International Journal of Medicine and Pharmaceutical Research

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R E V I E W A R T I C L E

Chemical ingredients pharmacological activities of *Strebulus Asper L*: A Review

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A B S T R A C T

Streblus asper L. is a small tree found in tropical countries, such as India, Sri Lanka, Malaysia, the Philippines and Thailand belonging to family moraceae. 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. The role of oxidative stress in the pathophysiology of diabetes and its associated complications are well known. The antioxidant system plays an important role in defending the cells against oxidants generated during metabolic processes and thus prevents the tissues from toxic response of the oxidants. The methanol extract of Streblus asper exhibited anti diabetic property as well as increased the levels of enzymatic and non enzymatic anti oxidant entities along with reduced MDA levels. The methanol extract of this plant did not exhibit any toxicity in the present study and thus it was concluded that the extract possesses antidiabetic as well as antioxidant properties without any adverse effect. This review presents the botany, chemistry, traditional uses and pharmacology of this medicinal plant.

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

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MS-ID: IJMPR4000

PAPER-QRCODE

A R T I C L E H I S T O R Y: Received 19 June 2019, **Accepted** 29 August 2019, **Available Online** 10 October 2019

Citation: *Navneet Kumar Verma, et al.* Chemical ingredients pharmacological activities of *Strebulus Asper* L: A Review. *Int. J. Med. Pharm. Res., 2019, 7(5): 146-152.*

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1. Introduction

Herbal medicines are the oldest remedies known to mankind. Herbs had been used by all cultures throughout history but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants [1]. In the present scenario, the demand for herbal products is growing exponentially throughout the

world and major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value. In many journals, national and international, we find an increasing number of research publications based on herbal drugs.

Herbal medicines form a major part of remedies in traditional medical systems such as Ayurveda, Rasa, Siddha, Unani, and Naturopathy. Hence all animal and clinical studies on herbal medicines were reviewed. The data for the years 1981-1983 were taken as baseline for the comparison of recent herbal drug research trends. The present study showed that interest has increased in herbal drug research in India, which supported the findings of Adithan (1996), with maximum utilization of the phytotherapeutic approach where in crude plant preparations were used.

The maximum work was observed with polyherbal preparations. Recently there has been a shift in global trend from synthetic to natural medicine, which we can say 'Back to nature'. Medicinal herbs have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agent for prevention of disease and ailment. India is perhaps the largest producer of medicine or herbs and is rightly called the "Botanical garden of the world". India in this regard has a very unique position in the world, where a number of recognized indigenous systems of medicine *viz.,* Ayurveda, Siddha, Unani, Homeopathic, Yoga and Naturopathy are practiced and utilized for the health care of the people [2].

India has an ancient heritage of traditional medicine. Materia medica of India provides lots of information on the folklore practices and traditional aspects of therapeutically important natural products. Indian traditional medicine is based on various system including Ayurveda, Siddha and Unani.

The evaluation of these drugs is mostly based on phytochemical, pharmacological and allied approaches including various instrumental techniques like chromatography, microscopy and others. These traditional systems of Indian medicine have their uniqueness no doubt but there is a common thread running through these systems in their fundamental principal and practices. With the emerging interest in the world to adopt and study the traditional system and to exploit their potentials based on different healthcare system, the evaluation of the rich heritage of the traditional medicine is essential.

The government and private sectors are trying their best to explore all possibilities for the evaluation of these systems to bring out therapeutic approaches available in original system of medicine as well as to help in generating data to put these products on national health care program [3].The World Health Organization (WHO) estimates that about 80% of the populations living in the developing countries rely almost exclusively on traditional medicine for their primary health care needs. In all most all the traditional medicine, the medicinal plants play a major role and constitute the backbone of traditional medicine. Indian materia medica includes about 2000 drugs of natural origin all most all of which derived from different traditional system and folklore practices. Out of these drugs derived from traditional system, 400 are of mineral origin while the rest are of vegetable origin. India has a rich heritage of traditional medicine and the traditional health care system namely Ayurveda, Siddha and Unani. Lot of efforts has been taken by the government and private sectors for the development of the traditional system based on these three methods [3].

The use of medicinal plants was compiled in Ayurveda, which listed more than 8000 herbal remedies. India is one of the world's twelve leading biodiversity centers with the presence of over 45,000 different plant species. Of these, about 15,000-20,000 plants have good medicinal properties, of which only 7000-7500 are being used by traditional practitioners. The Siddha system of medicine uses around 600, Ayurveda 700, Amchi 600, Unani 700 and modern medicine about 30 plant species. Projection is being made that next to information technology, herbal technology will be India's biggest revenue earner [4].

In the global perspective, there is a shift towards the use of medicine of herbal origin, as the dangers and the shortcoming of modern medicine have started getting more apparent, majority of Ayurvedic formulation are prepared from herbs [5]. It is the cardinal responsibility of the regulatory authorities to ensure that the consumers get the medication, which guarantee purity, safety, potency and efficacy. This duty is discharged by the regulatory authorities by rigidity following various standards of quality prescribed for raw materials and finished products in pharmacopoeias controlling manufacturing formulate through the use of formularies and manufacturing operation through statutory imposed "Good manufacturing practices".

Description of plant

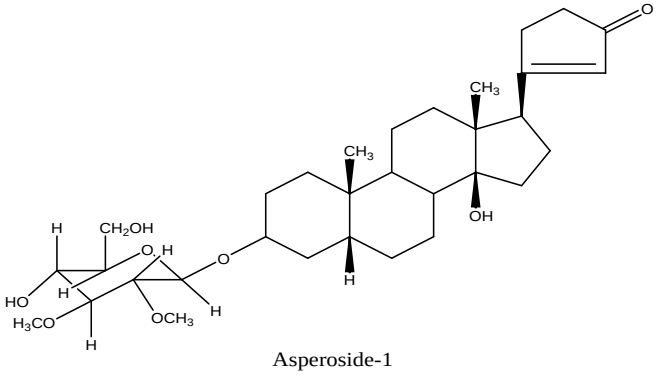
Streblus asper is a rigid shrub or gnarled evergreen tree; bark light grey or greenish with faint ridges, rough when old; juice milky; twings hairy, scabrid; leaves alternate, 2.5-10 cm long, rhomboid-elliptic, obovate or elliptic oblong, acute or shortly abruptly acuminate, more or less sinuate or crenate, scabrid on both surfaces but especially beneath; lateral nerves 4-6 pairs, prominent beneath, joined by intra marginal loops, petiole 1.3-3.8 mm. long, stipules rather longer than the petiole, obliquely lanceolate, acuminate; Flowers diocious, axillary. Male flowers in globose pedunculate heads 7.5 mm, peduncles 1-4 together, 7.5-13 mm long, Perianth campanulate, sepals 4, pubescent outside, imbricate in bud. Stamen 4, inflexed in buds, anthers rennin form, Female flowers solitary, inconspicuous, long peduncle; peduncles 1-4 together, 5-13 mm. long bracts 2-3 below peduncles; style 2, very long, filliform connate at the base. Fruit, one celled berry, loosely enclosed by the enlarged sepals, yellow when ripe, 5mm diameter [6].

Figure1: *Streblus asper leaves*

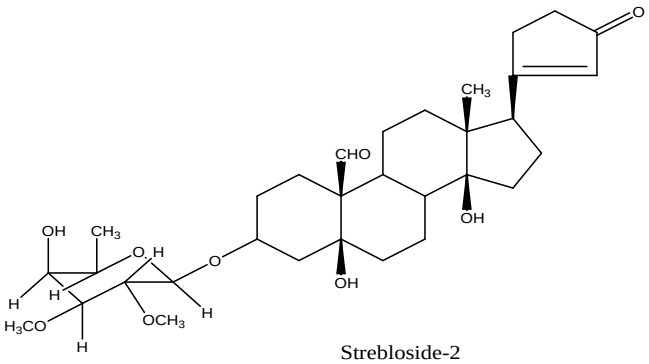
2. Chemical Constituents

Streblus asper is a rich source of cardiac glycosides. More than 20 cardiac glycosides from the root bark of *Streblus asper* have been reported and were able to structurally characterize about 15 such compounds, mainly as a result of the application of degradetive techniques, namely kamloside, asperoside, strebloside, cannodememoside, strophalloside, strophanolloside, glucogitomethoside, glucogitodimethoside, glucokamloside, sarmethoside, and glucostrebloside, some of them are summarized in the following table. Asperoside, Indroside, Kamloside, Cannodememoside, Strophalloside, Glucokamloside, Sarmethoside,Sarmethoside,Glucostrebloside,Vijaloside,Strebloside,α –amyrin, Lupeol acetate, β –sitosterol, Lupeol and diol, Sioraside, n-Triacontane, Stigma sterol, Betulin,Oleanolic acid, Phytol, Caryophyllene, Farnesyl acetate, Farnesyl acetate, α- farnesene, Farnesene, Farnesene, α –copaene, β –elemene, Geranyl acetone, Germacrene,α –copaene, Farnesene, β –elemene,Geranyl acetone, Germacrene [7].

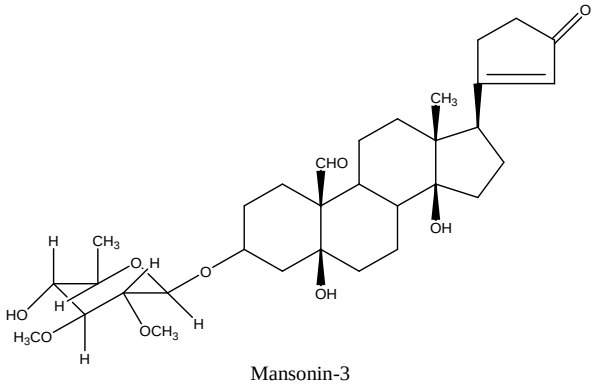
Chemical Structures



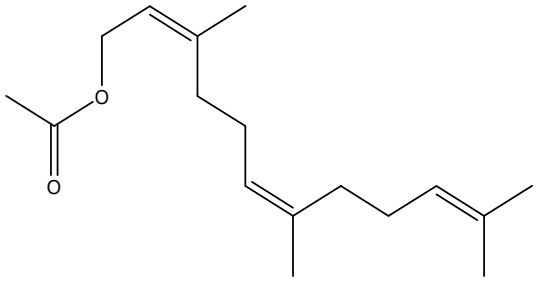
Asperoside-1



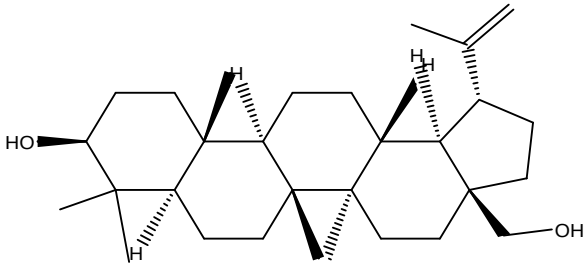
Strebloside-2



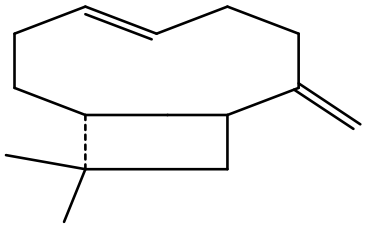
Mansonin-3



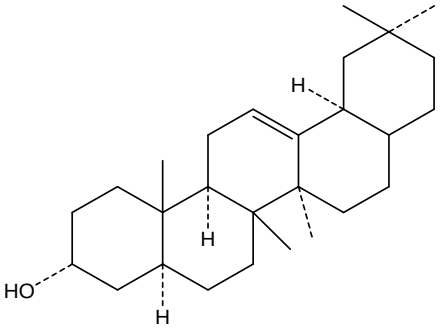
Farnesyl acetate-4



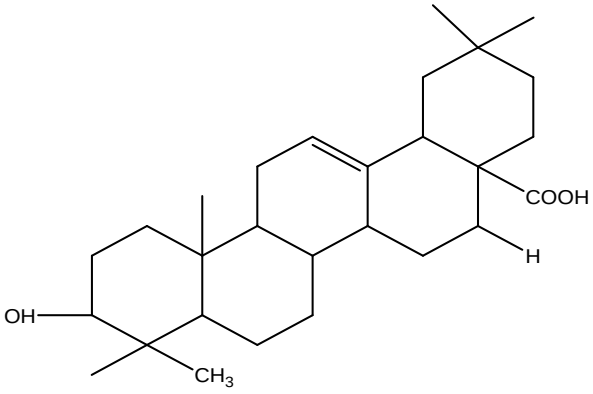
Betulin-5



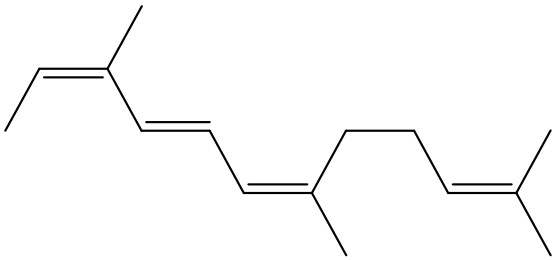
Caryophyllene-7



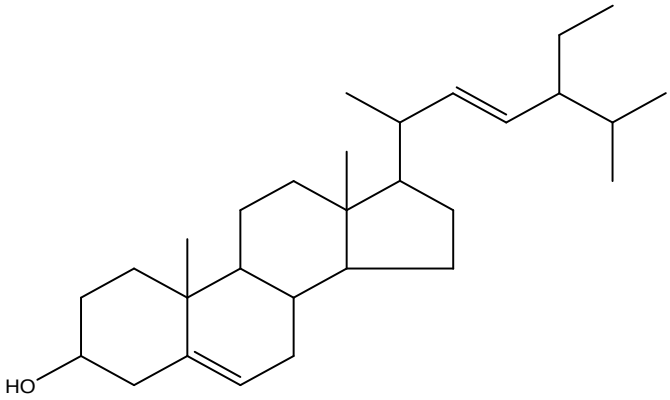
Alpha-amyrin-8



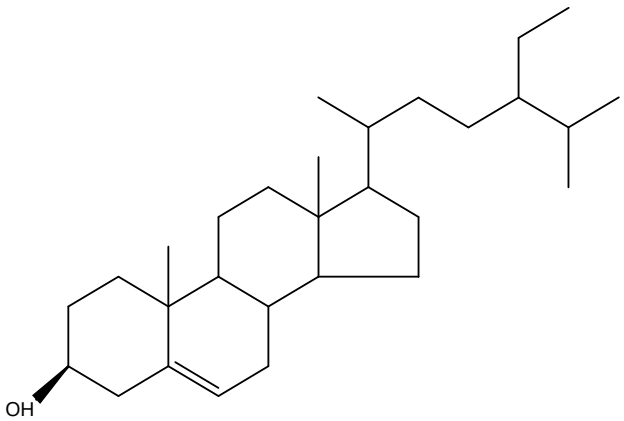
Oleanolic acid-9



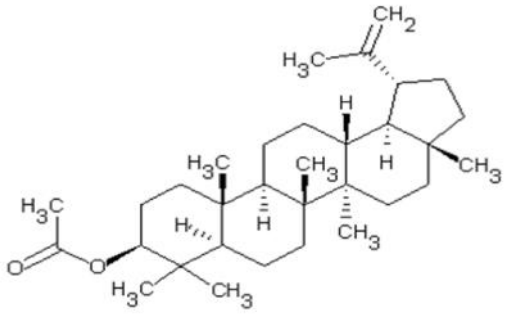
Farnesene-10



Stgma sterol-11



Beta-sitosterol-12



Lupeol acetate-13

3. Pharmacological Activities

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 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 [8]. Pharmacological studies carried out have indicated that the drug has got definite action on myocardium [9].

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 *Acanthocheilone maviteae* in masto mysnatalensis (>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*) [10]. *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 [11]. 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 [12]. 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 *Setariacervi*, 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 [13]. 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 [14]. 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 [15].A preliminary study of *S. asper* (shakhotak) as an antilymphoedematous agent was carried out by Baranwal*et al*. [16].

Anticancer Activity

Streblus asper has been reported to possess anticancer activity [17]. 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 ≤4 µg ml^{-1}. 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.

Antimicrobial Activity

Different studies were carried out to determine the antimicrobial potential of leaves of *S. asper*. Ethanol extracts from the sticks and leaves of *S. asper* have been shown to inhibit the growth of *Streptococcus mutans* [18].

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, *Serratiamarcescens*, *Klebsiellapneumoniae*, *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}[19]. *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 [20]. 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 [21]. *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 [22]. 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 [23]. The results revealed that when used in mouthrinse the *S. asper* leaf extract significantly affected 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 [24]. 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.) [25,26].

Insecticidal Activity

Insecticidal effects have been shown in extracts of the *S. asper* stem [27]. Extracts from the stem bark of *S. asper* possess insecticidal activity against the fifth instar of *Dysdercuscingulatus*. 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 [28].

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}[29]. However, it did not show any significant activity and was thus not taken up for *in vivo* studies. Das and Beuria [30] 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.

4. Conclusion

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. 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 iv ermectin, the drugs used commonly for filariasis are insufficient because of their inadequate effect on the adult parasites. 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.

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