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PHARMACOGNOSTIC AND PHYTO-PHARMACOTHERPEUTIC PROFILE OF *SPHAERANTHUS INDICUS*: A POTENT INDIAN FOLK LORE MEDICINAL PLANT

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ABSTRACT

Sphaeranthus indicus Linn. (SI) (Asteraceae) is widely used in Ayurvedic system of medicine to treat vitiated conditions of epilepsy, mental illness, hemicrania, jaundice, hepatopathy, diabetes, leprosy, fever, pectoralgia, cough, gastropathy, hernia, hemorrhoids, helminthiasis, dyspepsia and skin diseases. There are reports providing scientific evidences for hypotensive, anxiolytic, neuroleptic, hypolipidemic, immunomodulatory, anti-inflammatory, bronchodialatory, antihyperglycemic, hepatoprotective, anti-malarial, antioxidant, anti-microbial activities of this plant. A wide range of phytochemical constituents have been isolated from this plant including sesquiterpene lactones, eudesmenolides, flavanoids and essential oil. This comprehensive review explores the reported accountable investigations on the morphological studies, phytochemical studies, ethnobotanical uses and pharmacological activities of *Sphaeranthus indicus.* Therefore it is very significant to give the frontline position to this plant in the list of the most potent Indian traditional plant.

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INTRODUCTION

It is a well-known fact that traditional system of medicines have always played important role in meeting the global healthcare needs. They are continuing to do so at present and shall play major role in future as well. The system of medicines that are considered to be Indian in origin or the systems of medicine, which came to India from other countries and assimilated in Indian culture, are known as Indian Systems of Medicine. India has the unique distinction of having six recognized systems of medicine in this category. They are *Ayurveda*, *Siddha*, *Unani* and *Yoga*, Naturopathy and Homoeopathy. [1]

Among them, *Ayurveda* has been practiced for thousands of years. Considerable research on pharmacognosy, chemistry, pharmacology, and clinical therapeutics has been carried out on Ayurvedic medicinal plants. Natural products, including plants, animals, and minerals have been the basis of treatment of human diseases. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies. [2]

Plants have played a significant role in maintaining human health and improving quality of human life since long and have served humans well as valuable components of medicines, seasoning, beverages, cosmetics, and dyes. The popularity of herbal medicine in recent times is based on the premise that plants contain natural substances that can promote health and alleviate illness. Therefore, the focus on plant research has increased all over the world and a large body of evidence show immense potential of medicinal plants used in various traditional system. There are many herbs that are predominantly used to treat cardiovascular, liver, central nervous system (CNS), digestive, and metabolic disorders. Given their potential to produce significant therapeutic effect, they can be useful as drug or supplement in the treatment or management of various diseases. Herbal drugs or medicinal plants, and their extracts and isolated compounds have demonstrated a wide spectrum of biological activities. Ethnopharmacological studies on such herbs or medicinally imported plants continue to interest investigators throughout the world. [3]

Plant profile:

It is a wild plant and cultivated throughout the hotter parts of India and Ceylon. It is cultivated in all hot countries. [4]

Common names [4]

Sanskrit: *Mundi, Sravani Kadamba, Pus.pika, Alambusta*
Gujarati: Gorakhmundi
Hindi: Mundi
Marathi: Mundi, Baras Bondi
Kannada: Mirnagnee, Atookamanni, Mirangnee
Tamil: Kotook, Karandai, Kottakarthai
Urdu: Mundi

Taxonomic Classification [4]

Kingdom: Plantae
Subkingdom: Viridaeplantae
Phyllum: Tracheophyta
Subphyllum: Euphyllophytina
Infraphyllum: Radiatopses
Class: Magnoliopsida
Subclass: Asteridae
Superorder: Asteranae
Order: Asterales
Family: Asteraceae
Genus: Sphaeranthus
Species: S. indicus
Parts used: Entire plant

Figure 1. Morphology of *Sphaeranthus indicus* Linn.

Ayuervedic properties [5]
Rasa: Madhura, Katu, Tikta, Kasaya
Guna: Laghu
Virya: Usna
Vipaka: Katu
Karma: Medhya, Vit.aghna, Vatakaphahara, Arsadosa, Vinasaka.

Microscopic characteristics [4] **(Fig. 2)**
Leaf:

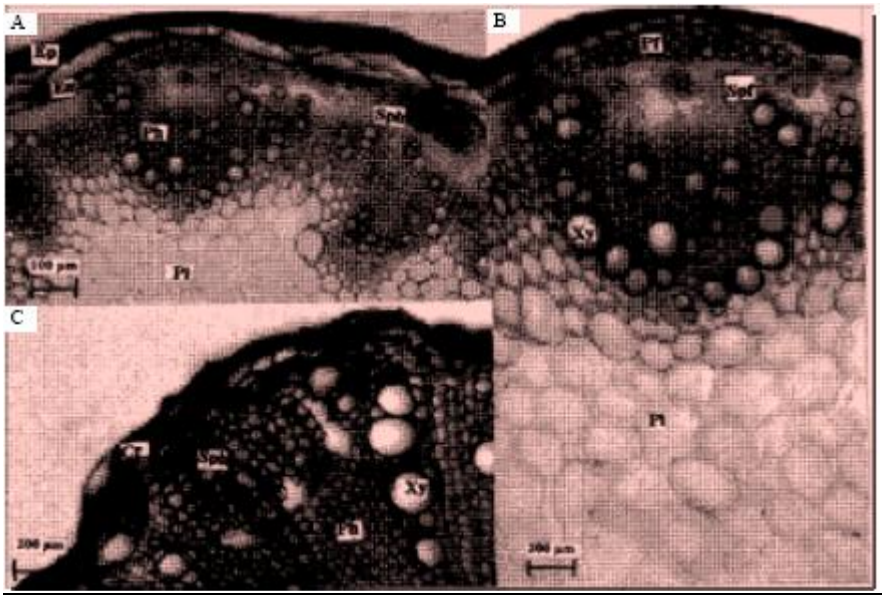
The leaf is dorsiventral and shows abundant trichomes of varying types on both the epidermis. Simple trichomes are three to four celled, thick walled and measure 130.8-145.2 µm in length and 29.0-43.5 µm in width. Trichomes are straight/knee shaped, with a swollen base and with collapsed cell at the middle or at the apex. Midrib shows three to four collateral vascular bundles associated with a group of sclerenchymatous cells on either side.

Stem:

The stem shows cork with two to three layers of parenchymatous cells covered with papillose cuticle having trichomes and can be distinguished by the presence of a discontinuous ring of lignified pericyclic fibers and a well-developed ring of bicollateral vascular bundle surrounding the pith. Medullary rays are pitted, lignified and about uni-tetraseriate.

Root:

The root shows on its outer side metaderm, a typical brown colored tissue. It consists of suberized cells, arranged irregularly and forms a protective layer. Radial groups of pericyclic fibers and few stone cells are seen alternating with radially arranged secretory canals in the secondary cortex. Phloem is parenchymatous and radially arranged. Medullary rays are pitted, lignified and about two to five seriate.



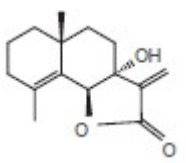
(A) Photomicrograph showing transverse section of the stolon of *S. indicus*, (B) A portion of vascular bundle of the stolon (enlarged) Ep-epidermis, En-endodermis, Pf-pericyclic fibres, Ph-phloem, Xy-xylem, Pi-pith, Sph-secondary phloem, Spf-secondary phloem fibres and (C) Microscopy of the root of *S. indicus* Cr-cork, Xy-xylem, Ph-phloem, Sph- secondary phloem.

PHYTOCHEMISTRY

Phytochemical analysis of roots and rhizome of SI reveals the presence of steroids, fats and oils in petroleum extract; carbohydrates, proteins, amino acids, tannins, phenols, steroids, fats and oils in the methanolic extract and carbohydrates, proteins, amino acids, tannins**,** phenolic compounds, saponins and alkaloids in the aqueous extract. [6, 7]

Phytochemical investigations/ reports
Sesquiterpene lactones

Rahman et al. (1994) isolated the sesquiterpene lactone, 7α-hydroxyfrullanolide (P-1) from the plant. [8] A new sesquiterpene lactone, 7α-hydroxyeudesm-4-en-6, 12-olide (P-2) and a new sesquiterpene acid, 2-hydroxycostic acid (P-3), along with the known compounds β-eudesmol (P-4) and ilicic acid (P-5) have been isolated from the acetone extract of the plant. [9]



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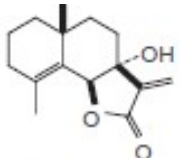

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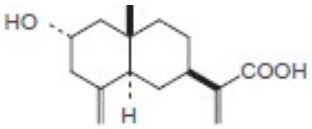

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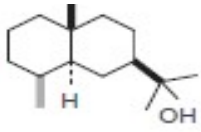

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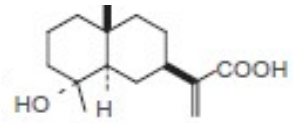
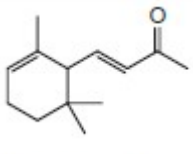


P-5

Volatile principles

The plant also contains the volatile principles mainly α-ionone (P-6), β-ionone (P-7), ocimene (P-8), δ-cadinene (P-9), α-terpinene (P-10), α-citral (P-11), geraniol (P-12), methyl-chavicol (P-13), p-methoxy cinnamaldehyde (P-14). [10, 11]



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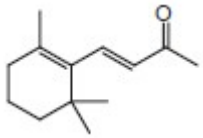

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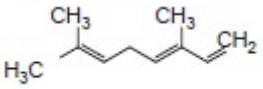

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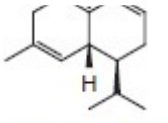

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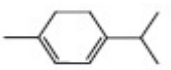

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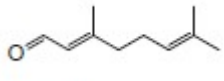

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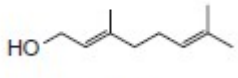

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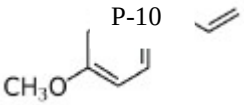

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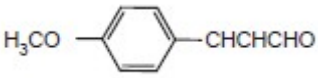
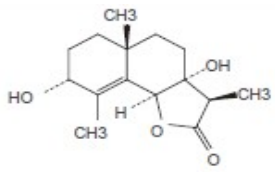


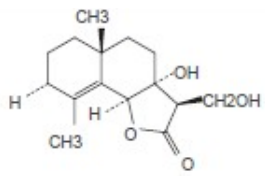
P-14

Eudesmanolides

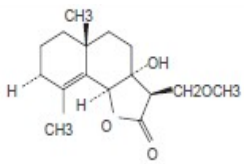
Shekhani et al. (1991) isolated three eudesmanolides, 11α, 13-dihydro-3α, 7α-dihydroxyfrullanolide (P-15), 11α, 13-dihydro-7α, 13-dihydroxyfrullanolide (P-16) and 11α, 13-dihydroxy-7α-hydroxy-13-methoxyfrullanolide (P-17) from the flower heads of *S. indicus*. He performed structural elucidation of those eudesmanolides by using various analytical techniques and found that the IR spectra of all those compounds showed characteristic 5-membered lactone absorptions (1752, 1745 and 1757 cm-1, respectively) and revealed the presence of -OH and non-conjugated olefin functions. Moreover the molecular ions were confirmed by Fast Atom Bombardment Mass Spectroscopy (FABMS) and Field Desorption Mass Spectrometry (FDMS).[12]



P-15

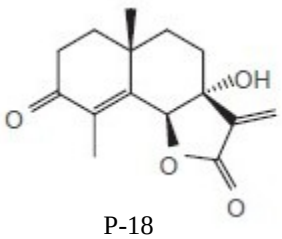


P-16

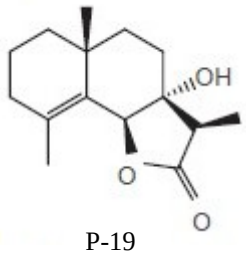


P-17

In addition to this, Jadhav et al. (2007) carried out isolation of two new eudesmanolides from the aerial part of *S. indicus* and their structures were established as 11α, 13-dihydro-3α, 7α-dihydroxyeudesm-4-en 6α, 12-olide (P-18) and 4-en-6β, 7α-eudesmanolide (P-19) on the basis of spectral data and comparison of spectral data with closely related compounds. Their chemical structures are as following. [13]



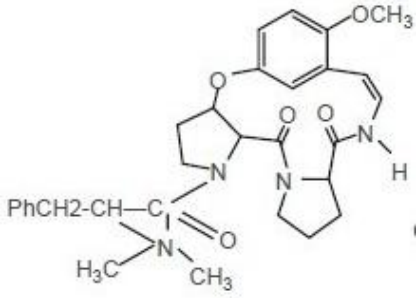
P-18



P-19

Alkaloids

Two peptide alkaloids (P-20 & P-21) have been isolated from flowers of the plant. [14]



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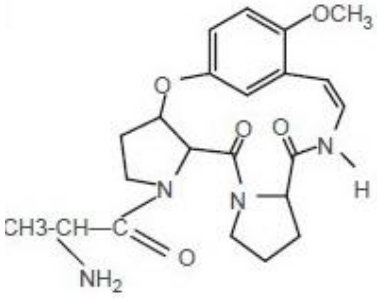
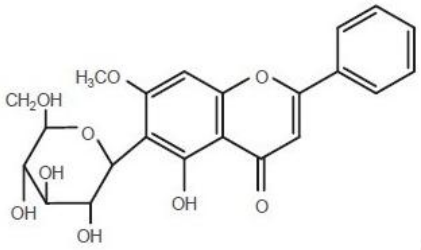


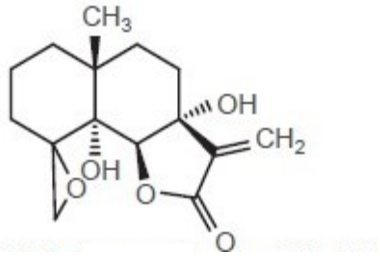
P-21

Flavonoids

Duraipandiyan et al. (2009) isolated a novel flavonoid C-glycoside, 5-hydroxy-7-methoxy-6-C-glycosylflavone (P-22), from the aerial part of *S. indicus*. The structure was established by Mass Spectroscopy (MS) and Proton Nuclear Magnetic Resonance (1H-NMR) studies. [15] Moreover a novel isoflavone glycoside, 5, 4'- dimethoxy-3'- prenylbiochanin 7-O-β-D-galactoside (P-23), was isolated from the leaves of the plant. [16]



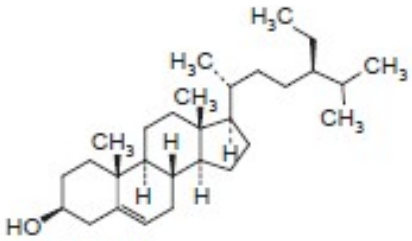
P-22



P-23

Phytosterols

The alcoholic extract of powdered drug contains sterols, stigmasterol (P-24) and β-sitosterol (P-25). [17, 18]



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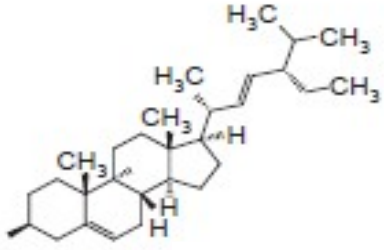
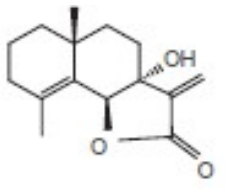


P-25

Glycosides

The plant is also reported to contain β-D-glucoside of 7-Hydroxyfrullanolide (P-26).[19] A new sesquiterpene glycoside, sphaeranthanolide (P-27), has been isolated from the flowers of the plant. [20]



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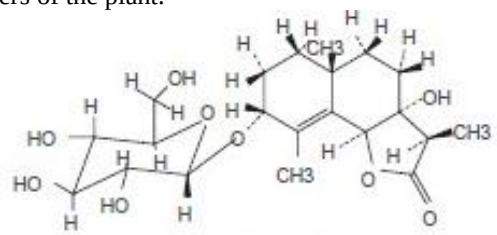

P-27

Amino acids

Yadav & Kumar (1998) reported the presence of amino acids like, glycine, alanine, valine, leucine, histidine, cysteine, lysine, aspartic acid and glutamic acids and sugars viz., D-arabinose, L-rhamnose, lactose, raffinose, D-galactose, maltose, D-fructose and D-glucose in the leaves of the plant.[21]

Garg K et al. (2019) preformed Gas Chromatography-Mass Spectrometry of the methanol and ethyl acetate extracts of SI fruits and identified various phytoconstituents. They detected and identified Totally 26 compounds. Among them 13 constituents were found in methanol extract and 13 constituents were in ethyl acetate extract. The authors focused more on two biopotent compounds, stigmasterol and lupeol and explained their importance in the treatment of arthritis and prove the anti-arthritic potential of the plant. [22]

ETHNOPHARMACOLOGY

Pharmacological Reports:

Neuroprotective potential

Anxiolyic action

Kaur R et al. (2017) reported anxiolytic activity of SI fruit and seed extracts. In their investigation they evaluated anxiolytic action by using elevated plus maze, open field test and foot-shock induced aggression test. The results showed that petroleum ether extract (10 mg/kg), alcoholic extract (10 mg/kg) and water extract (30 mg/kg) produced prominent anxiolytic activity in mice. The study showed an increase in the time spent percent entries and total entries in the open arm of the elevated plus maze; increased ambulation, activity at center and total locomotion in the open field test and decreased fighting bouts in the foot-shock induced aggression test suggesting anxiolytic activity of the plant.[23]

Neuroleptic activity

Neuroleptic activity of petroleum ether, alcohol and water extracts of flowers of SI (30, 100 and 300 mg/kg, *i.p.*) were investigated using apomorphine induced cage climbing and catalepsy in mice model. Only the petroleum ether extract (300 mg/kg, *i.p.)* reduced total time spent in apomorphine induced cage climbing. The aqueous (300 mg/kg, *i.p.*) and alcoholic (300 mg/kg, *i.p.*) extracts showed catalepsy while petroleum ether extract was devoid of it.[24]

Anti-psychotic potential

In 2009, Galani VJ & Patel BG evaluated the anti-psychotic potential of SI in rats and mice. They observed the effects hydroalcoholic extract of SI (100, 200 and 500 mg/kg, *p.o.*) on spontaneous motor activity, pentobarbital-induced sleeping time, motor coordination, exploratory behaviour and apomorphine-induced stereotypy in mice. The extract (100, 200 and 500 mg/kg, *p.o.*) reduced the cataleptic symptoms in rats induced by haloperidol. The extract showed significant reduction of spontaneous motor activity, exploratory behaviour and prolonged pentobarbital sleeping time in the mice. Narcoleptic potential was observed by the results in which the extract antagonized apomorphine-induced stereotypy in mice, produced catalepsy and potentiated haloperidol-induced catalepsy in rats. Moreover the extract had no effect on motor-coordination as determined by the rota rod test. These results provide evidence that the plant may contain neuroprotective phytocompounds. [25]

Extending the above research study, Galani & Patel (2010) also screened the neuroleptic activity of the hydroalcoholic extract of the whole SI plant at doses of 100, 200 and 500 mg/kg, *p.o.* According to the results of the study, the extract produced catalepsy, potentiated haloperidol-induced catalepsy and antagonized apomorphine-induced stereotypy. It also reduced locomotor activity, exploratory activity and potentiated pentobarbital induced sleep in mice. [26]

Anticonvulsant effect

Bikash Kumar Nanda et al. (2010) investigated anticonvulsant effect of the petroleum ether, benzene, chloroform, ethanol and triple distilled water extract of all parts of the plant of the on electrically and chemically induced seizures. During study all the extracts were administered at doses 200 and 400 mg/kg, *i.p.* body wt. to evaluate anticonvulsant effect on maximal electroshock-induced seizures and pentylenetetrazole-, picrotoxin-, bicuculline- and N-methyl-dl-aspartic acid-induced seizures in mice. The latency of tonic convulsions and the number of animals protected from tonic convulsions were noted. The results showed that ethanol extract (200- 400 mg/kg) significantly reduced the duration of seizures induced by maximal electroshock (MES). However, only 200 and 400mg/kg of the extract conferred protection (25 and 50%, respectively) on the mice. The same doses also protected animals from pentylenetetrazole-induced tonic seizures and significantly delayed the onset of tonic seizures produced by picrotoxin and N-methyl-dl-aspartic acid. The extract had no effect on bicuculline-induced seizures. The aqueous extract (400mg/kg) significantly reduced the latency, but did not alter the incidence of seizures elicited by maximal electroshock to any significant extent. The data suggests that the SI plant contain anticonvulsant activity via non-specific mechanisms since it reduced the duration of seizures produced by maximal electroshock as well as delayed the latency of seizures produced by pentylenetetrazole and picrotoxin. [27]

Anti-amnestic Activity

Patel MB & Amin D (2012) discovered novel Acetylcholinesterase (AChE) inhibitors from SI flower heads. In their study they performed *in vitro* AchE inhibitory activity of various extracts of the plant flower heads. The petroleum ether extract of SI flowers exhibited significant activity due to its sesquiterpene lactone content responsible for *in vitro* AChE inhibition. Further the antiamesic activities of SI flowers in mice on the learning and memory impairments induced by scopolamine (1.0 mg/kg, *i.p.*) were examined. The results exhibited that administration of SI pet. ether extract (10 mg/kg, *p.o.*) significantly reversed cognitive impairments in mice by passive avoidance test (P<0.05). It also reduced escape latencies in training trials and prolonged swimming times in the target quadrant during the probe trial in the water maze task (P<0.05). These results indicated that SI, due to its sesquiterpene lactones had shown anti-cholinesterase activity. Further a major sesquiterpene lactone, 7-hydroxy frullanolide along with other constituents were isolated from the extract and evaluated for AchE inhibitory activity. Though negative results were obtained in case of isolated compounds. [28]

Anticancer activity

Nahata A et al (2012) screened the anticancer activity of SI along with *Ganoderma lucidum* and *Urtica dioica* against human cancer cell lines. In the study petroleum ether, ethanolic, and aqueous extracts of SI, *G. lucidum*, *U. dioica* were subjected to cytotoxicity studies using 7 different cancer cell lines. Potent cytotoxicity was noted in petroleum ether extract of SI, which inhibited proliferation of various cancer cell lines. Growth inhibition was determined by sulforhodamine B assay. Two biochemical markers, namely β-sitosterol and 7-hydroxyfrullanolide were isolated and characterized using high-performance thin layer chromatography, melting point, Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, and mass analysis. Cytotoxicity of isolated β-sitosterol and 7-hydroxyfrullanolide were also determined. The IC_{50} of SIP was calculated in the HL-60 cells and was found to be 53µg/ml. Furthermore, SI plant induced apoptosis in human leukemia HL60 cells as measured by several biological end points. Cell cycle analysis and change in mitochondrial membrane potential was quantified by flow cytometry. Subsequently, using annexin V/PI assay, proportion of cells actively undergoing apoptosis was determined. Changes in DNA were observed by DNA ladder assay. SIP induced apoptotic bodies formation, induced DNA laddering, enhanced annexin-V-FITC binding of the cells, increased sub-G0 DNA fraction, and induced loss of mitochondrial membrane potential (ΔΨm) in HL-60 cells. SI plant also elevated the caspase 3 and caspase 9 levels in the HL-60 cells, which clearly indicates the involvement of the intrinsic proteins in inducing apoptosis. The results established that SI plant has apoptosis-inducing effect against HL-60 cells in vitro and can be a promising candidate for future anticancer agents. Further two biopotent compounds, β-Sitosterol and 7-hydroxyfrullanolide were isolated, responsible for anti-cancer activity.[29]

Anti-diabetic activity

The alcoholic extract of plant was reported to have anti-diabetic activity. In the study 50% ethanolic extract was screened in the nicotinamide (120 mg/kg, *i.p.*) and streptozotocin (60 mg/kg, *i.p.*) induced diabetes in rats. Fasting plasma glucose levels, serum insulin levels, serum lipid profiles, magnesium levels, glycosylated hemoglobin, changes in body weight and liver glycogen levels were evaluated in normal and diabetic rats. Fasting normal rats treated with the extract showed significant improvement in oral glucose tolerance test. Oral administration of the extract for 15 days resulted in a significant decrease in blood glucose levels and increase in hepatic glycogen and plasma insulin levels.[30]

Furthermore Gubrele D et al. (2018) also investigated hypoglycemic effect of various plant parts of SI by using *in vitro* α-amylase inhibition assay. The results revealed that methanolic extract of SI flowers showed the highest effect. Further during Liquid Chromatography-Mass Spectroscopy analysis active compound swietenine was detected in flower extract. Therefore the presence of swietenine is a clear indication of hypoglycemic activity of the plant.[31]

Hepatoprotective activity

Nayak SS et al. (2007) reported the hepatoprotective effect of aqueous and methanolic extracts of flower heads of the plant on acetaminophen-induced heptotoxicity. He observed a significant decrease in liver function markers such as serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), acid phosphatase (ACP) and alkaline phosphatase (ALP), bilirubin and total protein. The results suggested that the methanoloic extract was more effective compared to the aqueous extract. That result was also supported by studying the liver histopathology of treated animals. [32]

In addition, Tiwari BK et al. (2010) studied the effect of the plant methanolic extract in enhancement of the activities of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase and diminished the amount of lipid peroxides against acetaminophen-induced hepatotoxicity in these animals. [33]

Mansoori MH et al. (2018) investigated the antioxidant and hepatoprotective activity of SI leaves against the carbon tetrachloride (CCl_4)-induced hepatotoxicity using *in vitro* and *in vivo* models of liver injury. In the study they prepared the successive extracts of SI leaf powder and then administered to rats to evaluate *in vitro* human live hepatoma cell line study and *in vivo* hepatoprotective activity against CCl_4 intoxicated mice. The results indicated that all the extracts gave promising effect in dose dependent manner. Though ethanol extract gave the most significant results among all the extracts by preventing the hepatic malondialdehyde level by 22.22, 26.67, and 58.89% with the doses of 100, 200, and 400 mg/kg, respectively. Thus this study suggested that the presence of flavonoids in SI leaves exhibiting marked antioxidant and hepatoprotective activities. [34]

Immunomodulatory activity

Shekhani et al.(1990) investigated immunomodulatory activity of SI by evaluating its effect on antibody titre, delayed type hypersensitivity response, phagocytic function and cyclophosphamide-induced myelosuppression in mice. In his study, he found that the methanolic extract and petroleum ether, chloroform and remaining methanol fractions of flower heads of the plant were found to be effective in increasing the phagocytic activity, haemagglutination antibody titre and delayed type hypersensitivity.[35] Shekhani et al. (1991) proved that the eudesmanolides like sesquiterpenes, present in the plant are responsible for the immunostimulating activity.[12]

Moreover Bafna AR et al. (2004) also reported immunomodulatory activity of the methanolic extract of the plant flower heads. In his experiment, the methanolic extract was found potent in normalizing total WBC levels in the case of cyclophosphamide-induced myelosuppression in mice.[36]

Furthermore Anarthe SJ et al. (2015) investigated the plant for its immunomodulatory activity. In their study, they prepared extract and administered different dose levels 100, 200 and 400 mg/kg body wt. in healthy wistar albino rats. The assessment of immunomodulatory activity was done for humoral immunity (antibody titre, plaque forming cell assay and quantitative haemolysis of SRBC) and cellular immunity (delayed type hypersensitivity, T- cell population and drug induced myelosuppression) with antigen challenge by sheep RBCs. The Methanolic extract of the plant along with the antigen (sheep red blood cells) showed significant increase in the circulating antibody titer and the number of c in the spleen at the dose of 100 mg/kg body wt. as compared to 200 and 400 mg/kg body wt. The methanolic extract also showed significant (P<0.01) increase in the DTH response, restoration of histological parameters, increase in lymphocytes and rosettes formation in T-cell population at dose of 400 mg/kg body wt. as compare to 100 and 200 mg/kg body wt. Thus the present experiment reveals that SI can be used as immunomodulator for activation of both specific and non-specific immune responses.[37]

Antimicrobial activity

A bicyclic sesquiterpene lactone isolated from the petroleum ether extract of the aerial part of the plant was reported to have antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Fusarium sp.*, *Helminthosporium sp.* and other micro organisms.[38] Similarly, antimicrobial activity of alkaloidal and non-alkaloidal fractions of alcoholic extract of flowers was also reported.[39] Garg SC et al. (1983) isolated the volatile principles from the plant leaves and evaluated their antibacterial activity against *Salmonella paratyphi A, Salmonella paratyphi B, Salmonella paratyphi C, Schigella Flexneri, Salmonella Enteritidis, Salmonella typhimurium, Shigella sonnei* and *Vibrio cholea.* [40]

Vijaya K et al. (1997) proved the antibacterial activity of the plant against enteropathogens viz., *Bacillus cereus var. mycoides, Bacillus pumilus, Bacillus subtilis, Bordetella bronchiseptica, Micrococcus luteus, S. aureus, Staphylococcus epidermidis, Klebsiella pneumoniae* and *Streptococcus faecal*.[41]

In the year of 2000, Dubey KS et al. reported the antibacterial activity of the alcoholic and water extracts of the plant against *Alternaria solani*, *Fusarium oxysporum* and *Penicillium pinophilum.*[42] The plant fruits were also reported to exhibit excellent antibacterial activity against gram positive and gram negative bacteria as well as antifungal activity.[43]

Lalla PM et al. (2005) evaluated the petroleum ether, acetone, methanol (90%) and water extracts of the flowers for antibacterial and antifungal activities by diffusion method in bacterial and fungal test culture. In the experiment, all the extracts showed noticeable antibacterial and strong antifungal activities.[44]

Moreover Mohd. Irfan et al. (2014) tested SI plant against the uropathogenic organisms *Escherichia coli, Klebsiella pneumoniae, Proteus mirabils, Acetobector spp. and Pseudomonas aeroginosa.* The results of the study showed that the methanolic extract of SI possessed higher degree of antibacterial activity against *Escherichia coli*. However against *Klebsiella pneumonia* ethanolic extract of plant showed higher activity than any other extract, whereas against *Proteus mirabils*, Chloroform extract show similar inhibition zone as that with Kanamycin. Thus it was also observed that against *Acetobector* and *Pseudomonas,* methnolic and ethanolic extract of SI shows similar activity, however it was higher than chloroform extract.[45]

Moreover Mumtaz N et al. (2017) also investigated SI flowers against highly resistant pathogens such as *E. coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus* and *Candida albicans*. They evaluated antimicrobial activity against different bacterial and fungal cultures by disc diffusion method with respect to the selection of different solvents for phytoconstituents extraction and fractionation. The results showed that the ethanolic extract of the flowers has both antibacterial activity and antifungal activity. Moreover the greater antimicrobial activity of plant was observed against some highly resistant pathogens as compared to antibiotics. The statistical one-way anova and Tukey's Post Hoc test results also reflects the difference in antibacterial activity between antibiotics and plant extract. The phytochemical characterization results indicated the presence of different chemical constituents in flowers extract. This study concluded that SI may be a good source of antimicrobial agents to get more beneficial effects as compared to antibiotics.[46]

Recently Dhananjay & Gupta isolated and identified the bioactive compounds from SI stems, responsible for the antimicrobial and antioxidant activity. The antibacterial activity of hexane, ethyl acetate, methanol polar fraction and aqueous extract of SI stems was evaluated against MTCC bacterial strains *Bacillus* cereus-430, *B. subtilis*-441, *Staphylococcus aureus*-96, *S. epidermidis*-435, *Escherichia coli*-1687, *Klebsiella pneumoniae*-3384, *Pseudomonas aeruginosa*-741 and *Proteus vulgaris*-744 with their corresponding clinical isolates. The results revealed inhibitory activity of hexane extract against most of the bacterial pathogens except MTCC *K. pneumonia* and clinical *B. cereus*. The ethyl acetate extract inhibited growth of MTCC *B. cereus, B. subtilis, S. epidermidis, P. aeruginosa* and clinical isolates of *B. cereus, S. aureus, S. epidermidis, E. coli, K. pneumonia*. The methanol polar fraction exhibited activity against clinically isolated *S. aureus, S. epidermidis, P. aureginosa, P. vulgaris* while aqueous extracts had no activity against any of the organisms.

Among all the extracts showing antioxidant activity, aqueous extract was found to possess highest activity when tested by reducing power, DMPD and DPPH assay. Phytochemical analysis revealed that methanol polar fraction had highest quantity of terpenoids while aqueous extract was rich in phenols and flavonoids. The active compound from hexane extract was isolated by TLC and the active band was detected via bio autography. DPPH was used for detecting antioxidants in TLC plate. A total of 13 bands were obtained after separation in which two bands showed both the antibacterial as well as antioxidant activities. Hence it is speculated that bioactive compound showing antibacterial activity may also possesses antioxidant activity.[47]

Anti-inflammatory activity

Jain A et al. (2003) screened anti-inflammatory activity of the plant by suppressing the capacity of *Propioni bacterium* acnes induced reactive oxygen species and pro-inflammatory cytokines, the two important inflammatory mediators in acne pathogenesis. To prove the anti-inflammatory effects of *S. indicus*, polymorphonuclear leukocytes and monocytes were treated with culture supernatant of *P.* acnes in the presence or absence of the herb (5 and 50 µg/mL). The plant exhibited a smaller, still significant, suppression of reactive oxygen species. The aqueous extract obtained from the root of the plant was found to be moderately active in down-regulating *Propioni bacterium* acnes induced TNF-α and IL-8 production.[48]

Analgesic and antipyretic activity

Nanda et al. (2009) screened the petroleum ether, benzene, chloroform, ethanol and triple distilled water extracts of the whole plant for analgesic and antipyretic activity (200 and 400 mg/kg, *p.o.*), using Eddy's hot plate, tail immersion and brewer's yeast induced pyrexia methods, respectively. The petroleum ether, chloroform and ethanol extracts showed significant analgesic activity at both the doses from 1 hour onward as compared to the standard drug diclofenac sodium. The chloroform and ethanol extracts showed potential significant antipyretic activity from 1 hour onward, whereas the aqueous extracts exhibited activity from 2 hours onward as compared to the standard drug paracetamol amongst various extracts.[49]

Antihyperlipidemic activity

Antihyperlipidemic activity of alcoholic extract of plant flower heads in atherogenic diet induced hyperlipidemia was studied in rats. The plant extract (500 mg/kg/day) caused a marked decrease in body weight, total cholesterol, triglyceride, and low density lipoprotein and very low density lipoprotein. A significant increase in the level of high-density lipoprotein was observed after treatment with the plant extract.[50]

Anti-arthritic activity

Sarpate RV et al. (2009) tested the methanolic extract of the entire plant and its various fractions for their bronchodilatory effect against histamine-induced acute bronchospasm in guinea pigs. From the results of the experiment, he concluded that the extract and the all fractions were effective. Amongst the fractions acetone fraction showed the most potent effect.[51]

Badgujar LB et al. (2009) evaluated the anti-arthritic activity of the petroleum ether extract of the flowers in the doses 10, 30 and 100 mg/kg/day *p.o.* against complete Freund's adjuvant induced arthritis in laboratory rats. He concluded that the dose of 100 mg/kg/day *p.o.* showed significant anti-arthritic activity.[52]

Nephroprotective activity

Srinivasan VM et al. (2008) evaluated the ethanolic extract of the plant for nephroprotective screening in gentamicin-induced acute renal injury in rats. The injury resulted in elevated biochemical markers, namely, blood urea and serum creatinine followed by a decrease in total protein and serum albumin. The ethanolic extract of plant at a dose level 300 mg/kg was found to normalize the above mentioned biochemical markers and bring about near to normal recovery in the kidneys as evidenced histopathologically. [53]

Further Sundaresan PK et al. (2017) *reported* diuretic activity of SI plant by Lipschitz method in albino rats. In their experiment they divided thirty albino rats in 5 different groups. Further Groups III, IV and V received ethanolic extracts of *S. indicus* Linn in doses 100, 200 and 300 mg/kg respectively dissolved in isotonic saline orally. The mice were put in metabolic cages and urine samples were collected for all the groups up to 24 hours after dosing. Urine was analysed for volume, urinary excretion ratio, diuretic activity, sodium and potassium composition electrolytes. The results exhibited that the single dose administration of SI extract at doses of 100, 200 and 300 mg/kg as compared to Hydrochlorothiazide (25 mg/kg) have significantly ($P<0.001$) increased total urine output along with an increase in concentration of sodium and potassium, while at 300 mg/kg, the extract produced greater diuretic activity, which is comparable to the effect of standard. Thus the present study also supports and confirms the basis for folklore use of SI as a diuretic agent.[54]

Recently Pradeep S et al. (2019) evaluated the nephroprotective activity of the aqueous extract & ethanolic extract of SI. In the study they divided animals in total 6 experimental groups viz., Group-1 served ashealth control; received purified water (5 ml/kg, *p.o.*). Group-2 served as Nephrotoxic control; this group of animals received daily *i.p.* injection of gentamicin (80mg/kg body wt.) for eight days. Group 3,4,5,6 animals of this group received 80 mg/kg of gentamicin *i.p.* nearly for eight days in addition to this they also received aqueous extract low dose (200 mg), aqueous extract high dose (400mg), ethanolic extract low dose (200 mg) and ethanolic extract high dose (400mg) respectively which was started three days prior to the gentamicin injection and continued with 8 days gentamicin treatment. Histopathological studies on isolated kidney revealed that the aqueous extract & ethanolic extract of the plant reversed the kidney damage and also restored normal kidney architecture. The study concluded that the aqueous and ethanolic extracts of the plants showed statistically significant nephroprotective activity. The plant extract proved to have nephroprotective potentials may because of its known flavonoids, saponins, tannins, and phenolic compounds.[55]

Antioxidant activity

Shirwaikar et al. (2006) investigated *in vitro* anti-oxidant activity of the ethanolic extract of plant. He concluded that the extract showed maximum scavenging of the radical 2, 2-azinobis-(3-ethylbenzothiazoline-6-sulfonate) (ABTS), 1, 1-diphenyl, 2-picryl hydrazyl (DPPH), superoxide and nitric oxide radical. The extract also showed moderate scavenging activity of iron chelation.[56]

While Tiwari BK et al. (2009) reported *in vivo* antioxidant activity of methanolic extract of plant. The extract exhibited a significant effect showing increasing levels of superoxide dismutase, catalase and glutathione peroxides by reducing malondialdehyde levels in rats.[57]

Larvicidal action

Sharma M et al. (1996) reported the toxic effects of the plant extract on the second and fourth instar larvae of *Calex quinquefasciatar* mosquito at 100-500 ppm concentration. The fourth instar larvae were more susceptible than the second instar larvae.[58] Hameed SVS et al. (2003) screened the acetone extracts of the plant roots and leaves for their larvicidal action. He reported that the extracts were shown to cause more than 50% mortality in a predominant Indian mosquito species which acts as a vector of filarial worm. The root extract was found to be more effective than leaves extract.[59]

Anti-malarial action/ Mosquitocidal potential

Vidhya PT and Mathew N (2014) investigated the mosquitocidal potential of SI plant for the first time. They prepared soxhlet extracts of flowers, leaves and aerial parts of the plant with four solvents *viz*., hexane, chloroform, ethyl acetate, and methanol and further they were screened against the larvae of the vector mosquitoes *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus*. The commercially available synthetic insecticide temephos was used as positive control. The LC_{50} values for the hexane extract of the flowers, leaves and aerial parts were 75.62, 48.22, 70.23 mg/l; 18.61, 53.34, 33.04 mg/l and 191.9, 71.58, 116.21 mg/l respectively for *A. aegypti*, *A. stephensi* and *C. quinquefasciatus*. In addition to this they also performed bioactivity-guided fractionation of the hexane extract. The fractions were examined by thin layer chromatography using silica gel, 60 F254 plates using hexane-ethyl acetate (95:5), pooled the similar fractions and screened for mosquito larvicidal activity. The bioassay-guided fractionation showed that the fractions F3-F7 eluted with hexane showed 100% mosquito larvicidal activity against all the three species of mosquitoes at 10 mg/l. The FT-IR spectrum of this fraction revealed the presence of long-chain alkanes. Phytochemical analysis showed the presence of long-chain alkanes and terpenes in the bioactive fraction. Thus this investigation suggested that SI plant may be developed as a botanical insecticide for mosquito larval control. [60]

Nematocidal action

Nisha M et al.(2007) evaluated the plant methanolic extract (1-10 mg/ml) for *in vitro* macrofilaricidal activity by worm motility assay against adult *Setaria digitata*, the cattle filarial worm. Results of the evaluation showed remarkable macrofilaricidal activity at concentrations below 4 mg/ml and an incubation period of 100 minutes.[61]

Antitussive activity

Nayak SS et al. reported that the successive methanol extract of the plant exhibited antitussive activity and synergistic effects of sleeping time induced by standard sedatives using Swiss Albino mice. The extract (200, 300 and 400 mg/kg) showed maximum inhibition of cough by 71.24%, 76.84% and 77.92% and also exhibited significant synergistic effect (P<0.001) at the dose levels of 200, 250 and 300 mg/kg, when compared with control and standard sedative pentobarbitone and diazepam. The plant produced significant synergistic effects 3 times higher than that of standard sedatives. [62]

Wound healing action

Ethanolic extract of aerial part of plant was evaluated for wound healing activity in guinea pigs. In the study, the cream containing the extract was applied *in vivo* on the paravertebral area of six excised wounded models once a day for 15 days. The cream significantly enhanced the rate of wound contraction and the period of epithelialization and that effect was comparable to neomycin. According to one more report, various ointments of ethanolic extract of the flower heads of SI plant in various proportions were screened for the assessment of wound healing activity in albino rats. Based on the comparison made of the wound healing activity of various formulations, the formulation comprising 2% (w/w) alcoholic extract of flower head was found to be superior to that of control and standard formulation. The hydroxy proline content was also found greater in healed wounds as compared to control and standard formulation. [63]

Vijayalakshmi N & Mudiganti Ram (2019) evaluated antioxidant assays of SI leaves along with leaves of *Psophocarpus tetragonolobus.* In their study they prepared ethanol, methanol, hexane, and distilled water extracts by using dried leaves of both the plants. Antioxidant studies of the various extracts were performed by 1-diphenyl-2-picrylhydrazyl and Ferric Reducing Ability of Plasma assays. Te results indicated that among the two plants studied, SI showed better 2-diphenyl-1-picryl-hydrazyl (DPPH), scavenging activity than *P. tetragonolobus* with IC_{50} values of 174.380 and 262.313, respectively, as compared to that of the standard, ascorbic acid, IC_{50} value of which being 111.16. The FRAP assay results for both the plants indicated that the methanol fractions showed closer results when compared with standards, ascorbic acid and quercetin. The IC_{50} value of SI, *P tetragonolobus*, ascorbic acid, and quercetin was 70.065, 151.953, 85.162, and 79.647, respectively. Results concluded that *S. indicus* and *P. tetragonolobus* have excellent antioxidant activities, which could be the major contributing factors for their medicinal roles. [64]

Anti-ulcer activiy

Nanda Bikash Kumar et al. (2013) evaluated the anti-ulcer potential of SI plant. In study they performed successively extraction of aerial parts of the plant, using solvents of varying polarities. Further they investigated anti-ulcer effect in albino rats using pyloric ligation induced and aspirin induced ulcer model. Ranitidine at a dose of 25 mg/kg was used as standard drug for the gastric ulcer model. The gastric content was collected and volume was measured. The ulceration index was determined by examining the inner lining of each stomach. Moreover the effect was assessed by free acidity, total acidity and ulcer index. The results revealed that the ethanol and aqueous extracts exhibited more significant actions among all the extracts. Thus this study proves the traditional claim of the plant as anti ulcer drug. [65]

Skin protective action

Sharma S (2010) reported the potent effect of the plant on psoriasis type auto immune disorder. [66] Recently Yang S et al. (2020) formulated multiple emulsions containing the extract of *SI* flowers. During study they observed sufficient amount of polyphenols in the extracts possessing good antioxidant activity with mushroom tyrosinase inhibition activity. Further, stable multiple emulsion was developed and stability testing was performed for 180 days by keeping the multiple emulsion at 8°C ± 1, 25°C ± 1, 40°C ± 1, and 40°C ± 1 with 75% ± 1 RH. Parameters checked were color change, phase distribution, viscosity, droplet size and size distribution, pH determination, and electrical conductivity. Sun protection factor (SPF) was determined which also showed promising results. Skin testing on human volunteers was carried out for 3 months after biosafety profiling of the most stable multiple emulsions. The results showed that skin erythema, melanin, and sebum were reduced, while Skin hydration and elasticity were increased. There was also reduction in the number of skin large and small skin pores. Skin spot area was also reduced by the use of multiple emulsions loaded with SI flower extract. ANOVA test showed that all the effects produced on skin were significant. Thus this study proves that SI is used for skin beautification in folk medicine.[67]

Antiviral activity

Dhar ML et al. (1968) also proved the antiviral activity of the plant against the vaccinia and ranikhet viruses.[68] Further Vimalanathan S et al. (2009) also reported the anti-viral activity of the methanolic extract of the plant against the mouse corona virus and herpes simplex virus at the concentration as low as 0.4 µg/ml.[69]

Mast cell stabilizing action

Mahapatra A et al. (2013) reported mast cell stabilizing property of SI plant. In his investigation he prepared ethanol extract and ethyl acetate extract of the plant. The results of his study showed better protective action of mast cell degranulation in sheep serum induced allergy test and compound 48/80 induced allergy.[70]

Miscellaneous activity

The aqueous extract of the plant has been reported to inhibit hyaluronidase enzyme.[71]

CONCLUSION

Medicinal plants play an important role in the lives of rural people, particularly in remote parts of developing countries with few health facilities. The present review reveals that *Sphaeranthus indicus* is utilized for the treatment of various diseases. The plant is highly regarded as a universal panacea in the Ayurvedic medicine. It is one of the most versatile plants having a wide spectrum of medicinal activities. This versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. In the present review we have congregated information pertaining to botanical, phytochemical, pharmacological studies of *Sphaeranthus indicus*. As the global scenario is now changing towards the use of nontoxic natural alternative drugs derived from plants, having traditional medicinal uses, the efforts towards Research and development activity should be executed to prepare modern effective and safe drugs from *Sphaeranthus indicus*.

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Conflict of interest statement

We declare that we have no conflict of interest.

List of abbreviations

AChE : Acetylcholinesterase (AChE)
ACP : Acid Phosphatase
ALP : Alkaline Phosphatase
CNS : Central Nervous System
DPPH : 1, 1-diphenyl, 2-picryl hydrazyl
FABMS : Fast Atom Bombardment Mass Spectroscopy
FABMS : Field Desorption Mass Spectrometry
H NMR : Proton Nuclear Magnetic Resonance
MES : Maximal Electroshock Seizure
MS : Mass Spectroscopy (MS) and
SGOT : Serum Glutamate Oxaloacetate Transaminase
SGPT : Serum Glutamate Pyruvate Transaminase
SI : *Sphaeranthus indicus* Linn.
SPF : Sun Protection Factor

REFERENCES

1. Prasad LV. Indian System of Medicine and Homoeopathy Traditional Medicine in Asia. New Delhi: WHO- Regional Office for South East Asia; 2002: pp. 283-286.
2. Vishnukanta, Rana AC. 2008. A review on *Melia azedarach*. Pharmacog Rev. 2: 173-179.
3. Arulmozhi S, Mazumber PM, Ashok P, Narayanan LS. 2007. Pharmacological activites of *Alstonia scholaris* Linn. (Apocynaceae) – A Review. Pharmacog Rev. 1: 163-170.
4. Vikani KV, Dangar RD, Kapadia NS, Shah MB. 2008. A pharmacognostic study on *Sphaeranthus indicus*. J Nat Remed. 8: 61-67.
5. Anonymous. 2001. The Ayurvedic Pharmacopoeia of India. Part I. Vol. III. New Delhi: Department of ISM and H, Ministry of Health and Family Welfare, Government of India;. pp. 127-128.
6. Shriwaikar A, Prabhu KS, Punitha ISR. 2006. In vitro antioxidant studies on *Sphaeranthus indicus* (Linn). Ind J Exp Biol. 44: 993-996.
7. Ambavade SD, Mhetre NA, Tate VD, Bodhankar SL. 2006. Pharmacological evaluation of the extracts of *Sphaeranthus indicus* flowers on anxiolytic activity in mice. Ind J Pharmacol. 38: 254-259.
8. Rahman A, Choudhary MI, Ata A, Alam M, Farooq A, Perveen S, Shekhani S. 1994. Microbial transformations of 7α-hydroxyfrullanolide. J Nat Prod. 57: 1251-1255.
9. Sohoni JS, Rojatkar SR, Kulkarni MM, Dhaneshwar NN, Tavale SS, Gururow TN, et al. 1988. A new eudesmenolide and 2-hydroxycostic acid from *Sphaeranthus indicus* Linn. X-ray molecular-structure of 4α, 5α-epoxy-7α-hydroxyeudesmanolide. J Chem Soc Perkin Trans I. 1: 157-160.
10. Baslas KK. 1959. The essential oil from *Sphaeranthus indicus*. Perf Ess oil Res. 50: 765-768.
11. Lodha V. 2003. Chemical analysis of the essential oil of *Sphaeranthus indicus*: An Ayurvedic plant of India. Ind Perf . 47: 29-30.
12. Shekhani MS, Shah PM, Khan KM, Rahman AU. 1991. New eudesmanolides from *Sphaeranthus indicus*. J Nat Prod. 54: 882-885.
13. Jadhav RB, Sonawane KB, Deshpande NR, Rojatkar SR. 2007. Two new eudesmanolides from *Sphaeranthus indicus* L. Ind J Chem .46: 379-381.
14. Chughtai MI, Khokhar I, Ahmad A. 1992. Isolation, purification and structural determination of alkaloids from the flowers of *Sphaeranthus indicus*. Sci Int (Lahore). 4: 151-154.
15. Duraipandiyan V, Kannan P and Ignacimuthu S. 2009. Antimicrobial Activity of *Sphaeranthus indicus* L. Ethnobot Leaflets. 13: 320-325.
16. Yadava RN, Kumar S. 1999. A novel isoflavone glycoside from the leaves of *Sphaeranthus indicus*. Fitoterapia . 70: 127-129.
17. Kirtikar KR, Basu BD. Indian Medicinal Plants. Vol. II. Dehra Dun: International Book Distributors 1999. pp.1347-1348.
18. Makhija K, Richard L, Kirti SP, Saleemullah K, Jessy M, Shirwaikar A. *Sphaeranthus indicus*. 2011. A review of its chemical, pharmacological and ethnomedicinal properties. Int J Pharmacol. 7: 171-179.
19. Attaurrahman, Shekhani MS, Perveen S, Habiburrehman, Yasmin A, Ziaulhaque A, et al. 1989. 7-Hydroxyfrullanolide, an antimicrobial sesquiterpene lactone from *Sphaeranthus indicus* Linn. J Chem Res. 13: 68.
20. Shekhani MS, Shah PM, Yasmin A, Siddiqui R, Perveen S, Khan KM, et al. 1990. An immunostimulant sesquiterpene glycoside from *Sphaeranthus indicus*. Phytochemistry. 29: 2573-2576.
21. Yadava RN, Kumar S. 1998. Chemical examination of the leaves of *Sphaeranthus indicus*. Asian J Chem. 10: 764-766.
22. Garg K, Shrivastava B, Bhargava A. 2019. GC-MS Analysis of Methanol and Ethyl Acetate Extract of fruits of *Sphaeranthus indicus*. J Drug Deland Thera. 9(2): 28-30
23. Kaur R, Tiwari N, Patel S, Marvaniyar V. 2017. A review article for herbal drugs as anxiolytic activity. Int J of Allied Med Sci and Clin Res. 5(2): 636-647.
24. Mhetre NA, Ambavade SD, Bodhankar SL. 2006. Neuroleptic activity of extract of *Sphaeranthus indicus* in mice. Ind J Nat Prod. 22: 24-27.

25. Galani VJ, Patel BG. 2009. Psychotropic Activity of *Sphaeranthus indicus* Linn. In Experimental Animals. Phcog Res.1: 307-313.
26. Galani VJ, Patel BG. 2010. Effect of hydroalcoholic extract of *Sphaeranthus indicus* against experimentally induced anxiety, depression and convulsions in rodents. Int J Ayu Res. 1(2): 87-89.
27. Bikash Kumar Nanda, Jyotirmoyee Jena, Bhabagrahi Rath, Biswaranjan Behera. 2012. Anticonvulsant Activity of whole parts of *Sphaeranthus indicus* Linn. Extract in Experimental Mice. Drug Inv. 2(3): 202.
28. Patel MB & Amin D. 2012. *Sphaeranthus indicus* Flower Derived Constituents Exhibits Synergistic Effect against Acetylcholinesterase and Possess Potential Antiamnestic Activity. J Comple Int Medi. 9(1): 1-12.
29. Nahata A, Saxena A, Suri, Saxena A and Dixit V. 2012. *Sphaeranthus indicus* Induces Apoptosis Through Mitochondrial-Dependent Pathway in HL-60 Cells and Exerts Cytotoxic Potential on Several Human Cancer Cell Lines. Int Can Thera. 12(3): 236–247.
30. Prabhu KS, Lobo R, Shirwailer A. 2008. Antidiabetic properties of the alcoholic extract of *Sphaeranthus indicus* in streptozotocin-nicotinamide diabetic rats. *J* Pharm and Pharmacol. 60(7): 909-916.
31. Gubrele D, Singh R and Ayachi A. 2019. Hypoglycemic Effects of Different Extracts of *Sphaeranthus Indicus* and Presence of Swietenine. Int J Recent Sci Res. 10(10): 35363-35366.
32. Nayak SS, Maity TK, Maiti BC. 2007. Hepatoprotective activity of *Sphaeranthus indicus* Linn. Int J Green Pharm. 1: 32-36.
33. Tiwari Bk, Khosa RL. 2009. Hepatoprotective and antioxidant effects of *Sphaeranthus indicus* against acetaminophen induced hepatotoxicity in rats. J Pharm Sci Res. 1: 26-30.
34. Mansoori MH, Gupta MK , Mishra V, Yadav N , Vyas M. 2018. Estimation of antioxidant and hepatoprotective activity of *Sphaeranthus indicus* Linn. leaves extract. Int J Green Pharm . 2018 (Suppl); 2 (4): S855.
35. Shekhani MS, Shah PM, Yasmin A, Siddiqui R, Perveen S, Mohammed K, et al. 1990. An immunostimulant sesquiterpene glycoside from *Spharanthus indicus*. Phytochemistry. 29: 2573-2576.
36. Bafna AR, Mishra SH. 2004. Immunomodulatory activity of methanol extracts of flower heads of *Sphaeranthus indicus* Linn. Ars Pharmaceutica. 45: 281-291.
37. Anarthe SJ, Malavika E, Pravalika A, Ganga Raju M. 2015. Screening of Immuniomdulatory activity of *Sphaeranthus indicus* whole plant. Int J of Phytomed. 7: 432-440.
38. Singh SK, Saroj KM, Tripathi VJ, Singh AK, Singh RH. 1988. An antimicrobial principle from *Sphaeranthus indicus* L. (Family Compositae). Int J Crude Drug Res. 26: 235-239.
39. Shaikh D, Naqvi BS, Shaikh R. 1986. The antibacterial principles of *Sphaeranthus indicus*. Isolation, purification and anti-bacterial action. Pak J *Sci* Ind *Res*. 29: 366-371.
40. Garg SC, Kasera HL. 1983. In vitro antibacterial activity of the essential oil of *Spharanthus indicus* L. Fitoterapia. 54: 37-39.
41. Vijaya K, Anathan S. 1997. Microbiological screening of Indian Medicinal plants with special reference to enteropathogens. J Alt Compl Med. 3: 13-20.
42. Dubey KS, Ansari AH, Harduha M. 2000. Antimicrobial activity of the extract of *Sphaeranthus indicus*. Asian J Chem. 12: 577-578.
43. Naqvi BS, Hashmi K, Sheikh D, Mahdi A. 1998. Antibacterial activity in fruits and vegetables. Pak J Pharmacol. 15: 7-11.
44. Lalla PM, Deshpande AR, Musaddip M, Shahare NH, Ukesh CS. Antimicrobial activity of Medicinal plant *Sphaeranthus indicus*. International conference on modern trends in plant sciences with special reference to the role of biodiversity in conservation, Amravati, Maharashtra: 2005. pp.96.
45. Mohd. Irfan, Shakeel Ahmed and Manik Sharma. 2014. Antimicrobial activity of terpenoids from *Sphaeranthus* indicus. L. Asian J Plant Sci Res. 4(1): 1-6.
46. Mumtaz N, Baqir Shyum Naqvi S, Arif Asghar, Asif Asghar M. 2017. Assessment of antimicrobial activity of *Sphaeranthus indicus* L. Against highly resistant pathogens and its comparison with three different antibiotics. J Dis Glo Health. 10(3): 67-73.
47. Tandon D & Gupta AK. 2010. In vitro screening of antibacterial and antioxidant properties of stem of *Sphaeranthus indicus* Linn. ACCESS Microbiogy. 1(1A): 48.
48. Jain A, Basal E. 2003. Inhibition of Propionibacterium acnes-induced mediators of inflammation by Indian herbs. Phytomed . 10: 34-38.
49. Nanda BK, Jena J, Rath B, Behera BR. 2009. Analgesic and antipyretic activity of whole parts of *Sphaeranthus indicus* Linn. J Chem Pharm Res. 1: 207-212.
50. Pande VV, Dubey S. 2009. Antihyperlipidemic activity of *Sphaeranthus indicus* on atherogenic diet induced hyperlipidemia in rats. Int J Green Pharm. 3: 159-161.
51. Sarpate RV, Deore TK, Tupkari SV. 2009. Bronchodilatory effect of *Sphaeranthus indicus* Linn. against allergen induced bronchospasm in guinea pigs. Pharmacog Mag. 5: 74-77.
52. Badgujar LB, Ghosh P, Gaur V, Bodhankar SL. 2009. Effect of petroleum ether extract of *Sphaeranthus indicus* Linn. on complete freunds adjuvant induced arthritis in laboratory rats. Pharmacologyonline. 2: 281-291.
53. Srinivasan VM, Jessy KK, Alex AE. 2008. Effectof *Sphaeranthus indicus* Linn. on gentamicin induced acute renal failure in rats. Ind J Pharmacol . 40: 71.
54. Sundaresan PK, Prabhakaran SS, Palappallil DS, Chellappan D. 2017. Diuretic activity of ethanolic extract of whole plant of *Sphaeranthus indicus* linn in albino rats. Int J Basic Clin Pharmacol. 6: 265-270.

55. Pradeep S, Mahesh CD, Manjunath PM, Saraswathidevi HN. 2019. Nephroprotective activity of Mundi (*Sphaeranthus indicus* Linn.)- An Experimental Study. *J* Ayurveda Integr Med Sci. 5: 143-151.
56. Shriwaikar A, Prabhu KS, Punitha ISR. 2006. In vitro antioxidant studies on *Sphaeranthus indicus* (Linn). Ind J Exp Biol. 44: 993-996.
57. Tiwari Bk, Khosa RL. 2009. Antioxidant and Hepatoprotective effects of *Sphaeranthus indicus* against acetaminophen induced hepatotoxicity in rats. J Pharm Sci Res. 1: 26-30.
58. Sharma M, Saxena RC. 1996. *Sphaeranthus indicus* as mosquito larvicide. J Appl Zool Res. 7: 87-88.
59. Hameed SVS, Shah DS. 2003. Effect of aqueous extracts of *S. indicus* against *Culex fatigans*, weid (Diptera; calicidae). Ind J Exp Zool. 6: 279-284.
60. Vidhya PT and Mathew N. 2014. Bioassay guided fractionation of Sphaeranthus indicus extract against mosquito vectors. Int J Pharm Sci & Res. 5(9): 3965-3671.
61. Nisha M, Kalyanasundaram M, Paily KP, Abidha, Vanamail P, Balaraman K. 2007. In vitro screening of medicinal plant extracts for macrofilaricidal activity. Parasitol Res. 100: 575-579.
62. Nayak SS, Maity TK, Maiti BC. 2010. Antitussive and synergistic effects of sleeping time induced by standard sedatives of *Sphaeranthus indicus* plant extracts. J Adv Pharm Res. 1: 123-132.
63. Jha RK, Garud N, Nema RK. 2009. Excision and incision wound healing activity of flower head alcoholic extract of *Sphaeranthus indicus* Linn. in albino rats. Glob J Pharmacol . 3: 32-37.
64. Vijayalakshmi N, Mudiganti Ram Krishna Rao. 2019. The Antioxidant studies of two medicinal plants, *Sphaeranthus indicus* and *Psophocarpus tetragonolobus*. Asian J Pharm Clin Res.12(1): 321-327.
65. Nanda Bikash Kumar, Behera Biswa Ranjan, Mohapatra Tapas Kumar, Behera Bhupen Chandra, Nayak Reena Rani. 2013. Anti ulcer potential of *Sphaeranthus indicus* linn. On experimental animal. Inventi: pep. 798: 13.
66. Sharma S. 2016. *Sphaeranthus indicus* (East Indian globe thistle)- A promising natural remedy for psoriasis. J Am Acad Dermatol. 62: 131.
67. Yang S, Liu L, Han J and Tang Y. 2020. Encapsulating plant ingredients for dermocosmetic application: an updated review of delivery systems and characterization techniques. Inter J Cosmetic Sci. 42(1): 6-28.
68. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. 1968. Screening of Indian plants for biological activity. Ind J Exp Bio. 6: 232-247.
69. Vimalanathan S, Ignacimuthu S, Hudson JB. 2009. Medicinal plants of Tamil Nadu (Southern India) are a rich source of antiviral activities. Pharm Biol. 47: 422-429.
70. Mahapatra A, Ojha N, Kumar A. 2013. Therapeutic management of pediatric-allergic disorders by Indian Medicinal planys withmast cell stabilizing potential: A review. J Pharma Sci Innov. 2(2): 35-37.
71. Sadaf F, Saleem R, Ahmed M, Ahmad SI, Navaid-ul-Zafar. 2006. Healing potential of cream containing extract of *Sphaeranthus indicus* on dermal wounds in Guinea pigs. J Ethnopharmacol. 107: 161-163.