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Full Length Research Article

Medicinal Plants for the Treatment of Snake Envenomation in Sub-Saharan Africa: Opportunities and Challenges

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ABSTRACT
Snakes are primarily venomous animals that bite when frightened, which can be lethal. This is because snake venom is one of the most active biological fluids containing a wide range of peptides and proteins that can induce several effects, including hemo-, neuro-, cyto- and myotoxic effects, consequently becoming deleterious to life if untreated. Although snakes are found on almost all continents, the rural communities in sub-Saharan Africa are the most affected by snakebites, mainly due to increased human-snake interactions forced by their socioeconomic status and agricultural or rural practices. Consequently, this recently prompted the World Health Organisation to enlist snakebites envenoming among the category-A neglected tropical diseases with an estimated annual death of 7,300 in sub-Saharan Africa. Aside from mortality, snakebite envenomation also causes permanent disabilities in humans and a heavy burden on livestock, creating economic hardship for the already impoverished communities. Several animal-derived antivenoms have been developed for treating snakebites and wounds; they effectively attenuate venom-related toxicity, tissue necrosis, and deaths. However, despite the efficacy of these antivenoms, several issues, such as problems in production and distribution, exorbitant prices, and adverse effects of the antivenoms, have challenged their practical use in sub-Saharan Africa. This review highlights the challenges that make conventional antivenoms unavailable to prone populations. We also discuss the plants used in the treatment of snake bites laying emphasis on Mucuna pruriens (Velvet bean) and Allium sativum (Garlic) as the two most studied medicinal plants. The progress and bottlenecks of using herbal antivenoms as alternatives in treating snakebite envenomation in sub-Saharan Africa are also discussed.
Keywords: Antivenom, Envenomation, Plants, Snakebite, Traditional medicine.

INTRODUCTION
Snakes are among the most widely spread reptiles; they are legless carnivorous vertebrates found in all continents of the world. The specie distribution widely varies based on habitat and feeding habits (Kasturiratne *et al*., 2008; Reeder *et al*., 2015). Though they all are amniotic ectothermic serpents, some of these reptiles may possess scales, skulls, and mobile jaws (Wiens *et al*., 2006). Studies have shown that snakes prey on animals such as insects, rats/mice, frogs, birds, fishes, lizards, worms and other snakes. Certain snakes (such as the various species of *Dasypeltis*) solely feed on the eggs of birds (Branch, 2004), while giant snakes (e.g., *Pythonidae*) can feed on mammals (Hoyer *et al*., 2017). Snakes are believed not to be a threat to humans; they shun, evade, and rarely prey on humans. However, when frightened, injured, or attacked, they retaliate via a bite, lunge, hiss or even body rasp (Kasturiratne *et al*., 2008). The most dreadful among these reprisals is the snakebite, which can prove lethal, especially when the snake is venomous. The snakebite process involves using fangs to puncture tissue, which is then accompanied by the injection of venom (envenomation) (Gold *et al*., 2002). Venom is the proteinaceous saliva produced by a snake's advanced or modified parotid gland (Jackson, 2003; Fry *et al*., 2006). It is among the most active biological fluids with various pharmacological properties attributed to its composite proteins and peptides, in addition to 25 or more diverse enzymes (Zelanis and Tashima, 2014).

Snakebites envenoming was enlisted among the category A neglected tropical diseases (NTDs) by the World Health Organization (WHO) in June 2017, and the resolution was passed by the assembly in May 2018, renewing the impetus to ensure appropriate control and prevention interventions are implemented (Minghui *et al*., 2019; Schiermeier, 2019; WHO, 2019a). Although the exact number of snakebites is unknown, it is estimated that the annual global prevalence of snakebites is around 5.4 million and envenomation at about 1.8 to 2.7 million people. The yearly death rate is estimated to be between 81,000 to 138,000 deaths and nearly three times as many permanent disabilities and amputations caused by snakebites (Kasturiratne *et al*., 2008; Gutierrez *et al*., 2017; WHO, 2021). Among a million yearly snakebite cases in sub-Saharan Africa, 7,000 to 20,000 fatalities are documented of which 97% are in rural settlements where rapid antivenom therapy is scarce (Chippaux, 2011). These fatalities are alleged to be under-reported since 3,557 – 5,450 lives are lost in West Africa alone (WHO, 2019b). Apart from human fatalities and permanent disabilities caused by venomous snakebites, they can also cause a

heavy burden on livestock, creating economic hardship for the already impoverished communities (Rodríguez *et al*., 2016).

The rural communities in Asia and sub-Saharan Africa are the most affected by snakebites globally. This is due to the agricultural and other rural practices and socioeconomic status, which largely contribute to increased human-snake interactions (Harrison *et al.,* 2009). Longbottom *et al*. (2018) carried out a global mapping of hotspots with vulnerability to snakebite envenomation and showed that an overlap exists between identified vulnerable communities and existing burden estimates (Figure 1). Benin, Congo (Brazzaville), Nigeria, Myanmar, and Papua New Guinea, previously estimated to be burdensome countries (Chippaux, 1998), are identified as vulnerable communities. South Asia and sub-Saharan Africa, where these countries are located, have considerable morbidity and mortality associated with snakebite envenoming (Kasturiratne *et al.,* 2008).

For example, in Nigeria (the country with the largest population in Africa), the incidence of snakebites is most prevalent in its Savannah region, where an average of 20,000 snakebite cases occurs in 2020 alone, with about 2,000 fatalities and also 1,700 to 2,000 peoples' legs or arms are amputated in order to save their lives (Federal Ministry of Health, 2022). Although the exact figures of snakebite incidences in Nigeria are not known and often grossly underestimated; however, a single hospital reported 6687 snakebite-related cases within three years (Gutierrez *et al*., 2007). Common envenomation-causing snakes in Nigeria are *Viperidae*, *Elapidae*, *Columbridae* and *Actraspididae*. *Echis ocellatus* (carpet viper) account for 66% of the bites, while *Naja nigricollis* (black-necked spitting cobra) and *Bitis arietans* (puff adder) are also substantially important species (Habib, 2003; Mustapha, 2003; Ameen *et al*., 2015).

Several antivenoms have been developed, which have proved to be efficacious in neutralising the damaging effects of snake venoms. Their use or administration has been shown to reverse postsynaptic neurotoxicity, hypotension, and antihaemostasis effects. At the same time, early administration has offered to limit or prevent tissue necrosis, presynaptic neurotoxicity, and rhabdomyolysis (Warrel, 2004; WHO 2010). One of the significant limitations of these antivenoms is that they cannot be broadly used as they are precise. Thus, they only neutralise venoms used in their production. Therefore, appropriate antivenom must be administered based on the type of snake responsible for envenoming. Furthermore, these antivenoms are often scarce, expensive, poorly distributed, and usually require cold-chain transport and storage, which are lacking in communities most affected by snakebites (Habib and Warrel, 2013). Thus, this necessitates the production and use of alternative treatments, mainly from plants available in the habitats of prone populations to overcome the disadvantages posed by the dependence on conventional antivenoms.

This paper reviews the most widely used conventional antivenoms and highlights the disadvantages that make them not readily available to prone populations. It also highlights the need for alternatives – herbal antivenom remedies; especially the bottlenecks and progress made to date in terms of medicinal plants as antivenoms.

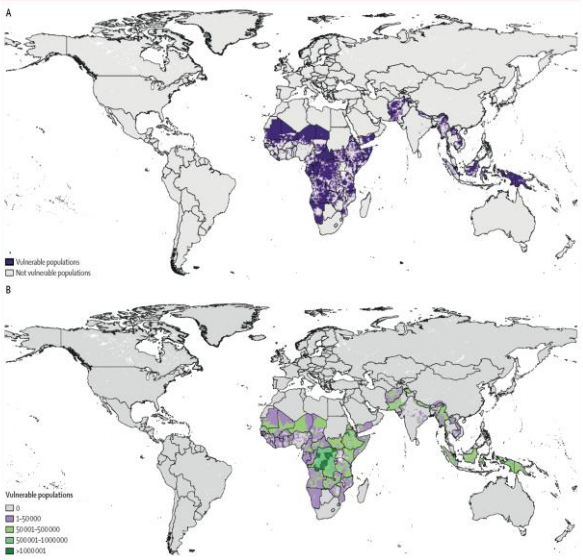

Figure 1: Hotspots of vulnerable populations to medically important venomous snake species. Hotspots are defined as people living in areas within the range of one or more medically important venomous snake species, and more than 3 h away from major urban centres with Healthcare Access and Quality index deciles of 1-3. **(A)** Pixel-level vulnerability surface (i.e., vulnerability to all species of medically important snakes). **(B)** Aggregated second administrative level vulnerability all species of medically important venomous snakes, as measured by the absolute number of people. Source: Longbottom *et al.* (2018)

Antivenoms

Snake antivenom (also referred to as antivenin, venom antiserum or antivenom immunoglobulin) is a drug used to treat snakebites and wounds. The administration of antivenoms has been the basis for the treatment of snakebite for almost 125 years (Potet *et al.,* 2021). However, about 45 years ago, the WHO recognized antivenoms as essential medicine (WHO, 1977). They are prepared from antibodies and considered essential medicines required in an effective or safe health system (Dart, 2004; Gad, 2007; WHO, 2015). These drugs are biochemically active against a composite mixture of the injurious pharmacologically functional venomous proteins such as phospholipases A2 (PLA2s), L-amino acid

oxidases (LAAOs), cardiotoxins, neurotoxins, snake venom metalloproteinases (SVMPs), nucleotidases, snake venom serine proteinases (SVSPs), acetylcholinesterase (AChE) nitrate, snake venom hyaluronidases (SVHs), phosphomonoesterase and phosphodiesterase (Kang *et al*., 2011; Janardhan *et al*., 2014). The primary clinical effects of these toxins are haemotoxicity and blood vessels degeneration, which can precipitate into spontaneous systemic bleeding, muscle paralysis, systemic myolysis, haemolysis, arrhythmias, coagulopathy, haemorrhage, cardiotoxicity as well as cardiac and renal damage/failure (Wangoda *et al*., 2004). These ultimately lead to imminent morbidity and mortality (White, 2005; Upasani *et al*., 2017). Though antivenoms do not reverse the defects caused by envenomation, they remain the most effective emergency treatment for attenuating venom-related toxicity, tissue necrosis and deaths (White, 1991).

Types of Antivenoms

Antivenoms are animal antibodies (principally from horses and sheep) that bind and neutralise snake venoms (Bochner, 2016). Based on composition, they are categorised into two broad groups; monovalent antivenoms (consisting of a single antivenin) and polyvalent antivenoms (composed of multiple antivenins). Most contemporary antivenoms are polyvalent; therefore, they are effective against venoms of numerous snake species (Nuchpraryoon and Garner, 2000). These agents have been useful for over a century, with evidence of acceptable safety profiles (Otero-Patino *et al*., 1998; Otero *et al*., 2006; Bochner, 2016). However, these antivenoms may cause adverse drug reactions depending on their quality, purity, and production technique. Some exhibit less than 10% adverse effects, while others can be beyond 50%. Due to this reason, premedication with corticoids, antihistamines, or adrenaline (most rarely) is recommended or obligatory before administering antivenoms in certain countries (De Silver *et al*., 2011; Leon *et al*., 2013; De Silver *et al*., 2016).

Production and Distribution of Antivenoms

Despite the proven efficacy of antivenom therapy in suppressing morbidity and mortality from snakebites, several issues have challenged its effective use. The production of these essential life saving drugs has been neglected or under-financed by governments, non-profit organizations, and related manufacturers (Heakston and Warrell, 2000). An estimated 10 million or more antivenom vials are required annually (WHO, 2007). Nonetheless, about 50 laboratories are accredited by WHO as active producers of animal-derived antivenoms globally. Most manufacturers are in Asia, America, and Europe (Table 1) (WHO, 2019c). These factors have increasingly made antivenoms inaccessible or accessed at an extortionate cost, especially in Africa (Williams *et al*., 2011). The exorbitant prices of antivenoms have consequently led to a decrease in demand which has caused a significant decline in the availability of antivenoms, especially in Africa. Thus, an impending shortage or failure of antivenom supply is imminent in Africa (WHO, 2021). Shortfalls have been shown to promote the sale and use of non-specific and substandard or fake antivenom products (Warrell, 2008), further undermining public confidence in antivenom therapy. In addition, poor distribution chain, strained storage facilities/logistics and diverse snake species frustrate the proper distribution and use of antivenom therapy, especially in impoverished regions (Bawaskar, 2004; Morals and Massaldi, 2008; Gutierrez *et al*., 2011).

A clear-cut example of the snags mentioned above is epitomised in the instances of Fav-Afrique (produced by Sanofi Pasteur, France; certified by Stringent Regulatory Authorities and French National Regulatory Authority). It is the safest, most effective, and most widely used antivenom agent in sub-Saharan Africa (Chippaux *et al*., 1999; Wolf *et al*., 2011). This polyvalent antivenom is highly effective against envenomation from several indigenous African snakes, especially *Echis ocellatus* (the West African saw-scaled viper), which majorly account for morbidity and mortality in West and Central African savannah (Chippaux *et al*., 1999). It has been successfully used by Medecins Sans Frontieres (MSF) in Paoua of the Central African Republic (CAR), where *E. ocellatus* envenoming is recurrent (Gras, 2011). Though several other alternatives are available, the production of Fav-Afrique was unfortunately terminated for unknown/undisclosed reason(s); the last batches produced are said to have expired in June 2016.

Adverse Effects of Antivenoms

The use of conventional drugs, vaccines, and antibodies comes with repercussions in the form of adverse reactions. For antivenoms, the adverse reactions can be either acute (anaphylactic or pyrogenic) or chronic/delayed (serum sickness type) (Gutierrez *et al*., 2006). The mechanism of acute antivenom adverse effects is equivocal, causing many obstacles for medics to curtail while treating envenomation. The effects may be mild (such as hives/urticaria, fever, headache, nausea, and vomiting) or severe, as seen in systemic anaphylaxis, which can prompt hypotension, cyanosis and syncope in about half of treated patients (Lalloo and Theakston, 2003; Theakston *et al*., 2003; Sampson *et al*., 2006). Low-quality antivenoms can have high pyrogenicity, commonly due to microbial lipopolysaccharides, causing fever, rigour or chill, myalgia, and possibly tachycardia or hypotension (Leon *et al*., 2013). Some of the common causes of antivenom adverse reactions are highlighted below:

i. Complement activation that is IgE-mediated or non-IgE-mediated often causes anaphylactic reactions (Isbister *et al*., 2008; De Silva *et al*., 2011; Leon *et al*., 2013).
ii. The composite nature of antivenom confers to it substantial amount (almost 70%) of venom non-

specific immunoglobulins and antigen-binding fragments that are targeted against other antigens, which could cause unwarranted reactions and complications (Segura *et al*., 2013; Laustsen *et al*., 2015; Laustsen *et al*., 2016a; Rodriguez-Rodriguez *et al*., 2016).

iii. Human anti-horse antibodies (IgGs and IgMs) binding to a substantial amount of antivenom antibodies can generate immune complexes having an extended half-life. When deposited in tissues (such as blood vessels, glomeruli, and joints), these immune complexes can trigger inflammatory or autoimmune responses linked to Type III hypersensitivity (Descotes and Choquet-Kastylevsky, 2001).

Given the challenges mentioned above relating to cost, distribution, storage, and the adverse effects of antivenom, novel therapies are being exploited for snakebite treatment. Emerging therapies include immunisation with DNA, epitope strings or recombinant toxins (Alvarenga *et al*., 2002; Araujo *et al*., 2003; Harrison, 2004; Laustsen *et al*., 2016a; Laustsen *et al*., 2016c). Compared to basic antivenoms, production techniques for these emerging therapies are not cost-effective, especially in sub-Saharan Africa, where poverty is endemic. Thus, the African populace resorts to traditional folk medicinal practices and mostly to herbs as alternatives to the inaccessible conventional antivenom therapies (Laustsen *et al*., 2016b; Laustsen *et al*., 2017).

Folk Medicine and Plant Antidotes against Snakebite

In Africa and other developing countries, an enormous population (up to 80%) depend on herbal medicines to treat several diseases. This dependence on herbal medicines is likely due to the absence of conventional healthcare services due to poverty or remoteness of the settlements, coupled with negligence by governments (WHO, 2002; Calixto, 2005; Bhattacharjee and Bhattacharyya, 2013). Alam *et al.* (2014) estimated that 70% of the global population depended on plant-based formulations as herbal drugs. Plants are inexpensive sources of a plethora of bioactive compounds employed for the treatment/management of infectious, chronic, and degenerative diseases, as well as poisoning and envenomation (Willcox *et al*., 2004; Mahato and Sharma, 2019; Magaji *et al*., 2020). These forms of folk practice are also resorted to for treating snakebites due to the increasing difficulty in accessing conventional antivenom agents, especially in poor rural African communities. Their use is ordinarily attributed to availability, low price, non-requirement for sophisticated logistics systems, impeccable stability, and broad-spectrum antivenom activity besides tissue antinecrotic effects (Gomes *et al*., 2010; Santhosh *et al*., 2013; Butt *et al*., 2015; Sulochana *et al*., 2015).

Masticated leaves, leaf juice, seed or root paste as antidotes are applied topically and consumed as decoction or concoction; this may be singly or combined with other materials before administration (Harsha *et al*., 2002; Parinitha *et al*., 2005; Samy and Thwin, 2008). This technique has drawn the interest of toxicologists around the globe and has promoted the search for potent inhibitors or attenuators of venoms (Butt *et al*., 2015). Several formulations inhibit snake venoms, mitigating tissue damage and successfully attenuating systemic diffusion. Hence, buying time for possible antivenom therapy and ultimately increasing the longevity and survival of victims (Félix-Silva *et al*., 2017; Isabel *et al*., 2019). Although the exact antivenom mechanism and active compounds are unknown, an excess of seven hundred plants have been identified/documented to be active against snake envenomation (Gomes *et al*., 2010; Giovannini *et al*., 2017; Upasani *et al*., 2017). Rizzini *et al.* (1988) identified 83 plant species with snake venom antidote action. After that, Mors (1991) and Martz *et al.* (1992) registered 578 and 11 plant species, respectively. A higher number of plants species (470 plants) with antivenom activities were subsequently recorded within a year by Duke (1993). Moreover, scientists have made giant strides by evolving and enriching databases for plants with antivenom effects and as well elaborating the amino acid sequence of venoms (Gomes, 2010; Amui *et al*., 2011; Dey and De, 2012).

The plants used against Snakebite and Envenomation in Sub-Saharan Africa

Traditional antivenom remedy is widely practised in sub-Saharan Africa due to convenience, affordability, broad specificity, cultural dogmas, and non-requirement for specialised logistics (Mander, 1998; Meenatchisundaram *et al*., 2008; Venkata *et al*., 2015). They proved to be lifesaving antidotes with a substantial impact on human life, consequently referred to as essential herbs in communities where snakebite is endemic. However, very few of these documented indigenous anti-envenomation herbs and folk medicines have been put to pharmacological and toxicological scrutiny (Ismaila and Adamu, 2012; Ameen *et al*., 2015). Some studies suggest that extracts from these plants antagonise multitudinous snake venoms and purified toxins (Da Silva *et al*., 2005; Maiorano *et al*., 2005; Oliveira *et al*., 2005; Ticli *et al*., 2005). Twenty-seven plants used as antidotes against snakebite and snake antivenom in diverse locations of sub-Saharan Africa are presented in Table 2.

Among the 27 plants specie that belongs to 19 families listed in Table 2, *Mucuna pruriens, Allium sativum, Guiera senegalensis, Aristolochia sp., Tamarindus indica* and *Securida calongipedunculata* are perceived to be the most effective plants with anti-snake effect.

Mucuna pruriens is a known tropical legume usually identified as "Velvet bean", which belongs to the family Fabeaceae.*Mucuna pruriens* is widely cultivated due to its

dietary protein and mineral composition. The plant is considered the most widely studied with anti-snakebite effect (Gurumoorthi *et al.,* 2003; Janardhanan *et al.,* 2003; Pugalenthi *et al.,* 2005). All its parts exhibit diverse pharmacological effects and show antidiabetic, aphrodisiac, antineoplastic, antiepileptic, and antimicrobial activities in addition to antivenom effects (Sathiyanarayanan and Arulmozhi, 2007). The seeds of *Mucuna pruriens* act as an antidote against snake venoms (Guerranti *et al*., 2002). In Nigeria, a swallowed whole seed of the plant is believed to act as an oral antivenom prophylactic agent, with herbalists professing it to protect against snakebite envenomation for about a year (Aguiyi, 1999; Guerranti *et al*., 2002; Fung *et al*., 2009; Tan *et al*., 2009; Scire *et al*., 2011; Kavitha *et al*., 2014). Vaccination with aqueous seed extracts of *M. pruriens* protects against envenomation from the *Elapidae*and *Viperidae* family snakes (Aguiyi, 1999; Guerranti *et al.,* 1999). An *in vivo* study by Guerranti *et al*. (2008) showed that the multiform glycoprotein (gpMuc) of the *M. pruriens* seeds possess short- and long-term protection against snake venom toxicity. Furthermore, it has been reported to stimulate the synthesis of antibodies capable of cross-reacting with venomous proteins and inhibits the venom proteolytic apparatuses, thus mitigating toxicity (Guerranti *et al.,* 2004; Kumar *et al.,* 2016). This immunogenic glycoprotein (gpMuc) has a molecular weight of 20.3 to 28.7 kDa and pI of 4.8 to 6.5 (Di Patrizi *et al.,* 2006; Hope-Onyekwere, 2012) and has Seven (7) different N- terminal isoforms, some of which possess structural similarities to PLA_2 of venoms (Lucia *et al.,* 2012). Recent investigations by Kumar *et al.* (2016) substantiated that a specific purified protein from *M. pruriens* code-named MP-4 (20.9 kDa) reacts with antibodies against *Echiscarinatus* venom, though contrarily, the MP-4 protein exhibited no direct protease inhibitory action. They further reported that this validates the potentiality of the plant to induce immunological response and prevent toxicity via an antibody-mediated mechanism. Consequently, the researchers concluded that MP-4 could be used as an active adjuvant to improve prophylactic and therapeutic approaches against the physiological effects of snake envenomation.

Allium sativum is the second most extensively studied plant in anti-snake venom properties after *Mucuna pruriens*. *Allium sativum* is commonly known as Garlic, one of the most widely used flavouring agents in food preparation; hence it is a special spice and a known therapy for numerous diseases and physiological disorders in different parts of the world (Rubatzky and Yamaguchi, 1997; Dandare *et al.,* 2014). *Allium sativum* belongs to the genus *Allium* and is a member of the family *Alliaceae.* It is described to contain at least Thirty-Three (33) sulfur compounds (higher than any other *Allium* species), Seventeen (17) amino acids and their glycosides, including arginine and others, and several enzymes such as allinase, peroxidases, myrosinase, and minerals including selenium, germanum, tellurium and other trace minerals (Londhe *et al.,* 2011; Bhandari, 2012). These sulfur compounds and their precursors (ajoene, allicin, alliin, allyl sulfides, allyl disulfides, allyl trisulfides, cysteine, cycloalliin, cysteine sulfoxides, cystine, diallyl sulfides, dimethyl sulfides, glutathione, disulfides, methionine, methyl sulfides, sulfanes, pseudoscordinine, thiosulfinates, scordinine, trisulfides and tetrathiol) as revealed by Choudhary (2008) and Butt *et al.* (2009) and also the presence of peptides, steroids, terpenoids, flavonoids, and phenols are responsible for the plant's strong odour and most of its nutraceutical and medicinal properties (Mikaili *et al.* 2013; Dandare *et al.* 2014). Besides this, *Allium sativum* (garlic) is reported to contain volatile oils, which contribute to its pharmacological properties, as Kaschula *et al*. (2010) reported. Because of its biologically active constituent named "allicin" and its derivative, *Allium sativum* is used as a medicinal plant for the treatment of a wide range of ailments and disorders related to the heart and blood system, including high blood pressure, high cholesterol, coronary heart disease, heart attack, and atherosclerosis (Mikaili *et al*., 2013). However, Mikail (2010) reported the presence of phytochemical compounds such as saponins, steroids, tannins, carbohydrates, and cardiac glycosides, which conformed to similar studies by Otunola *et al.* (2010) and Divya *et al.* (2017), who reported the presence of phenolic, alkaloids, flavonoid, saponin, steroid, carotenoids and glycoside which are considered as active medicinal chemical constituents in the *A. sativum*. Studies on *Allium sativum* by Touloupakis and Ghanotakis (2010); Nicastro *et al.* (2015), and Divya *et al.* (2017) revealed the existence of essential mineral elements such as Potassium (K), Phosphorus (P), Magnesium (Mg), Calcium (Ca), Zinc (Zn), Aluminium (Al), selenium (Se), iron (Fe) and germanium (Ge) which are vital elements for many regulatory systems in the body, hence increasing its potential as therapeutic agent plant. Fourier Transform Infrared Spectroscopic (FTIR) study by Divya *et al.* (2017) showed the presence of specific functional groups such as Hydroxyl, carbonyl, carboxylic organosulfur and aromatic compounds in garlic methanolic extract. *Allium sativum* has also been reported to contain important antioxidants, Vitamins A, C and E, as well as Vitamins B_1, B_2 and B_6 (Goncagul, and Ayaz, 2010; Capasso, 2013; Kovarovic *et al.,* 2019). Pharmacological studies by Borges *et al.* (2001) and Lin *et al.* (2003) on some selected medicinal plants, including *Allium sativum,* used for treating snakebites, showed that the plants could antagonise the activity of several crude venoms and purified toxins. The proposed mechanism by which the activity of snake venoms is neutralised by antivenin is through antigen-antibody interaction, as reported by Omara *et al.* (2020). Other reported mechanisms of snake venom neutralisationinclude precipitation or inactivation of the toxic venom proteins, inactivation, or enzyme inhibition, chelation, adjuvant action, antioxidant activity or synergistic

interaction of these mechanisms (Castro *et al.,* 1999; Hung *et al.,* 2004; Januario *et al.,* 2004; Vale *et al.,* 2008), though the enzyme inhibition and protein precipitation are reported to be the most conservatively recognised mechanisms (Alam and Gomes, 1998).

Furthermore, the phytochemical compounds in *Allium sativum* such as flavonoids, phenols, saponins, tannins, carotenoids, steroids, and alkaloids are reported to snuggly bind to lethal proteins of snake venoms, hence counterweighing their injurious effects (Omara *et al.,* 2020). These phytochemical constituents of *Allium sativum* are reported to have analogous functions (Bruno *et al.,* 2009). Additional possible mechanism of snake venom inactivation by the plant is through inhibition of the active enzymes such as phospholipase A2, metalloproteases, and hyaluronidases by polyphenolic compounds such as tannins which interact with the venom enzymes by non-specific binding proteins (Gupta and Peshin, 2014) through hydrogen bonding with hydroxyl groups in the protein molecules thereby generating chemically stable complexes (Leanpolchareanchai *et al.,* 2009). In the case of antioxidation mechanism, phytochemical metabolites (flavonoids, terpenoids, tannins and polyphenols), vitamins A, C, E, and minerals elements (such as selenium) present in *A. sativum* are believed to thwart, stop or diminish oxidative damage due to phospholipase A2 activity via selective binding to the active sites or altering the conserved residues that are inevitable for phospholipase A2 catalytic action, which will subsequently alter the entire activity of the enzyme (Gupta and Peshin, 2014).

Opportunities and Challenges of Herbal Antivenoms

Herbal medications, including herbal antivenoms, have been extensively used worldwide since time immemorial and have been identified by physicians and patients for their healthy therapeutic importance as they have fewer adverse effects when compared with contemporary medicines (Devi *et al*., 2010; Sofowora *et al.,* 2013; Abdel-Aziz *et al.,* 2016). Medicinal plants used as a complementary therapy for the treatment of snakebites are reported to be rich sources of natural inhibitors and pharmacologically active compounds (Santhosh *et al.,* 2013; Guimaraes *et al.,* 2014; Shabbir *et al.,* 2014), hence used against snakebites around the globe, particularly in tropical and subtropical regions including sub-Saharan Africa (Gomes *et al.,* 2010; Dey and De, 2012). The use of medicinal plants for the treatment of snakebite is famous practice all over human history from generation to generation; consequently, people residing in rural communities significantly depend on folk medicines as a remedy for snakebites from any venomous snakes (Butt *et al.,* 2015; Sulochana *et al.,* 2015). Currently, this development in the use of traditional medicine as herbal antidotes against snake venom has yielded positive results, particularly with significant attention received from toxicologists all over the globe as a device to design potent inhibitors of snake venom toxins (Juliana *et al.,* 2017). Parts of the advantages of herbal snake antivenoms include:

i. **Availability and affordability:** herbal medicines are readily available at a cheaper price than synthetic medicines, hence the only alternative for low-income clients to solve their health problems (Walter *et al.,* 2005). In Africa and globally, herbal medicines are considered more affordable and cost-effective than conventional pharmaceutical products (Parasuraman, 2018). Due to their availability and affordability, the use of herbal antidotes against snake venoms is increasing both in developed and developing countries; thus, WHO estimated that more than 80% of the world's population relies on traditional herbal medicines for the treatment of numerous diseases (Bhattacharjee and Bhattacharyya, 2013). Herbal medicinal plants that neutralise snake venom are found worldwide, particularly in tropical or subtropical regions of Asia, the Americas, and Africa (Juliana *et al.,* 2017).
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ii. **Storage at room temperature:** another advantage of herbal plants used against snake venom is they are stable at room temperature compared to synthetic antivenoms (Gomes *et al.,* 2010). Medicinal plants are generally resistant to heat and light compared to synthetic drugs that are considered susceptible to degradation when exposed to heat and light (Lowe *et al.,* 2011). Conventional snake antivenoms are recommended to be stored at temperatures of 2 to 8°C, which is considered not feasible, particularly in rural areas where the cold chain is frequently interrupted due to inconsistent power supply (Andreas, 2018). Heat stability for long-term storage is particularly vital in tropical regions where most snake envenomation occurs (Warrell, 2007). Thus, this necessitated using herbal medical plants to treat snakebites, which are stable and effective at room temperature.

iii. **Broad spectrum efficacy:** herbal antivenom plants possess the ability to neutralise a wide range of snake venoms, including those that induce local tissue damage. And they can achieve this without side effects (Gomes *et al.,* 2010; Santhosh *et al.,* 2013; Butt *et al.,* 2015; Sulochana*et al.,* 2015).

Table 1: Available snake antivenom products in sub-Saharan Africa

S/NO	ANTIVENOM	COMPANY	COUNTRY ASV ACCESSIBLE
1	EchiTabG	Micro Pharm, UK	Nigeria
2	ViperaTab	Micro Pharm, UK	Nigeria
3	SAIMR Boomslang antivenom	South African Vaccine Producers	South Africa
4	SAIMR Echis antivenom	South African Vaccine Producers	South Africa.
5	SV antiserum Echisocellatus	VINS Bioproducts, India	Kenya, Nigeria, Ghana.
6	ASNA-C	Bharat Serums and Vaccines, India	Ghana, Nigeria, Kenya, Benin, Burkina Faso, Sudan.
7	ASNA-D	Bharat Serums and Vaccines, India	Ghana, Nigeria, Kenya, Benin, Burkina Faso, Sudan
8	SV Antiserum (Pan-African)	VINS Bioproducts, India	Kenya, Nigeria, Ghana, Burkina Faso, Angola, Mozambique, Sudan.
9	Antivipmyn-Africa (Antivip-A)	InstitutoBioclon/Silanes, Mexico	West Africa; Post clinical trials.
10	InoserpPanAfrica	Inosan, Spain	West Africa, East Africa.
11	Fav-Afrique	Sanofi Pasteur, France*	West Africa, East Africa.
12	SAIMR Polyvalent SAV	South African Vaccine Producers	South Africa.
13	EchiTabPlus	Instituto Clodomiro Picado, Costa Rica	West Africa; Post clinical trials.
14	Poly; equine; lyophilised (10 ml)	Serum Institute of India, India*	Burkina Faso, Angola, Mozambique, Sudan, Ghana, Tanzania, Ethiopia, Kenya.

Key: * Manufacturer has now stopped antivenom production; ASV- Anti Snake Venom; SVA-Snake Venom Antiserum; SAV- Snake Anti-venom; SV-Snake Venom. Adapted from Alirol *et al.* (2015) and Potet *et al.* (2019).

Table 2: Plants with anti-envenomation, antivenom, or anti-snake effects used in sub–Saharan Africa

S/NO	PLANT NAME (FAMILY)	ENGLISH NAME	PART/EXTRACT USED	NAME OF SNAKE	REFERENCES
1	Ageratum conyzoides L. *(Asteraceae)*	White weed	Leaves	*Cobra* and *Viper*	Jeetendra and Kumar (2012). Vashistha and Kaur (2013).
2	*Allium cepa* (Amaryllidaceae)	Onion	Bulbs	*Cobra* and *Viper*	Alagesaboopathi (2013); Panghal (2010).
3	*Allium sativum* (Amaryllidaceae)	Garlic	Bulbs	*Cobra* and *Viper*	Sarkhe (2014) Ismail and Adamu (2012).
4	*Aloe vera* (Asphodelaceae)	Aloe vera	Leaf extracts	*Cobra* and *Viper*	Coe and Anderson (2005); Dharmadasa *et al.* (2016).
5	*Annona senegalensis* (Annonaceae)	Custard-apple	Root extract	*Cobra* and *Naja nigricollis*	Chinyere *et al.* (2016); Amlabu *et al.* (2014).
6	*Aristolochia bracteolate,* Aristolochia indica L. (Aristolochiaceae)	Pipevine	Leaves and roots extracts	*Daboia russelli* and *Naja naja*	Marandi *et al.* (2015); Alagesaboopathi (2013).
7	*Azadirachta indica* (Meliaceae)	Nimtree	Methanolic leaf extract	*Cobra* and *Viper*	Khan *et al.* (2014); Mukherjee *et al.* (2008).
8	*Balanites aegyptiaca* (Zygophyllaceae)	Desert date	Extract of stem back	*Echis carinatus*	Wufen*et al.* (2007)
9	*Calotropis gigantea (L.)* (Apocynaceae)	Crown flower	Roots	*Cobra* and *Viper*	Bhat *et al.* (2012); Rao and Sunitha (2011).
10	*Calotropis procera (Ait.)* (Apocynaceae)	Apple of Sodom	Leaves	*Cobra* and *Viper*	Khan *et al.* (2014); Jeetendra and Kumar (2012).
11	*Curcuma longa* (Zingiberaceae)	Turmeric	Rhizome	*Naja naja*	Mathur and Joshi (2013); Chethankumar and Srinivas (2008).
12	*Curcuma zedoaroides* (Zingiberaceae)	Curcuma longa	Rhizome	*Ophiophagus hannah*	Lattmann *et al.* (2010).
13	*Guiera senegalensis* (Combretaceae)	Evergreen shrub	Leaves extracts	*Echis carinatus and Naja nigricollis*	Ameen *et al.* (2015); Abubakar *et al.* (2000).
14	*Heliotropium indicus* (Boraginaceae)	Indian heliotrope	Root extract	*Cobra* and *Viper*	Marandi *et al.* (2015); Sahu*et al.* (2014).
15	*Hibiscus aethiopicus* (Malvaceae)	Yellow hibiscus	Whole plant	*Echis ocellatus and Naja nigricollis*	Hasson *et al.* (2010).
16	*Hibiscus sabdariffa L* (Malvaceae)	Sorrel	Seed extract	*Cobra* and *Viper*	Jasmeet *et al.* (2017).

17	*Mangifera indica* (Anacardiaceae)	Mango	Aqueous extract of stem back, ethanolic extract from seed kernels.	*Calloselasma rhodostoma, Naja kaouthia.*	Bhattacharjee and Bhattacharya (2013); Dhananjaya *et al.* (2011).
18	*Moringa oleifera* (Moringaceae)	Moringa	Root & Seed extract	*Cobra* and *Viper*	Satish *et al.* (2012), Sarkhe (2014).
19	*Morus alba* (Moraceae)	White mulberry	Leaf extract	*Daboia russelii*	Chandrashekara*et al.* (2009).
20	*Mucuna pruriens* (Fabaceae)	Velvet bean	Seed extract	*Naja kaouthia, Naja nivea, Calloselasma rhodostoma* and *Echis carinatus.*	Isabel *et al.* (2019); Kunjam *et al.* (2013); Scire *et al.* (2011).
21	*Nicotiana tabacum L.* (Solanaceae)	Cultivated tobacco	Leaf extracts	*Cobra* and *Viper*	Samy*et al.,* 2008; Omara*et al.* (2019).
22	*Pluchea indica* (Asteraceae)	Indian camphorweed Indian fleabane.	Root extract	*Cobra* and *Viper*	Bhattacharjee and Bhattacharya (2013);
23	*Pluchea indica* (Asteraceae)	Pluchea Indica	Root extract	*Cobra* and *Viper*	Gomes *et al.* (2007)
24	*Securidaca longipedunculata* (Polygalaceae)	Violet tree	Root extract	*Cobra* and *Viper*	Wannang (2005); Ameen *et al.* (2015).
25	*Tamarindus indica* (Fabaceae).	Tamarind	Seed extract	*Cobra* and *Viper*	Ushanandini *et al.* (2006).
26	*Tephrosia purpurea (L.) Pers.* (Fabaceae).	Purple tephrosia	Roots and leaves	*Cobra* and *Viper*	Kunjam *et al.* (2013); Patel *et al.* (2010).
27	*Vitis vinifera* (Vitaceae)	Grapevine	Seed extract	*Daboia russelli and Echis carinatus*	Mahadeswaraswamy *et al.* (2009).

iv. **Easy administration:** Unlike conventional anti-snake venoms that are primarily administered either by slow intravenous injection, intravenous infusion, or intramuscular (Ahmed *et al.,* 2008), most herbal snake antivenoms are administered orally. Nearly, 80% of herbal products are commonly administered orally (Boadu and Asase, 2017). Oral administration is considered the most convenient and accessible route, as drugs administered via this route are more suitable for individuals.

v. **Shelf life:** Medicinal plants have no shelf life unless they are spoilt. Mostly, medicinal herbs have no duration to which they can stay before being discarded.

vi. **Fewer side effects:** It has been reported by Devi *et al.* (2010) that natural components of herbal medicines are simply and readily metabolised by the body; consequently, resulting in fewer, if any, side effects which subsequently improve absorption in the bloodstream thereby leading to more systematic and effective treatments.

Additionally, Schmidt *et al.* (2008) reported that herbal antivenoms have a more significant advantage due to their complex composition of different components; therefore, they perform several biological activities that lead to greater total activity in the biological system. Williamson (2001) reported that possible reasons include synergy, enhanced bioavailability, cumulative effects, or simply the addictive properties of the constituents, but he recommended that advanced study is needed. Natural constituents of herbal medicine, including herbal antivenoms, are different from synthetic antivenoms by the frequency of other atoms, radicals, and spatial configuration (Koehn and Carter, 2005). These natural products are reported to contain less nitrogen, phosphorus, sulfur, and halogens and more overall molecular complexity, scaffold variety, stereochemical richness, ring system diversity, and carbohydrate constituents compared to synthetic ones (Schmidt *et al*., 2008).

Despite these benefits derived from the use of herbal antivenoms for the treatment/management of snakebites, they need to be used with great caution due to the following challenges:

i. **Safety and efficacy:** Cao *et al.* (2008) and Saleh *et al.* (2012) reported serious concerns on the safety of herbal and herbal related products in recent times. This may be the reason why the two (2) major professional bodies in the health sector: the medical community and the pharmaceutical industry, have not well accepted plant medication because herbal medication lacks safety and efficacy validation and due to improper regulations by regulatory authorities, as well as poor standardisation, quality control, confusing nomenclature, and the accurate identification of plants (Houghton, 1998).

ii. **Interactions:** herbal medicinal plants might elicit some adverse reactions, mainly when consumed in high or bearable doses/quantities over a long period. Adverse reactions may also occur due to herbal-drug interactions when herbal remedies are co-administered with synthetic drugs (Janetzky and Morreale, 1997; Miller, 1998). Similarly, if herbal antivenoms are used in combination with other plants, the effects can be complicated as various interactions can occur among the individual plant components resulting in herbal-herbal interactions. Therefore, because of the presence of numerous constituents in the herbal plants, the effects as a result of herbal-drug or herbal-herbal interactions are frequently unpredictable and complicated (Che *et al.,* 2013).

iii. **Dosage disparity:** This dosage disparity has been reported to impose greater effects on children because of their smaller body size and inability to detoxify chemicals than adults (Roulet *et al.,* 1988; Woolf, 2003)

iv. **Contaminants and adulterants:** Plant medicines are known to contain contaminants and adulterants that are pharmacologically active and responsible for unexpected toxicity (Saad *et al*., 2006). Contaminants and adulterants found in medicinal plants, including herbal antivenoms, are among the leading factors of adverse reactions that may be occasionally deadly to patients (Ernst, 1999; Fugh-Berman, 2000; Abu-Irmaileh and Afifi, 2003). The reported toxic effect of medicinal plants may be as a result of numerous factors, which include contamination with pesticides, microbes, heavy metals, toxic organic solvents, radioactivity or adulteration with conventional drugs (Fugh-Berman, 2000; El-Nahhal, 2004), hence the liver toxicity from herbal therapies may lead to mild elevations of liver enzymes and subsequently to total liver damage necessitating liver transplantation (Woolf, 2003).

v. **Poor regulatory standard:** most of the herbal antivenoms currently in use in sub-Saharan Africa are not subjected to the same regulatory standards or scrutiny by the regulatory bodies as done to synthetic antivenoms to ensure their safety and efficacy (Kuete, 2014).

vi. **Purity of the plant:** uncertainties in recognising the plant's active ingredients and accessing their

complex modes of action (Raskin and Ripoll, 2004). Furthermore, it has also been reported by Saad *et al.* (2006) that the concentration of active constituents and other chemicals in plants differs by the part of the plant harvested; the maturity of the plant at the time of harvest; the time of year during harvest; geography and soil conditions; soil composition and its contaminants; and year to year variations in soil acidity, water, weather conditions and other growth factors. Azaizeh *et al.* (2005) in their study reported that fertilization affects the antioxidant activity of some medicinal plants used in traditional medicine; therefore, increasing the quantity of fertiliser may lead to a substantial reduction in the antioxidant activity of the plants. Hence the exact amount of active ingredients taken is often flexible, unpredictable or unknown (Woolf, 2003).

Conclusion and Future prospects

The high prevalence rate of snakebites in Africa and the lack of adequate treatment made snakebite envenomation listed as a category A Neglected Tropical Disease (NTD) by the WHO. Despite the need for synthetic antivenoms in subduing morbidity and mortality from snakebites, these important drugs are unavailable for decades or inadequate to meet the high demands annually. Poor financing from Governments of various African countries, which consequently led to poor infrastructure (poor/inadequate roads, storage facilities, power supply, distribution chains), is the key factor that resulted in the shortage or reduced efficacy of antivenoms in sub-Saharan Africa. This shortage or unavailability of synthetic antivenoms, coupled with their vague severe adverse reactions, prompted Africans, particularly those in rural communities to resort to herbal antivenoms as alternatives to the inaccessible conventional therapies.

Though herbal antivenoms are widely used for the treatment of snakebites due to their numerous advantages (such as their pharmacological effects, availability & affordability, broad-spectrum efficacy, ease of administration, etc.); however, some of them are reported to exhibit apparent toxicity. Therefore, there is a need to conduct extensive pharmacological and toxicological evaluations of each potential antivenom plant to establish its safety and efficacy. Furthermore, it is important to isolate the biologically active compounds or antivenins from the potential candidates to test their effectiveness and efficacy in the treatment/management of snake envenoming. The Governments, especially in sub-Saharan Africa, need to finance research in herbal antivenoms and establish regulations and standards for the use of herbal remedies for the treatment and management of snake envenoming.

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