Journal of The Gujarat Research Society

ISSN: 0374-8588
Volume 22 Issue 1, January 2020

Snake Venom Antidote Using Plants: The Review

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ABSTRACT: Death & morbidity due to snake bite is due to the improper storage, usage and lack of specificity of the snake antidote. The snake venom is composed of serine proteases (SVSP), phospholipase A2 (PLA2), metallo-proteases (SVMP) & L-amino acid oxidases. Snake envenomation treatments involves intravenous administration of snake anti-venoms or snake venom anti-dote which are antibodies isolated from the plasma of a large mammal like horse that had been previously immunised with non-lethal doses of snake venom. These antibodies then bind to and neutralized the snake venom. However, being foreign proteins they can cause fatal hypersensitivity reactions. In view of these disadvantages, this review has tried to show case information about the anti-snake venom activity of plants. Various phytomolecules of plants exhibit snake anti-venom properties by directly binding with the proteins present in the snake venom, inhibiting the enzymatic activity of metallo-protease, PLA. However, to make it a viable mode of treatment, pharma industry must isolate, characterize and check the efficacy of such phyto-molecules in a clinical setting.

KEYWORDS: Antidote, Botanical origin, Plants, Phytochemicals, Phytomolecules, Snake venom.

1. INTRODUCTION

WHO has agreed that Snake envenomation causes severe mortality & morbidity which requires hospitalisation and many a times leading to disability and death. The main causes of death and disability occurs due to the lack of specific anti- snake venom antidote or anti-serum and also due to the poor quality of the same. Death and disability due to snake venom is a major cause of distress in the rural community and has been labelled as a neglected tropical disease (NTD). Mainly 3 families of snakes are venomous, namely Elapidae, Viperidae & Atractaspididae. Moreover, Viperidae family has 2 sub-families namely; Crotalinae (pit vipers) & Viperinae (true vipers). Snake venoms are a mixture of polypeptides, proteins long with carbohydrates, inorganic salts, lipids & amines (Table 1 & Table 2)[1].

Polypeptides & proteins have been grouped into (1) enzymes [viz., serine proteases (SVSP), phospholipase A_2 (PLA_2), metalloproteases (SVMP) & L-amino acid oxidases (LAAO)], & (2) non-enzymatic matter [viz., disintegrins (DIS), 3-finger toxins (3FTx) & kunitz peptides (KUN)]. Constitution of snake toxins depends upon the taxonomy, geographical location, family of the snake etc. Moreover, it's been found that snake toxins have 10 protein families out of which 4 were from the main protein families (3FTx, PLA_2, SVMP & SVSP) and 6 were from the secondary (2°) protein families (Natriuretic peptides (NP), Cysteine-rich secretory proteins (CRiSP), etc.). Having knowledge of the various aspects of the snake venom would help in more accurate e treatment of the victims of snake envenomation[2].

Table 1: Enzymes found in the snake venom: Name, biological effects and the family of snakes having such enzymes. All the enzymes are not found in all the families of the snake[3]**.**

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Enzymes	Biological effects	Families of snakes
Phospholipase A_2 (PLA_2)	Myotoxicity, hypotension	Elapidae, Viperidae
Snake-venom metallo-proteases (SVMP)	Bleeding, Necrosis	Mostly Viperidae
Serine proteases (SVSP)	Homeostasis disruption	Viperidae
L-amino acid oxidases (LAAO)	Apoptosis	Elapidae, Viperidae
5'-Nucleotidases	Inhibition of platelet aggregation	Elapidae, Viperidae
Acetylcholinesterases	Neurotransmission terminated	Elapidae
Hyaluronidases	Extra-cellular matrix altered	Elapidae, Viperidae

Table 2: Non-Enzymes found in the snake venom: Name, biological effects and the family of snakes having such chemicals. All the non-enzymes are not found in all the families of the snake[4]**.**

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Non-Enzymatic parts	Biological effects	Families of snake
3 finger toxins (3FTx)	Neurotoxicity	Elapidae
Kunitz peptides (KUN)	Homeostasis disrupted	Elapidae, Viperidae
Cysteine rich secretary proteins (CRiSP)	Inhibition of contraction in smooth muscles	Viperidae
C-type lectins (CTL)	Prevents coagulation	Viperidae
Disintegrins (DIS)	Platelet aggregation inhibited	Viperidae
Natriuretic Peptides	Vasodilation	Viperidae> Elapidae

Snake envenomation treatments involves intravenous administration of snake anti-venoms or snake venom anti-dote which are antibodies isolated from the plasma of a large mammal like horse that had been previously immunised with non-lethal doses of snake venom. These antibodies then bind to and neutralized the snake venom. However, being foreign proteins they can cause fatal hypersensitivity reactions. Moreover, antidotes are not only expensive but also many times lack specificity towards all types of snake venom, which further negates its effectiveness. Also, a large number of antibodies are produced in large mammals in response to administration of non-lethal doses of snake toxin which are mostly non-specific. However, they are the only mode of treatment recognized by WHO. In view of these disadvantages, this review has tried to show case information about the anti-snake venom activity of plants[5].

2. DISCUSSION

2.1 Traditional system of Medicine for treating Snake envenomation:

In many societies, botanical formulations are used on snake bite cases however it suffers from type of usage, stability of composition etc. Such difficulties can be solved by proper extraction of phyto-molecules from plants having anti-snake venom properties (Figure 1). Thereby the isolation & identification of phyto-molecular groups from botanical sources are, very important. There are nearly 15 main chemical groups namely flavonoids, glucosides, etc.), like, flavones which includes> 9000 structures. Secondary (2°) metabolites from botanical origin having therapeutic activity can become a basis for designing snake venom's antidote. In absence of proper primary (1°) heath care systems in most parts of the world,

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ISSN: 0374-8588
Volume 22 Issue 1, January 2020

many people have relied on plants which are known to have anti-snake venom activity, some of which has been tabulated in Table 3[6].

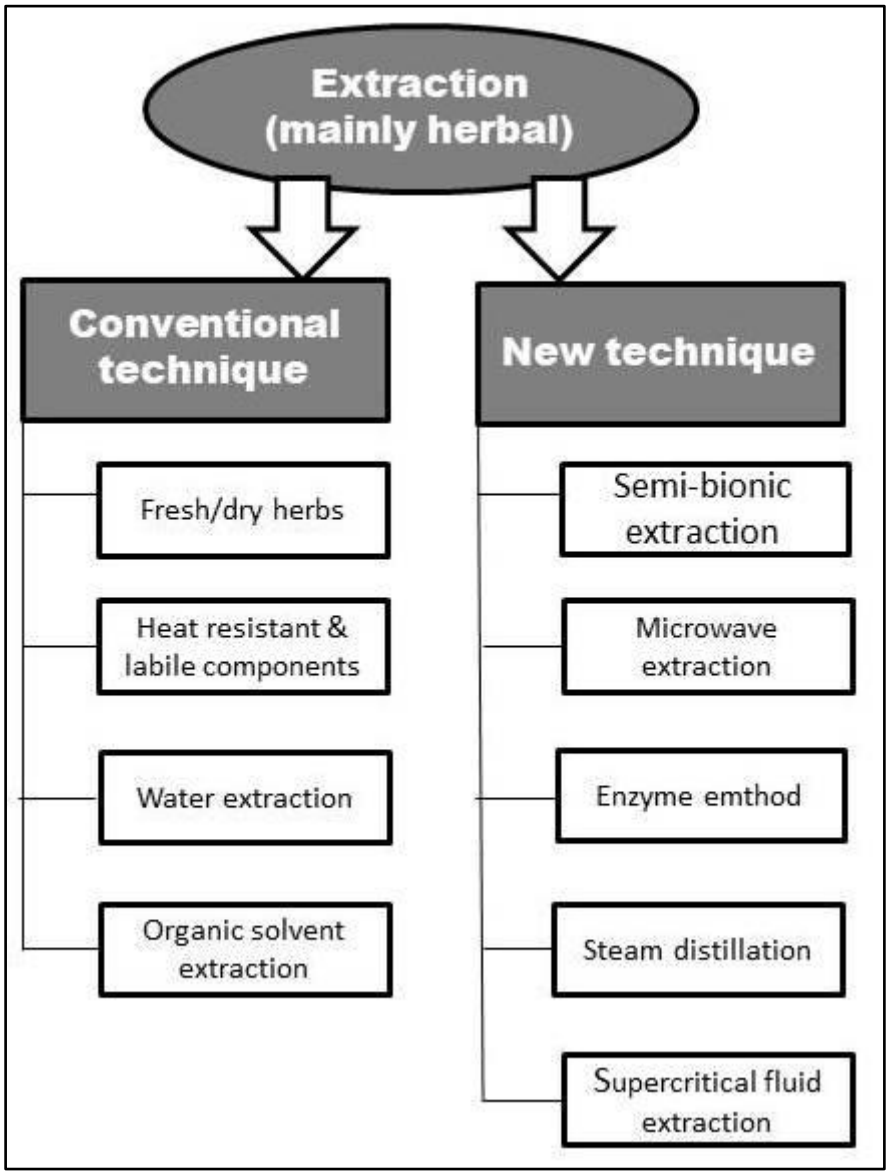

Figure 1: Techniques for extraction of phytomolecules[7]**.**

The procedure for developing a therapeutic agent from a botanical origin requires at nearly 3 stages:

- Isolation of compound from natural sources;
- Evaluation of its efficacy & safety;
- Regulatory approval of the isolated compound.

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ISSN: 0374-8588
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Table 3: Ethno-pharmacological survey of various nations regarding treating snake envenomation. India being a rich source of medicinal plants has many plants showing anti-venom activity[8]**.**

Nation	Plant	Study description
India	*Morus alba*	Prevents Hemorrhagic, procoagulant
India	*Vitis vinifera*	Inhibition of D.russelli venom
India	*Mangifera indica*	Inhibition of D.russelli venom
India	*Nicotiana rustica*	Inhibition of Naja venom
India	*Anacardium accidentale*	Inhibition of D.russelli venom
India	*Tamarindus indica*	Inhibited enzymes in snake venom

2.2 Role of herbal anti-venoms:

Though neutralization of snake's venom occurs by the antidote antigen–antibody reaction however, plant small molecules tend to have antidote activity via protein inactivation, chelation, enzyme's inhibition, antioxidant activity, adjuvant action etc. Among these, precipitation of proteins & inhibition of enzyme activity are accepted mostly. The following mode of action of the antidote property of phyto-molecules has been briefly described below:

2.2.1 Protein Precipitation:

Many 2° metabolites having properties of protein binding towards snake venom & their receptors include saponins, flavonoids, polyphenols, etc., for example, the flavanone pinostrobin, from *Renealmia alpinia*, has antimyotoxic and anti-hemorrhagic activities, with its protein binding activity[9].

2.2.2 Inactivation of enzyme:

Phospholipase A_2 (PLA_2), hyaluronidases & metalloproteases, are some enzymes whose inactivation is very important. Polyphenolic compounds like tannin's interaction between the

ISSN: 0374-8588
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sanke venom's enzymes & the hydroxyl groups (via hydrogen bonds) of polyphenols, results in the creation of a stable compound.

- *Chelation Activity:*

Plant extracts disturbs the metal ion interactions with metalloproteases & PLA_2, resulting in their hydrolytic activity's inactivation.

- *Adjuvant Action:*

The 2-hydroxy-4-methoxybenzoic acid from *Hemidesmus indicus* neutralized the snake venom by adjuvant effects and potentiation of the antiserum.

- *Antioxidant Activity:*

Many compounds of botanical origin by binding to the conserved residues of the PLA_2 can reduce the oxidative damage caused by PLA_2 enzyme activity[10].

2.3 Antivenom Agents from natural products:

It has been well reported that phytochemicals neutralizes snake enzymes, like protease, L-amino acid oxidase, phospholipase A_2 (PLA_2), hyaluronidase & 5′ nucleotidase, etc. A list of phyto-chemicals having snake venom neutralizing capabilities have been tabulated in Table 4. Figure 2 demonstrates the chemical structure of phenolic compounds having anti-venom activity, Figure 3 demonstrates the chemical structure of flavonoids having anti-venom activity, Figure 4 illustrates the chemical structure of terpenoids having anti-venom activity, Figure 5 illustrates the chemical structure of saponins having anti-venom activity and Figure 6 illustrates the chemical structure of alkaloids having anti-venom activity

Table 4: Natural compounds that neutralize venom with their manner of action. Most of the phytomeolecules are quite well known for their other biological activity[10]**.**

Compound	Action's mechanism	Plant source
Aristolochic acid	Anti-lethality	*Aristochia indica*
Rosmarinic acids	Anti-haemorrhagic activity	*Cordia verbenacea*
Chlorogenic acid	Inhibition of PLA_2	*Euphorbia hirta*
Pinostrobin	Inhibition of PLA_2	*Renealmia alpinia*
Undisclosed	Inhibition of PLA_2	*Azadirachta indica*
2-hydroxy-4-methoxy benzoic acid	Inhibition of haemorrhagic activity	*Hemidesmus indicus*
ß-sitosterol	Enzyme neutralization	*Edipta prostrata*
ß-methoxy coumesterol	Edema inhibition	*Medicago sativa*
Resveratrol	Inhibition of PLA_2	*Crinum jagus*
Campesterol	Anti-haemorrhagic activity	*Croton urucurana*
Ellagic acid	Edema inhibition	*Casearia sylvestris*

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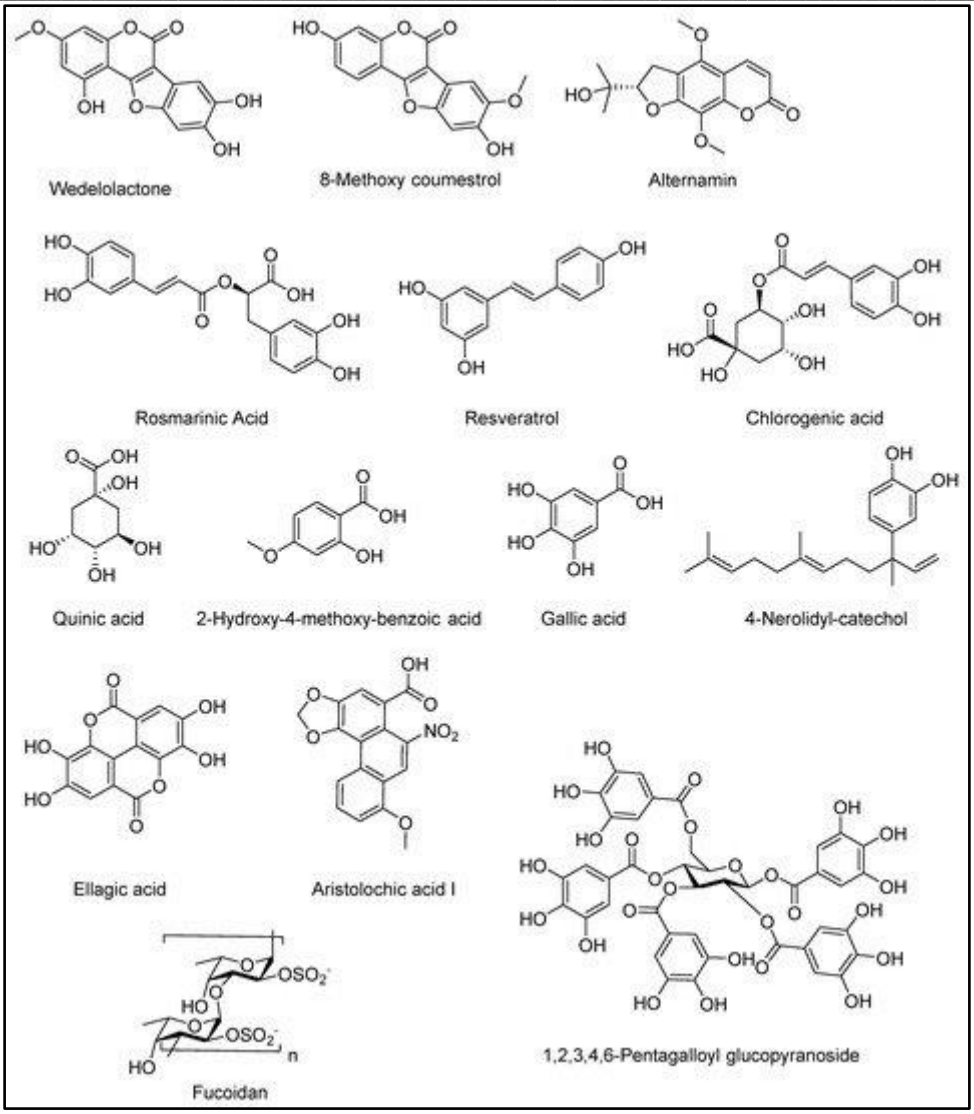

Figure 2: Some of the phenolic compounds having fucoidan sugar with antivenom role. They are namely; Wedelolactone, 8-methoxy coumestrol, Alternamin, Rosmarinic acid, Resveratrol, Chlorogenic acid, Quinic acid, 2-Hydroxy-4-methoxy benzoic acid, Gallic acid, 4-Nerolidyl-catechol, Ellagic acid, Aristolochic acid, Fucoidan, 1,2,3,4,6-Pentagalloyl glucopyranoside Figure courtesy[11]**.**

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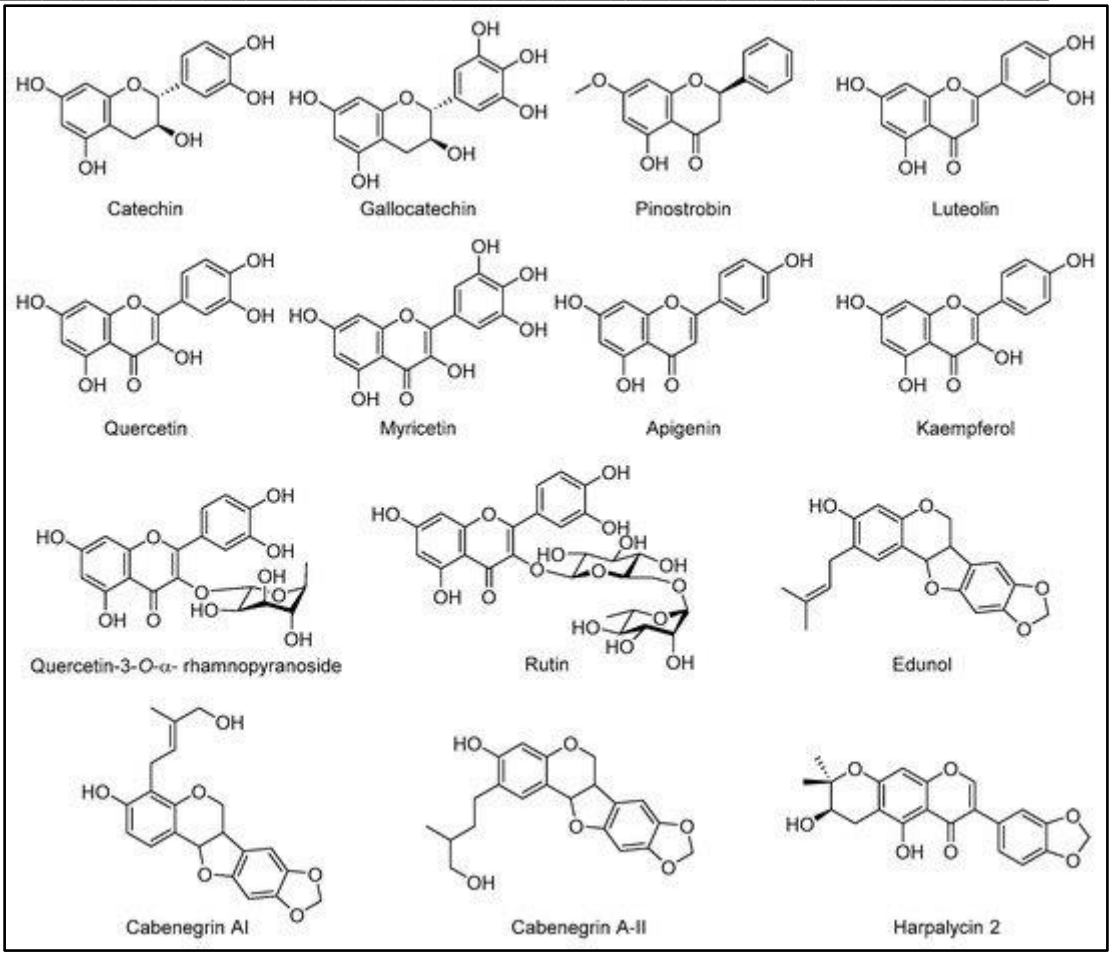

Figure 3: Some of the flavonoids having antivenom activity which are namely: Catechin, Gallocatechin, Pinostrobin, Luteolin, Quercetin, Myricetin, Apigenin, Kaempferol, Quercetin-3-o-α-rhamnopyranoside, Rutin, Edunol, Cabenegrin AI, Cabenegrin AII, Harpalycin 2 Figure courtesy[11]**.**

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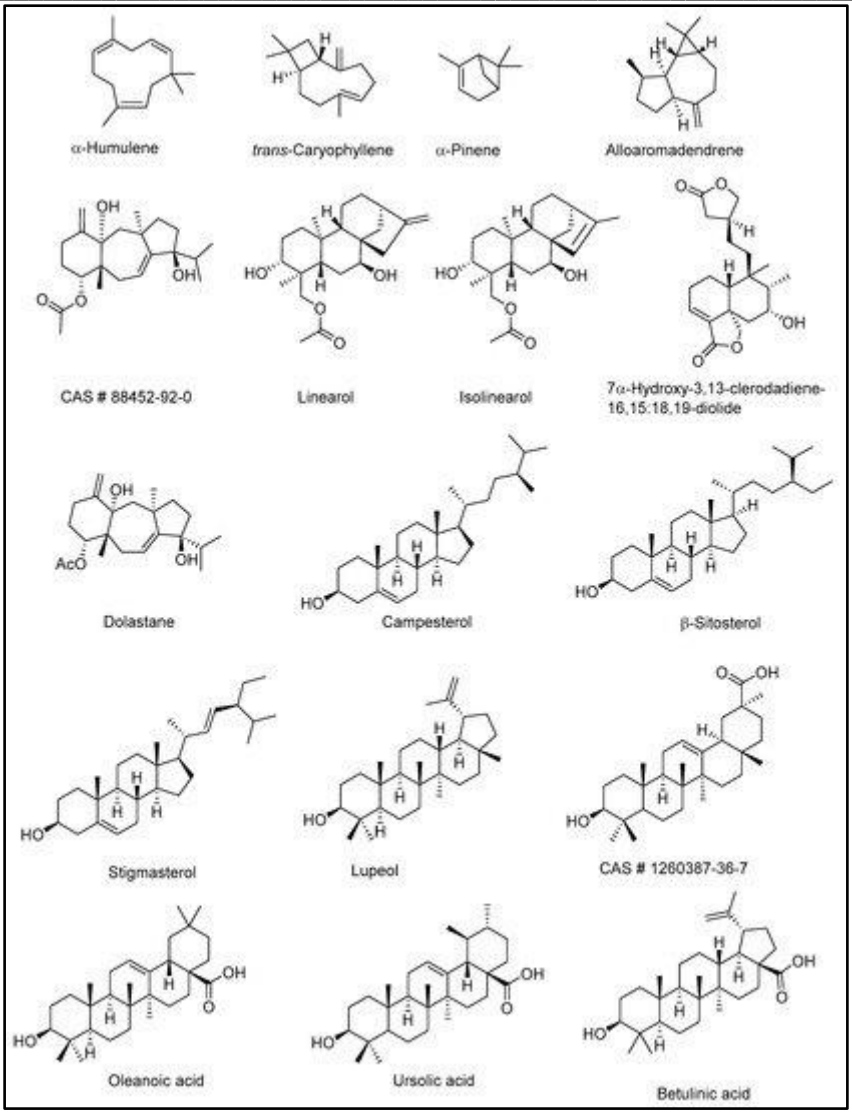

Figure 4: Some of the terpenoids having antivenom activity are α Humelin, trans-Caryophyllene, α-Pinene, Alloaromadendrene, CAS # 88452-92-0, Linearol, Isolinearol, 7α-Hydroxy-3,13-clerodadiene-16,15, 18,19-diolide, Dolastane, Campesterol, ß-Sitosterol, Stigmasterol, Lupeol, CAS # 1260387-36-7, Oleanoic acid, Ursolic acid, Betulinic acid Figure courtesy[7].

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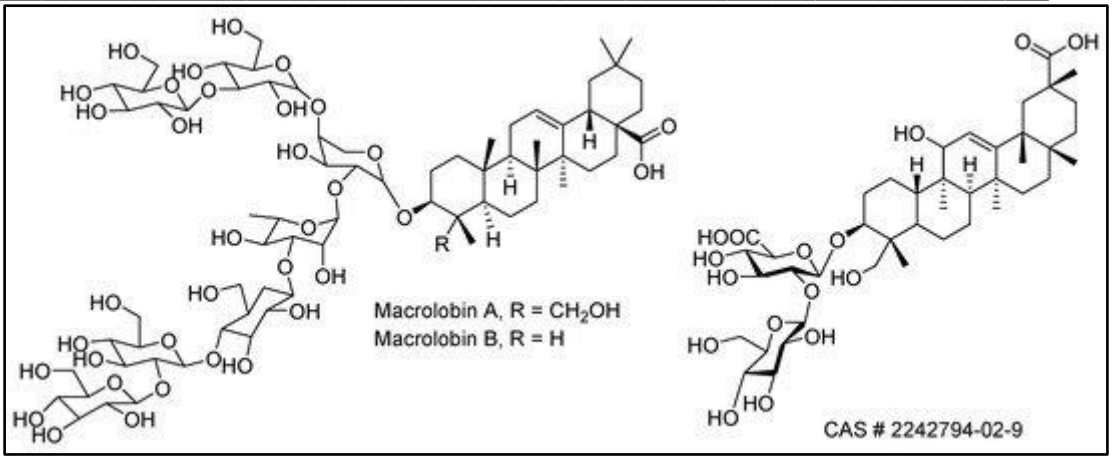

Figure 5: Some of the saponins having antivenom role namely Macrolobin A, Macrolobin B, CAS # 2242794-02-9 Figure courtesy.

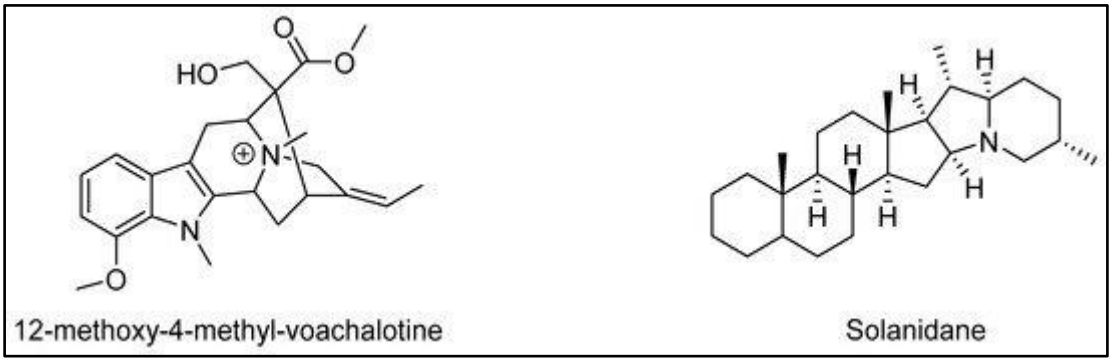

Figure 6: Some of the alkaloids having antivenom role namely 12-methoxy-4-methyl-voachalotine & Solanidane Figure courtesy.

2.4 Loopholes regarding botanical products regarding treating of Envenomation by snake:

One of the major drawbacks of finding a phyto-molecule of importance is the plethora of phytomolecules in a plant extract. Moreover, getting to know of plants having a traditional medicinal use is also a difficult task. In this regard, some of the databases like the Traditional Knowledge Digital Library (TKDL), Traditional Chinese Medicine Information Database (TCHM-ID), along with PubChem, DrugBank, etc. are of great help to researchers[8].

2.5 Obstacles in the invention of novel antivenoms:

The invention of novel antidote should involve newer methods like the usage of recombinant DNA technologies which would require the expression of an antibody protein in E.coli. Peptide library would be needed. The reason for the adoption of newer methods of production of snake antidotes should be used so as to minimize the chances of non-specific antibodies being produced. Another challenge lies in identification of plants and also their phytomolecules that show snake venom antidote activity[9].

3. CONCLUSIONS

The WHO has classified that death and morbidity due snake envenomation constitutes a neglected tropical disease (NTD). The reason for this is due to improper usage, handling and storage of the snake venom antidote and also due to non-specificity of antidote towards all

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types of snake venom. Of late, plants have been reported to have anti-snake venom properties. Various phytomolecules of plants exhibit sanke anti-venom properties by directly binding with the proteins present in the snake venom, inhibiting the enzymatic activity of metallo-protease, PLA_2. As most of the tissue damage occurs due to the activity of metallo-protease, PLA_2 thereby inhibition of these 2 enzymes help to alleviate the problems occurring due to snake envenomation.

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