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Andrographis paniculata Experimental Evidence as a Natural Anti-Venom: A Comprehensive Review

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Abstract
Snakebite remains a significant public health concern, particularly in rural regions where access to timely medical care and antivenom is limited. *Andrographis paniculata*, a traditionally valued medicinal herb, has gained attention for its potential supportive role in snakebite management. Its major constituents are especially andrographolide, exhibit anti-inflammatory, antioxidant, and enzyme-inhibitory activities that may counteract venom-induced tissue damage. Experimental evidence from in vitro and in vivo studies demonstrates its ability to inhibit key venom enzymes, reduce local inflammation, and protect organs from oxidative stress. While extracts show activity against venoms of species such as *Naja naja* and *Daboia russelii*, their efficacy remains partial and inconsistent. Limitations include variable extract quality, low bioavailability, rapid metabolism, and lack of clinical trials. Although *A. paniculata* shows promise as a complementary therapy, standardised formulations and human studies are essential before it can be considered a reliable adjunct in snakebite treatment.

Keywords: Snakebite, public health, rural healthcare, *Andrographis paniculata*, andrographolide, venom enzymes

Introduction

Fig 1: Complete budding plants of *A. paniculata*

- Snakebite envenomation remains a major problem, yet an often overlooked global health challenge, particularly in rural areas of tropical and subtropical countries.
- Each year, an estimated 5.4 million people experience snakebites, and roughly 1.8 to 2.7 million of these cases involve a significant venomous bite. Tragically, this leads to around 81,000 to 138,000 deaths per year, while thousands of survivors are left with long-term complications, including limb loss and other permanent disabilities.

- The burden is especially high in low and middle-income regions of Asia, where limited access to timely medical care leads to higher mortality.
- According to the Global Burden of Disease (2019) assessment, snakebite envenoming ranks among the most fatal and neglected tropical diseases worldwide.
- Currently, antivenom serums remain the primary treatment for snakebite, but they still have several drawbacks. Many patients experience side effects such as allergic reactions or serum sickness after administration. In addition, antivenoms usually work well against systemic effects but are less effective in preventing or reversing local tissue damage at the bite site. Their production is also challenging, and they are expensive to manufacture, have stability issues, and sometimes fail to neutralise all venom components completely. These limitations emphasise the need for safer, more efficient, and more accessible antivenom therapies in the future.
- There is growing interest in using plant-based compounds as supportive or alternative options to conventional antivenoms. Medicinal plants contain a wide range of bioactive molecules, and many of them tend to cause fewer side effects compared to serum-based treatments.
- Some research has shown that phytochemicals such as flavonoids, polyphenols, triterpenes and steroids may help to counteract the harmful effects of snake venom. These natural compounds demonstrate the potential to neutralise various venom components and reduce tissue damage, highlighting their value as promising complementary anti-venom agents.
- Among them, most widely used traditional plant Kalmegh, or Andrographis paniculata, is a well-regarded medicinal herb known for its wide range of therapeutic benefits and across many Asian traditions and has long been valued for its healing properties.
- In traditional systems such as Ayurveda, Traditional Chinese Medicine, and Unani, the plant is commonly used for its anti-inflammatory, detoxifying, and blood-cleansing effects and also used to support digestion, strengthen the immune system, and protect the liver, largely due to its strong anti-inflammatory and antioxidant actions.
- Its primary bioactive compound, andrographolide, along with other diterpenoid lactones, is responsible for many of these effects, including antimicrobial and liver-protective activities. Because of these versatile properties, Kalmegh has gained attention in modern research, particularly for its potential role in reducing venom-induced toxicity, so it has been used in managing snakebite symptoms, either taken orally or applied to the affected area.
- Because of this long-standing traditional use and its rich phytochemical profile, *Andrographis paniculata* has become an important candidate in current research exploring plant-based complementary anti-venom therapies.

Fig 2: Andrographis paniculata growing in field conditions

Botanical Description and Traditional Uses

Botanical Description

Andrographis paniculata (Kalmegh), widely recognized as the "King of Bitters," is an annual herbaceous species valued for its medicinal relevance across traditional and modern systems of medicine.

Table 1: Botanical Description, Taxonomy, Distribution, and Uses *of Andrographis paniculata*

Parameter	Description
Scientific Name	*Andrographis paniculata* (Burm.f.) Nees
Common Names	Kalmegh, King of Bitters, Green Chiretta
Family	Acanthaceae
Taxonomic Classification	Kingdom: Plantae Division: Tracheophyta Class: Magnoliopsida Order: Lamiales Family: Acanthaceae Genus: *Andrographis* Species: *A. paniculata*
Habit	Annual, erect, branched herb
Height	30–110 cm
Stem	Slender, quadrangular with longitudinal ridges and winged angles; dark green
Leaves	Opposite, simple, lanceolate, glabrous; 2–12 cm × 1–3 cm; acute apex and entire margin
Flowers	Small, white with rose-purple spots; arranged in loose axillary or terminal racemes/panicles
Fruits	Linear-oblong capsules (~1.9 cm long)
Seeds	Yellowish-brown, sub-quadrate
Flowering & Fruiting Period	December to April
Habitat	Moist, semi-shaded areas in plains, foothills, forest edges, and wastelands
Geographical	Native to South and Southeast Asia (India, Sri Lanka, Bangladesh, Myanmar, Thailand, Malaysia, Indonesia, China); now

Distribution	also cultivated in Africa, the Caribbean, and tropical regions worldwide
Major Uses	Widely used in traditional and modern medicine for its anti-inflammatory, antipyretic, hepatoprotective, immunomodulatory, antimicrobial, and antioxidant properties. Commonly employed for treating liver disorders, fevers, digestive issues, upper respiratory infections, and general immune support. Extracts and andrographolide compounds are also studied for antiviral, anticancer, and antivenom potential.

Major Bioactive Constituents of *Andrographis paniculata*

- Phytochemical screening of *Andrographis paniculata* usually contains the following steps:
- preparing a soft extract using a suitable solvent such as methanol or ethanol in a Soxhlet apparatus, the solvent is used to capture the plant's major chemical constituents.
- This extract is then examined to identify different groups of natural compounds, such as flavonoids, alkaloids, saponins, terpenoids, phenolics, and the characteristic diterpenoids for which the plant is well known. To make sure the material being studied is genuinely Andrographis paniculata, researchers often confirm the plant's identity through DNA barcoding, commonly using the rbcL gene.
- The actual testing involves a mix of traditional and modern techniques. Simple colour-based reactions, like Wagner's test for alkaloids or the Shinoda test for flavonoids, offer quick initial insights. More precise tools like TLC, HPLC, and various spectroscopic methods are then used to verify and measure specific chemical constituents, especially andrographolide. Together, these approaches provide a clear picture of the plant's chemical makeup and help explain its strong antimicrobial and anti-inflammatory activities.
- *Andrographis paniculata* contains a rich profile of bioactive constituents, particularly diterpenoid lactones and flavonoids. The major diterpenoids include andrographolide, which is the most abundant and can constitute up to about 4% of the dried plant material, along with neoandrographolide, dehydroandrographolide, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydroandrographolide.
- In addition to these diterpenoids, the plant also contains several flavonoids and polyphenolic compounds, such as 7-O-methylwogonin, apigenin, onysilin, 5-hydroxy-7,8-dimethoxyflavone, and other related polyphenols. Together, these constituents contribute to the plant's wide spectrum of therapeutic properties.

Table 2: Major Chemical Constituents of *Andrographis paniculata* and Their Reported Uses

Constituent	Class	Key Biological / Medicinal Uses
Andrographolide	Diterpenoid lactone	Strong anti-inflammatory, antioxidant, hepatoprotective, immunomodulatory, antidiabetic, antiviral, and anticancer activities.
Neoandrographolide	Diterpenoid lactone	Antioxidant, hepatoprotective, anti-inflammatory; supportive in immune enhancement and liver protection.
14-Deoxyandrographolide	Diterpenoid	Antimicrobial, anti-inflammatory, and potential antitumor effects.
14-Deoxy-11,12-didehydroandrographolide	Diterpenoid	Antioxidant, cytotoxic, and anti-inflammatory properties.
Dehydroandrographolide	Diterpenoid lactone	Antiviral, antibacterial, and anti-inflammatory effects.
Apigenin	Flavonoid	Antioxidant, antimicrobial, anticancer, and anti-inflammatory; supports digestive health.
7-O-Methylwogonin	Flavonoid	Anti-inflammatory, antioxidant, and potential neuroprotective effects.
Onysilin	Flavonoid	Antioxidant and antimicrobial potential (less commonly studied).
5-Hydroxy-7,8-dimethoxyflavone	Flavonoid	Anti-inflammatory, antioxidant, and cytotoxic activities.
Polyphenols (various)	Polyphenolic compounds	General antioxidant, antimicrobial, and immune-supportive roles; contribute to overall therapeutic activity.

Structures of constituents

Andrographolide

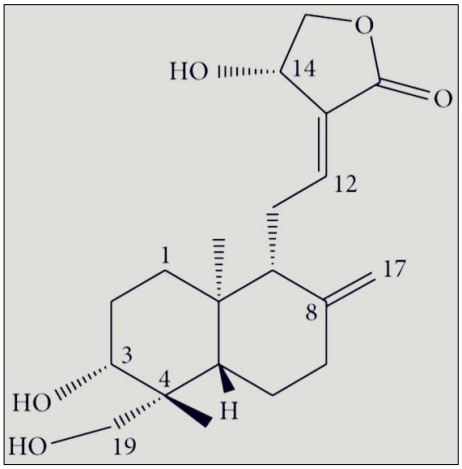

Fig 3: Structure of Andrographolide

Neoandrographolide

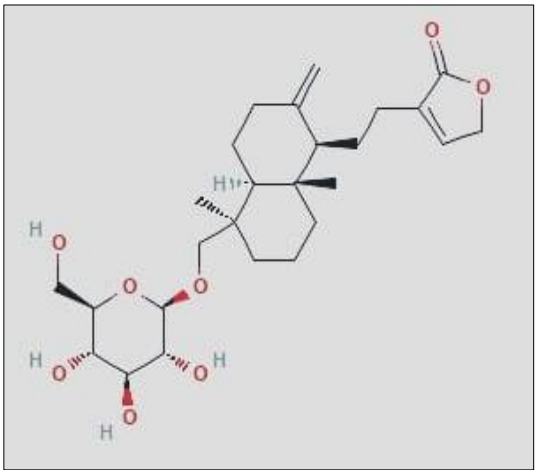

Fig 4: structure of Neoandrographolide

14-Deoxyandrographolide

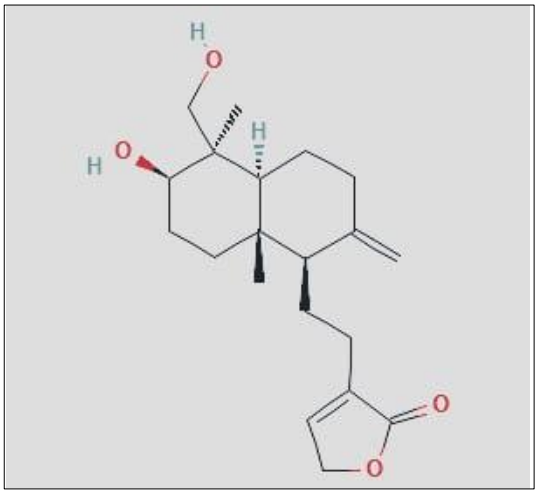

Fig 5: structure of 14-Deoxyandrographolide

14-Deoxy-11,12-didehydroandrographolide

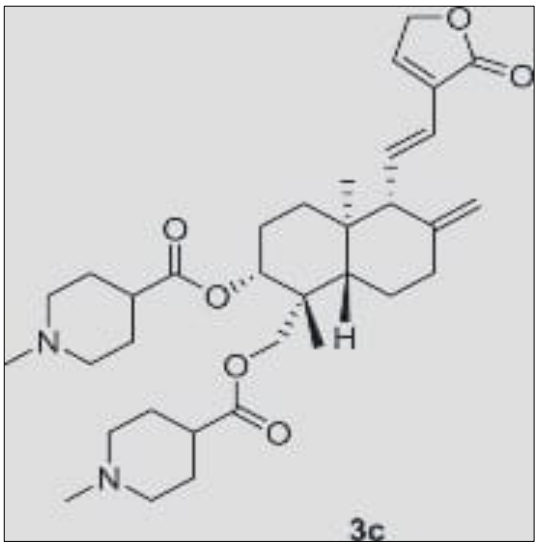

Fig 6: Structure of 14-Deoxy-11,12-didehydroandrographolide

Dehydroandrographolide

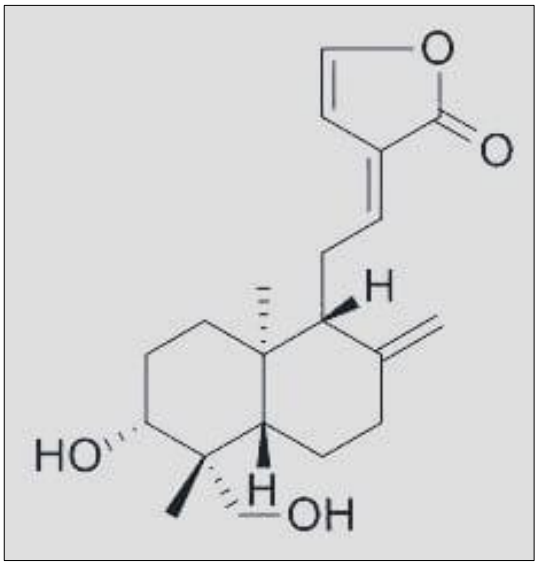

Fig 7: Structure of Dehydroandrographolide

Apigenin

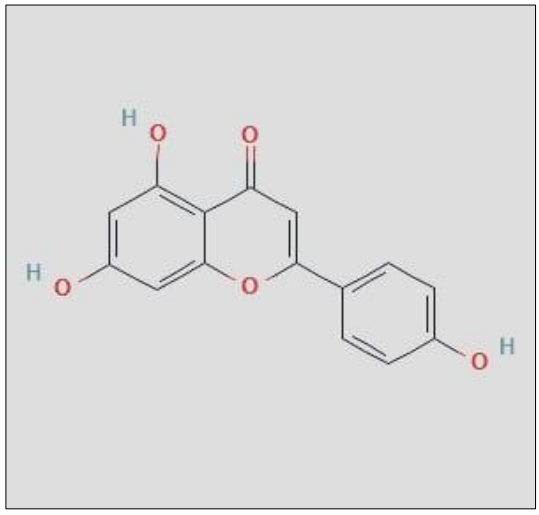

Fig 8: Structure of Apigenin

7-O-Methylwogonin

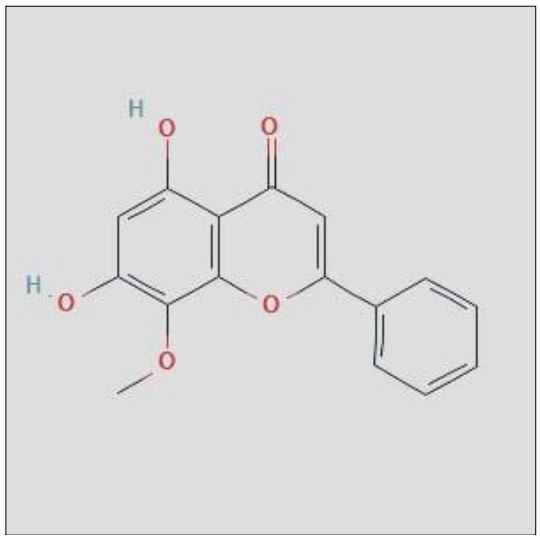

Fig 9: Structure of 7-O-Methylwogonin

Onysilin

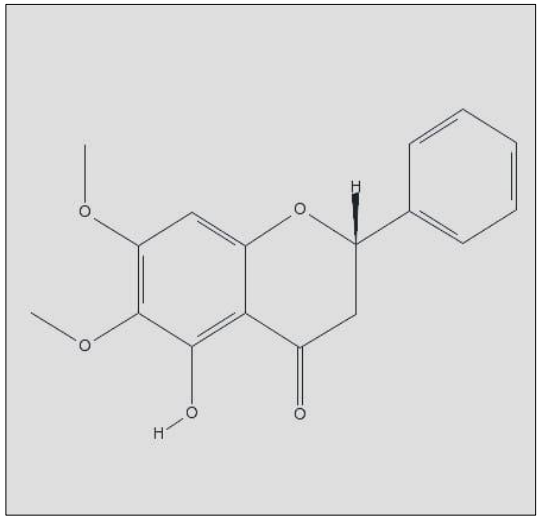

Fig 10: Structure of Onysilin

5-Hydroxy-7,8-dimethoxyflavone

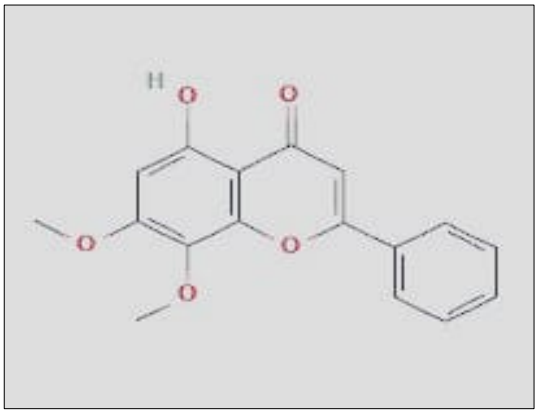

Fig 11: Structure of 5-Hydroxy-7,8-dimethoxyflavone

Polyphenols

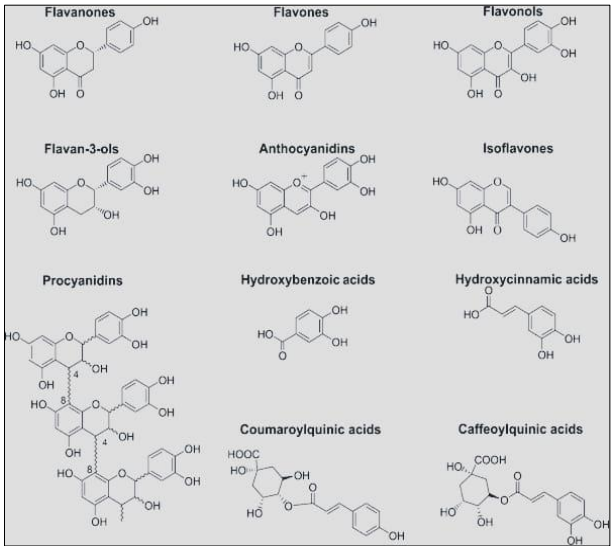

Fig 12: Structure of Polyphenols

Variation in Anti-Venom Potential Across Snake Species
Venom Types Shown to Respond to *A. paniculata*

1. Indian cobra — *Naja naja* (and other Naja spp.)

- Multiple studies have shown that in vitro enzyme inhibition (e.g., inhibition of acetylcholinesterase and hyaluronidase) and animal protection when ethanolic/methanolic extracts of *A. paniculata* are tested against *Naja naja* venom. These findings indicate the extract can reduce some neurotoxic and spreading-factor activities of cobra venom in laboratory models

2. Russell's viper — *Daboia russelii*

- Several shown that that methanolic extracts of A. paniculata neutralized enzymatic activities (e.g., phospholipase A2, proteases) and reduced lethality in animal models challenged with *D. russelii* venom. Some reports state full neutralisation of specified LD-units in controlled in-vivo assays

3. Other cobra species / Naja philippinensis (and venoms from other regions)

- Work on *A. paniculata* root constituents and leaf extracts indicates inhibition of secretory PLA2 from *Naja* spp. (for example, studies that look at Philippine cobra venom components). These are specific biochemical or docking/assay studies rather than human trials.

Venoms Not Adequately Neutralised by *Andrographis paniculata*

1. Summary of In-Vitro Studies

- In vitro experiments have mainly focused on assessing whether extracts of the plant can block specific venom enzymes that contribute to toxicity.
- These studies often test the extract against phospholipase A_2, proteases, hyaluronidase, and other venom-associated enzymes.
- Across multiple publications, researchers have observed that *A. paniculata,* especially in its methanolic and ethanolic extract forms, can inhibit some of these enzymes in a dose-dependent manner.
- The reduction in enzyme activity suggests that the plant contains compounds capable of interacting with venom proteins before they cause extensive tissue damage.
- However, the degree of inhibition varies by venom type, extraction method, and the concentration of the plant extract. This means that while in-vitro results are encouraging, they cannot be generalised to all venoms or clinical situations.

2. Summary of In-vivo Studies

- Animal studies have been conducted to determine whether the plant can reduce the severity of envenomation in living organisms. In these experiments, venoms from vipers and cobras are often used to test the plant's protective effects.
- In several studies, *A. paniculata* extracts have been shown to decrease local swelling, reduce haemorrhagic effects, and improve certain biochemical markers associated with tissue damage. Some experiments also reported that combining the plant extract with conventional antivenom provided better improvement than antivenom alone.
- Despite these positive findings, complete protection against venom-induced death is not consistently achieved, and the plant shows limited benefit in cases involving strong neurotoxins.
- This highlights that *A. paniculata* may help with supportive or localized reactions but does not replace standard antivenom therapy.

Extract Types Used in Anti-Venom Research

Researchers have tested several extract types to understand which solvent pulls out the most active phytochemicals:

1. **Methanolic Extracts:** These are the most widely used in laboratory studies. They generally show stronger enzyme-inhibiting activity because methanol extracts a broad range of active compounds, including andrographolide and related diterpenoids.
2. **Ethanolic Extracts:** Ethanol extracts often demonstrate similar activity to methanolic extracts and are considered effective for isolating anti-inflammatory and antioxidant molecules that may contribute to venom neutralization.
3. **Aqueous Extracts (Water-based):** These resemble traditional herbal preparations. They do show some anti-venom activity, but usually at a lower potency than alcoholic extracts, likely due to differences in the types of phytochemicals that water can extract.

Anti-Venom Mechanisms of *Andrographis paniculata*

A snakebite injects venom into the body, and Scientific studies suggest that the extract of *Andrographis paniculata* possesses anti-venom properties, primarily due to its ability to neutralise the toxic components of the venom, such as specific enzymes and toxins, which act by following mechanisms:

It slows down venom enzymes

- Snake venom contains aggressive enzymes like PLA_2, metalloproteases, and hyaluronidase, which damage tissues rapidly.
- *Andrographis paniculata* extracts can bind to or block these enzymes, reducing their ability to destroy cells and spread through tissues.

It limits local tissue destruction

- Because the harmful enzymes are weakened, the herb helps in:
- Reducing bleeding under the skin
- decreasing muscle breakdown
- protecting red blood cells from bursting
- This slows down the typical swelling and necrosis that occur after venom entry.

Inflammatory reaction

Snakebite triggers a heavy inflammatory response. Andrographolide naturally switches off major inflammatory pathways like NF-κB and slows the release of TNF-α, IL-6, and other cytokines. This results in: less swelling, less pain, reduced secondary tissue injury

It boosts the antioxidant defence system

- Venom produces a burst of oxidative stress that damages organs.
- The herb increases natural antioxidants in the body, such as superoxide dismutase (SOD), catalase, glutathione
- This helps protect cells from oxidative damage and supports tissue recover

It protects major organs and also supports the immune system

- Studies show that *A. paniculata* can shield the heart, liver and kidneys from venom-induced stress.
- This protective effect is due to its combination of anti-inflammatory, antioxidant, and membrane-stabilising properties.
- The plant enhances macrophage activity, which is responsible for cleaning up venom components and repairing tissue.
- It may also help preserve important blood proteins (like α2-macroglobulin), which naturally neutralise venom proteases.

Experimental Evidence

In Vitro Assays

In vitro systems are commonly used as the first step in screening anti-venom activity. These tests involve direct interaction between the plant extract and purified venom or isolated venom enzymes under controlled laboratory conditions.

Typical in vitro evaluations include:

- Phospholipase A_2 (PLA_2) inhibition tests: These measure how well the extract suppresses PLA_2, an enzyme that contributes to inflammation, myotoxicity, and cell membrane damage.
- Protease and metalloprotease inhibition: These assays examine whether the extract can limit venom-induced protein degradation, haemorrhage, or tissue necrosis.
- Homolysis and coagulation tests: These assess whether the plant compounds can prevent venom-induced red blood cell damage or disturbances in blood clotting.

These assays help identify specific biochemical pathways affected by the extract and determine whether the plant has potential for further in vivo testing.

Animal Models (Mice/Rats)

Animal studies offer insight into the systemic and physiological effects of the extract after venom exposure. These models simulate real envenomation conditions and provide data on survival, toxicity, inflammation, and organ protection.

Common animal model applications include:

- Lethality neutralisation studies: Animals are injected with venom and treated with crude plant extract or purified compounds to determine whether the treatment increases survival time or reduces mortality.
- Edema and inflammation models: These measure how effectively the extract reduces venom-induced swelling or tissue injury in paws, skin, or muscle.
- Histopathological analysis: Tissues are examined microscopically to evaluate whether *A. paniculata* protects organs such as the liver, kidneys, heart, and muscle from venom damage.
- Biochemical markers: Blood tests are used to monitor oxidative stress, liver enzymes, clotting factors, and other indicators of systemic envenomation.

Animal models are essential for determining whether in vitro activity translates into real therapeutic potential.

Venom Fractions and Enzyme Assays

Because snake venom is a complex mixture, studies frequently separate venom into individual components or enzyme fractions to understand which elements are affected by the plant extract.

These experiments typically include:

- Fractionation of venom using chromatography: This allows researchers to test the extract against specific toxin groups such as PLA_2, three-finger toxins, neurotoxins, proteases, and cardiotoxins.
- Direct enzyme assays: These measure the extract's ability to inhibit venom enzymes responsible for haemorrhage, myotoxicity, coagulopathy, or cytotoxicity.
- Kinetic studies: These determine the nature of inhibition (competitive, non-competitive, or mixed), providing insight into how plant molecules interact with venom components.
- Neutralisation of biological activities: Extracts are tested for their ability to reduce hemotoxic, cytotoxic, or myotoxic effects of isolated venom fractions.

Safety & Limitations

Toxicity and Safety Profile

- Preclinical and clinical evidence indicate that *Andrographis paniculata* generally has a wide safety margin when used at customary therapeutic doses, with several animal studies reporting very high median lethal dose (LD_{50}) values (often >5000 mg/kg for certain standardised extracts), which supports low acute toxicity in rodents.
- Ex Clinical reviews and systematic analyses of human trials report that short-term oral administration is usually well tolerated;
- Most adverse events are mild and transient, the commonest being gastrointestinal complaints (nausea, abdominal discomfort, diarrhoea) and occasional skin reactions
- However, safety is influenced by extract type, dose, and formulation: injectable andrographolide derivatives and highly concentrated standardised extracts have been associated with more severe adverse reactions, including rare but serious allergic reactions and anaphylaxis, so route and preparation matter for risk
- Although multiple experimental studies show hepatoprotective actions of andrographolide in models of chemical liver injury, there are case reports and theoretical concerns that very high or prolonged exposures could stress hepatic function in some settings; overall the clinical hepatotoxicity risk appears low but remains incompletely characterized Regulatory and herbal monographs (WHO and allied reviews) advise caution or avoidance during pregnancy and lactation and in individuals with known allergy to Acanthaceae plants, and they highlight the need for standardized, GLP-compliant toxicology and long-term safety studies before recommending use in specialized indications such as anti-venom therapy.

Limitations of *A. paniculata* as an Anti-Venom

Poor aqueous solubility and low oral bioavailability

Andrographolide is poorly soluble in water and undergoes extensive first-pass metabolism and efflux (P-glycoprotein), which together produce low and sometimes nonlinear oral bioavailability. This limits the ability of simple oral extracts to deliver reliable systemic levels

Rapid metabolism / short systemic half-life

Andrographolide is subject to metabolic transformation and rapid clearance, which reduces the duration of effective plasma concentrations and complicates dosing for systemic indications.

Variable quality/lack of standardisation of herbal preparations

plant source, harvest conditions, extraction method and assay differences cause large batch-to-batch variability in andrographolide content. This undermines reproducible dosing, regulatory approval, and clinical efficacy. Pharmacopoeias and analytical studies show differing content standards across regions

Safety signals and rare but serious adverse reactions (especially with injectables)

A. paniculata preparations have an acceptable safety profile at usual doses. Still, injectable andrographolide derivatives (used clinically in some countries) have been associated with allergic reactions, including anaphylaxis, and systemic AEs (GI, skin). Regulatory safety reviews and systematic reviews flag caution for injections and recommend monitoring

Potential for clinically relevant herb–drug interactions

Andrographolide/extracts can modify the pharmacokinetics of co-administered drugs (e.g., warfarin) by affecting hepatic metabolism (CYPs) or transporters; this raises bleeding risk or altered drug exposure in polypharmacy situations.

Inconsistent or limited clinical efficacy evidence for many indications

There are many preclinical reports and some clinical trials for respiratory/inflammatory indications, high-quality evidence for some therapeutic claims remains limited and heterogeneous. This complicates claims for new indications and regulatory approval pathways.

Translation from in-vitro/animal activity to human therapeutic outcomes

Many promising in-vitro or animal model effects do not reliably translate to humans because of PK/PD differences, dosing, and target exposure issues.

Applications & Future Prospects

Complementary Therapy

Extracts of *Andrographis paniculata* show anti-inflammatory, antioxidant, and mild antivenom-related activities in laboratory studies. Because of these properties, the plant may serve as a supportive remedy alongside standard antivenom treatment. It does not replace antivenom but may help reduce local tissue damage and inflammation in the early stages of envenomation.

Use in Rural and Tribal Medicine

- Traditional healers in several regions of Asia use *A. paniculata* preparations for managing fever, infections, and sometimes snakebite-related symptoms.
- Its inclusion in folk practices is mainly due to its ability to reduce swelling, pain, fever, and local inflammation, which are common complications after bites. However, traditional use varies widely and is not uniform across all communities.

Anti-inflammatory and Tissue-Protective Potential

- Phytochemicals like andrographolide and related diterpenoid lactones have been reported to suppress inflammatory pathways and protect cells against oxidative stress.
- These properties could contribute to the slower progression of venom-induced tissue necrosis, improved healing, and reduced secondary infections. While promising, these effects are based on preclinical data and require deeper validation.

Research Gaps and Future Directions

Need for Standardisation

Herbal preparations of *A. paniculata* differ considerably in their chemical composition depending on cultivation conditions, extraction method, and plant part used. Future research must establish standardised dosages, extraction protocols, and quality-control markers to ensure reproducible therapeutic effects.

Molecular Docking and Computational Studies

Modern computational tools can help identify which venom enzymes or proteins potentially interact with andrographolide and other constituents. In silico studies may guide targeted experiments by predicting binding affinity to toxins like phospholipases, metalloproteinases, or hyaluronidases.

Nano formulations

Nano-based delivery systems—such as nanoparticles, nano emulsions, or liposomes—can enhance the solubility, stability, and bioavailability of andrographolide. These approaches aim to improve its efficiency in reducing venom-induced local damage and to make herbal formulations more effective at lower doses.

Human Clinical Evaluation

Despite extensive lab and animal studies, human clinical trials are almost non-existent. Future research must evaluate safety, effective doses, interactions with antivenom, and actual therapeutic outcomes in controlled clinical settings. Without this evidence, the use of *A. paniculata* for snakebite remains experimental.

Conclusion

Andrographis paniculata emerges as a promising plant with measurable anti-inflammatory, antioxidant, and enzyme-inhibitory properties that may help reduce certain toxic effects of snake venom. Experimental evidence from in-vitro enzyme assays and animal models consistently shows that its diterpenoid-rich extracts, particularly those containing andrographolide, can partially neutralise venom-associated enzymes such as PLA_2, proteases, and hyaluronidase, while also limiting oxidative stress and local tissue injury. These findings support the plant's potential role as a complementary therapy alongside conventional antivenom. However, its effectiveness varies considerably across snake species, and it does not provide reliable protection against potent neurotoxic venoms. Limitations such as poor bioavailability, variable extract quality, scarce human studies, and occasional adverse reactions highlight the need for further standardisation, advanced formulation strategies, and rigorous clinical evaluation. Overall, while *A. paniculata* cannot replace antivenom, it holds value as a supportive, tissue-protective, plant-based adjunct that merits deeper scientific exploration.

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