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Emblica officinalis (Amla) as an adjunct in the cobra snake envenomation

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Abstract

Snakebite envenomation is a neglected yet severe global health challenge, causing an estimated 1.8-2.7 million cases and over 80,000 deaths annually, with India accounting for nearly half of this burden. Among venomous snakes, cobras (*Naja* spp.) are particularly feared for their potent neurotoxic and cytotoxic effects, which can lead to paralysis, respiratory failure, and irreversible tissue necrosis. Current treatment relies on equine -derived antivenoms, but these present critical limitations-restricted species-specific efficacy, inadequate protection against local tissue injury, high cost, and limited availability in rural regions. Such gaps highlight the urgent need for complementary or alternative interventions. *Emblica officinalis* (amla), a cornerstone of Ayurvedic medicine, has gained attention as a promising candidate due to its rich phytochemical profile, including ascorbic acid, tannins, polyphenols, flavonoids, and alkaloids. These confer potent antioxidant, anti-inflammatory, and protein-binding activities. Preclinical studies demonstrate that amla extracts, particularly from the peel and roots, can neutralize venom effects by inhibiting phospholipase A2, reducing oxidative stress, stabilizing membranes, and limiting cytotoxin-induced necrosis and haemorrhage. Such multi-targeted mechanisms suggest its potential as an adjunct to Antivenom, especially as a cost-effective option for underserved populations. Despite encouraging laboratory evidence, clinical application remains challenging. Standardized extract formulations, mechanistic validation, safety profiling and rigorously designed clinical trials are essential before therapeutic application. This review consolidates evidence on cobra venom pathology, shortcoming of existing therapies, and the emerging role of *Emblica officinalis* as a potential adjunct in snakebite management, paving the way toward integrative and sustainable treatment strategies.

Keywords: Antivenom, cytotoxin, phospholipase A2, neurotoxic

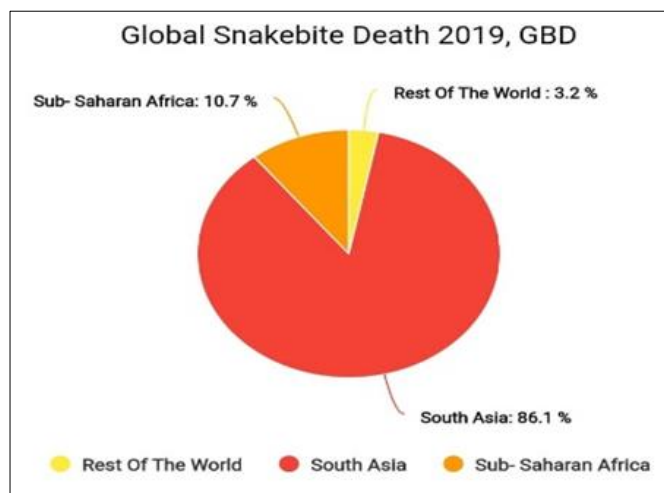
Introduction

Venom being the most lethal, nature has amazed us with its some of the biochemical weapons. The cobra venom is the most feared among the individuals as it has the capability to induce paralysis and death within hours^[1]. The modern antivenom though are very effective they come with a lot of hinderance such as causing allergic reactions, high production cost and due to their limited amount of availability in the remote and the local regions^[2]. This has awakened a profound impulse to seek healing from the nature own. One such fruit that is considered to have the potential in the snake neutralizing factor and the treasured fruit in Ayurveda is the Embilica Officinalis often referred to as Amla. Though this fruit is widely used as a rejuvenator the latest scientific researches have revealed that it has been marked to have remarkable potential in the neutralizing the antivenom activity and can counteract the tissue damage caused by the snake bite^[3]. In this review the need for a natural remedy against the venomous activity of snakes has been discussed mainly focusing on the fruit often referred to as the “divine nector” that is Amla.

Global and national impact of snakebite

Snake bites according to the WHO is the most neglected disease with an inordinate mortality and disability. The overall snakebite has been estimated to caused 1.8-2.7 million envenomings and 81000-138000 deaths annually with India counting for roughly half of the mortality^[4]. Many of the snake bite survivors suffer with either permanent disability or amputations. India has been profound to have mainly 58000 deaths per year which indirectly reflects to the neglected topical disease and the call for improved strategies^[5]. Based on the population level modelling and systematic reviews have shown a greater variance in this ratio. A current meta analysis has estimate a global incidence of 69.4 bites per 100,000 population with a predicted mortality of about 0.33 deaths per 100,000. According to the parallel level modelling using

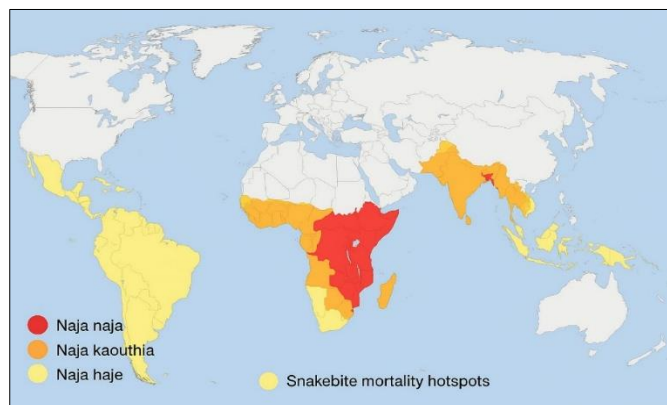
Global Burden of Disease which estimates for about 63,400 deaths in 2019 and this number remains large and uneven^[6]. This burden is mostly seen geographically and particularly in the South Asia and the Sub-Sahara Africa which carry the highest mortality and the mortality. In India the estimated of about 1.2 millions snakebites deaths between the 2000-2019 which equivalent to about 58,000 deaths per year^[7]. These findings mainly focus on the single-country. But beyond mortality it has even produce substantial morbidity, physical disabilities, chronic wounds and scarring. A rough estimate of people with physical disability is around 2 to 3 times the number of deaths^[8].



Cobra Snake: Biological Traits and Venom Mechanisms

The cobras belong to the family of Elapidae which has over 20 species in the genus which are mainly widely distributed in the asia and African regions. They are mainly medium to large terrestrial snakes. They belong to Naja species, various species include Naja Naja (Indian species), Naja Kaouthia (Southeast Asia), Naja Haje (North Africa) these species are mainly categorized by their hoods⁹. They also have the ability to spilt venom in the eyes of the attackers as their defensive mechanism. The venom of the cobra species are considered as complex but are much of small, highly potent protein families. It typically comprises of 70-90% of proteins. The major components of their venom includes the three- finger toxins (3FTx) and the snake-venom phospholipase A2 (svPLA2)^[10]. These two components are considered as important in the cobra toxins. The 3FTxs like the alpha - neurotoxins and these are capable of blocking the acetylcholine receptors in the body potentially leading to paralysis, cardiotoxins that disrupt and damage the cell membranes leading to necrosis and cardiac arrest. The svPLA2 that causes inflammation and hemolysis and the metalloproteinases that eventually tend to cause tissue necrosis^[11]. There are variations in the venom composition according to the geographical distributions for example many of the N. Kaouthia species contains venom that are dominated by more of 3FTx^[12]. However the cobra bites have a pattern such as neurotoxic symptoms, cytotoxic effects and then the systemic issues. if the bites are left untreated they have the potential to cause coagulopathy and myoglobinuria and infection of wounds^[13]. The lethal doses for the species Naja greatly vary LD50 ranges from 0.2-0.6 mg/kg in mice along with some human deaths if there has caused a delayed in the treatment^[14]. The geographical distribution greatly varies in the treatment of the cobra bite because the composition of venom varies greatly. This variation has greatly influenced in

the challenges faced and often documented while properly curating a anti-venom^[15].



Phyllanthus emblica: Botany and Phytochemistry

Phyllanthus emblica commonly known as Amla or the Indian Gooseberry is often considered a plant of significant medicinal and cultural benefits. It has its wide application in the Ayurveda system of medicines and often traces its rootes in the ancient system of medicines. Amla is rich in bioactive compounds. Its phytochemical profile has high ascorbic acid, polyphenols, tannins, flavonoids and alkaloids. These varities of constituents have potent antioxidant capacities to reduce the oxidative stress and for the scavenging of free radicals^[16]. The fruits of amla are edible and have a huge applications in Ayurveda, the roots, bark and leaves have distinct phtochemical profiles and the roots and the peel of the amla fruit have consistently reported with anti- venom signals^[17]. The some of the major chemical constituents of Amla that hava a huge medicinal benefits are listed as -

- Protein binding -they are mainly the tannins that can cut off the toxins.
- Antioxidents- they may have the capacity to eliminate the venom triggered oxidative damage.
- Enzyme inhibition -they have reportedly shown effects on sPLA2 and have shown cross activity against the sPLA^[18].

Medically, Amla exhibits anti-inflammatory effects by inhibiting the cytokines and also have shown the antimicrobial activity against a wide range of bacteria and fungi and also contains some of the hepaprotective activity used in the protection of liver. It also have shown to protect the cardiovascular health by lowering the lipids and prohibiting the oxidative damage to the vessels. The immunomodulatory actions of Amla enhance WBCs while the diabetics effects regulate the blood sugar level, often consumed for digestion, skin health and has a major anti-aging benefits^[19].

Table 1.1: Chemical constituents in different parts of Amla

Plant parts	Major chemical constituents
Leaves	Gallic acid, flavonoids,phenols and alkaloids
Fruit Peel	Ascorbic acid,Pectins,Flavanoids,Ellagic acids
Seeds	Fixed oils, fatty acids, tannins, proteins
Roots	Tannins, phenolic compounds, alkaloids
Flower	Flavonoids, phenolics, glycosides
Fruit Pulp	Ascorbic acid,Pectins,Flavanoids,Ellagic acids

The phytochemical richness of amla is well -documented with over a 180 identified compounds across the plant, but the peel of the fruit stands as a exceeding compounds and has been

observed to have high density of bioactive molecules. The peel has a highest concentration of ascorbic acids with a level contributing to overall 600 to 13,000 mg per 100 g of fresh weight which is often stabilized by tannins to prevent its oxidation^[20]. It has a dominating hydrolysable tannins which accounts for upto 45% of the fresh fruit tannins then 14% in the dried form. Often variations in the peel concentrations are seen due to various factors such as altitude, drying methods, processing parameters^[21]. These phytochemical mostly found in the peel are relevant to snake poisoning as it has been in scientific research that the tannins and the phenolics can bind to venom proteins, inhibiting enzymes like the phospholipases and the proteases that have reported to cause the tissue necrosis and the systemic damage^[22].

Table 1.2: Parts of Amla and their role in venom neutralization

Amla Part	Reported activities related to venom neutralization
Fruit	Neutralizes oxidative stress caused by venom
Stem	Supports anti-inflammatory effect post venom exposure
Peel	Binds venom proteins and reduces the oxidative stress
Seed	Protein precipitation and neutralizes venom enzymes
Leaves	Inhibits venom -induced haemorrhage and edema
Root	Interferes with venom protease

Relation Between Amla Peel and The Cobra Snake Venom

The neutralizing properties of amla against the venom of cobra snake are mainly influenced by the phytochemical constituents which is mainly concentrated in the various parts of the Amla. However the peel of amla is considered as a richer part in the medicinal application. It is particularly due to its high content of antioxidants, tannins, flavonoids and other phenolic compounds^[23]. The cobra venom contains mostly the PLA2 and the cytotoxins that have found to generate reactive oxygen species leading to the oxidative stress and the cellular damage. The peel of amla is considered as a rich source of ascorbic acid and also has phenolic compounds. These antioxidants effectively scavenges the ROS and hence preventing the oxidative damage caused by the venom. The polyphenols in the peel further enhance the effect by inhibiting the ROS- mediated signalling pathways and helps to reduce the inflammation^[24]. The mainly antioxidant are critical in protecting against the neurotoxin and the cardiotoxins effects of the venom. The cobra venom contains 3FTxs and the PLA2 and the metalloproteinases. So the tannins that are present in the peel they form stable complexes with the venom proteins through various bonding such as the hydrogen bonding, hydrophobic interactions and the metal chelation which carefully alters their structure and inhibit their receptor binding property^[25]. The venom also induces several inflammatory responses which many a times cause hypotension, edema and multiple organ failure. The peel of amla particularly the gallic acid and the ellagic acids they exhibit the potent anti-inflammatory effects by inhibiting the Cox enzymes^[26]. The peel has found to show a higher efficacy in the reducing of the anti-inflammatory property then the fruit pulp. Additionally the peels fibrous matrix may act as a reservoir for slow- release delivery of bioactives and prolonged their action^[27]. Modern researches have combined these practices with various parts of the amla fruit which

shows greater inhibition of venom- induced deaths and the hemorrhagic activity in the animal models.

Investigations of venom neutralization by Amla

The major health hazard that leads to high mortality rate especially in India is Snakebite. A large number of deaths occur due to envenomation by snakes like *Vipers russellii* and *Naja kaouthia*. The only therapeutic agent available throughout the world is Antiserum. Even Antiserum sometimes does not provide overall protection against venom-induced necrosis, haemorrhage, nephrotoxicity and produce hypersensitivity reactions. Development of Antiserum in animal is time consuming, not cost effective, and requires ideal conditions for storage. Extensive research has led to numerous attempts to develop snake venom antagonists with a focus on exploring plant based resources. As per the present investigations to neutralize snake venom in rodents, plant extracts of (*Vitex negundo* and *Emblica officinalis*) are been explored^[28]. The Indian medicinal plant *Emblica officinalis* Linn. root extract and its active compound (phthalate in nature) are used against snake venom in experimental animals. Through silica gel column chromatography a compound was isolated and the structure was determined by UV, IR, ¹H-NMR, ¹³C-NMR, and EIMS studies. Pthalate was the active fraction been determined which could be able to neutralize viper and cobra venom. Which induced hemorrhagic, lethal, proinflammatory, defibrinogenating, PLA2, neurotoxic and cardiotoxic activity in animal experimental models. The present study highlighted the therapeutic potential of the compound present in *Emblica officinalis* root against snake venom properties^[29].

Chemistry between *Emblica officinalis* Peel (Amla Peel) And Snake Venom (Cobra)

Following are the Neutralizing mechanisms of *Emblica officinalis* peel against Cobra venom

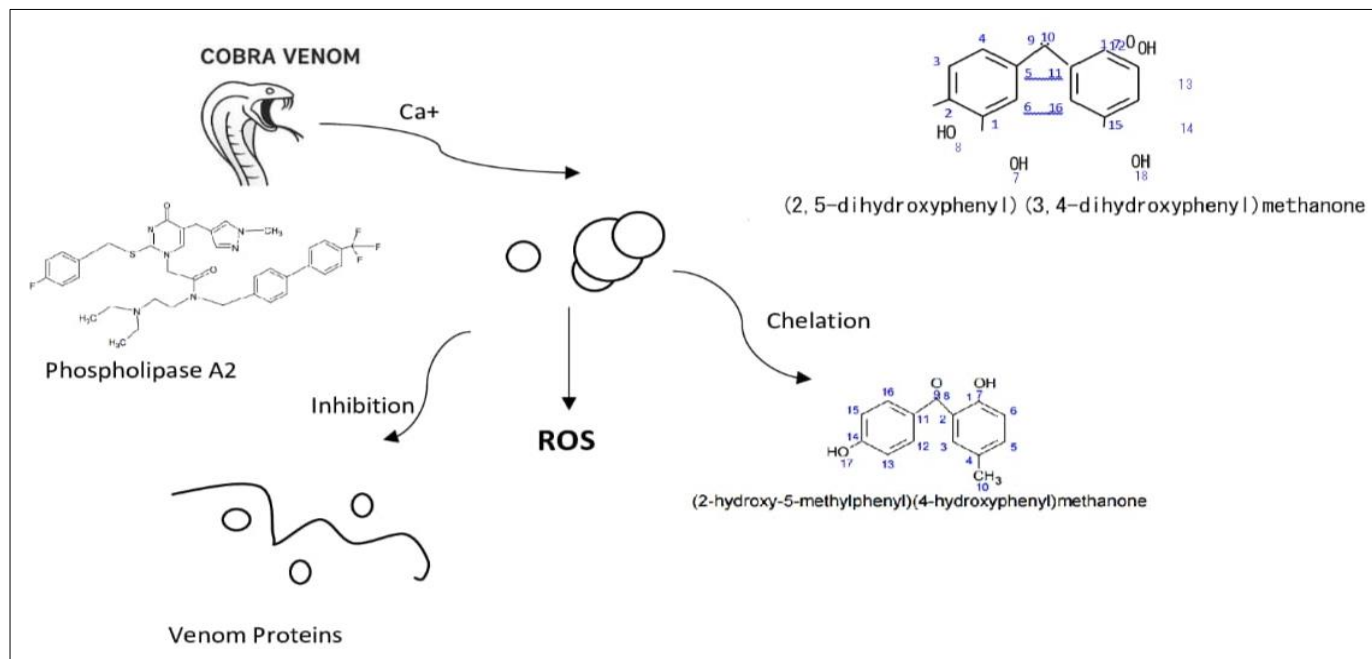
1. Protein binding and inactivation
2. Chelation of Metal Ion
3. Antioxidant Protection
4. Stabilization of Membrane

Protein binding and inactivation: The protein binding capacity is strong of Tannins and flavonoids. The binding of these molecules to venom neurotoxins and PLA2 helps in altering their conformation and preventing them from interacting with receptors^[30].

Chelation of Metal Ion: The combination of polyphenols and vitamin C acts as a potent inhibitor of Cobra venom enzymes by chelating Ca²⁺ and Zn²⁺ ions leading to enzymes inactive^[31].

Antioxidant Protection: L-amino acid oxidase (LAAO) is a major protein component of many snake venoms which is responsible to increase ROS production, but the antioxidants Vitamin C and Tannins play a crucial protective role against Cobra venom by neutralizing ROS generated by L-amino acid oxidase^[32].

Stabilization of Membrane: The polyphenols has membrane stabilizing property which help mitigate the destructive effects of PLA2, by effectively reducing hemolysis and inflammation^[33].



Limitations of Conventional Antivenom

Despite of saving countless lives, conventional antivenoms face limitations, such as

- Limited Spectrum of Neutralization - Conventional antivenoms generally have limited cross-neutralization, they are effective only against closely related species used for immunization^[34].
- Poor Efficacy against Local Tissue Damage - Antivenoms are less effective in reversing local tissue damage whereas effective mainly against systemic toxicities^[35].
- Delay In Access and Requirement for Hospital Administration- In rural areas where snake bite occur the most reaching a medical facility (hospital) in such emergency cases is difficult as the Antivenom needs to be administered through Intravenous route in a hospital setting with intensive monitoring^[36].
- Greater Risk of Adverse Reactions- As the conventional antivenoms are animal-derived they may cause: hypersensitivity reactions and late reactions may take place^[37].
- High Cost and Limited Supply- Production of conventional antivenom is highly expensive. The major requirement is maintenance of the venomous snakes, immunization of animals, storage and purification. As conventional antivenoms are expensive they face a shortage to supply mainly in developing countries^[38].
- Dose Variability- The yield of the venom vary among the species, the geographic regions and even individual snakes. Thus, the standardization of dose is difficult and there meets a requirement of large or repeated doses^[39].
- Not effective After Venom Binding- Free circulating venom is only neutralized by Antivenom. Once the toxins of the venom bind to the tissues, NM Junctions, or enzymes in the body. Antivenom has limited ability to restore tissue already damaged by venom^[40].

Potential Herb-Drug Interaction for *Embilica officinalis* (Amla) With Cobra

Preclinical neutralization

Several In-vitro and In-vivo studies report that the methanolic/aqueous extracts of fractions of part of *Embilica*

officinalis can neutralize some toxic activity of snake venoms including Naja (Cobra) species and viper venoms in rodent models. The effects that are reported include:

- Decrease in haemorrhage activity.
- Decrease in coagulant effects.
- Decrease in inflammatory responses^[41].

Interactions with conventional Antivenom-

As per the theoretical concerns potential interaction between plant compounds and venom proteins might reduce free venom, but they could also potentially form immune complexes which might impact on antivenom efficacy^[42].

Herb-drug (and safety) considerations for *Embilica officinalis* -

Amla is known for its own known pharmacological effects. The potential interactions between amla and certain medications, such as anticoagulants and antidiabetics could raise interaction concerns in theory. Although evidence is largely based on theoretical concerns, herbal databases, and case reports rather than clinical trials. The variation in quality, dose and preparation of herbal supplements across studies makes it difficult to translate findings directly to clinical practice due to differences in extracts, dosages, and plant part used^[43].

Clinical recommendation based on the evidence

In cases of cobra envenoming, antivenom therapy should be given a priority and amla or its compounds may offer potential for future drug development^[44].

Clinical and Public-Health Positioning of *Embilica Officinalis* in Cobra Bites

- Rapid administration of antivenom with airway/ventilator support act as lifesaving for neurotoxic cobra bites: cobra bites can affect nervous system, danger is paralysis of breathing muscles. So after antivenom probed ventilation support if patient can't breathe^[45].
- Amla-based products serve as adjuncts in snakebite: Amla extracts reduce harmful effect of cobra and viper venom by Reduce local tissue damage like swelling, bleeding, and muscle breakdown. Also neutralised venom's enzymes that cause inflammation and muscle damage^[46].

And reduce blood clotting problem caused by venom

- Clinical trials should prioritize functional outcomes^[47]. (time to extubation, debridement rate, wound healing, neuromuscular recovery) in addition to tradition endpoint^[48].

Conclusion

Cobra bites are still a very serious health problem in south asia, causing many cases of illness and death each year. The main and most important treatment still equine antivenom, which neutralised venom in blood. But does not always work equally well against all cobra species found in different regions, and is less effective in preventing or reversing the local tissue damage like swelling, bleeding or tissue death around the bite. Because of this gap scientists are searching for adjuncts alongside antivenom.

One most promising natural option is *Embilica officinalis* lin (commonly know as amla). Among many plants amla stands out most consistent laboratory evidence, makes sense in terms of biological mechanisms, has good potential into a medical - grade product. Research evidence-especially one well-known animal study showing that amla protected mice from death caused by cobra (*Naja kaouthia*) venom, supported by *in vitro* assays-suggest multiple mechanistic pathways, include Blocking venom's enzymes like svPLA2 that damage cells and tissues.

Stabilizing cell membranes so they are less easily destroyed by venom.

Binding venom proteins, reducing their activity.

Reducing inflammation and oxidative stress, which otherwise make tissue injury worse,

While this findings are encouraging, but are still early-stage. Before amla reco ended for patients required more research. This includes preparing extracts under Good Manufacturing Practice (GMP) standards, clearly mapping out the exact mechanisms, studying the pharmacokinetics and pharmacodynamics, safety testing in animals (GLP toxicology) and finally running clinical trials to test amla alongside antivenom in snakebite patients.

Discussions

The use of the peel of the *Embilica Officinalis* as a venom nutrizer in snakebite management offers a promising and the most effective alternative against the conventional anti venom used. Here the use of *Embilica Officinalis* offers a wide range of benefits because of its rich chemical constituents mainly the tannins, flavonoids and ascorbic acids. These are said to neutralize the venom enzymes like the phospholipase A2 and also neutralizing the reactive oxygen species and also effectively reducing the inflammatory response. This plant based antivenom offers various advantages and additionally when these are combined with the conventional antivenom their therapeutic action gets enhanced and also they help in the herb- drug interactions studies. Hence by integrating *E. Officinalis* in the treatment of snakebites could pave a road for a sustainable and a cost friendly approach. Hence the future of research is in the formulation, preparation and a well developed clinical trials in exhibiting the useful effects of the amla peel in the neutralizing effect of snake venom.

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