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Review

Streblus asper Lour. (Shakhotaka): A Review of its Chemical, Pharmacological and Ethnomedicinal Properties

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Streblus asper Lour is a small tree found in tropical countries, such as India, Sri Lanka, Malaysia, the Philippines and Thailand. Various parts of this plant are used in Ayurveda and other folk medicines for the treatment of different ailments such as filariasis, leprosy, toothache, diarrhea, dysentery and cancer. Research carried out using different *in vitro* and *in vivo* techniques of biological evaluation support most of these claims. This review presents the botany, chemistry, traditional uses and pharmacology of this medicinal plant.

Keywords: antifilarial – cardiac glycosides – Moraceae – Shakhotaka – *Streblus asper*

Introduction

Streblus asper Lour (Family: Moraceae) is a small tree (Fig. 1) which is indigenous to tropical countries such as India, Sri Lanka, Malaysia, the Philippines and Thailand. It is known by various names, e.g. Bar-inka, Berrikka, Rudi, Sheora, Koi, Siamese rough bush and Tooth brush tree (1). In India it is known by its several vernacular names, the most commonly used ones being Shakhotaka (Sanskrit), Siora (Hindi), Sheora (Bengali) and Piray (Tamil) (2). It is used traditionally in leprosy, piles, diarrhea, dysentery, elephantiasis (3) and cancer (4). It is a rigid shrub or gnarled tree; branchlets tomentose or pubescent. Leaves are 2–4 inch, rigid, elliptic, rhomboid, ovate or obovate, irregularly toothed; petiole 1/12 inch. Male heads globose, solitary or 2-nate, sometimes androgynous; peduncle short scabrid, flowers minute. Female flowers longer peduncled. Fruit pisiform; perianth yellow. It is found in the drier parts of India, from Rohilkund, eastward and southwards to Travancore, Penang and the Andaman Islands (5).

The pharmacognostical studies of its stem bark as well as its root bark have been carried out (6,7). It finds place in the Ayurvedic Pharmacopoeia of India (8) and has also been described in some monographs (9), but none have described the complete chemistry and pharmacology of this important ethnomedicinal plant. Therefore, we aimed to compile an up-to-date and comprehensive review of *S. asper* that covers its traditional and folk medicinal uses, phytochemistry and pharmacology.

Ethnomedicinal/Traditional Uses

Streblus asper is a well known ethnomedicinal plant which is also used in Ayurveda (2,10–14). Its use in the Indian traditional folk medicine is also well documented. Table 1 gives the various traditional uses of different parts of this species and the sources of information.

Phytochemistry

Streblus asper is a rich source of cardiac glycosides. Reichstein and co-workers (15–18) have isolated more than 20 cardiac glycosides from the root bark of *S. asper* and were able to structurally characterize ~15 such compounds, mainly as a result of the application of degradative techniques, namely kamloside, asperoside, strebloside, indroside, cannodimemoside, strophalloside, strophanolloside, 16-*O*-acetylglucogitomethoside, glucogitodimethoside, glucokamloside, sarmethoside and glucostrebloside. The other glycosides

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Figure 1. *S. asper*. (**A**) Whole tree. (**B**) Flowering twig.

Table 1. Ethnomedicinal uses of different parts of *S. asper*

S. no.	Plant part	Traditional uses	Sources
1	Root	As an application to unhealthy ulcers and sinuses and as antidote to snake bite (2), in epilepsy and obesity (10)	(2,10)
2	Stem	Toothache (11)	(11)
3	Stem bark	Given in fever, dysentery and diarrhea (2,10), stomachache and urinary complaints (11), useful in piles, edema and wounds (10), decoction effective against lymphadema, chylurea and other effects of filariasis (10,12,13)	(2,10–13)
4	Leaves	Eye complaints (11)	(11)
5	Milky juice/latex	Antiseptic, astringent, applied to chapped hands and sore feet (2), in pneumonia and swells of cheek (11)	(2,11)
6	Fruit	Eye complaints (11)	(11)
7	Seeds	Epistaxis and diarrhea (14)	(14)
8	Part not specified	Cancer, cholera, colic, diarrhea dysentery and menorrhagia (4), epilepsy and inflammatory swellings (11)	(11)

reported from the roots include β-sitosterol-3-*O*-β-D-arabinofuranosyl-*O*-α-L-rhamnopyranosyl-*O*-β-D-glucopyranoside (19), lupanol-3-*O*-β-D-glucopyranosyl-[1-5]-*O*-β-D-xylofuranoside (20) and vijaloside, i.e. periplogenin-3-*O*-β-D-glucopyranosyl-[1-5]-*O*-β-D-xylopyranoside (21).

From the stem bark of this plant, α-amyrin acetate, lupeol acetate, β-sitosterol, α-amyrin, lupeol and diol (22), strebloside and mansonin (23) have been isolated. A pregnane glycoside named sioraside (24) has also been isolated. *n*-Triacontane, tetraiacontan-3-one, β-sitosterol, stigmasterol, betulin and oleanolic acid were identified from the aerial parts (25). An unidentified cardenolide (26), β-sitosterol, α-amyrin and lupeol were isolated from root bark and leaves (27). Figure 2 gives the structures of a few biologically active compounds that have been isolated from *S. asper*.

The volatile oil (28) from fresh leaves of *S. asper* was obtained in 0.005% yield as a brown liquid. The major constituents of the volatile oil were phytol (45.1%), α-farnesene (6.4%), *trans*-farnesyl acetate (5.8%), caryophyllene (4.9%) and *trans-trans*-α-farnesene (2.0%). The other constituents were α-copaene, β-elemene, caryophyllene, geranyl acetone, germacrene, δ-cadinene, caryophyllene oxide and 8-heptadecene.

Pharmacological Properties

Several workers have reported the different biological activities of *S. asper* in various *in vitro* and *in vivo* test models. Different parts of this plant have been found to exhibit cardiotonic, antifilarial, anticancer, antimicrobial, anti-allergic and antimalarial activities. These have been described in greater detail in the following.

Cardiotonic Activity

The total ethanolic extract of the root bark of *S. asper* was found to indicate interesting activity on blood pressure, isolated frog heart, isolated rabbit intestine and guinea pig uterus. An αβ-unsaturated lactone was isolated which when administered by i.v. route gave the LD_{50} of 4.8 mg kg^{-1} in white mice. Studies on isolated frog heart showed that it induces a positive ionoptropic effect in 10^{-5} dilution and a systolic response in 10^{-4} dilution. Pronounced *in vitro* spasmodic effect of the compound was seen on the smooth muscles of the rabbit intestine and guinea pig uterus in those high dilutions (14). Pharmacological studies carried out have indicated that the drug has got definite action on myocardium (29).

Antifilarial Activity

The crude aqueous extract of the stem bark of *S. asper* revealed significant macrofilaricidal activity against *Litomosoides carinii* and *Brugia malayi* in rodents. The study revealed two cardiac glycosides, asperoside and strebloside, of the extract to be responsible for antifilarial activity. Of the two glycosides, the more effective macrofilaricide was asperoside which was active at 50 mg kg^{-1} orally against *L. carinii* in cotton rats

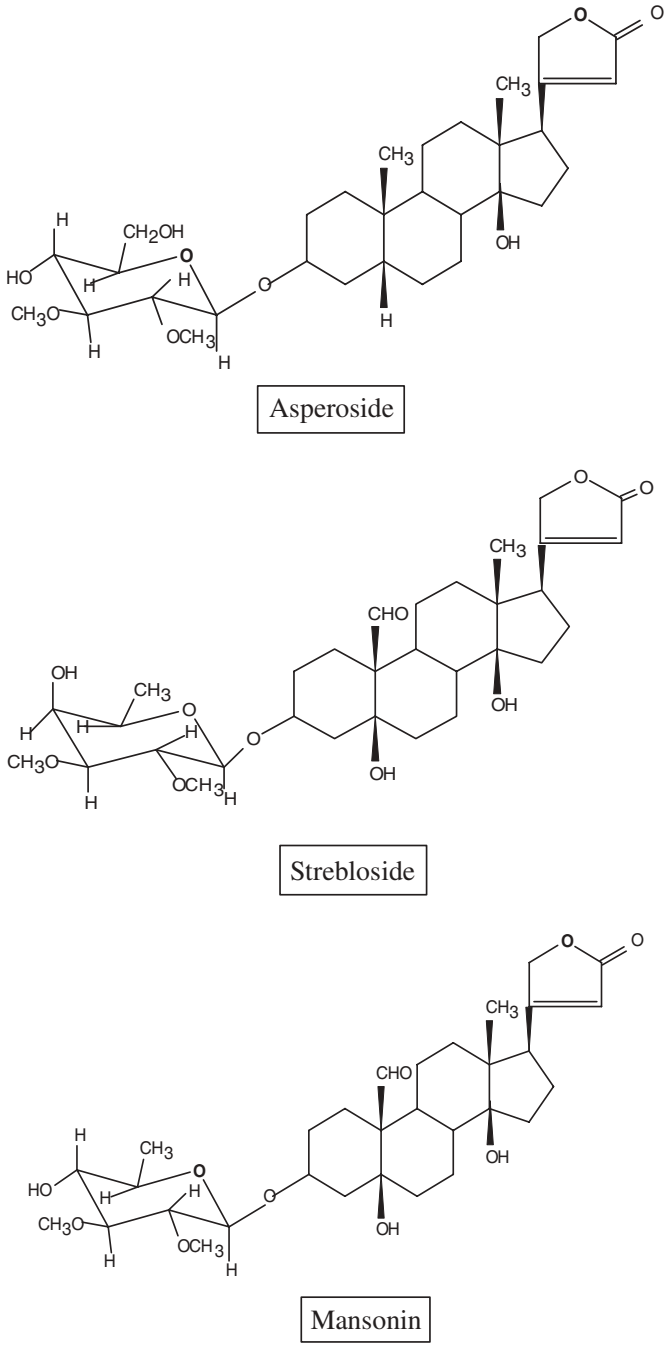

Figure 2. Structures of the biologically active compounds isolated from *S. asper*.

(>90%), *B. malayi* in mastomys (>70%) and *Acanthocheilonema viteae* in mastomys natalensis (>70%). The glycosides were also active *in vitro* against all the three filarial species. Significantly weak activity was detected in glycon and aglycon portions of the parent glycosides (asperoside and strebloside). Several cardiac glycosides of other origins did not show any comparable antifilarial efficacy. The aglycosidic portion of the extract, however, showed poor adulticidal activity (44.5% activity at 1 g kg^{-1} against *L. carinii*) (30). *Streblus asper* has been used in the preparation of a few formulations also. Shakhotaka Ghana Vati prepared from its stem bark was found to be useful in filariasis (31). Besides this, another safe and effective filaricide from the stem bark of *S. asper*, 'Filacid' has also been reported. A series of extraneous investigations involving hundreds of patients infested with filarial parasites have also established its efficacy against filariasis (32).

The effect of aqueous and alcoholic extract of *S. asper* was also studied on the spontaneous movements of the whole worm and nerve-muscle preparation of *Setaria cervi*, the bovine filarial parasite, and on the survival of microfilariae *in vitro*. Aqueous as well as alcoholic extract caused inhibition of spontaneous motility of the whole worm and the nerve-muscle preparation of *S. cervi* characterized by decreased tone, amplitude and rate of contractions. The concentration required to inhibit the movements of the nerve-muscle preparation was l/25 for aqueous and l/160 for alcoholic extract suggesting a cuticular permeability barrrier. The stimulatory response of acetylcholine was blocked by alcoholic and not by aqueous extract of *S. asper*. Both alcoholic as well as aqueous extracts caused death of microfilariae *in vitro*, LC_{50} and LC_{90} being 90 and 33.5 ng ml^{-1}, respectively (33). The *in vitro* effects of asperoside and strebloside on *S. cervi* females were also studied. Both asperoside and strebloside caused death of the worms within 2–3 h at concentrations of 10 g ml^{-1} (1.7 pmol) and were found to inhibit motility and glucose uptake of the parasites at lower concentrations (0.1 g ml^{-1}; 0.17 pmol). These glycosides also inhibited the incorporation of [U-14] C-glucose into macromolecules of *S. cervi* females. Parasites preincubated with either asperoside and strebloside had lowered profiles of glucokinase (EC 2.7.1.2), malate dehydrogenase (EC 1.1.1.37) and succinate dehydrogenase (EC 1.3.99.1) activities, suggesting that the lethal effects of the glycosides were owing to effects on glucose metabolism (34). It was found that asperoside and strebloside interfere with the glutathione metabolism of the adult *S. cervi*, which cause disturbance in various vital activities of the parasites that ultimately results in the death of the parasites (35).

A preliminary study of *S. asper* (shakhotak) as an antilymphoedematous agent was carried out by Baranwal *et al*. (36).

Anticancer Activity

Streblus asper has been reported to possess anticancer activity (37). KB cytotoxicity was found to be concentrated sequentially in the methanol and dichloromethane extracts of *S. asper* stem bark. Two cytotoxic cardiac glycosides, strebloside and mansonin, were isolated which displayed significant activity in KB cell culture system with ED_{50} values of 0.035 and 0.042 μg ml^{-1}, respectively. An isolate is considered to be active in this system if it shows an ED_{50} of $\leq$4 μg ml^{-1} (23).

The volatile oil from fresh leaves of *S. asper* showed significant anticancer activity ($ED_{50} \ll 30$ μg ml^{-1}) from cytotoxicity primary screening tests with P388 (mouse lymphocytic leukemia) cells but no significant antioxidant activity (IC_{50} values $\gg 100$ μg ml^{-1}) in a DPPH radical scavenging assay (28).

Antimicrobial Activity

Different studies were carried out to determine the antimicrobial potential of leaves of *S. asper* (38–44). Ethanol extracts from the sticks and leaves of *S. asper* have been shown to inhibit the growth of *Streptococcus mutans* (38).

For Oral Hygiene

Studies demonstrated the antimicrobial activity of *S. asper* leaf extract upon various microorganisms involving oral and nasopharyngeal infections, especially *S. mutans*. Bactericidal activity was found in the 50% ethanol (v/v) extract of *S. asper* leaves. The extract possessed a selective bactericidal activity towards *Streptococcus*, especially to *S. mutans* which has been shown to be strongly associated with dental caries. The extract had no effect on cultures of *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa, Staphylococcus* coagulase positive, *Staphylococcus* coagulase negative, *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter*, *P. aeruginosa*, *Burkholderia pseudomeallei* and *Candida albicans*. The minimum growth inhibitory concentration and the minimum bactericidal concentration of *S. asper* extract against 10^8 CFU per ml of *S. mutans* was 2 mg ml^{-1} (39).

In vitro study was carried out to determine the effects of a sublethal concentration of *S. asper* leaf ethanolic extract on adherence of *C. albicans* to human buccal epithelial cells (HBEC). The findings indicated that the sublethal concentration of this extract may modulate candidal colonization of the oral mucosa thereby suppressing the invasive potential of the pathogen (40). An *in vivo* one group time series design and single blind study was carried out to determine the antimicrobial effectiveness of a mouthrinse containing *S. asper* leaf extract on *S. mutans* and total salivary bacteria following single 60 s rinse. The results concluded that the mouthrinse containing *S. asper* leaf extract can reduce *S. mutans* without changing an oral ecology (41). *Streblus asper* extract solution at 0.5% concentration (w/v) was investigated for inhibitory effect on adherence of *S. mutans* on glass surfaces. However, it did not show significant inhibitory effect on bacterial adherence to glass surfaces (42). A single blind and crossover design study was also carried out to study the effect of the mouthrinse containing *S. asper* leaf extract on gingivitis and plaque formation (43). The results revealed that when used in mouthrinse the *S. asper* leaf extract significantly effected only the gingival health. It reduced the gingival index but no significant effect was seen on plaque growth.

Against Anaerobic Bacteria

In vitro study was also carried out to determine the antibacterial effects of leaf extract of koi (*S. asper*) against the following six anaerobic bacteria: *Porphyromonas gingivalis* W50, *Prevotella intermedia*, *Actinomyces naeslundii* (T14V), *Peptostreptococcus micros*, *Actinobacillus actinomycetemcomitans* ATCC 43717 and ATCC 43718 (44). It was demonstrated that 15 µl of the leaf extract at 250 and 500 mg ml^{-1} had inhibitory effects towards all bacterial strains tested except *A. actinomycetemcomitans* ATCC 43717. The extract had no bactericidal activity against *P. intermedia* and *A. naeslundii* (T14V). Although the extract did not show inhibitory effect towards *A. actinomycetemcomitans* ATCC 43717 by disc diffusion method, but it did inhibit growth of *A. actinomycetemcomitans* ATCC 43717 by using broth microdilution method.

Anti-allergic Activity

Streblus asper showed promising anti-allergic activity in experimental models. Anti-PCA (passive cutaneous anaphylaxis) and mast cell stabilizing activity of *S. asper* were investigated in mice and rats. Disodium cromoglycate (DSCG) was used as standard anti-allergic drug. *Streblus asper* (50–100 mg kg^{-1}, p.o.) in mice showed 60–74% anti-PCA activity. In rats it showed dose-dependent (50–200 mg kg^{-1}, p.o.) anti-PCA activity (56–85%). The mast cell stabilizing activity in rats (10 mg kg^{-1}, p.o. × 4 days) showed 62% protection against comp. 48/80 induced degranulation. In egg albumin induced degranulation in sensitized rats there was 67% protection with *S. asper*. These results were comparable with that of DSCG (50 mg kg^{-1}, i.p.) (45).

Insecticidal Activity

Insecticidal effects have been shown in extracts of the *S. asper* stem (46). Extracts from the stem bark of *S. asper* possess insecticidal activity against the fifth instar of *Dysdercus cingulatus*. Methanolic extract showed an LC_{50} value of 5.56 µg per insect. Partition with chloroform increased the insecticidal activity (LC_{50} 2.01 µg per insect). Three polyphenolic rich fractions were obtained from silica gel column chromatography of the chloroform fraction and found to have noteworthy insecticidal activity (LC_{50}: 1.82, 2.70 and 2.26 µg per insect) by topical application. This may provide a useful beginning for the development of biopesticides (47).

Antiparasitic

In vitro antitrypanosomal activity of aqueous extract of leaves of *S. asper* was studied at 5, 50, 500 and 1000 mg ml^{-1} (48). However, it did not show any significant activity and was thus not taken up for *in vivo* studies.

Das and Beuria (49) have studied the antimalarial property of the extract of *S. asper* in murine malaria. Giving the stem bark extract of *S. asper* intraperitoneally has been shown to stimulate a host immune response against *Plasmodium berghei* in mice.

Summary and Conclusion

Streblus asper is a well-known plant used in the Indian System of Medicine. In Ayurveda, the use of *S. asper* stem bark is recommended against elephantiasis for which there is no

effective cure in the modern system of medicine. Besides this, folklore medicine also claims its use in cancer, ulcer, diarrhea, dysentery, toothache, etc. Research carried out using different *in vitro* and *in vivo* techniques of biological evaluation support most of these claims.

Filariasis, a disease of considerable public health importance, is a vector-borne helminthic infection occurring in tropical and subtropical regions of the world. Diethylcarbamazine (DEC) and ivermectin, the drugs used commonly for filariasis are insufficient because of their inadequate effect on the adult parasites. The high antifilarial activity of asperoside derived from the stem bark of *S. asper* against *L. carinii*, *Brugia malayi* and *A. viteae* in their respective hosts is unique as for the first time a cardiac glycoside has exhibited antifilarial activity. However, since the active antifilarial compounds are cardiac glycosides, they are sure to produce cardiotoxicity and thus it is necessary to dissociate the two activities. Attempts in this direction were made by the authors (50) by subjecting strebloside and asperoside to hydrogenation so as to reduce the α–β unsaturated lactone ring. The results showed that at a dose of 50 mg kg^{-1} orally, although there was a decrease in the macrofilaricidal activity exhibited by dihydroasperoside as well as dihydrostrebloside, but there was a marked absence of cardiotonic activity as compared to the parent compounds. Also the dihydro derivatives affected the reproductive ability of the female worms as they were found to be sterilized. A fraction, 'Streblofil', containing these two dihydro compounds was also prepared which also exhibited macrofilaricidal action as well as sterilized the female worms (51,52). Asperoside and strebloside were also found to be effective against *S. cervi*, the bovine filarial parasite. These studies give credance to the ethnomedicinal claims of *S. asper* being an antifilarial agent.

The branch of *S. asper* has been used as a tooth brush for strengthening teeth and gums (53). Studies have also proven that it exhibits selective bactericidal activity towards *Streptococcus*, especially to *S. mutans* which has been shown to be strongly associated with dental caries. *Streblus asper* extract thus has the potential for being used as a natural product for controlling dental caries. The anticancer principles have been identified as strebloside and mansonin. Besides, the volatile oil from the fresh leaves has also shown significant anticancer activity. Studies have shown that *S. asper* possesses cardiotonic, antimalarial, anti-allergic antitrypanosomal as well as insecticidal properties. It is, therefore, in itself a very important ethnomedicinal plant whose potential is yet to be scientifically exploited.

Presently there is an increasing interest worldwide in herbal medicines accompanied by increased laboratory investigation into the pharmacological properties of the bioactive ingredients and their ability to treat various diseases (54–56). Numerous drugs have entered the international market through exploration of ethnopharmacology and traditional medicine. Although scientific studies have been done on a large number of Indian botanicals, a considerably smaller number of marketable drugs or phytochemical entities have entered the evidence-based therapeutics. Efforts are therefore needed to establish and validate evidence regarding safety and practice of Ayurvedic medicines (57).

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