity as the experimental challenge; evaluation of antivenom-related outcomes, such as enzymatic inhibition, neutralization of local or systemic toxicity, modulation of inflammation, coagulation, hemorrhage, myotoxicity, neurotoxicity, nociception, edema, dermonecrosis, fibrinolysis, or defibrinogenation; and presentation of original experimental data. Studies were excluded when they did not involve *Jatropha* species, did not assess venom-related activity, were based exclusively on *in silico* predictions, or corresponded to review articles, editorials, book chapters, conference abstracts without sufficient experimental data, ethnobotanical surveys without pharmacological validation, or studies with unavailable full text.

Article screening was performed in Rayyan and independently conducted by two reviewers to minimize selection bias and ensure adherence to the eligibility criteria established for this review (Table 1). Disagreements between reviewers were resolved by consensus among the authors. The selection process followed three stages, as summarized in Fig. 1. Initially, 541 records were identified and imported into Rayyan. After duplicate removal, 134 articles were screened based on titles, keywords, and abstracts. Subsequently, 15 studies were assessed in full text, of which 13 met the eligibility criteria and were included in the final qualitative synthesis. The included studies investigated *Jatropha* species with venom-inhibitory activity using *in vitro*, *ex vivo*, and/or *in vivo* experimental models (Table 2).

Table 1. Inclusion and exclusion criteria for selected articles.



Parameters	Inclusion	Exclusion

Type of publication	Original articles and full articles	Reviews, Letters, book chapters, conference abstracts, indexes
Study design	Nonclinical studies, *in vitro* and/or *in vivo* antivenom assay	Clinical trials on humans, non-laboratory studies and entirely predictive studies.

Figure 1. PRISMA flow diagram for the literature search and study inclusion.

2.3. Data Extraction And Synthesis

Data extraction was performed independently by the reviewers using a standardized form specifically developed for this review. The following information was extracted from each included study: author and year of publication; *Jatropha* species investigated; plant part used; type of plant-derived material, including extract, latex, fraction, powder, nanoemulsion, gel, or other formulation; extraction method or preparation procedure; venom or toxin evaluated; experimental model; route of administration, when applicable; dose, concentration, or venom-to-sample ratio; type of antivenom-related activity assessed; main biological outcomes; use of positive or negative controls; comparison with commercial antivenom or reference drugs, when available; phytochemical data; and major limitations reported or identified.

The extracted data were organized according to *Jatropha* species, venom source, experimental model, and biological activity. Because of the heterogeneity among the included studies regarding plant species, extraction methods, venom types, experimental designs, doses, outcome measures, and reporting formats, a meta-analysis was not performed. Therefore, the findings were synthesized qualitatively and narratively.

The synthesis prioritized the identification of recurring biological patterns among the included studies, including inhibition of key venom enzymes, such as proteases, phospholipases A_2, and hyaluronidases, as well as attenuation of venom-induced inflammatory, hemorrhagic, edematogenic, nociceptive, myotoxic, neurotoxic, dermonecrotic, fibrinolytic, and defibrinogenating effects. When available, phytochemical evidence was also considered to discuss possible mechanisms involved in the antivenom activity of *Jatropha*-derived products.

2.4. Methodological Quality Assessment/Risk Of Bias

The quality and risk of bias of the included studies were assessed qualitatively, considering the experimental nature and methodological heterogeneity of preclinical antivenom research. The assessment focused on key aspects relevant to *in vitro*, *ex vivo*, and *in vivo* studies, including clarity of the experimental design, botanical identification of the plant material, description of plant part and extraction method, characterization of the venom or toxin used, adequacy of control groups, use of dose-response or ratio-response approaches, description of experimental conditions, reporting of statistical analyses, reproducibility of the methods, and presence of phytochemical and toxicological characterization.

For *in vivo* studies, additional aspects were considered, including animal model description, route of venom administration, route and timing of treatment, use of pre-treatment, post-treatment, or pre-incubation protocols, sample size reporting, ethical approval, randomization, blinding, and comparison with commercial antivenom or reference drugs when applicable.

The risk of bias assessment was used to support the interpretation of the evidence rather than to exclude studies from the review. Particular attention was given to limitations commonly observed in preclinical studies involving medicinal plants and venom inhibition, such as reliance on crude extracts, insufficient phytochemical standardization, lack of isolated bioactive compounds, absence of toxicity assessment, limited comparison with commercial antivenoms, and experimental protocols based predominantly on pre-incubation models, which may not fully reproduce real clinical conditions of envenomation.

Table 2. List of studies with *Jatropha* spp. L. species investigated for antivenom activity.

n°	Scientific name	Common Name	Plant part	Preparation	Activi inhibit
1	*J. elliptica*	erva de lagarto	R	hydroalcoholic	procoa ant
2	*J. elliptica*	erva de lagarto	L, S	decoction	hemor gic, hemoly procoa ant ar enzyma

⚠ Esta tabela possui muitas colunas e foi cortada para impressão. Para visualizá-la completa, acesse o artigo original em: https://revistatopicos.com.br/artigos/antivenom-potential-of-the-genus-jatropha-l-euphorbiaceae-a-systematic-review-of-preclinical-evidence-on-natural-inhibitors-of-animal-venoms?noblockage

L: leaves. LA: latex. R: root. RZ: rhizomes. S: stem.

3. RESULTS

3.1. Study Selection

The database search retrieved 541 records, which were imported into Rayyan for screening. After duplicate removal, 134 articles were screened based on titles, keywords, and abstracts. Of these, 15 studies were assessed in full text, and 13 met the eligibility criteria and were included in the final qualitative synthesis. The included studies evaluated the antivenom potential of *Jatropha* species using *in vitro*, *ex vivo*, and/or *in vivo* experimental models. The study selection process is summarized in Fig. 1.

3.2. General Characteristics Of Included Studies

The 13 included studies investigated six species of the genus *Jatropha* L.: *Jatropha gossypiifolia* L., *Jatropha mollissima* (Pohl) Baill., *Jatropha elliptica* (Pohl) Müll.Arg., *Jatropha curcas* L., *Jatropha foetida* (Kunth) Steud., and *Jatropha mutabilis* (Pohl) Baill. The studies evaluated different plant-derived materials, including aqueous, hydroethanolic, methanolic, and chloroform extracts, latex, plant powders, nanoemulsions, and topical gel formulations.

The experimental models involved venoms from snakes and scorpions, with emphasis on *Bothrops jararaca*, *Bothrops erythromelas*, *Bothrops jararacussu*, *Bothrops moojeni*, *Bothrops alternatus*, *Lachesis muta*, *Naja naja*, and *Tityus stigmurus*. The main biological activities assessed included inhibition of proteolytic, phospholipase A_2, hyaluronidase, hemolytic, coagulant, hemorrhagic, edematogenic, myotoxic, nociceptive, dermonecrotic, fibrinolytic, defibrinogenating, and neurotoxic effects.

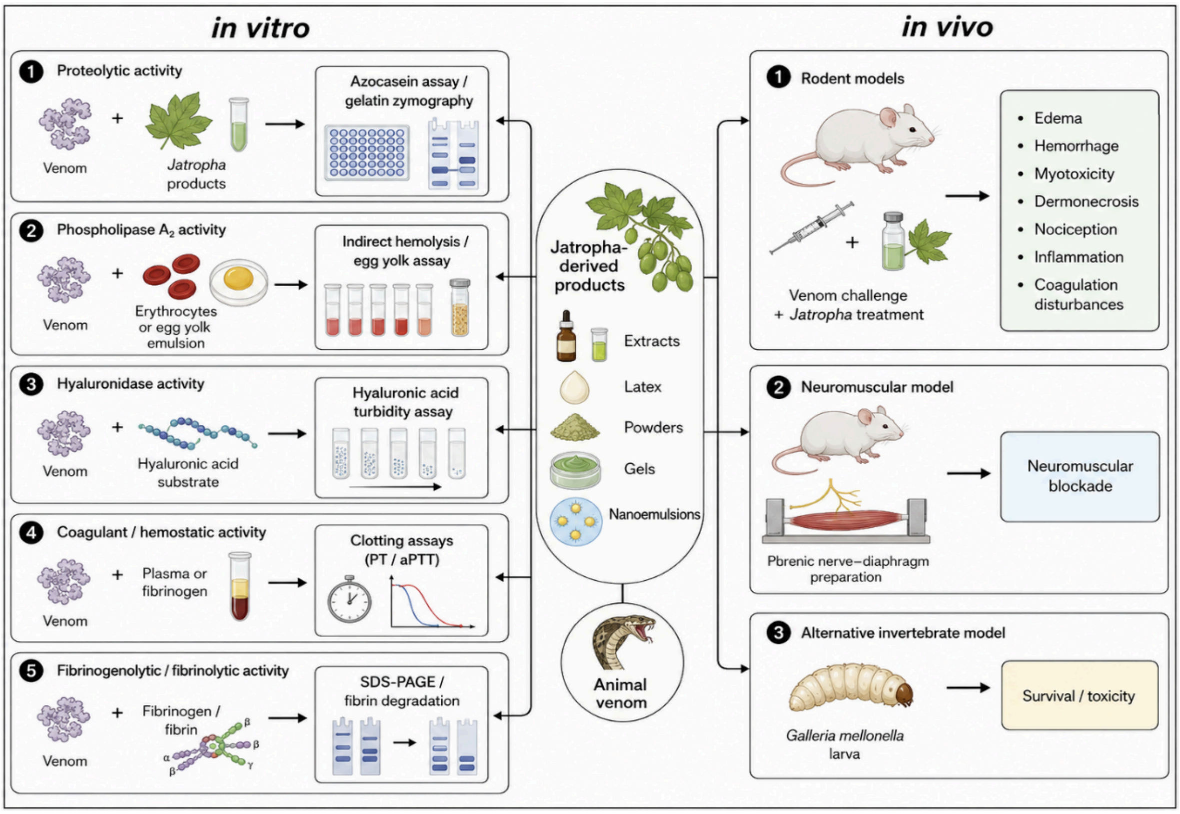
Overall, the available evidence indicates that *Jatropha*-derived products may interfere with key venom-induced pathological events, especially those associated with local tissue damage, inflammation, enzymatic degradation, hemostatic disturbances, and neuromuscular impairment. However, the studies varied considerably in terms of plant part used, extraction method, venom source, experimental protocol, venom-to-sample ratio, route of administration, and comparison with commercial antivenoms or reference drugs.

3.3. Antivenom Activities Of Jatropha Species

The anti-venom activity of *Jatropha* species was not restricted to a single venom type, experimental model, or toxicological endpoint. Across the included studies, *Jatropha*-derived products interfered with multiple venom-induced events, particularly enzymatic activities, local tissue damage, inflammatory responses, hemostatic disturbances, and neuromuscular impairment. This broad biological profile reflects the complexity of animal venoms, whose toxic effects result from the combined action of proteases, phospholipases A_2, hyaluronidases, coagulant toxins, hemorrhagins, myotoxins, and inflammatory mediators.

The evidence was therefore organized by species to preserve the ethnopharmacological and botanical context of each preparation, while allowing comparison among plant parts, extraction methods, venom sources, experimental protocols, and biological outcomes. Overall, the strongest and most recurrent findings involved inhibition of proteolytic, phospholipase A_2, hyaluronidase, hemolytic, coagulant, hemorrhagic, edematogenic, myotoxic, dermonecrotic, fibrinolytic, defibrinogenating, and neurotoxic activities. The main anti-venom effects reported for each *Jatropha* species are described below and summarized in Fig. 2.

Figure 2. Schematic representation of *in vitro*, *ex vivo*, and *in vivo* assays used to evaluate the antivenom potential of *Jatropha*-derived products against enzymatic, hemostatic, inflammatory, and local pathological effects induced by animal venoms.



3.3.1. Jatropha gossypiifolia L.

Jatropha gossypiifolia L., also known as “pinhão-roxo”, is a shrubby species widely distributed in tropical and subtropical regions. This species is characterized by purplish leaves, intense red flowers, and the presence of latex in its tissues (Félix-Silva et al., 2014a). In traditional medicine, it is used to treat inflammatory conditions, skin infections, and gastrointestinal disorders (Wu et al., 2019).

An aqueous extract obtained from the leaves of *J. gossypiifolia* was evaluated for its ability to neutralize defibrinogenating, edematogenic, hemorrhagic, and myotoxic activities, as well as to inhibit enzymatic components of *Bothrops jararaca* venom (BjV) (Félix-Silva et al., 2014b). Initial *in vitro* assays showed that the extract completely inhibited proteolytic activity on azocasein at the highest venom-to-extract ratios tested (1:75 and 1:100, w/w) (Félix-Silva et al., 2014b). In addition, gelatin zymography revealed preservation of the C-terminal regions of the Aα and Bβ fibrinogen chains, indicating effective inhibition of venom proteases (Félix-Silva et al., 2014b).

The extract also fully abolished the procoagulant activity of BjV in plasma assays (Félix-Silva et al., 2014b). Although fibrinogen clotting was not completely prevented, the extract-maintained plasma anticoagulant activity for up to 10 min after venom addition, suggesting that its effects are not restricted to snake venom thrombin-like enzymes (SVTLEs), but may also involve inhibition of other coagulation factor–activating toxins (Félix-Silva et al., 2014b). Moreover, activated partial thromboplastin time (aPTT) and prothrombin time (PT) performed in the absence of venom showed that the extract prolonged aPTT nearly threefold, indicating interference with the intrinsic and/or common coagulation pathways, while exerting no effect on the extrinsic pathway (Félix-Silva et al., 2014b).

In vivo assays further supported the protective effects of the extract against *B. jararaca* envenomation (Félix-Silva et al., 2014b). Oral administration inhibited venom-induced defibrinogenating activity at all tested doses (50, 100, and 200 mg/kg), restoring blood coagulation similarly to the PBS control group, whereas animals receiving venom alone exhibited incoagulable blood (Félix-Silva et al., 2014b). In the anti-edematogenic assay, intraplanar injection of BjV induced marked edema, which was reduced by approximately 40% after oral treatment with the extract at doses of 100 and 200 mg/kg (Félix-Silva et al., 2014b). Notably, intraperitoneal administration completely abolished edema within the same period (Félix-Silva et al., 2014b). Consistent with these findings, reduced myeloperoxidase (MPO) activity in paw tissues indicated decreased inflammatory cell infiltration, with reductions of approximately 20% after oral administration and 50% after intraperitoneal administration, supporting an anti-inflammatory effect (Félix-Silva et al., 2014b).

The anti-hemorrhagic potential of the extract was also evident, since oral administration significantly inhibited venom-induced local hemorrhage, achieving up to 56% inhibition at the 100 mg/kg dose, as determined by hemoglobin content in cutaneous tissue (Félix-Silva et al., 2014b). This reduction suggests inhibition of hemorrhagic snake venom metalloproteinases (SVMPs), which are primarily responsible for basement membrane degradation and vascular damage (Félix-Silva et al., 2014b). Similarly, in the anti-myotoxic assay, the aqueous extract significantly attenuated venom-induced muscle damage (Félix-Silva et al., 2014b). Oral treatment reduced serum creatine kinase (CK) levels by approximately 50% at 200 mg/kg, whereas intraperitoneal administration resulted in a pronounced reduction of up to 96.5% at 50 mg/kg (Félix-Silva et al., 2014b). These findings indicate that intraperitoneal treatment provided strong protection even at the lowest doses tested (Félix-Silva et al., 2014b).

In the same year, Reddi et al. (2014) investigated the antivenom potential of different botanical parts of *J. gossypiifolia*, including roots, leaves, and stems, extracted using solvents of increasing polarity, namely aqueous, methanolic, and chloroformic extracts. These preparations were evaluated against *Naja naja* venom using an indirect hemolytic assay with human erythrocytes and chicken egg yolk emulsion as substrates, a model associated with phospholipase A_2 (PLA_2) activity (Reddi et al., 2014). A pre-incubation protocol was employed, in which each extract was incubated with one minimum indirect hemolytic dose (MIHD) of *N. naja* venom before hemolysis assessment, and venom-induced erythrocyte lysis was quantified by measuring hemoglobin release (Reddi et al., 2014).

The results demonstrated that all tested plant parts exhibited inhibitory effects against venom-induced hemolytic activity, with notable differences depending on the solvent and plant organ (Reddi et al., 2014). Among aqueous extracts, leaves, roots, and stems showed high inhibition rates of 85.9%, 84.5%, and 81%, respectively (Reddi et al., 2014). In methanolic extracts, leaves displayed the highest inhibition among all preparations, reaching approximately 89.8%, whereas roots and stems exhibited comparatively lower inhibitory activity (Reddi et al., 2014). Similarly, among chloroformic extracts, leaf-derived preparations showed the greatest inhibition of PLA_2-associated hemolytic activity, reaching 87.5%, followed by stems and roots (Reddi et al., 2014). Overall, extracts derived from *J. gossypiifolia* leaves consistently showed the highest percentages of hemolytic inhibition, irrespective of the solvent used (Reddi et al., 2014).

Subsequently, the aqueous leaf extract of *J. gossypiifolia* was shown to be effective against enzymatic activities and local pathological effects, including edematogenic and hemorrhagic responses, induced by *Bothrops erythromelas* venom (BeV) (Félix-Silva et al., 2017). The inhibitory capacity of the extract against major venom enzyme classes was assessed using *in vitro* assays: proteolytic activity was evaluated colorimetrically using azocasein as substrate, PLA_2 activity was determined turbidimetrically in 96-well microplates using an egg yolk suspension, and hyaluronidase activity was assessed turbidimetrically using hyaluronic acid as substrate (Félix-Silva et al., 2017). In all assays, venom was used as the positive control, PBS as the negative control, and commercial bothropic antivenom (BAv; Butantan Institute, São Paulo, Brazil) as a reference treatment (Félix-Silva et al., 2017).

In the proteolytic assay, BeV was pre-incubated with different venom-to-extract ratios (1:25, 1:50, and 1:100, w/w), while BAv was tested at ratios of 1:0.25, 1:0.5, and 1:1 (w/v) (Félix-Silva et al., 2017). Under these conditions, the extract inhibited approximately 83% of protease activity, whereas BAv did not show significant inhibition (Félix-Silva et al., 2017). Similarly, in the PLA_2 assay, pre-incubation of BeV with the extract resulted in complete inhibition of enzymatic activity at the highest tested ratio, while BAv exhibited only limited inhibition, approximately 16% (Félix-Silva et al., 2017). In the hyaluronidase assay, pre-incubation of BeV with the extract at ratios of 1:1, 1:2.5, and 1:5 (w/w), or with BAv, led to complete inhibition of enzymatic activity, with the extract being effective at the highest tested ratio and BAv at all concentrations (Félix-Silva et al., 2017).

The extract was also effective in attenuating local effects of BeV envenomation *in vivo* (Félix-Silva et al., 2017). For these experiments, a dose of 400 mg/kg was employed (Félix-Silva et al., 2017). In the anti-edematogenic assay, intraplantar injection of BeV induced marked edema, which was evaluated over 2 h using pre- and post-treatment protocols (Félix-Silva et al., 2017). In the pre-treatment protocol, administration of the extract reduced edema by approximately 90% within 2 h, yielding results comparable to those observed with BAv (Félix-Silva et al., 2017). Notably, in the post-treatment protocol, the extract was more effective than BAv, reducing edema by 67% after 2 h, whereas the antivenom did not produce a statistically significant reduction (Félix-Silva et al., 2017).

These findings were corroborated by MPO activity measurements in paw tissue (Félix-Silva et al., 2017). In the pre-treatment protocol, both the extract and BAv significantly reduced MPO activity, by 70% and 42%, respectively (Félix-Silva et al., 2017). However, in the post-treatment protocol, only the extract remained effective, reducing MPO activity by 63% (Félix-Silva et al., 2017). Hemorrhagic activity was evaluated after subcutaneous injection of BeV, with assessment of both the hemorrhagic halo and hemoglobin content in the affected tissue after 3 h (Félix-Silva et al., 2017). In the pre-treatment protocol, BAv showed greater efficacy than the extract in reducing the hemorrhagic halo, with reductions of 50% and 41%, respectively (Félix-Silva et al., 2017). In contrast, in the post-treatment protocol, the extract maintained a comparable inhibitory effect, whereas BAv did not achieve statistically significant inhibition, reaching approximately 26% (Félix-Silva et al., 2017). Hemoglobin quantification confirmed these observations, with the extract reducing hemoglobin content by 41.9% and 30.8% in the pre- and post-treatment protocols, respectively, while BAv was more effective only in the pre-treatment protocol, reducing hemoglobin content by 52.3%, and showed limited inhibition in the post-treatment protocol, approximately 25% (Félix-Silva et al., 2017).

These findings are consistent with another study by Félix-Silva et al. (2018), in which the aqueous leaf extract of *J. gossypiifolia* was also evaluated against BeV. In this study, the extract was tested at 200 mg/kg and compared with the aqueous extract of *Jatropha mollissima*, dexamethasone at 5 mg/kg, and PBS in a BeV-induced paw edema model (Félix-Silva et al., 2018). Treatments were administered orally or intraperitoneally, and animals were euthanized after 2 h for edema and MPO analyses (Félix-Silva et al., 2018). The aqueous extract of *J. gossypiifolia* reduced edema by 50% after oral pretreatment and by 76.4% after intraperitoneal administration (Félix-Silva et al., 2018). These results were comparable to those obtained with dexamethasone, which reduced edema by 55% after oral administration and 44% after intraperitoneal administration (Félix-Silva et al., 2018). Regarding MPO activity, the extract was more effective than dexamethasone after intraperitoneal administration, reducing MPO by 78.2% compared with 57.3%, whereas dexamethasone was more effective after oral administration, reducing MPO by 83.9% compared with 69.5% for the extract (Félix-Silva et al., 2018).

Unlike previous studies, Batista et al. (2024) evaluated a hydroethanolic extract (JgE) and a nanoemulsion formulation (JgNe) prepared from *J. gossypiifolia* leaves against enzymatic activities and dermonecrotic effects induced by BeV. The inhibitory effects of JgE and JgNe were assessed against PLA_2 activity using an egg yolk substrate at venom-to-extract/formulation ratios of 1:50, 1:75, and 1:100 (BeV:JgE/JgNe, w/w), and against hyaluronidase activity using hyaluronic acid as substrate at ratios of 1:0.0625, 1:0.125, and 1:0.25 (BeV:JgE/JgNe, w/w) (Batista et al., 2024).

The hydroethanolic extract inhibited PLA_2 activity by approximately 25% across all tested ratios, whereas the nanoemulsion exhibited a concentration-dependent inhibitory effect, reaching up to 24% inhibition at the highest ratio evaluated (1:100) (Batista et al., 2024).

These findings indicate that incorporation of the extract into a nanostructured delivery system does not eliminate its antivenom activity, although it modifies the response profile compared with the crude extract (Batista et al., 2024). Regarding hyaluronidase activity, both formulations displayed dose-dependent inhibition; however, the crude extract exerted more pronounced effects, achieving approximately 47% inhibition at the highest tested concentration, whereas the nanoemulsion reached approximately 23% (Batista et al., 2024). This difference may be associated with the release kinetics of bioactive metabolites from nanoemulsion, potentially influencing their short-term bioavailability (Batista et al., 2024).

Antidermonecrotic activity was further confirmed *in vivo* using an intradermal model in which dermonecrosis was induced by BeV injection (Batista et al., 2024). Topical treatment with JgNe significantly reduced the venom-induced necrotic halo, with reductions of 64.79% after 24 h and 78.78% after 72 h compared with the venom control group (Batista et al., 2024). In contrast, treatment with commercial bothropic antivenom achieved a reduction of only 45.27% over the same period, highlighting the superior efficacy of the nanoemulsion in mitigating local tissue damage (Batista et al., 2024). Notably, combined treatment with JgNe and antivenom resulted in an intermediate effect, suggesting that adjunctive use of nanostructured plant-based formulations may enhance therapeutic strategies for the management of local effects of snakebite envenomation (Batista et al., 2024).

3.3.2. Jatropha mollissima (Pohl) Baill.

Is a shrubby species endemic to northeastern Brazil (Crepaldi et al., 2016). Popularly known as “pinhão-bravo”, this species is adapted to semi-arid environments and is characterized by densely pubescent, velvety leaves and showy pink flowers. In traditional medicine, *J. mollissima* is used to treat inflammatory conditions, wounds, and gastrointestinal disorders, although potentially toxic compounds have also been reported (Dias et al., 2019; Queiroz Neto et al., 2019).

The aqueous leaf extract of *J. mollissima* has been evaluated for its ability to attenuate local effects induced by *Bothrops erythromelas* venom (BeV) and *Bothrops jararaca* venom (BjV), including inflammatory, hemorrhagic, and myotoxic activities (Gomes et al., 2016). In this study, the extract was prepared by decoction of dried leaves at 10% w/v for 15 min at approximately 100 °C and assessed *in vivo* using Swiss mice as experimental models of bothropic envenomation (Gomes et al., 2016).

Inflammatory responses were evaluated using paw edema and leukocyte migration assays (Gomes et al., 2016). Animals were pretreated intraperitoneally with different doses of *J. mollissima* extract (50, 100, or 200 mg/kg), dexamethasone (2 mg/kg), or PBS before venom challenge (Gomes et al., 2016). In the paw edema model, intraplantar injection of BeV or BjV induced significant edema, which was markedly reduced by extract treatment at 120 min post-envenomation (Gomes et al., 2016). The maximum edema inhibition reached 46.41% at 50 mg/kg for BeV and 25.19% at 200 mg/kg for BjV, although these effects were lower than those observed with dexamethasone, which reduced edema by 57.58% and 30.65%, respectively (Gomes et al., 2016).

Consistent with these anti-edematogenic findings, venom administration significantly increased leukocyte migration into the peritoneal cavity, whereas pretreatment with *J. mollissima* extract effectively reduced leukocyte infiltration induced by both venoms (Gomes et al., 2016). Maximum inhibition reached 80% at 100 mg/kg for BeV and 80.18% at 200 mg/kg for BjV (Gomes et al., 2016). Dexamethasone showed slightly higher inhibitory effects, particularly against BeV, reinforcing the anti-inflammatory relevance of the extract while indicating that its activity was less pronounced than that of the reference anti-inflammatory drug in some experimental conditions (Gomes et al., 2016).

The anti-hemorrhagic potential of *J. mollissima* extract was also investigated after subcutaneous venom injection (Gomes et al., 2016). Pretreatment with the extract resulted in moderate inhibition of hemorrhagic activity induced by both venoms, with maximum inhibition of 44% for BjV at 200 mg/kg (Gomes et al., 2016). In contrast, inhibition of hemorrhage induced by BeV was observed at lower doses, although these effects were not statistically significant (Gomes et al., 2016).

The myotoxic effects of both venoms were assessed by measuring plasma creatine kinase (CK) levels (Gomes et al., 2016). Pretreatment with *J. mollissima* extract significantly reduced CK levels compared with venom-only control groups (Gomes et al., 2016). The greatest reduction for BeV was observed at 200 mg/kg, reaching 81.70%, whereas for BjV the maximum reduction reached 72.73% at 100 mg/kg (Gomes et al., 2016). As expected, dexamethasone produced more pronounced protective effects, reducing CK levels by more than 90% for both venoms (Gomes et al., 2016).

More recently, Passos et al. (2024) developed and evaluated a topical gel formulated with a hydroethanolic leaf extract of *J. mollissima* for its therapeutic potential against BjV-induced local damage. In this study, edematogenic, hemorrhagic, and dermonecrotic activities induced by BjV were treated using a semi-solid topical formulation containing the leaf extract at 5.0% w/w (Passos et al., 2024).

The gel was prepared using a polymeric base composed of hydroxypropylmethylcellulose, propylene glycol, poloxamer F-127, and methylparaben, with the lyophilized extract previously solubilized in water before incorporation into the formulation (Passos et al., 2024). A base gel without the extract was used as a placebo control (Passos et al., 2024). After preparation, the formulations were homogenized by ultrasonication and stored under refrigerated conditions before use (Passos et al., 2024). For the *in vivo* assays, 20 mg of each formulation was applied, based on previous studies conducted by the research group and evidence available in the literature (Passos et al., 2024).

Edema inhibition induced by BjV was evaluated after treatment with the *J. mollissima* extract gel, Bothropic-Crotalic antivenom (BCAv), or their combination (Passos et al., 2024). The extract gel significantly reduced edema at all evaluated time points, from 0.5 to 4 h, with inhibition ranging from approximately 33% to 60% compared with venom-only controls (Passos et al., 2024). Both BCAv alone and the combined treatment significantly inhibited edema from 1 h onward (Passos et al., 2024). Area under the curve analysis demonstrated that the extract gel alone produced an anti-edematogenic effect comparable to BCAv, whereas the combined treatment showed superior efficacy, achieving nearly complete edema resolution, approximately 90%, at 4 h (Passos et al., 2024).

Phytochemical analysis revealed a high flavonoid content in the *J. mollissima* leaf extract (Passos et al., 2024). These metabolites are known to inhibit snake venom toxins, including PLA_2s, either through direct enzymatic inhibition or indirectly through immunomodulatory effects (Passos et al., 2024). In addition, phenolic compounds can chelate metal ions, thereby inhibiting metalloproteases that depend on metal cofactors for catalytic activity (Passos et al., 2024). This study was the first to report a topical gel formulation containing *J. mollissima* extract capable of markedly reversing BjV-induced edema, highlighting its potential as an accessible complementary strategy for managing local effects of bothropic envenomation (Passos et al., 2024).

The anti-hemorrhagic activity of the topical gel was assessed by quantifying hemoglobin content in muscle tissue after local hemorrhage induction by BjV (Passos et al., 2024). Treatment with *J. mollissima* extract gel, BCAv, or their combination significantly reduced hemoglobin levels compared with venom-only controls, indicating effective inhibition of hemorrhagic activity (Passos et al., 2024). These findings are consistent with previous studies from the same research group demonstrating the anti-hemorrhagic potential of aqueous leaf extracts from *J. gossypiifolia* and *J. mollissima* against BjV (Passos et al., 2024).

Dermonecrosis is a severe local consequence of bothropic envenomation and is associated with the direct action of zinc-dependent metalloproteases and myotoxic PLA_2s, which degrade basement membrane components and disrupt tissue integrity (Passos et al., 2024). In this study, the *J. mollissima* extract gel significantly reduced the dermonecrotic halo induced by BjV, both when applied alone and in combination with BCAv (Passos et al., 2024). In contrast, BCAv alone did not significantly reduce dermonecrosis compared with venom-only controls (Passos et al., 2024).

These findings corroborate previous results reported by Félix-Silva et al. (2018), who also investigated the antivenom activity of *J. mollissima*. In that comparative study, evaluating *J. mollissima* and *J. gossypiifolia*, the aqueous leaf extract of *J. mollissima* demonstrated pronounced antivenom activity, particularly against local pathological effects induced by *Bothrops* envenomation (Félix-Silva et al., 2018). *In vivo* assays showed that the extract significantly inhibited venom-induced edema and hemorrhage, supporting its marked anti-inflammatory and local protective potential (Félix-Silva et al., 2018).

3.3.3. Jatropha elliptica (Pohl.) mull

Is a species native to the semi-arid region of Brazil. Popularly known as “pinhão-do-cerrado” or “erva de lagarto”, it is recognized for its medicinal properties and ornamental potential. This species is a shrub of variable size, with dry tricoccous fruits exhibiting explosive dehiscence and oval seeds with a smooth, marbled testa (Añez et al., 2005).

The first study evaluating the antivenom potential of *J. elliptica* was reported by Trebien et al. (1988), who investigated the effects of a crude hydroalcoholic extract prepared from chopped tubers. The plant material was extracted with 50% ethanol-water (1:3, w/v), mechanically agitated at room temperature for 24 h, filtered, dehydrated, and resuspended in 0.9% saline solution (Trebien et al., 1988). The extract was assessed in an *in vivo* model of venom-induced vascular permeability, a key pathological feature of

Bothrops jararaca envenomation (Trebien et al., 1988). Male rats were orally pretreated with the extract at 1 g/kg or saline 60 min before intradermal injection of BjV, and vascular leakage was quantified by Evans blue extravasation (Trebien et al., 1988).

Under these experimental conditions, pretreatment with *J. elliptica* extract did not significantly inhibit the increase in cutaneous vascular permeability induced by BjV, indicating an absence of direct protective activity against venom-mediated endothelial disruption (Trebien et al., 1988). In parallel assays, the extract also failed to reduce vascular permeability elicited by classical inflammatory and vasoactive mediators, including histamine, serotonin, dextran, and platelet-activating factors (Trebien et al., 1988). These findings suggest that the pharmacological effects of this preparation are not associated with stabilization of the vascular barrier or inhibition of mediator-driven plasma extravasation (Trebien et al., 1988).

Thus, despite the ethnomedicinal use of *J. elliptica* for snakebite treatment, the crude hydroalcoholic tuber extract did not neutralize the acute vascular effects induced by BjV in this model (Trebien et al., 1988). Since these effects are primarily mediated by hemorrhagic metalloproteinases and other vasoactive toxins, the results argue against a direct antivenom action of this preparation in the vascular permeability model (Trebien et al., 1988). Accordingly, any therapeutic benefit associated with its traditional use may depend on other plant parts, extraction methods, venom types, or indirect symptomatic mechanisms rather than direct inhibition of venom-induced vascular leakage (Trebien et al., 1988).

De Paula et al. (2010) reported inhibitory activity of aqueous leaf and stem extracts of *J. elliptica* against *Lachesis muta* venom. In this study, *J. elliptica* was included among twelve plant species whose aqueous extracts were evaluated for antivenom-related activities using *in vitro*, *ex vivo*, and *in vivo* approaches (De Paula et al., 2010). The extracts demonstrated inhibitory effects on phospholipase A_2 and proteolytic activities, assessed by indirect hemolytic and azocasein-based assays, respectively (De Paula et al., 2010). Interference with venom-induced coagulation was also observed in human plasma assays, and anti-hemorrhagic activity was evaluated by measuring hemorrhagic lesion formation in mice after intradermal venom injection (De Paula et al., 2010). These effects were assessed after incubation of the extracts with venom at venom-to-plant ratios of 1:10 and 1:20 (w/w) (De Paula et al., 2010).

Anti-proteolytic activity was detected for J. *elliptica* extracts (De Paula et al., 2010). The leaf extract completely inhibited the proteolytic activity induced by *L. muta* venom, whereas the stem extract promoted approximately 91% inhibition using azocasein as substrate (De Paula et al., 2010). These findings indicate that *J. elliptica* contains metabolites capable of efficiently neutralizing venom proteases, likely including metalloproteases and serine proteases involved in tissue necrosis, inflammation, and hemorrhage (De Paula et al., 2010).

The extracts showed only moderate inhibition of the indirect hemolytic activity induced by *L. muta* venom (De Paula et al., 2010). The leaf extract inhibited approximately 44% hemolysis, whereas the stem extract showed a more pronounced effect, reaching approximately 74% inhibition when preincubated with the venom at a 1:10 venom-to-plant ratio (w/w) (De Paula et al., 2010). These results suggest partial interference with phospholipase A_2 activity, with stem-derived constituents showing stronger neutralizing potential against venom phospholipases (De Paula et al., 2010).

Regarding venom-induced coagulant activity, both *J. elliptica* extracts demonstrated low inhibitory efficacy (De Paula et al., 2010). The leaf extract reduced coagulation by approximately 20%, while the stem extract achieved approximately 18% inhibition, without preventing clot formation within the experimental period (De Paula et al., 2010). These data indicate that the metabolites present in the extracts do not strongly interfere with the venom components responsible for plasma coagulation, including serine proteases or metalloproteases involved in hemostatic disturbance (De Paula et al., 2010).

Marked differences between plant parts were observed in the hemorrhagic assay (De Paula et al., 2010). According to the authors, the leaf extract did not significantly reduce the hemorrhagic halo induced by *L. muta* venom (De Paula et al., 2010). In contrast, the stem extract showed high anti-hemorrhagic activity, inhibiting approximately 94% of hemorrhage and providing substantial protection against local vascular damage (De Paula et al., 2010). This finding suggests that compounds concentrated in the stems may be particularly effective against hemorrhagic metalloproteases, consistent with the strong anti-proteolytic activity observed in the same study (De Paula et al., 2010).

Another study investigated a hydroalcoholic root extract of *J. elliptica* against *Bothrops jararacussu* venom (BjuV) (Ferreira-Rodrigues et al., 2016). In this work, the extract demonstrated pronounced protective effects against key toxic activities of the venom, particularly neurotoxicity, myotoxicity, and inflammation (Ferreira-Rodrigues et al., 2016). The extract was prepared from roots using 70% ethanol, and the suspension was percolated at 20 drops/min, producing a 20% (w/v) hydroalcoholic extract (Ferreira-Rodrigues et al., 2016).

In neuromuscular assays using the mouse phrenic nerve-diaphragm preparation, the *J. elliptica* extract significantly attenuated venom-induced neuromuscular blockade (Ferreira-Rodrigues et al., 2016). The preincubated concentration of 500 µg significantly reduced the neuromuscular blockade induced by BjuV, preserving approximately 86% of the contractile response, which was higher than the protection observed when the extract was added after the onset of venom action (approximately 64%) (Ferreira-Rodrigues et al., 2016). These findings suggest that constituents of the extract may act primarily through direct interaction with venom neurotoxins, limiting their ability to disrupt neuromuscular transmission (Ferreira-Rodrigues et al., 2016).

The extract also exhibited marked anti-myotoxic activity (Ferreira-Rodrigues et al., 2016). Histomorphometry analysis of diaphragm muscle fibers revealed that BjuV alone induced substantial muscle damage, with a myotoxic index of 44.4% (Ferreira-Rodrigues et al., 2016). In contrast, treatment with the *J. elliptica* extract, particularly under preincubation conditions, significantly reduced muscle injury, lowering the myotoxic index to approximately 17% (Ferreira-Rodrigues et al., 2016). This nearly three-fold reduction highlights the capacity of the extract to protect skeletal muscle against venom-induced degeneration (Ferreira-Rodrigues et al., 2016).

In addition to its effects on neuromuscular function and muscle integrity, the extract displayed potent anti-inflammatory activity (Ferreira-Rodrigues et al., 2016). In the venom-induced paw edema model, oral administration of the extract resulted in a significant and dose-dependent reduction of edema, beginning within the first hour after venom inoculation and persisting for up to 5 h (Ferreira-Rodrigues et al., 2016). At the highest tested dose, the anti-inflammatory effect was comparable to that observed with dexamethasone, used as a positive control (Ferreira-Rodrigues et al., 2016). These results indicate that the extract may interfere with inflammatory pathways activated by the venom, possibly through modulation of prostanoids and cellular mediators involved in vascular permeability and edema formation (Ferreira-Rodrigues et al., 2016).

Jatropha elliptica was also evaluated for its ability to counteract the neurotoxic effects of *Bothrops moojeni* venom (Ferreira-Rodrigues et al., 2021). In this study, starch was obtained from the rhizome of *J. elliptica* by decantation (Ferreira-Rodrigues et al., 2021). After removal of the supernatant, the remaining material was dried at room temperature, sieved, diluted in Tyrode solution, and tested against *B. moojeni* venom using a mouse phrenic-diaphragm neuromuscular preparation (Ferreira-Rodrigues et al., 2021).

The crude venom of *B. moojeni* exhibited proteins with molecular masses ranging from 10 to 60 kDa, consistent with toxin families commonly associated with neurotoxic and myotoxic effects observed in *Bothrops* envenomation (Ferreira-Rodrigues et al., 2021). When applied at 50 μg/mL, the venom induced a marked neuromuscular blockade characterized by a progressive reduction in muscle contractile response, reaching 50% blockade (T50) after 71.5 ± 8.9 min (Ferreira-Rodrigues et al., 2021).

The antivenom potential of *J. elliptica* powder (JeP) was evaluated using three experimental protocols designed to simulate different exposure scenarios: pre-venom, post-venom, and pre-incubation models (Ferreira-Rodrigues et al., 2021). In the pre-venom and post-venom protocols, JeP was added before or after venom exposure, respectively, allowing assessment of both prophylactic and therapeutic effects (Ferreira-Rodrigues et al., 2021). At 100 μg/mL, JeP demonstrated a significant protective effect on neuromuscular function (Ferreira-Rodrigues et al., 2021). In the pre-venom protocol, this concentration increased the time required to reach 50% neuromuscular blockade to 100.9 ± 7.6 min, representing a significant prolongation of contractile activity compared with venom alone (Ferreira-Rodrigues et al., 2021). Similarly, in the post-venom protocol, JeP extended T50 to 97 ± 6.1 min, indicating partial attenuation of neurotoxic effects even after venom exposure had begun ($p < 0.05$) (Ferreira-Rodrigues et al., 2021). However, increasing the concentration to 1000 μg/mL did not enhance the protective effect, as blockade times were not significantly different from those observed with venom alone, suggesting the absence of a clear dose-dependent relationship or possible physicochemical interference in the experimental preparation (Ferreira-Rodrigues et al., 2021).

In the pre-incubation protocol, in which venom was incubated with JeP for 30 min before tissue exposure, no statistically significant differences were observed compared with venom alone (Ferreira-Rodrigues et al., 2021). T50 values were 78.2 ± 9.2 min for 100 μg/mL and 86.5 ± 8.9 min for 1000 μg/mL, values comparable to those obtained with commercial bothropic antivenom used as a control

(80.2 ± 14.1 min) (Ferreira-Rodrigues et al., 2021). These findings suggest that JeP did not act mainly through direct venom neutralization under pre-incubation conditions, although it partially delayed venom-induced neuromuscular impairment in pre- and post-venom protocols (Ferreira-Rodrigues et al., 2021).

Additionally, a dose-response curve was generated to evaluate the direct effects of JeP on neuromuscular activity (Ferreira-Rodrigues et al., 2021). Concentrations of 100, 200, and 1000 µg/mL were tested, and the 100 µg/mL concentration produced the smallest baseline alteration in contractile response, justifying its selection for the neutralization assays (Ferreira-Rodrigues et al., 2021). Interestingly, the 200 µg/mL concentration reduced neuromuscular activity more markedly than the highest concentration tested, 1000 µg/mL (Ferreira-Rodrigues et al., 2021). This unexpected result was attributed to possible methodological factors, such as insufficient sonication, which may have affected powder dispersion in the experimental medium (Ferreira-Rodrigues et al., 2021).

Collectively, these findings demonstrate that *B. moojeni* venom induces significant neuromuscular blockade in the mouse phrenic-diaphragm model and that JeP, particularly at 100 µg/mL, can partially protect neuromuscular function by delaying venom-induced paralysis (Ferreira-Rodrigues et al., 2021). This protective effect was observed when the powder was administered both before and after venom exposure, suggesting potential use as an adjuvant agent in the management of snakebite envenomation (Ferreira-Rodrigues et al., 2021). Although the mechanism underlying this activity remains unclear, it may be associated with residual secondary metabolites present in the rhizome starch or with phenolic compounds capable of exerting antioxidant effects or modulating cellular responses to venom toxins (Ferreira-Rodrigues et al., 2021).

3.3.4. Jatropha curcas L.

Is a shrubby to medium-sized plant commonly found in arid and semi-arid environments and widely distributed across Africa, Asia, and the Americas, although it is originally native to the Americas (Abdelgadir and Van Staden, 2013). Popularly known in Brazil as “pinhão-de-cerca”, this monoecious species produces simple, often lobed leaves, inflorescences with unisexual flowers, and tricoccous capsular fruits that typically contain three large oil-rich seeds (Ruatpuia et al., 2024).

Preclinical studies have demonstrated the antivenom potential of *J. curcas* using different venom models and extract preparations. Reddi et al. (2014) evaluated methanolic extracts obtained from leaves, stems, and roots against the indirect hemolytic activity induced by *Naja naja* venom, using human erythrocytes and egg yolk emulsion as substrates. The extracts, tested at 25 μg and pre-incubated with the minimum indirect hemolytic dose (MIHD; 10 μg/mL) for 30 min at 37 °C, produced approximately 80% inhibition of hemolysis across all plant parts analyzed (Reddi et al., 2014). These findings indicate the presence of bioactive compounds capable of interacting with venom components and reducing their cell-lytic and hemolytic effects (Reddi et al., 2014).

In contrast, aqueous extracts of *J. curcas* displayed the opposite effect, enhancing venom-induced hemolysis compared with the positive control group exposed only to crude venom (Reddi et al., 2014). This result suggests the presence of water-soluble constituents capable of intensifying venom-associated cytotoxicity (Reddi et al., 2014). Chloroform extracts exhibited low neutralizing capacity, with inhibition ranging from 2.6% to 22.4%, indicating limited efficacy against PLA_2-associated hemolytic activity under the tested conditions (Reddi et al., 2014).

Xavier et al. (2019) investigated the antivenom activity of lyophilized leaf extracts of *J. curcas* against *Bothrops alternatus* and *Bothrops moojeni* venoms, assessing *in vitro* parameters, including phospholipase and coagulant activities, as well as *in vivo* hemorrhagic effects. The extract significantly inhibited *B. alternatus* phospholipase A_2 activity at a 1:0.5 venom-to-extract ratio (w/w), with complete inhibition achieved at a 1:1 ratio (Xavier et al., 2019). Regarding plasma coagulation, the extract significantly prolonged clotting time at 1:1 and 1:5 ratios and induced complete plasma incoagulability at 1:10 and 1:20 ratios, demonstrating marked interference with venom-induced coagulation pathways (Xavier et al., 2019).

In vivo assays, *B. alternatus*-induced hemorrhage was fully inhibited at a 1:10 venom-to-extract ratio (Xavier et al., 2019). For *B. moojeni* venom, the extract also significantly reduced enzymatic and hemostatic activities, although the magnitude of inhibition varied according to the specific activity evaluated and the extract concentration used (Xavier et al., 2019). Taken together, these results suggest that *J. curcas* contains bioactive compounds capable of interacting with protein components of snake venoms, particularly phospholipases and procoagulant factors, thereby attenuating enzymatic, hemostatic, and local toxic effects (Xavier et al., 2019).

3.3.5. Jatropha foetida (Kunth) Steudel

The antivenom potential of *Jatropha foetida* (Kunth) Steud. was also evaluated by Reddi et al. (2014), in comparison with *J. gossypiifolia* and *J. curcas*. In that study, the inhibitory activity of different *J. foetida* extracts was assessed against phospholipase A_2 (PLA_2)-associated cytotoxicity induced by crude *Naja naja* venom, using an indirect hemolytic assay as the experimental model (Reddi et al., 2014). Distinct biological responses were observed according to the plant part and extraction solvent used (Reddi et al., 2014).

Aqueous extracts obtained from the stem and root of *J. foetida* markedly enhanced venom-induced hemolysis when pre-incubated with the minimum indirect hemolytic dose (MIHD) of *N. naja* venom, indicating potentiation of PLA_2-associated cytotoxicity rather than inhibition (Reddi et al., 2014). In contrast, the aqueous leaf extract exhibited measurable antivenom activity, partially inhibiting PLA_2-induced hemolysis, although with lower efficacy than that observed for *J. gossypiifolia* extracts under similar experimental conditions (Reddi et al., 2014).

Methanolic extracts of *J. foetida* showed improved inhibitory efficacy, suggesting a solvent-dependent extraction of bioactive constituents with PLA_2-neutralizing potential (Reddi et al., 2014). Among the plant parts tested, the methanolic root extract produced substantial inhibition of PLA_2-mediated hemolysis, reaching approximately 74.5%, whereas the leaf extract displayed moderate inhibitory activity (Reddi et al., 2014). These findings suggest that secondary metabolites capable of interfering with venom-induced hemolysis may be more efficiently extracted using organic solvents, particularly from the roots of *J. foetida* (Reddi et al., 2014).

Chloroform extracts of *J. foetida* exhibited a contrasting activity profile (Reddi et al., 2014). The chloroformic root extract showed high inhibition of PLA_2-associated hemolysis, reaching approximately 81.7%, whereas the leaf extract showed minimal inhibitory activity (Reddi et al., 2014). Phytochemical screening indicated the presence of alkaloids, terpenoids, tannins, and phenolic compounds in *J. foetida* extracts, which may contribute to the observed modulation of venom activity (Reddi et al., 2014). However, the enhancement of hemolysis by some aqueous extracts suggests the presence of polar constituents capable of facilitating PLA_2 activity or increasing membrane susceptibility to venom-induced damage (Reddi et al., 2014).

Overall, the findings reported by Reddi et al. (2014) indicate that *J. foetida* exhibits a dual, extract-dependent effect on *N. naja* venom activity, acting either as a partial inhibitor or as a potentiator of PLA_2-associated cytotoxicity. Although qualitative phytochemical screening indicated the presence of similar major classes of secondary metabolites across different plant parts, the markedly distinct biological outcomes suggest that differences in relative abundance, plant organ distribution, and solvent-dependent extractability are critical determinants of activity (Reddi et al., 2014). Organic solvent extracts, especially those obtained from roots, may concentrate bioactive phenolic or terpenoid constituents capable of interacting with PLA_2 and reducing hemolysis, whereas aqueous stem and root extracts may preferentially contain polar components that enhance venom-induced cytotoxicity (Reddi et al., 2014). Thus, the modulation of venom activity by *J. foetida* appears to depend not merely on the presence of secondary metabolite classes, but on their distribution, extractability, and functional interaction with venom components (Reddi et al., 2014).

3.3.6. Jatropha mutabilis (Pohl) Baill.

Species endemic to the Caatinga biome, occurring in hyperxerophilous areas of the semi-arid region of northeastern Brazil. Popularly known as "pinhão-de-seda", this monoecious species presents inflorescences containing male and female flowers arranged in protogynous dichasial clusters and exhibits adaptations to the water stress typical of dry environments. Previous studies have investigated extracts of this species for phytochemical composition and biological activities, reporting antioxidant and photoprotective properties (Costa et al., 2021).

The latex of *J. mutabilis* has also demonstrated antivenom activity. Unlike previous studies focused mainly on snake venoms, De Souza et al. (2024) described, for the first time, the antiscorpion potential of *J. mutabilis* latex against *Tityus stigmurus* venom (TstiV), a scorpion venom of significant medical importance in northeastern Brazil. The authors employed a combination of *in vitro* and *in vivo* assays to evaluate whether the latex could interact with venom components and attenuate TstiV-induced toxic effects (De Souza et al., 2024).

In vitro analyses indicated a strong interaction between *J. mutabilis* latex and proteins present in TstiV (De Souza et al., 2024). Protein precipitation, assessed by SDS-PAGE at all tested doses, suggested that latex constituents were able to interact directly with venom proteins (De Souza et al., 2024). This interaction was further supported by alterations in venom protein profiles detected by UV-Vis spectroscopy (De Souza et al., 2024). According to the authors, this protein precipitation may contribute to the reduction of venom enzymatic activity (De Souza et al., 2024).

The enzymatic inhibitory potential of the latex was evaluated against hyaluronidase and fibrinolytic activities of TstiV (De Souza et al., 2024). Hyaluronidase activity was assessed using hyaluronic acid as substrate, whereas fibrinolytic activity was evaluated by SDS-PAGE based on the degradation profile of fibrinogen chains (De Souza et al., 2024). These assays confirmed a marked reduction in venom enzymatic activity, with complete inhibition of both hyaluronidase and fibrinolysis at higher venom-to-latex ratios, particularly 1:25 and 1:50 (w/w) (De Souza et al., 2024). Notably, hyaluronidase inhibition exceeded 50% even at the lowest ratio tested (De Souza et al., 2024). These findings are relevant because hyaluronidase acts as a "spreading factor" during envenomation, facilitating venom diffusion through tissues, whereas fibrinolytic activity is closely associated with hemostatic disturbances and tissue damage (De Souza et al., 2024).

The *in vivo* assays evaluated the ability of *J. mutabilis* latex to attenuate nociceptive and edematogenic effects induced by TstiV (De Souza et al., 2024). Latex administration significantly reduced both nociception and edema induced by the venom (De Souza et al., 2024). In the pre-incubation protocol, reductions reached up to 56.5% for the nociceptive response and 50% for edema formation (De Souza et al., 2024). In the pre-treatment protocol, reductions reached 46% and 48.7%, respectively, whereas in the post-treatment protocol, reductions of up to 36.2% for nociception and 34.6% for edema were observed (De Souza et al., 2024).

According to De Souza et al. (2024), these biological responses may be associated with the phytochemical composition of *J. mutabilis* latex. The latex exhibited a diverse chemical profile comprising 75 identified secondary metabolites, including flavonoids, terpenoids, alkaloids, glycosides, and notably cyclic peptides, especially orbitides (De Souza et al., 2024). These compound classes are known for antioxidants, anti-inflammatory, and protease-inhibiting properties, which may contribute to the attenuation of venom-induced local effects (De Souza et al., 2024).

Taken together, these findings indicate that *J. mutabilis* latex exerts antivenom effects through at least two complementary mechanisms: direct toxin neutralization through physicochemical interaction with venom proteins and attenuation of local pathological effects through modulation of inflammatory responses (De Souza et al., 2024). This study expands the antivenom relevance of the genus *Jatropha* beyond snakebite models and supports the potential of *J. mutabilis* as a source of bioactive compounds against scorpion venom-induced toxicity (De Souza et al., 2024).

4. DISCUSSION3.8. ETHNOPHARMACOLOGICAL RELEVANCE OF MEDICINAL PLANTS IN ANIMAL ENVENOMATION

4.1. Ethnopharmacological Relevance Of Medicinal Plants In Animal Envenomation

In many tropical and subtropical regions, medicinal plants remain widely used in the management of envenomation caused by venomous animals, particularly in medically underserved rural communities. The use of these natural resources constitutes a longstanding community-based therapeutic practice across different continents and remains an important component of traditional healthcare systems. The persistence of these practices across generations has been strongly associated with limited access to antivenom therapy in rural areas, socioeconomic vulnerability, and the intergenerational transmission of traditional ecological knowledge (Longbottom et al., 2018; Seabra et al., 2023; Bandé et al., 2025).

Different ethnic groups, including Indigenous peoples of the Americas, have historically used leaves, bark, roots, latex, and other plant-derived materials as traditional first-aid interventions following bites or stings from snakes, scorpions, spiders, and other venomous animals (Agra et al., 2007; Schneider et al., 2021). These preparations are commonly administered as topical applications, infusions, decoctions, or macerated extracts applied directly to the affected site. Such practices have increasingly attracted scientific interest because plant-derived metabolites may modulate venom-induced toxic, enzymatic, inflammatory, and tissue-damaging responses.

Ethnomedical systems across Africa, Asia, and Latin America document the extensive use of medicinal plants for the management of envenomation, especially in rural and medically underserved regions (Kunjam et al., 2013). These therapeutic practices are frequently embedded within culturally structured healing systems and are supported by the intergenerational transmission of traditional medical knowledge. Although traditional systems such as Ayurveda and Traditional Chinese Medicine are based on conceptual frameworks distinct from contemporary biomedicine, they share an empirical understanding that plant-derived preparations may alleviate local and systemic manifestations associated with envenomation, including inflammation, hemorrhage, pain, edema, and tissue damage (Lai et al., 2024).

Ethnobotanical surveys conducted in developing countries consistently demonstrate the continued reliance of local populations on medicinal plants as part of primary healthcare strategies (Nath and Mukherjee, 2023). In India, for example, Ayurvedic practices have historically incorporated plant-based remedies for the management of snake and scorpion envenomation, whereas in Mexico, rural communities employ a diverse repertoire of medicinal species to treat scorpion stings, with representatives of Fabaceae, Lamiaceae, and Asteraceae among the most frequently reported families (Carrera-Fernández et al., 2023). Species such as *Aristolochia elegans*, *Bouvardia ternifolia*, and *Mimosa tenuiflora* have been traditionally administered as infusions, decoctions, or topical preparations for symptoms associated with envenomation (Carrera-Fernández et al., 2023). Despite the widespread ethnomedical relevance of these practices, pharmacological validation and clinical standardization remain limited for many traditionally used species.

The therapeutic use of medicinal plants in envenomation is primarily associated with the management of local and systemic manifestations induced by venom toxins, including pain, edema, erythema, hemorrhage, myonecrosis, and inflammatory responses. These effects have been largely associated with the extensive phytochemical diversity found in medicinal species traditionally employed in ethnomedical practices (Romanelli et al., 2025). Several classes of secondary metabolites, including flavonoids, alkaloids, tannins, saponins, and glycosides, have demonstrated potential to modulate venom-induced toxic pathways in experimental studies (Singh et al., 2017; Romanelli et al., 2025).

Pharmacological investigations suggest that these compounds may interfere with multiple biochemical mechanisms involved in envenomation, including enzymatic activity, oxidative stress, inflammatory signaling, and proteolytic tissue damage (Singh et al., 2017; Romanelli et al., 2025). Among the venom targets most frequently investigated are phospholipases A_2 (PLA_2s), snake venom metalloproteinases (SVMPs), snake venom serine proteases (SVSPs), and other hydrolytic toxins commonly associated with local and systemic toxicity. Polyphenolic compounds, particularly flavonoids and tannins, have been reported to inhibit venom enzymes through mechanisms such as metal ion chelation, protein precipitation, and modulation of inflammatory mediators (Konrath et al., 2022). These interactions may contribute to the attenuation of pathological effects associated with envenomation, including hemorrhage, edema, proteolysis, necrosis, and myotoxicity, as demonstrated in *in vitro* and *in vivo* experimental models (Konrath et al., 2022).

Despite these promising findings, most available evidence remains restricted to preclinical investigations. Therefore, the clinical applicability of plant-derived antivenom compounds is still limited by insufficient toxicological evaluation, lack of phytochemical standardization, limited mechanistic validation, and scarcity of controlled clinical studies. This reinforces the need for systematic approaches capable of integrating ethnopharmacological knowledge, experimental pharmacology, natural products chemistry, and translational toxicology in the search for complementary antivenom strategies.

4.2. Ethnopharmacological And Phytochemical Relevance Of The Genus Jatropha L

The genus *Jatropha* L., belonging to the family Euphorbiaceae and the tribe Jatropheae, comprises approximately 170–180 species distributed across tropical and subtropical regions of the Americas, Africa, and Asia (World Flora Online, 2025). The generic name derives from the Greek terms *iatros* ("physician") and *trophe* ("nourishment"), reflecting the longstanding medicinal relevance attributed to several species within the genus. Although most *Jatropha* species are native to the Americas, their current pantropical distribution has been facilitated by both natural dispersion and anthropogenic introduction, particularly for ornamental, medicinal, and agricultural purposes (Martins et al., 2015). Several species have become well adapted to disturbed and semi-arid environments, where they are frequently incorporated into traditional healthcare systems and ethnomedical practices.

Species of *Jatropha* exhibit considerable morphological and ecological diversity, encompassing trees, shrubs, subshrubs, and herbaceous forms adapted to a wide range of environmental conditions. In general, these species are characterized by perennial root systems, oil-rich seeds, and physiological adaptations associated with drought tolerance and survival in nutrient-poor soils. Such adaptive traits include deep root architecture, water-storage tissues, and high-energy seed reserves, which contribute to the successful establishment of the genus in seasonally dry tropical ecosystems, including the Cerrado and Caatinga biomes of Brazil (Divakara et al., 2010). In addition to their ecological relevance, several *Jatropha* species have attracted growing scientific interest due to their ethnopharmacological applications and diverse phytochemical composition.

Ethnomedicinal reports indicate that *Jatropha* species have traditionally been employed for the treatment of inflammatory disorders, gastrointestinal diseases, infectious conditions, skin lesions, wounds, parasitic infections, and envenomation in different regions of Africa, Asia, and Latin America (Sabandar et al., 2013).

Experimental investigations have further demonstrated that extracts and isolated compounds from several species exhibit a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, antioxidant, cytotoxic, wound-healing, gastroprotective, antiparasitic, and analgesic effects (Cavalcante et al., 2020). These biological properties have been mainly associated with structurally diverse secondary metabolites, particularly diterpenoids, cyclic peptides, flavonoids, alkaloids, coumarins, lignans, and phenolic compounds (Souza et al., 2024). Among these metabolites, diterpenes represent one of the most characteristic and pharmacologically relevant classes within the genus, exhibiting remarkable structural diversity and a wide range of bioactivities (Souza et al., 2024).

Among the most extensively investigated species, *Jatropha curcas* L. stands out due to its economic, pharmacological, and industrial relevance. Popularly known in Brazil as "pinhão-de-cerca", this species is widely cultivated for biodiesel production because of its oil-rich seeds, which also serve as raw material for soaps, varnishes, lubricants, and other industrial products (Melo et al., 2020). In traditional medicine, different parts of the plant have been used in both human and veterinary healthcare. Phytochemical investigations have identified a chemically diverse repertoire of secondary metabolites, especially diterpenoids such as phorbol esters, as well as flavonoids, tannins, saponins, and alkaloids (Sabandar et al., 2013; Souza et al., 2024; Majeed et al., 2025). Preclinical studies have suggested antimicrobial, anti-inflammatory, antioxidant, purgative, cytotoxic, and wound-healing properties associated with these compounds (Sabandar et al., 2013; Souza et al., 2024; Majeed et al., 2025). However, the therapeutic applicability of *J. curcas* requires careful toxicological consideration due to the presence of highly bioactive and potentially toxic constituents, particularly phorbol esters, which have been associated with irritative, cytotoxic, and tumor-promoting effects (Sabandar et al., 2013; Souza et al., 2024; Majeed et al., 2025).

Another species of considerable ethnopharmacological relevance is *Jatropha gossypiifolia* L., popularly known in Brazil as “pinhão-roxo”. Native to the Americas and later introduced into several tropical regions, this species is widely employed in traditional medicine for the management of inflammatory conditions, wound healing, infectious diseases, hypertension, gastrointestinal disorders, and venomous animal bites (Albuquerque et al., 2007; Anani et al., 2016; Upasani et al., 2018). Pharmacological investigations have reported anti-inflammatory, antimicrobial, antiviral, antioxidant, and wound-healing activities associated with extracts obtained from its leaves, roots, stems, and latex (Utshudi et al., 2022). In particular, the latex has received attention due to the occurrence of cyclic peptides and diterpenes with potential biological activity. Nevertheless, despite promising experimental findings, many pharmacological reports remain restricted to preclinical models, and important limitations persist regarding toxicological evaluation, phytochemical standardization, dosage safety, and clinical validation of therapeutically active compounds derived from *Jatropha* species.

Collectively, the available evidence highlights the ethnopharmacological and pharmacological relevance of the genus *Jatropha*, particularly due to the structural diversity of its secondary metabolites and their broad spectrum of experimentally reported biological activities. In the context of envenomation, this chemical diversity provides a plausible basis for the traditional and experimental use of *Jatropha* species as sources of venom-modulating agents. However, the validation of these traditional applications requires reproducible preclinical data, phytochemical standardization, toxicological assessment, and mechanistic studies, especially because some natural products may also contain constituents capable of worsening toxic effects under specific conditions.

4.3 Phytochemical Evidence And Putative Mechanisms Of Antivenom Activity

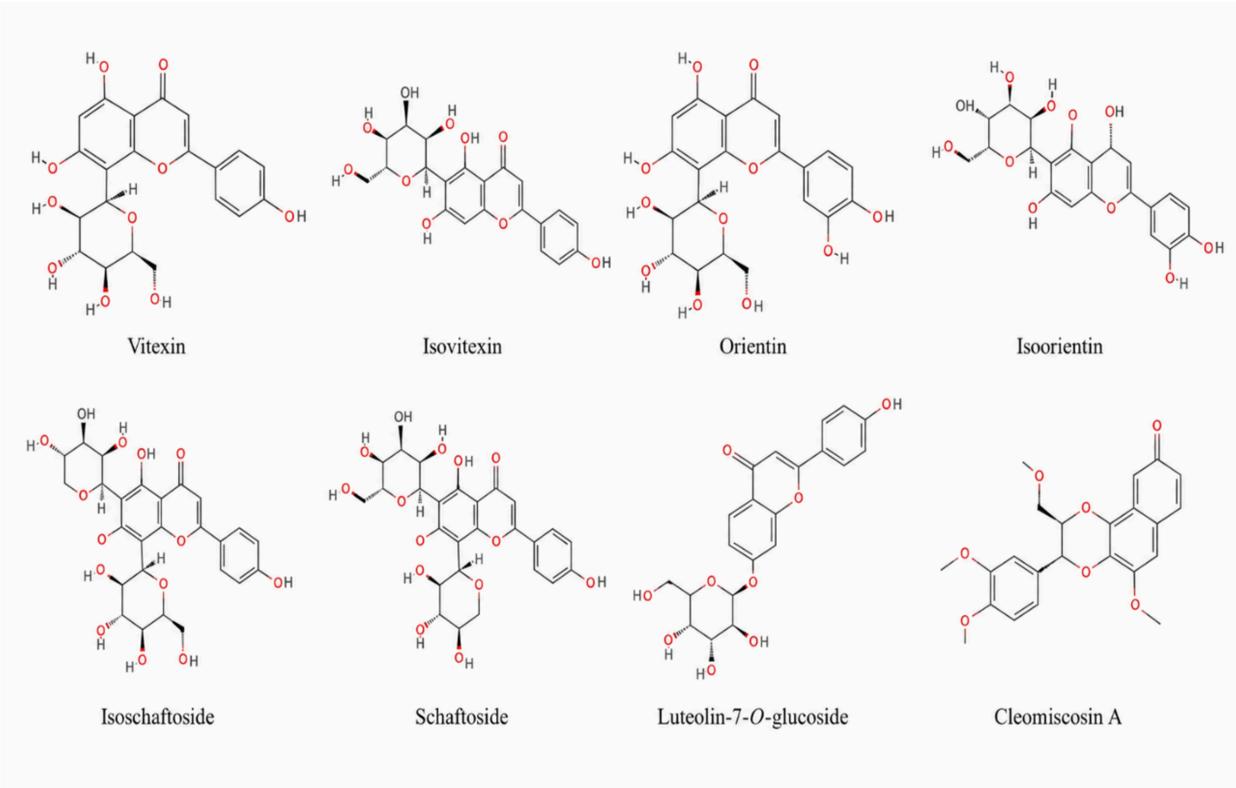
Despite the historical and widespread use of medicinal plants in the traditional management of envenomation caused by venomous animals, the identification of bioactive phytoconstituents capable of directly neutralizing venom toxins has become one of the central objectives of contemporary antivenom research. This growing interest is supported by accumulating evidence showing that several classes of plant-derived secondary metabolites exhibit inhibitory activity against key toxic components of snake venoms, including phospholipases A_2 (PLA_2s), proteases, and hyaluronidases.

Currently, antivenom immunotherapy based on polyclonal antibodies remains the only specific treatment for envenomation caused by animals such as snakes, spiders, and scorpions. Although antivenoms are effective in neutralizing circulating toxins and reducing mortality, conventional formulations present important limitations, particularly their restricted efficacy against local tissue damage, high production costs, cold-chain dependency, batch variability, limited par specificity, and the occurrence of early or delayed hypersensitivity reactions (Albulescu et al., 2020a). Furthermore, the biochemical complexity and interspecific variability of snake venoms substantially compromise the broad-spectrum neutralization capacity of antibody-based therapies.

Recent advances in toxin-oriented therapeutic approaches have reinforced the potential application of small-molecule inhibitors as complementary or adjunctive therapies for envenoming (Albulescu et al., 2020a; Albulescu et al., 2020b). In this context, natural products have emerged as promising sources of venom-neutralizing compounds due to their chemical diversity and multitarget pharmacological properties (Adrião et al., 2022; Romanelli et al., 2025). Phenolic compounds, particularly flavonoids and tannins, have been extensively reported as inhibitors of venom-induced toxic effects through mechanisms involving metal ion chelation, protein precipitation, antioxidant activity, and direct interactions with catalytic domains of venom enzymes (Puzari et al., 2022). Experimental evidence suggests that several polyphenols can inhibit the catalytic activity of PLA_2s and SVMPs by interacting with conserved residues within enzymatic active sites or by chelating divalent metal ions, especially Zn^{2+}, which is essential for metalloproteinase activity. These mechanisms have been associated with attenuation of hemorrhagic, proteolytic, myotoxic, inflammatory, and edematogenic effects induced by viper venoms. Additionally, flavonoids may modulate membrane destabilization, lipid peroxidation, oxidative stress, and inflammatory signaling pathways involved in venom-induced tissue damage.

Among the 13 studies included in this review, there are only seven reported phytochemical investigations of *Jatropha* species. These studies revealed a chemically diverse profile of secondary metabolites distributed across different plant organs, including latex, leaves, stems, and roots. Phytochemical analyses identified alkaloids, terpenoids, steroids, amines, phenolic compounds, particularly flavonoids and tannins, and cyclic peptides in species such as *Jatropha gossypiifolia*, *Jatropha mollissima*, *Jatropha elliptica*, and *Jatropha mutabilis* (Table 3). Among the identified metabolites, C-glycosyl flavonoids such as vitexin, isovitexin, orientin, isoorientin, schaftoside, and isoschaftoside were the compounds most frequently reported across the studies, especially in *J. mollissima* and *J. gossypiifolia* (Fig. 3).

Figure 3. Representative secondary metabolites identified in *Jatropha* extracts, including C-glycosyl flavonoids and related phenolic compounds. Chemical structures were adapted from the National Institutes of Health/National Library of Medicine databases.



Collectively, these findings underscore two major trends. First, they indicate a progressive refinement of phytochemical methodologies toward increasingly robust analytical characterization of *Jatropha*-derived preparations. Second, they reveal the predominance of phenolic metabolites among the identified compounds, reinforcing previous evidence that these constituents may be directly associated with the inhibitory potential of *Jatropha* extracts against venom-associated enzymes and inflammatory mediators described in the included studies.

Table 3. Summary of Phytochemical constituents and analytical techniques reported in preclinical studies of antivenom *Jatropha* species.

n°	species	Plant part	Preparation	Phytochemical analysis method	Compounds identif
1	*Jatropha gossypiifolia*	L	decoction	Classical qualitative phytochemical screening and thin-layer	Sugar alkaloi flavono tannin terpen teroid and

⚠ Esta tabela possui muitas colunas e foi cortada para impressão. Para visualizá-la completa, acesse o artigo original em: https://revistatopicos.com.br/artigos/antivenom-potential-of-the-genus-jatropha-l-euphorbiaceae-a-systematic-review-of-preclinical-evidence-on-natural-inhibitors-of-animal-venoms?noblockage

L: leaves. LA: latex. R: root. RZ: rhizomes. S: stem.

Importantly, although the studies included in this review demonstrated promising *in vitro* and *in vivo* antivenom activities associated with *Jatropha*-derived extracts and fractions, significant methodological limitations remain. Most investigations relied on crude extracts, with limited phytochemical standardization and incomplete characterization of isolated bioactive compounds. This limitation compromises a deeper understanding of the phytochemical basis and molecular mechanisms underlying the observed biological effects, as further discussed in the following section.

4.4. Limitations And Translational Challenges Of Jatropha-derived Antivenom Candidates

The diversity of biological activities reported for botanical taxa is well documented in scientific literature. Historically, natural products, particularly those of plant origin, have played an important role in drug discovery and development, serving as strategic sources of chemical scaffolds with inhibitory, modulatory, or adjuvant properties. In the context of envenomation, the broad repertoire of plant secondary metabolites provides a pharmacological basis for the biological effects observed in traditional medicine, including the attenuation of venom-induced inflammation, hemorrhage, edema, myotoxicity, and enzymatic tissue damage.

However, despite their ethnopharmacological relevance, plant-based therapeutic strategies remain only marginally incorporated into conventional clinical practice. Antivenom therapy remains the gold standard for the treatment of envenomation caused by venomous animals, particularly because it is the only specific therapy capable of neutralizing circulating venom toxins. Nevertheless, conventional antivenoms have limited efficacy against local tissue damage, which is often established rapidly after venom injection. This limitation reinforces the potential value of plant-derived products not as substitutes for antivenom therapy, but as complementary or adjunctive approaches aimed at reducing local morbidity and long-term sequelae.

The translation of *Jatropha*-derived products into therapeutic candidates is still limited by several methodological and pharmacological challenges. Although the studies included in this review demonstrated promising *in vitro* and *in vivo* activities, most investigations relied on crude extracts, latex, powders, or semi-purified preparations. This restricts the identification of specific active compounds and complicates the interpretation of structure–activity relationships. In addition, the chemical composition of plant-derived preparations may vary according to species, plant organ, developmental stage, environmental conditions, extraction solvent, and preparation method. Such variability represents a major obstacle to reproducibility, standardization, quality control, and dose definition.

Another important limitation is the incomplete toxicological characterization of *Jatropha* preparations. Some species of the genus contain highly bioactive and potentially toxic constituents, including diterpenes and phorbol ester-related compounds, which may produce irritative, cytotoxic, or pro-inflammatory effects depending on concentration and route of administration. This concern is particularly relevant because some extracts may not only fail to neutralize venom activity but may also potentiate toxic effects under specific experimental conditions. Therefore, any translational application of *Jatropha*-derived products requires rigorous assessment of acute and chronic toxicity, cytotoxicity, genotoxicity, local irritation, systemic safety, pharmacokinetics, and therapeutic window.

A further challenge concerns the experimental design of pre-clinical anti-venom studies. Many investigations employ pre-incubation protocols, in which venom and plant extract are mixed before administration to the biological system. Although this approach is useful for identifying direct toxin–inhibitor interactions, it does not fully reproduce the clinical scenario of envenomation, in which treatment is administered after venom injection and after the onset of local tissue damage. Pre-treatment protocols also have limited translational relevance, as they simulate prophylactic exposure rather than therapeutic intervention. Therefore, future studies should prioritize post-treatment designs, time-course analyses, dose-response curves, and comparisons with commercial antivenoms or clinically relevant anti-inflammatory drugs.

The scarcity of mechanistic studies also limits the interpretation of the anti-venom effects attributed to *Jatropha* species. Although flavonoids, tannins, terpenoids, alkaloids, phenolic compounds, and cyclic peptides have been proposed as possible contributors to venom inhibition, few studies have isolated, quantified, and tested individual compounds against purified venom toxins. As a result, it remains unclear whether the observed effects are mediated by direct enzymatic inhibition, protein precipitation, metal ion chelation, antioxidant activity, anti-inflammatory modulation, membrane stabilization, or synergistic interactions among multiple constituents. Advanced metabolomic profiling, bioassay-guided fractionation, molecular interaction studies, and validation using purified toxins are therefore essential to clarify the molecular basis of activity.

Formulation development represents a promising but still emerging translational pathway. The nanoemulsion of *J. gossypiifolia* and the topical gel of *J. mollissima* indicate that pharmaceutical technologies may improve local delivery, stability, tissue retention, and practical applicability of *Jatropha*-derived preparations. These approaches are particularly relevant for local manifestations of envenomation, such as edema, hemorrhage, dermonecrosis, and inflammatory tissue damage, which are often poorly neutralized by systemic antivenom therapy. However, these formulations still require further evaluation regarding stability, skin permeation, dose uniformity, toxicity, scalability, regulatory feasibility, and performance in clinically realistic post-envenomation models.

Overall, the available evidence supports the potential of *Jatropha* species as sources of bioactive compounds with antivenom or adjuvant properties. Nevertheless, the current data remain predominantly preclinical and heterogeneous. The development of *Jatropha*-derived antivenom candidates will require a multidisciplinary strategy integrating ethnobotany, toxinology, pharmacology, natural products chemistry, pharmaceutical technology, and translational toxicology. Future studies should move beyond crude extract screening and prioritize standardized preparations, isolated compounds, validated mechanisms of action, rigorous toxicological profiling, and comparative efficacy against commercial antivenoms. Only through this integrated approach will it be possible to determine whether *Jatropha*-derived products can become safe, reproducible, and clinically useful adjuncts in the management of animal envenomation.

5. CONCLUSION

This systematic review demonstrates that species of the genus *Jatropha* have relevant preclinical anti-venom potential, particularly against local and enzymatic effects induced by snake and scorpion venoms. The evidence indicates that different plant-derived preparations, including extracts, latex, powders, gels, and nanoemulsions, can reduce venom-induced edema, hemorrhage, dermonecrosis, myotoxicity, nociception, coagulation disturbances, and inflammatory responses. The antivenom activity of *Jatropha* species appears to be associated with both direct inhibition of venom toxins and modulation of inflammatory processes. These effects are probably related to the presence of phenolic compounds, flavonoids, tannins, terpenoids, alkaloids, and cyclic peptides, although the active compounds and their mechanisms remain insufficiently characterized.

Overall, *Jatropha* species should be regarded as promising sources of adjuvant agents for antivenom research, especially for local tissue damage that is poorly neutralized by conventional antivenoms. However, their therapeutic application still depends on phytochemical standardization, toxicological validation, identification of active compounds, and studies using clinically realistic post-treatment models. Therefore, the available evidence supports the scientific relevance of *Jatropha* as a source of natural venom inhibitors, but not yet its direct clinical use. Future studies should move from crude extract screening toward standardized, safe, and mechanistically validated preparations.

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