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STREBLUS ASPER LOUR. (SHAKHOTAKA): A REVIEW, OF TRADITIONAL USES, PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

Streblus asper (family-Moraceae) is a small tree which is native to tropical countries, such as India, Sri Lanka, Malaysia, the Philippines, and Thailand. In India it is found in the Himalayas from Himachal Pradesh to West Bengal and Assam to Tripura. Different parts of this plant are used in Ayurveda and other folk medicines for the treatment of different ailments such as toothache, diarrhoea, dysentery. leprosy, filariasis, epilepsy. and Cancer. This review presents the chemistry, traditional uses, and pharmacology of *Streblus asper.*

KEYWORDS: *Streblus asper*, Shakhotaka, Pharmacology, Traditional uses, Toothache.

INTRODUCTION

Streblus asper Lour (Family: Moraceae) is a small tree, which is indigenous to tropical countries such as India, Sri Lanka, Malaysia, the Philippines, and Thailand. It is a rigid shrub or gnarled tree; It is known by various names, e.g., Bainka, Berrikka, Rudi, Sheora, Koi, Siamese rough bush, and Tooth brush tree.[1] Medicinal plants have been widely used in traditional system to treat several diseased conditions in the world. In ancient days it was used as tooth brush due strengthing effect of gums and teeth. The various parts of the plant like extract of roots reported against cardiac activity, extract of leaves reported against epilepsy, leprosy, extract of stem reported as antimicrobial, antibacterial. The various chemical constituents reported were glycosides like cardiac glycosides, steroidal glycosides, terpenoids etc. 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, diarrhoea, dysentery, elephantiasis[3] and cancer.[4] It is found in the drier parts of India, from Rohilkund, eastward and southwards to Travancore, Penang and the Andaman Islands.[5] It finds place in the Ayurvedic Pharmacopoeia of India.[8] 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. All the properties are filed and updated information as well gathered to complete review study on *S. asper* up to date.

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 kamloside, asperoside, strebloside, indroside, strophalloside, strophanolloside, cannodimemoside, glucokamloside, glucogitodimethoside, sarmethoside, 16-O acetylglucogitomethoside, and glucostrebloside. The other glycosides reported from the roots include b-sitosterol-3-O-b-d-arabinofuranosyl- O-a-l-rhamnopyranosyl-O-b-d-glucopyranoside, lupanol-3-O-b-d-glucopyranosyl- [1-5]-O-b-d xylofuranoside and vijaloside, i.e. periplogenin-3-O-b-d-glucopyranosyl-[1-5]-O-b-d-xylopyranoside . From the stem bark of this plant, a-amyrin acetate, lupeol acetate, b-sitosterol, a-amyrin, lupeol and diol, strebloside and mansonin have been isolated. A pregnane glycoside named sioraside has also been isolated. n-Triacontane, tetraiacontan-3-one, b-sitosterol, stigmasterol, betulin and oleanolic acid were identified from the aerial parts. An unidentified cardenolide. b-sitosterol, a-amyrin and lupeol were isolated from root bark and leaves. The volatile oil 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%), a-farnesene (6.4%), trans-farnesyl acetate (5.8%), caryophyllene (4.9%) and trans-trans-a-farnesene (2.0%). The other constituents were a-copaene, b-elemene, caryophyllene, geranyl acetone, germacrene, d-cadinene, caryophyllene oxide and 8-heptadecene.

TRADITIONAL USES

Streblus asper reported in many articles regarding uses of this plant, which can be seen in Ayurveda, pharmacopeia and even in many articles that is published and also it has various uses in the Indian traditional medicinal and parts which posses' different activity is mentioned in the below.

LEAVES - Against eye complaints, cardiac glycosides.
STEM - Toothache
STEMBARK - Used fever, diarrhoea, Dysentery, Filariasis, lymphedema, against wounds
ROOT - Against unhealthy ulcer, sinuses, epilepsy, obesity.
LATEX - Antiseptic, Astringent, sore feet, Pneumonia.
FRUITS AND SEEDS - Epistaxis, Epilepsy, diarrhoea.

PHARMACOLOGICAL ACTIVITES

Several workers have reported the different biological activities of S. asper in various in vitro and in vivo test models. These have been described in greater detail in the following.

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.

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 108 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. 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. 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. 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.

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 LC50 value of 5.56 mg per insect. Partition with chloroform increased the insecticidal activity (LC50 2.01 mg per insect). Three polyphenolic rich fractions were obtained from silica gel column chromatography of the chloroform fraction and found to have noteworthy insecticidal activity (LC50: 1.82, 2.70 and 2.26 mg per insect) by topical application. This may provide a useful beginning for the development of biopesticides.

Antiparasitic activity

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

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 ab-unsaturated lactone was isolated which when administered by i.e., route gave the LD50 of 4.8 mg kg_1 in white mice. Studies on isolated frog heart showed that it induces a positive ionotropic 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. Pharmacological studies carried out have indicated that the drug has got definite action on myocardium. 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 (>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. 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. 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 nervemuscle 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, LC50 and LC90 being 90 and 33.5 ng ml_1, respectively. 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. 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. A preliminary study of S. asper (shakhotak) as an antilymphoedematous agent was carried out by Baranwal et al.

Antitumor activity

The study of Suresh Kumar RB, Biswakanth KA showed that EASA (ethanoic extract of *Streblus asper*) treatment was found to significantly reduce tumor proliferation. From this study, it can be concluded that the ethyl acetate fraction of defatted methanol extract from *S. asper* bark demonstrated remarkable antitumor efficacy against Dalton's ascitic lymphoma in *Swiss albinomice*, mediated plausibly by virtue of ameliorating oxidative stress by augmenting the endogenous antioxidant status13. Cardiac glycoside, (+)-strebloside, has been characterized as the main cytotoxic component of *S. asper*, which binds to Na+/K+-ATPase and inhibits the activity of this enzyme. However, (+)-17β-hydroxystrebloside, C-17 hydroxylated (+)-strebloside which was isolated from *S.asper* doesn't provide an efficient action against Human cancer cell line by using Na+/K+-ATPase enzyme, and this work was proved by Ren Y, et.al., and their team .They also proved by docking studies that is structure 4:**(+)**-strebloside has an efficient action as antitumor moiety on comparing with reference ouabain,*i,e* structure 5, for the docking studies8.The work done by Dan Miao and his team on cytotoxic and melanogenesis-inhibitory activities was provided a proof that *Streblus asper* root as action against cancer14 which further their team done work on isolation of chemical derivatives with various substitutions, which are mentioned as structure 6 and structure 7. Later it was proved by using COSY, NOSY for identification as well for determination about the structure that has been isolated. The major constituents of the volatile oil of *S. asper* were phytol (45.1%), α -farnesene (6.4%), trans-farnesyl acetate (5.8%), caryophyllene (4.9%) and trans- α -farnesene (2.0%). In addition, the volatile oil showed significant anticancer activity at effective dose *i.e.* (ED< 30μg/ml) from cytotoxicity primary screening tests with P388 (mouse lymphocytic leukemia) cells. This work was done by Phutdhawong W and their team and, they described about dose required to exhibit anticancer activity.

Antiallergic Activity

Streblus asper showed promising enemy of hypersensitive action in exploratory models. Hostile to PCA (Passive cutaneous anaphylaxis) and pole cell settling action of *S. asper* were researched in mice and rodents. Structure 6: -Disodium cromoglycate (DSCG) was utilized as standard antiallergic drug. *Streblus asper* (50–100 mg kg p.o.) [Where p.o.; - parenterally or orally] in mice appeared 60–74% enemy of PCA action. In rodents it showed portion subordinate (50–200 mg kg−1, p.o.) against PCA action (56–85%). The pole cell balancing out action in rodents (10 mg kg−1, p.o. × 4 days) showed 62% security against comp. 48/80 initiated degranulation. In egg whites-initiated degranulation in sharpened rodents there was 67% security with *S. asper*. Therefore, work of Amarnath Gupta and their team tried to prove that *Streblus asper* showed prominent role against hyper sensitive reactions**.**

Antifilarial Activity

The work done by Chatterjee, R.K and their team tried to prove that the crude extract of the stembark of *Streblus*

asper, a traditionally used medicinal plant of India, revealed significant macrofilaricidal activity against *Tifomosoidescariniiand Brugiamalayi* in rodents. The study revealed two cardiac glycosides, structure 1: - Asperoside and Structure 2: - Strebloside of the extract to be responsible for antifilarial activity. Of the two glycosides, the more effective macrofilaricide was KO29 which was active at 50 m/kg orally against *L. carinii* (>9o %), *B. malayi* (>70%), and Acanfhocheilonemavifeae (>70%) in their respective hosts. The glycosides were also active in vitro against all the three filarial species that were selected for their studies and report was compared by using reference Structure 11: DEC (Diethylcarbamazine). The aqueous and alcoholic extract of Streblus asper was studied on the spontaneous movements of the whole worm and nerve-muscle preparation of Setariacervi 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 work done by Nazneen and their team stated that Streblus asper posse's antifilarial activity**.**

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 ED50 values of 0.035 and 0.042 mg ml_1, respectively. An isolate is active in this system if it shows an ED50 of _4 mg ml_1.[23] The volatile oil from fresh leaves of S. asper showed significant anticancer activity (ED50 _ 30 mg ml_1) from cytotoxicity primary screening tests with P388 (mouse lymphocytic leukemia) cells but no significant antioxidant activity (IC50 values _ 100 mg ml_1) in a DPPH radical scavenging assay.

CONCLUSION

This review is concerned about the collection of information about the updated work that has been carried out using an raw material of *Streblus asper* and also includes about the various information like traditional uses, phytochemistry, pharmacological activity etc. Although, it is evident that *S. asper* contains several important phytochemical constituents that are responsible for various pharmacological action. Hence, isolation of phytochemical constituents from selected species is important as they can act as lead molecules or pharmacophores for synthesizing novel agent in dry lab synthesis or can be used for the various Ayurveda formulations which can possess a good pharmacological activity and get desired action for the diseases condition.

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