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REVIEW ARTICLE

BIOCHEMICAL PROPERTIES AND BIOACTIVE COMPOUNDS WITH MULTIPLE THERAPEUTIC VALUES OF *SENNA ALATA* (L.), AN ORNAMENTAL SHRUB FROM THE BOTANICAL FAMILY OF FABACEAE (LEGUMINOSAE) – A PHARMACOLOGICAL OVERVIEW

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ABSTRACT

Senna alata (L) is an ornamental flowering plant which is mostly used as antifungal agent as an oral preparation by traditional practitioners. The juice of fresh leaves of *Senna alata* is universally recognized by local healers as a remedy for parasitic skin disease and is used in the treatment of many eruptive and pustular skin condition by simply rubbing the crushed leaves either alone or mixed with oil on the skin. Root is taken in Nigerian and Guinea Bissau to regulate menstrual flow. Decoction with rock salt and other dry medicinal plants is taken in Nigeria thrice weekly on an empty stomach for effective treatment of chronic gonorrhoea. Though it has much therapeutic options traditionally, the most of these information are still under research for experimental evidences. There are some more research is going on to screen and to understand the existence of bioactive compounds with free radical scavenging activity, anticancer property and antidiabetic potency. In this critical time, we have sum up almost all the details of current and completed research on this plant as review here for the idea about *Senna alata* (L).

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INTRODUCTION

Senna alata is a large branched shrub with height upto 16 ft. Leaves are usually present like 7–14 pairs, rounded tip with 2.5 inches long and larger toward tip. The Branches are hairy and green in colour. The Flowers of *Senna alata* is yellow coloured and are arranged one above the other like upward spike, a candle. Pods upright, thick, leathery, straight, narrow and 4-angled, winged, containing up to 60 tan to brown flattened seeds. Bark has been used for tanning and as medicine for skin diseases, poisonous bites, and fevers. *Senna alata* is a pantropical shrub, cultivated throughout Thailand. The leaves contain anthraquinones such as emodin, aloe-emodin, and rhein1 and possess laxative activity. In Thai Traditional Medicine, *S. alata* leaves are used for the treatment of Tinea versicolor and ringworm infections by crushing fresh leaves with or without alcohol. The Thai Ministry of Public Health recommends the plant for the use in the primary health care system for skin disease treatment.

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Universal distribution

Cassia alata Linn. [Synonym: *Senna alata* (L.) Roxb.] (*Caesalpiniaceae*) is a shrub commonly known as "Ath thora", "Eth thora" (in Sri Lanka), candle bush/tree (Malaysia), candle stick, Carrion Crow Bush, Winged Senna, Empress Candle plant, Dadmardan (India), Roman Candle tress (Fiji), and ringworm shrub since it is in the effective use for the treatment of ringworm infections (USDA, 2012). The plant is native to South America but is now introduced and naturalized in many pantropical countries of Southeast Asia, Africa, and North America (Protabase, 2012).

It is also occurs in Andhra-Pradesh State of India (commonly called as Simavisi), is used as a traditional medicine to treat bronchitis and asthma (Savithramma *et al*., 2007). It is an important medicinal tree as well as an ornamental flowering plant and is commonly known as 'candle-tree'. This shrub also grows in the tropical climate of Philippines (locally called as 'Akapulko') and has been used in the form of herbal tea, lotion and ointment for different purposes (Khare, 2007).

Phytochemical composition

Guajava, like most *Cassia* and *Senna* plants, contain a group of chemicals called anthraquinones. These chemicals are well known for their laxative effect. Guajava leaves also contain a chemical called adenine which has been documented as an effective platelet aggregating inhibitor (reduces sticky blood and arterial plaque). Other chemicals in guajava include chrysoeriol - 7- O- (2" -O- beta -D-mannopyranosyl)-beta-Dallopyranoside, kaempferol, kaempferol 3-O-gentiobioside, naringenin, quercetin, and rhamnetin-3-O-(2"-O-beta-D-mannopyranosyl)-beta-D-allopyranoside (Borbalan *et al*., 2003). Extracts of *Senna alata* were investigated for antioxidant phenolic compounds using High Performance Liquid Chromatography (HPLC).

The dried aerial plant parts were macerated into powder and extracted in different organic solvent systems consisting of methanol, hexane, chloroform, ethyl acetate, butanol and water. Each extract was dried under reduced pressure using a rotary evaporator, freeze-dried and stored at a temperature of 4°C. The extracts were then subjected to high performance liquid chromatography studies. Two major phenolic compounds Naringin and Apigenin, were identified in some of the fractions of *Senna alata*. The presence of these flavoniods in *Senna alata* may explain its wide use in ethnomedicine practice for the treatment of hypertension, sickle cell anemia and diabetes in Southwestern Nigeria.

Phenols are a class of low molecular weight secondary metabolites found in most land plants. These compounds are of great importance in foods and drinks because they are responsible for their organoleptic properties. Polyphenols such as anthocyanins, add colour to food which may be purple, black or red (Aliyu *et al*., 2009) and this is desirable in red wines. Phenolic compounds are the largest group of phytochemicals and accounts for most of the antioxidant activity in plants or plant products (Osawa, 1999). Phenolic substances such a flavonols, naringin, apigenin, myricetin, coumarins and caffeic acids are known to possess antioxidant properties which play important roles in protecting foods, cells and organs from oxidative degeneration and are considered as antioxidants (Manach *et al*., 2004).

Antioxidants are able to scavenge free radicals and thereby prevent free radicals from causing damage. Reports indicate that diets rich in phenolic compounds play pevotal role in the prevention of various diseases associated with oxidative stress such as cancer, cardiovascular and neurodegenerative diseases etc (Hang *et al*., 2004; Middleton *et al*., 2000) In addition, phenols constitute the active substances found in many medicinal plants with important pharmacological activities and modulate the activities of a wide range of enzymes and cell receptors (Adedayo *et al*., 2001). Therefore, the isolation and identification of these compounds are of great interest and importance because of their role in drug development and in management of many chronic diseases. *Senna alata* Linn. Roxb (*Leguminosae*) synonym Cassia alataLinn. commonly referred to as *Asunwon oyinbo* by the Yoruba ethnic stock in Southwestern Nigerian, is indigenous to Africa. In Cameroon, the leaves and stem bark of *S. alata* are used to treat hepatitis, skin diseases, jaundice, gastroenteritis, eczema and ringworm. The young leaves are used in rural areas of Nigeria to treat constipation and food poisoning (El-Mahmood *et al*., 2008).

In Northern Nigeria, the root, stem and leaves are used to treat burns, wounds, skin infection, diarrhoea and upper respiratory tract infection (Wegwu *et al*., 2005). The bioactivity of the plant include antibacterial, antifungal, antimicrobial, diuretic, analgesic and choleretic (Reezal *et al*., 2002). There are studies on the antioxidant activity of the leaves of this plant (Akinyemi, 2000) reported that Senna alata was able to induce antioxidant effects in the serum of rats exposed to carbon tetrachloride (CCl4) with a concentration-dependent decrease in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In this study, High Performance Liquid Chromatographic (HPLC) analysis coupled to an UV (Ultra violet) detector was done to identify and determine the phenolic contents of fractions of Cassia alata.

A reversed-phase high-performance liquid chromatographic method is described for the simultaneous determination of four anthraquinones: rhein, aloe-emodin, emodin, and chrysophanol in Senna alata leaves. The method involves the use of a TSK-gel ODS-80Tm column (5 μm, 4.6 × 150 mm) at 25°C with the mixture of methanol and 2% aqueous acetic acid (70:30, v/v) as the mobile phase and detection at 254 nm. The parameters of linearity, precision, accuracy, and specificity of the method were evaluated. The recovery of the method is 100.3–100.5%, and linearity (r2 > 0.9998) was obtained for all anthraquinones. A high degree of specificity as well as repeatability and reproducibility (relative standard deviation values less than 5%) were also achieved. The solvent for extraction of anthraquinones from *S. alata* leaves was examined in order to increase the anthraquinone content of the leaf extract. It was found that a solution of 5% hydrochloric acid (v/v), 5% ferric chloride (w/v), and 15% water in methanol (v/v) was capable of increasing the anthraquinone content in the leaf extract up to 1.67% (w/w) (Pharkphoom Panichayupakaranant *et al*., 2009)

Toxicity

The toxicity data for hydro-alcoholic extract of *Cassia alata* in albino rats has been already known. The reported LD_{50} value is 18.5 g/kg, indicating the safe use of *Cassia alata* extract (Pieme *et al*., 2006).

Antimicrobial Quality

It was observed in a study that, the antimicrobial activity of the root and leaf extracts of the *Senna alata* plant against some infectious bacteria (Escherichia coli, Proteus mirabilis, *Pseudomonas aeruginosa* etc) and fungi (*Spergillus flavus, Aspergillus niger*, *Candida albicans* etc) as well as the physiochemical and microbiological quality of the plant was determined using the cup plate agar diffusion method. The freshly collected fresh mature leaves and roots were chopped into pieces and shade-dried at 32-35^{0}C to constant weight for 5 days. 50g each of the plant parts was coarsely powdered using a mortar and pestle and finely powdered using an electric blender. Each of the powdered air-dried plant material was extracted with water, acetone and methanol. All the extracts

demonstrated considerable activity against both Gram negative and Gram positive bacteria and some fungi with the organic extracts showing higher activity than the aqueous extracts. *Stretococus pyogenes* and *S. aureus* were the most susceptible to all the extracts followed by *Salmonella typhi* and *Escherichia coli.* The most susceptible fungi were *Cryptococcus neoformans* and *Candida albicans* while the least susceptible was *Aspergillus flavus*. The minimum inhibitory concentration and minimum bactericidal concentration of the methanol extracts ranged between 3-10 mg/ml and 25-50 mg/ml for bacteria and fungi respectively. Preliminary phytochemical analysis showed that the extracts contained tannins, saponins, glycosides, flavonoids and phenols. The results obtained show the basis for the local usage of *S. alata* Linn as an antimicrobial. Phytochemical result showed ethanol to be a better solvent for the extraction of the bioactive agents in *Senna alata* which include: glycosides, alkaloids, saponins, tannins, flavonoids and volatile oil. Despite the significant progress made in microbiology and the control of microorganisms, sporadic incidents of epidemics due to drug resistant microorganisms pose an enormous threat to public health. The use of medicinal plants for antimicrobial activities needs to be given more attention (Ehiowemwenguan *et al*., 2014).

Antioxidant Property

Isolation and characterisation of the active antioxidant compound in the methanol extracts from the aerial parts of *Cassia alata* led to identification of the flavonol named Kaempferol. Kaempferol reduces the DNA damage induced by mutagenic compounds in the human comet assay. Pre-treatment of human lymphocytes with kaempferol reduced the oxidative damage induced by hydrogen peroxide. This flavonol helps to prevent oxidative damage to cells and DNA. No genotoxic effect of aqueous ethanolic extract of *Senna alata* on the model used has been detected. Therefore, the results obtained encourage studies on its pharmacological properties (P. Panichayupakaranant and S. Kaewsuwan, 2004). In another attempt, using DPPH radical scavenging assay to investigate the antioxidant activity of crude methanol extracts from the leaves, flowers and pods of Cassia alataL. found that the leaf extract exhibited a stronger antioxidant activity than the extracts from the flowers and pods.

On the basis of DPPH radical scavenging assay-guided isolation, the methanol extract of *C. alata* leaves was separated by silica gel vacuum chromatography and Sephadex LH-20 gel filtration chromatography afford a light yellowish powder (CA1), which was identified as kaempferol. This compound exhibited antioxidant activity (ED_{50} 9.99 μM) that was six times stronger than that of BHT (ED_{50} 57.41 μM) and fifty eight times stronger than that of emodin (ED_{50} 578.87 μM) (Panichayupakaranant and Kaewsuwan, 2004).

Anti-inflammatory effects

Anti-inflammatory activities of heat-treated *Cassia alata* leaf extract and kaempferol 3-O-gentiobioside (K3G) isolated from *C. alata* as an abundant flavonoid glycoside were studied by comparing their activities with the activities of sun-dried *C. alata* leaf extract. It was observed strong inhibitory effects on Concanavalin A induced histamine release from rat peritoneal exudate cells both in the extracts of heat-treated and sun-dried *C. alata* leaves. Furthermore, the heat treated leaf extract exhibited stronger inhibitory effects than the effects of the sun-dried leaf extract at low concentrations in the studies of Concanavalin A-induced histamine release, 5-lipoxygenase inhibition, and also inhibition of cyclooxygenases (COX-1 and COX-2), whereas K3G showed weak inhibitory effects on Concanavalin A-induced histamine release, 5-lipoxygenase, and COX-1. No anti-hyaluronidase effect was detected in any of the materials tested (Hiroyoshi Moriyama *et al*., 2003).

Anti-allergic Property

Antiallergic activity of hydroalcoholic extract of *Cassia alata* along with its two components rhein and kaempferol was evaluated using in vivo mast cell stabilization assay. Inhibitory effect on lipoxygenase (LOX) enzyme was also evaluated in vitro. Further chemical standardization of Cassia alataextract was done using rhein and kaempferol by HPTLC-densitometric method. The hydroalcoholic extract of Cassia alatasignificantly inhibited mast cell degranulation at 200 mg/kg dose. Both chemical constituents rhein and kaempferol also showed potent (>76%) inhibition of mast-cell degranulation at 5 mg/kg. Extract and rhein inhibited LOX enzyme with IC50 values of 90.2 and 3.9 μg/mL, respectively, whereas kaempferol was inactive. (B. Singh *et al*., 2012)

Anticancer Property

In an attempt to explore Philippine plants traditionally used for therapeutic purposes, extracts from *Cassia alata* were tested in vitro for cytotoxicity against selected cancer cell lines. C. alata, commonly called “akapulko” in the Philippines, belongs to family Leguminosae. It has been studied for its antimicrobial, antifungal, anti-inflammatory, antimutagenic, and hypoglycemic activities (Ibrahim and Osman, 1995; Villaseñor *et al*., 2002). However, its therapeutic and preventive effects against cancer remain relatively unexplored. A strong cancer chemopreventive potential was reported by Jacinto *et al*. (2005) when C. alata hexane leaf extract was observed to induce quinone reductase with specific activity comparable to bromoflavone, a known chemopreventive agent. Quinone reductase is a Phase II enzyme that helps to inactivate carcinogenic compounds in vivo. This enzyme mediates the conversion of quinones into enols, which are easily metabolized and excreted by the body.In another attempt, Leaf extracts of Cassia alataL (akapulko), traditionally used for treatment of a variety of diseases, were evaluated for their potential antitumor properties in vitro. MTT assays were used to examine the cytotoxic effects of crude extracts on five human cancer cell lines, namely MCF-7, derived from a breast carcinoma, SK-BR-3, another breast carcinoma, T24 a bladder carcinoma, Col 2, a colorectal carcinoma, and A549, a nonsmall cell lung adenocarcinoma. Hexane extracts showed remarkable cytotoxicity against MCF-7, T24, and Col 2 in a dose-dependent manner. This observation was confirmed by morphological investigation using light microscopy. Further bioassay-directed fractionation of the cytotoxic extract led to the isolation of a TLC-pure isolate labelled as f6l. Isolate f6l was further evaluated using MTT assay and morphological and

biochemical investigations, which likewise showed selectivity to MCF-7, T24, and Col 2 cells with IC50 values of 16, 17, and 17µg/ml, respectively. Isolate f6l, however, showed no cytotoxicity towards the non-cancer Chinese hamster ovarian cell line (CHO-AA8). Cytochemical investigation using DAPI staining and biochemical investigation using terminal deoxy nucleotidyl transferase-mediated dUTP nick end labelling (TUNEL)-a method used to detect DNA fragmentation-together with caspase assay, demonstrated apoptotic cell death. Spectral characterization of isolate f6l revealed that it contained polyunsaturated fatty acid esters. Considering the cytotoxicity profile and its mode of action, f6l might represent a new promising compound with potential for development as an anticancer drug with low or no toxicity to non-cancer cells used in this study (Elizabeth *et al*., 2013).

Pregnancy Termination Effects in induced rats

The abortifacient claim of *Senna alata* (*S. alata*) was scientifically validated recently with alkaloids speculated to be the bioactive agent. This speculation is yet to be substantiated or refuted by scientific evidence. This study was aimed to investigate the pregnancy terminating effects of the alkaloids from *S.alata* leaves. Twenty four Pregnant rats (143.99±1.21 g) allocated randomly to four groups: A, B, C and D respectively received, 0.5 ml of distilled water, 250, 500 and 1000 mg/kg body weight of the S. alata extracted alkaloids orally, once daily from day 10 until day 18 post-coitum. The indices of abortifacient were evaluated at the end of the exposure period. The results were analyzed by both the analysis of variance and Duncan's multiple range test and $p<0.05$ was considered as statistically significant. Thin-layer chromatographic separation produced five spots with Rf values of 0.28, 0.33, 0.39, 0.47 and 0.55 which gave positive reaction with Meyer's and Wagner's reagents, respectively. The number of implantation sites and corpora lutea, as well as the concentrations of FSH, LH, progesterone, weight of uterus, uterine/ body weight ratio, glucose and cholesterol decreased significantly ($p<0.05$) whereas the resorption index, pre- and post-implantation losses, uterine protein content and alkaline phosphatase activity increased significantly. None of the alkaloid treated animals presented with provoked vaginal opening or bleeding except fetal deaths. The alkaloid decreased the maternal weight gain, as well as feed and water intake. Overall, the alkaloids from *S. alata* leaves exhibited anti-implantation, anti-gonadotropic, anti-progesteronic, embryonic resorptive, feto-maternal toxic activities but not complete abortifacient. The alkaloids alone may not be the sole abortifacient bioactive agent in the leaf extract (Yakubu and Musa, 2012).

Anti-dermatophilosis property

A study describes interesting preliminary results on the therapeutic effects of ointments prepared with extracts of medicinal plants on bovine dermatophilosis. Our results show that the use of ointments made with ethanolic extracts of leaves of *Senna alata, Lantana camara* and *Mitracarpus scaber*, as topical treatments on chronic crusty or acute lesions of dermatophilosis, induces healing of the disease in the nine infected animals treated without recurrence. This is opposed to what is observed by using oxy tetracycline, Terramycin long-acting (TLA), or procaine-penicillin, antibiotics commonly used parenterally for the treatment of dermatophilosis in the Republic of Benin which could not prevent the recurrence of the disease. These ointments, when applied once a day for 8–15 days, provoked the falling off of the crusts after 3–4 days of treatment. Hair grows on the treated areas, which heal without scarring, within 3–4 weeks after the end of the treatment. The healed animals became free of dermatophilosis without recurrence for more than 3 years and were in good health (N. Ali-Emmanuel *et al*., 2003). It is the first report of the use of these plants to cure dermatitis in animals. Furthermore, these ointments are cheaper, easier to produce and give better results than antibiotics used parenterally, but further experiments have to be performed on a larger scale to capture the full range of severity of the disease and analyse possible resistance to that treatment.

Antidiabetic Properties

The methanol extract of leaves of *S.alata*, which showed potent α-glucosidase inhibitory activity (IC50, 63.75 ± 12.81 µg/ml), was fractionated. Active fractions were taken for further analysis by a variety of techniques including HPLC and Combiflash chromatography. The identity of the isolated compounds was established by spectroscopic analysis while their potential antidiabetic activity was assessed by in vitro enzyme inhibition studies. The α-glucosidase inhibitory effect of the crude extract was far better than the standard clinically used drug, acarbose (IC50, 107.31 ± 12.31 µg/ml). A subsequent fractionation of the crude extract was made using solvents of ascending polarity (petroleum ether, chloroform, ethyl acetate, n-butanol and water). The ethyl acetate (IC50, 2.95 ± 0.47µg/ml) and n-butanol (IC50, 25.80 ± 2.01 µg/ml) fractions which contained predominantly kaempferol (56.7 ± 7.7 µM) and kaempferol 3-O-gentiobioside (50.0 ± 8.5 µM), respectively, displayed the highest carbohydrate enzyme inhibitory effect (G. K. Varghese *et al*., 2013).

Wound healing property

In a recent study, the wound healing effects of the leaf ethanolic extract of the plant on excision wound in laboratory Rats was observed. 5 groups (n= 6 per group) were used. A wound area of 2 x 2cm was experimentally induced at the depilated dorsal portion of the animals. There concentrations of 125, 250 and 500mg of the leaf extracts were slated for the treatment of the wound topically. Group 1, 2 and 3 were treated with the ethanolic leaf extract, group 4 was treated with spray plus (as standard drug) while group 5 was left untreated which served as the control group. Wounds were measured from the day of excision and every other 2 days interval till complete epithelialisation. The wound size in animals treated with the leaf extracts were significantly reduced ($p<0.05$) when compared with the negative control group. This study showed that the ethanol leaf extracts of *Senna alata* promoted significant wound healing in excision wound model compared to the negative control (Midawa *et al*., 2010).

Summary and Conclusion

Though this plant has wide range of pharmaceutical values, it has obtained many attentions among scientists and research scholars for more in depth research for exploring its bioactive compounds as biopharmaceutical agent for various diseases.

This is the foremost reason behind in preparation of this collective review for the easy attention for those who need it really.

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