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Review

Sida acuta Burm. f.: a medicinal plant with numerous potencies

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***Sida acuta* is shrub belonging to *Malvaceae* family. The plant is widely distributed in the subtropical regions where it is found in bushes, in farms and around habitations. Surveys conducted in indigenous places revealed that the plant had many traditional usages that varied from one region to another. The most cited illnesses are fever, headache and infections diseases. Indeed, many laboratory screening have been conducted to show the scientific rationale behind these usages and many compounds have been isolated from the plant. In the present review we listed the plant usages in folk medicine in some regions where the plant grows and we discussed on the confirmed *in vitro* activities after laboratory screenings. The review ended with the pharmacological properties of several compounds isolated from *S. acuta* principally alkaloids.**

Key words: Ethnomedicine, medicinal plants, natural substances.

INTRODUCTION

Sida acuta is a malvaceous weed that frequently dominates improved pastures, waste and disturbed places roadsides (Mann et al., 2003). The plant is native to Mexico and Central America but has spread throughout the tropics and subtropics (Holm et al., 1977). In traditional medicine, the plant is often assumed to treat diseases such as fever, headache, skin diseases, diarrhea, and dysentery. Referring to the traditional knowledge, studies have been carried out to confirm the activities the plant is assumed to exert *in vivo*. The described pharmacological properties of the plants involve the antiplasmodial, antimicrobial, antioxidant, cytotoxic activities and many other properties. Some studies resulted in the isolation of single compounds while the others just demonstrated the activity of the crude extracts. The present review is focused on the traditional usages of the plant, the *in vitro* laboratory screening results and the pharmacological properties of some compounds isolated from the plant.

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TRADITIONAL USAGES

S. acuta is widely distributed in pantropical areas and is widely used as traditional medicine in many cases. The plant is also used for spiritual practices. Table 1 displays the traditional usages of the plant in some regions where it grows. Among illnesses the plant is used to cure, fever is the most cited. The administration may be by oral route for example in the case of fever or by external application of the paste directly on the skin for skin diseases or snake bites (Kerharo and Adam, 1974). The plant may be used alone or in combination with other plants according to the diseases or to the healers.

IN VITRO ACTIVITIES AND ISOLATED COMPOUNDS OF *SIDA ACUTA*

Isolated compounds of the plant

Several phytochemical screenings resulted in the isolation of various compounds from the plant involving alkaloids and steroidal compounds (Cao and Qi, 1993;

Table 1. Traditional usages of *Sida acuta* in several regions.

Locality	Local name	Used part	Traditional usages	Reference
Guatemala, Nicaragua	-	WP	Asthma, renal inflammation, colds, fever, headache, ulcers and worms	(Caceres et al., 1987 ; Coee and Anderson, 1996)
India (Ghats)	Pilla valatti chedi	WP	Fever, bronchitis, ulcer, diarrhea, dysentery, skin diseases. The paste of leaves is mixed with coconut oil and applied on head regularly for killing dandruffs and also for strengthening hair	(Ignacimuthu et al., 2006; Malairajan et al., 2006)
Kenya (Digo)	Mbundugo	WP	The plant is used to prepare "Bundugo", a supplementary strength magically added to a person	(Pakia, 2005)
Nigeria	Iseketu	WP, L	malaria, ulcer, fever, gonorrhea, abortion, breast cancer, poisoning, inflammation, feed for livestock, stops bleeding, treatment of sores wounds antipyretic	(Kayode, 2006; Edeoga et al., 2005 Saganuwan and Gulumbe, 2006)
Togo	-	L	Eczema, kidney stone, headache	(Anani et al., 2000)
Western Colombia	-	WP	Snakebites	(Otero et al., 2000)
Sri Lanka	-	R, L	Hemorrhoids, fevers, impotency, gonorrhea, and rheumatism. In mixture as aphrodisiac and for boils and eye cataracts	(Dash, 1991; Pal and Jain, 1998)
Burkina Faso (Mossi Central Plate)	Zon-Raaga	WP	Fever, diarrhea, pulmonary affection, snakebites, insects' bites. Paste of leaves mixed with salt is applied on skin to cure panaris	(Nacoulma/Ouedraogo, 1996)

-: non available data, L: leaves, R: roots, WP: whole plant.

Dinan et al., 2001). Figure 1 lists the chemical structure of some. The alkaloids occurring in the plant belong to the indoloquinolines family. The main alkaloids are cryptolepine and its derivatives such as quindoline, quindolinone, cryptolepinone and 11-methoxy-quindoline (Jang et al., 2003). The major steroids of the plant are ecdysterone, beta-sistosterol, stigmaterol, ampesterol. Phenolic compounds such as evofolin-A, and B, scopoletin vomifoliol, loliolid and 4-ketopinoresinol have also been isolated (Jang et al., 2003).

Antiplasmodial activity

The *in vitro* antiplasmodial activity of the plant was first reported by Karou et al. (2003). The test was performed on fresh clinical isolates of *Plasmodium falciparum* using the *in vitro* semi microtest by light microscopy as described by Le Bras and Deloron (1983). Ethanolic extract of the plant was tested both with ethanolic extract of four other plants. As *S. acuta* was the most active plant of the study (IC_{50} value of 4.37 µg/mL), its extract was brought under liquid-liquid separation between petroleum ether, chloroform and water resulting in three fractions. These fractions tested on the parasites revealed that the chloroformic fraction and the aqueous fraction had similar activities while the ether fraction was devoid of intrinsic antiplasmodial activity. This suggested that alkaloids of the plant may be responsible for the activity. The issue of the study confirmed that the activity of the plant was related to its alkaloids which displayed IC_{50} value of 0.05 µL/mg. Banzouzi et al. (2004) continued the work in the same way using one reference strain of *P. falciparum*: FcM29-Cameroon (chloroquine-resistant strain) and a Nigerian chloroquine-sensitive strain. The antiplasmodial assay was performed with ethanolic and aqueous extract by flow cytometry with incorporation of [^{3}H] hypoxanthine (Desjardins et al., 1979; Schulze et al., 1997). The ethanolic extract showed good activity on the two strains with IC_{50} values between 3.9 and 5.4 µg/mL. The purification of this active extract led to the identification of cryptolepine as the antimalarial agent of the plant.

It is evidence that the plant showed a good in vitro antimalarial activity related to its alkaloid contents. Referring to the traditional practices where the drug is often prepared by boiling plant material in water, this activity may be reduce *in vivo* since alkaloid solubility in water is pH-dependant.

Antibacterial activity

The antimicrobial screening of *S. acuta* revealed that many compounds might be responsible for the activity of the plant. The first antimicrobial screening of the plant was conducted by Anani et al. (2000) using the disk diffusion assay. The authors found that the methanolic extract of the plant had a significant activity on *Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Mycobacterium phlei,* however the extract was not active on *Streptococcus faecalis, Klebsiella pneumoniae, Salmonella thyphimurium, Pseudomonas aeruginosa* and *Candida albicans*. The same findings were confirmed in another study using methanolic extract and similar microorganisms (Rajakaruna et al., 2002). Polyphenols and alkaloids of the plant were tested separately on several pathogenic bacteria including clinical strains and reference strains of *Enterobacteriaceae* and *Staphylococcaceae* families. The tests were performed by agar well diffusion (Perez et al., 1990) and the NCCLS (2000) broth microdilution assays. The results revealed that the phenolic compounds had a good *in vitro* antimicrobial activity and this activity was much influenced by the storage of the extract probably because of the phenolic compounds oxidization. The inhibition zone diameters varied from 11 to 25 mm for 250 µg polyphenols and MBC values ranged from 20 to 2000 µg/mL (Karou et al., 2005). Alkaloids of *Sida acuta* also displayed a good antibacterial activity. The recorded inhibition zone diameters varied from 16 to 38 mm for 100 µg alkaloids and the MBC values from 80 to 400 µg/mL (Karou et al., 2006). In another study, leaf/flower combination was evaluated for antimicrobial activity using hexane, chloroform, methanol and aqueous extraction methods. The antibacterial activities were exhibited by the four extract on *E. coli, S. pyogenes, Pasterella multocida* and *S. typhimurium* as there was no activity exhibited on *S. typhi, S. pneumoniae and K. pneumoniae* (Sanganuwan and Gulumbe, 2006).

As many other plants with antibacterial properties, *S. acuta* contains phenolic compounds that are responsible for the activity of the plant. The current problem with phenolic compounds is the fact that they are vulnerable to polymerization in air through oxidation reactions. This oxidization may first affect the extractability of the phenolic compounds that is crucial in drug preparation; in this topic some authors suggested extracting the compounds directly on fresh material in order to enhance the yield (Scalbert, 1992). However, in our enquiries many traditional healers always dry their plant materials before the use, particularly when the plant does not grow around habitations (Karou et al., 2007). Secondly, an important factor governing the activity of phenolic compounds is their polymerization size. Oxidized condensation of phenols may result in the toxification of microorganisms, while the adverse effects can be observed in some cases (Scalbert, 1991; Field and Lettinga, 1992). Recently in the case of S. acuta we observed that the tested microorganisms were particularly susceptible to the stored extract (Karou et al., 2006). Therefore, it is now the time to think about how to prepare phenolics-based drugs with traditional healers.

Other *in vitro* activities

Since *S. acuta* has several usages in folk medicine it has been involved in many other pharmacological screenings. The plant has been screened for its cancer chemo-preventive properties by Jang et al. (2003). The study resulted in the isolation of several compounds, among them quindolinone, cryptolepinone and 11-methoxyquindoline was found to induce quinone reductase activity, while cryptolepinone, N-transferuloyltyramine exhibited a significant inhibition of 7, 12-dimethylbenz-[a]anthracene-induce preneoplastic lesions in mouse mammary organ culture model. These observations suggested that cryptolepinone was a potential chemopreventive agent.

The polyphenol extract of the plant was tested together with polyphenol extract of other medicinal plants for antioxidant activity through free radical scavenging. The tests were performed using the phosphomolybdenum reduction (Prieto et al., 1998) and the ABTS radical cation decolorization assays (Re et al., 1999) with trolox as standard antioxidant. The results showed that there was a good correlation between the two methods (r = 0.9) and *S. acuta* had a weak free radical scavenging according to values recorded with bark extracts of *K. Senegalensis*, *P. erinaceus* and *C. micranthum* in the same study. The activities were highly correlated with the total phenolic content determined by the Folin-Ciocalteu reagent (Singleton et al., 1999) with gallic acid as standard (r = 0.94 and r = 0.91 with the two assays respectively).

In another study, Otero et al. (2000a, b) showed that the ethanolic extract of the plant had a moderate activity against the lethal effect of *Bothrops atrox* venom. In Western Kenya where the plant is consumed as legume, a study using Brine shrimp lethality tests revealed that the plant was toxic (LC_{50} = 99.4 µg/ml). The author concluded that the plant can cause acute or chronic toxicities when consumed in large quantities or over a long period of time (Orech et al., 2005).

Malairajan et al. (2006) had demonstrated the analgesic properties of the whole plant extract in animal model. The authors conducted the tests using two methods the hot plate method described by Woolfe and Mac Donalds (1944) and the tail immersion method described by Dykstra and Woods (1986). The screening did not result in the isolation of single compounds but the authors suggested that the observed analgesic activity may be due to steroidal compounds the plant contains (Figure 1).

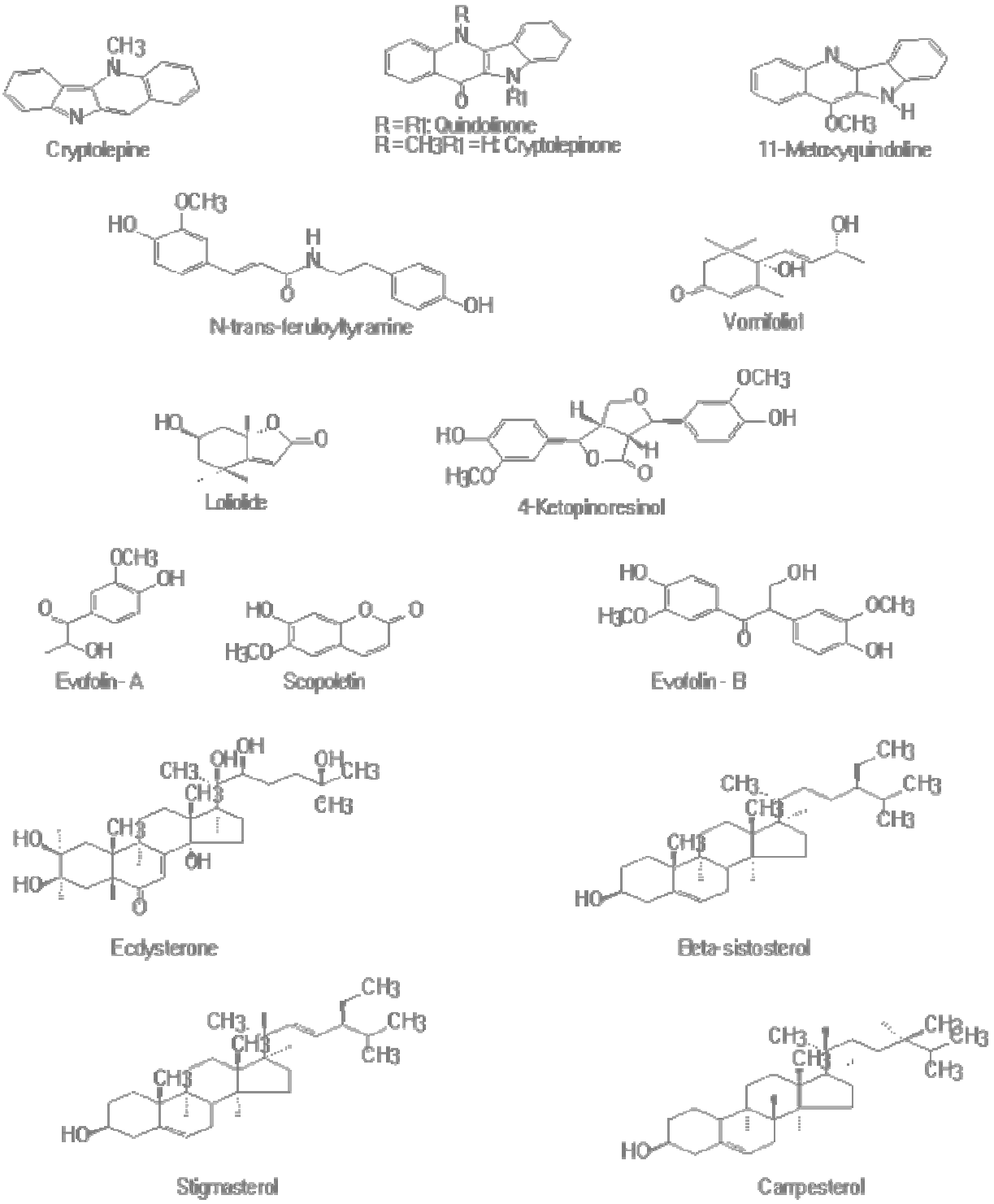

Figure 1. Chemical structure of compounds isolated from *S. acuta*.

PHARMACOLOGICAL PROPERTIES OF TWO SINGLE COMPOUNDS ISOLATED FROM *S. ACUTA*: CRYPTOLEPINE AND SCOPOLETIN

Cryptolepine

Cryptolepine (5-methyl indolo [2,3b]-quinoline) is a natural alkaloid occurring in *S. acuta*, that was first isolated from the roots of *Cryptolepis triangularis*. This compound is the main alkaloid present in the roots of *Cryptolepis sanguinolenta*, a plant traditionally used in Central and West Africa for the treatment of rheumatism, urinary and respiratory infections. Cryptolepine presents a large spectrum of biological properties, including hypotensive and antipyretic, antimuscarinic, antibacterial and anti-inflammatory effects (Bonjean et al., 1998). It also possesses potent *in vitro* activity against *P. falciparum*, the main parasite species responsible for malaria. The mechanism of action of this antimalarial product remains unclear; at least two independent effects may together lead to a potent activity. First, it behaves like a DNA intercalator (Bonjean et al., 1998). Second, it may act like chloroquine by inhibiting the detoxification of heame in red blood cells (Wright et al., 2001). This is supported by a fluorescent microscopy study, which suggested that cryptolepine accumulates into parasite structures that may correspond to the parasite nucleus (Arzel et al., 2001). However, cryptolepine failed to cure malaria in mice by oral route, by intra peritoneal injection the compound showed toxic effects. These observations led to the investigation of its synthetic analogues such as 2,7-dibromocryptolepine (Wright, 2005).

It has been proposed that crytolepine exerts its cytotoxic action via the inhibition of DNA synthesis and stabilization of topoisomerase II-DNA covalent complexes. In a study conducted to elucidate the strength and mode of binding to DNA of cryptolepine and two other alkaloids by spectroscopy, Dassonneville et al. (1999) found that the alkaloid binds tightly to DNA and behaves as typical intercalating agent, thus it stabilizes the topoisomerase II-DNA covalent complex and stimulates the cutting of DNA by topoisomerase II, but the drug does not exhibit a preference for cutting at a specific base. However, the flow cytometry analysis showed that the drug alters the cell cycle distribution, but no sign of drug-induced apoptosis was detected when evaluating the internucleosomal fragmentation of DNA in cells. The authors suggested that cryptolepine-treated cells probably die via necrosis rather than via apoptosis and there was evidence that DNA and topoisomerase II are the primary targets of cryptolepine. In another study, the same authors found later that Cryptolepine induce apoptosis in HL_{60} leukaemia cells (Dassonneville et al., 2000). Recently, the structure of a cryptolepine-DNA complex was elucidated by X-ray crystallography. Lisgarten et al. (2002) demonstrated that the drug interacts with the CC sites of the d(CCTAGG)2 oligonucleotide.

Scopoletin

Scopoletin (6-methoxy-7-hydroxycoumarin) is a coumarin that has been isolated from many plants species. The compound has been tested for many pharmacological properties, we list below few examples of the described properties of the compound. Yang et al. (2007) observed that the compound significantly increased lipoprotein lipase activity 3T3-L1 adipocytes in dose- and time-dependent manners. Scopoletin did not release the enzyme from the adipocyte membrane and, instead, decreased the enzyme mRNA level, suggesting a post transcriptional control. In the same study the compound was also found to partially reverse tumor necrosis factor-alpha-induced suppression of lipoprotein lipase activity, thus the compound may act as a facilitator of plasma triglyceride clearance. Looking for the possible mode of action of scopoletin in the inflammatory cytokine production using CCRF-CEM leukemia cells, Moon et al. (2007) found that scopoletin was a potential regulatory of inflammatory reactions mediated by mast cells. Scopoletin was also found to inhibit leukemia cell proliferation. Tested against multidrug resistant subline CEM/ADR5000 cells together with standard cytostatic drugs, doxorubicin, vincristin and paclitaxel the cells did not exhibit cross resistance to the compound in contrast with what was observed with the standard drugs (Adams et al., 2006). However the compound was also found to exert a cytotoxic effect on tumoral lymphocytes (Manuele et al., 2006). Finally, scopoletin was found to inhibit the thyroid function and hyperglycemia without hepatotoxicity according to the study conducted by Panda and Kar (2006).

CONCLUDING REMARKS

S. acuta is a plant of wide usage in traditional medicine. Following these traditional usages many studies have been conducted in laboratories for the efficiency of the plant. It is now evident that the plant has a good antiplasmodial activity due to its alkaloids principally cryptolepine the main alkaloid of the plant. It is also demonstrated that the plant is active on several bacterial strains. Many other compounds which are demonstrated to have interesting pharmacological properties alone have been isolated from the plant, in addition the plant may have many other properties since it has not been tested for all desired pharmacological activities. However it should be noted that all laboratory screenings have been carried out with laboratory classical extractions as it is often observed with other medicinal plants. No study has been conducted with traditional preparation; this must be the priority for two reasons. First people still use the plant even if laboratory screenings do not confirm the assumed activity, so the laboratory results in the conditions of the traditional usage is more pertinent and can directly improve this usage. Secondly most of theses

extracts act sometimes by synergistic effects so the fractionation may result in the lost of the activity, in addition the establishment of the drug from pure single compound may be too expensive so the drug may not be affordable for our populations.

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