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Review article

A mini-review on the pharmacognosy and phytochemistry of a tropical medicinal plant: *Annona senegalensis* Pers. (Annonaceae)

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Abstract: The aim of this mini-review was to collect data obtained from various studies carried out by different authors concerning the phytochemistry and pharmacognosy of *Annona senegalensis* (Annonaceae). This review has been compiled using references from major databases such as PubMed, PubMed Central, Science Direct and Google scholars. An extensive survey of literature revealed that *A. senegalensis* is a good source of health promoting secondary metabolites such as terpenoic acids (kaurenoic acid) among others that could have many wonderful applications (like antisickling properties).Traditionally, the plant is used as stimulant, pain reliever etc. whereas the plant possess beneficial effects such as anti-oxidant, antimicrobial, Antidiarrheal, anti-inflamatory, anti-parasitic, anticonvulsant, antimalarial, anti-trypanosomal, antisnake venom and Antinociceptive and many other medicinal properties. The results of the present review of literature makes *A. senegalensis* an interesting candidate for advanced anti-sickle cell anemia investigations such as erythroid differentiation and fetal hemoglobin induction effects of this plant using K562 cell lines as model system.

Keywords: Traditional Medicine - *Annona senegalensis* - Phytochemicals - Scientific validation - Biodiversity valorization.

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INTRODUCTION

As per the records of World Health Organization, it is assumed that more than 60% of global population is using the traditional medicine system to overcome several health related issues (Farnsworth 1994, Cotton 1997). This percentage goes up in the developing countries where, rural and tribal population is higher because of its low cost (Mehra *et al.* 2014, Bajpai *et al.* 2016). Recent findings revealed that over 80% of the African population relies on medicinal plant species for their primary healthcare (Ngbolua *et al*. 2011a, b).

In the case of Sickle cell disease (SCD) treatment based plants, Bianchi *et al.* (2009) reported that phytochemicals (like resveratrol) are able to ameliorate the state of SCD patients by shifting from monthly blood transfusion dependency to a stable transfusion-free condition. The correlation between *in vitro* effects of such fetal hemoglobin (HbF) inducers and *in vivo* treatment is well established. The complementary and alternative medicine constitutes therefore a solution for the management of this hemoglobinopathy. Thus, the

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search and the development of antisickling herbal drugs are a priority agenda in Africa, where SCD is endemic. In such region, herbal medicines are widely used to relieve the symptoms of SCD. In our efforts to search for novel and bioactive antisickling hits from indigenous plants, we recently investigated plant species indigenous to Democratic Republic of the Congo which are prescribed by traditional healers or sold in the markets for the management SCD (Ngbolua *et al.* 2014a, Ngbolua *et al.* 2016). *Annona senegalensis* Pers. is one of the plants traditionally used for this purpose. The aim of the present review is to document research results on the pharmacognosy and phytochemistry of this promising medicine. These findings are highlighted in this mini review. Such informations should pave the way for future directional research on this plant species as valuable source of new hits against Sikle cell anemia (epigenetic modulator agents) and associated pathogenic bacteria (antibacterial agents).

BOTANY AND DESCRIPTION

Annona senegalensis Pers. is a tropical plant species also known as 'wild custard apple' or 'wild soursop'. It is a shrub (2–6 m) or small tree (11 m) under some suitable ecological conditions. The bark is smooth to roughish, silver grey or grey-brown. The leaves of this medicinal plant are alternate, simple, oblong, ovate or elliptic, green to bluish green, mostly lacks hairs on upper surface, with brownish hairs on lower surface. Flowers are up to 3 cm in diameter on stalks 2 cm long, solitary or in groups of 2–4, arising above the leaf axils. The fruits are formed from many fused carpels, fleshy, lumpy, egg shaped, 2.5–5.0 by 2.5–4.0 cm, ovoid or globose, unripe fruit green, turning yellow to orange on ripening. Wild fruit trees of this species are found in semi-arid to sub-humid regions of Africa, it is native to tropical east and northeast, west and west- central, and southern Africa, as well as southern subtropical Africa, and islands in the western Indian Ocean. The species occur along river banks, fallow land, swamp, forests and at the coast. It commonly grows as a single plant in the understorey of savannah woodlands (Orwa *et al.* 2009).

ETHNOBOTANY

Annona senegalensis Pers. (Annonaceae) is a multipurpose plant with a high traditional and medicinal uses for the maintenance of free health life. Traditionally the plant is used as stimulant, pain reliever etc. Several uses of the plant species is reported for example anti-oxidant, antimicrobial, antidiarrheal, antiinflammatory, antiparasitic, anticonvulsant, antimalarial, antitrypanosonal, anti-snake venom and antinociceptive properties and many other biomedical properties of pharmaceutical relevance. These properties of the plant possess is due to its important phytochemical constituents like triterpenes, anthocyanes, glucids, coumarins, flavonoids and alkaloids etc. (Samuel *et al.* 2016).

As per the traditional medicine practices, all the plant parts of *A. senegalensis* are useful in several diseases. The leaves have been used in treating yellow fever, tuberculosis, and small pox (Ajaiyeoba *et al.* 2006, Mustapha *et al.* 2013). The stem bark has been used in snakebite and hernia treatment (Dambatta & Aliyu 2011). The root is used in conditions such as difficulty in swallowing, gastritis, snake bites, male sexual impotence, erectile dysfunction, tuberculosis, and as antidote for necrotizing toxins; the root bark is effective in infectious diseases (Ofukwu *et al.* 2008, Jiofack *et al.* 2009, Noumi & Safiatou 2015). Juice from the tree is used in the treatment of chicken pox (Faleyimu & Akinyemi 2010). Many of the plant parts are used as antidotes for venomous bites and in the management of diabetes (Ogoli *et al.* 2011, Ahombo *et al.* 2012). In Guinea, *A. senegalensis* has been employed in the treatment of malaria (Traore *et al.* 2013). Among the Igede people of Benue State in North Central Nigeria, the plant is used in combination with *Ageratum conyzoides* for diarrhoea and in combination with *Nauclea latifolia* for dysentery (Igoli *et al.* 2005).

PHARMACOGNOSY

Antidrepanocytary (antisickling) activity

Annona senegalensis Pers.from Democratic Republic of the Congo was reported to possess antidrepanocytary (anti-sickle cell anaemia) activity (Mpiana *et al.* 2007, Mpiana *et al.* 2012).

Antidiarrhoeal activity

The methanol stem-bark extract of *Annona senegalensis* was investigated using both *in vivo* and *in vitro* models by oral application of effective dose (5000 $mg.kg^{-1}$). In order to investigate intestinal transit time, the plant extract was given by oral route to mice fed with charcoal as meal. The extract decreased intestinal transit time by decreasing the spontaneous contractions of the intestine, thus the findings provided a scientific basis for

the use of Annona *senegalensis* stem bark extract in the treatment of diarrhoea. Therefore, *A. senegalensis* is a potent phytomedicine for diarrhoea (Suleiman *et al.* 2008).

Antimalarial and filarial mosquito vectors activity

The methanol extract of *Annona senegalensis* possess antimalarial activity against *Plasmodium berghei* and the extract showed better antimalarial activity than compared to the standard reference drug Chloroquine disphosphate which had a 96.2% chemosuppression activity (Ajaiyeoba *et al.* 2006). In DRC antimalarial and cytotoxic activities of tested plant extract moderate *in vitro* (*i.e.* 10< IC_{50} < 50 µg/mL: *A. senegalensis* IC_{50} = 32, 52±6, 97 µg.ml^{-1}) and weak *in vivo* (*i.e.* %I < 33, 00±2: %I=16, 93±2, 00). The ethanolic crude extract from the leaves of *A. senegalensis* displayed also cytotoxic effect towards P-388 cells (IC_{50} < 10 µg.ml^{-1}, therapeutic index= 0, 27). The observed cytotoxic effect of the leaves could be due to presence of aporphine alkaloid (Ngbolua *et al.* 2014b**).** These results are not consistent with previously reported research work. Indeed (Ajaiyeoba *et al.* 2006) reported that *A. senegalensis* harvested in Nigeria had intrinsic antimalarial property that was dose- dependent. They found that, at dose of 100 mg.kg^{-1} body weight of mice, methanolic extract produced significant chemosuppression of parasitemia (> 57%) when administered orally. It had the highest activity at 800 mg.kg^{-1} weight of mice (91.1%). Their extract exhibited low cytotoxicity against A2780 ovarian cancer cells (with an IC50 of 28, 8 µg.ml^{-1}).The antimalarial effectiveness of *A. senegalensis* from DRC has not formerly demonstrated *in vivo*, it could be a question of a plant which used by traditional healers to alleviate or prevent a wide range of malaria symptoms because of its anti-inflammatory, immunostimulant, antipyretic or vasorelaxant effects or a plant species which potentiates other plants and thus its effectiveness would depend on associations of the plants (Rasoanaivo *et al.* 2004, Ngbolua *et al.* 2014b).

Spermatogenic activity

Oladele *et al.* (2014) tested the aqueous leaf extract of *A. senegalensis* at different doses of 200, 300, and 500 mg.kg^{-1} body weight for its spermatogenic effect. Results showed the weight of the testes and epididymis increased significantly for the 300 and 500 mg.kg^{-1} doses. The sperm concentration for the 200, 300 and 500 mg.kg^{-1} doses also significantly increased and the sperm motility at 300 and 500 mg.kg^{-1} also increased significantly. Decrease in abnormal sperm morphology was not significant for any of the doses. However, another study revealed that aqueous leaf extract of *A. senegalensis* may possess the potential to adversely affect testicular function in rat (Nwonuma *et al.* 2015)**.**

Antimicrobial activity

In a study of methanol-methylene chloride extract of the root bark of *A. senegalensis*, the ethyl acetate fraction on further fractionation gave two active subfractions, a lipophilic oily and another fraction (AS2) which on purification precipitated white crystalline compound, later characterized to be kaurenoic acid. MICs of the ethyl acetate fraction, the lipophilic oily fraction and kaurenoic acid against *Bacillus subtilis* were 180, 60, and 30 µg.ml^{-1} respectively. AS2 exhibited activity against *Staphylococcus aureus* with an MIC of 150 µg.ml^{-1}, while the lipophilic oily fraction was active against *Pseudomonas aeruginosa* with an MIC of 40 µg.ml^{-1}. However, the extract and kaurenoic acid exhibited no effects against *Candida albicans* and *Aspergillus niger* (Jada *et al.* 2015).

Ethanol extract of the plant had *in vitro* antimicrobial activity against some oral pathogens (More *et al.* 2008). An extract of recipe containing six plants including *A. senegalensis* had significant antibacterial activity with (MIC) of 62.5 µg.ml^{-1} against *Staphylococcus aureus* and 250 µg.ml^{-1} against *Candida albicans* (Aiyeloja & Bello 2006).

Antioxidant activity

It is concluded that antioxidant activity and drug detoxification activity of *Annona senegalensis* leave in carbon tetrachloride-induced hepatocellular damage in rats using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical, superoxide ion, hydrogen peroxide (H_2O_2), 2, 2'-azinobis-(3-ethylbenzthiazoline-6-sulfonate) (ABTS) and ferric ion models decreased significantly. The responsible chemical constituent of antioxidant activity may be due to the presence of flavonoids in the extracts (Ajboye *et al.* 2010).

Anti-inflammatory activity

Anti-inflammatory activities of the leaves extract of *A. senegalensis* were determined in rats in inflammatory models. The extract induced a significant decrease in the number of inflammatory cells. This effect is probably due to higher concentrations of tannins and phenolic compounds in the extract of plant (Yeo *et al.* 2011).

Haemostatic activity

A. senegalensis is sold by herbalists in South Benin for treatment of bleeding. Dandjesso *et al.* (2012), in a bid to find scientific evidence for this use, performed *in vitro* haemostatic tests on hydro alcoholic extracts of the leaves. Results confirmed its anticoagulant properties, as indicated by a 39% reduction of plasma re-calcification time. *A. senegalensis* was also shown to have astringent property, so it could act on primary haemostasis through vasoconstriction.

Anticonvulsant activity

Anticonvulsant activities of the root bark extract on pilocarpine-induced seizures in animal model was evaluated. The results proved the efficacy of *A. senegalensis* in the treatment of epilepsy and convulsions (Konate *et al.* 2012). Kaurenoic acid (KA) was identified as the anticonvulsant principle in the root bark extract of *A. senegalensis*. The anticonvulsant effect of KA is most likely being mediated through central inhibitory mechanisms.

In vivo trypanocidal activity

The aqueous extract of *A. senegalensis* possesses trypanocidal activity against *Trypanosoma brucei* in infected mice (Ogbadoyi *et al.* 2007).

Anti-snake venom activity

(Adzu *et al.* 2005), tested the power of the methanol extract of the root bark of the *Annona senegalensis* was tested on brine shrimp (Artemia saline Leach) against cobra (*Naja nigricotlis nigricolis* Wetch) venom in rats. They further reported that the reduction in the induced hyperthermia directly detoxified the snake venom used by 16–33%. However, the extract doesn't restore the liver functions.

Antinociceptive activity

The methanolic extract of *Annona senegalensis* was reported to display antinociceptive property in a various test models. The analgesic effect of the methanolic this plant extract might be through peripheral mechanisms. This pharmacological property justifies the use of the plant species in traditional medicine to treat rheumatic pain (Adzu *et al.* 2003).

Anthelmintic activity

Alawa *et al.* (2003) investigated the efficacy of the extract of *Annona senegalensis* against Haemonchus contortus eggs and was shown a significant reduction in the egg hatch and larval recovery as the concentration increases.

Hypnotic activity

Effect of extract and fractions of *A. senegalensis* leaves on pentobarbitone-induced sleeping time was assessed. The extract and fractions significantly ($p<0.05$) shortened the sleep onset time (sleep latency) and prolonged sleeping time in a dose-related manner. A bioactive fraction significantly ($P<0.05$) prolonged sleep time but increased sleep latency in a dose-related manner (Okoli *et al.* 2010). Extracts of the root bark also potentiated the central nervous system depressant effect of phenobarbitone in a dose dependent fashion (Otimenyin & Omeri 2014).

PHYTOCHEMISTRY

Phytochemical screening of *Annona senegalensis* revealed the presence of various secondary metabolites including tannins (Jada *et al.* 2014), flavonoid (Jada *et al.* 2015), saponins (Afolabi & Afolabi 2013), alkaloids (You *et al.* 1995), glycosides, steroids (Ijaiya *et al.* 2014), volatile oil (Ngamo *et al.* 2007), anthocyanins (Mpiana *et al.* 2012), triterpenes and coumarins. GC/MS study of stem bark of *A. senegalensis* showed the presence of 1, 2 benzenediol, butylated hydroxytoluene (BHT), Phenol, 2, 6 bis (1, 1-dimethylethyl-4methyl, methylcarbamate, n hexadecanoic acid, hexadecane, 13- hexyloxacyclotridec-10-en-2one, oleic acid, tetracosane, 9- octylheptadecane, heneicosane, 12-mehtyl-E, E-2, 13- octadecadien-1-ol, octadecanoic acid, 9, 17-octadecandienal, pentadecane, tetratriacontane and squalene (Awa *et al.* 2012). Biochemist in Ahmadu Bello University, Zaria, Nigeria has been reported that a hydroxylated phenol which is 2-benzenediol or catechol is toxic to microorganisms (Awa *et al.* 2012).

The diterpenoid, kaur-16-en-19-oic acid or kaurenoic acid was reported as phytochemical constituent responsible for the antibacterial effects of root bark (Okoye *et al.* 2012). *A. senegalensis* has also been found to contain various minerals such as Ca, K, Mg, Zn, Fe, Cu, Mn, Pb, Cr as well as ascorbic acid and amino acids, making it an important source of nutrients (Yisa *et al.* 2010).

The GC and GC–MS analyses showed that p-cymene (36.0%), α-phellandrene (25.0%), α-pinene (8.3%), Z-sabinol (6.9%) and limonene (4.8%) are the major compounds *A. senegalensis* stem bark essential oil (Khallouki *et al.* 2002). In another study, the leaf essential oil of *A. senegalensis* had oxygenated monoterpenes (65.0%) as the major compounds and contains also citronellal (30.0%), citronellol (14.8%), geranial (17.2%), thymol (8.1%), β–caryophyllene (7.8%) and carvacrol (6.92%) (Ameen *et al.* 2011). The GC and GC/MS analyses of the essential oil of *A. senegalensis* from Burkina Faso displayed the presence of germacrene D (19.2%), β-caryophyllene (19.1%), γ- cadinene (11.1%) and α-humulene (9.7%) as major components (Nébiéa *et al.* 2002). In Brazzaville (Congo), essential oils were found in all parts of *A. senegalensis* including leaves, stem bark, root bark, epicarp and mesocarp (Nkounkou *et al.* 2010).

In Nigeria, nineteen monoterpenes and sesquiterpenes were identified in the essential oils of the leaves and fruits of *A. senegalensis*. The major constituents were car-3-ene in the fruit oil and linalool in the leaf volatile oil (Ekundayo & Oguntimein 1986).

Two new cyclopeptides, cyclosenegalin A, cyclo (Pro^1-Gly^2-Leu^3-Ser^4-Ala^5-Val^6-Thr^7-) (**1**) and cyclosenegalin B, cyclo (Pro^1-Gly^2-Tyr^3-Val^4-Tyr^5-Pro^6-Pro^7-Val^8-) (**2**), were isolated and structurally characterized from the methanol extract of the seeds of *Annona senegalensis* Pers., along with the known cyclic peptide, glabrin A. The structures of the isolated compounds were characterized on the basis of the MS/MS fragmentation, using a Q-TOF mass spectrometer equipped with an ESI source, chemical degradation and extensive 2D-NMR (Alassane *et al.* 2002). Bioactive-guided fractionation of the methanol-methylene chloride root bark extract (MME) of *A. senegalensis* using pentylenetetrazole (PTZ)-induced seizures in mice, afforded ethyl-acetate fraction (EF) with anticonvulsant activity. The chromatographic fractionation of the EF yielded eight sub-fractions (F_1–F_8) which were submitted to anticonvulsant screening assay. The white crystals from the sub-fraction F2 were purified to afford *A. senegalensis* crystals, AS2. The AS2, which exhibited potent anticonvulsant effects, was characterized by 1D and 2D NMR spectroscopy, mass spectroscopy and X-ray crystallography (Okoye *et al.* 2013). Chromatographic fractionation of the methanol-methylene chloride root bark extract of *A. senegalensis* afforded a potent antibacterial ethyl acetate soluble fraction (EF) which gave after additional column chromatography, two active sub-fractions F1 and F2. F1 yielded a lipophilic liquid component while F2 on purification, precipitated a white crystalline compound that was characterized by proton NMR and X-ray crystallography as kaur-16-en-19-oic acid. F1 was analyzed using GC-MS to obtain 6 major constituents: 1- dodecanol, kaur-16-en-18-oic acid, 1-Naphthalenemethanol, 6, 6-dimethyl-bicyclo [3.1.1] hept-2-ene-2-ethanol,3,3-dimethyl-2-(3-methylbuta-1,3-dienyl) cyclohexan-1-methanol and 3-hydroxyandrostan-17-carboxylic acid (Okoye *et al.* 2012).

CONCLUSION

The pharmacological relevance and diversity of compounds reviewed in this manuscript demonstrate that there is much to be discovered in this medicinal plant. As an anti-sickling plant candidate, there is therefore an urgent need to evaluate this plant species for it biological activity and modes of action of derived organic acids extracts which may shelter some epigenetic modulators drugs for the management of SCD in the future.

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