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Snake venom detoxification potential of selected Nigerian medicinal plants: a review

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Snake envenomation is one of the neglected public health problems with high morbidity and mortality rate across the globe. Snakebite has led to several major health complications such as numbness and flaccid paralysis, damage to local tissue which eventually results in temporary and/or permanent physical impairment. In Nigeria however, lack of access to emergency treatment for snake envenomation has in no small measure contributed to the high rate of snake incidence. Though, a lot of drawbacks and limitations associated with the use of standard antisnake venom (ASV) include storage, side effects, expire in short time coupled with short supply. These factors made snake venom detoxification with ASV unaffordable to victims especially to people living in rural areas who are at high risk of snakebites. Therefore, the use of medicinal plants remains the only alternative for snake venom detoxification (SVD) in Nigeria especially in rural areas. This mini review reported the detoxification potentials of different medicinal plants (parts: leaves, stem bark, root, seed) of creeping foxglove (*Asystasia gangetica L.*), Resurrection plant (*Bryophullum pinnatum Lam*), Hammattan lily (*Crinum jagus*) wild custard apple (*Annona sengalensis*), plantain (Musa *paradiasia*) and finger root (*Uvaria chamate*), used to treat snakebite in Nigeria. Majority of these medicinal plants used by herbalists were validated by recent scientific works conducted on snake venom detoxification potentials. Bioactive antivenin compounds such as aristolochic acid, quercetin, kaempferol, resveratrol isolated from common Nigerian medicinal plants show very promising detoxification potential against snakebites. The authors of this review paper suggest that, more ethnomedicinal survey should be done to explore more plants with SVD potential for the development of effective medications.

Keywords: Bioactive compounds, Medicinal plants, Nigeria, ASV, Snakebite, phytochemicals.

1. Introduction

Historically, the importance of natural products either as food, medicine, dyes, etc. cannot be overemphasized (Hassan *et al.,* 2020a). Since time immemorial, when there was no drugs or conventional medications for the treatment of common ailments such as headache, stomach violent, and wounds, our ancestors chewed on certain herbs to relieve pain, or wrapped leaves around wounds to improve healing, boil leaf/root of certain plant(s) for emergency treatment of snakebites (Hassan *et al.,* 2020a). For several decades, natural substances particularly those obtained from plants have been used for the management of diseases and this has been the major reasons for the discovery of the modern pharmaceutical drugs (Clark, 1996). Today, approximately 40% of medicines used for various clinical and pharmaceuticals therapies have their sources from medicinal plants (Hanson, 2003; Butler, 2004). Many of these medicinal plants (commonly known as traditional medicine) formulations are still used in many developed and developing countries especially in the rural areas across the world. Majority famous drugs of pharmaceutical and medicinal importance that saved the lives of millions of people across the world are derived from natural products (plants or microoganisms). Some of these drugs, like acetylsalicyclic acid **1** (aspirin) derived, salicin **2**, isolated from the bark of the willow tree *Salix alba L.,* morphine **3,** and codeine **4** isolated from *Papaver somniferum* L. (opium poppy), digitoxin **5** isolated from *Digitalis purpurea* L. (*foxglove*), paclitaxel **6** obtained from yew tree etc. have played important role in medicines (Marderosian and Beutler, 2002; Hassan, *et al.,* 2020a; Clark, 1996).

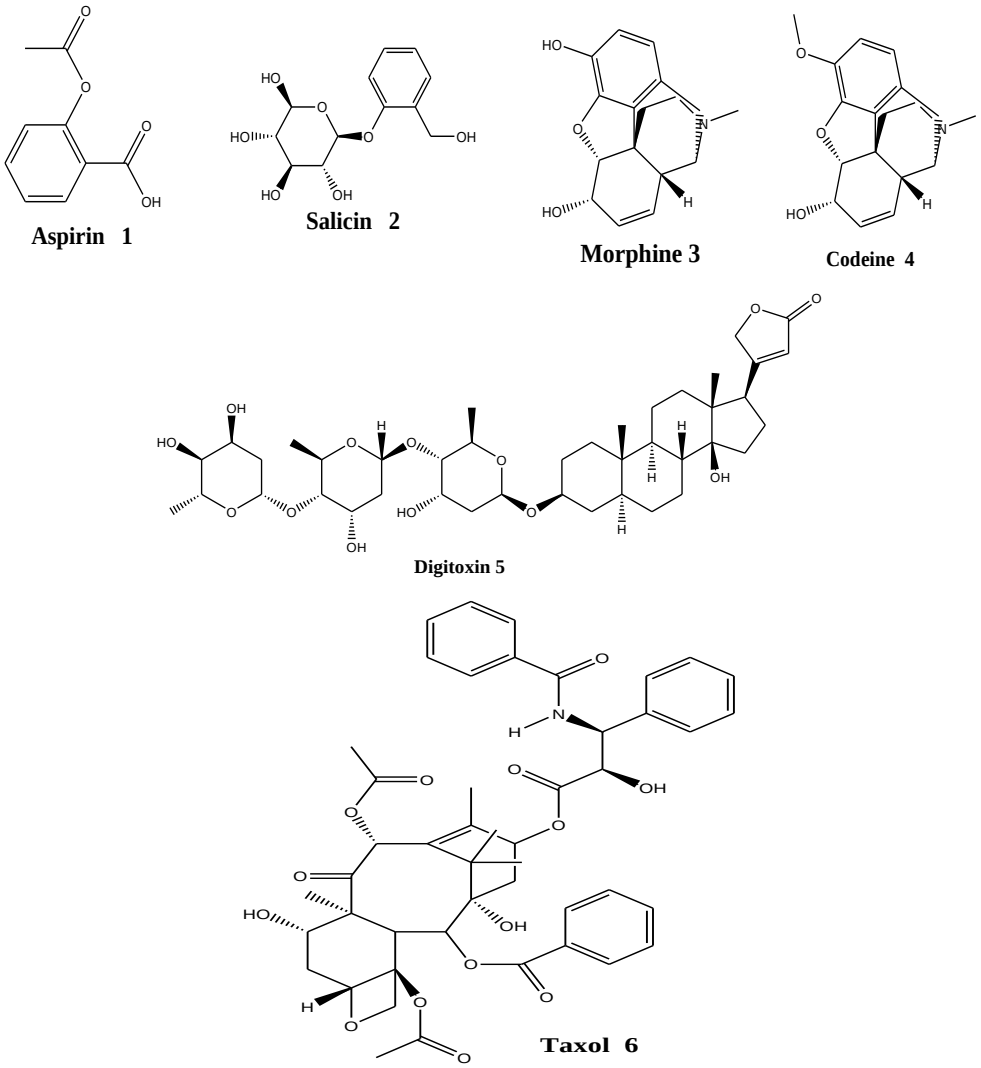

Figure 1: Pharmaceutical drugs of plants origin

Snake (Maciji in Hausa) is one of the few living organisms which educe a positive or negative response once seen or hear of the word snake *Maciji*. This sudden pizzazz upon hearing the name *maciji* arise from the fatal nature and deadly effect of their venoms, which when injected into the victim cause a variety of physiological reactions such as paralysis, myonecrosis and often death (Sani *et al.,* 2020a, Menez, 1998). Envenomation from snakebite is one of the severe but neglected public health problems responsible for high morbidity and mortality rate across the globe; especially in the rural areas where access to modern health facilities are very limited (Sani *et al.,* 2020b; Code *et al.,*2010; Yusuf *et al.,* 2019). An estimate number of more than 100,000 people die each year of snake poisons, approximately, 5 million cases of snake incidence have been documented worldwide, and more than 20,000 cases and 2000 deaths from snakebites are recorded in Nigeria from January to September, 2021 (Premium Times, 2021). Although, poor documentations of the snake incidence in rural areas made these figure not acceptable from the majority of scientists in the snake researchers. The burden of snake bite in Nigeria is more common in northern region (rural areas) whose livelihood depends on farming and rearing of animals (Oyinbuomwan *et al.,* 2018). This is the reason why most of the scientific researches on snakebites in Nigeria have come from this region.

Snake venoms is a complex mixture of proteins, enzymes which served both “as offensive weapons in incapacitating and immobilizing their prey (the primary function), as defensive tools against their predators (the secondary function) and to aid in digestion” (Sani *et al.,* 2020b). The most common and abundant toxic component of this complex mixture called venom is

phospholipase A_2 (PLA_2). Nearly, all families of poisonous snakes have PLA_2, this toxic enzyme hydrolyzes the sn-2 ester bond of membrane glycero-phospholipids generating fatty acids such as, arachidonic acid and lysophospholipids, which are precursors of eicosanoids such as prostaglandins, thrombaxanes, leukotrienes and lipoxins participating in inflammatory process (Morais, 2018; Sani *et al.,* 2020b). According to Sani *et al.,* (2020b), PLA2 from poisonous snakes could lead to local tissue damage, the effect which in many cases cannot be neutralized even by antivenoms and eventually cause disability or amputation to victims (Sani *et al.,* 2019). Majority of victims from the snakebite in rural areas are treated with root, leaf or stem-bark of certain plants or due to high cost of conventional antivenom immunotherapy and its side effects. However, the use of antivenins which is the only known medications worldwide is associated with many drawbacks such as cost, storage, side effects (serum sickness) short term expiry etc. Several efforts have been made by scientist in the area of natural products to develop potent antisnake venom (ASV) from medicinal plants that could be used in the future instead of antivenin immunotherapy.

2. Antivenom Immunotheraphy (Antiserum)

Antivenom immunotherapy also known as snake antivenom immunoglobulin is currently the only known medication for emergency treatment against snakebite across the world. Despite its role as life-saving medication, the use of ASV is associated with several factors which limit its use. These factors includes high cost, required proper storage, short expiry date, short supply and side effect such as anaphylactic shock, pyrogen reaction and serum sickness (Kumar and Khamar, 2014). Majority of these side effects could be due to high concentrations of non-immunoglobulin proteins present in commercially available hyper immune antivenom (Maya *et al.,* 2002). Though, the recent guidelines for the production, control and regulation of snake antivenom immunoglobulins by World Health Organization (WHO, 2016) have improved the quality of antivenom productions from horse and sheep. For instance, an intravenous administration of antisnake venom, prepared from immunoglobulin (IgG) of venom-immunized horses or sheep, shows an effective treatment for systemic envenoming (WHO, 2016; Kumar and Khamar, 2014).

According to WHO (2016) guidelines, the productions of snake antivenom immunoglobulin are divided into:

i. **Monospecific antisnake venoms:** This is antisnake venom produced from a single venomous snake species, and their effectiveness is largely restricted to that snake species. Monospecific antisnake venoms can be effective in treating snakebite cause by a few but closely related species whose venoms show clinically effective cross-neutralization. However, this requires preclinical and clinical confirmation. Therefore, the usage of this antisnake venom depends on areas where:
   a. Only one medically-important snake species (e.g. *Vipera berus* in the United Kingdom and Scandinavia) or where one species is accountable for the majority of incidence (e.g. *Oxyuranus scutellatus* in southern Papua New Guinea).
   b. A simple blood test, suitable for use even in under-resourced health care centres, can define the biting species (e.g. detection of incoagulable blood by the 20-minute).
   c. There is a reliable and affordable rapid immunodiagnostic test readily available allowing the toxins to be identified unambiguously (currently only available in Australia).

ii. **Polyspecific antisnake venoms**: This is antisnake venom produced from multiple venomous snake species. It is applicable to tropical countries with several medically-important snake species, it therefore make no meaning and also commercially unrealistic to develop multiple monospecific antisnake venoms. Thus, production of polyspecific antisnake venoms is highly recommended. The production of polyspecific antisnake venoms include:
   a. Mixing venoms from multiple snake species/genera (sometimes in amounts quantitatively associated with medical importance, immunogenicity etc) and immunizing donor animals with this mixture.
   b. Immunizing groups of donor animals with distinct venom mixtures and then mixing the hyper-immune plasma from each group of animals.
   c. Immunizing groups of donor animals with distinct venom mixtures and then mixing the monospecific antisnake venom immunoglobulins (IgGs) to formulate the final polyspecific antisnake venom.

3. Nigerian Medicinal plants Used for the Treatments of Snakebites

The limitations associated with the use of serum antivenin are well known and this necessitates the search for alternative for the snakebite treatment from cheap and easily available natural herbs such as medicinal plants (Sani *et al.,* 2020a). Ethnobotanical data of some Nigerian medicinal plants (used for local snake treatment) and methanol extracts of the selected medicinal plants against *Naja nigricollis, Echis ocellatus* and *Bitis arietans* are summarized in Table 1:

Table 1: Selected Medicinal Plants used for treatment of Snakebite in Nigeria

Scientific Name of the plant	Local Name	Plant Part	Dose (mg/kg)	Snake	References
Annona senegalensis	H-Gwandan daji F-Dukuuhi Y-Abo	Stem bark Root	100	*N. nigricollis*	Ameen *et al.,* 2015
Neocarya macrophylla	H-Gawasa	Stem bark	40-80	*N. nigricollis*	Yusuf *et al.,* 2019
Moringa oleifera	H-Zogale F-Gaware	Leaves	400	*Echis ocellatus*	Yusuf *et al.,* 2021
Calotropis procera	H-Tumfafiya F-Tumpaapahi Y-Bomu bomu	Leaves	NSW	NSW	Sani *et al.,* (2020a)
Adansonia digitata L	H-Kukaa F-Bokiki	Fruit	UID	*Naja nigricollis*	Ameen *et al.,* (2015)
Allium cepa	H-Albasa F-Tingyere	Bulb	NSW	NSW	Ameen *et al.,* (2015)
Allium sativum	H-Tafarnuwa F-Amgalaa-re	Bulb	NSW	NSW	Sani *et al.,* (2020a)
Acacia senegal wild	H-Dakwanaa F-Dibee-lu	Stem bark	NSW	NSW	Sani *et al.,* (2020a)
Hibiscus sabdariffa L	H-Yakuwa F-Fullere	Seeds	NSW	NSW	Sani *et al.,* (2020a)
Guiera senegalensis J.F Gmel	H-Sabaraa F-Geeloki jelloki	Leaves	NSW	NSW	Sani *et al.,* (2020a)
Parkia biglobosa	H-Dorawa F-Narahee	Stembark Root	400	*Naja nigricollis*	Sani *et al.,* (2020a)
Tamarindus indica L.	H-Tsamiyaa F-Jabbi	Seeds	NSW	NSW	Ameen *et al.,*(2015)
Musa parasidiaca	H-Agade	Juice	UID	*Echis ocellatus & Crotalae*	Borges *et al.,* (2005); Muanya (2021)
Azadirachta indica	H-Dogon yaro/Darbejiya	Leaf	20	*Naja nigricollis*	Faruq*et al.,* 2002
Crinum jagus	H & F-Gadali	Bulb	1000 250	*Naja nigricollis* *Echis ocellatus*	Ode, 2006
Bryophullum pinnatum Lam	Y-Odundun	Leaves	100	*Bitis arietans* *Naja nigricollis*	Gbolade *et al.,* 2020
Catunaregam nilotica	H-Chibra F-gil-al-godi	Root and stem bark	3mg/mL	*Naja nigricollis*	*Hassan et al.,* 2023

Key: H=Hausa, **F**= Fulfulde, **Y**= Yoruba, **NSW=** No Scientific Work, **UID**= Unidentified Dose

4. Bioactive Snake Anti-venom Compounds

Nigeria is blessed with different species of plants majority of which are used either as a source of food, dye, or herbs. The phytoconstituents of these important plants were reported, but active antivenom compounds from these Nigerian medicinal plants are seldom reported. Recently, Gbolade (2021) reported few classes of bioactive

antivenom compounds which include flavonoids, phenolic compounds, terpenes, steroids and to a lesser extent organic acids and alkaloids. Some Bioactive antivenom with PLA_2 and hyaluronidase activities were reported from *Bryophyllum pinnatum, Schum anniophyton magnificum, Mucuna pruriens, Annona species, Aristolochia species and Crinum jagus* (Gbolade, 2021; Yusuf *et al.,* 2021). The following are the structures of few antivenom compounds isolated from Nigerian medicinal plants:

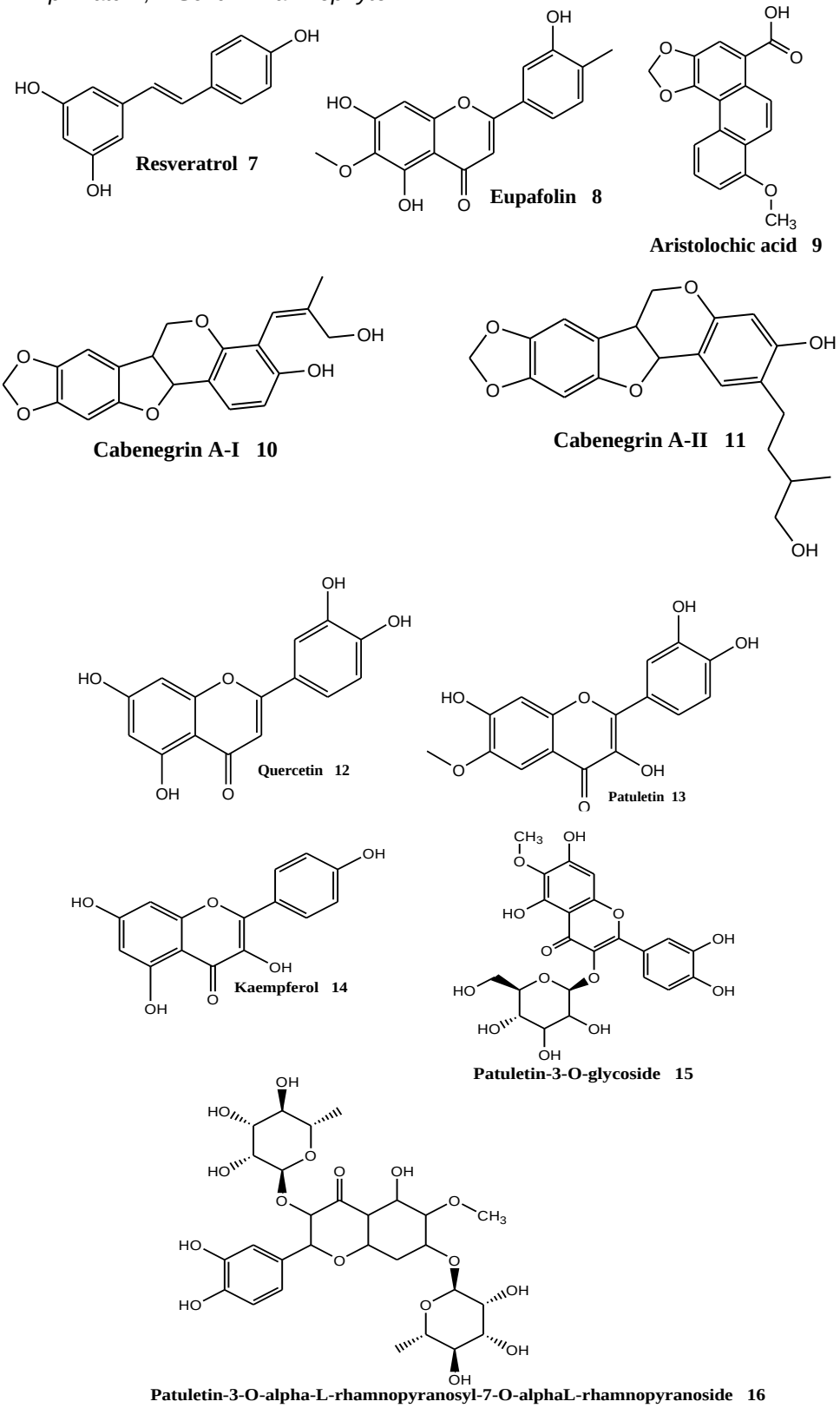

Figure 2: Structures of bioactive antisnake venom compounds from Nigerian medicinal plants

5. Conclusion

Medicinal plants are currently the only alternative for the development of effective and safer substances against snakebite, because it is cheap and available natural habitat.This is because of the limitations and effects associated with the use of serum antivenin (the only available medication) against snakebite especially victims in the rural areas who cannot afford the ASV. In this review, the ethnobotanical data of some Nigerian medicinal plants used by local herbalists alongside the scientific proof (methanol extracts) against *Naja nigricollis, Echis ocellatus* and *Bitis arietans*are compiled. Bioactive antivenin compounds such as aristolochic acid, quercetin, kaempferol, resveratrol etc. isolated from common Nigerian medicinal plants are also highlighted. The authors suggest that, more ethnomedicinal survey should be conducted to explore more plants with antisnake venom potential for the development of effective medications.

Conflict of Interest

The author declares that there is no conflict of interest.

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