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Review of Phytochemical, Pharmacological and Toxicological Profile of *Stereospermum kunthianum*

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Authors' contributions

This work was carried out in collaboration between all authors. Author JJO designed the study and wrote the first draft of the manuscript. Author FO reviewed the study design and presentation of the work. Authors JJO and GOO managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: The review is directed at the phytochemical, pharmacological and toxicological activities of the medicinal plant *Stereospermum kunthianum,* Cham, (Bignoniaceae) widely distributed in the Guinean-savannah.
Results: A survey of previous scientific publications and available literatures revealed that tannins, saponins, flavonoids, terpenoids, glycosides, sterols, coumarins, quinones and higher fatty acids have been isolated with various solvents from different parts of the plant. Extracts from the plant have shown antibacterial, antiplasmodial, analgesic, anti-inflammatory, antidiarrhoeal, anticonvulsant and antioxidant activities pharmacologically. Sub-acute and acute toxicity studies

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showed that *Stereospermum kunthianum* has a wide safety margin up to 1000 mg/kg b. wt. and can be used for long term treatment of disease conditions for which it is indicated.
Conclusion: Result emerging from the review of scientific studies unveil the therapeutic potential of *Stereospermum kunthianum* extracts and isolated compounds thereby justifying the use of the plant in traditional medicine as a remedy for treatment of various diseases in humans.

Keywords: Medicinal plants; extracts; activity; isolated.

1. INTRODUCTION

The use of medicinal plants is as old as human civilization [1]. Medicinal preparations derived from plants have been in widespread use and considered in ancient times as a connection to the divine [2,3]. Medicinal plants have been used as a means of curing or preventing diseases and traditional medicine is still the first point of healthcare for many people in sub-Saharan Africa where there has been a long and rich tradition of obtaining treatments from herbs and trees [3,4]. Although incorporating traditional medicine into the national health system is not a priority in Nigeria, WHO recognizes traditional medicine as a vital health-care resource [5].

Scientifically proven therapeutically active substances are present in different medicinal plants, one of which is *Stereospermum kunthianum (S. kunthianum)*. *S. kunthianum* (Cham, Sandrine Petit), family Bignoniaceae, synonyms; *Stereospermum dentatum* A. Rich, *Bignonia lanata* R.Br, *Dolichandrone smithii*, *Stereospermum arguezona* A. Rich, *Stereospermum cinereoviride* K. Schum, *Stereospermum integrifolium* A. Rich [6].

S. kunthianum is a small woody tree of about 5 or 15 m high and diameter 25 cm. It is found in the Sudano-Guinea savannah regions of Africa and Asia, where the plant parts are used to treat various ailments [7]. It has thin, grey-black bark, smooth or flaking in patches, the trunk is rarely straight, with twisted branches with abundant, fragrant, precocious, pink or purplish flowers, making the tree a spectacular sight. The alternate leaves are imparipinnately compound and some 25 cm long; leaflets are nearly opposite with one terminal leaflet, and with short, soft hairs, oblong to oblong-elliptic in shape, green and hairless above, yellowish-green with prominent venation below, apex somewhat attenuate, and the base tapering. The leaf margin may be entire or sometimes toothed in coppice shoots, while petiolules are virtually absent. Petioles may be up to 7 cm long, and are caniculate. Immature leaves are occasionally toothed and hairy [6].

The pods are chewed with salt to treat coughs and are used in treatment of ulcers, leprosy, skin eruptions and venereal diseases, while the stem bark decoction or infusion is used to cure bronchitis, pneumonia, cough, rheumatic arthritis and dysentery [7]. The roots and leaves have been found useful in treating venereal diseases, respiratory ailments, gastritis [7]. Analgesic and anti-inflammatory activities of stem bark [8], as well as the anthelmintic activity of ethanol leave extract has been reported [9]. Other pharmacologic activities such as, antibacterial, antidiarrhoeal and antiplasmodial activity of lipophilic root bark extract have also been reported [10-12]. Parts of the plant often used for ethnomedicinal purpose are leaves, stem bark and root bark.

Numerous scientific studies which unveil the therapeutic potentials of the plant extract or isolated active phytochemical compounds such as tannins, saponins, flavonoids, glycosides, sterols, terpenoids, coumarins, naphthaquinones and anthraquinones which account for the medicinal value of the plant have been elucidated. But the isolation and characterization of phytochemical constituents and the mechanisms by which it exerts some of its pharmacological and toxicological activity have only been partly investigated. Thus, this study is a thorough review of phytochemical, pharmacological and toxicological studies of *S. kunthianum* aimed at providing information available in scientific literatures thereby revealing opportunities for further research work required for complete assessment of the therapeutic benefits of the plant.

2. PHYTOCHEMICALS OF *S. kunthianum*

Phytochemical analysis of the plant extracts of *S. kunthianum* was done using standard tests; Wagner test for alkaloids, foam test for saponins, ferric chloride, gelatin and lead acetate tests for

the presence of phenolic compounds and flavonoids. Data from phytochemical studies of extracts of *S. kunthianum* verifies the presence of tannins, saponins, flavoniods, terpenoids, polyphenols, higher fatty acids, coumarins, sterols, naphthaquinones, anthraquinone and glycosides in the plant [10,11,13-15]. Three phytochemicals of utmost interest in this species are glycosides, flavonoids and quinones.

2.1 Glycosides of *S. kunthianum*

There is a wide distribution of iridoid ester glycosides and recognized as one of the important markers in plants belonging to Bignoniaceae family [16]. These glycosides have been associated with antimicrobial activity thereby justifying its use as antiseptic in traditional medicine [17]. Iridoid glycosides isolated from the stem bark extracts of the plant were 6-O-trans-p-coumaroyl-decinnamoylglobularimin (stereospermiside; 1), (3,4-dihydroxyphenyl)-ethyl-O-α-rhamnopyranosyl-3′,4′-dihydroxycinnamoyl-β-D glucopyranoside (stereospermin; 2), 1,6-di-O-cinnamoyl-β-glucopyranoside {stereostin; 3} [13] and phenylpropanoid glycosides. The chemical structures are shown in Fig. 1.

2.2 Flavonoids of *S. kunthianum*

Flavonoids are partly responsible for the anti-diarrheal activity of *S. kunthianum* [17,12]. The preliminary phytochemical screening of the petroleum extracts revealed that the antidysenteric and antidiarrheal properties of medicinal plants were due to tannins, alkaloids, saponins, flavonoids, steroids, terpenoids and reducing sugars [11,15]. Flavonoids that have been isolated and characterized from stem bark and leave extracts of *S. kunthianum* by MS, UV and NMR spectra are compound 4; quercitin, 5; luteolin, 6; rutin, 7; 3,7,4′-trihydroxy-3′- (8′-acetoxy-7′-methyloctyl)-5,6-dimethoxyflavone, 8; isoquercetin and 9; kaemferol (Fig. 2) [18,14,12,19]. An example of flavonoid isolated from *S. kunthianum* with antidarrhoeal activity is dimethoxyflavone [12].

2.3 Sterols of *S. kunthianum*

In a review [20] reported that compound 10 (β-sitosterol) shown in Fig. 3 and β-sitosterol glucoside exhibited good pharmacologic activity in hypercholesteremia, wound healing, inflammation, helminthiasis, management of pain, diabetes, as an antioxidant and in certain types of cancers. Petroleum ether extract of *S. kunthianum* containing sterols subjected to thin layer chromatography, using normal phase silica gel as stationary phase and petroleum ether: chloroform, hexane: ethyl acetate or chloroform: methanol as mobile phase, the chromatograms show identical zones for steroidal nucleus with reagents. Structural elucidation carried out by various spectral data from 1H- and 13C-NMR, IR and Mass spectroscopy confirmed the presence of two phytosterols; β-sitosterol and β-sitosterol glucoside [13].

2.4 Quinones of *S. kunthianum*

Five naphthoquinones; pinnatal, sterekunthals A, sterekunthal B, pyrankunthone A, pyrankunthone B and one anthraquinone; anthrakunthone were isolated from lipophilic root bark extract of *S. kunthianum* (Table 1) were reported to exhibit antiplasmodial activity [10].

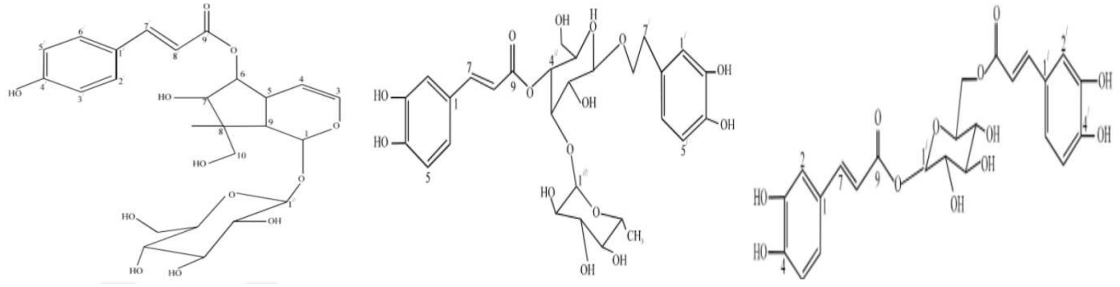

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Fig. 1. Chemical structures of *S. kunthianum* glycosides

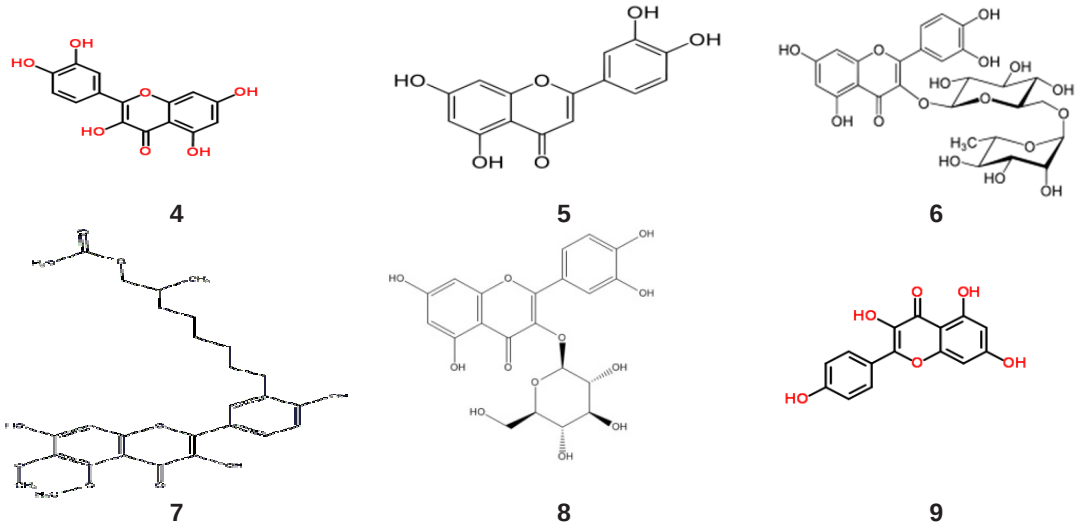

Fig. 2. Chemical structures of flavonoids of *S. kunthianum*

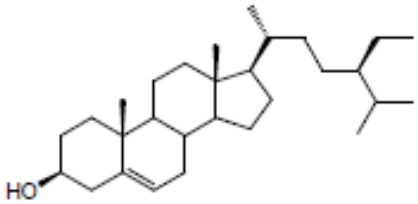

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Fig. 3. Chemical structure of sterol *S. kunthianum*

Table 1. Phytochemical profile of *S. kunthianum*

Plant part	Type of extract	Phytochemical	Reference
Root bark	Petroleum ether	Naphthoquinone (sterekunthals A, sterekunthal B, pyrankunthones A, pyrankunthones B, pinnatal) Anthraquinone (anthrakunthone)	[10,17,22]
Stem bark, leave	Methanol extract	Glycoside (stereospermiside, stereospermin and stereostin) Glycosides of ferulic acid	[13,22,18,21]
Stem bark, leave	Aqueous-acetone	Flavonoids (rutin, isoquercitin, quercitin and luteolin) Kaepferol Dimethoxyflavone	[22,18,14,21]
	Aqueous-acetone	Coumarin (sinapic *p*- coumaric acid)	[11,18,21]
Leave	Petroleum ether, methanol, aqueous	Phytosterol (β-sitosterol, β-sitosterol glucoside)	[11,13,18,21,20]

Ground root bark of *S. kunthianum* was extracted with petrol ether–ethylacetate 1:1 each at room temperature. The solvent was evaporated under reduced pressure at 40°C and the residue subjected to column chromatography over silica gel. It was eluted with increasingly polar mixtures of cyclohexane–ethylacetate and methanol. Eluents of 30% ethylacetate in cyclohexane on further fractionation using reversed-phase HPLC (methanol–H_2O 45:55 to 80:20) gave various weights of fractions whose structures (Fig. 4) were elucidated by comprehensive analysis of

their 1D and 2D NMR data as compound 13 (sterekunthal B), 14 (pyranokunthone A) and 15 (pyranokunthone B). Further purification yielded compound 11 (pinnatal), 12 (sterekunthal A) and 16 (anthrakunthone) [10].

3. PHARMACOLOGICAL PROFILE OF *S. kunthianum*

Scientific investigation of ethnomedicinal claims of *S. kunthianum* have been carried out pharmacologically. Some of the pharmacologic parameters investigated using crude extracts or isolated compounds were antibacterial, anti-inflammatory, analgesic, antiplasmodial, antdiarrhoeal, antconvulsant and antioxidant activities, Table 2.

3.1 Antibacterial Activity

Antibacterial activity of *S. kunthianum* was evaluated using ethanol, ethyl-acetate and petroleum ether of leaves and stem bark extracts by well diffusion method against *Staphylococcus. aureus, E. coli, Salmonella typhi, Klebsiela spp*, and *Aeromonas hydrophila* [11,15]. Results emerging from the study show that lipophilic leaf extracts of *S. kunthianum* exhibited significant antibacterial activity against tested organisms [11]. The zones of inhibition of bacterial growth of the extract at 30 mg/ml were *Staphylococcus aureus* 35 mm, *E. coli* 23 mm, *Salmonella typhi* 25 mm, *Klebsiela spp* 28 mm and *Aeromonas hydrophila* 28 mm. However, *Pseudomonas aeruginosa* was resistant to the extract. The mechanism by which *S. kunthianum* exert antibacterial activity is unknown. More definitive comparative study and resistance profile is required to ascertain the efficacy of the extracts and isolated compounds of *S. kunthianum* as antibacterial agent before introduction to clinical setting.

3.2 Anti-inflammatory Activity

The anti-inflammatory activity of aqueous extract of stem bark of *S. kunthianum* was investigated by [23] in rats using Carrageenan-induced paw oedema, leucocytes migration and granuloma air pouch test at 3 h post-treatment showed pronounced effect of the extract at a dose of 400 mg/kg b. wt. and comparable to indomethacin at 10 mg/kg b. wt. Treatment with extract (400 mg/kg b. wt.) or indomethacin (10 mg/kg b. wt.) prior to Carrageenan induced paw oedema reduced peritoneal exudates volume by 24.93% and 26.88% of control respectively [23].

Carrageenan-induced oedema is a model of acute inflammation in the study of non-steroidal anti-inflammatory drugs and suitable for evaluating the anti-oedematous effects of natural products [24,25]. The model is believed to be biphasic; phase one involves the release of inflammatory mediators such as serotonin and histamine while phase two is associated with prostaglandin release mediated by kinin. The anti-inflammatory activity of *S. kunthianum* is probably due to the inhibition of prostaglandin synthesis and cyclooxygenase products [23,22]. This makes *S. kunthianum* a target for search for potential anti-inflammatory drug to add to existing ones.

The *in vivo* anti-inflammatory activities of β-sitosterol and β-sitosterol glucoside which are phytosterols of *S. kunthianum* have been reported [20]. [26] (2006) reported the *in vivo* effect of β-sitosterol in a model of delayed-type hypersensitivity in which they reveal the cell-mediated modulation of oedema via a mechanism other than the arachidonic acid and leukocyte inhibitory pathways.

3.3 Analgesic Activity

Thermal stimulus (hot plate test), mechanical stimulus (tail flick test) and chemically induced tissue damage (acetic acid-induced writhing and formalin pain test) in mice/rats were employed to evaluate analgesic activity of aqueous extract of *S. kunthianum*. The aqueous extract (100, 200 or 400 mg/kg b. wt.) produced a significant dose-dependent increase in pain threshold, increased tail flick latency in rats, inhibition of abdominal writhes in mice and inhibited both phases of formalin pain test in mice with more effect on the first phase [8,22]. The analgesic effect of *S. kunthianum* is typical of central and peripheral analgesic acting agents. Perhaps, this suggests that aqueous extract of *S. kunthianum* acts via similar mechanism and may find use as analgesic agent.

3.4 Antiplasmodial Activity

Evaluation of the antiplasmodial activity of petroleum ether fraction of root extract of *S. kunthianum in vitro* against two strains of *P. falciparum* carried out by [10] using the method described by [27], (1979). Isolated quinones from *S. kunthianum* showed different degrees of antiplasmodial activity against chloroquine resistant strain of *P. falciparum* and chloroquine sensitive strain of *P. falciparum* with sterekunthal

A being the most active against both strains [10]. Mean IC_{50} values obtained for the fractions were 5.6±0.6 µg/ml and 3.6±0.96 µg/ml pinnatal 1.3±0.1 µg/ml and 0.4±0.1 µg/ml sterekunthal A, 23.3±4.2 µg/ml and 15.2±1.7 µg/ml sterekunthal B, 14.7±0.25 µg/ml and 14.7±05.3 µg/ml anthrakumthone, 11.7±4.0 µg/ml and > 25.0 µg/ml pyranokunthal A, 8.9±1.2 µg/ml and 7.8±1.3 µg/ml pyranokunthone B against chloroquine resistant and chloroquine sensitive *P. falciparum* respectively [10]. The result is indicative of a probable "lead" to a novel and potent antimalarial thus making available to clinicians an additional "armour" to combat malaria a disease with high mortality rate among under five and pregnant women in the tropics.

3.5 Antidiarrhoeal/Antispasmolytic Activity

The antidiarrhoeal effect of 3,7,4′-trihydroxy-3′-(8′-acetoxy-7′-methyloctyl)-5,6-dimethoxyflavone a flavonoid isolated from the stem bark aqueous extract of *S. kunthianum* was investigated using rodent models of castor oil-induced gastrointestinal motility and castor oil-induced diarrhoea. The result indicate that pre-treatment with dimethoxyflavone (25 mg/kg b. wt. or 50 mg/kg b. wt.) caused a delay in the onset of diarrhoea, reduction in the frequency and weight of wet stools compared to distilled water used as negative control [12].

The antispasmolytic effect at doses of 25 mg/kg b. wt. or 50 mg/kg b. wt. was higher than 10 mg/kg b. wt. of morphine but with no effect on castor oil-induced intestinal fluid accumulation in rats and on normal gastrointestinal transit in mice [12]. Although flavonoids are known for their ability to inhibit intestinal motility and hydro-electrolytic secretions induced by prostaglandins E_2 [28,12], the result from this study suggest that the antidiarrhoeal activity of *S. kunthianum* is due to antispasmolytic effect rather than inhibition of hydro-electrolytic secretion [12]. Investigation of the cellular mechanism by which dimethoxyflavone exerts antispasmolytic activity is necessary to know if it will be most suitable compared to clinically used antispasmolytic agents with pronounced undesirable antimuscarinic side effects.

3.6 Anticonvulsant Activity

The anticonvulsant activity of *S. kunthianum* was reported by [29]. In the study aqueous extract of stem bark of *S. kunthianum* at the dose of 100 to 400 mg/kg b. wt. demonstrated anticonvulsant activity in rodents [29]. This result validates the use of the aqueous stem bark extract by traditional medicine dealers for the treatment of childhood convulsions.

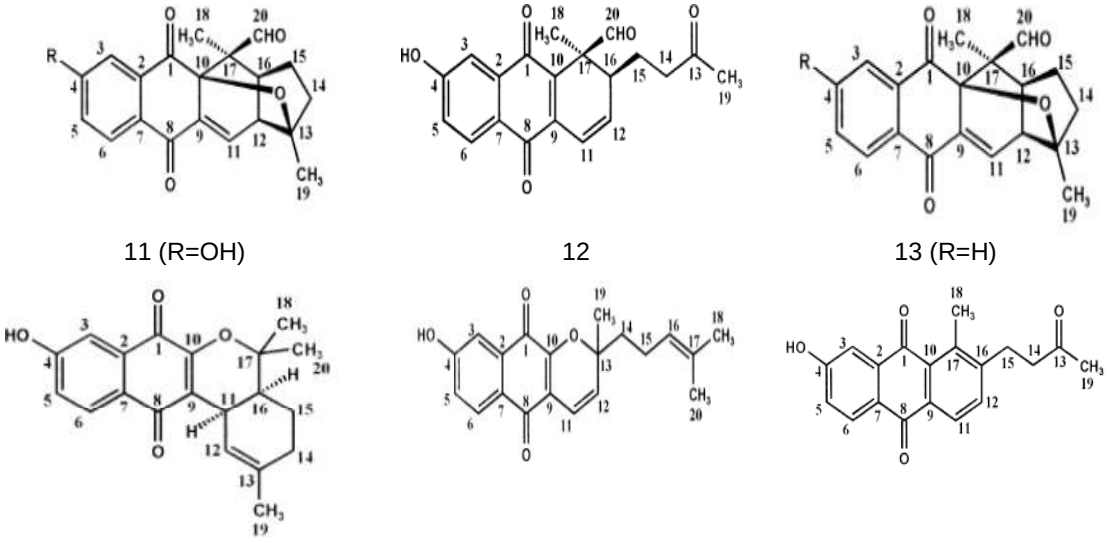
3.7 Antioxidant Activity

Phytocompounds like flavonoids and phenolic acid commonly found in plants have been shown to possess antioxidant activities and multiple biological effects by different mechanisms [30,31,21,19]. Antioxidants with free radical scavenging activities of extracts of *S. kunthianum* may have great relevance in the prevention and therapeutics of several diseases in which free radicals are implicated. The antioxidant activity of three (aqueous, methanol and aqueous-acetone) extracts of *S. kunthianum* was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing/antioxidant powder (FRAP) and 2,2′-azinobis(3-ethylbenzoline-6-sulphonate (ABTS) methods.

Results from the study carried out by [18] (2011) showed that the aqueous acetone extract had the best antioxidant and xanthine oxidase inhibitory activities. The antioxidant and xanthine oxidase inhibitory activities may be due to the mixture of flavonoids and polyphenols present in the aqueous acetone extract as quantified using high-performance liquid chromatography-mass spectrometry (HPLC-MS) [18,21].

4. TOXICITY PROFILE OF *Stereospermum kunthianum*

Acute and sub-acute toxicity studies of the aqueous extract of *S. kunthianum* stem bark show that the aqueous extract has a wide safety margin as no adverse effect was observed in experimental animals when used at doses up to 1000 mg/kg b. wt. as reported by [33]. Marginal enlargement of organs such as liver, kidney, heart and spleen with no histological changes was observed in rats treated with aqueous extract of *S. kunthianum*. Parameters such as liver enzymes and serum biochemical components evaluated; alanine aminotransferase (ALT), alkaline phosphatase (AST), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides showed no significant deviation from the normal range [33]. *S. kunthianum* extract could therefore be used for long term treatment or management of acute or chronic conditions which it is pharmacologically indicated.



11 (R=OH) 12 13 (R=H)

14 15 16

Fig. 4. Chemical structures of quinones of *S. kunthianum*

Table 2. Pharmacological profile of *Stereospermum kunthianum*

Plant part	Type of extract	Pharmacologic activity	Reference
Leave	Petroleum ether extract, methanol extract, hexane extract	Antibacterial	[11,22,32,15]
Stem bark	Aqueous extract Petroleum ether extract	Anti-inflammatory	[29,22,20]
Stem bark	Aqueous extract	Analgesic	[8,22]
Leave	Petroleum ether extract	Antiplasmodial	[10,22]
Stem bark	Aqueous extract	Antidiarrhoael	[12,22]
Stem bark	Aqueous extract	Anticonvulsant	[29]
	Aqueous acetone extract Petroleum ether extract	Antioxidant	[18,19,20]

The cytoxicity proliferation assay of the isolated quinones from petroleum ether root extract showed that pinnatal, sterekunthal A, sterekunthal B, anthrakunthone exhibited marked non selective cytotoxicity against human endothelial (ECV-304) cell [34]. Mean IC_{50} values obtained was 2.2±0.3 µg/ml pinnatal, 0.9±0.02 µg/ml sterekunthal A, 16±1.0 µg/ml sterekunthal B, 7.9±0.5 µg/ml anthrakunthone, while pyranokunthone A >200.0 µg/ml and pyranokunthone B 88.2±4.6 µg/ml display much less cytotoxicity and more selective against *P. falciparum* [34].

5. CONCLUSION

S. kunthianum is a medicinal plant widely distributed and used in the Sudano-Guinea savannah regions of Africa and Asia. This review is an appraisal of the phytochemical, pharmacological and toxicological profile of the plant species which revealed the presence of tannins, saponins, glycosides, sterols and various phenolic compounds. Isolation and characterization of chemical compounds from the various part of the plant revealed that iridoid glycosides, flavonoids and quinones are predominant phytochemicals present in the plant. Isolated compounds of coumarins and sterols are not uncommon. Extracts and pure compounds from *S. kunthianum* have been shown to exhibit numerous pharmacological activities. The therapeutic potentials of various fractions and isolated compounds of *S. kunthianum* as validated in the studies so reviewed provides a platform for further investigation on the

pharmaceutical formulation studies, pharmacodynamic studies and pharmacokinetics studies of each of the fractions and compounds before use in clinical setting. Although this review is limited to phytochemical, pharmacological and toxicological profile of *S. kunthianum*, more studies may be required for inclusion of possible candidates to serve as alternative drugs or part of combination therapy and as such may enhance therapeutic efficacy, decrease toxicity or mitigate drug resistance development in the treatment/management of human and animal diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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