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# *Targeting Snake Venom Metalloproteinases with Natural Compounds: A Systematic Review of Mechanism and Experimental Evidence*

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## ABSTRACT
Snakebite envenomation remains a major public health problem in tropical regions, with local tissue damage largely mediated by snake venom metalloproteinases (SVMPs). Conventional antivenom therapy shows limited effectiveness against these local effects, prompting interest in complementary therapies derived from natural products. This study is a systematic literature review that evaluates the inhibitory effects of natural compounds against SVMP activity. The literature search was conducted using PubMed, ScienceDirect, Google Scholar, and Garuda databases, focusing on experimental *in vitro*, *in vivo*, and *in silico* studies published within the last 15 years. From the screened articles, six studies met the inclusion criteria and consistently demonstrated that plant-derived secondary metabolites, particularly flavonoids, tannins, and phenolic compounds, effectively inhibited SVMP-related activities such as hemorrhage, proteolysis, edema, and tissue necrosis. The inhibitory mechanisms were mainly associated with zinc chelation, direct binding to catalytic domains, and structural destabilization of SVMPs. These findings indicate that natural SVMP inhibitors have strong potential as complementary therapeutic agents to reduce local tissue damage following snakebite envenomation.
**Keywords:** snakebite, snake venom metalloproteinase, SVMP inhibitor, natural compounds, systematic review

## ABSTRAK
Envenomasi gigitan ular masih menjadi masalah kesehatan masyarakat yang signifikan di wilayah tropis, dengan kerusakan jaringan lokal terutama dimediasi oleh snake venom metalloproteinases (SVMP). Terapi antivenom konvensional memiliki keterbatasan dalam menetralkan efek lokal tersebut, sehingga mendorong pencarian terapi komplementer berbasis bahan alam. Penelitian ini merupakan systematic review yang mengevaluasi efek penghambatan senyawa alami terhadap aktivitas SVMP. Penelusuran literatur dilakukan pada basis data PubMed, ScienceDirect, Google Scholar, dan Garuda dengan fokus pada studi eksperimental in vitro, in vivo, dan in silico yang dipublikasikan dalam 15 tahun terakhir. Dari artikel yang diseleksi, enam studi memenuhi kriteria inklusi dan secara konsisten menunjukkan bahwa metabolit sekunder tanaman, terutama flavonoid, tanin, dan senyawa fenolik, mampu menghambat aktivitas SVMP seperti perdarahan, proteolisis, edema, dan nekrosis jaringan. Mekanisme penghambatan terutama berkaitan dengan khelasi ion seng, ikatan langsung pada domain katalitik, dan perubahan struktur SVMP. Temuan ini menunjukkan bahwa inhibitor SVMP berbasis bahan alam berpotensi sebagai terapi komplementer untuk mengurangi kerusakan jaringan lokal akibat gigitan ular.
**Kata kunci:** gigitan ular, snake venom metalloproteinase, inhibitor SVMP, senyawa alami, systematic review

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## INTRODUCTION
Snakebite envenomation remains a major global public health problem, particularly in tropical and subtropical regions where access to timely antivenom therapy is limited (1). The World Health Organization classifies snakebite envenomation as a *Neglected Tropical Disease* due to its high burden of mortality, morbidity, and long-term disability (2). In addition to systemic toxicity, local tissue damage such as hemorrhage, edema, necrosis, and permanent functional impairment constitutes a major clinical challenge and is often inadequately controlled by conventional antivenom therapy (3).
Snake Venom Metalloproteinases (SVMPs) are among the most abundant and pathogenic toxins in viperid venoms and play a central role in venom-induced local tissue injury (4). SVMPs degrade extracellular matrix components, disrupt vascular integrity, and induce severe hemorrhage and

inflammation. Importantly, antivenoms show limited efficacy in neutralizing SVMP-mediated local effects once the enzymes have bound to tissue targets, highlighting the need for complementary therapeutic strategies that directly inhibit SVMP activity(5).

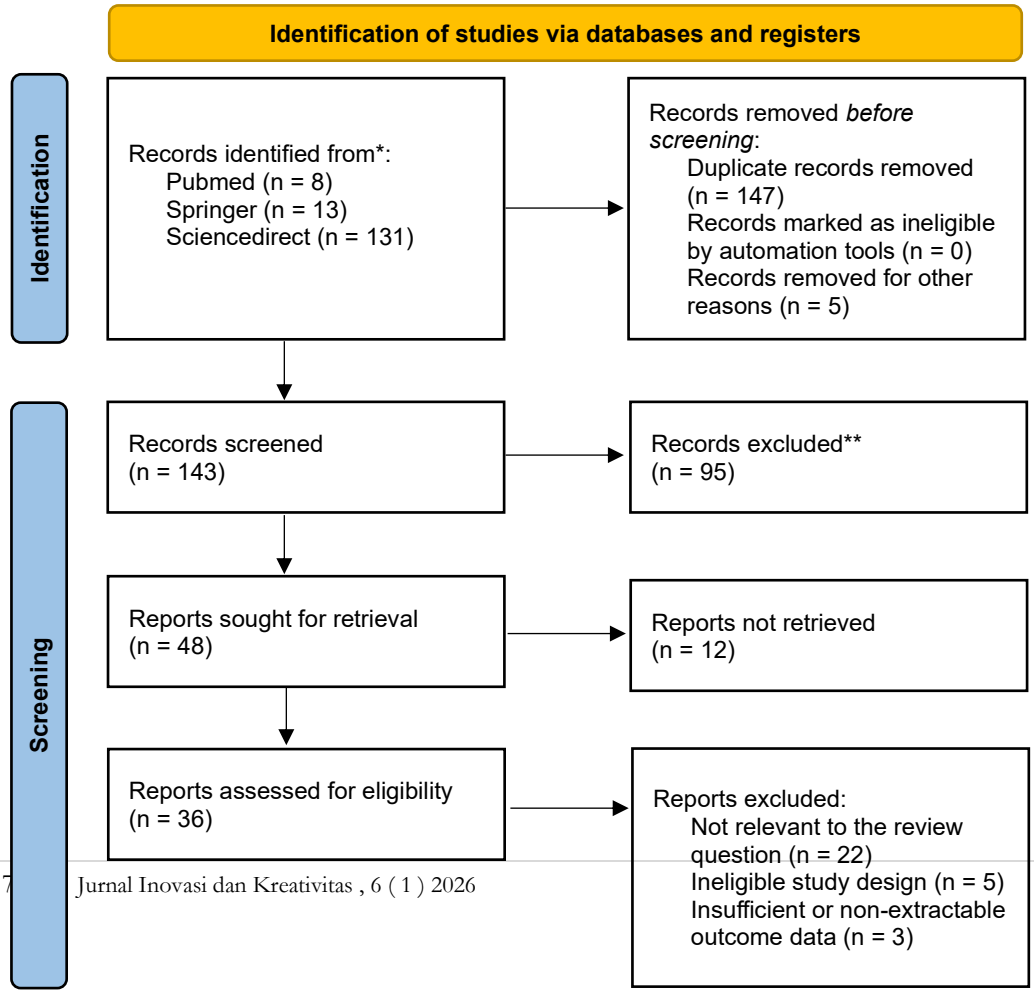
In recent years, increasing attention has been directed toward natural compounds and plant-derived extracts traditionally used in snakebite management (6). Several experimental studies have reported that secondary metabolites such as flavonoids, tannins, alkaloids, and phenolic acids can inhibit SVMP activity through metal ion chelation, enzyme conformational alteration, or direct binding to catalytic domains. Advances in *in vitro*, *in vivo*, and *in silico* approaches have further contributed to understanding the molecular mechanisms underlying SVMP inhibition by these compounds (7,8).

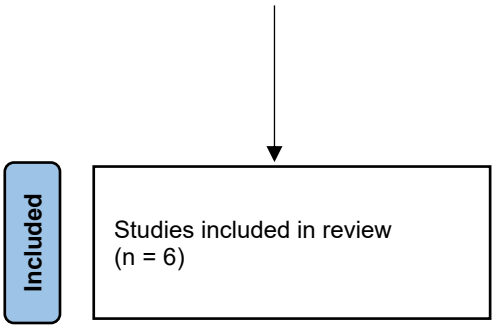
Despite the growing body of evidence, data on SVMP inhibitors remain fragmented across studies with heterogeneous designs, experimental models, and outcome measures. To date, no systematic synthesis has specifically focused on SVMP-targeted interventions derived from natural products. Therefore, this systematic review aims to critically evaluate and synthesize existing evidence on the inhibitory effects of natural compounds against snake venom metalloproteinases, with the goal of identifying promising candidates and mechanistic insights that may support the development of adjunctive therapies for snakebite envenomation.

## MATERIALS AND METHODS

This systematic review focuses on evaluating the inhibitory potential of natural compounds and plant extracts against Snake Venom Metalloproteinases (SVMPs) as a complementary strategy in snakebite management. Articles were identified through database searches in PubMed, ScienceDirect, and SpringerLink using the keywords *"snake venom metalloproteinase"*, *"SVMP inhibitor"*, *"natural compound"*, *"plant extract"*, *"anti-snake venom"*, and *"hemorrhagic toxin"*, combined with Boolean operators.

Only full-text original research articles published in English were included. Eligible studies comprised *in vitro*, *in vivo*, and *in silico* investigations that explicitly evaluated SVMP inhibition or SVMP-related biological effects. Studies focusing primarily on non-SVMP toxins such as phospholipase $A_2$ or neurotoxins were excluded. The study selection process was conducted through title and abstract screening followed by full-text assessment, in accordance with PRISMA guidelines, and is summarized in the corresponding flow diagram.






## RESULTS AND DISCUSSION

| No. | Author (Year) | Study Design | Population / Model | Intervention | Comparator | Instruments / Assessed Parameters | Primary Outcome | Secondary Outcome | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Vieira et al. (2021) (9) | In vitro & in vivo experimental | *Bothrops pauloensis* venom; Swiss mice | Isohemigossypolone (ISO) isolated from *Pachira aquatica* | Untreated venom | SVMP-induced hemorrhagic activity, fibrinogenolysis, molecular docking and molecular dynamics | Significant reduction in hemorrhagic and fibrinogenolytic activities | Inhibitory effects remained evident in post-envenomation treatment | ISO effectively and directly inhibits SVMP and shows potential as an adjuvant therapy |
| 2 | De Moura et al. (2016) (10) | In vitro & in vivo experimental | *Bothrops jararaca* venom; mice | *Jatropha gossypiifolia* extract | Conventional antivenom | SVMP proteolytic activity, edema, hemorrhage | Significant inhibition of SVMP-mediated local effects | More effective than antivenom in post-treatment setting | Plant extract shows potential to complement limitations of conventional antivenom |
| 3 | Ribeiro et al. (2019) (11) | In vitro + proteomic analysis | *Bothrops atrox* venom | *Aniba fragrans* extract | Untreated venom | SDS-PAGE, Western blot, SVMP fibrinolytic activity | SVMP protein precipitation and inactivation | Additional antibacterial activity observed | Primary mechanism involves SVMP binding and protein precipitation |
| 4 | Silva et al. (2016) (12) | In vivo experimental | Swiss mice; *Bothrops jararacussu* venom | *Schwartzia brasiliensis* plant fraction | Untreated venom | Coagulant activity, hemorrhage, SVMP-induced lethality | Significant reduction in tissue damage | No toxicity detected in animal models | Plant fraction is effective as an adjuvant anti-SVMP therapy |
| 5 | Passos et al. (2024) (13) | In vitro + chemometric analysis | *Bothrops jararaca* venom | *Siparuna* spp. alkaloids | Negative control | SVMP proteolytic activity, coagulation assays, UHPLC-MS/MS | SVMP inhibition exceeding 90% | Identification of specific active alkaloids | Certain alkaloids show strong correlation with SVMP inhibition |
| 6 | De Souza et al. (2020) (14) | In vivo experimental | Mice; *Bothrops erythromelas* venom | *Jatropha gossypiifolia* extract | Antivenom | Hemorrhage, edema, SVMP proteolytic activity | Significant reduction in SVMP-mediated local effects | Antivenom failed to inhibit local tissue damage | Phytotherapy demonstrates superiority for SVMP-driven local effects |

Based on the six studies analyzed in this systematic review, a relatively consistent pattern emerges indicating that Snake Venom Metalloproteinase (SVMP) represents a critical and relevant molecular target in the management of local effects of venomous snake envenomation. All included studies demonstrated that inhibition of SVMP activity, using either plant extracts or isolated natural compounds, was associated with a significant reduction in local toxic effects, particularly hemorrhage, edema, and tissue damage. These outcomes were consistently observed through *in vitro* assays assessing SVMP proteolytic activity as well as *in vivo* evaluations showing reduced hemorrhagic area and decreased severity of tissue necrosis in animal models.

The reported effectiveness of SVMP inhibition is closely related to the biochemical properties of SVMP as a $Zn^{2+}$-dependent metalloproteinase. Most studies indicated that the tested bioactive compounds—

predominantly polyphenols and flavonoids—are capable of directly interacting with the SVMP active site through metal ion chelation or stable protein–ligand complex formation. This interaction results in diminished proteolytic degradation of extracellular matrix components such as collagen and gelatin, thereby contributing to vascular stabilization and attenuation of local tissue injury following envenomation.

In addition to the primary outcomes of hemorrhage and proteolytic activity inhibition, several studies reported supportive secondary outcomes, including improved histopathological tissue architecture, reduced inflammatory cell infiltration, and enhanced venom protein stability as demonstrated by spectroscopic analyses and *in silico* modeling. Studies integrating *in vitro*, *in vivo*, and *in silico* approaches provided more comprehensive evidence of a causal relationship between molecular interactions with SVMP and the observed biological effects, compared to studies employing a single experimental approach.

Nevertheless, this systematic review also identified considerable methodological heterogeneity among the included studies, particularly regarding study design, animal models, intervention dosages, and outcome assessment methods. All analyzed studies remain at the preclinical stage, with relatively small sample sizes and no clinical validation in human subjects. Furthermore, the absence of standardized protocols for SVMP activity measurement and uniform outcome criteria precluded quantitative meta-analysis. Therefore, although the findings consistently indicate promising inhibitory effects, further research employing standardized methodologies and more robust experimental designs is required to strengthen the evidence supporting SVMP inhibitors as complementary therapeutic strategies in snakebite envenomation management.

## CONCLUSION

This systematic review demonstrates that Snake Venom Metalloproteinase (SVMP) is a critical molecular target in the management of local tissue damage following snakebite envenomation. Across the six included preclinical studies, natural compounds and plant-derived extracts consistently exhibited significant inhibitory effects on SVMP activity, leading to marked reductions in hemorrhage, edema, proteolytic tissue degradation, and necrosis in experimental models. The inhibitory efficacy of these agents is largely attributed to direct interactions with SVMP, including metal ion chelation and protein–ligand complex formation, which impair the proteolytic function of the enzyme. Several studies further indicate that SVMP inhibitors retain effectiveness even when administered after envenomation, highlighting their potential as complementary or adjuvant therapies alongside conventional antivenom.

Although current evidence is limited to in vitro, in vivo, and in silico studies, the findings collectively support the therapeutic promise of SVMP-targeted phytochemicals in mitigating local venom-induced pathology. Future research involving standardized methodologies and clinical validation is required to translate these findings into practical therapeutic applications.

## CONFLICT OF INTEREST

The author declares no conflict of interest in this study.


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