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Ethnopharmacological and pharmaco-toxicological data of *Sarcocephalus latifolius* and *Crateva adansonii* DC, two plants used in traditional malaria treatment in Benin

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Abstract

Antimalarial drug resistance is worsening the management of malaria in Africa, increasing the use of new alternatives, including medicinal plants. *Sarcocephalus latifolius* and *Crateva adansonii DC* are of paramount importance in dealing with various diseases, especially malaria. Therefore, this study aims at analyzing some ethnopharmacological and pharmaco-toxicological data of these species as a starting point and orientation for the value addition to the treatment of malaria. A bibliographic search was conducted in scientific databases and the Boolean operators AND and OR were used. From the Sixty studies, it appears that *Crateva adansonii DC* is known for the traditional treatment of malaria, boils, infections and gastrointestinal problems. Bioactive molecules such as flavonoids, alkaloids, triterpenes, fatty acids and steroids have been found in its organs. Pharmacologically, extracts of *Crateva adansonii DC* have been shown to be active on bacterial strains (*Shigella sonei, Staphylococcus aureus, Pasteurella pestis, V. Cholerea* and *P. vulgaris*) and fungal (*Candida albicans, Aspergillus parasiticus*). *Sarcocephalus latifolius*is traditionally is also used in the treatment of malaria, diabetes, ascites, hernias, fevers and convulsions. Tannins, flavonoids and cyanogenic glycosides, saponins and alkaloids have been found in its organs. Anti-inflammatory, analgesic and antipyretic, antihypertensive, antibacterial (*S. aureus, P. aeruginosa, S. aureus, Bacillus subtilis, P. aeruginosa*) and antifungal (*Aspergillus niger*) activities have been demonstrated. Both species inhibit DPPH free radicals and show no toxicity. *Crateva adansonii DC* and *Sarcocephalus latifolius* may be good candidates for the discovery of new bioactive molecules. Their valorization in the management of malaria, through antiplasmodial activity tests is essential.

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Introduction

Malaria is one of the most common infectious diseases in the world (Filisetti & Monassier, 2012). In 2010, 106 countries were listed in areas at risk of malaria and nearly half of the world's population is exposed to this scourge, 216 million cases being recorded with 2-3 million of serious cases and 500 000 to 900 000 deaths(OMS, 2018). It is a major public health problem in endemic countries, particularly sub-Saharan African countries with tropical and sub-tropical climates (Lusakibanza Manzo, 2012). Malaria is a major contributor to underdevelopment in Africa, particularly in endemic areas. According to one estimate it would cost Africa more than 12 billion US dollars each year(Dorsey *et al.*, 2000; Bloland,2001).The overwhelming majority of deaths (90%) from malaria occur in Africa, south Sahara (Banerjee, 2003). In Benin, according to the National Malaria Control Program(PNLS), Malaria accounted for 39.7% of the reasons for seeking medical care in 2006 and the leading reason for hospitalization (18%) in health facilities (PNLS, 2007).

Currently the fight against malaria integrates different preventive (use of insecticides, mosquito nets) and curative (uses of antimalarial) strategies. However, the limited number of antimalarial drugs and especially the emergence of resistance of *Plasmodium falciparum* strains to most commonly used antimalarial tablets are major handicaps in the fight against malaria.(Nassirou *et al.*, 2015).

Alternatives to conventional antimalarial drugs available are limited. African pharmacopeia plants can be regarded as one of the alternatives and which have been intensively used traditional medicine for the treatment of malaria. For example, quinine and artemisinin come from medicinal plants: *Cinchona spp.* and *Artemisia annua,* from the traditional Peruvian and Chinese pharmacopoeia, which have been used for centuries to treat malaria (Wright, 2005).These examples highlight the potential and the opportunity of using medicinal plants in the management of malaria.

In Benin, several plants are commonly used for the traditional treatment of malaria. For instance, *Sarcocephalus latifolius* and *Crateva adansonii DC* are used intensively in the traditional treatment of malaria, sometimes alone or in combination with other herbs. (Adomou *et al.*, 2012; Kouchadé *et al.*, 2016). In a socio-economic context where access to conventional antimalarial is not affordable, the utilization of these two medicinal plants in the treatment of malaria is necessary. Henceforth, the analysis of scientific literature data on their traditional use, chemical composition, biological activities and toxicity are fundamental before considering their valorisation.

This is what motivates this research work in analyzing the ethnopharmacological and pharmaco-toxicological parameters of Sarcocephalus latifolius and *Crateva adansonii* DC. This database will serve as a starting point and orientation for the value addition to the treatment of malaria.

Material and methods

The methodology used is a bibliographic search based on the use of specific keywords, followed by a systemic analysis of the bibliographic data.

Key words and bibliographic search equations

The keywords were chosen to target the most relevant sources. These are "*Sarcocephalus latifolius*", "*Crateva adansonii* DC " and variants. With regard to *Crateva adansonii* DC, the key word" *Crateva religiosa* Forst " was also used, since it is a synonym of the species. The search was then refined by the use of Boolean operators AND and OR.

Scientific databases

The different keywords and equations generated with Boolean operators were introduced in PubMed and Google Scholar.

Inclusion criteria

Types of documents

Theses, dissertations, articles and scientific reference documents were considered.

Information sought

Botanical characteristics, geographical distribution, systematics, ethnopharmacological uses, pharmacological data (all sorts of biological activities), phytochemical data (quantitative and qualitative), and toxicological data were sought.

Fig. 1. Distribution of Crateva adansonii DC in Africa (Nielsen, 2001).

Region

Mostly African countries.

Analysis and synthesis of data

Complementarity between documentary sources were used to produce a more or less complete synthesis according to the targeted information.

Results

Crateva adansonii DC

Taxonomy and nomenclature

Crateva adansonii DC belongs to the family Capparaceae and the genus Crateva. The genus Crateva comprises about 9 species, most of them in tropical Asia, about 3 in Madagascar, 1 in Africa and 1 in tropical America(Nielsen, 2001). *C. adansonii* DC is called " varum " and " garlic pear " in English, " migingirgingir " in Giziga and " scramataihi " in Foufoulde(Zingue *et al.*, 2016), " Crateva sacré " in French, " wontonzounzin " in fon and goun, " Tanya ", " Egun-Erun " in Yoruba and Nago, " gorigiberu " in Bariba.

Distribution

Crateva adansonii DC is found in Mauritania, Senegal, Gambia, Eritrea, Ethiopia, and south Tanzania and Zambia (Figure 1).

Botanical description

Crateva adansonii DC is a small deciduous tree up to 10 -15 m tall; the bole is usually irregular and short, up to 50 cm in diameter; the surface of the bark is smooth and gray to brown while the inner bark is thin, yellow-brown with brown streaks.

The crown is rounded, more or less open, and the branches are glabrous, brown with gray lenticels. The wood is pale yellow, light and relatively soft. The specific density (at 0% humidity) of the wood is about 0.39.

Leaves and inflorescence

They are alternate but grouped at the end of twigs, composed of 3 leaflets; the stipules are minute, quickly deciduous; the petiole is 2.5 to 8.5 cm long with petiolules up to 8 mm long.

The leaflets are elliptical to ovate or lanceolate. The inflorescence is a short terminal raceme up to 2.5-7.5 cm long, glabrous, bearing up to 15 flowers.

Flowers

They are bisexual, almost regular, 4-mothers; the pedicel is 1.5-4 cm long; sepals are free, deltoid to lanceolate, 3-9 mm long, equal; the petals are free, ovate, slightly unequal, 1.5-3 cm long, yellowish-white, sometimes with red-purple apex; the stamens 15-20, are also free, 2-3.5 (-5) cm long, with violet anthers; ovary superior, long-termed, ellipsoid, glabrous, 1-celled, sessile stigma, capitate.

Fruit a globose berry, distinctly pedunculate, 4-5 (-8) cm, smooth, yellow to brown, with whitish floury pulp, up to 15 (-20) seeds. Seeds are kidney-shaped, 0.5-1 cm long, brown to black. (Figure 2).

Traditional therapeutic uses

Crateva adansonii DC is subject to intense traditional therapeutic uses (Table 1).

Table 1. Some medicinal use of *Crateva adansonii*.

Diseases	Organs used	Processing and usage	References
Malaria	leaves	Put in suppository the crushed of some young leaves and a pepper or a shea nut; Drink a decoction of the leaves.	(DA, 2009)
Earache	leaves	To put the liquid of the mash of some young leaves in the sick ear.	(DA, 2009)
Abscess and various wounds	leaves	Squeeze and crush the leaves and put the juice in the wound	(DIALLO, 2013)
Belly ache, diarrhea	leaves	Purge with fresh leaves, drink a decoction of the leaves.	(DA, 2009)
Eye damage	leaves	Put a few drops of decoction of the leaves in the eyes.	(DA, 2009)
Cough	leaves	Drink a decoction of the leaves	(DA, 2009)
Blood pressure	leaves	Regularly drink a decoction of the leaves.	(DA, 2009)
Whitlow	roots	Apply on powdery mildew the powder of dried roots and slightly moistened.	(DA, 2009)
Diarrhea, stomach ache	roots	Drink the powder of dried roots.	(DA, 2009)
Constipation and intimate washing of postmenopausal women	Leaves and twigs of stems	Infusion	(Borokini & Omotayo, 2012)
Kidney, bladder and urinary disorders	Bark	Bark powder	(Gupta *et al.*, 2006)

Chemical composition

From the aerial parts, kaempferol-3-glucoside and phenolic acids were isolated. The leaves contain flavonoids, tannins, saponins, cardiac glycosides, terpenes and alkaloids (Abdullahi *et al.*, 2012; Akanji, 2013; Borokini & Omotayo, 2012). The trunk bark contains; phenols, saponins, flavonoids, tannins, terpenoids, alkaloids and cardiac glycosides (Patil, 2011). The main constituents of the essential oil of *Crateva adansonii* DC are linalool (30%) and nonanal (17%) from Nigeria.

One of the isolated compounds is lupeol, known for its anti-inflammatory activity and its reducing action on renal tubular lesions in the rat with induced hyperoxaluria (Nielsen *et al.*, 2001).

Table 2. Some medicinal use of *Sarcocephalus latifolius*.

Diseases	Organs used	Processing and usage	References
Teethache	Roots	Chewed	(Malgras, 1992)
Gastrointestinal disorders, constipation, indigestion	Roots	Macerated and mixed with honey	Malgras, 1992)
diarrhea	Root bark	Decoction	(Tona *et al.*, 2004)
Malaria	Roots		(Adjanohoun *et al.*, 1989; Haidara *et al.*, 2016; Traore *et al.*, 2013)
Ascites	roots	sauce with powdered calcined roots in association with those of other plants	(Adjanohoun *et al.*, 1989)
Hernias	roots	Root bark powder is used to treat hernias	(Adjanohoun *et al.*, 1989)
Fevers, seizures, headaches, inflammatory pain and neuropathic pain	roots	the root decoction is used	(Taïwe *et al.*, 2011)
Hypertension	roots		(Jazy, Karim, Morou, Sanogo, & Mahamane, 2017)
Burns with urination, jaundice	Root	The root of this plant is used in the recipes used for the treatment of burns with urination and jaundice	(Nworgu *et al.*, 2008)
Menstrual disorders	roots	Decoction	(Koko *et al.*, 2011)
Diabetes	leaves		(Gidado, Ameh, Atawodi, & Ibrahim, 2008)

The phytocompounds with anti-inflammatory activity identified in the leaf extracts of methanol and chloroform are respectively gentioside and epinephrine (Rathinavel *et al.*,2017).

Toxicity

Organic and aqueous extracts of *Crateva adansonii* DC were non-cytotoxic to Crustacea *Artemia salina* larvae (Nounagnon *et al.*, 2018). Leaf extract causes

slight, selective and reversible changes in hematological profile and biochemical parameters in rats (Akanji *et al*., 2013).

Pharmacological and toxicological data

Antibacterial and antifungal activities

Some experiences carried out in Benin, leaf extract showed in vivo antibacterial activity in grass cutter (*Thryonomyss winderianus*). The extract was active against *Escherichia coli, Shigella sonei, Staphylococcus aureus, Pasteurella pestis* and *Yersinia enterocolitica*. The ethyl acetate extract was the most potent(Lagnika *et al*., 2011). The antibacterial and antifungal properties of crude extracts of Crateva adansonii DC have been demonstrated in Nigeria in 2011(Agboke *et al*., 2011). The ethanolic extracts obtained by maceration of the leaves in ethanol showed their activity on six bacterial strains (*Pseudomonas aeruginosa, Escherichia coli, Salmonella* Typhii, *Staphylococcus aureus, Klebsiella pneumoniae, Bacillus subtilis*) and two fungal strains (*Aspergillus niger* and *Candida albicans*).

In Benin, the aqueous extract of *Crateva adansonii DC* was active on *S. aureus, V. Cholerea* and *P. vulgaris* (Lagnika *et al*., 2011). Another study carried out in Benin in 2016, showed an interesting antifungal power of *Crateva adansonii DC* on Aspergillus strains *A. Clavatus, A. fumugatus, A. parasiticus, A. Ochraceus* (Patil *et al*., 2011).

Fig. 1. Leaves and flowers of Crateva adansonii DC (Akoègninou, Burg, & Maesen, 2006).

Anti-inflammatory activities

Extracts from the leaves of Crateva adansonii DC showed anti-inflammatory activity on *S. aureus* infected keratinocytes by reducing the expression and production of IL6, IL8 and TNFα(Ahama-Esseh *et al*., 2017).

Anti-urolithiasis activity

an anti-urolithiasis activity of the bark petroleum ether extract was observed in the rat(Gupta *et al*., 2006).

Antitumor properties

In vitro, the CC50 values for in vitro tests were 289 mg / ml against MCF-7 cells and 4500 mg / ml in other cells. In vivo, C. adansonii DC extract significantly reduced cumulative tumor yield (87.23%), total tumor burden (88.64%), mean tumor weight (71.11%)) and tumor volume (78.07%) at a dose of 75 mg / kg(Zingue *et al*., 2016).

Antitroformic activities

Crude extracts of hexane and ethyl acetate or phytoconstituants isolated from leaves exhibited moderate in vitro antitrypanosomal activity(Igoli *et al*., 2014; Peace Igoli *et al*., 2012).

Anti-analgesic activities

The extract at doses of 100, 200 and 400 mg / kg demonstrated significant anti-analgesic activity ($p < 0.05$) (Udeh & Onoja, 2015).

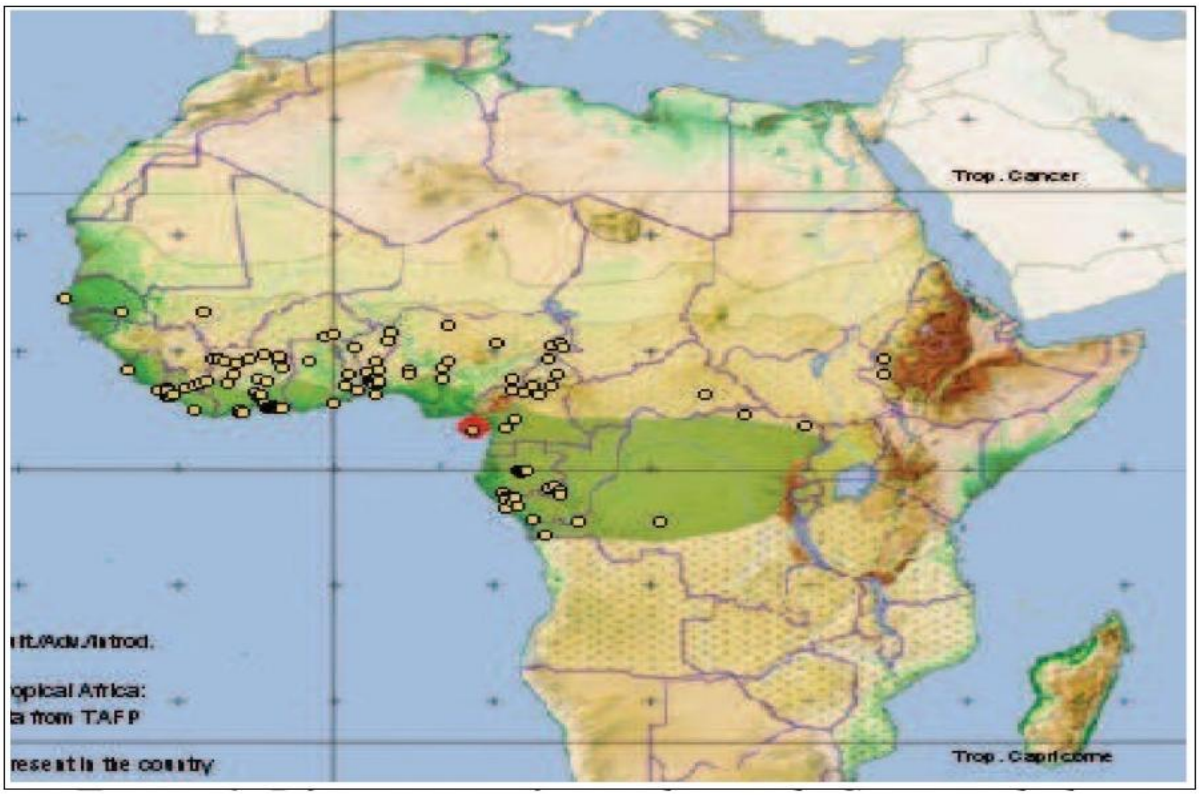

Fig. 3. Distribution of Sarcocephalus latifolius in Africa (Nielsen, 2001).

Antioxydant activity

Extracts of *Crateva adansonii* DC have a strong antioxidant activity(Patil *et al.*, 2011; Agboke *et al.*, 2011; Igoli *et al.*, 2014).

Antiplasmodial activities

Crateva adansonii extracts caused a significant decrease in parasitaemia in Plasmodium berghei-infected mice (Tsado *et al.*, 2015).

Sarcocephalus latifolius

Taxonomy and nomenclature

Of the family Rubiaceae, *Sarcocephalus latifolius* is a plant species native to sub-Saharan Africa. It belongs to the genus Sarcocephalus which comprises to date according to The Plant List two species originating from tropical Africa: *Sarcocephalus latifolius* (Sm) Bruce and *Sarcocephalus Pobeguinii* Hua ex Pobeg. The genus Sarcocephalus is closely related to the genus Nuclea; these two genera can be differentiated by the placentation and the form of their stipules. *Sarcocephalus latifolius* is known in French under the name of Pêcher africain, in fon and goun under the name of Codô, in Peulh under the names of Bauré, Bakuré, Bakuri, and Dundunké(Plassart, 2015).

Origin and distribution

The species *Sarcocephalus latifolius* is found exclusively in tropical Africa, particularly in sub-Saharan West Africa, extending from Senegal to Zaire. It is also often found in eastern Sudan (Sudano-Guinean zone). More specifically, Sarcocephalus latifolius occurs in Senegal, Côte d'Ivoire, Benin, Cameroon, Angola, Congo, Zaire, Central African Republic, Guinea, Gabon, Ghana, Liberia, Mozambique, Togo, Mali, Nigeria, Sierra Leone and Uganda.(Arbonnier, 2009). The map below shows the distribution of the species in Africa, the yellow dots representing the precise locations where it occurs (Figure 3).

Botanical description

(Badiaga,2011; Walker et Sillans, 2003) *Sarcocephalus latifolius* is an evergreen shrub, 5 to 6 m tall, sometimes up to 9 m, bushy, stunted with tortuous bole 30 cm in diameter. The branches are flexible, lianascent, intermingled, erect and drooping. The bark is fibrous, the wood is white or yellow rather

soft. The flowers, small, whitish, are grouped in inflorescence cyme type forming a spherical head. The fruit, fleshy, edible, is in fact an infructescence forming a syncarp (Figure 4).

Leaves

Leaves are simple, opposite, ovate, sometimes overbodicular, glabrous, 10 to 17 cm long and 6 to 14 cm wide.

They contain deltoid stipules 3-5 mm long, plain or biapiculated, glabrous and more or less adorned with a thin hull. The petiole is purple in color and 8-20mm long. The foliage is green and shiny on the top.

Fig. 4. *Sarcocephalus latifolius(A : shrub ; B : leaves and fruits).*

Flowers

The flowers are arranged in inflorescences at the top of the branches with a short peduncle of 1.5- 2.5 cm, all forming a spherical floral bouquet of about 4-5cm in diameter. The flowers are white or yellowish-white, exhaling a pleasant odour of orange blossoms and bloom especially from January to May. The ovary has two more or less distinct compartments, the ovules are numerous with long funicules when they are inserted towards the top or the bottom of the placenta.

Fruit

The fruit is actually a spherical infructescence of 5 to 8 cm in diameter. Fleshy and red, it has the consistency and appearance of a large red-black strawberry, stained brown at maturity, leathery epidermis, rough and hollow shallow cells, pink flesh inside.

Traditional therapeutic uses

The reported medicinal uses are numerous. Some are listed in Table II below.

Chemical composition

Tannins are present in trace amounts; concentrations of flavonoids and cyanogenic glycosides are not negligible. On the other hand, saponins and alkaloids are particularly abundant in the bark of roots and trunk(AtangwhoI.JE gbungG & OdeyIwaraI, 2013).

Pharmacological and toxicological data

Anti-inflammatory, analgesic and antipyretic action

Sarcocephalus latifolius is in great demand in the treatment of malaria, fever and abdominal pain in several countries. Several studies have focused on the demonstration of the anti-inflammatory, analgesic and antipyretic properties of this plant.

The overall results obtained provided a scientific justification for the use of *Sarcocephalus latifolius* for the treatment of malaria by allowing the reduction of

fever and pain (Abbah *et al.*, 2010; Amouzoun, Agbonon, Eklu-Gadegbeku, Aklikokou, & Gbéassor, 2008; Taïwe *et al.*, 2011). Indeed the administration of the decoction, aqueous or hydroalcoholic extracts of *Sarcocephalus latifolius* roots to mice or rats, leads to a reduction in the number of abdominal cramps induced by acetic acid (analgesic action), the decrease of the inflammatory response induced by ovalbumin (anti-inflammatory action) and the significant decrease in fever induced by the yeast of beer to 20% (antipyretic action).

Antihypertensive action

The hypertensive activity of this plant was confirmed by a study in 2008 which revealed that they decreased systolic and diastolic arterial pressures in hypertensive and normotensive rats(Nworgu *et al.*, 2008).

Antibacterial and antifungal activities

Aqueous and alcoholic extracts of leaves and roots of *S. latifolius* showed inhibitory and bactericidal activity on *S. aureus and P. aeruginosa*.

The antibacterial constituents of the plant are mainly concentrated in the leaves, according to the work of Okwori *et al.*(Okwori, Okeke, & Uzoechina, 2008), the leaf extracts showed a strong inhibition of bacterial growth. In addition, the methanolic extract of the leaves showed activity against E. coli, *Shigelle dysenteriae*, *S. aureus, Bacillus subtilis, P. aeruginosa* and against the fungus *Aspergillus niger*, with an efficiency comparable to the reference drugs. Alcoholic extracts are often more active on *S. aureus* and *E. coli*.(Boucherle *et al.*, 2016).

Antioxydant activities

Aqueous and ethanolic extracts of *Sarcocephalus latifolius* exhibited a dose-dependent inhibition of DPPH(2,2-diphenyl-1-picrylhydrazyl) radical activity. The phytochemical analysis of plants revealed a wealth of antioxidative substances such as vitamins A and C, minerals such as zinc, iron, copper and flavonoids which also contribute to strengthening the antioxidant properties of the plant(Enemor, Okaka, & Opeyemi, 2013). The leaves of *S. latifolius* would have a strong antioxidant activity than that of the fruits(Ayeleso, Oguntibeju, & Brooks, 2014). However, studies have shown that the fruits of this plant have a real antioxidant activity and their consumption could be an easily accessible source of antioxidants of natural origin(Yesufu *et al.*,2014).

Antiplasmodial activity

on decoctions and infusions of stems and roots of *Sarcocephalus latifolius*, Benoit-Vical *et al.* found similar activity levels for both extraction modes (IC50 of stem infusion is 3.1 µg mL-1, IC50 decocted in stem is 3.6 µg mL-1) *Plasmodium falciparum* susceptible and resistant to chloroquine)(Benoit-Vical *et al.*, 1998). An aqueous extract removed hepatic and cerebral parasites in mice infected with P. berghei(Onyesom, Osioma, & Okereke, 2015). Strictosamide (a molecule isolated from *Sarcocephalus latifolius*) has been described as a potent inhibitor of the chloroquine-resistant K1 strain and the chloroquine-sensitive strain NF54 (IC50 of 0.90 mM and 0.74 mM, respectively). In recent studies, it has been inactive on K1 cells (IC50> 500 mM) and shows only moderate activity with respect to chloroquine-sensitive D6 strains and chloroquine-resistant W2 strains (IC50> 20 mM)(Abreu & Pereira, 2001; del Rayo *et al.*, 2004; He *et al.*, 2005).

Therapeutic potential of Crateva adansonii DC and Sarcocephalus latifolius, to be valued in the management of malaria

Traditional uses reported on Crateva adansonii D.C and Sarcocephalus latifolius place them in a strategic position in the traditional pharmacopoeia. The treated diseases varied, including malaria. Produced pharmaco-toxicological data give a less empirical image to the use of these two medicinal plants. Indeed, antibacterial, antifungal, antioxidant, antimalarial activities have been demonstrated and attributed to the presence of large families of chemical molecules such as flavonoids, polyphenols and tannins. Antimalarial tests carried out on plasmodium strains show that the pharmaco-toxicological valorization of these two medicinal

plants in the management of malaria has been initiated. When it is known that in vitro experiments of a natural substance are not sufficient to attest to the safety in vivo, it is necessary to guide future work in a more in-depth approach by using resistant strains of Plasmodium and prioritizing in vivo work.

Conclusion

This study has highlighted the traditional uses and phytochemical and pharmacological properties of *Crateva adansonii* DC and *Sarcocephalus latifolius*, two plants used in Benin in the traditional treatment of malaria as well as other diseases. both species are widely used in the Beninese and African pharmacopoeia for the treatment of various diseases, including malaria. Their interesting chemical composition as well as toxicological and bioactive properties have been reported. These data prove that the valorisation of these medicinal plants in fighting malaria requires efficacy tests in vitro and in vivo.

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