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Canarium schweinfurthii Engl. (Burseraceae): An Updated Review and Future Direction for Sickle Cell Disease

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ABSTRACT
The aim of the study was to collect data obtained from various studies carried out by different authors concerning the phytochemistry and pharmacology of *Canarium schweinfurthii*. This review has been compiled using references from major databases such as PubMed, PubMed Central, ScienceDirect and Google scholars Databases. An extensive survey of literature revealed that *C. schweinfurthii* is a good source of health promoting secondary metabolites such as phenolic and terpenoic acids among others that could have many wonderful applications (like antisickling properties). The plant has been reported to possess several pharmacological activities such as analgesic, antimicrobial and antioxidant, anti-diabetic and anti-inflammatory activities. The plant is also belongs to the great apes (GA) feeding. Humans and great apes (bonobos, chimpanzees, gorillas, etc.) share a common gut anatomy. Although, some diseases that cause countless deaths in humans (like malaria) are ineffective or have minor non disturbing effects in GA. They represent therefore a good model for human pathology and physiology. This GA plant based food could protect human sickle erythrocyte against hemolysis by inhibiting the polymerization of sickle hemoglobin and radical oxygen species formation within sickle erythrocyte as it does for *Plasmodium falciparum* infected erythrocytes in bonobos. The results of the present review of literature makes *C. schweinfurthii* an interesting candidate for advanced antisickling pharmacological investigations such as antisickling, anti-hemolytic and membrane stabilizing effects of this plant.

Keyword: *Sickle cell Disease, ethno-pharmacology, zoopharmacognosy, chemotaxonomy, Canarium schweinfurthii*

INTRODUCTION:
The World Health Organization (WHO) recognizes that traditional and complementary medicines (TCM) are a vital part of the global health care system [1]. In Africa, it is estimated that over 80% of the population continues to rely on medicinal plant species to meet their basic health care needs [2, 3]. Although, the weakness of TCM is the reluctance of traditional healers to share their secrets in order to allow scientists to streamline and integrate them into the modern health system. In this regard, the pharmacopoeia of great apes or zoopharmacognosy is a very promising strategy because of the phylogenetic closeness between humans and non-human primates (NHP) such as Bonobos (*Panpaniscus*) [4-6]. These NHP are endemic to rainforest (central basin) of Democratic Republic of the Congo. They have a social behavior close to the one of man and constitute a good model for the understanding of human disease. As for humans, bonobos would have coevolved with malaria parasite in Tropical regions. These animals adopt a particular feeding when they are having some symptoms by selecting specific plants for controlling malaria parasite infection while this one cause hemolytic anemia of human red blood cells (like does the polymerization of hemoglobin S in sickle erythrocytes) [5, 7]. Thus, plant species (like *Canarium schweinfurthii)* which belongs to the bonobo feeding [8] are potentially non-toxic to man and could provide new sources of anti-sickle cell hemolytic compounds.

Canarium schweinfurthii is a large forest tree of ethno-pharmacological relevance in African Traditional Medicine. The plant is traditionally used to treat various ailments [9]. Since *C. schweinfurthii* is reported to contain phenolic and terpenoic acids [10-12], it can therefore, be hypothesized by chemotaxonomy that this plant could possess hemolytic inhibitory effects on sickle red blood, thus justifying the present extensive literature survey on it phytochemistry and pharmacology with the aim of integrating this plant species in a future program of plants screening research for their antisickling activity. Indeed, in Democratic Republic of the Congo, almost 2% of the population suffers from Sickle cell disease [5]. The animal self medication based selection in combination with the chemo-taxonomical approach, the identification of the active principles and their pharmaceutical validation through *in vitro* biological and toxicological experiments could enhance the standardization of affordable recipes for the management of SCD. This review of literature makes *C. schweinfurthii* a good candidate for an advanced study.

BOTANICAL DESCRIPTION AND ORIGIN
The genus *Canarium* L. belongs to the family of Burseraceae Kunth. in the order Sapindales Juss. ex Bercht. & J. Pearl. This family consists of 18 genera and about 700 species of tropical trees. This genus is probably originated from the North American continent but not Gondwanaland. The members of the genus

Canarium L. consist of medium to large buttressed trees up to 40-50m tall, or rarely a shrub [13].

According Orwa et *al*. [14], *Canarium schweinfurthii* is a large forest tree with its crown reaching to the upper canopy of the forest, with a long clean, straight and cylindrical bole exceeding 50 m. Diameter above the heavy root swellings can be up to 4.5 m. Bark thick, on young tree fairly smooth, becoming increasingly scaly and fissured with age. The slash is reddish or light brown with turpentine like odor, exuding a heavy, sticky oleoresin that colors to sulphur yellow and becomes solid. Leaves are pinnate, clustered at the end of the branches, and may be 15-65 cm long, with 8-12 pairs of leaflets, mostly opposite, oblong, cordate at base, 5-20 cm long and 3-6 cm broad, with 12-24 main lateral nerves on each side of the mid-rib, prominent and pubescent beneath. The lower leaflets are bigger than the upper ones. The lower part of the petiole is winged on the upper side. The creamy white unisexual flowers about 1 cm long grow in inflorescences that stand in the axils of the leaves and may be up to 28 cm long. The fruit is a small drupe, bluish-purple, glabrous, 3-4 cm long and 1-2 cm thick. The calyx is persistent and remains attached to the fruit. The fruit (figure 1) contains a hard spindle-shaped, trigonous stone that eventually splits releasing 3 seeds. The seeds are mainly dispersed by hornbills and elephants. Flowers are unisexual.

Figure 1 : Fruits of Canarium schweinfurthii

ETHNOBOTANY

Canarium schweinfurthii Engl. is traditionally used in African Traditional Medicine as Insecticide or against dysentery, gonorrhea, coughs, chest pains, pulmonary affections/*Mycobacterium tuberculosis*, stomach complaints, food poisoning, purgative and emetic, roundworm infections and other intestinal parasites, emollient, stimulant, diuretic, skin-affections, eczema, leprosy, ulcers; diabetes mellitus; colic, stomach pains, pains after child birth, gale; fever, constipation, malaria, sexually transmitted infection and rheumatism [15, 16].

PHARMACOGNOSY

ANTI-DIABETIC ACTIVITY

Stem bark extracts of *Canarium schweinfurthii* Engl. are used in Africa for the treatment of various ailments, including diabetes mellitus. The anti-diabetic effects of the methanol/methylene chloride extracts of the stem barks on streptozotocin (STZ)-induced diabetes revealed that at 300 mg/kg, *Canarium schweinfurthii*), significantly showed at least 69.9% reduction in blood glucose level. The authors reported also that this plant species can reverse hyperglycemia; polyphagia and polydipsia provoked by streptozotocin, and thus, has anti-diabetic properties [17].

ANALGESIC ACTIVITY

The essential oil obtained by hydro-distillation of the resin of *Canarium schweinfurthii* from Central African Republic revealed that at the doses of 1, 2 and 3 ml/kg i.p. essential oil shows a significant analgesic effect using acetic acid-induced writhing and hot plate methods. However, it was unable to reduce inflammatory process in cotton pellet induced granuloma method [18].

ANTI-INFLAMMATORY ACTIVITY

Essential oils of the resins of *Canarium schweinfurthii* from Cameroon revealed anti-lipoxygenase activity with an IC_{50} of 62.6 µg/ml [19].

ANTIOXIDANT ACTIVITY

The antioxidant activity of the essential oil extracted (from *C. schweinfurthii* resin) assessed using 2,2-diphenylpicrylhydrazyl radical scavenging assay and the carotene bleaching test revealed interesting antioxidant and radical scavenging activities and the inhibition of lipid peroxidation [20].

The methanol extract from the fruit mesocarp oil of *C. schweinfurthii* has very strong antioxidant and radical scavenging activities on hypoxanthine/xanthine and 2-deoxyguanosine assay models as a result of its richness in polyphenols and might play a key role in the chemoprevention of cancers and other oxidative damage-induced diseases [10].

ANTIBACTERIAL ACTIVITY

The essential oil of *Canarium schweinfurthii* from Centrafrican Republic were evaluated for it antibacterial and antifungal activities against bacteria and fungi (*Bacillus cereus* LMG 13569, *Enterococcus faecalis* CIP 103907, *Escherichia coli* CIP NCTC 11609, *Listeria innocua* LMG 1135668, *Salmonella enteric* CIP105150, *Shigella dysenteria* CIP 5451, *Staphylococcus aureus* ATCC9244, *Proteus mirabilis* 104588 CIP, *S. aureus* ATCC25293 BHI, *Staphylococcus camorum* LMG13567 BHI, *E. faecalis, Pseudomonas aeruginosa,Candida albicans* ATCC10231 and *C. albicans* ATCC90028) using agar diffusion and broth microdilution methods. The essential oil displayed antimicrobial activity against almost the strains studied suggesting that *C. schweinfurthii* essential oil could be a natural antimicrobial [20].

The leaves were reported for their antimycobacterial activities [21]; Moshi et *al*. [22] reported also the antimicrobial activities of dichloromethane, ethyl acetate and ethanol leave extracts against gastrointestinal pathogenic bacteria.

PHYTOCHEMISTRY

USED TECHNIQUES

The isolation and separation technique used dependent on the type of fractions. Essential oils are analyzed with gas chromatography (GC) and mass spectroscopy (MS). Other substances are separated with liquid chromatography using different solvent mixtures with silica gel, charcoal, sephadex, etc. Other analytical techniques include thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). X-rays crystallography is also a powerful technique used in phytochemistry to elucidate the structure of secondary metabolites without ambiguity. Although, the structures secondary metabolites are mainly established by a combination of chromatographic and spectroscopic techniques such as ultra-violet spectroscopy (UV), mass spectroscopy (MS), infrared spectroscopy (IR) and ^{1}H and/or ^{13}C nuclear magnetic resonance (NMR). ^{1}H and/or ^{13}C spectroscopy is probably the most useful method in structure elucidation [13].

REPORTED RESULTS

Ngbede et *al*. [23] reported that, chemical screening of the leaves of *Canarium schweinfurthii* revealed the presence of secondary metabolites such as Saponins, Tannins, Cardiac glycosides, steroids and flavonoids. Although, Alkaloid and anthraquinone were not detected from the leave extract. The GC and GC/MS analyses of essential oil obtained by hydrodistillation of the resins of *Canarium schweinfurthii* growing in Central African Republic revealed the presence of octylacetate (60%) and nerolidol (14%) as major constituents. While essential oils of the resins of *Canarium schweinfurthii* harvested in Cameroon were reported to be composed mainly of monoterpenes. The major compounds were p-cymene, limonene and α-terpineol [19].

The oils of *Canarium schweinfurthii* Engl. extracted from the mesocarp and endocarp using hexane to remove the free flowing lipid (FFL) and successive extraction with $CHCl_3$-MeOH followed by water saturated butanol to remove bound lipid (BL) revealed that the mesocarp contained 68.3% FFL and 13.7% BL while the endocarp contained 67.0% FFL and 13.0% BL. The quality characteristics of the mesocarp oil extracts were 151.9–195.3 mg KOH/g fat saponification value (SV), 20–40 mEq peroxide/kg fat peroxide value (PV), 71.1–94.9 g iodine/100 g fat iodine value (IV) and 1.33–8.30 mg KOH acid value (AV). Characteristics for the endocarp oil extracts were 95.4–184.3 mg KOH/g fat SV, 4.0–8.0 mEq peroxide/kg fat PV, 100.1–118.3 g iodine/100 g fat IV, and AV of 0.48–8.70 mg KOH. The fatty acid composition of the first hexane extracts indicated that the oils were primarily C16 and C18s. The mesocarp contained 31.7% hexadecanoic acid, 30.0% 9-octadecenoic acid, 30.1% 6,9-octadecadienoic acid and 8.2% 9,12,15-octadecatrienoic acid, while the endocarp, contained 31.2% hexadecanoic acid, 28.9% 9-octadecenoic acid and 31.3% 6,9-octadecadienoic acid [24].

The *Canarium schweinfurthii* fruit pulp from Côte d'Ivoire was found to contain 5.6% protein, 30–50% fat, 8.2% starch, 11.8% cellulose and 8.3% ash (the highest mineral elements being potassium, 1.2% and calcium, 0.4%). The melting and solidification points of the extracted fat (44.5°C and 35.2°C, respectively) are higher than those of all the commercial and other *Canarium*-species oils. This oil shows low iodine, peroxide and carotene values (36, 17 meq-g and 2 mg, respectively). The fatty acid composition of the oil revealed a high content of oleic (89.4%) or stearic (67.7–84.0%) acids in the liquid, semi-solid and solid forms of the oil. Consequently, the content of these two acids is much higher in *Canarium schweinfurthii* oil than in any other vegetable oil [25].

Kamdem et *al*. [26] isolated a triterpene with an unprecedented carbon backbone from *C. schweinfurthii*. It is the first member of a new class of triterpenoids, for which the name "canarane" was proposed. Its structure was unambiguously deduced by single-crystal X-ray diffraction technique.

The analyses of the fruit mesocarp oil of *C. schweinfurthii* by HPLC-UV, HPLC-MS and GC-MS techniques revealed the presence of phenolic compounds such as catechol, p-hydroxybenzaldehyde, dihydroxyphenylacetic acid, tyrosol, p-hydroxybenzoic acid, dihydroxybenzoic acid, vanillic acid, phloretic acid, pinoresinol, secoisolariciresinol (figure 2) [10].

Kouambou et *al*. [27] reported that the bark of *C. schweinfurthii* contains triterpenes, steroids, saponins, lipids and glycosides. The seeds contain various secondary metabolites like schweinfurthinol, p-hydroxybenzaldehyde, coniferaldehyde, p-hydroxycinnamaldehyde, ligballinol, amantoflavone [28].

Yousuf et *al*. [11, 12] isolated three triterpenoic acids namely 3a-Hydroxytirucalla-8,24-dien-21-oic acid, 3α-hydroxytirucalla-7,24-dien-21-oic acid (or epielemadienolic acid, I) and 3β-fluorotirucalla- 7,24-dien-21-oic acid (II) from the resin of *Canarium schweinfurthii* Engl. (figure 3).

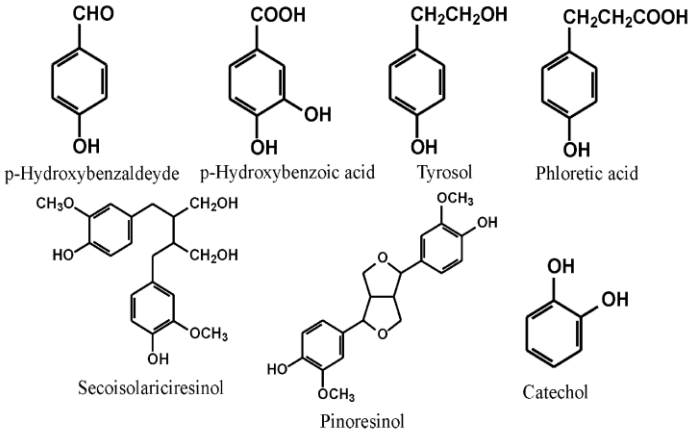

Figure 2 : Chemical structure of some phenolic compounds

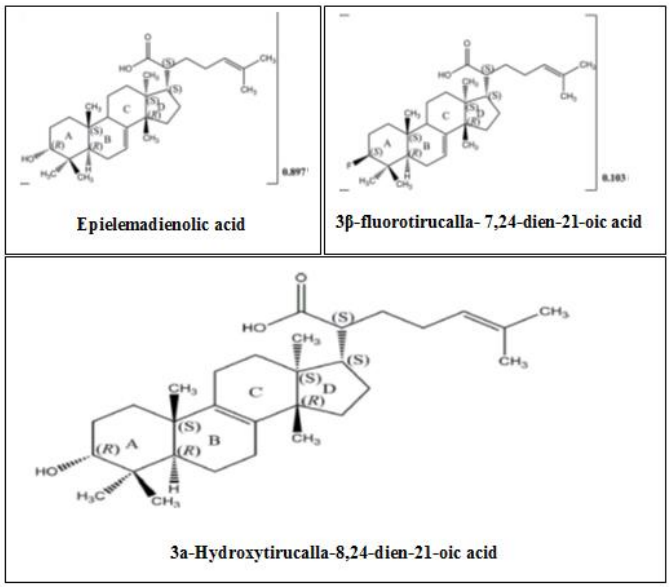

Figure 3: Chemical structure of some triterpenoic acids from *Canarium schweinfurthii*

Compared to many other medicinal plant species of pharmacological relevance like *Noronhia divaricata*) [29], *Ocimum gratissimum* [30], *Callistemon viminalis*, *Meulaleuca bracteata* var. Revolution Gold *Syzygium guineense* and *Syzygium cordatum* [31], *Canarium schweinfurthii* also contain antisickling phytomarkers such as phenolic and triterpenoic acids and merit more attention for a bio-prospecting program. Thus, this plant could serve according to chemo-taxonomical approach as promising source of antisickling new lead compounds.

CONCLUSION

The diversity of secondary metabolites and pharmacological properties reviewed in this manuscript demonstrate that there is much to be discovered in this medicinal plant. As an antisickling plant candidate, there is therefore a compelling need to evaluate this plant species for it biological activity and modes of action of derived organic acids extracts which may shelter some antisickling drugs for the future.

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