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Functional properties of *Streblus asper* Lour.: a review

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Abstract

Plants are the major sources of food and medicine for humans. *Streblus asper* Lour is a small tree belonging to the Moraceae family and is commonly found in tropical countries. *S. asper* plant is used in several folk medicines, especially Ayurveda and Siddha, to treat several diseases and disorders. This review summarizes the medicinal and economical properties of this medicinal plant. Scientific literature dealing with *S. asper* was collected from scientific databases without any year limit and was included in this review. About twenty potential active compounds were isolated from *S. asper*. The study revealed that *S. asper* is an important medicinal plant with several proven therapeutic potentials *in vitro* and *in vivo*, including anti-cancer, antibacterial, anti-fungal, anti-diarrhoeal, anti-macrofilaricidal, anti-diabetic, anti-inflammatory, anti-aging, and neuroprotective effects. Additionally, the plant can be used as animal feed and bio-insecticide. It also helps in the coagulation of skimmed milk and cheese production. Further, it has some economic uses, including vermicompost production and papermaking and its use as a fuel. However, there are no prescribed *S. asper*-based therapeutic agents to manage any disease condition, and some adverse effects were observed in human trials. Enough studies are available to prove the potential of *S. asper in vitro* and *in vivo* models; however, further clinical studies are required to develop safe therapeutic agents using the phytoconstituents of *S. asper*.

Keywords: *Streblus asper* Lour.; antifilarial; cardiac glycosides; moraceae.

Practical Application: The review may help researchers develop and formulate the functional ingredients with pharmacological applications using *Streblus asper* Lour.

1 Introduction

Plants are the major sources of food and medicine for humans. So far, it has been reported that more than 7000 species of plants are considered edible (Lim, 2012), either found in the wild or can be cultivated manually. The presence of different phytochemicals in plants aids them in extending various health benefits (Shikov et al., 2017). These bioactive phytochemicals are chemical components (mostly secondary metabolites) present in smaller amounts than macronutrients such as carbohydrates, proteins, and lipids. Depending on the specific application and benefits, these phytochemicals are classified into various categories, such as medicinal, functional foods, nutraceuticals, and botanicals (Okoro et al., 2021).

Many countries promote medicinal plants in the diet as daily food or functional food, thereby promoting overall health. In Eastern countries, food and medicine come from the same source, and they are equally important in maintaining and improving health, preventing, and curing diseases. For instance, countries such as China, Japan, Korea, and Southeast Asia, use medicinal plants as daily foods (cereals, vegetables, and fruits) and as functional foods for replacement and medical purposes (Shi et al., 2011). Europe has also introduced different varieties of exotic fruits and other diverse species from other continents in the last few decades (Franz et al., 2011; Shikov et al., 2017). By the 1600s, almost all the important old World food crops had been introduced to the Americas and were available as medicinal resources for Indigenous, Mestizo and European migrants for the last 400 years (Crosby, 1972; Kujawska & Pieroni, 2015).

Various plants and their by-products have become a major area of investigation for bioactive compounds with health benefits. Approximately half of the new chemical molecules introduced during the last two decades have come from natural products. Therefore, the industry's efforts have been directed toward isolating and characterizing the active principles and clarifying the relationship between structure and activity (Álvarez et al., 2022). In this regard, many plant species known to have traditional health benefits are analyzed by researchers to identify the different pharmacological potential of the plants and to identify the phytochemicals responsible for it.

Streblus asper Lour. is one such plant that belongs to the family Moraceae and the subfamily of Moroideae with the 4th tribe Strebleae and *Taxotrophis, Phyllochlamys,* and *Maillardia. Streblus* consists of a total of 22 species (Willis, 1973). This plant

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is commonly known as "sheora" in Bengali (Datta & Datta, 1984; Mukherjee & Roy, 1983) and "khoi" in Thai (Phutdhawong et al., 2004). *S. asper* is known for its medicinal properties; it is known as "Shakhotaka" in Ayurveda and "Piraayan" in Siddha. The plant is grown widely in Asia, majorly in India, Thailand, Sri Lanka, Philippines, China, and Malaysia, in open, wet, and dry fields, along with coastal regions (Fiebig et al., 1985; Chaudhuri, 1968). Several studies have reported the phytochemical constituents of *S. asper* (Rastogi et al., 2006). The present manuscript summarizes the recent updates on the medicinal properties of *S. asper*.

2 Methodology

Scientific documents were searched and retrieved from Scopus, PubMed, Google Scholar, and Science Direct databases, with no specific timeline, using the search term "*Streblus asper*." The available and relevant documents in English dealing with the health benefits were selected without any chronological restrictions to prepare the review. A total of 130 articles were available, among which 51 were excluded, which were published in other languages or were duplications. The remaining 79 articles were further narrowed down to 50 by excluding articles that did not deal with the medicinal properties of *S. asper*. The plant had benefits in extending anticancer, antioxidant, antibacterial, antifungal, oral hygiene, antimacrofilaricidal, neuroprotection, antidiabetic, hepatoprotective, anti-inflammatory, anti-diarrheal, anti-aging, and anti-analgesic properties.

3 Traditional uses of *S. asper*

S. asper is said to be useful in treating approximately around 20 types of diseases by traditional practitioners, which is described in Table S1 (Supplementary material), that includes cardiac disorders, epilepsy, oedema, leprosy, dysentery, elephantiasis, and tuberculous glands; in addition, it is employed in treating fever, diarrhoea, dysentery, and disinfecting wounds (Fiebig et al., 1985; Das & Beuria, 1991). Also, its bark has been observed to induce an immune response (Das & Beuria, 1991). The root is used to treat epilepsy, cardiac disorders, oedema, ulcers, and sinuses; further, it acts as an antidote to snakebite and affects the myocardium (Gaitonde et al., 1964). The latex is used as an antiseptic and astringent agent, which can be applied on chapped hands, sore heels, and glandular swellings (Datta & Datta, 1984; Mukherjee & Roy, 1983). The leaf treats fever, regulates blood pressure, and reduces pain during labour. The seed is used in treating epistaxis, piles, and diarrhoea. Twigs were used as toothbrushes, which could be chewed to clean the teeth and cure pyorrhoea (Datta & Datta, 1984; Kadir et al., 2014; Sharkar et al., 2013; Kritsaneepaiboon, 1989; Lewis, 1980). Different tribal groups use *S. asper* as traditional medicine for the treatment of dysuria, dysentery (Mia et al., 2009), oedema, rheumatic pain, elephantiasis, toothache, dental caries, impotence (Hossan et al., 2009), prevention of infections caused by burns (Rahmatullah et al., 2012a; Rahmatullah et al., 2012b), and treatment of dysentery (Rahmatullah et al., 2012b).

4 Commercial uses of *S. asper*

Commercial use of different parts and products of *S. asper* has been reported, which adds value to the plant, apart from its medicinal properties. The extract of the stem bark of *S. asper* was observed to exhibit insecticidal activity on *Dysdercus cingulatus* and can act as a biopesticide (Hashim & Devi, 2003). Fibre obtained from the bark of *S. asper* is used for papermaking and slate-making. A collection of old Lanna medicinal-plant recipes from different parts of Thailand were majorly based on the leaves of *S. asper* along with palm and mulberry (Manosroi et al., 2006). In the southern parts of India, wood is used to make yokes and cartwheels and used as fuel. Interestingly, the tree's twigs were stuck in and around thatched roofs of houses to ward off lightning (Datta & Datta, 1984).

The dry leaves of *S. asper* can be converted to vermicompost with a high nutritional value containing nitrogen, phosphorus, sodium, calcium, and sulphur (Sannigrahi, 2009). *S. asper* is a host for *Cuscutare flexa* Roxb., an epiphytic parasitic plant that has been widely used as a functional food (Tanruean et al., 2019). Twigs of *S. asper* produce a rennin-like milk-clotting protease, which can be potentially used for cheese production (Senthilkumar et al., 2006). It can also be applied in the cheese industry as it is stable in alkaline pH values (Tripathi et al., 2011). The leaves of *S. asper* can be used as feed for ruminants (Khan et al., 2008), as they are a good source of fiber, which improves milk production (Chumpawade & Pimpa, 2009), and the plant foliage can be efficiently used as a source of proteins (Paengkoum, 2011). *S. asper* leaves can be used as a nutritious feed for cattle and are more beneficial than green grass (Akbar & Alam, 1991). The fruit juices of *S. asper* could act as a cooling agent or refrigerant when given orally to ruminants like cows or goats (Aziz et al., 2018).

5 Phytoconstituents of *S. asper*

Several bioactive phytoconstituents of *S. asper* have been reported. *S. asper* leaf extract contains fatty acids, phytosterol, triterpenoids, polyol, sugar acid, aldehyde, diterpene, terpene, carboxylic compounds, acid, and sugar. The reported phytoconstituents have been listed (Supplementary material: Table S2) and their structure was illustrated (Supplementary material: Figure S1 and Figure S2). Also, phytol, α-farnesene, α-copaene, β-elemene, α-d-glucopyranoside, glycerol, myo-inositol, butanedioic acid, hexadecanoic and octadecanoic acids, β-sitosterol, and α-d-glucopyranoside were found in the leaves of *S. asper* (Phutdhawong et al., 2004; Fiebig et al., 1985; Gaitonde et al., 1964; Rawat et al., 2018). LC-MS analysis reported many phytoconstituents, and the major ones are andrographolide, carnosic acid, α-linolenic acid, and oleoyl oxazolopyridine (Prasansuklab et al., 2017). Asperoside, strebloside, and indroside are the major cardiac glycosides identified in the plant's root. Lupeol, α-amyrin, mansonin, siaroside, and betulin were isolated from the stem bark, and lignans were isolated from the root. The heartwood of the plant has been reported to exhibit various pharmacological properties, such as anticancer, neuroprotection and antimicrobial effects (Phutdhawong et al., 2004; Fiebig et al., 1985; Gaitonde et al., 1964).

6 Medicinal properties

S. asper has been reported to possess various medicinal properties in *vitro, in vivo,* and clinical trials explained in

detail in this section and Table S3 (Supplementary material). The plant has reported anti-cancer, antioxidant, anti-bacterial, anti-fungal, oral hygiene, anti-macrofilaricidal, neuroprotective, anti-diabetic, anti-hepatitis, anti-inflammatory, anti-diarrheal, anti-aging, anti-parasitic and analgesic properties.

6.1 Anti-cancer activity

Fresh leaves of *S. asper* were subjected to hydrodistillation to isolate the volatile oil, containing phytol, α-farnesene, trans-farnesyl acetate, caryophyllene and trans-trans-α-farnesene at 45.1%, 6.4%, 5.8%, 4.9% and 2.0%, respectively. This oil expressed anti-cancer properties significantly (ED50 << 30 µg/mL) in P388 (mouse lymphocytic leukemia) cells (Phutdhawong et al., 2004). The leaf and flower extract of *S. asper* in combination with cyclophosphamide (CTX) significantly potentiated the antitumor activity in P388 cells (Ganu et al., 1991).

(+)-Strebloside is a cardiac glycoside isolated from the stem bark of *S. asper*. It was found to inhibit the proliferation of ovarian cancer cells by blocking cell cycle progression at the G2 phase by inhibiting Na+/K+-ATPase and inducing apoptosis by initiating caspase signaling and PARP (Poly) ADP-ribose) polymerase) cleavage. In addition, (+)-strebloside also potently inhibits the mutant p53 expression by inducing ERK pathways. It also inhibits the NF-κB activity in human ovarian cancer cells (Chen et al., 2017). The cytotoxicity of (+)-strebloside against cancer cells was attributed to the C-10 formyl, C-5, C-14 hydroxy groups, and C-3 sugar unit (Ren et al., 2017). Further, the cardiac glycosides strophanthidin-3-O-α-L-rhamnopyranosyl-(1→4)-6-deoxy-β-D-allopyranoside, 5βH-16β-acetylkamaloside, and mansonin-19-carboxylic acid isolated from the root of *S. asper* exhibited significant cytotoxicity in A549 cells (IC_{50}:0.01 to 3.77 mM) (Miao et al., 2018).

The methanolic extract and fractions of *S. asper* leaves showed antiproliferative activity against human cancer cell lines (A-549, Hep-G2 and K-562) (Rawat et al., 2018). Likewise, the methanolic extract of the stem bark of *S. asper* showed significant anti-tumour activity. It extended the lifespan of Swiss albino mice inoculated with Ehrlich ascites carcinoma mediated through antioxidant activity (Kumar et al., 2013a). Likely, the ethyl acetate fraction of the methanolic extract of the bark of *S. asper* exhibited an anti-tumour effect against Dalton's ascitic lymphoma in Swiss albino mice. Intraperitoneal injection of lymphoma cells was done in mice, and from the next day, the plant extract (200 and 400 mg/kg) was inoculated through the same route for 9 consecutive days. The plant extract supplementation increased the survival rate of mice compared to the tumour-bearing controls. The plant extract expressed a significant and dose-dependent decrease in different growth parameters such as tumour weight and volume. The altered haematological, biochemical and tissue antioxidant parameters, including the RBC (red blood cells), WBC (white blood cells) and haemoglobin count, were restored by the plant extract (Kumar et al., 2015).

6.2 Antioxidant activity

Almost every plant in the plant kingdom possesses antioxidant activity due to phenolic compounds, which act as the first line of defence against pathogens, injury, or any other external factors. An increase in ROS level is one such defence mechanism, and the antioxidant mechanism present in plants will protect the plants from ROS-mediated damages. In this regard, even if plants exhibit antioxidant properties, it's still debatable whether the antioxidant potential of plants can have any impact on human health (Gafner, 2018). However, in this section, the reported antioxidant properties of *S. asper* are described.

The *in vitro* antioxidant activity of the aqueous extract of the leaves of *S. asper* was reported against hydrazyl, nitric oxide, hydroxyl, and superoxide radicals. The reductive ability of the extract was also described. Qualitative analysis of the extract indicated the presence of phytoconstituents with reported *in vitro* antioxidant activity. The individual phytoconstituents of the extract may probably exhibit better antioxidant capability in higher concentrations than the mixture of the extract of *S. asper* (Choudhury et al., 2009).

Cell-free *in vitro* studies using various parts of *S. asper* extract exhibit significant antioxidant activities as determined by DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging, lipid peroxidation inhibition, hydroxyl radical scavenging, and nitric oxide scavenging. The dose dependent Fe^{3+} to Fe^{2+} transformation indicated the reductive ability of the extract (Kakoti et al., 2007; Ibrahim et al., 2013; Prasansuklab et al., 2018). The administration of *S. asper* extract (250 or 500 mg/kg) four days before the single-dose intoxication of carbontetrachloride (CCl_4) significantly increased the glutathione (GSH) and catalase (CAT) levels. The thiobarbituric acid reactive substances (TBARS) level was significantly reduced in the extract-treated groups compared to the CCl_4 control group. In addition, serum biochemical parameters such as transaminases, phosphatase, and total bilirubin levels were significantly restored to normal by administering *S. asper* extract, indicating its significant antioxidant and hepatoprotective properties (Kakoti et al., 2007).

The aqueous extract of *S. asper* leaf at different concentrations significantly decreased the intracellular ROS levels in H_2O_2-treated SK-N-SH cells without making any changes in cell viability (Singsai et al., 2015). Further, the methanolic extract of the root bark of *S. asper* expressed antioxidant activity in rats, which could help reduce the blood glucose levels (Kumar et al., 2012). In addition, the methanolic extract of the stem bark of *S. asper* exhibited significant antioxidant activity in Swiss albino mice inoculated with Ehrlich ascites carcinoma as it effectively modulated the hepatic and renal antioxidant parameters (Kumar et al., 2013a).

6.3 Anti-bacterial activity

The ethanolic extract of the leaves of *S. asper* at concentrations of 250 and 500 mg/ml was observed to express *in vitro* antibacterial activity against *Porphyromonas gingivalis* W50, *Prevotella intermedia*, *Actinomyces naeslundii* (T14V), *Peptostreptococcus micros*, and *Actinobacillus actinomycetemcomitans* ATCC 43718 (Taweechaisupapong et al., 2005a). The acidic fraction of the ethanolic extract of *S. asper* exhibited antibacterial activity against *S. aureus* and *B. subtilis* at the strongest level, with MIC (minimum inhibitory concentration) value of 125 µg/

ml, which was determined by the broth microdilution method (Prasansuklab et al., 2018). Similarly, the methanolic extracts of *S. asper* exhibited antibacterial activity against *Staphylococcus aureus* and *Salmonella Typhi*, which was observed through the agar diffusion method (Mahida & Mohan, 2006).

The aqueous, ethanolic, and methanolic extracts of *S. asper* exhibited antibacterial activity against *Streptococcus agalactiae*, a major fish pathogen causing streptococcosis, at MICs of 125, 250 and 250 µg/ml, respectively (Rattanachaikunsopon & Phumkhachorn, 2009). The aqueous, petroleum ether, ethyl acetate and methanolic extracts of the leaves of *S. asper* exhibited antibacterial activity against *S. paratyphi*, *Staphylococcus epidermidis*, *Shigella dysenteriae*, *Enterococcus faecallis*, *Mycobacterium tuberculosis* and *Candida albicans*, which were monitored by Agar well diffusion method (Arulmozhi et al., 2018).

Lignans (a kind of polyphenol) isolated from the root of *S. asper* revealed antimicrobial activity against *Saccharomyces cerevisiae*, *S. aureus, Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli* with MIC values ranging from 0.0150 to 0.0940 µM (Nie et al., 2016).

The leaf extracts of *S. asper* exhibited 70% anti-biofilm activity at 90 mg/ml against subgingival pathogens (Taweechaisupapong et al., 2014). The aqueous extracts of *S. asper* exhibited *in vitro* antibacterial activity against supragingival plaque-causing bacteria (Rao et al., 2014).

6.4 Anti-fungal activity

The ethanolic extract of the leaves of *S. asper* was observed to exhibit antimicrobial activity against *C. albicans* in human buccal epithelial cells. A brief pre-treatment of the cells with *S. asper* extract could significantly reduce the adhesion of fungal cells to the epithelial cells. Interestingly, pre-treatment of the fungal cells with the leaf extract also reduced their ability to adhere to the epithelial cells. The leaf extract at 125 and 250 mg/ml concentrations exhibited 41 and 61% inhibition of germ tube formation, respectively, which could have affected adherence (Taweechaisupapong et al., 2005b). The adhesion of *C. albicans* to an *in vitro* medium, acrylic strips, was significantly reduced following a 4h exposure to sub-lethal concentrations of 62.5 and 125 mg/ml of *S. asper* extract. Yeast cells, which are commonly found on the palatal surface of a denture acting as a reservoir for *Candida* (Davenport, 1970), were also pre-treated with 62.5 mg/ml of *S. asper* extract, which led to an almost 80% reduction in adherence to the acrylic strips (Taweechaisupapong et al., 2006a). This could, in turn, prevent denture stomatitis, an inflammatory reaction taking place in dental prostheses (Casaroto & Lara, 2010). The extract may also alter the cell surface hydrophobicity of *Candida* species, which may reduce the adhesive properties of the fungi (Taweechaisupapong et al., 2006a; Casaroto & Lara, 2010; Klotz et al., 1985).

6.5 Oral hygiene

The ethanolic extracts isolated from the sticks and leaves of *S. asper* inhibited the growth of *Streptococcus mutans* (Triratana & Thaweboon, 1987), and 50% (v/v) extracts at concentrations of 2-100 mg/mL were found to inhibit the growth of *Streptococci in vitro*. A short (2 min) *S. asper* extract treatment (30 mg/mL) can also be used to reduce the number of *S. mutans* in the oral cavity thereby reducing the chances of dental caries (Wongkham et al., 2001). Interestingly, the same extract was not able to inhibit the growth of other bacteria, namely *S. aureus*, *E. coli*, *P. aeruginosa* and clinical isolates of *Staphylococcus* coagulase-positive, *Staphylococcus* coagulase-negative, *Serratia marcescens, Klebsiella pneumonia, Enterobacter, Burkholderia pseudomeallei* and *C. albicans* (Wongkham et al., 2001). Traditional medical formulations made with *S. asper* and other medicinal plants were scientifically proven to reduce the growth of *S. mutans in vitro* by disc diffusion assay (Joycharat et al., 2012). Ethanolic extracts from the leaves and bark of *S. asper* were able to reduce and inhibit the growth of *S. mutans* and *Streptococcus intermedius,* respectively (Wongkham et al., 2001; Phumat et al., 2018).

A single-blind study was done by Taweechaisupapong et al. to evaluate the antibacterial properties of *S. asper* against *S. mutans* in the oral microbiota. A mouth rinsing solution was prepared with *S. asper* extract (80 mg/mL) and was used once for 60 seconds by 30 healthy human subjects. Saliva samples were collected after 0, 0.5, 1, 3, 5 and 6 h post rinsing and were compared to the samples collected before rinse. The population of *S. mutans* and the total bacteria in the mouth were calculated from the saliva samples. It was observed that *S. asper* leaf extract significantly reduced the count of *S. mutans* without changing the oral ecology or the salivary pH compared with distilled water (Taweechaisupapong et al., 2000).

Another single-blind study was done using the same rinsing solution to analyze its effect on gingivitis and plaque formation on 35 subjects having moderate gingival inflammation. A professional teeth cleaning was done for all the participants, and then they were asked to rinse twice for 60 seconds for 4 days, followed by monitoring the gingival index. The same procedure was repeated after an incubation period of 10 days. The mouth rinse containing *S. asper* promoted gingival health by significantly reducing the gingival index without having a significant effect on plaque growth compared to distilled water (Taweechaisupapong et al., 2000). Similarly, 42 chronic periodontitis subjects were treated with subgingival irrigation with *S. asper* leaf extract, which effectively reduced the gingival inflammation (Taweechaisupapong et al., 2006b). The effect of *S. asper* on the promotion of gingival health was recently examined. A randomized controlled trial was done involving 76 subjects with moderate gingival inflammation. The subjects were divided into 4 groups, and each group received chlorohexidine (positive control), placebo (negative control), *S. asper* alcoholic extract and *S. asper* aqueous extract, respectively, as a mouth rinse. Saliva samples were collected before the rinse and 2, 30, 60 and 120 minutes after the rinse. The results pointed out that the extract could significantly affect gingival health without significantly affecting plaque growth (Gunjan et al., 2020).

6.6 Anti-macrofilaricidal activity

Lymphatic filariasis is a vector-borne tropical disease that could lead to abnormally swollen limbs, enlarged scrotum, breasts, and clitoris. The stem bark of *S. asper* was observed to act against filarial parasites *in vitro* and *in vivo*. Two cardiac glycosides,

asperoside and strebloside, identified from the chloroform and ethyl acetate fractions, respectively, exhibited significant antifilarial activity. The *in vitro* antifilarial activity of asperoside was found to be significantly higher against *Brugia malayi* (at 0.06 pg/mL) than *Acanthocheilonema viteae* (at 0.975 pg/mL) (Chatterjee et al., 1992). Additionally, asperoside and strebloside were able to act upon another bovine filarial parasite, *Setaria cervi*. At higher concentrations (10 µg/mL), both glycosides were able to cause the death of parasites in a couple of hours, whereas lower doses were also active against the parasites as they were able to inhibit the glucose uptake, glutathione metabolism and motility (Singh et al., 1998; Singh et al., 1994).

6.7 Neuroprotective activity

The ethanolic extracts of the leaves of *S. asper* exhibited positive effects against glutamate-induced toxicity in HT22 hippocampal neuronal cells in a dose-dependent manner. The extract was also able to reduce oxidative stress induced by glutamate, an excitatory amino acid whose excess activation results in neuronal dysfunction and cell death. Additionally, the extract could dose-dependently reduce the levels of intracellular ROS, thereby protecting the cells from ROS-mediated cytotoxicity. Interestingly, these activities were mediated by the Nrf2 mediated pathway inside the cells, which was confirmed with the mRNA and protein analysis (Prasansuklab et al., 2017). Further, basic and neutral fractions of the extract exhibited cholinesterase inhibitory effect in a dose-dependent manner, indicating the possibility of ameliorating Alzheimer's disease (Prasansuklab et al., 2018).

The ethanolic extract of *S. asper* extended the lifespan of the Aβ transgenic strain of *C. elegans*. It reduced the paralysis phenotype of the strain, which further validated the neuroprotective potential (Prasanth et al., 2021). The aqueous extracts of *S. asper* leaves were reported to have anti-Parkinson's activity against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity in mice. MPTP is a neurotoxin known to induce Parkinson-like symptoms in laboratory animals in preclinical trials. Male C57BL/6 mice were inoculated with MPTP intraperitoneally to induce Parkinson's-like symptoms. These animals were fed with 200 mg/kg of *S. asper* extract daily for 32 days. This extract could antagonize the motor and cognitive function deficits induced by MPTP, which was evident through the assessment of catalepsy, beam balance ability, olfactory discrimination, social recognition, and spontaneous locomotor activity. Additionally, the antioxidant capacity of the extract, which was observed in SK-N-SH cells, could also have aided in the anti-Parkinson's activity since ROS can play a major role in accelerating neurodegenerative diseases (Singsai et al., 2015).

Verma et al. explored the constituents of the stem bark of *S. asper* by using the microwave-assisted extraction (MAE) technique and analyzed their efficacy in treating neuro-pharmacological disorders by using BALB/c mice. Betulin isolated from the stem bark of the plant and n-hexane fraction exhibited a protective effect against electroshock-induced convulsions. Moreover, the n-hexane and dichloromethane fractions (400 mg/kg) significantly showed antidepressant activity (Verma et al., 2016). A dose-dependent diminution of epileptic seizures was detected, which could be due to the presence of betulin, which could penetrate the blood-brain barrier and competitively bind with the $GABA_A$ receptor to exhibit anticonvulsant activity (Verma et al., 2016).

6.8 Anti-diabetic activity

The petroleum ether extract of the leaves of *S. asper* displayed anti-diabetic activity and potential control over peripheral glucose utilization in diabetic rats. Treatment with the extract for 30 days resulted in a significant reduction in the fasting blood sugar level and restoration of glycolytic and gluconeogenic enzyme activities along with glycogen content and insulin level in diabetic rats. Analysis of the petroleum ether extract showed the presence of apiol, which accounts for the anti-diabetic activity of the extract (Choudhury et al., 2012).

Likewise, the petroleum ether extract of the root of *S. asper* exhibited anti-diabetic activity against alloxan-induced diabetes in mice. The extract was found to reduce glucose in the blood, which was observed in the glucose tolerance test. The maximum reduction in the level of glucose in the blood was observed after 4 h in mice treated with 250 mg of extract/kg of body weight. Long-term treatment (subacute study) with the extract showed a significant reduction in blood glucose levels as measured on 0, 1, 7, 14, 21 and 28th days, indicating the anti-diabetic activity of the extract (Karan et al., 2012).

The petroleum ether extract of the stem bark of *S. asper* also expressed significant anti-diabetic properties in streptozotocin-induced diabetes in rats. Streptozotocin is a broad-spectrum antibiotic compound used to induce diabetes in experimental animals. The administration of α-amyrin acetate, which was found to be the active constituent of the extract, was also able to lower the glucose level in the plasma and prevent liver damage. Additionally, oral administration of α-amyrin acetate exhibited a significant anti-hyperglycaemic effect, lower total cholesterol, and triglycerides, and increased the HDL-cholesterol level in diabetic rats. Overall, the stem bark extract and the α-amyrin acetate effectively controlled glycemia, which was evident in the significant reduction in glycosylated hemoglobin (HbA1c) level and the significant increase in the level of insulin (Karan et al., 2013). Similarly, the methanolic extract of root bark of *S. asper* reduced the blood glucose level in diabetes-induced wistar rats (Kumar et al. 2012).

6.9 Anti-Hepatitis activity

Lignans from the heartwood of *S. asper* were analyzed for their cytotoxicity and potential anti-hepatitis B virus (HBV) activity, and the results suggested that 6-hydroxyl-7-methoxyl-coumarin and ursolic acid could inhibit the secretion of HBV surface antigen (HBsAg) and HBV e-antigen (HBeAg). The neolignans reduced HBeAg and HBsAg expression. These neolignans exhibited low or no cytotoxicity (Li et al., 2012a). Neolignans such as (7'R,8'S,7"R,8"S)-erythro-streblus lignanol G, isomagnolol, magnolol, and isolariciresinol displayed anti-HBV activity in HBV transfected HepG2.2.15 cell lines (Li et al., 2012b).

The methanolic extracts of the heartwood, bark, and root of *S. asper* exhibited potential anti-HBV activities. Their inhibitions ranged from 14.1% to 64.7%, 15.1% to 65.9% and 16.0% to 66.5%, respectively for HBsAg with low or no cytotoxicity.

The solvent fractions of these methanolic extracts, especially the ethyl acetate and n-butanol fractions of the root, exhibited significant anti-HBV activity (Chen et al. 2012).

6.10 Anti-inflammatory activity

The anti-inflammatory action of *S. asper* extract was attributed to the suppression of LPS-induced expression of COX-2 and iNOS in RAW 264.7 macrophages. A dose-dependent reduction in the expression of mRNA levels of COX-2 and iNOS was observed on treatment with *S. asper* extract, indicating its anti-inflammatory effect (Sripanidkulchai et al., 2009). The ethanolic extract of the leaves of *S. asper* exhibited anti-inflammatory activity against carrageenan-induced paw oedema in rats. Intraperitoneal administration of the extract showed a dose-dependent inhibition of oedema and related mechanisms. At the highest dose tested (500 mg/kg), the inhibition of oedema was like the standard non-steroidal anti-inflammatory drug diclofenac (Sripanidkulchai et al., 2009).

6.11 Anti-diarrhoeal activity

The methanolic extract of *S. asper* was observed to exhibit anti-diarrhoeal activity in Swiss albino rats. Diarrhoea was induced in rats using castor oil or magnesium sulfate. In both cases, *S. asper* extract (100, 200 and 400 mg/kg) intervention significantly reduced the total number of diarrhoeal feces in a dose-dependent manner (Shahed-Al-Mahmud et al., 2020).

6.12 Anti-aging activity

The ethanolic extract of the leaves of *S. asper* exhibited anti-aging activity in the model nematode *Caenorhabditis elegans* as it could significantly extend the survival of the nematode larvae (Prasansuklab et al., 2017), which the Mitogen mediated activated protein kinase (MAPK) pathway and SKN-1 (ortholog of mammalian Nrf-2) transcription factor (Prasanth et al., 2021).

6.13 Anti-parasitic activity

The aqueous extract of the leaves of *S. asper* showed moderate activity at concentrations of 5, 50, 500 and 1000 μg/mL against *Trypanosoma evansi,* the causative agent of surra in animals (Talakal et al., 1996).

6.14 Analgesic activity

The ethanolic extract of *S. asper* aerial parts was evaluated for analgesic activity using the hot plate and acetic acid-induced abdominal constrictions in mice. The results proved that the extract (100 and 200 mg/kg) has significant analgesic properties (Basuri, 2011).

7 Health hazards

The bark of *S. asper* was used to prepare home-grown sun-dried tobacco in the northern parts of Thailand (Khan et al., 2008).

The chloroform extract of the root of *S. asper* was observed to be lethal as it leads to the death of canines and rats when administered intravenously (Gaitonde et al., 1964).

The methanolic extract of the bark of *S. asper* was fed to Zebrafish embryos to analyze the extract's developmental toxicity and behavioral safety. As the dosage of the extract was increased, the heart rate of the zebrafish was also increased proportionately along with slight oedema of the heart muscle at a higher dose, indicating the possible health hazards of consuming the plant extracts (Basuri, 2011).

Studies on lymphatic filariasis treatment using *S. asper* extracts showed positive results (Chatterjee et al., 1992; Singh et al., 1998; Singh et al., 1994). However, while analyzing the effects of the same extracts in human subjects, adverse levels of vomiting were observed, which could be due to the presence of cardiac glycosides (strebuloside and asperoside) in the bark (Kumar et al., 2013b).

8 Conclusions and future perspectives

Although reports on the pharmacological activities of phytoconstituents are on an exponential rise, only a comparative study of compounds on a particular aspect would provide a better understanding and lead to a conclusion on which compound works better than the other. Each compound has its mechanism of action, and a single compound may not exert all the pharmacological activities when used alone. Still, it could show synergism or additive effect when used in combination. The compounds identified from *S. asper* are equally efficient in extending various health benefits compared to other major and widely accepted active compounds and available drugs.

However, we think that standardized plant extracts would be more beneficial than pure compounds because they contain diverse macro and micro compounds in a defined ratio, which would exert synergistic beneficial activity in various health situations; this may not be achieved at the same level through individual compounds. Additionally, the chances of side effects are lesser with plants than with pure compounds. However, the plant's bioavailability, the extract's stability, and limited clinical trials are some of the key issues that must be investigated.

The study revealed that *S. asper* is an important medicinal plant with several proven therapeutic potentials *in vitro* and *in vivo*. However, there are no prescribed *S. asper*-based therapeutic agents to manage diseases. Enough studies are available in *vitro* and *in vivo* models to prove the potential of *S. asper*; however, further clinical studies are required for the development of safe and effective therapeutics. Presently, the clinical trials are limited and focus more on oral hygiene properties, which needs to be further extended to analyze other medicinal properties. Many plants have been identified to possess similar biological and health benefits. The development of strategies to identify the activity level will aid the listing of plants with the highest health benefits. It could help have more plants as therapeutics for the same disease, which could eventually reduce the problem of bioavailability.

Conflict of interest

There are no conflicts of interest.

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Supplementary Material

Supplementary material accompanies this paper.

Table S1. Traditional use of S. asper.

Table S2. The major phytoconstituents of S. asper.

Table S3. Medicinal Properties of S. asper.

Figure S1. The major phytochemicals of S. asper (Andrographolide, carnosic acid, α-d-glucopyranoside, linolenic acid, α-farnesene, lupenyl acetate, β-sitosterol, and farnesyl acetate). The chemical structures were adapted from PubChem, National Center for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/).

Figure S2. The major phytochemicals of S. asper (Octadecanoic acid, hexadecanoic acid, phytol, acteoside, strophanthidin, oleoyl oxazolopyridine, mansonin, β-caryophyllene, butanedioic acid, myo-inositol, and glycerol). The chemical structures were adapted from PubChem, National Center for Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/).

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