Review

Strophantus (Apocynaceae): Composition and Biochemical Properties with a Focus on S. sarmentosus

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Review

Strophantus (Apocynaceae): Composition and Biochemical Properties with a Focus on *S. sarmentosus*

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Abstract: The genus *Strophantus* belongs to the Apocynaceae family of flowering plants which grows primarily in tropical Africa. The plants are widely used in traditional herbal medicine. *S. sarmentosus*, in particular, is used for the treatment of, e.g., joint pain and rheumatoid arthritis, wound infections, head lice, diarrhoea, snake bite, and eye conditions. Despite the widespread use, dedicated research characterizing bioactive plant components is scarce. Investigations focussed mainly on the cardenolides, because of their cardioactivity and historical use as cardiotonic. There are also studies concerning the antibacterial, antioxidant and anti-inflammatory activity of plant extracts. This review summarizes the present knowledge about the biochemical and analytical reserach on *Strophantus*, in general, and *S. sarmentosus*, in particular, and describes the current state-of-the-field based on the available sientific literature.

Keywords: ethnomedicine; cardiac glycoside; bioactivity

1. Introduction

Members of the Apocynaceae family of flowering plants can be found on all continents with moderate or warm climate. *Strophantus* grows primarily in tropical Africa with some species also native in Asia (for morphology and geographical distribution of all 38 species, see [1]). The genus *Strophantus* was described by deCandolle in 1802, but Linnaeus had already reported on *S. caudatus* in 1767 [1]. The plants have been used for thousands of years in traditional herbal medicine and, interestingly, also as an arrow poison [2,3]. Their ethnopharmacological significance extends to dermatological diseases and skin care [4], treatment of tuberculosis [5] and ulcers [6], anti-protozoal [7], antibacterial, antioxidant [8] and anti-inflammatory [9] activity, as well as hypoglycemic effects [10].

Medicinal plants contain a variety of substances with potentially useful activity including hydrocarbons, organic acids, polysaccharides, proteins and peptides, fatty acids and essential oils, alkaloids, tannins, saponins, glycosides, bitter substances and vitamins [11]. Apocynaceae, in particular, are a source of indoline and steroidal alkaloids, cardioactive and cyanogenetic glycosides, saponins, tannins, coumarins, phenolic acids, and triterpenoids (see review [12]; it includes, for *Strophantus, S. kombe*).

The cardiotoxins, which were isolated from *Strophantus* seeds and which were the main reason for the use of the plant extracts as a poison, gained increasing interest in Western medicine as an alternative to digitoxin, the cardiac glycoside from the foxglove, at the turn of the 19th century [13]. They were used in purified form in clinics to treat congestive heart failure and arrhythmias for many years [2]. Practitioners of alternative medicine still advertise strophantin for its cardiotonic effects [14].

The interest in *Strophantus* grew further, when, in the late 1940s, a precursor of corticosteroids was needed for the production of cortison and was found in the seeds of ***S. sarmentosus*** in the form of sarmentogenin (Figure 1) [15]. A difficulty at the time was the distinction of the seeds from different *Strophantus* species, not all of which contained sufficient amounts of the desired

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compounds, promping efforts for classification of commercial seeds [16]. For a review of commercially important African medical plants including *S. gratus*, see [17].

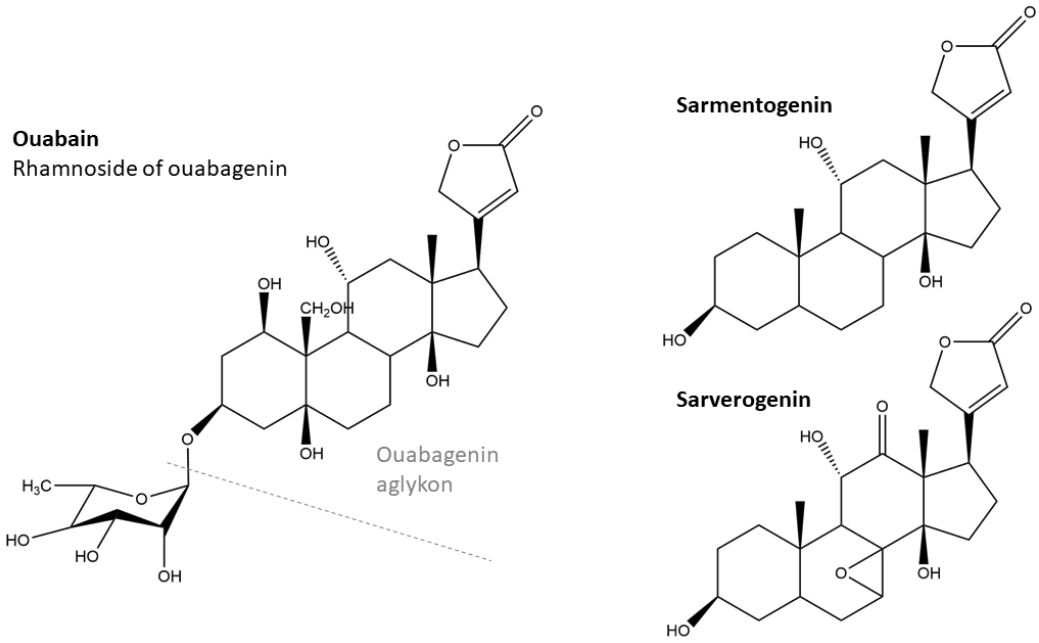

Figure 1. Structure of ouabain, the cardenolide found in *S. gratus* seeds, sarmentogenin (PubChem CID 6437) and sarverogenin [18] from ***S. sarmentosus***.

In addition to the cardiac glycosides, there are many bioactive compounds in *Strophantus*, only few of which have been identified or scientifically characterized. In a collaborative project with a student from Nigeria who was searching for such substances in ***S. sarmentosus*** (also called spider tresses or poison arrow vine), I found the state of knowledge unsatisfactory, in particular, because many publications were not referenced in standard scientific databases like PubMed. ***S. sarmentosus*** is widely distributed in Nigeria and tropical Africa, in general, and has numerous ethnomedicinal uses including treatment of joint pain and rheumatoid arthritis, wound infections, head lice, gonorrhoea, leprosy, scabies, venereal disease, diarrhoea, snake bite, and eye conditions such as conjunctivitis and trachoma [19], but dedicated research studies are scarce. In order to obtain a comprehensive overview, I screened the literature from the viewpoint of an analytical chemist with the goal of generating a summary of the identified molecules from *Strophantus* extracts and their bioactivity with a particular focus on our species of interest, ***S. sarmentosus***.

2. Bioactive Compounds

2.1. Cardiac Glycosides and Their Activity

Cardiotoxins such as strophoside, cymarin and ouabain (Figure 1) have been isolated from *S. kombe*, *S. hispidus* and *S. gratus*, respectively [3]. Many more of these so-called cardenolides are known; for introductory reading on their structures, biochemistry and pharmacology, see "Cardiac Glycosides 1785-1985" [20] and review (with *S. kombe*) [21].

Cardenolides consist of steroid and sugar; only steroids containing 23 or 24 carbon atoms have cardiac activity [3]. Figure 1 shows the prominent representative ouabain, which can be isolated from *S. gratus* seeds. Like several members of this substance class, it is toxic when injected into the bloodstream, but not when given orally [3] as a result of low absorption [22]. Cardenolides can bind to and inhibit Na+/K+-ATPase causing the cardiotonic activity [23]. For the aglykon of ouabain, ouabagenin (Figure 1), it has also been shown that the oxysterol is a liver X receptor ligand [24].

Glycoside composition in *Strophantus* seeds is genetically determined as proven for four geographically separate chemical forms of ***S. sarmentosus*** [1,25]. Exemplarily, sarmutoside and musaroside (from aglykon sarmutogenin) were isolated from two rare single plants in Senegal,

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which differed slightly in composition from the typical native *Strophantus* representatives in that region [26]. Differences in the cardenolide contents of *S. kombe* seeds from Zimbabwe and Malawi were also reported [27].

Analyses in *S. divaricus* proved that cardenolides occur in different parts of the plant and that their concentrations there vary; most glycosides were isolated from the leaves in that study [28]. Based on their seed glycosides, *Strophantus* species were assigned to four groups [1]:

- ouabain group: *S. gardeniiflorus*, *S. gratus*, *S. thollonii*
- sarmentogenin/sarverogenin group: *S. welwitschii*, *S. amboensis*, *S. gerrardii*, *S. congoensis*, *S. petersianus, S. courmontii*, ***S. sarmentosus***
- strophanthidin/strophanthidol/periplogenin group: *S. arnoldianus*, *S. hispidus*, *S. mirabilis*, *S. barteri*, *S. hypoleucos*, *S. mortehanii*, *S. eminii*, *S. kombe*, *S. nicholsonii*, *S. gracilis*, *S. ledienii*, *S. preussii*
- divaricoside/caudoside group: *S. caudatus*, *S. divaricatus*, *S. wightianus*

S. kombe and *S. hispidus* dried ripe seeds are rich in cardiac glycosides (8–10%) [12] and were an early and important commercial source for these molecules; the purified total mixture of these substances was widely used as an injectable solution (strophantin K) for treatment of cardiac deficiencies [29,30]. Research has been ongoing for more than 100 years, but new cardenolides are still being isolated such as glycosides of 17α-strophadogenin in *S. kombe* [29,30]. A dedicated electrospray mass spectrometry (MS)-method characterized strophantidin and six different glycosides including cymarin, helveticoside, erysimoside and neoglucoerysimoside in strophantin K [31].

Strophanthidin glycosides of *S. kombe* seed extracts changed upon storage over 12 months [27]. Cardenolides exhibiting two or three saccharide moieties were degraded presumably by β-glucosidase activities, originating from the plant material or lactobacilli, releasing the corresponding monoglycosides. They were further degraded into the corresponding aglycons probably by acid hydrolysis as a result of lactic acid accumulation [27].

For ***S. sarmentosus*** [32], the Reichstein group contributed many structural investigations in the 1950s and 1960s, identifying 20 glycosides including bipindogenin, lokundjosid and thollosid in a sarmentoside mixture of water-soluble glycosides (see [18,33] and references therein). The cardioactivity of sarmentoside extracted from the seeds was tested on rabbit heart preparations [34]; it compared favorably with digoxin increasing the force and rate of heart contractions. These effects were antagonized by potassium chloride solution.

The cardioactivity of the bark extract of *S. cumingii* and its sub-fractions was determined on isolated frog hearts [35]. The hexane fraction was the most cardioactive with a maximum of 31% increase in the force of contraction and 38% increase in the frequency of contraction. The non-polar fraction of the crude extract from the bark elicited a positive inotropic and negative chronotropic effect on the hearts.

S. hispidus is used in treatment of myocardial infarction in Nigerian ethnomedicine. A study of the hearts from male Wistar rats daily pretreated with *S. hispidus* extract for 14 days before isoprenaline hydrochloride injection (ISO) demonstrated that the pretreatment not only protected against excessive release of cytochrome c but also resulted in decreased caspase 3 activation, which prompted the decrease in excessive apoptosis [36]. The reduction in lipid peroxidation levels in ISO-induced myocardial infarction in rats correlated with the decrease in creatine kinase and aspartate aminotransferase levels.

In another study, the use of *S. hispidus* against ischemia-reperfusion myocardial infarction and renal artery occluded hypertension in rats suggested significant cardiac protective and anti-hypertensive activity for the ethanolic extract [37]. Infarction size, blood pressure and heart rate were reduced.

Modern analytical technologies such as high-resolution MS and nuclear magnetic resonance spectroscopy accelerated the identification process of natural substances in recent years and led, e.g., to the description of six new cytotoxic cardenolide glycosides from *S. boivinii* (boivinides),

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which, on a side note, exhibited antiproliferative activity in a human ovarian cancer cell line [38]. In fact, several cardiac glycosides were found to exert potent antitumor activity; ouabain, e.g., showed antiproliferative effects on SW13, H295R and five primary adrenocortical tumor cells [39]. Of 109 isolated and identified Apocynaceae cardenolides, about a quarter had the capability to regulate cancer cell survival (for review with limited information about *Strophantus*, see [40]). *S. gratus* and *S. caudatus* extracts, e.g., showed no anticancer and antifungal activity in a study of 23 Indonesian plant families [41]. The choice of the sugar moieties at position C-3 is fundamental for a high growth inhibition against cancer cells, and the cytotoxic effects are decreased with the length of the sugar chain [40].

Divaricoside from *S. divaricatus* inhibited cell growth in a dose- and time-dependent manner in SCC2095 and oral squamous cell carcinoma OECM-1 OSCC cells [42]. It induced autophagy, S and G2/M phase arrest accompanied by downregulation of phosphorylated CDC25C, CDC25C, and CDC2 in SCC2095 cells, and apoptosis by activating caspase 3 and downregulating the expression of Mcl-1. These findings suggest a translational potential as a therapeutic agent for OSCC treatment [42].

Testing the hypothesis that they may provide patients with baseline protection to cancers and/or adjuvant treatment of chemotherapy-resistant cancers, 27 popular herbal infusions widely used in Nigeria for diabetes were studied on a panel of liver (HepG2), colon (Caco2), and skin (B16-F10) cancer cells [43]. The results showed that *S. hispidus* stem extract was preferentially toxic against the human colon carcinoma Caco2 cell line. It was concluded that its regular intake by diabetic patients may provide a baseline protection against colon cancer.

Not only the cardenolides exhibit bioactivity, but also the steroid core structures. For example, from twigs, stem and leaves of *S. divaricus,* cytotoxic steroids were described [44,45].

Interestingly, on a side note, Apocynaceae cardenolides have been detected in monarch butterflies [46]. These insects sequester cardiac glycosides from milkweed plants as part of their adaptive strategy. The substances elicit vomiting in birds, who learn to avoid this prey.

2.2. Triterpene Glycosides and Other Substances

In contrast to cardiac glycosides, triterpene glycosides were not as extensively investigated although *Strophantus* extracts have been used as emetic and for treatment of respiratory diseases by native Africans for long [2]. Saponins (water-soluble foam-forming plant components) are credited with emetic, secretolytic and expectorant activity. For a recent review on *Strophantus* saponins and triterpene glycosides in *S. gratus*, see [2].

In ***S. sarmentosus*** and other *Strophantus* species, echinocystic acid (Figure 2) was isolated from fermented seed extract as a core structure, e.g., of bidesmoside in *S. gratus* [2]. Echinocystic acid as a natural extract is widely used in the treatment of inflammatory diseases and reported to alleviate ischemia/reperfusion injury via inhibiting the JNK signaling pathway in mice [47].

Phytochemical screening for the various substance groups in *Strophantus* plant extracts is typically performed with specific assays [48,49]. Different plant parts vary in their composition; ***S. sarmentosus*** stem methanol extract, for instance, tested positive for flavomoids, saponins, phenolics, tannins, carbohydrates, glycosides, alkaloids, steroids and terpenoids, while leave extract only showed five of these substance classes [50,51].

Gas chromatography (GC)-MS of the seed oils of *S. kombe* characterized mainly fatty acids, especially oleic acid and linoleic acid, as well as phytosterols, the latter representing intermediates of cardenolide biosynthesis [30]. In seed oil of ***S. sarmentosus***, major component acids were palmitic (12%), oleic (38%), and linoleic (30%) acids; the minor components included stearic acid (9%), some saturated acids (4%) higher than stearic, and an unsaturated hydroxy-acid (7%) not previously reported [52]. In addition, triglycerides and 2-monoglycerides have been investigated in that species [53]. Another GC-MS study of methanol extracts suggested the presence of six more compounds such as octadecyl vinyl ether and hexadecanal diisopentyl acetal without validation [51]. The compound 2-hydroxy-4-methoxy-benzaldehyde has been described in the methanolic extract of *S. wallichii* [54].

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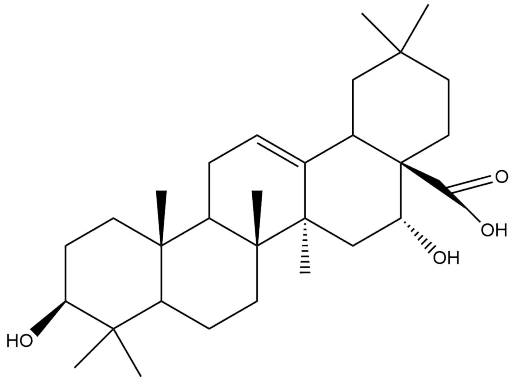

Figure 2. Structure of echinocystic acid, which was isolated from fermented seed extract of several *Strophantus* species including ***S. sarmentosus*** [2].

From *S. gratus* stem bark, lignans (pinoresinol; olivil, Figure 3) [55] and from the leaves, cyclitols (bornesitol, dambonitol, generally found in Apocynaceae) [56,57] have been structurally analysed. From stem and roots of *S. divaricatus,* sesquiterpenoids (Figure 3) were characterized, one of which (neridienone A) exhibited significant cytotoxicity against human cancer cell lines [58,59].

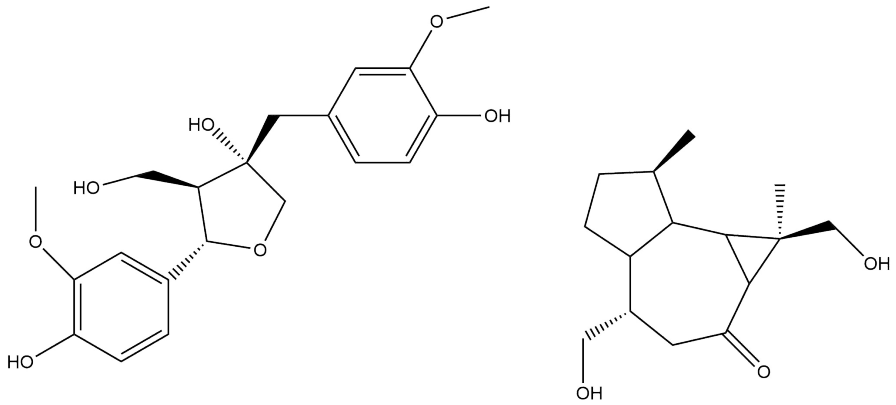

Figure 3. Structures of olivil (left) from *S. gratus* [55] and strophantoid A from *S. divaricatus* [58].

Seeds of *S. kombe* and *S. hispidus* contain, besides the cardioglycosides, about 30% of oil and other constituents such as kombic acid, the alkaloids, choline and trigonelline, resin, mucilage, and calcium oxalate [12]. In *S. hispidus,* chromatographic finger-printing of a methanol stem bark extract detected seven major compounds including ascorbic acid, quercetin, resorcinol and gallic acid represented in large amounts [60][61]. *S. hispidus* stem ethanolic extract contained polyphenol, flavonoids, tannins, alkaloids, terpenoids and saponines [62]. In a study of plants used against diabetes mellitus [63], *S. hispidus* exhibited much less compared to the other plants of several phenolic compounds such as rutin, gallic acid, and ellagic acid.

3. Bioactivity

3.1. Toxicity and Mutagenicity

Despite the fact that numerous plants are used in ethnomedicinal practice, scientific studies about their undesirable and toxic effects are limited. A report concerning plants used in Guinean traditional medicine [64] mentioned adverse or toxic effects for *S. hispidus* and associated them with the presence of the cardiotonic heterosides, which are known to have a narrow therapeutic margin.

A sub-chronic toxicological investigation of aqueous root extract of *S. hispidus* in rats showed no significant alterations in body weight of treated compared to control rats [65]. At doses of 500 and 1,000 mg/kg, treated rats had a significant increase in white blood cells and decrease in liver weight, but the extract demonstrated otherwise a good safety profile for oral administration.

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A study of the sub-chronic effects of the *S. hispidus* aqueous and ethanol extracts in normal rats indicated that higher doses were dangerous to liver and heart with the ethanol extract posing greater risk [66]. The plant extracts caused significant increases in liver proteins (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyltransferase, albumin) and heart enzymes (lactate dehydrogenase, creatine kinase) whereas liver markers decreased significantly in relation to the control. These alterations were in most cases seen at doses higher than 800 mg/kg. Histology revealed mild to marked morphological changes with increasing dosage.

Over half of the most frequently used medicinal plants (110 of 53 families) in Ghana showed moderate to high mutagenicity, but the *Strophantus* representative in this project, *S. gratus,* was not among them [67].

3.2. Anti-inflammatory, Antibacterial and Antioxidant Activity

Free radicals and oxidative stress play a major role in the development of tissue damage and pathological processes, which result in inflammation. *S. gratus* is used in Ghana for managing inflammation-related conditions. A study detected anti-inflammatory (carrageenan-induced paw edema model in 7-day old chicks) and antioxidant activities (phosphomolybdenum assay) in the sub-ethyl acetate fraction of the leave ethanolic extract [68].

The leaves and root of *S. preusii* proved to be potent natural antioxidants, which justified their traditional use in the management of stress-related diseases. The antioxidant and AchE-inhibitory properties of the methanol extracts (leaves, stem, root) were evaluated by standard in vitro methods viz: 2,2-diphenyl-1-picrylhydrazine (DPPH), nitric oxide (NO), hydroxyl radical (OH-) and hydrogen peroxide (H_2O_2) radical scavenging assays as well as reducing power, Fe2+/ascorbate-induced lipid peroxidation (LPO) and acetylcholinestrase (AChE) inhibition assays with catechin as standard [69]. High phenolic and flavonoid contents were found in the aerial parts. All extracts showed antioxidant activities in vitro. Leave extract had the highest DPPH, H_2O_2 and OH radical scavenging ability and root extract most reducing power. All extracts significantly inhibited LPO in rat liver by 30-40% and in rat brain by 30-70% similarly to the standard. Only the stem extract produced significant NO scavenging effects. The percentage inhibition of AChE activity was significant for leave and root extract [69].

Several studies for *S. hispidus* reported that the entire plant (stem bark, leaves, roots) had therapeutic applications including the treatment of skin diseases, gonorrhea, dysentery, leprosy, diabetes, oedema, malaria, ulcers, rheumatism, and urine retention [6]. Significant antioxidant activity using DPPH was detected for the methanol extract of *S. hispidus* stem bark [61]. The in vitro antibacterial activity was better against Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) than *Staphylococcus aureus* in that work. Also in another study, *S. hispidus* aqueous and organic (cyclohexane, chloroform, ethyl acetate, ethanol) stem extracts exhibited strong and broad spectrum antimicrobial activity against these three microbes [62]. Only the ethanolic extract had appreciable antioxidant activity as evaluated using DPPH. In contrast, other research did not find any activity against 10 Gram-positive and three Gram-negative (*Proteus vulgaris, Klebsiella pneumoniea*, *E. coli*) bacteria [8], and low antioxidant activity of the extract was measured in comparison to the reference antioxidant (ascorbic acid).

A total of 211 plant species from 56 families are used in West Africa for several skin conditions such as aphthous ulcers, burns, eczema, scabies, sores, and wounds (for review, see [4]). Among these, *S. hispidus* leaf, stem bark and root methanol extracts showed significant wound-healing as well as antimicrobial (against two Gram-positive, two Gram-negative bacteria and a fungus) and antioxidant (DPPH) properties [70]. Wound tissues treated with the extracts exhibited improved collagenation, re-epitheliazition and rapid granulation formation compared with untreated wound tissues.

Cytoprotective properties are typically associated with the release of free radical scavengers. Anti-ulcer activity was shown for the root ethanolic extract investigated in albino rats in three ulcer models (ethanol, HCl, and pylorus ligation) [6]. Results from the ethanol-induced ulcer model

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indicated a marked reduction in ulceration compared to misoprostol, a standard drug. Results from the HCl-induced ulcer model showed a marked reduction in ulceration comparable to cimetidine. Moreover, in the pyloric ligation-induced ulcer model, *S. hispidus* extract demonstrated an effective reduction in gastric ulcers compared to omeprazole. Reduced ligation of gastric acid and its accumulation in the stomach of the albino rats were also observed. Investigations conducted in the aspirin-induced ulcer model using an aqueous antiulcer drug formulated with *S. hispidus* as a constituent in albino rats found that the formulated drug markedly reduced ulceration compared to omeprazole [6].

Extracts from multiple plants are often combined in ethnomedicine to achieve synergistic effects. As aqueous extracts from *S. hispidus* (roots) and *Aframomum meleguta* (seeds) are topically co-administered in the nasal cavities for the management of chronic sinusitis, a study assessed the anti-inflammatory, antimicrobial and antioxidant effects of such preparations [71]. The individual plant extracts showed comparable potency to that of the mixture with regard to antimicrobial activity and DPPH radical scavenging activity. The an anti-inflammatory activity (inhibition of carrageenan-induced 7-day old chick feet oedema) evoked by mixed extracts was, however, greater than the sum of the individual potencies of the two extracts [71].

Only two studies, both from Nigeria, investigated ***S. sarmentosus*** in more detail with regard to the anti-inflammatory, antimicrobial and cytotoxic activities of different plant extracts [50,51]. The crude extracts of the leaf, root bark and stem (n-hexane, dichloromethane, methanol) had a significant anti-inflammatory effect against egg albumin-induced inflammation of rat paw edema in comparison to the standard drug (aspirin) with root bark working best [51]. The highest dose of 400 mg/kg was lethal to the animals.

In the other study [50], cold extracts (hexane, ethyl acetate, methanol) of plant parts (leaf, stem, roots) demonstrated considerable activity against both Gram-positive and Gram-negative bacteria as well as fungi. Thereby, *Candida albicans*, *Staphylococcus typhimonium*, *S. aureus*, and *P. aeruginosa* were inhibited most, while the least susceptible were *K. pneumonia* and *Bacillus subtilis*. The stem methanol and the root ethyl acetate extracts were the most active and comparable to the standard drug (gentamycin). The cytotoxic activity (brine shrimps method) of the extracts ranged within the medium toxic level according to Clarksons toxicity index.

Part of the antioxidant capacity of a plant may be originating from endosymbiontic species. In a study of 292 morphologically distinct endophytic fungi isolated from 29 traditional Chinese medicinal plants including *S. divaricus*, the antioxidant capacities of the endophytic fungal cultures were significantly correlated with their total phenolic contents and phenolics were major antioxidant constituents of the endophytes [72].

3.3. Hypoglycemic Effects

In type 2 diabetes mellitus, inhibition of α-glucosidase is a useful treatment to delay the absorption of glucose after meals. In a study, the α-glucosidase inhibitory activity of 80% ethanol extracts of leaves and twigs of some plants from the Apocynaceae, Clusiaceae, Euphorbiaceae, and Rubiaceae were determined. Compared with the control acarbose, 37 samples of 45 were shown to be more potent α-glucosidase inhibitors including the *Strophantus* representatives (*S. gratus* folium, *S. caudatus* cortex) [73].

For *S. hispidus*, contrasting results pro and con hypoglycemic activity have been published. One investigation demonstrated the hypoglycemic and antioxidant effects of aqueous root extract in streptozotocin-induced diabetic rats using the activities of superoxide dismutase, total peroxidases, gamma glutamyl transferase, glutathione-S-transferase, glutathione peroxidase, glutathione reductase, as well as the concentrations of glucose, glutathione, vitamin C, nitric oxide, total thiols and malondialdehyde as indices [74]. The concentrations of blood glucose, NO and malondialdehyde were significantly decreased in all groups that received extract. These results were supported by other work proving beneficial antidiabetic activity of aqueous root extract in rats [75]; the extract produced a day-dependent reduction in glucose level. It significantly increased the level of high-density lipoprotein, total protein, catalase, superoxide dismutase and reduced

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glutathione and reduced the levels of triglycerides, low-density lipoprotein, total cholesterol, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, creatinine and urea compared to diabetic control rats. It significantly inhibited α-amylase and α-glucosidase enzymes compared with acarbose. Another study found significant concentration-dependent hypoglycemic effects of both the ethanol and chloroform extracts of *S. hispidus* leaf, stem, and root in Wistar male rats in streptozotocin-induced diabetes mellitus with the ethanol leaf extract working best [76]. Chloroform root extracts exhibited more prolonged hypoglycemic effects.

Furthermore, aqueous and ethanol extracts of *S. hispidus* stem bark showed hypoglycemic, anti-hyperlipidemic and antidiabetic activities [77]. There was a significant progressive decrease in fasting blood glucose concentration on the 2nd-12th weeks and 4th-12th weeks in normal and diabetic treated rats, respectively. Total cholesterol, low density lipoprotein and triglyceride levels were lowered significantly by the extracts in normal and diabetic treated rats, whereas high density lipoprotein levels were elevated in diabetic treated rats. The activity of serum α-amylase, the inhibition of which is an important therapeutic target in the regulation of postprandial increase of blood glucose in diabetic patients, was also elevated by the extract in diabetic treated rats in this work.

In contrast, in a study of the α-amylase inhibitory and antioxidant potential of selected herbal drugs used in the treatment of diabetes by traditional healers in Nigeria, *S. hispidus* methanol crude extracts did not show potent free radical scavenging and efficient reducing power as compared with other plant samples and exhibited no α-amylase inhibition [78]. In another investigation of the aqueous extracts of 27 Nigerian plants for their in vitro effects on glutathione levels within HepG2 cells, P-gp-mediated Rh-123 efflux activity in Caco-2 vincristine-resistant cells, and modulation of glibenclamide transport in Caco-2 monolayers [63], only three plants had a significant effect at the same level as the reference drug verapamil and the *Strophantus* representative *S. hispidus* was not among them.

3.4. Anti-Nociceptive Effects

Decoction of the root of *S. hispidus* is highly valued in Africa herbal medicine. A study evaluated the anti-nociceptive effect of the aqueous root extract in Swiss albino mice with various models (acetic acid-induced writhing, formalin, Haffner's tail clip, hot plate, tail immersion tests) [79]. The extract was administered orally to the animals and possessed, in each of the models, a significant anti-nociceptive effect in a dose-dependent manner. The involvement of opioid and dopamine receptors in anti-nociception was established. The effect of the extract was comparable to that produced by peripheral analgesics, the NSAIDs (aspirin) and centrally acting analgesic opioids (morphine), both used as positive control. These findings showed that *S. hispidus* provides anti-nociceptive effects mediated both peripherally and centrally.

Other work reported anti-nociceptive, anti-inflammatory and anti-ulcerogenic properties for the ethanol root extract of *S. hispidus* [80]. Anti-nociceptive activity was evaluated using acetic acid-induced writhing and formalin tests in mice. The carrageenan- and egg albumin-induced rat paw edema tests were used to investigate the anti-inflammatory actions, whereas the antiulcer activity was investigated using ethanol, HCl- and pyloric ligation-induced gastric ulcer models in rats. The extract given orally produced significant inhibition of writhing reflex and attenuated formalin-induced early and late phase of nociception. It caused significant inhibition of edema development in the carrageenan and egg albumin models and showed potent antiulcer activity [80].

3.5. Anti-Venomenous Activity

Snakebite envenomation causes about 5-10,000 deaths and results in more than 5-15,000 amputations in sub-Saharan Africa alone every year. Antiserum is not easily accessible in these regions thus more than 80% of all patients seek the help of ethnomedicine. It is important to elucidate whether the medical plants contain compounds against the necrosis-inducing enzymes of snake venom. A total of 226 extracts from 94 traditionally used plant species from Congo, Mali and South Africa were tested in hyaluronidase, phospholipase A2 and protease enzyme bioassays using

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Bitis arietans and *Naja nigricollis* venoms as enzyme source [81]. Forty plant species showed more than 90% inhibition in one or more assay, but the *Strophantus* representatives (***S. sarmentosus***, *S. speciosus*) had low to medium effects in comparison [81].

In other work, aqueous extracts of the leaves of *S. gratus* and *S. hispidus* prolonged the time taken to clot for blood treated with the venom of *Echis carinatus* with *S. hispidus* being the most potent [82].

3.6. Anti-Phytoviral, Anti-Herpetic, Anti-Trypanasomal, Anti-Protozoal, Anti-Malarial and Hydroxynitrile Lyase Activities

The tuber necrotic strain of potato virus Y (PVYNTN) causes widespread disease and has severe negative effects on the growth and yield of plants. Ethanolic extracts of the fruits and leaves of *S. speciosus* showed significant inhibition of PVYNTN in vivo and in vitro and thus, have the potential to be used as an anti-phytoviral treatment [83].

Aqueous ethanol (80%) extracts of six plants used traditionally for treatment of malaria including *S. eminii* were screened for anti-malarial activity [84]. This extract exhibited low activity in mice inoculated with red blood cells parasitized with *Plasmodium berghei*. It was innocuous to the mice and not toxic up to 2400 mg/kg body weight, suggesting it may be safe for short-term use.

An investigation reported significant anti-trypanosomal activity of ***S. sarmentosus*** methanolic stem extract with a median lethal dose of 100 mg/kg body weight in mice, but no inhibition of *P. vulgaris, E. coli, S. aureus* and *Enterobacter spp* [85].

In an ethnobotanical survey of 41 Guinean plant species widely used in the traditional treatment of fever and malaria, *S. hispidus* showed no in vitro anti-protozoal activity or cytotoxicity on MRC-5 cells [7].

Herpes simplex virus infection is associated with oral mucocutaneous lesions and/or genital infections. The methanolic extract of *S. hispidus* (stem bark) had good anti-herpetic activity against anti-herpes simplex virus (1 and 2) but it was also highly toxic [60].

Hydroxynitrile lyases are used for the synthesis of enantiomerically pure cyanohydrins, which are of technical importance as building blocks for the pharmaceutical and fine chemical industries. In over 3000 plant species, cyanohydrin is broken down by this enzyme, but no such activity or cyanogenic properties were found for *S. amboensis* and other members of the Apocynaceae [86].

4. Methods

Information was obtained by searching the literature using the SciFinder and Google Scholar tools as well as regular internet browsers for publications with the search term *Strophantus*. ***S. sarmentosus*** is printed in bold throughout the manuscript for faster locating the species of interest.

5. Conclusions

Strophantus is a plant of high ethnomedicinal importance and considerable commercial interest. Its cardiotoxin components have been in the focus of many past investigations. Scientific research regarding further isolated bioactive compounds is, however, sparse and, in some cases, contrasting. Different extract quality may be associated with varying compositions of uncultured plants collected in the wild. A number of studies report biochemical properties of plant extracts, but the way to an individual purified substance is long and not often taken. Many species of the genus are underresearched including ***S. sarmentosus***. Nevertheless, properties such as antibacterial, antioxidant and even anti-cancerous and anti-venomenous activity have been reported for aqueous and organic extracts of plant parts and it is promising to study them further.

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