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Anti-venom Potential of Traditionally used Medicinal Plants of East Africa: A Perspective on the Phytotherapeutics

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ABSTRACT: The East African diversity constitutes of the highly diverse flora of medicinal plants and traditional medicinal knowledge about their application to treat snakebite which is majorly neglected issue of concern all across the world. Nowadays, researchers emphasize plant-based anti-dotes by assessing traditional medicinal knowledge which is used in treating snakebite. The present investigation documented the plant-based snake venom antagonists based on limited literature available due to lack of access to traditional knowledge. The present study aims to compute and documenting possible available data on plant for anti-venom potential. Among the East African countries, Uganda and Kenya express key interest to used herbal medicine against snakebite and roots are used extensively, although numerous species from the family Aristolochiaceae and Fabaceae are used as a remedy against snake venom. The study assists to draw an attention towards the need of identifying and scientifically validating East African anti-venom plants for future use.

Keywords: Africa, Antivenin, Ethnomedicinal plants, Pharmacological activity, Snakebite

INTRODUCTION

From thousands of years' treatment of numerous human diseases and for mankind plant have been used traditionally and are still utilizing chiefly. Traditional herbal medicine is the foremost medical care a patient took in treating ailments since antiquity. Plants are the integral component of various traditional medicinal systems and are still predominantly used all across the world due to their accessibility, affordability, ethics and fewer side effects as compared with modern systems of treatment utilizing synthetic drugs. Around 2,50,000 species have been delivered to attention for healthcare in all nations of the world (Balkrishna *et al.*, 2021; Petrovska, 2012). According to a report presented by World Health Organization (WHO), 60% of the global population depend on herbal treatments as a form of primary health care (Williams *et al*., 2019). The African area with tropical and subtropical climate is privileged with vast biodiversity resources with an estimation of about 40 to 45,000 species, out of which only 5,000 species are predominately used as medicinal (Mahomoodally, 2013). A recent study on East African Natural Products Database showed a collection and pharmacoinformatic analysis of 1870 natural products of 302 medicinal species which belongs to 58 families with traditional medicine usage during 1962 to 2019 (Simoben *et al*., 2020). The vascular flora listed was estimated to have 3125 species with 70 endemic species. A total of 207 species were identified as part of the traditional pharmacopeia of the Comoros archipelago (Saive *et al*., 2020). Ethiopia has rich medicinal plant lore with 60% of the flora have estimated to be medicinal while, more than 230 angiosperms species categorized under 168 genera from 69 families are being used extensively in Uganda for treatment of numerous human diseases (Omara *et al.*, 2020).

Roundabout, 80% of the world's population utilizes medicinal plants to treat different diseases due to concept acceptance of cultural healers, local pharmacopeia's, as well as difficult access to modern health care facilities and comparatively low cost (Ayele, 2018). The most common and frequent diseases encountered here in East Africa are skin infections, diarrhea, respiratory diseases malaria, HIV/AIDS and tuberculosis and snake bite (Fig. 1).

Fig. 1. Region of study (East Africa).

In 2009, WHO recognized and enlightens snakebite as a most neglected tropical concern (Guidelines for Registration of Traditional Medicines in the WHO African Region, 2010) with recent estimates of about 80–140,000 fatalities/year, 400,000 amputations, long-term incapacities and disabilities occur due to snake envenomation (Ralph *et al*., 2019). Approximately, 85% of snakebite victims in Kenya undergo treatment from traditional healers or use other basic elementary means to eliminate the venom due to affordability, reliability and difficult exposure to modern medicinal facilities (Ochola *et al*., 2018). It is difficult to estimate the exact number of cases in few countries of East Africa because they don't seek government dispensaries for medical treatment, thereby merely little data is available (Birhanu Hurisa, 2014). In May 2019, WHO introduced a layout plan to minimize these fatalities and amputations by 2030, executive on the development of anti-dotes and distribution of anti-venom plants in the highly affected countries (Williams *et al*., 2019). The different ethnic groups in East Africa utilizes different plant species belonging to either same or different family as an anti-dote in treating snakebite which is related to their snakebite perception and etiology (Simoben *et al*., 2020).

Myriad recent studies have been published on the therapeutic potentials of medicinal plants and their pharmacological activities to combat against a wide range of snake venoms and its associated factors that cause lethality (Okot *et al*., 2020; Omara *et al*., 2020). East Africa contains huge biodiversity of medicinal plants, being this reason, indigenous people and several herbalists of this territory are used medicinal herbs against snakebite and to downgrade the venom-induced complications (Saive *et al*., 2020). This review aims to provide a conversant explanation of the usages of medicinal plants to overcome snake venom-induced health challenges. The study also unifies the information regarding the practices of herbal medicine by the tribal and indigenous people of East Africa. The study will help to explore an arena of phytoconstituents and their actions on snake venom, and also open opportunities for the uses of phytotherapeutic agents against the snake venoms.

A. Pathologies caused by snakebite

Snakebite fatalities are relatively common in rural areas than urban ones and are a major reason of morbidity and death among children, farmers, hunters and pastoralists (Maregesi *et al*., 2013). Snake species are capable of producing a severe combination of cytotoxic, neurotoxic and hemotoxic effects resulting in multifactorial pathologies in patients. The envenoming consequences present in snake venom, which can be limited to local effect (pain, edema, bruising) or maybe critical and lethal if left unoperated (Massey *et al*., 2012). Snake venom is a combination of inorganic ions, organic compounds like bradykinin potentiating peptide, disintegrins, histamine, serotonin, and proteins with or without catalytic activity including hyaluronidases, L-amino acid oxidases, lectins, metalloproteases, phospholipases A2 and serine proteases (Carvalho *et al*., 2013).

The snake venom causes to damage the local tissues (necrosis), predominantly due to the formation of neutrophil extracellular traps (NETs) which block blood vessels thereby conducting cytotoxic pathologies (Katkar *et al*., 2016).

The hydrolytic enzymes present in venom such as metalloproteinase (SVMPs) and PLA2, and non-enzymatic three-finger toxins (3FTXs) are responsible for pathologies in the victim(Rivel *et al*., 2016). The various proteins belonging to PLA2 and 3FTX families of toxins are generally considered as neurotoxic. These zootoxins are targeting multiple side (pre or post-synaptic junction, blocking potassium or sodium ion channels, or in behaving antagonists to nicotinic or muscarinic receptors) (Casewell *et al*., 2013). Hemotoxic venoms can have cardiovascular and hemostatic effects and decreased in blood pressure with increase in toxins(Gutiérrez *et al*., 2016). The vasodilator effects are induced directly with induction of bradykinin potentiating peptides (BPPs) and this effect was further enhanced by specific serine protease (SVSP) toxins present in snake venom exhibiting kallikrein-like functionalities, promoting and release of bradykinins from plasma kininogens. However, spontaneous systemic bleeding can also result in mortality due to hypovolemic shock (Camargo *et al*., 2012).

B. Traditional Medicines for snake bite

Magical and Mystical therapies. The traditional healers keep their medicinal knowledge in great secrecy, other communities involve mystical therapies and spiritual herbal skills for the treatment of snake bite (Omara, 2020). Some healers use *Opilia amentacea* roots burnt powder to mix with crushed snake teeth and applied to the bitten area (Kipkore *et al*., 2014).

Plant-based traditional treatment. Species can be used in alleviating associated symptoms of respiratory tract infection, or as a tonic to 'restore strength', treating stomach cramps, skin condition, and also as toward off the 'evil-eye' effect (Belayneh *et al*., 2012; Omara *et al*., 2020). The treatment is applied to snakebite for either wound healing or to prevent the bitten area from the invasion of any pathogen microbe like *Clostridium tetani* introduced to the wound from the snake's saliva and fangs (Okot *et al*., 2020). Some herbalist considers the use of polyherbal formulations as *Pseudocedrela kotschyi*, *Gardenia ternifolia*, *Zanthoxylum chalybeum*, *Indigofera arrecta* and *Capsicum frutescens* collectively an antivenin formulation. *Clerodendrum myricoides* also exhibited remarkable anti-venom efficacy against the snakebite (Table 1). The herbalists from the Uganda followed by Kenya used herbal medicine abundantly as a remedy against snake bite (Fig. 2). The farmers, wanders, hunters and herdsmen of some communities (Ik) usually travel with small amount of *Gladiolus dalenii* powder as ready to use a stable medicine which can be applied to small cuts made on the snake-bitten area.

Table 1: Distribution of ethnomedicinal anti-venin plants in East Africa.

Species	Family	Occurrence	Local Name	Parts Used	Mode of administration	Anti-venom activity	Ref.
Allium cepa L.	Amaryllidaceae	Uganda, Kenya	Butungulu, Kitunguu	Bulb, Leaves or Root tubers	Pounded sap applied externally, bulb chewed	Stabilized human red blood corpuscles membrane (anti-hemolytic), neutralized PLA2	(Omara *et al*., 2020)
Allium sativum L.	Amaryllidaceae	Uganda	Katunguluccumu	Bark	Decoction made and sprinkled around wound	Neutralized PLA2	(Omara *et al*., 2020; Tugume *et al*., 2016)
Annona senegalensis Pers. ssp. *senegalensis*	Annonaceae	Kenya	Obolo, Obolobolo	Leaves	Rubbed crushed leaf or chewed, and the juice swallowed	Neutralized lethal toxicity, haemorrhage and fibrinogen clotting activity.	(Emmanuel *et al*., 2014)]
Aristolochia albida Duch.	Aristolochiaceae	Mozambique	……………	Root	Crushed roots applied on snake bite	Neutralized anticoagulant, hemolytic, and phospholipase activity of crude venom.	(Omara, 2020)
Aristolochia bracteolata L.	Aristolochiaceae	Djibouti	Suqsuuqi	Leaves	Soaking crushed fresh leaves in water and the water is taken orally	Anti-phospholiphase A2.	(Hassan-Abdallah *et al*., 2013; Mahomoodally, 2013)
Aristolochia elegans Mast.	Aristolochiaceae	Uganda	…………	Root	Infusion drunk or root chewed	Against *Bothropsatrox* venom	(Hassan-Abdallah *et al*., 2013; Mahomoodally, 2013)
Aristolochia odoratissima L.	Aristolochiaceae	Uganda	…………	Leaves	----	PLA2, hyaluronidase, gelatinolytic, collagenase, peroxidase, nuclease, L-amino acid oxidase and protease inhibitory potencies. Inhibition of lethality.	(Omara, 2020)
Asystasia gangetica L.	Acanthaceae	Uganda	Isihobo	Leaves	----	80% protection against snake venom PLA2.	(Omara, 2020)
Balanites aegyptiaca (L.) Del.	Zygophyllaceae	Somalia	Shilan, Kulun.	Rootbark	Decoction is drunk.	Increased survival time; Inhibition of hyaluronidase and PLA2 activity.	(Molander *et al*., 2015)
Bidens pilosa L.	Asteraceae	Uganda, Kenya	Kalala, Nyanyiek mon, Onyiego	Leaves	Crushed and rubbed on cuts as an astringent, snake bite antidote	Effective against venom, Neutralized PLA2.	(Omara, 2020)
Burkea africana Hook.	Fabaceae	Mozambique	Mucaratimussimbe	Leaves	----	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Isabel *et al*., 2018; Molander *et al*., 2015)
Calendula officinalis L.	Asteraceae	Mauritius	Pissenli	Flowers	----	anti-hemorrhagic, ant-necrosis	(Saive *et al*., 2020)
Calotropis procera (Ait.) Ait. f.	Apocynaceae	Somalia	Booc	Root	Root decoction is drunk	Increased survival time	(Sani *et al*., 2020)
Capparis tomentosa Lam.	Capparidaceae	Uganda	Muzingani	Root	Infusion drunk	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020)
Carica papaya L.	Caricaceae	Uganda	Mupapaliomusaiza	Root	Chew, poultice applied to bite wound	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020)
Carissa spinarum L..	Apocynaceae	Ethiopia	Agam	Shoot buds	Chewed	Inhibition of acetylcholinesterase, PLA2, hyaluronidase, phosphomonoesterase, phosphodiesterase,5- nucleotidase enzymes.	(Enyew *et al*., 2014)

Cassia occidentalis L.	Fabaceae	Uganda	Etiaatia, Omwita-njoka, Ekayeriyer, Umuthanjoka	Leaves, Root	----	Stimulated angiogenesis, inhibition of epidermal hyperplasia, and minimized venom local effects	(Omara, 2020)
Cissampelos mucronata A. Rich.	Mnesparmaceae	Uganda	Kavamagombe	Plant	Pound leaves and tie on affected part	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020; Tugume *et al*., 2016)
Citrus limon L. Burm. F	Rutaceae	Uganda	…………….	Root, ripe fruits	----	Neutralized the anticoagulant effect induced by weak PLA2 enzymes. Inhibition of lethality	(Omara, 2020)
Clerodendrum myricoides (Hochst)	Lamiaceae	Eritrea	Sur-betri /Ugandense	Stem bark, leaves	----	Inhibition of hyaluronidase.	(Félix-Silva *et al*., 2017; Meresa *et al*., 2017)
Clerodendrum myricoides R. Br.	Lamiaceae	Rwanda	Umukuzanyana	Bark	----	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015)
Colocasia esculenta (L.) Schott	Araceae	Mauritius	Songe, Taro	Leaves	Leaves applied to snake bite wound	Inhibition of hyaluronidase and PLA2 activity.	(Molander *et al*., 2015)
Combretum molle G. Don	Combretaceae	Kenya, Uganda	Muama, Kiama, Loro	Root or bark	Infusion drunk	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020)
Commiphora africana (A. Rich.) Engl.	Burseraceae	Zambia	……………..	Bark	Chewed	Neutralizing of crude venom.	(Li *et al*., 2021)
Crinum jagus (J. Thomps.) Dandy	Amaryllidaceae	Uganda	……….	Bulb	----	Prevention against hemorrhage, prolonged death time.	(Omara, 2020)
Cynodon dactylon (L.) Pers	Poaceae	Eritrea, Ethiopia	Romadi, Serdo	Plant, Root.	----	Prevent haemolysis	(Gnanaselvan & Sivaraman, 2020; Yirgu & Chippaux, 2019)
Datura stramonium L.	Solanaceae	Uganda	Yat two	Root, Leaves, Seeds	----	Inhibition of PLA2 activity	(Molander *et al*., 2015; Omara *et al*., 2020)
Flueggea virosa (Roxb. ex Willd.) Voigt	Euphorbiaceae	Zimbabwe	Mushagahuwe	Root	Dried root powder is used as snake antidote	Inhibition of PLA2, proteolytic, hyaluronidase activity	(Félix-Silva *et al*., 2017; Maroyi, 2013)
Grewia mollis Juss.	Malvaceae	Kenya	Powo	Leaves	----	Inhibition of hyaluronidase, PLA2 and proteolytic activity.	(Molander *et al*., 2015)
Imperata cylindrica (L.) P. Beauv.	Poaceae	Uganda	Lubembe, Lusenke	Plant, Root	Chew	Inhibition of hyaluronidase enzyme activity	(Omara, 2020; Saraswat *et al*., 2021)
Indigofera capitata Kotschy	Fabaceae	Uganda	………..	Leaves	----	Prevention against hemorrhage and coagulation.	(Omara, 2020)
Indigofera pulchra Willd.	Fabaceae	Uganda	………….	Leaves	----	Inhibition anticoagulant, hemolytic and PLA2 activities	(Omara, 2020)
Maesa lanceolata Forssk.	Primulaceae	Kenya	Katera	Root	Decoction administered as follow up treatment	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015)
Pergularia daemia L.	Apocynaceae	Ethiopia	Yeayit Hareg	Root	Created small cut at the location and root juice inserting	Antagonize PLA2 and left atrial appendage occlusion activities	(Kaushik *et al*., 2013)
Portulaca oleracea L.	Portulacaceae	Somalia	Jijimoole, Canyo	Plant	Roots are chewed or pounded and soaked in water	Inhibition of hyaluronidase and proteolytic activity	(Molander *et al*., 2015)
Pupalia lappacea (L.) Juss.	Amaranthaceae	Somalia	Geed-beered or Sariibiye	Root	Decoction of roots is drunk	Inhibition of hyaluronidase and PLA2	(Molander *et al*., 2015)

Securidaca longepedunculata Fresen.	Fabaceae	Zimbabwe, Eritrea	Mufufu	Root or Root bark	Infusion drunk	Inhibition of hyaluronidase and PLA2	(Maroyi, 2013; Meresa *et al*., 2017; Molander *et al*., 2015)
Securnega virosa (Willd) Baill.	Euphorbiaceae	Uganda	Ilakara	Root	----	Neutralize venom toxicity.	(Omara, 2020)
Senna singueana (Del.) Lock	Fabaceae	Uganda	Musumbilabafele	Root	Infusion drunk	Inhibition of hyaluronidase enzyme activity.	(Omara, 2020; Park *et al*., 2020)
Solanum incanum L.	Solanaceae	Somalia, Eritrea, Ethiopia, Uganda, Kenya, Rwanda	Makarumbey, Uengule, Yabesha Embuay, Ntonka, Mutongu, Umukuku, Ocokock	Plant, leaves, Fruit, Root, Stem	Leaves, stem, fruits, fruits sap applied externally or use as a Infusion drunk	Inhibition of acetylcholine response like atropine.	(Enyew *et al*., 2014; Meresa *et al*., 2017; Omara, 2020)
Strychnos innocua Del.	Loganiaceae	Uganda	Akwalaakwala	Root	----	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020)
Strychnos spinosa Lam.	Loganiaceae	Zambia, Mozambique	Muzimbilili, Mutamba, Ntupa, Massala	Root, Leaves	Decoction and ash taken orally	Inhibition of PLA2 and proteolytic activity	(Molander *et al*., 2015)
Zingiber officinale Roscoe	Zingiberaceae	Comoros	……….	Resins	----	Inhibition of PLA2	(Félix-Silva *et al*., 2017; Saive *et al*., 2020)
Ziziphus mucronata Willd.	Rhamnaceae	Kenya	Oloilalei	Roots	Infusion drunk	Inhibition of hyaluronidase, PLA2 and proteolytic activity	(Molander *et al*., 2015; Omara *et al*., 2020)

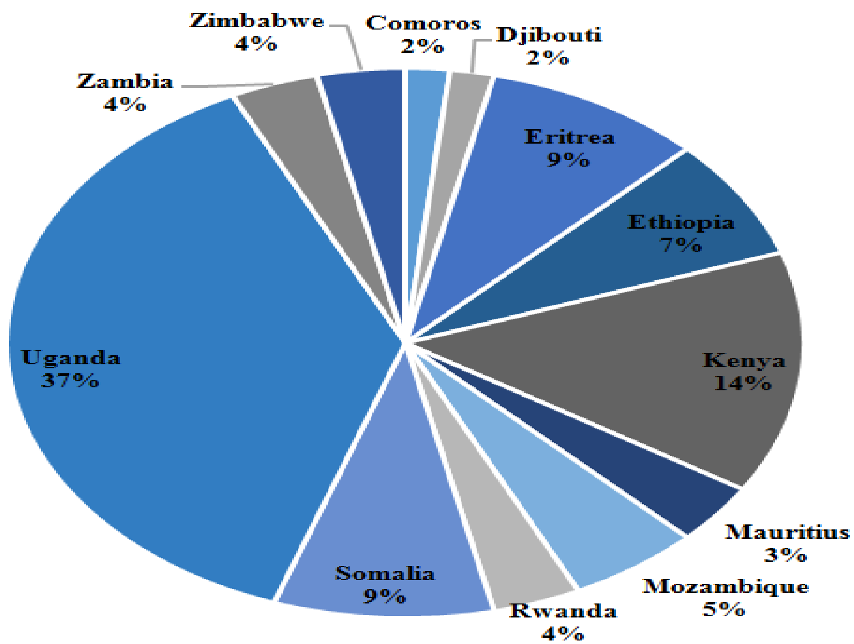

Fig. 2. Country wise uses of herbal medicine against snake bite.

The Ik community of Uganda uses some unique plants such as *Cyathula uncinulata, Gladiolus dalenii* and *Steganotaenia araliaceae* which are not used by other communities as antivenin (Yemane *et al.*, 2017).
Bidenspilosa is used as a snake venom antagonist and is also used for the treatment of cancer, inflammation, infectious diseases, immunological disorders, digestive disorders and other metabolic syndromes (Omara *et al.*, 2020). However, some antivenin plants are reported to exhibit noticeable toxicity for instance *Jatropha carcus* (leaves and latex) comprise some phytochemicals as curcin which has protein translation inhibitory (N-glycosidase) effect, amphiphilic molecules phorbol esters which can bind phospholipid membrane receptors are responsible for irritant purgative oil of the species. Thus, the antivenin preparations are applied topically or ingested in small amounts (Devappa *et al.*, 2010).

C. Scientific validation of traditionally used plants for snake bite

Plants that are recommended in snake bite treatment showed inhibition of pain, edema, hemorrhaging and necrosis which are observed as pathologic processes in indirect intervention antagonizing venom action. Many traditional healers consideration powder, paste, extract and dried parts mix with butter, honey and cow milk, these are used either externally (rubbing on skin or contact with mucus membrane) or internally by oral administration (Shahid *et al.,* 2016; Yirgu & Chippaux, 2019). Several studies showed the extended uses of different plant parts like root, leaves, bark and tuber, while most of the studies indicated that root showed highest efficacy against snake venom (Fig. 3). The majority of the species belonging to the predominantly antivenin category of plants is *Allium cepa*, *Carica papaya*, *Harrisonia abyssinica*, *Nicotiana tabacum* and *Securidacalongi pedunculata* belongings to various families namely Fabaceae, Euphorbiaceae, Asteraceae, Amaryllidaceae and Solanaceae as demonstrated in Fig. 4. Approximately, 226 extracts from 94 sub-Saharan Africa plants are reported to have an inhibitory effect against *Bitis arietans* and *Naja nigricollis* venoms hyaluronidase, phospholipase and proteases enzymatic actions(Molander *et al.*, 2015).

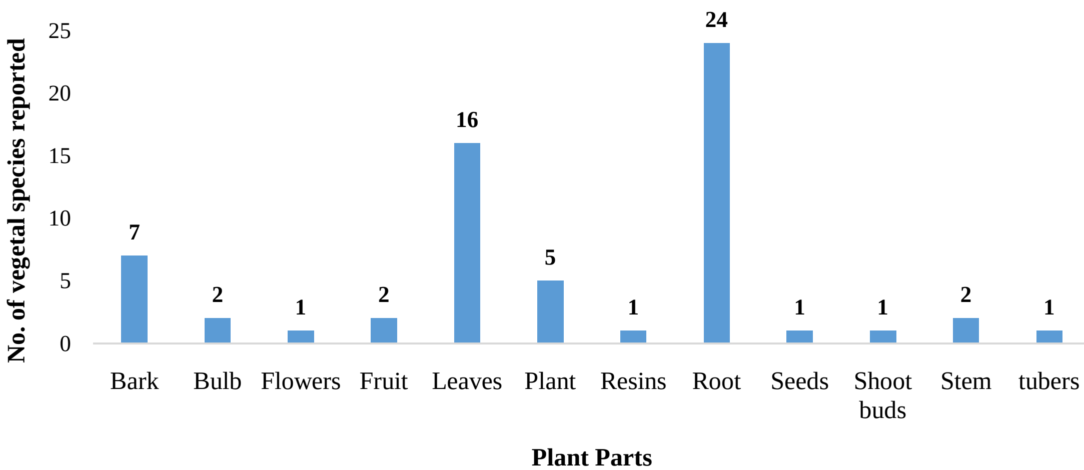

Fig. 3. Ethno-medicinal plant parts used against snakebite in East Africa.

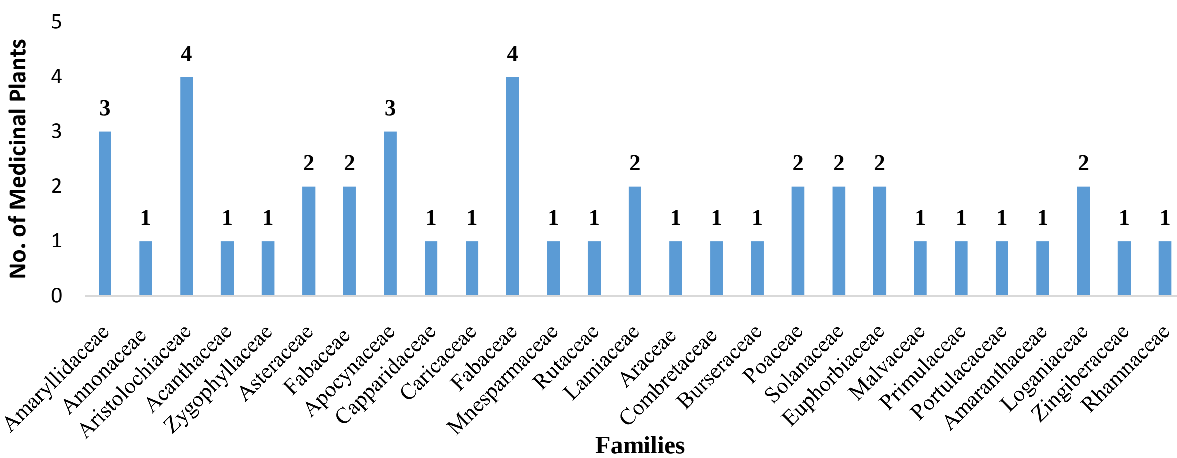

Fig. 4. Major families from which vegetal antivenins are obtained in East Africa.

The inhibitory action observed due to having of divalent cations such as Calcium (II), Barium (II) ions or quercetin-like compounds and Strontium (II) which are described to have phospholipase A2 augmentation potential by inducing conformational changes in substrate binding sites (Rathnakar Reddi *et al.*, 2014). Another conceivable inactivation mechanism of snake venom is through inhibition of hyaluronidase, phospholipase A2, and metalloproteases active enzymes by the implementation of different phytochemicals especially tannins. These phytoconstituents upon interaction with non-specific binding enzyme proteins leading to the formation of chemically stable complexes mediated through hydrogen bonding with hydroxyl groups. These different compounds are also susceptible to divalent metal ions (chelation) binding and disrupting the enzyme metal ion bondage inhibiting enzymatic action in venom. Phytoconstituents have shown potencies in reducing, stopping and even preventing oxidative damage either presenting competitive inhibition or even allosteric inhibition of venom enzymatic action (Gupta, 2014; Joshi *et al.*, 2014).

CONCLUSION AND FUTURE PROSPECTIVE

The plant parts (roots, leaves, whole plant, bark and tuber) are commonly used, although root showed highest usages against the snake venom followed by leaves and bark. The buds, flowers, fruits and seeds although are also rich in phytochemicals but are less frequently used. Highest number of medicinal species from the family Aristolochiaceae and Fabaceae are used as a remedy against snakebite. The plant is mostly administered orally in the form of paste, its infusions as a drink, juice, decoctions, concoction and in powdered form and it can be applied topically. Several studies showed the key interest of investigators to screen new plants for their anti-venom actions. Among the East African countries, Uganda and Kenya shows the highest interest to use the traditional herbal medicine against snake venom. The emerging trends in the research also focus on the clinical aspects of these plant-based medicines trials. The untiring efforts to procure information about phytochemical and pharmacological aspects of antivenin plants used by traditional healers are also acknowledged. The ongoing research all across the globe in the lure to scientifically validate the antivenin plants is in progress but besides this more information on these traditional plants has to be collected from many countries of East African regions. The outcomes of this study may be helpful to identify the potential phytoconstituents of East African plant that can be used against snakebite. Moreover, these phytochemicals may be useful in the drug discovery and related phytopharmaceuticals.

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