Review on *Sphaeranthus indicus* Linn. (Koṭṭaikkarantai)

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ABSTRACT

Sphaeranthus indicus Linn. is from the aroma family Asteraceae. It is also known with other synonyms such as Munditika, Mundi, Shravana, Bhikshu, Tapodhana, Mahashravani, Shravanahva, Shravanashirshaka. It is abundantly distributed in damp areas in plains and also as a weed in the rice fields. In the Indian system of medicine, the plant as a whole plant or its different anatomical parts viz., leaf, stem, bark, root, flower and seed are widely used for curing many diseases. The plant is bitter, stomachic, restorative, alterative, pectoral, demulcent and externally soothing. The whole plant and its anatomical parts have been reported with different types of secondary metabolites which include eudesmanolides, sesquiterpenoids, sesquiterpene lactones, sesquiterpene acids, flavone glycosides, flavonoid C-glycosides, isoflavone glycoside, sterols, sterol glycoside, alkaloid, peptide alkaloids, amino acids and sugars. The essential oils obtained from the flowers and whole plants were analyzed by different authors and reported the presence of many monoterpene hydrocarbons, oxygenated monoterpenes, sesquiterpene hydrocarbons and oxygenated sesquiterpenes. The whole plants, its isolated secondary metabolites and different anatomical parts have been reported for ovicidal, antifeedant, anthelmintic, antimicrobial, antiviral, macrofilaricidal, larvicidal, analgesic, antipyretic, hepatoprotective, antitussive, wound healing, bronchodilatory, mast cell stabilizing activity, anxiolytic, neuroleptic, immunomodulatory, anti-diabetic, antihyperlipidemic and antioxidant, antioxidant, central nervous system depressant, anti-arthritic, nephroprotective, anticonvulsant activities and many other activities. It is also effective on psoriasis. In the present paper, the plant is reviewed for its phytochemical and pharmacological reports in detail.

Key words: 5,4′-Dimethoxy-3′-prenylbiochanin-7-O-β-D-galactoside, 7-hydroxy eudesmanolide, Koṭṭaikkarantai, Munditika churna, Veezhi Ennai

INTRODUCTION

Sphaeranthus indicus Linn. is known as Koṭṭaikkarantai in Tamil. It is a multi-branched aromatic herb 1-2 feet in height, distributed widely in plains all over India and up to an altitude of 50 feet in hills. It is an important medicinal plant used for the treatment of styptic gastric disorders, skin diseases, anthelmintic, glandular swelling, nervous depression, analgesic, antibiotics, antifungal, laxative and diuretic properties. The decoction of the plant is said to be active against bronchitis, asthma, leucoderma, jaundice and scabies. The powdered bark along with whey is useful in the treatment of piles. Flowers have alterative, depurative and stimulant characters. Roots and seeds are anthelmintic. Juice of fresh leaves is taken for cough. The plant is also useful in preservation of food grains as it possess insecticidal property.[1-6] Earlier, the plant has been reviewed by some authors.[7-10] However, in the present paper author aims to describe the plant on Siddha as well as Ayurvedic aspects, phytochemical and pharmacological aspects.

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REGIONAL NAMES

S. indicus Linn. is known in different names in different Indian languages as mentioned below:[11]

- Sanskrit: Mundi, Śrāvani Kadamba, Puṣpikā, Alambusta
- Assamese: Kamadarus
- Bengalese: Surmuriya, Chhagal Nadi, Mudmudiya
- Gujarati: Gorakhmundi
- Hindi: Mundi
- Kannada: Mirnagnee, Atookamanni, Mirangnee
- Marathi: Mundi, Baras Bondi
- Oriya: Buikadam
- Punjabi: Gorakhmundi

- Tamil: Kotook, Karandai, Kottakarthai
- Telelugu: Bodasaramu, Bodataramu
- Urdu: Mundi.

SIDDHA PROPERTIES

S. indicus Linn. is used in Siddha system of medicine in the name of Kot.t.aikkarantai. Other properties as described in this system are listed below. It is used as one of the ingredient in the siddha preparation, "Veezhi Ennai (or Veezhi oil)."[12] Though this plant finds place in many preparations, this is the only preparation mentioned in the official publication.

- Suvai (Taste): Kaippu (Bitter)
- Tanmai (Potency): Veppam (Hot)
- Gunam: Ilaku (Soft)
- Pirivu (Transformation): Kārppu (Pungent)
- Ceikai (Action): Uḷḷalalārri (Demulcent), Uṭarterri (Restorative), Puzhukkolli (Anthelmintic), Uramaakki (Tonic).

AYURVEDIC PROPERTIES

- Rasa: Madhura, Kaṭu, Tikta, Kasāya
- Guna: Laghu
- Virya: Usna
- Vipaka: Kaṭu
- Karma: Medhya, Viṭaghna, Vātakaphahara, Arśadosa, Vināśaka.[11]

IMPORTANT AYURVEDIC FORMULATIONS

Navaratnarāja, Mṭgānka Rasa, Arka Muṭṭī, Guduchyadi taila, Vatagajankusha rasa, Munditika churna, Guduchi taila.[11]

AYURVEDIC THERAPEUTIC USES

Gant.amālā, Apaci, Kut.t.ha, Kt.mi, Pāt.t.u, Slipada, Medaroga, Apasmara, Kasa, Mutrakrcchra, Tvaka Roga, Stana Saithalya, Yonirogā, Āmātisara, Āmaroga, Vātaroga, Gudaroga, Plīhāroga, Chardi, Āmavāta, Gātradurgandhya, Sūryāvarta, Ardhāvabhāvabhedaka.[11]

DOSE

3-6 g of the drug.[11]

PHARMACOGNOSTIC STUDY

The physico-chemical parameters and estimation of 7-hydroxy eudesmanolide (1), a major sesquiterpene lactone had been carried ouṭ *S. indicus* was described as a branched, hairy and strongly scented herb; leaves spathulate, sessile; flowers pinkish purple. Leaf shows uni-multicellular and club and clavate type of trichomes. Ring of deltoid vascular bundles and well-developed pith with few pitted cells are found in stem. Metaderm and radially arranged fibers are seen in root; in the cortical region secretory canal are alternatively arranged. Powder shows large number of different types of trichomes, pollen grains in pollen sacs and cruciferous stomata. 7-hydroxy eudesmanolide was quantified (0.0658% w/w) by high performance thin layer chromatography method using the solvent system of n-hexane: diethyl ether (3:7) at λ 213 nm.[13]

PHYTOCHEMICAL STUDIES

Spaeranthine, an alkaloid of molecular formula $C_{13}H_{19}O_5$ (m.p. 166-168°C) was isolated from the plant. The essential oil from the fresh flowering plant was isolated and it was characterized for physical and chemical properties viz., specific gravity at 30° (0.9419 68), refractive index at 20° (1.512), optical rotation (nil), acid value (2.4030), ester value (47.80), ester value after acetylation (74.15).[14]

The essential oil from the plant was reported to contain methyl chavicol (12), δ-cadinene (11), α-ionone (2), para-methoxycinnamaldehyde (4), α-terpinene (9), citral (6), geraniol (7), geranyl acetate (8), β-ionone (3), oscimene (10), eugenol (5), sphaeranthene, sphaeranthol, estragole, indicusene.[15,16]

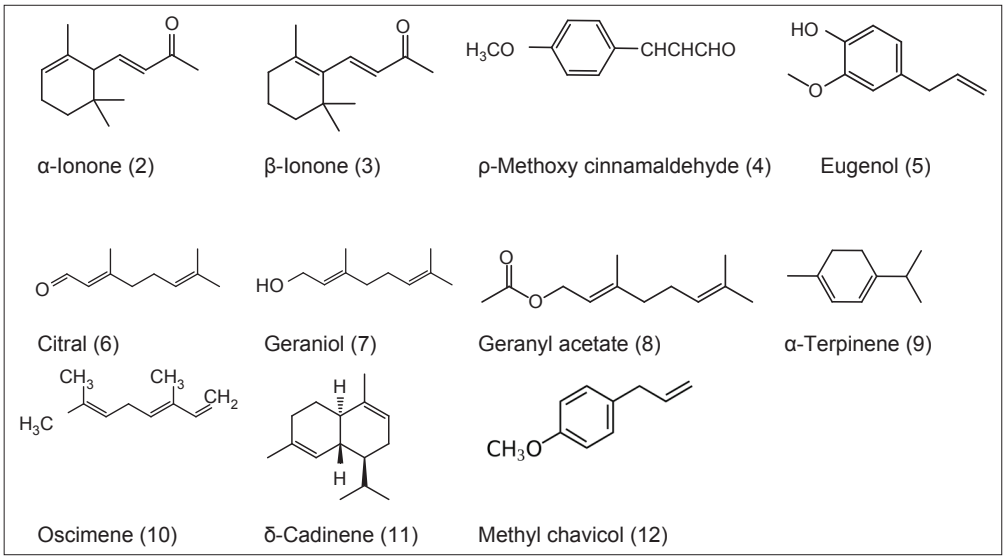
β-Sitosterol, n-triacontanol, phenylurethane, n-pentacosane were isolated from oil.[17] The alcoholic extract yielded sterols, viz., stigmasterol (13) and β-sitosterol (14).[18]

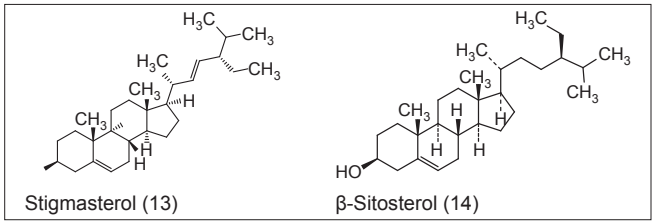
Phytochemical analysis of *S. indicus* yielded three interesting hydroxy lactones (15-17).[19]

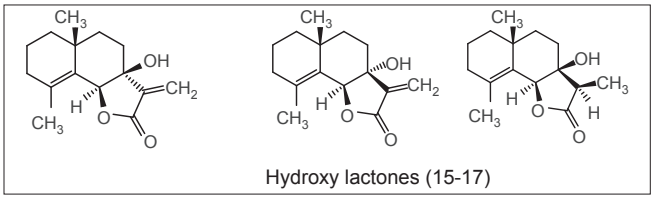
A bicyclic sesquiterpene lactone (18) was isolated from the petroleum ether extract of the aerial part.[20]

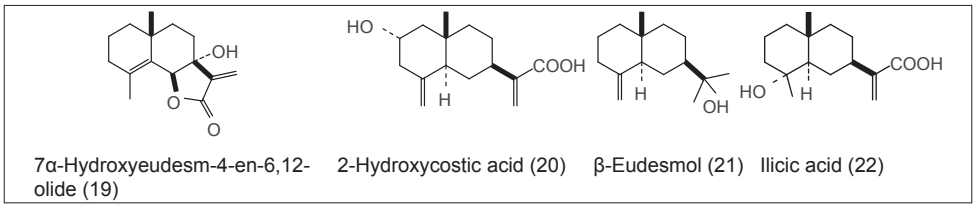
A new sesquiterpene lactone, 7α-hydroxyeudesm-4-en-6, 12-olide (19) and a new sesquiterpene acid, 2-hydroxycostic acid (20), along with the known compounds β-eudesmol (21) and ilicic acid (22) have been isolated from the acetone extract of *S. indicus* L.[21]

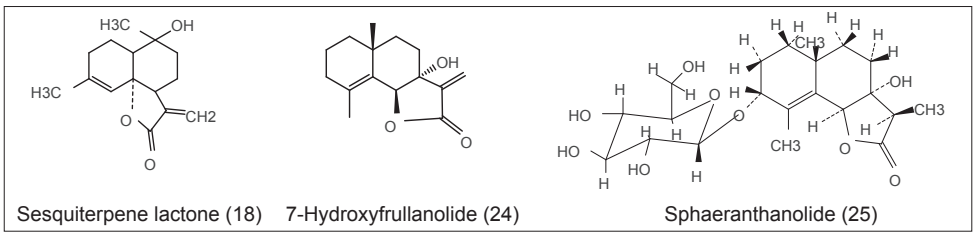
A sterol glycoside has been isolated and characterized as β-D-glucoside of (24S)-24-ethylcholesta-4,22-dien-3-β-ol (23).[22] 7-Hydroxyfrullanolide (7HF) (24), was reported from *S. indicus* Linn.[23] A new sesquiterpene glycoside, sphaeranthanolide (25), has been isolated from the flowers of *S. indicus*.[24]

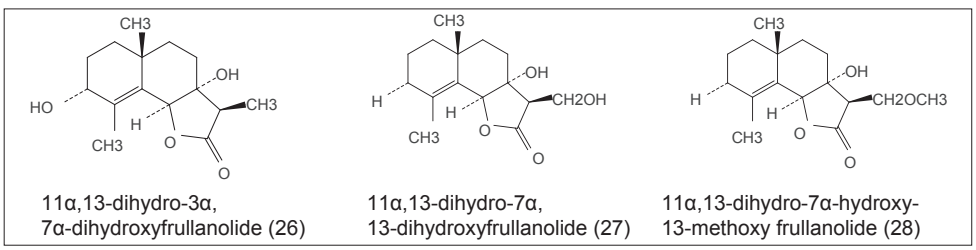












Three new eudesmanolides, 11α,13-dihydro-3α,7α-dihydr oxyfrullanolide (26), 11α,13-dihydro-7α,13-dihydroxyfrul lanolide (27) and 11α,13-dihydro-7α-hydroxy-13-methoxy frullanolide (28) were isolated from the flowers of *S. indicus*. Their structures were determined by 2D nuclear magnetic resonance and other spectroscopic techniques.[25]

Two *Sphaeranthus* peptide alkaloids (1 and 2) (29,30) have been isolated from flowers.[26]

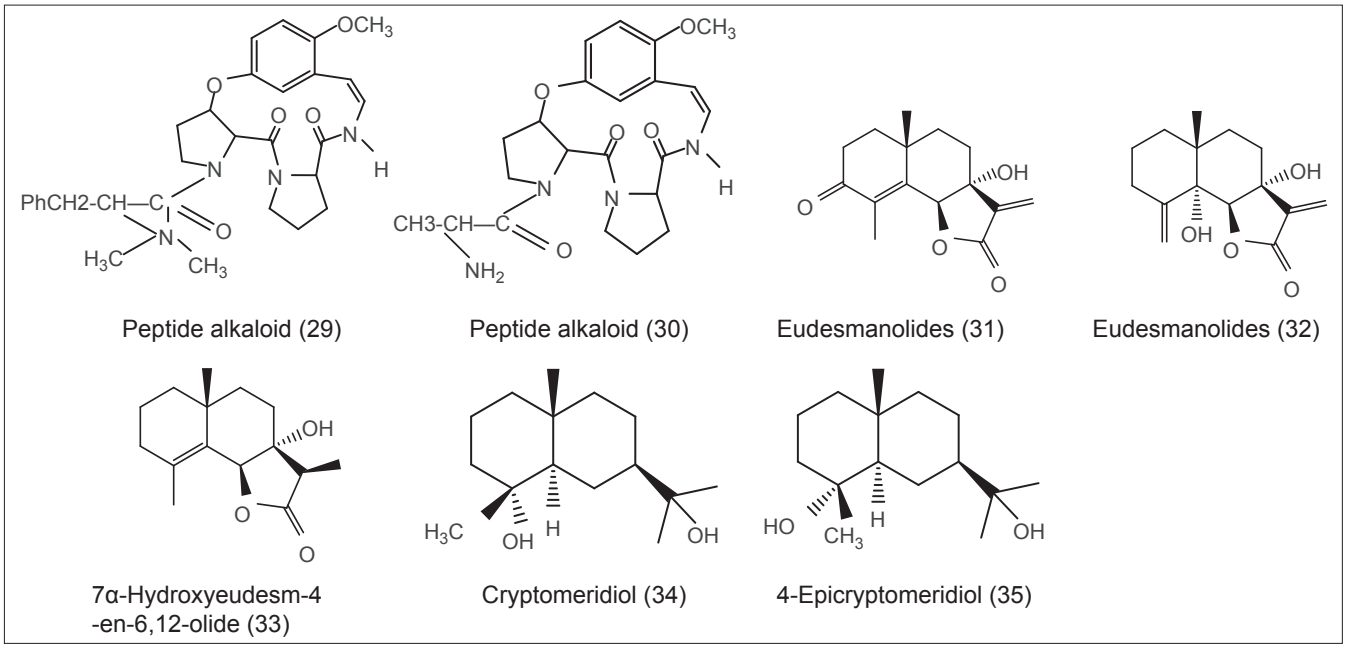
Two new eudesmanolides (31 and 32) along with 7α-hydr oxyeudesm-4-en-6,12-olide (33) and two sesquiterpenoids, cryptomeridiol (34) and 4-epicryptomeridiol (35) have been isolated from *S. indicus*.[27]

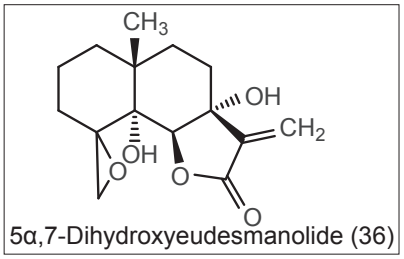
A new 5α,7-dihydroxyeudesmanolide (36) along with two known eudesmanolides (31,32) have been obtained from the photo-oxidation of a known 7-hydroxyeudesmanolide.[28]

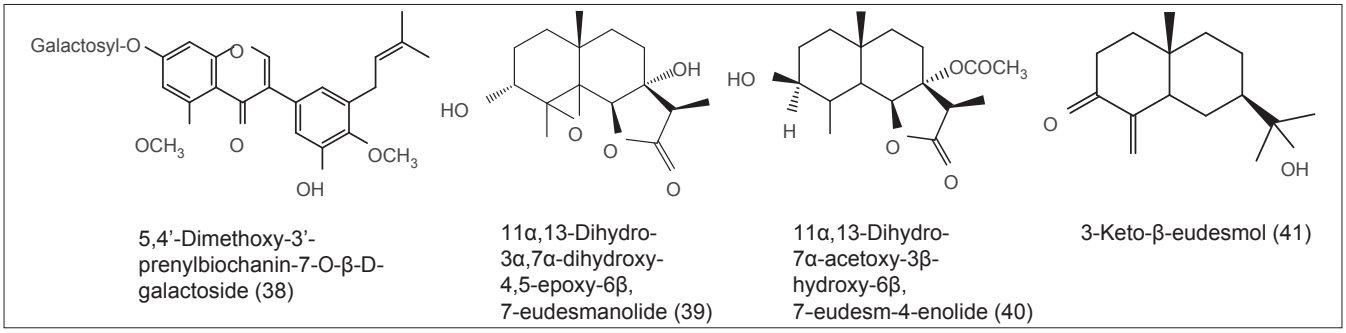
Amino acids, viz., glycine, alanine, valine, leucine, histidine, cysteine, lysine, aspartic acid and glutamic acids and sugars viz., D-arabinose, L-rhamnose, lactose, raffinose, D-galactose, maltose, D-fructose and D-glucose were reported the chemical examination of the leaves of *S. indicus*.[29]

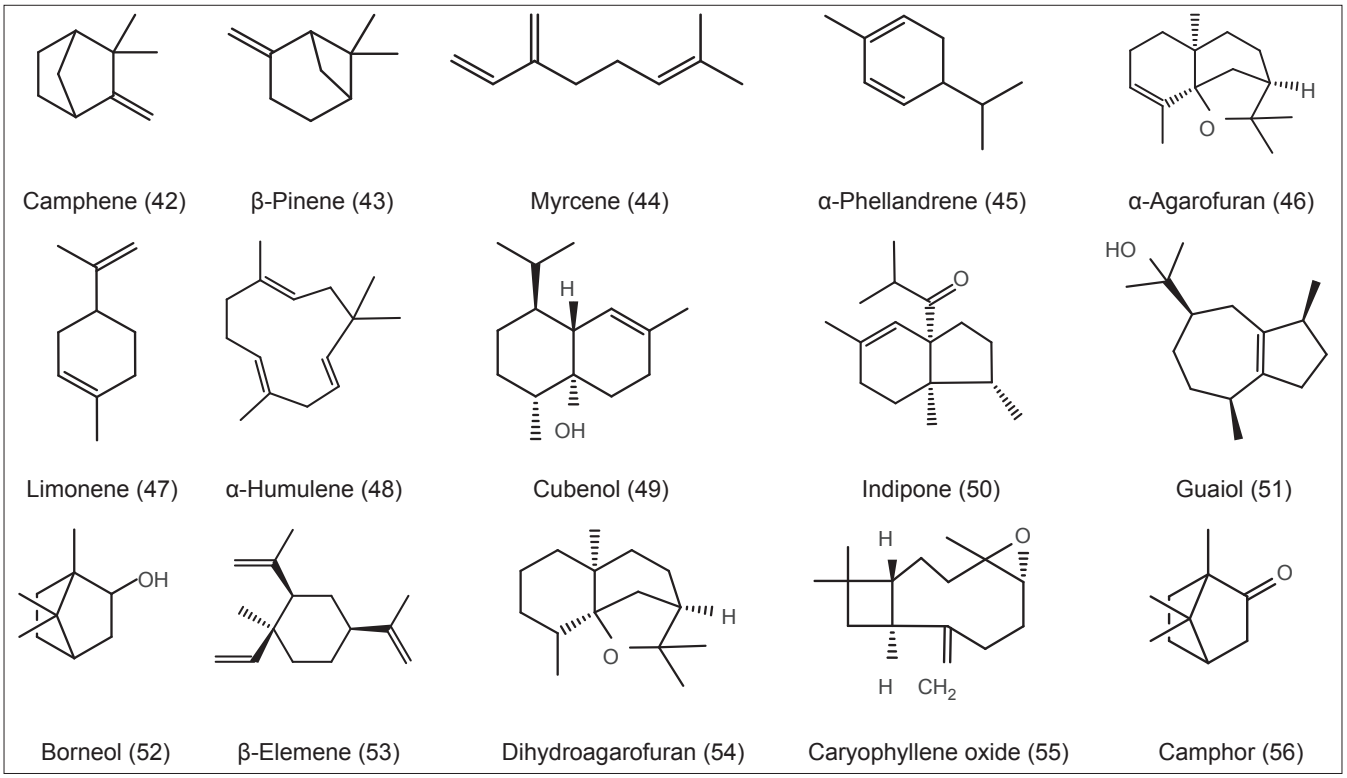
A new flavone glycoside, 7-hydroxy-3′,4′,5,6-tetramethoxy flavone 7-O-β-D-diglucoside (37) was isolated from the stem.[30] A novel isoflavone glycoside, 5,4'-dimethoxy-3'-prenylbiochanin 7-O-β-D-galactoside (38), was isolated from the leaves of *S. indicus*.[31]

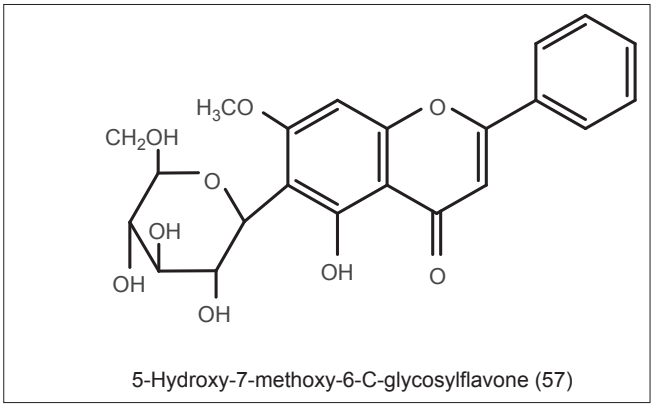
Three new eudesmanoids have been isolated from whole plant and their structures were established as 11α,13-dihydr o-3α,7α-dihydroxy-4,5-epoxy-6β,7-eudesmanolide (39), 11α, 13-dihydro-7α-acetoxy-3β-hydroxy-6β,7-eudesm-4-enolide











(40) and 3-keto-β-eudesmol (41) by comparison of spectral data with those of other 7α-hydroxyeudesmanolides.[32]

The hydro distilled essential oil of *S. indicus* was analyzed by gas chromatography (GC) and GC/mass spectrometry. Thirty-eight compounds making up 84.0% of the oil were identified. The major compounds were: 2,5-dimethoxy-ρ-cymene (18.2%), α-agarofuran (11.8%) (46), 10-epi-γ-eudesmol (7.9%) and selin-11-en-4α-ol (12.7%). Other detected compounds were (Z)-3-hexenol, (E)-2-hexenol, α-pinene, camphene (42), 6-methyl 5-hepten-2-one, β-pinene (43), myrcene (44), α-phellandrene (45), ρ-cymene, limonene (47), α-ρ-dimethylstyrene, linalool, camphor (56), borneol (52), terpinen-4-ol, nerol, neral, geraniol, geranial, maaliene, β-cubebene, β-elemene (53), β-caryophyllene, 2,5-dimethoxy-1-isopropenyl-4-isopropylbenzene, α-humulene, dihydroagarofuran (54), indipone (52), caryophyllene oxide (55), globulol, cis-arteannuic alcohol, guaiol (51), trans-arteannuic alcohol, cubenol (49), α-muurolol, α-eudesmol and valianol.[33]

A novel flavonoid C-glycoside, 5-hydroxy-7-methoxy-6-C-glycosylflavone (57), was isolated from the aerial part. Its structure was elucidated by spectroscopic methods.[34]

Two new eudesmanolides have been isolated[35] from the aerial part and their structures have been established as 11α,13-dihydro-3α,7α-dihydroxyeudesm-4-en-6α,12-olide, 4-en-6β,7α-eudesmanolide, based on the spectral data and in comparison of spectral data with those of reported data of 11α,13-dihydro-3α,7α-dihydroxyfrullanolide,[25] eudesmanolide-4[19] and γ-cyclocostunolide.[36]

PHARMACOLOGICAL STUDIES

Ovicidal activity

Sesquiterpene lactone, isolated from a petroleum ether extract of *S. indicus*, was screened for its effects on the hatching of eggs and the metamorphosis of larvae of *Culex quinquefasciatus* at concentration of 50-250 ppm. Rates of fecundity and fertility were found to be affected in the larval-treated adult females. Egg hatching was also significantly lowered. Mortality in the larvae, pupae and adults produced a marked decrease in mosquito populations in laboratory experiments.[37]

Hepatoprotective activity

The protective effectof methanolic extract of *S. indicus* Linn. (MES) against CCl_4 induced hepatotoxicity was studied in animal models. It showed a significant protective effect by lowering the serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (ALP).[38]

The aqueous (AQS) and methanolic (MES) extracts of flower head of *S. indicus* L. were evaluated for the hepatoprotective and antioxidant effect on acetaminophen (APAP)-induced heptotoxicity in rats. Oral dose of MES (300 mg/kg) showed a significant hepatoprotective effect (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), acid phosphatase (ACP) and ALPthan aqueous extract. MES exhibited significant antioxidant activity showing increasing levels of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) by reducing malondialdehyde levels.[39]

Ethanolic extract in the doses 200 and 300 mg/kg bw, of aerial parts of *S. indicus* L. was investigated for hepatoprotective activity against paracetamol induced liver damage of rat. 300 mg/kg of extract showed significant protection against paracetamol-induced hepatocellular injury.[40]

Aqueous extract (200 and 300 mg/kg b/w) of root of *S. indicus* L. was evaluated for hepatoprotective activity against APAP induced hepatotoxicity in rats. The activity of 300 mg/kg of the extract was comparable to standard drug, silymarin (50 mg/kg body weight).[41]

Antitussive activity

The successive methanol extract of *S. indicus* (MESI) exhibited antitussive activity and synergistic effects of sleeping time induced by standard sedatives using Swiss Albino mice. The MESI of (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 MESI produced significant synergistic effects three times greater than that of standard sedatives.[42]

Wound healing activity

A cream containing ethanolic extract of aerial parts of *S. indicus*, L. (Asteraceae) was evaluated for wound healing activity in guinea pigs. The cream 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 comparable to neomycin.[43]

The wound healing activity of ointments comprising various percentage of alcoholic extract of *S. indicus* flower head was tested for protection against microbial invasion by providing better tissue formation. The formulation comprising of 2% (w/w) alcoholic extract was found to be superior to control and standard formulation.[44]

A randomized placebo controlled single blind study was conducted on 45 patients ($n = 30$ test and $n = 15$ control groups) to test the efficacy and safety of *S. indicus* L., cream of *Lawsonia inermis* L. and *Plumbi oxidum*. The test drug formulations were found to be effective in healing and relieving the symptoms of cervical erosion with cervicitis.[45]

Anxiolytic activity

The petroleum ether (10 mg/kg), alcohol (10 mg/kg) and water extracts (30 mg/kg) of flowers were tested to assess the anxiolytic activity in mice. Petroleum ether extract of *S. indicus* flowers produced prominent anxiolytic activity.[46]

Neuroleptic activity

Neuroleptic activity of extract of flowers was evaluated in apomorphine induced cage climbing and catalepsy in mice models. The petroleum ether extract (300 mg/kg, i.p.) reduced total time spent in apomorphine induced cage climbing. Aqueous and alcoholic extracts showed catalepsy while petroleum ether extract was devoid of it.[47]

Immunomodulatory activity

Immunostimulant activity of sphaeranthanolide was tested by Jerne plaque assay method. This compound was found to be an immune modulator.[24]

Methanol extract, its petroleum ether, chloroform and remaining methanol fractions, of flower heads were found effective in increasing phagocytic activity, hemagglutination antibody titer and delayed type hypersensitivity, whereas only remaining methanol fraction was found active in normalizing total white blood celllevels in case of cyclophosphamide induced myelosuppression in mice. The study, therefore, revealed that the drug holds promise as immunomodulatory agent, which acts by stimulating both humoral as well as cellular immunity and phagocytic function.[48]

The bioactive fraction exhibited dose dependent increase in immoral and cell-mediated immunity and offers protection against immunosuppression induced by the cytotoxic agent cyclophosphamide.[49]

The petroleum ether extract from the flower heads of *S. indicus* Linn. was found to be effective in increasing phagocytic activity, hemagglutination antibody titer and delayed type hypersensitivity. The extract acts by stimulating both humoral and cellular immunity as well as phagocytic function.[50]

Antifeedant activity

MESI showed antifeedant activity against 4th instar larvae of *Spodoptera litura*. Among the compounds isolated from this

fraction, 7-hydroxy frullanolide had high antifeedant activity at 1,000-ppm. Deformities in larvae, pupae and adult were also observed.[51]

Anthelmintic activity

The anthelmintic activities of ethanolic and aqueous extracts (10, 50, 100 mg/ml concentration levels) of the whole plant were tested against *Pheretima posthuma* and *Ascardia galli*. Both extracts exhibited anthelmintic activity in a dose-dependent manner. The most significant activity was observed at the highest concentration of 100 mg/ml against both types of worms.[52]

Analgesic Activity

The ethanol extracts of the whole plant *S. indicus* Linn. exhibited dose dependent analgesic activity with 66.6 and 67.4% of protection when tested with 250 mg and 500 mg/kg b.w. by tail immersion method in rat models using pentazocine 10 mg/kg as standard.[53]

Analgesic and antipyretic activity

The analgesic and antipyretic activity of the successive taking petroleum ether, benzene, chloroform, ethanol and triple distilled water extracts (200 mg/kg and 400 mg/kg b.w) of whole plant was screened for analgesic and antipyretic activities on Albino rats by Eddy's hot plate, Tail immersion and Brewer's yeast induced pyrexia method. The petroleum ether, chloroform and ethanol extracts showed significant analgesic activity in both doses as compared to the standard drug diclofenac sodium. The chloroform and ethanol extracts showed potential significant antipyretic activity from 1 h onward whereas aqueous extracts exhibited activity from 2 h onward as compared to the standard drug paracetamol amongst various extracts.[54]

Anti-diabetic activity

The anti-hyperglycemic effect of *S. indicus* extract was carried out in diabetic rats induced by nicotinamide (120 mg/kg i.p.) and streptozotocin (STZ) (60 mg/kg i.p). Oral administration of alcoholic extract of *S. indicus* for 15 days exhibited in significant reduction in blood glucose levels and increases in hepatic glycogen and plasma insulin levels and significant improvement in oral glucose tolerance test. Glibenclamide was used as a reference standard.[55]

The ethanol extract of aerial part was evaluated for anti-diabetic activity using the glucose uptake by isolated rat hemi-diaphragm *in-vitro* model. *S. indicus* increased the uptake of glucose by isolated rat hemi-diaphragm significantly ($P < 0.01$) and was found to be more effective than insulin and it will be alternative choice for the treatment of diabetes mellitus caused in the consequences of resistance to stimulatory effect of insulin on glucose transporter type 4 protein.[56]

The effect of the methanol extract in dexamethasone-induced insulin resistance in mice was studied. The mice were treated with dexamethasone for 22 days. The *S. indicus* extract showed significant decrease in plasma glucose and serum triglyceride levels at doses, of 400 and 800 mg/kg, p.o. and stimulated insulin assisted and non-insulin assisted glucose uptake in skeletal muscle. The extract significantly restored dexamethasone induced body weight loss thereby suggesting its effect in the treatment of type II diabetes mellitus.[57]

Dried petroleum ether (60-80°C) extract of flower head of *S. indicus* was screened for activity against alloxan induced hypoglycemea in Wistar rats. The oral administration of flower head extract at doses of 200 mg/kg lead to a significant blood glucose reduction.[58]

The anti-diabetic effect of MES in alloxan induced diabetic rabbits in comparison with 80 mg/kg of diamicron standard was studied. The extract at the dose of 300 mg/kg body weight significantly reduced the blood glucose level, plasma total cholesterol, triglycerides and low density lipoprotein (LDL) in treated rabbits as compared to diabetic rabbits; also significantly increased the level of high density lipoprotein (HDL) (36.95 ± 2.95); SGOT and SGPT also significantly decreased.[59]

Anti-diabetic, antihyperlipidemic and antioxidant

The anti-diabetic, antihyperlipidemic and *in-vivo* antioxidant properties of the root in STZ-induced type 1 diabetic rats was studied. The ethanolic extract 100 and 200 mg/kg to the diabetic rats showed significant reduction in blood glucose and increase in body weight compared with diabetic control rats. Both doses showed significant alteration in elevated lipid profile levels, significant increase in SOD, CAT, GPX and decrease in thiobarbituric acid reactive substances levels than diabetic control rats. 200 mg/kg produced significant higher antioxidant activity than 100 mg/kg. These activities are possibly due to the presence of biomarkers gallic acid and quercetin revealed by high performance liquid chromatography analysis of the extract.[60]

Antimicrobial activity

The bicyclic sesquiterpene lactone isolated from the petroleum ether extract of the aerial part has been found to be potent against *Staphylococcus aureus, Escherichia coli, Fusarium* sp., *Helminthosporium* sp., and other microorganisms.[20] 7HF, a sesquiterpene lactone showed antimicrobial activity.[23] Alcoholic and aquous extracts of the plant were highly effective against *Alternaria solani, Fusarium oxysporum* and *Penicillium pinophilum* by preventing their growth to a greater extent.[61] Antimicrobial activity of terphenoidal compound isolated from *S. indicus* showed activity against *Bacillus subtilis*.[62] The *in-vitro* antimicrobial activity of aqueous extract of flower was evaluated against coliforms *E. coli* (10,536) and total coliforms by using disc diffusion method. The extracts showed significant inhibition against coliform strains.[63]

Leaves, flower stem and roots were extracted separately with methanol, ethanol, chloroform, petroleum ether and hot water and the extracts were screened for its phytochemical constituents. The plant revealed the presence of alkaloids, saponins, tannins, flavonoids, steroids, terpenoids, cardiac glycosides, amino acids, mono saccharides and reducing sugar. Leaves extracts showed significant amount of phytochemicals and hence antimicrobial studies of leaves extracts were carried out against bacterial species such as *Bacillus* sp. *Staphylococcus* sp., *Klebsiella* sp., *E. coli*, *Pseudomonas* sp., using filter paper and agar well diffusion method at 4 different concentrations. MES and AQS of leaf showed the highest inhibitory effect compared to all other extracts and it showed good inhibitory activity against *Bacillus* sp., followed by *Staphylococcus* sp. The gram-positive bacteria were found to be more susceptible than gram-negative bacteria. Antifungal activity of methanol and ethanol extracts were tested against *Penicillum* sp., and *Aspergillus* sp. and the growth was found to decreasewith increase in concentration of the extracts.[64,65]

Hexane, benzene, chloroform, ethyl acetate and acetone extracts of the aerial parts and flowers showed activity against *B. subtilis, S. aureus* and *Staphylococcus epidermidis.* Benzene and chloroform extracts of flower and benzene and acetone extracts of aerial parts were not active against *Enterococcus faecalis;* all extracts of flower and aerial part were not active against *E. coli* and *Klebsiella pneumonia* when tested by disc diffusion method.[66]

Four new alkaloids have been isolated from the alcoholic extract of flowers. The crude extract showed antibacterial activity against 18 different gram-positive and gram-negative bacteria. Both alkaloidal and non-alkaloidal fractions showed the activity. The isolated two alkaloids showed broad spectrum activity.[67]

Ten Indian medicinal plants were screened for antibacterial activity specific to enteropathogens. Diffusion and dilution methods were used to measure the antibacterial activity. *Allium sativum*, *Camellia sinensis* and *Chamaesyce hirta* showed higher activity when compared to the rest. They had a minimum bactericidal concentration of <100 μg/ml and gave inhibition zones of more than 2 cm. Among the pathogens studied, *Vibrio cholerae* and *Shigella flexneri* were found to be highly susceptible to the plant extracts.[68] The essential oil from the leaves exhibited antibacterial activity against *Salmonella paratyphi* A, B and C, *S. flexner*, *Salmonella enteritidis*, *Salmonella typhimurium*, *Shigella sonnei* and *Vibrio cholera.*[69] The fruits showed very good antibacterial activity against gram-positive and gram-negative bacteria.[70] The plant also exhibited antifungal activity.[71] The petroleum ether, acetone, methanol (90%) and aqueous extracts of flowers also exhibited remarkable antibacterial and strong antifungal activities.[72]

The hexane, chloroform, ethyl acetate, ethanol, methanol and aqueous extract of entire part including flower heads exhibited antimicrobial activity compared with gentamycin and nystatin as standards. The chloroform, methanol and aqueous extracts showed high antibacterial activity against *S. aureus*; chloroform, methanol and ethanol extract against *P. aeroginosa*, methanol, chloroform and hexane against *B. substilus*, aqueous, methanol, ethyl acetate and chloroform against *E. coli*.[73]

Antiviral activity

The methanol extract was found to exhibit inhibitory activity against *Mouse corona* virus and *Herpes simplex* virus at a concentration of 0.4 μg/ml.[74] The plant also showed antiviral activity against vaccinia and ranikhet viruses.[75]

Macrofilaricidal activity

The methanolic extract showed macrofilaricidal activity (4 mg/ml) against adult *Setaria digitata*, the cattle filarial worm when tested by worm motility assay method.[76]

Larvicidal action

Acetone extract of root and leaf caused $>50\%$ mortality in an Indian mosquito specie, which acts as a vector of filarial worm. Root extract was more active than leaf extract.[77] Purified fraction of acetone extract showed mosquito larvicidal effect. Methanolic extract showed repellent and feeding deterrent activities against *Tribolium castaneum* in the lower concentration of 1%; complete feeding deterrent activity at 5 ml and repellent activity at 4 ml dose.[78]

Antioxidant activity

The free radical scavenging potential of the plant was studied by using different antioxidant models of screening. The ethanolic extract at 1,000 μg/ml showed maximum scavenging of the radical cation, 2,2-azinobis-(3-ethylbenzothiazoline-6-sulphonate) observed up to 41.99% followed by the scavenging of the stable radical 1,1-diphenyl, 2-picryl hydrazyl (33.27%), SOD (25.14%) and nitric oxide radical (22.36%) at the same concentration. However, the extract showed only moderate scavenging activity of iron chelation (14.2%). Total antioxidant capacity of the extract was found to be 160.85 nmol/g ascorbic acid. The results justify the therapeutic applications of the plant in the indigenous system of medicine, augmenting its therapeutic value.[79]

Attenuation effect on prostatic hypertrophy

The attenuating effect of petroleum ether, ethanolic, aqueous extracts and β-sitosterol on prostatic hyperplasia induced by testosterone in Albino rats. Finasteride was used as a positive control (1 mg/kg p.o.). The petroleum ether extract exhibited the best activity, although the ethanol and aqueous extracts also exhibited significant activity thereby indicating the potential use of *S. indicus* in the treatment of prostatic hyperplasia.[80]

Anxiolytic, central nervous system depressant and anticonvulsant activities

The hydroalcoholic extract in the doses of 100, 200, 500 mg/kg, p.o. was experimented on induced anxiety, depression and convulsions in rodents; anticonvulsant effect on pentylenetetrazole-induced convulsions in mice; and maximal electroshock-induced convulsions in rats. *S. indicus* demonstrated anxiolytic, central nervous depressant and anticonvulsant activities in rodents; thus, supporting the folk medicinal use of this plant in nervous disorders.[81]

Effect on psoriasis

The effect of *S. indicus* on psoriasis was studied and found to exhibit the potent activity.[82]

Bronchodilatory effect

The methanolic extract and its fractions viz. petroleum ether, benzene, chloroform and ethyl acetate exhibited significant protection against bronchospasm, induced by histamine in guinea pigs. Significant protection exhibited by methanolic extract was comparable with the standard chlorophenarmine maleate (2 mg/kg).[83]

Mast cell stabilizing activity

The protective effect of different extracts of whole plant against the compound 48/80 and sheep serum induced mast cell degranulation was evaluated. The ethanol extract at the dose levels of 150 mg/kg and 300 mg/kg and ethyl acetate extract at the dose levels of 100 mg/kg, 150 mg/kg and 300 mg/kg showed slightly better protection of mast cell degranulation (77-86%) than ketotifen (75%) in the sheep serum model. These extracts also showed better mast cell stabilizing activity (77-88%) than the standard drug (69%) when peritoneal mast cells are treated with compound 48/80. These results suggest that *S. indicus* has potent mast cell stabilizing effects thereby inhibiting mediator release from mast cells.[84]

Antihyperlipidemic activity

The alcoholic extract of flower heads in atherogenic diet induced hyperlipidemia in rats was investigated for the dose of 500 mg/kg/day, p.o. for 8 days. The extract effectively suppressed the hyperlipidemia by decreasing total cholesterol, triglyceride, LDL and very low density lipoprotein (VLDL); increasing the HDL.[85]

Anti-arthritic activity

The anti-arthritic activity of the petroleum ether extract of the flowers in the doses 10, 30 and 100 mg/kg/day p.o. was investigated against complete Freund's adjuvant induced arthritis in laboratory rats. Indomethacin (2 mg/kg/day p.o.) was the standard drug. The dose of 100 mg/kg/day p.o. showed significant anti-arthritic activity.[86]

Anti-inflammatory activity

The anti-inflammatory effect of ethanolic extract was evaluated. The extract in different doses (100, 200 and 400 mg/kg, p.o.) exhibited dose dependent and significant anti-inflammatory activity in acute (carrageenan induced hind paw edema, $P < 0.05$) and chronic (cotton pellet granuloma formation, $P < 0.05$) model of inflammation.[87]

Anti-inflammatory and analgesic activity

The anti-inflammatory and analgesic activities of ethanolic extract of *S. indicus* flowers in doses of 300 and 500 mg/kg was tested on Albino mice and rat of either sex. Anti-inflammatory activity was evaluated by measuring the mean decrease in hind paw volume after the sub planter injection of carrageenan. The analgesic activity was tested against acetic acid induced writhing response using Albino rats. At the end of 1 h, the inhibition of paw edema was 42.66 and 50.5% respectively and the % of protection from writhing was 62.79 and 68.21 respectively.[88]

Anti-inflammatory, anti-migratory and anti-proliferative activity

Chronic inflammation induced hyper-proliferation and migration of keratinocytes are pathological hallmarks of psoriasis. Extracts from *Sphaeranthus* spp. demonstrate pharmacological activity *in-vitro* and *in-vivo*. However, the activity in modulating disease relevant pathways in psoriasis has not been reported. In the current study a standardized herbal extract from *S. indicus* (NPS31807) was used to study the mechanistic activity under conditions of inflammation, keratinocyte proliferation and migration using cell based and gene expression assays. NPS31807 treatment reduced levels of pro-inflammatory cytokines from human macrophages and activated epidermal keratinocytes in a dose dependent manner. Treatment with NPS31807 diminished NFκB and AP-1 transcription activity in human macrophages. Lowered nuclear translocation of p65 sub-unit in macrophages by treatment confirmed reduced activity of NFκB. Gene expression profiling showed attenuated expression of genes involved with inflammation such as tumor necrosis factor (TNF) signaling and angiogenesis by NPS31807. Inhibition of angiogenesis and matrix metalloproteinase production in keratinocytes was confirmed using real-time quantitative-polymerase chain reaction assays. Pretreatment with NPS31807 led to significant reduction of signal transducer and activator of transcription 3 phosphorylation and mitogen induced cellular migration. NPS31807 induced inhibition of proliferative genes and BrdU uptake in epidermal keratinocytes. In summary, our study provides novel molecular insights into the anti-inflammatory, anti-migratory and anti-proliferative properties of NPS31807. In summary, NPS31807, an extract from *S. indicus* can be used as therapeutic option in inflammatory and auto-immune conditions such as psoriasis.[89]

The anti-inflammatory effect *S. indicus* was found to be potent in suppressing the proinflammatory cytokines interleukin-8 (IL-8) and TNF-α induced by the culture

supernatant of *Propionibacterium acnes* in polymorphonuclear leukocytes and monocytes than that of other tested plants, viz., *Rubia cordifolia, Curcuma longa, Hemidesmus indicus* and *Azadirachta indica*.[90]

7HF significantly reduced the production (induced/spontaneous) of TNF-α and IL-6 from freshly isolated human mononuclear cells, synovial tissue cells isolated from patients with active rheumatoid arthritis and BALB/c mice. Oral administration of 7HF significantly protected C57BL/6J mice against endotoxin-mediated lethality. In the dextran sulfate sodium (DSS) model of murine colitis, oral administration of 7HF prevented DSS-induced weight loss, attenuated rectal bleeding, improved disease activity index and diminished shortening of the colon of C57BL/6J mice. Histological analyses of colonic tissues revealed that 7HF attenuated DSS-induced colonic edema, leukocyte infiltration in the colonic mucosa and afforded significant protection against DSS-induced crypt damage. 7HF was also significantly efficacious in attenuating carrageenan-induced paw edema in Wistar rats after oral administration. In the collagen-induced arthritis in DBA/1J mice, 7HF significantly reduced disease associated increases in articular index and paw thickness, protected against bone erosion and joint space narrowing and prominently diminished joint destruction, hyperproliferative pannus formation and infiltration of inflammatory cells. These results provide evidence that 7HF-mediated inhibition of pro-inflammatory cytokines functionally results in marked protection in experimental models of acute and chronic inflammation.[91]

Hypolipidemic activity

The effect of AQS (300 mg/kg/day, i.p) against dexamethasone (10 mg/kg/day, s.c) induced changes in lipid profile was studied in rat. *S. indicus* decreased the serum total cholesterol, triglyceride, LDL and VLDL significantly but not HDL; it also reduced atherogenic index significantly thus indicating its lipid lowering effect.[92]

Nephroprotective effect

The ethanolic extract was screened for nephroprotectivity in gentamicin induced acute renal injury in rats. The extract in the dose of 300 mg/kg was found to increase blood urea, serum creatinine and decrease the total protein and serum albumin of the treated group compared to normal group.[93]

Other activities

The plant was also found to exhibit anticancer activity and antiprotozoal activity against *Entamoeba histolytica*.[75] The alcoholic extract of the flower exhibited hypotensive, peripheral vasodilatory and cathartic activities.[94] The extract of the plant was found to inhibit hyaluronidase.[95] The extract effected toxicity on second and fourth instar larvae of *Calex quinquefasciator* mosquito at 100-500 ppm concentration.[96] The methanolic extract of dried fruit exhibited nematocidal activity.[97] The methanolic extract (<4 mg/mL) showed macrofilaricidal activity within an incubation period of 100 min by the worm motility assay against adult *S. digitata*, a cattle filarial worm.[78]

CONCLUSION

From the literature survey it is evident that *S. indicus* Linn. has been exhaustively worked out for both chemical and pharmacological studies. In all the reported pharmacological activities, it is found to be more potent. It finds a broad spectrum of therapeutic usage. As the plant is widely distributed, it could be considered for new drug formulations.

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