Medicinal plants of sandy shores: A short review on *Vitex trifolia* L. and *Ipomoea pes-caprae* (L.) R. Br.

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Two plant species of sandy shores, namely, *Vitex trifolia* L. (Beach vitex) and *Ipomoea pes-caprae* (L.) R. Br. (Beach morning glory), have been selected for review. Both species have ethno-pharmacological relevance and have been traditionally utilised by local people in remedies for various ailments. Endowed with diterpenes and flavonoids as major constituents, *V. trifolia* has trypanocidal, antimicrobial, anti-quorum sensing, mosquito larvicidal and repelling, hepatoprotective, anti-inflammatory, vascular relaxation, antimalarial, trachea-spasmolytic, wound healing, estrogenic, antinociceptive, anti-tubercular, molluscidal, and mice repelling properties. It is noteworthy that casticin or vitexicarpin isolated from *V. trifolia* displays potent cytotoxicity against a wide range of cancer cell lines via different modes of molecular action. Chemical constituents of *I. pes-caprae* include resin glycosides, flavonoids and phenolic acids. It exhibits antimicrobial, anti-inflammatory, antinociceptive, antispasmodic, insulinogenic, hypoglycemic, hypolipidemic, anti-collagenase and immuno-stimulatory activities. With an increasing number of people being stung by jellyfish while swimming in the sea of Thailand, clinical trials have been conducted to test the efficacy of *I. pes-caprae* extracts in treating jellyfish dermatitis.

Keywords: Beach morning glory, Beach vitex, *Ipomoea pes-caprae* (L.) R. Br., Pharmacology, Phytochemistry, *Vitex trifolia* L.,

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Introduction

Occurring worldwide, sandy shores are among the most dynamic landscapes, shifting with the winds, waves and tides1,2. Sand delivered to the beach by waves is dried by the sun and transported inland by wind to form dunes. Coastal dunes serve as reservoirs of sand to re-nourish the beach during storms as erosion transports the sand offshore, act as buffers to winds and waves, and shelter human habitation in the hinterland. They are also important habitats for plants and animals including the nesting of sea turtles. Plant communities of sandy shores, also referred to as strand vegetation, consist of the pioneer zone with primary stabilising herbs and grasses, the shrub zone with secondary stabilising shrubs and the forest zone consisting of shrubs and trees3,4.

In this short review, two plant species of the pioneer zone of sandy shores, namely, *Vitex trifolia* L. and *Ipomoea pes-caprae* (L.) R. Br. have been selected. Both these coastal species have ethno-pharmacological relevance and have been utilised by local people in remedies for various ailments. There is sufficient knowledge on their phytochemistry and pharmacology in the literature. In addition, some information on clinical trials using *I. pes-caprae* is available. To date, both plants have been reviewed as *V. trifolia*4 and as *I. pes-caprae*5 and under the genera of *Vitex*6-8 and *Ipomoea*9.

*Vitex trifolia*

Botany and uses

*Vitex trifolia* syn. *V. rotundifolia* L. f. and *V. ovata* Thunb.10 (Beach vitex) of the family Lamiaceae is widely distributed throughout sandy beaches of the tropics and sub-tropics. Occurring in South, Southeast and East Asia, the species is a low sprawling shrub, producing radiating stems with adventitious roots and short erect flowering branches at the nodes11. Leaves are greyish-green and flowers borne on erect inflorescences are purplish-blue or lilac (Plate 1).
species grows behind the frontal dunes, forming dense stands and can withstand moderate salt spray and sand blasting. It is a useful secondary sand-stabilising species because of its sprawling growth habit and sand-binding ability.

In Southern Thailand and in Northeastern Peninsular Malaysia, local communities prepare a traditional dessert made from rice flour. The leaf extract of *V. trifolia* is added to give colour and flavour and the dessert is served with grated coconut and granulated sugar. In folk medicine, *V. trifolia* is used as an anti-inflammatory drug and for treating cancer in China and Korea to treat asthma and other allergic diseases. In folk medicine, *V. trifolia* is used as an anti-inflammatory drug and for treating cancer in China.

**Phytochemistry and pharmacology**

From the fruits of *V. trifolia*, labdane diterpenes (vitexilactone and previtexilactone), phenolic acids (p-hydroxybenzoic acid and vanillic acid), flavones (casticin, luteolin and artemetin), flavonoids (luteolin, crysosplenol-D and penduletin), halimane diterpenes (vitetrolons-D–G), and ten new labdane diterpenes have been isolated. From the leaves, flavone glycosides, luteolin, ursolic acid and m-hydroxybenzoic acid and flavonoids such as casticin, vitexin, artemetin, coniferaldehyde and vanilin have been reported.

Analysis of the acetone fruit extract led to the isolation of two new norditerpene aldehydes along with known diterpenes (vitexifolin E, vitexifolin F, vitexilactone and previtexilactone). When tested against epimastigotes of *Trypanosoma cruzi*, the two new aldehydes displayed trypanocidal activity with minimum lethal concentrations of 11 and 36 µM. Values of the known diterpenes were 34 or 66 µM with previtexilactone showing no activity.

Using the disc diffusion method, the methanol extract of the aerial part (500 µg/mL) inhibited the growth of *Bacillus cereus* and *Pseudomonas aeruginosa* with minimum inhibitory concentration (MIC) of 62 and 125 µg/mL, respectively. Against six fungal species of *Aspergillus* and *Candida*, MIC ranged from 125–250 µg/mL. Recent studies on the leaf extracts reported antibacterial activity and anti-quorum sensing activity against *P. aeruginosa*.

The mosquito larvicidal activity of *V. trifolia* has also been reported. Methanol and fatty acid methyl ester (FAME) leaf extracts were tested against early fourth instar larvae of *Culex quinquefasciatus*, the vector of lymphatic filariasis. LC50 was 41 ppm for the methanol leaf extract and 9.3 ppm for the FAME leaf extract. Against the larvae of *Aedes aegypti* and *C. quinquefasciatus*, methyl-p-hydroxybenzoate from the leaves exhibited 100% mortality of both the larval species at 20 ppm with LC50 of 4.7 and 5.8 ppm, respectively. Earlier, rotundial from *V. trifolia* has been reported to be an effective natural mosquito repellent against *A. aegypti*.

Leaves of *V. trifolia* display cytotoxic activity. Study has shown that the hexane and the dichloromethane extracts of aerial parts were cytotoxic to SQC-1, OVCAR-5, HCT-15 and KB cancer cells. When tested against MCF-7 breast cancer cells, HT-29 colorectal cancer cells and WRL-68 normal liver cells, the methanol leaf extract showed positive cytotoxicity with IC50 values 78.9, 77.5 and 78.3 µg/mL, respectively. Against HepG2 and HeLa cancer cells, the IC50 value of the hexane fraction of the leaf extract was 80 µg/mL for both. Methanol, ethyl acetate and chloroform extracts of the aerial part have been reported to be cytotoxic to brine shrimp with LC50 values 140, 165 and 180 mg/mL, respectively.

At 100 µg/mL, flavonoids (persicogenin, artemetin, luteolin, penduletin, casticin and chrysosplenol-D) isolated from the leaves of *V. trifolia* inhibited the proliferation of mouse tsFT210 cancer cells. Strongest activity was observed in casticin and chrysosplenol-D with IC50 values of 0.3 and 3.5 µg/mL, respectively. Casticin also induced apoptosis...
of human leukaemia K562 cells. Concurrently, casticin was also reported to inhibit the proliferation of A2780, HCT-15, HT-1080 and K562 human cancer cells. For K562 cells, casticin induced apoptosis via the mitochondrial pathway. In a related study, labdane-type diterpenes (vitexilactone, rotundifuran, vitetrifolin D and vitetrifolin E) isolated from leaves induced apoptosis of tsFT210 and K562 cells at higher concentrations and inhibited cell cycle progression at lower concentrations.

Fruits of V. trifolia have also been reported to possess anticancer properties. From the fruits, casticin inhibited all nine cancer cell lines with IC\textsubscript{50} values ranging from 0.2–2.0 \(\mu\text{M}\), while rotundifuran inhibited the growth of human leukaemia HL-60 cells with an IC\textsubscript{50} value of 22.5 \(\mu\text{M}\).

Of all the compounds isolated from the fruits and leaves of V. trifolia with anticancer properties, casticin (also called vitexicarpin) is the most studied including their molecular modes of action. In polymethoxylavones, the C3 hydroxyl and C8 methoxyl groups are not essential for the anticancer activity but the C3' hydroxyl group and the C2-C3 double bond are important for the anti-proliferative and apoptotic activities. In casticin, it has been shown that the C3' and C5 hydroxyl groups as well as the C3 and C4' methoxyl groups contribute to its significant anti-proliferative activity (Fig. 1). Apart from casticin, other flavones such as apigenin, chrysin, luteolin and quercetin can also cause oxidative stress in cancer cells, resulting in their cytotoxicity.

Recently, an increasing number of pharmacological studies have reported that casticin induces growth inhibition, cell cycle arrest and apoptosis in many human cancer cell lines like in leukaemia HL-60, carcinoma KB, leukaemia K562, cervical cancer HeLa, hepatocellular carcinoma HepG2, lung epithelial A549, prostrate carcinoma PC-3, pancreatic carcinoma PANC-1, ovarian cancer SKOV3 and A2780, colon cancer Col2 and breast cancer MCF-7 and MDA-MB-231.

Molecular mechanism studies have shown that casticin induces apoptosis via the mitochondrial pathway of caspase-3 activation, activation of c-Jun N-terminal kinase, inactivation NF-\(\kappa\)B and MAPK signalling, death receptor 5 up-regulation, G2/M phase arrest, FOXO3a activation by repression of FoxM1, up-regulation of Bax, down-regulation of Bcl-2 followed by activation of caspase-3 and potentiation of apoptosis through activation of mitochondrial pathway and induction of DR5. A review of the pharmacological and therapeutic applications of casticin with emphasis on its anticancer, anti-proliferative and pro-apoptotic functions and its related molecular mechanisms is available for further reading.

With V. trifolia being a promising candidate for anticancer drug development, research is much needed to raise its seedlings for cultivation on a commercial scale. In this context, a protocol has been developed to mass propagate plantlets through in vitro culture using leaf and inter-nodal explants. However, in a review article on coastal vegetation as an underexplored source of anticancer drugs, V. trifolia was not amongst the 16 species identified.

Leaves and flowers of V. trifolia have also been reported to possess potent hepatoprotective activity against carbon tetrachloride (CCl\textsubscript{4})-induced liver damage in rats. Supported by histopathological evidence, aqueous and ethanol leaf extracts and ethanol flower extract of V. trifolia, significantly reduced total bilirubin, total protein and activities of serum enzymes in the CCl\textsubscript{4}-treated groups.

Other pharmacological properties of V. trifolia include anti-asthma, analgesic, vascular relaxation, anti-inflammatory, anti-malarial, trachea-spasmolytic, wound healing, estrogenic, antinociceptive, anti-tubercular, anthelmintic, molluscidal, mice repelling and anti-allergic activities.

**Ipomoea pes-caprae**

**Botany and uses**

*Ipomoea pes-caprae* (Beach morning glory) of the family Convolvulaceae is a perennial creeping vine with milky sap and a sweet taste. Roots are produced at the nodes. Leaves are alternate, oval-shaped and notched at the end, resembling the footprint of a goat. Borne on long stalks, flowers are attractive, bell-shaped, pink, purple...
or violet with deeper colour at the centre (Plate 2). Fruits are a flattened capsule with four black and densely hairy seeds. The species is pan-tropical and common along sandy beaches of Asia and the Pacific. It is a primary sand-stabilising species, being one of the earliest plants to colonise the sand dunes including the seaward dune slopes. Growing in association with other plant species, *I. pes-caprae* is a useful sand-binder, thriving under conditions of sand blast and salt spray.

In China, the leaves of *I. pes-caprae* are topically applied to treat pain, boils and bedsores. In Thailand, local fishermen use the plant as antidote to jellyfish stings by applying the leaves to relieve pain, inflammation and allergic reactions. The preparation involves pounding the leaves and mixing with distilled vinegar to make a paste. After straining, the liquid is applied to the affected area. In India, leaves have been used in ritual baths to dispel evil spirits. With diuretic and laxative properties, leaves are used as stomachic and tonic and for treating rheumatism. In Papua New Guinea, leaves are chewed to relieve stomach ache and young leaves are heated over a fire and applied to sores. The sap from the stem is used to treat sore eyelids, boils and earache. In Mauritius, the vine has been traditionally used to treat stone fish stings and haemorrhoid infections.

**Phytochemistry and pharmacology**

Chemical investigations of *I. pes-caprae* have revealed the presence of resin glycosides such as pescapreins I–IX, stoloniferin III, pescaprosides A and B, and pescapreins X–XVII. Recently, flavonoids and phenolic acids (7-hydroxy-6-methoxycoumarin, 5,7,4′-trimethoxykaempferol, 3,7,8,3′,4′-pentahydroxyflavone, *trans*-3-(4′-hydroxyphenyl)-2-propenoic acid, isoquercitrin and isochlorogenic acids A–C) have been reported in methanol and ethanol extracts of *I. pes-caprae*.

The constituents of the essential oils from leaves of *I. pes-caprae* in Mauritius were analysed using GC-MS and 70 compounds were identified. Major components were 8-cedren-13-ol (13 %) in fresh leaves and β-caryophyllene (37 %) in dried leaves.

From the aerial parts of *I. pes-caprae*, 10 new pentasaccharide resin glycosides (pescapreins XXI–XXX), along with the known pescapreins I–IV and stoloniferin III were isolated. These new compounds have a pentasaccharide core, esterified and lactonized to form a macrocyclic lactone. Evaluation of their inhibitory effects against human breast cancer MCF-7/ADR cells showed that each of the pescapreins XXI–XXX (5 µg/mL) when combined with doxorubicin increased cytotoxicity of the latter by 1.5–3.7 fold.

Leaf extracts of *I. pes-caprae* have been reported to possess antimicrobial properties. Using the disc diffusion method, methanol, butanol, acetone and chloroform leaf extracts (100 µg/mL) were tested against five bacterial species and six fungal species. The methanol extract inhibited *Escherichia coli* and *Salmonella paratyphi* with diameters of inhibition zone (DIZ) of 20 mm and 13 mm, respectively. The acetone extract was found to inhibit *Mucor* sp. and *Candida albicans* with DIZ of 22 mm and 16 mm, respectively. Tested against five human pathogens, methanol extract exhibited strong antibacterial activity, whereas hexane, dichloromethane and ethyl acetate extracts showed no activity.

Two studies reported on the antinociceptive effects of aerial parts of *I. pes-caprae* on mice. Using the writhing and formalin tests, the methanol extract, and ethyl acetate and aqueous fractions exhibited antinociceptive activity against pain and inflammation. Of the constituents isolated from the plant, isoquercetin, β-amyrin acetate, α-amyrin acetate, betulinic acid and glochidone showed pronounced antinociceptive properties. A follow-up study on the antinociceptive and anti-inflammatory actions was conducted aimed at optimising maceration and extraction protocols.

An extract of *I. pes-caprae* was shown to inhibit the contraction of the guinea-pig ileum stimulated by four different spasmogens. β-Damascenone and (E)-phytol were later isolated and found to possess antispasmodic activity. In addition, eugenol,
(--)-mellein and 4-vinylguaiacol were isolated and found to exhibit anti-inflammatory properties via the inhibition of prostaglandin activity\textsuperscript{97}. The extract also demonstrated the ability to neutralize crude jellyfish venom\textsuperscript{98}. When incubated with active venom, the extract inhibited the actions of jellyfish venoms with IC\textsubscript{50} values of 0.3–0.8 mg extract per mg of venom for proteolytic action and with 10 times lower IC\textsubscript{50} values for the neutralization of haemolytic action.

The leaf extract of \textit{I. pes-caprae} has anti-inflammatory effects on ear oedema in rats\textsuperscript{99,100}. Actinidols 1a and 1b, isolated from the extract together with other compounds of (--)mellein, eugenol and (E)-phytol reduced oedema formation. Results showed that the extract contains active compounds which interfere with the process of inflammation.

Recently, extracts of \textit{I. pes-caprae} were found to exhibit significant anti-inflammatory activities in rats using the cotton pellet-induced granuloma test\textsuperscript{101}. Based on percentage inhibition, treatment with 400 mg/kg of leaf extract (53 %) was the most effective followed by 400 mg/kg of stem extract (44 %) and 200 mg/kg of leaf extract (38 %). The percentage inhibition of 400 mg/kg of leaf extract was comparable with 5 mg/kg of diclofenac sodium (60 %) used as the standard. In a related study, application of an ointment made from the ethanol extract of \textit{I. pes-caprae} on the shaved dorsal part of rats showed no dermal toxicity at 2 g/kg\textsuperscript{81}.

Other pharmacological properties of \textit{I. pes-caprae} are antioxidant\textsuperscript{102}, insulinogenic, hypoglycemic and hypolipidemic\textsuperscript{103,104}, collagenase inhibitory\textsuperscript{105} and immuno-stimulatory\textsuperscript{106} activities.

**Clinical trials**

In recent years, an increasing number of victims have been stung by the box jellyfish while swimming in the sea of Thailand with fatal cases reported due to its massive envenomation\textsuperscript{107}. In fatal cases, victims experience severe burning pain before becoming unconscious which leads to cyanosis and eventual death within minutes\textsuperscript{108}. In severe non-fatal cases, victims have extensive skin lesions followed by cardio-pulmonary failure. These fatal and non-fatal cases of jellyfish stings have prompted the Thai Government to undertake clinical trials in search of a remedy for jellyfish dermatitis.

In the 1980s, a clinical trial involving 12 patients was conducted at the Siriraj Hospital of Mahidol University in Bangkok, Thailand, to test the efficacy of a cream containing leaf extract of \textit{I. pes-caprae} in the treatment of jellyfish dermatitis\textsuperscript{109}. Topical application of the cream yielded promising results. Five patients with mild infections were relieved of itching the following day and the dermatitis disappeared after two days. Seven patients with severe infections showed 50 % improvement within a week and complete recovery after 30–45 days, leaving few hypertrophic scars.

Currently, another clinical trial is being conducted at the Hospital for Tropical Diseases of Mahidol University, using an ointment of \textit{I. pes-caprae} as an add-on therapy for patients with jellyfish dermatitis\textsuperscript{110}. Each patient received a standard medical treatment depending on the severity of dermatitis with the ointment applied as an add-on to the test area in comparison with the control area. Preliminary results could not demonstrate the efficacy of the ointment in the treatment of dermatitis but was effective in reducing the duration of itching.

**Conclusion**

Research has shown that both the coastal species have pharmacological properties that support their use in folk medicine. For \textit{V. trifolia}, there is scientific evidence affirming the anticancer properties of castacin. However, further studies and pre-clinical trials are needed to determine its toxicology, specific intracellular sites of action and derivative targets before this candidate anticancer drug can progress to clinical trials. For \textit{I. pes-caprae}, the modes of action of isolated compounds with antiinociceptive, anti-inflammatory and antispasmodic activities warrant further investigation. The outcome of the on-going clinical trial of using an ointment made from the species as an add-on therapy for patients with jellyfish dermatitis in Thailand is much awaited. The flora of sandy shores does comprise species with promising and exciting medicinal potentials.

**References**


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