

Advances on Ethnomedicinal Uses, Phytochemistry, and Pharmacology of *Spathodea campanulata* P. Beauv

Pone Kamdem Boniface*

Department of Organic Chemistry, Institute of Chemistry, University of Rio de Janeiro, Avenida Athos da Silveira Ramos, Rio de Janeiro (RJ), Brazil

*Corresponding Author: Pone Kamdem Boniface, Department of Organic Chemistry, Institute of Chemistry, University of Rio de Janeiro, Avenida Athos da Silveira Ramos, Rio de Janeiro (RJ), Brazil.

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Abstract

Spathodea campanulata (*S. campanulata*) is a plant mostly found in the tropics and used for the traditional treatment of infectious and metabolic disorders. Scientific studies during the past few decades signify the prospective use of this plant for restorative purpose. The current work encompasses published data on the phytochemical composition of *S. campanulata* in addition to its ethnomedicinal and pharmacological potential. The literature available in various recognized databases including Google Scholar, Elsevier, PubMed, SciFinder, Scopus, Springer and Web of Science, as well as from books, reports and other relevant websites (www.theplantlist.org), are surveyed, analysed and included in this review. The literature related to chemical constituents, pharmacological activities and toxicology dates from 1953 to 2017. The phytochemical information indicates the presence of several compounds including terpenoids, sterols, cerebroside, flavonoids, phenolic acids and iridoids in *S. campanulata*. The identified compounds exhibit antioxidant, anti-inflammatory, antibacterial, antifungal and anti-convulsant properties. The present work infers the scope of future studies directed towards anti-infectious conditions.

Keywords: *Spathodea campanulata*; Medicinal Uses; Phytochemistry; Ethnobotany; Toxicology

Introduction

S. campanulata is an African plant which is used in tropical and subtropical areas for ornamental purposes as well as for the treatment of a range of diseases [1]. *S. campanulata* grows commonly in several countries including Ghana, Nigeria, Uganda, Gabon, Cameroon and Senegal. The decoction from the leaves and stem bark of *S. campanulata* is traditionally used to cure some types of wounds including skin rashes, haemorrhoids and stomach ulcer in Ghana [2]. Other ethnomedicinal uses of *S. campanulata* in Ghana include the treatment of malaria (leaves and stem bark) [3]; dyspepsia (stem bark and leaves); arthritis and fracture (leaves, root bark and fruit); toothache and stomach ache (stem bark) [4]. The decoction of *S. campanulata* bark is prepared by boiling until the water is half reduced, and is taken orally thrice a day for five days by inhabitants of Uganda for the treatment of malaria [5]. Likewise, Nigerian tribes use the bark of this plant for malaria treatment [6]. Moreover, *S. campanulata* flowers and bark are used to treat fever, convulsion, bacterial infections, HIV, poor blood circulation, gastro-intestinal diseases, respiratory ailments, genital-urinary system disorders, filaria, gonorrhoea, epilepsy and mental disorders [7].

S. campanulata was reported for its wound healing [8-11]; antimalarial [12-15]; molluscicidal [16,17]; antibacterial [8,11,18]; anti-inflammatory [19]; antioxidant [9,20]; hypoglycemic, anticomplement as well as anti-HIV [21,22] activities.

Along with its growing reputation, the chemical constituents of *S. campanulata* have been extensively studied. Terpenoids, flavonoids, sterols, phenolics and iridoid glucosides as the main constituents were isolated and identified. Among them, spathoside, *p*-hydroxybenzoic acid, verminoside and 1-*O*-(*E*)-caffeoyl- β -gentiobiose are some examples that have been proven to possess pharmacological activities [20,23].

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Despite the scientific contribution highlighted in the literature towards *S. campanulata*, no comprehensive review is reported so far on the chemistry, pharmacology and medicinal use of *S. campanulata* in the treatment of multifactorial diseases.

The present study summarizes the comprehensive information pertaining to the ethnomedicinal uses, phytochemistry and pharmacology of *S. campanulata* from 1953 till 2017, and discusses the possible trend and scope for future research of *S. campanulata*.

Methodology

The data on *S. campanulata* were retrieved through an internet search in SciFinder, Elsevier, Scopus, Springer, Web of Science, Pubmed, Wiley, Science direct, Scielo, PROTA and Google scholar. The search terms used for this systematic review include *S. campanulata*, pharmacology, traditional uses, phytochemistry and toxicity. 'The plant List' (www.theplantlist.org) was used to validate the scientific names of *S. campanulata*. Besides, dissertations, books and reports from classic literature, articles published in peer reviewed journals as well as unpublished materials related to *S. campanulata* were also examined and searched. Reference lists of all the included reviews and other archives of the located publications were hand-searched for further relevant articles. No limitations were set for languages.

Scientific classification

S. campanulata belongs to the kingdom Plantae and is unranked successively as Angiosperm, Eudicots and Asterids. *S. campanulata* belongs to Lamiales order while its family and tribe are termed as Bignoniaceae and Tocomeae respectively. The genus of this plant is *Spathodea* whereas the species is termed as *S. campanulata*. The binomial name is *Spathodea campanulata* P. Beauv [24].

Botanical description and distribution

S. campanulata, which is native of West tropical Africa, develops between 7-25 meters tall [25]. It is extensively planted throughout the tropics and possess campanulated flowers [26]. From their original region, *S. campanulata* flowers are pollinated by birds [27] and by lemurs as well [28]; but in Panama, bats pollinate them [29]. The growth of *S. campanulata* is rapid in full sun especially on soil with good drainage and fertility. The plant propagation is by seeds, root suckers or softwood cuttings [30].

Phytochemical constituents of *S. campanulata*

Alkane and alcohols

GC-MS analysis of *S. campanulata* allowed the identification of octacosanol and triacontanol [31] on one hand and butane 1,1-diethoxy-3-methylene as well as *n*-hexadecanoic acid on the other hands [32]. Some other volatile compounds including alkanes and alkenes, acids, terpenoids, esters and lactones were also reported from buds and flowers of *S. campanulata* [33].

Anthocyanins

Studies of Sharma and Seshadri [34] led to the identification of some anthocyanins including diglucosides and 3,5-dimonoside from *S. campanulata* flowers. Likewise, the presence of anthocyanins in *S. campanulata* flowers was identified by Banerjee and Bratati [35].

Cerebroside, terpenoids and sterols

Successive extraction of the stem bark of *S. campanulata* with chloroform followed by the fractionation of the residue obtained from column chromatography led to the isolation of a mixture of sterols and 4 triterpenoids. The triterpenoids were termed as 3 β -acetoxyoleanolic acid (1), siaresinolic acid (2), 3 β -acetoxy-12-hydroxyoleanan-28,13-olide (3), and oleanolic acid (4) [36,37] (Figure 1).

Ngouela, *et al.* [38] isolated spathodic acid (5) and sitosterol-3-*O*- β -D-glucopyranoside (6) from *S. campanulata* stem bark (Figure 1). A dihydroxylated sterol named as spathodol (8) was also isolated from the leaves of *S. campanulata* along with some triterpenoids including 3 β -acetoxyoleanolic acid, siaresinolic acid, 3 β -acetoxy-12-hydroxyoleanan-28,13-olide, oleanolic acid and β -sitosterol-3-*O*- β -D-glucopyranoside [37]. However, the unsaponifiable part from ethanol extract was mostly rich in hydrocarbons from (C₁₄-C₂₈), cholesterol

(7), campesterol (9), stigmasterol (10) and α -amyrin (11) [39] (Figure 1). Furthermore, the bioassay guided fractionation of *S. campanulata* yielded β -sitosterol, *n*-alkanes, linear aliphatic alcohols, (12) as well as their esters, β -sitosterol-3-*O*- β -D-glucopyranoside, oleanolic acid, pomolic acid (13), *p*-hydroxybenzoic acid (14) and some phenylethanol esters [23]. In this study, a cerebroside named as spathoside [23] (15) was also isolated (Figure 2).

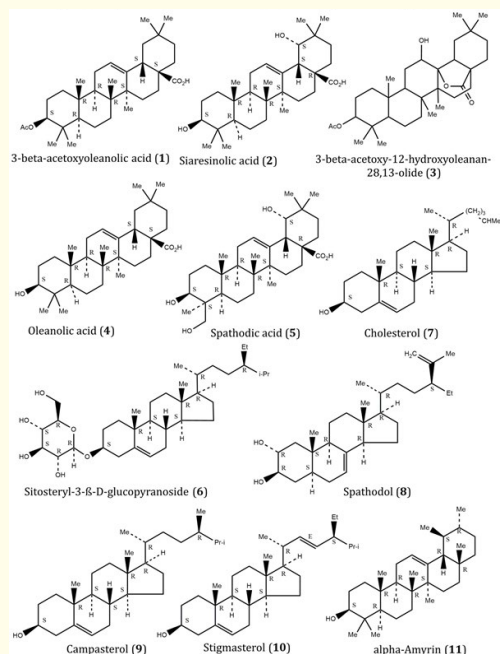


Figure 1: Terpenoids and sterols isolated so far from *Spathodea. campanulata*. 3-beta-Acetoxyoleanolic acid (1); Siarsinolic acid (2); 3-beta-acetoxy-12 hydroxyoleanan-28,13-olide (3); Oleanolic acid (4); Spathodic acid (5); Sitosteryl-3-beta-D-glucopyranoside (6); Cholesterol (7); Spathodol (8), Campesterol (9), Stigmasterol (10) and alpha-Amyrin (11) previously isolated from *S. campanulata*.

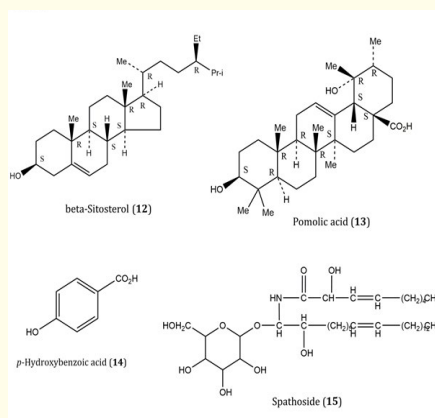


Figure 2: Sterols and cerebroside derived from *S. campanulata* in previous phytochemical studies. Beta-Sitosterol (12), Pomolic acid (13), *p*-Hydroxybenzoic acid (14) and Spathoside (15) isolated so far from *S. campanulata*.

Flavonoids, phenolics and iridoids of *S. campanulata*

Reviewing the current literature, *S. campanulata* revealed the presence of flavonoids, phenolics and iridoids. A flavonoid namely quercetin (16) and a phenolic acid termed as caffeic acid (17) were isolated from *S. campanulata* in 1972 and 1973 respectively [40,41].

Further studies including, fractionation of the alcoholic extract of *S. campanulata* aerial parts through column afforded chloroform/EtOAc and EtOAc/MeOH fractions. The purification of chloroform/EtOAc fraction afforded phenolic acids including caffeic acid and ferulic acid (18) while that of EtOAc/MeOH fraction yielded 3 flavonoids including quercetin 3-methyl ether (19), 8-methoxy kaempferol 3-*O*-glucoside (20) and kaempferol 3-*O*-glucoside (21) [39] (Figure 3). Likewise, *S. campanulata* was reported to contain free phenols as well syringyl group compounds (22) [42] (Figure 3). The following sets of compounds including phenolic acids [gallic (23), protocatechuic (24), chlorogenic (25), *p*-hydroxybenzoic, caffeic, *p*-coumaric (26) and ferulic acids] and flavonoids [quercetin, quercetin 3- β -*O*-D-glucoside (27) and quercetin 7-*O*- β -D-glucoside (28)] were isolated from *S. campanulata* by El Hela [43] (Figure 3). Moreover, the fractionation and purification of methanol extract from *S. campanulata* leaves afforded 6 compounds identified as: 1-*O*-caffeoyl- β -D-glucopyranoside (29), kaempferol 3-*O*-(2-*O*- β -D-xylopyranosyl)- β -D-galactopyranoside (30), kaempferol 3-*O*-(6-*O*- α -L-rhamnopyranosyl)- β -D-galactopyranoside (31), acteoside (32), kaempferol 3-*O*- β -D-(6''-*O*- α -L rhamnopyranosyl)- β -D-glucopyranoside (33) (Figure 3), and quercetin 3-*O*-(2-*O*- β -D-xylopyranosyl)- β -D-galactopyranoside (34) [44].

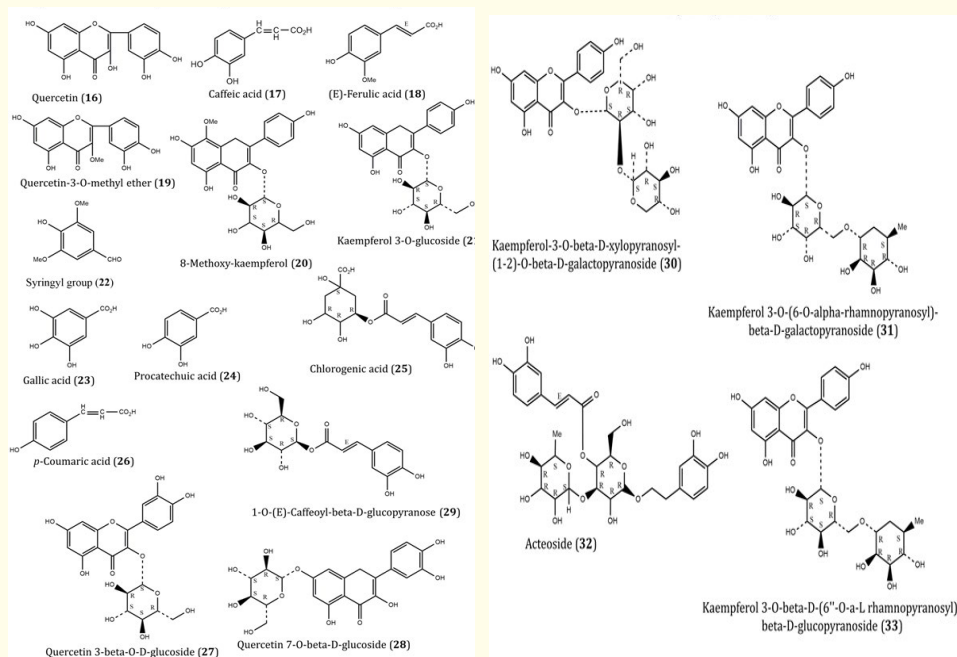


Figure 3: Flavonoids and phenolic compounds isolated so far from *S. campanulata*. Quercetin (16), Caffeic acid (17), (*E*-Ferulic acid (18), Quercetin-3-*O*-methyl ether (19), 8-Methoxykaempferol (20), Kaempferol 3-*O*-glucoside (21), Syringyl group (22), Gallic acid (23), Procatechuic acid (24), Chlorogenic acid (25), *p*-Coumaric acid (26), Quercetin 3- β -*O*-D-glucoside (27), Quercetin 7- β -*O*-D-glucoside (28), 1-*O*-(*E*)-Caffeoyl- β -D-glucopyranose (29), Kaempferol-3-*O*- β -D-xylopyranosyl-(1-2)-*O*- β -D-galactopyranoside (30), Kaempferol 3-*O*-(6-*O*- α -rhamnopyranosyl)- β -D-galactopyranoside (31), Acteoside (32), Kaempferol 3-*O*- β -D-(6''-*O*- α -L rhamnopyranosyl)- β -D-glucopyranoside (33) isolated in previous phytochemical studies from *S. campanulata*.

In addition, seven iridoids were isolated from *S. campanulata* leaves. Among them, three were characterised as 6-*O*-trans-caffeoyl-decinnamoyl globularimin, 6-*O*-trans-caffeoyl-asystasioside E and 6-*O*-trans-caffeoyl-5,7-bisdeoxycynanchoside and were provisionally named spatheosides A (35), B (36) and C (37) respectively [45]. The four others were reported as 6'-*O*-trans-caffeoyl-loganic acid (38) [46], verminoside (39), catalpol (40) and ajugol (41) [45] (Figure 4). In another study, some iridoid glucosides were also reported from various parts of *S. campanulata*. Specioside (42) was isolated from the flowers whereas verminoside was isolated from leaf, stem bark and flowers. Meanwhile, kampeferol diglucoside and (*E*)-phytol (43) (leaf) (Figure 4), caffeic acid (leaf and fruits) and ajugol (stem bark and fruits) were also identified [46].

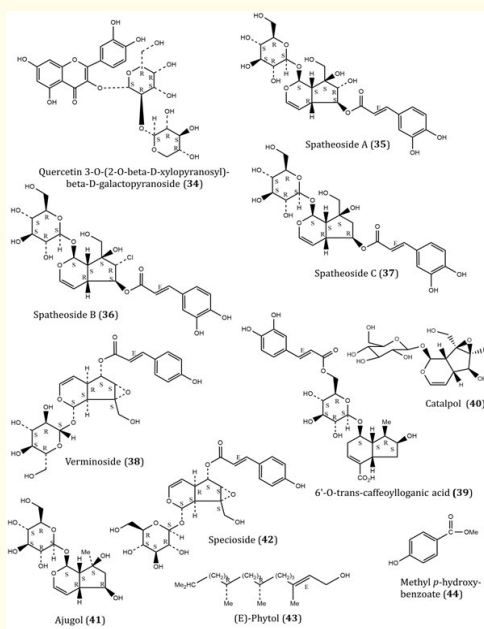


Figure 4: Iridoids glucosides and some other phenolic compounds isolated so far from *S. campanulata*. Quercetin 3-*O*-(2-*O*-beta-*D*-xylopyranosyl)-beta-*D*-galactopyranoside (34), Spatheoside A (35), Spatheoside B (36) and Spatheoside C (37), Verminoside (38), 6'-*O*-trans-caffeoylloganic acid (39), Catalpol (40), Ajugol (41), Specioside (42), (*E*)-Phytol (43) and Methyl *p*-hydroxybenzoate (44) isolated from *S. campanulata*.

Prior to the studies of Elusiyani, *et al.* [47], the presence of ajugol in *S. campanulata* root peels was identified whilst two phenolic derivatives termed as *p*-hydroxybenzoic acid and methyl *p*-hydroxybenzoate (44) were isolated [48].

Pharmacological studies

Antimalarial activity

The antimalarial activity of *S. campanulata* stem bark extract on *P. berghei* in mice was reported [12]. *S. campanulata* in combination with *Conyza sumatrensis* decreased the percentage of parasitaemia in *P. berghei* infected mice [15].

Molluscicidal effects

Aqueous (macerated and boiled), hexane and ethanol extracts from *S. campanulata* leaves were tested for their molluscicidal activity against *Biomphalaria glabrata* at 1, 10, 100 and 1000 ppm. The macerated extract showed 100% of inhibition at 1000 ppm. At 100 ppm,

hexane and ethanol extracts displayed 60 and 100% inhibition respectively. The molluscidal activity was found significant [16]. Likewise, Shams., *et al.* [49] reported the molluscicidal activity of the extract from *S. campanulata* leaves.

Anti HIV, anti-complement and hypoglycemic activities

The decoction of the stem bark from *S. campanulata* and the fraction thereof were tested for their anti-HIV, anti-complement and hypoglycemic effects. The extract, as well as the fractions exhibited significant hypoglycemic, anti-HIV and anti-complement activities [22].

Insecticidal properties

Trigo and Dos Santos [25] investigated the insecticidal activity of *S. campanulata* flowers in different varieties of insects that inhabited five trees located at Ribeirão Preto region, Sao Paulo, Brazil. In this study, *S. campanulata* flowers significantly induced the dead of insects including 97.0% of Meliponinae mostly *Scaptotrigona postica*; 1.7% of Diptera and Vespidae, 1.0% of Formicidae and 0.3% of Orthoptera [25]. In another investigation, *S. campanulata* was effective against immature stages of *Anopheles albimanus* [50] and some species of bees including *Melipona fasciculata* and *Melipona seminigra* [1].

Wound healing activity

Wound healing involves a variety of processes such as inflammation, cell proliferation and contraction of the collagen lattice formed [51]. Infected wounds are prone to infection and heal less rapidly but often result in the formation of unpleasant exudates and toxins that eliminates the regenerating cells [9].

Ofori-Kwakye., *et al.* [52] investigated the wound healing activity of *S. campanulata* stem bark in Sprague Dawley rats. 28 days treatment of wounded rats with cream formulation containing 20% w/w of methanol extract from *S. campanulata* induced a complete wound contraction in treated rats [52]. In another study, the methanol extract ointment from *S. campanulata* stem bark decreased the score damage at the burn site in rat model [10]. The use of *S. campanulata* in the treatment of wound healing was also confirmed through an *in vitro* study [53].

Antimicrobial and antifungal properties

Methanol and ethanol extracts from *S. campanulata* exhibited significant antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* [54]. Likewise, *S. campanulata* extract exhibited antifungal activity against some trychophyton species with optimum IC₅₀ value of 1.39 mg/ml [11]. Adriana., *et al.* [48] studied the antifungal activity of ajugol, as well as two phenolic compounds including methyl *p*-hydroxybenzoate and *p*-hydroxybenzoic acid, isolated from *S. campanulata* roots against *Cladosporium herbarum*. Only the phenolic compounds were found active against this pathogen [48]. In another study, the aqueous extract of *S. campanulata* inhibited the microbial growth of eight important species of *Fusarium* [55]. In addition, spathoside and *p*-hydroxybenzoic acid, isolated from the stem bark of *S. campanulata* inhibited significantly the growth of both Gram positive and Gram negative bacteria [23].

Anticonvulsant activity

Ilodigwe., *et al.* [56] have carried out the anticonvulsant activity of ethanol leaf extract and urs-12-en-27 α , 30-dioic acid 3-*O*- α -L-rhamnopyranosyl-(1 \rightarrow 2)- α -L-arabinopyranoside isolated from this extract against pentylenetetrazole-, maximum electroshock- and picrotoxin-induced convulsion in mice. The extract and the compound abolished the seizures in treated mice [56].

Anti-inflammatory activity

Kulkarni., *et al.* [57] reported the *in vitro* anti-inflammatory activity of aqueous and methanol extracts from *S. campanulata* leaves [57], while Ilodigwe and Peter [58] described the *in vivo* anti-inflammatory activity of ethanol extract from *S. campanulata* leaves against acute inflammation induced by carrageenan in mice and rats [58]. More recently, two compounds namely 1-*O*-(*E*)-caffeoyl- β -gentiobiose and

(2S)-1,2-di-*O*-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-*O*-[α -D-galactopyranosyl-(1"→6')-*O*- β -D-galactopyranosyl] glycerol isolated from *S. campanulata* were reported to possess significant anti-inflammatory activity [19].

Antioxidant properties

The antioxidant activity of *S. campanulata* leaves, flowers, stem bark and the whole plant was described [9,59-61]. Extracts and compounds (caffeic acid, ferulic acid, kampferol 3-*O*-glucoside, quercetin 3-methyl ether and 8-methoxy kampferol 3-*O*-glucoside) from the aerial parts of *S. campanulata* were found to possess significant antioxidant activity [39]. Some other antioxidant principles from various parts of *S. campanulata* including verminoside (leaf, stem bark and flowers), specioside (flowers), kaempferol diglucoside (leaf) and caffeic acid (leaf and fruits) were also reported [47]. Likewise, Boniface, *et al.* [20] emphasized the antioxidant activity of two compounds namely verminoside and 1-*O*-(*E*)-caffeoyl- β -gentiobiose isolated from *S. campanulata* leaves.

Cardioprotective effects

Abubaker, *et al.* [62] reported the cardioprotective effects of ethanol extract of *S. campanulata* stem bark in Wistar albino rats.

Cytotoxic activity

Stem barks, roots and leaves of *S. campanulata* are used to treat cervical, bone, breast, colorectal and skin cancer in Kakamega County, Kenya [63]. In order to substantiate the ethnomedicinal use of *S. campanulata* for the treatment of cancer, Eid, *et al.* [33] reported the cytotoxic effects of volatiles from *S. campanulata* buds and expanded flowers against (MCF7) and (HCT116) cell lines.

Kuete, *et al.* [64] reported the cytotoxic effects of the methanol extracts of bark, leaves and roots of *S. campanulata* against leukemia CCRF-CEM cells. These extracts were found cytotoxic to CCRF-CEM cells with IC₅₀ values of 58.08; 63.29 and > 80 μ g/ml for methanol extracts of roots, barks and leaves, respectively.

Toxicological studies

Torres-Estrada, *et al.* [50] explored the toxicity of aqueous extract of *S. campanulata* leaves in *Anopheles albimanus*. In this study, the extract inhibited the growth of larvae and pupae of *Anopheles albimanus* with 99% mortality after 7 days. In another study, nectar and pollen from *S. campanulata* significantly affected the survival of two species of bees namely *Melipona fasciculata* and *Melipona seminigra* [1].

However, *S. campanulata* has been proven to be safe, with no evidence of any distinct toxicity or side effects in *in vivo* studies. For example, in acute and sub-chronic toxicity studies of ethanol extract from *S. campanulata* leaves in mice, no sign of toxicity was observed at the doses tested (100 - 250 mg/kg). The medium lethal dose (LD₅₀) was found to be higher than 250 mg/kg [65]. Moreover, acute and sub-chronic toxicities of *S. campanulata* were investigated at the dose range of 1000 - 5000 mg/kg and 750 - 3000 mg/kg, respectively. The estimated LD₅₀ of the extract was 4466.84 mg/kg. There was no mortality during the period of study though the animals showed some physical and biochemical changes. However, these changes showed recovery after 28 days post-treatment [66]. These studies showed that *S. campanulata* is safe up to 5000 mg/kg when taken orally at a single dose. Meanwhile, in-depth toxicological studies are expected for the prediction of the therapeutic index so as to ensure safe use of *S. campanulata*.

Discussion

From the available literature on the ethnomedicinal use of *S. campanulata*, it is likely that various parts of this plant are employed for the traditional treatment of many diseases.

Though several investigations have focused on the pharmacology of *S. campanulata*, there are some plant parts such as the fruits which have not yet been studied. Indeed, *S. campanulata* fruits are used traditionally to treat arthritis and to relieve fractures in Ghana. Thus, it is suggested to carry out further research on the pharmacological activity of fruits from *S. campanulata* in order to assess their ethnomedicinal use in the treatment of arthritis.

The literature survey reveals that *S. campanulata* is mostly rich in terpenoids, sterols, cerebroside, flavonoids, phenolic acids and iridoids. However, the connection between activity and specific compound is unclear. Therefore, more research is required to elucidate the relations between the isolated compounds and the therapeutic applications of *S. campanulata* in ethnomedicine.

Reports on the toxicity of *S. campanulata* are relatively few. At present, none of the research has indicated that *S. campanulata* has any side effects. Indeed, most of the reports are directed towards the adverse effects of crude extracts from *S. campanulata* rather than its constituents. Henceforth, it is suggested to investigate the toxicity profile of active constituents of *S. campanulata*. The possible side effects following long term oral administration of *S. campanulata* is not yet reported. It is therefore recommended to carry out chronic toxicity studies in order to support the safe use of *S. campanulata*.

Conclusion

From an ethnopharmacological point of view, the use of *S. campanulata* as a remedy has been extensively researched, and related information has been comprehensively compiled in this study. The medicinal properties of *S. campanulata* particularly its anti-inflammatory, antimalarial, wound healing, antiproliferative, anticonvulsant and oxidant activities, have been studied by using *in vitro* and *in vivo* models. Besides, the phytochemical study of this plant has led to the identification of several compounds that exhibited various pharmacological activities such as antioxidant, anti-inflammatory, antibacterial, antifungal and anti-convulsant. *S. campanulata* was found to be toxic in some insects such as *Anopheles albimanus* and some species of bees including *Melipona fasciculata* and *Melipona seminigra* inferring that *S. campanulata* possesses anti-insecticidal activity. However, *S. campanulata* was found to be safe *in vivo* as the plant did not induce any sign of toxicity or mortality up to 5000 mg/kg in rat model.

Although phytochemical and pharmacological studies on *S. campanulata* have received considerable interest, the following gaps are still noteworthy. First, regarding the chemical constituents contributed to therapeutic values, there is not enough evidence regarding purified molecules and their pharmacological activities. Therefore, further study is required to elucidate the bioactivity of the constituents from *S. campanulata*. Secondly, various pharmacological activities of the extracts and compounds were mainly conducted to test *in vitro* assays, and less carried out *in vivo* assays using laboratory animals. Thirdly, there are few reported data focusing on toxicity, side effects and clinical efficiency, and the results obtained may not be accurate and applicable to humans. More studies should undoubtedly have the priority to clearly dissect the molecular mechanism of the pharmacological effects of bioactive constituents from *S. campanulata*.

All in all, *S. campanulata* is a valuable herb that is worth additional attention because of its wide uses and extensive biological activities. Deep phytochemical and pharmacological investigation of *S. campanulata*, especially its mechanism of action, to illustrate its ethnomedicinal use will certainly be the focus of future research.

Conflict of Interest

The author declares no conflicts of interest.

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