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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, analgesic, vascular relaxation, antimalarial, trachea-spasmolytic, wound healing, estrogenic, antinociceptive, anti-tubercular, anthelmintic, 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 tides[1,2]. 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 trees[1,3].

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].

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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 nodes[11]. Leaves are greyish-green and flowers borne on erect inflorescences are purplish-blue or lilac (Plate 1). The

Plate 1—Leaves and flowers of *Vitex trifolia*

species grows behind the frontal dunes, forming dense stands and can withstand moderate salt spray and sand blasting[3]. 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[12]. 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[13-15]. Having anti-inflammatory and sedative properties, fruits of this shrub have been used to treat headache, rheumatism, migraine, sore eye and cold in Asian countries[16-18]. Dried fruits have long been used in China and Korea to treat asthma and other allergic diseases[19].

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)[20], *p*-hydroxybenzoic acid, β-sitosterol, β-sitosterol-3-*O*-glucoside, casticin and 3,6,7-trimethyl quercetagetin[21], vitexfolins A–C[22], flavonoids (luteolin, crysosplenol D and penduletin)[23], halimane diterpenes (vitetrifolins D–G)[16] and ten new labdane diterpenes[17] have been isolated. From the leaves, flavone glycosides[24], luteolin, ursolic acid and *m*-hydroxybenzoic acid[25] and flavonoids such as casticin, vitexin, artemetin, coniferaldehyde and vanillin[26,27] 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)[18]. 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[28]. Against six fungal species of *Aspergillus* and *Candida*, MIC ranged from 125–250 µg/mL. Recent studies on the leaf extracts reported antibacterial activity[29] and anti-quorum sensing activity against *P. aeruginosa*[30].

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. LC_{50} was 41 ppm for the methanol leaf extract[31] and 9.3 ppm for the FAME leaf extract[32]. 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 LC_{50} of 4.7 and 5.8 ppm, respectively[33]. Earlier, rotundial from *V. trifolia* has been reported to be an effective natural mosquito repellent against *A. aegypti*[34].

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[35]. 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 IC_{50} values 78.9, 77.5 and 78.3 µg/mL, respectively[12]. Against HepG2 and HeLa cancer cells, the IC_{50} value of the hexane fraction of the leaf extract was 80 µg/mL for both[36]. Methanol, ethyl acetate and chloroform extracts of the aerial part have been reported to be cytotoxic to brine shrimp with LC_{50} values 140, 165 and 180 mg/mL, respectively[37].

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[14]. Strongest activity was observed in casticin and chrysosplenol-D with IC_{50} values of 0.3 and 3.5 µg/mL, respectively. Casticin also induced apoptosis

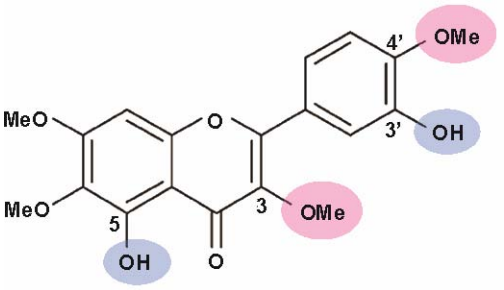

Fig. 1—Molecular structure of casticin (vitexicarpin)

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[38]. 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[15].

Fruits of *V. trifolia* have also been reported to possess anticancer properties. From the fruits, casticin inhibited all nine cancer cell lines with IC_{50} values ranging from 0.2–2.0 μM[27], while rotundifuran inhibited the growth of human leukaemia HL-60 cells with an IC_{50} value of 22.5 μM[39].

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 polymethoxyflavones, 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[40,41]. 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[42] (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[41], carcinoma KB[42], leukaemia K562[38,43], cervical cancer HeLa[44,45], hepatocellular carcinoma HepG2[46,47], lung epithelial A549[48], prostrate carcinoma PC-3[49], pancreatic carcinoma PANC-1[50], ovarian cancer SKOV3 and A2780[13], colon cancer Col2[51] and breast cancer MCF-7 and MDA-MB-231[52,53].

Molecular mechanism studies have shown that casticin induces apoptosis via the mitochondrial pathway of caspase-3 activation[38,43], activation of c-Jun N-terminal kinase[45], inactivation NF-κB and MAPK signalling[48,54], death receptor 5 up-regulation[46], G2/M phase arrest[14,42,49], FOXO3a activation by repression of FoxM1[13,47,52], up-regulation of Bax, down-regulation of Bcl-2 followed by activation of caspase-3[50] and potentiation of apoptosis through activation of mitochondrial pathway and induction of DR5[51,55]. 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[56].

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[57]. However, in a review article on coastal vegetation as an underexplored source of anticancer drugs, *V. trifolia* was not amongst the 16 species identified[58].

Leaves and flowers of *V. trifolia* have also been reported to possess potent hepatoprotective activity against carbon tetrachloride (CCl_4)-induced liver damage in rats[59,60]. Supported by histopathological evidence, aqueous and ethanol leaf extracts[59] and ethanol flower extract[60] of *V. trifolia*, significantly reduced total bilirubin, total protein and activities of serum enzymes in the CCl_4-treated groups.

Other pharmacological properties of *V. trifolia* include anti-asthma[19], analgesic[22], vascular relaxation[23], anti-inflammatory[61-64], anti-malarial[65,66], trachea-spasmolytic[67], wound healing[68], estrogenic[69], antinociceptive[70], anti-tubercular[71], anthelmintic[72], molluscidal[73], mice repelling[74] and anti-allergic[75] 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[3,11]. 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

Plate 2—Leaves and flowers of *Ipomoea pes-caprae*

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[76]. In Thailand, local fishermen use the plant as antidote to jellyfish stings by applying the leaves to relieve pain, inflammation and allergic reactions[77,78]. The preparation involves pounding the leaves and mixing with distilled vinegar to make a paste[79]. After straining, the liquid is applied to the affected area. In India, leaves have been used in ritual baths to dispel evil spirits[80,81]. 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[82]. 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[83].

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[84,85] and pescapreins X–XVII[86]. 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*[87,88].

The constituents of the essential oils from leaves of *I. pes-caprae* in Mauritius were analysed using GC-MS and 70 compounds were identified[83]. 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[89]. 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[90]. 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[91].

Two studies reported on the antinociceptive effects of aerial parts of *I. pes-caprae* on mice[92,93]. Using the writhing and formalin tests, the methanol extract, and ethyl acetate and aqueous fractions exhibited antinociceptive activity against pain and inflammation[92]. Of the constituents isolated from the plant, isoquercetrin, β-amyrin acetate, α-amyrin acetate, betulinic acid and glochidone showed pronounced antinociceptive properties[93]. A follow-up study on the antinociceptive and anti-inflammatory actions was conducted aimed at optimising maceration and extraction protocols[94].

An extract of *I. pes-caprae* was shown to inhibit the contraction of the guinea-pig ileum stimulated by four different spasmogens[95]. β-Damascenone and (*E*)-phytol were later isolated and found to possess antispasmodic activity[96]. In addition, eugenol,

(−)-mellein and 4-vinylguaiacol were isolated and found to exhibit anti-inflammatory properties via the inhibition of prostaglandin activity[97]. The extract also demonstrated the ability to neutralize crude jellyfish venom[98]. When incubated with active venoms, the extract inhibited the actions of jellyfish venoms with IC50 values of 0.3–0.8 mg extract per mg of venom for proteolytic action and with 10 times lower IC50 values for the neutralization of haemolytic action.

The leaf extract of *I. pes-caprae* has anti-inflammatory effects on ear oedema in rats[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 *I. pes-caprae* were found to exhibit significant anti-inflammatory activities in rats using the cotton pellet-induced granuloma test[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 *I. pes-caprae* on the shaved dorsal part of rats showed no dermal toxicity at 2 g/kg[81].

Other pharmacological properties of *I. pes-caprae* are antioxidant[102], insulinogenic, hypoglycemic and hypolipidemic[103,104], collagenase inhibitory[105] and immuno-stimulatory[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[107]. In fatal cases, victims experience severe burning pain before becoming unconscious which leads to cyanosis and eventual death within minutes[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 *I. pes-caprae* in the treatment of jellyfish dermatitis[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 *I. pes-caprae* as an add-on therapy for patients with jellyfish dermatitis[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 *V. trifolia*, there is scientific evidence affirming the anticancer properties of casticin. 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 *I. pes-caprae*, the modes of action of isolated compounds with antinociceptive, 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

1 Craft C B, Bertram J and Broome S, Coastal zone restoration, *In*: Encyclopedia of ecology, S E Jorgensen and B Fath, Eds, Elsevier Ltd, 2008, 637-644.

2 Moreno-Casasola P, Ecosystems: Dunes, *In*: Encyclopedia of ecology, S E Jorgensen and B Fath, Eds, Elsevier Ltd, 2008, 971-976.

3 Chan H T and Baba S, Manual on Guidelines for rehabilitation of coastal forests damaged by natural hazards in the Asia-Pacific Region, ISME and ITTO, Japan, 2009.

4 Kulkani L A, Pharmacological review on *Vitex trifolia* L. (Verbenaceae), *PharmacologyOnline*, 2011, **3**, 858-863.

5 Manigauha A, Ganesh N and Kharya M D, Morning glory: A new thrust in-search of *de-novo* therapeutic approach, *Int J Phytomed*, 2010, **2**, 18-21.

6 Ganapaty S and Vidyadhar K N, Phytoconstituents and biological activities of *Vitex* – A review, *J Nat Remed*, 2005, **5**, 75-95.

7 Meena A K, Niranjan U S, Rao M M, Padhi M M and Babu R, A review of the important chemical constituents and medicinal uses of *Vitex* genus, *Asian J Tradit Med*, 2011, **6,** 54-60.

8 Rani A and Sharma A, The genus *Vitex*: A review, *Pharmacogn Rev*, 2013, **7**, 188-198.

9 Meira M, da Silva E P, David J M and David J P, Review of the genus *Ipomoea*: Traditional uses, chemistry and biological activities, *Brazil J Pharmacogn*, 2012, **22**, 682-713.

10 The Plant List, *Vitex*, 2013, Database available online at http://www.theplantlist.org.

11 Giesen W, Wulfraat S, Zieren M and Scholten L, *Vitex ovata*. *In*: Mangrove guidebook for Southeast Asia, FAO and Wetland International, 2007, 768-769.

12 Aweng E R, Nur Hanisah N, Mohd Nawi M A, Nurhanan Murni Y and Shamsul M, Antioxidant activity and phenolic compounds of *Vitex trifolia* var. *simplicifolia* associated with anticancer, *ISCA Int J Biol Sci*, 2012, **1**, 65-68.

13 Jiang L, Cao X C, Cao J G, Liu F, Quan M F, Sheng X F and Ren K Q, Casticin induces ovarian cancer cell apoptosis by repressing FoxM1 through the activation of FOXO3a, *Oncol Lett*, 2013, **5**, 1605-1610.

14 Li W X, Cui C B, Cai B, Wang H Y and Yao X S, Flavonoids from *Vitex trifolia* L. inhibit cell cycle progression at G2/M phase and induce apoptosis in mammalian cancer cells, *J Asian Nat Prod Res*, 2005, **7**, 615-626.

15 Li W X, Cui C B, Cai B and Yao X S, Labdane-type diterpenes as new cell cycle inhibitors and apoptosis inducers from *Vitex trifolia* L., *J Asian Nat Prod Res*, 2005, **7**, 95-105.

16 Ono M, Ito Y and Nohara T, Four new halimane-type diterpenes, vitetrifolins D–G, from the fruit of *Vitex trifolia*, *Chem Pharm Bull*, 2001, **49**, 1220-1222.

17 Ono M, Yamamoto M, Yanaka T, Ito Y and Nohara T, Ten new labdane-type diterpenes from the fruit of *Vitex rotundifolia*, *Chem Pharm Bull*, 2001, **49**, 82-86.

18 Kiuchi F, Matsuo K, Ito M, Qui T K and Honda G, New norditerpenoids with trypanocidal activity from *Vitex trifolia*, *Chem Pharm Bull*, 2004, **52**, 1492-1494.

19 Bae H, Kim Y, Lee E, Park S, Jung K H, Gu M J, Hong S P and Kim J, *Vitex rotundifolia* L. prevented airway eosinophilic inflammation and airway remodeling in an ovalbumin-induced asthma mouse model, *Int Immunol*, 2012, **25**, 197-205.

20 Kondo Y, Sugiyama K and Nozoe S, Studies on the constituents of *Vitex rotundifolia* L., *Chem Pharm Bull*, 1986, **34**, 4829-4832.

21 Zeng X, Fang Z, Wu Y and Zhang H, Chemical constituents of the fruits of *Vitex trifolia* L., *China J Chin Mater Medic*, 1996, **21**, 167-168.

22 Okuyama E, Fujimori S, Yamazaki M and Deyama T, Pharmacologically active components of viticis fructus (*Vitex rotundifolia*). II. The components having analgesic effects, *Chem Pharm Bull*, 1998, **46**, 655-662.

23 Okuyama E, Suzumura K and Yamazaki M, Pharmacologically active components of viticis fructus (*Vitex rotundifolia*). I. The components having vascular relaxation effects, *Nat Med*, 1998, **52**, 218-225.

24 Ramesh P, Nair A G R and Subramanian S S, Flavone glycosides of *Vitex trifolia*, *Fitoterapia*, 1986, **57**, 282-283.

25 Ramli I, Hamzah A S, Aimi N and Lajis N H, Chemical constituents of *Vitex ovata* (Verbenaceae), *Pertanika J Sci Technol*, 1997, **5**, 105-109.

26 Chen H Y, Cheng W X, Feng Y, Gu K, Yang L J and Zhang Y P, Studies on flavonoid constituents of *Vitex trifolia* L. var. *simplicifolia* Cham., *Nat Prod Res Dev*, 2008, **20**, 582-584.

27 Kim H, Yi J M, Kim N S, Lee Y J, Kim J, Oh D S, Bang O S and Lee J, Cytotoxic compounds from the fruits of *Vitex rotundifolia* against human cancer cell lines, *J Korean Soc Appl Biol Chem*, 2012, **55**, 433-437.

28 Ali A M, El-Sharkawy S H, Hamid J A, Ismail N H and Lajis N H, Antimicrobial activity of selected Malaysian plants, *Pertanika J Trop Agric Sci*, 1995, **18**, 57-61.

29 Hossain M M, Paul N, Sohrab M H, Rahman E and Rashid M A, Antibacterial activity of *Vitex trifolia*, *Fitoterapia*, 2001, **72**, 695-697.

30 Mary R N I and Banu N, Screening of antibiofilm and anti-quorum sensing potential of *Vitex trifolia* in *Pseudomonas aeruginosa*, *Int J Pharm Pharm Sci*, 2015, **7**, 242-245.

31 Kannathasan K, Senthilkumar A, Chandrasekaran M and Venkatesalu V, Differential larvicidal efficacy of four species of *Vitex* against *Culex quinquefasciatus* larvae, *Parasitol Res*, 2007, **101**, 1721-1723.

32 Kannathasan K, Senthilkumar A, Venkatesalu V and Chandrasekaran M, Larvicidal activity of fatty acid methyl esters of *Vitex* species against *Culex quinquefasciatus*, *Parasitol Res*, 2008, **103**, 999-1001.

33 Kannathasan K, Senthilkumar A and Venkatesalu V, Mosquito larvicidal activity of methyl-*p*-hydroxybenzoate isolated from the leaves of *Vitex trifolia* Linn., *Acta Tropic*, 2011, **120**, 115-118.

34 Watanabe K, Takada Y, Matsuo N and Nishimura H, Rotundial, a new natural mosquito repellent from the leaves of *Vitex rotundifolia*, *Biosci Biotechnol Biochem*, 1995, **59**, 1979-1980.

35 Hernández M M, Heraso C, Villarreal M L, Vargas-Arispuro I and Aranda E, Biological activities of crude plant extracts from *Vitex trifolia* L. (Verbenaceae), *J Ethnopharmacol*, 1999, **67**, 37-44.

36 Vasanthi V J, Radhjeyalakshmi R and Nasrin F, Evaluation of anticancer activity using hexanic extract of *Vitex trifolia* on two different cancer cell lines, *Int J Pharmacogn Phytochem Res*, 2014, **6**, 449-453.

37 El-Kousy S, Mohamed M and Mohamed S, Phenolic and biological activities of *Vitex trifolia* aerial parts, *Life Sci J*, 2012, **9**, 670-677.

38 Wang H Y, Cai B, Cui C B, Zhang D Y and Yang B F, Vitexicarpin, a flavonoid from *Vitex trifolia* L., induces apoptosis in K562 cells *via* mitochondria-controlled apoptotic pathway, *Acta Pharmacol Sinica*, 2005, **40**, 27-31.

39 Ko W G, Kang T H, Lee S J, Kim Y C and Lee B H, Rotundifuran, a labdane type diterpene from *Vitex rotundifolia*, induces apoptosis in human myeloid leukaemia cells, *Phytother Res*, 2001, **15**, 535-537.

40 Kawaii S, Tomono Y, Katase E, Ogawa K and Yano M, Antiproliferative activity of flavonoids on several cancer cell lines, *Biosci Biotechnol Biochem*, 1999, **63**, 896-899.

41 Ko W G, Kang T H, Lee S J, Kim N Y, Kim Y C, Sohn D H and Lee B H, Polymethoxy-flavonoids from

Vitex rotundifolia inhibit proliferation by inducing apoptosis in human myeloid leukemia cells, *Food Chem Toxicol*, 2000, **38**, 861-865.

42 Kobayakawa J, Sato-Nishimori F, Moriyasu M and Matsukawa Y, G2-M arrest and antimitotic activity mediated by casticin, a flavonoid isolated from viticis fructus (*Vitex rotundifolia* Linn.), *Cancer Lett*, 2004, **208**, 59-64.

43 Shen J K, Du H P, Yang M, Wang Y G and Jin J, Casticin induces leukemic cell death through apoptosis and mitotic catastrophe, *Ann Hematol*, 2009, **88**, 743-752.

44 Chen D, Cao J, Tian L, Liu F and Sheng X, Induction of apoptosis by casticin in cervical cancer cells through reactive oxygen species-mediated mitochondrial signalling pathways, *Oncol Rep*, 2011, **26**, 1287-1294.

45 Zeng F, Tian L, Liu F, Cao J, Quan M and Sheng X, Induction of apoptosis by casticin in cervical cancer cells: reactive oxygen species-dependent sustained activation of Jun N-terminal kinase, *Acta Biochim Biophys Sinica*, 2012, **44**, 442-449.

46 Yang J, Yang Y, Tian L, Sheng X F, Liu F and Cao J G, Casticin-induced apoptosis involves death receptor 5 upregulation in hepatocellular carcinoma cells, *World J Gastroenterol*, 2011, **17**, 4298-4307.

47 He L, Yang X, Cao X, Liu F, Quan M and Cao J, Casticin induces growth suppression and cell cycle arrest through activation of FOXO3a in hepatocellular carcinoma, *Oncol Rep*, 2012, **29**, 103-108.

48 Koh D J, Ahn H S, Chung H S, Lee H, Kim Y, Lee J Y, Kim D G, Hong M, Shin M and Bae H, Inhibitory effects of casticin on migration of eosinophil and expression of chemokines and adhesion molecules in A549 lung epithelial cells *via* NF-κB inactivation, *J Ethnopharmacol*, 2011, **136**, 399-405.

49 Meng F M, Yang J B, Yang C H, Jiang Y, Zhou Y F, Yu B and Yang H, Vitexicarpin induces apoptosis in human prostate carcinoma PC-3 cells through G2/M phase arrest, *Asian Pac J Cancer Prev*, 2012, **13**, 6369-6374.

50 Ding C, Khan M, Zheng B, Yang J, Zhong L and Ma T, Casticin induces apoptosis and mitotic arrest in pancreatic carcinoma PANC-1 cells, *Afr J of Pharm Pharmacol*, 2012, **6**, 412-418.

51 Tang S Y, Zhong M Z, Yuan G J, Hou S P, Yin L L, Jiang H and Yu Z Y, Casticin, a flavonoid, potentiates TRAIL-induced apoptosis through modulation of anti-apoptotic proteins and death receptor 5 in colon cancer cells, *Oncol Rep*, 2013, **29**, 474-480.

52 Liu L P, Cao X C, Liu F, Quan M F, Sheng X F and Ren K Q, Casticin induces breast cancer cell apoptosis by inhibiting the expression of fork-head box protein M1, *Oncol Lett*, 2014, **7**, 1711-1717.

53 Garbi M I, Osman E E, Kabbashi A S, Saleh M S, Yuosof Y S, Mahmoud S A and Salam H A A, Cytotoxicity of *Vitex trifolia* leaf extracts on MCF-7 and Vero cell lines, *J Sci Innov Res*, 2015, **4**, 89-93.

54 Liou C J, Len W B, Wu S J, Lin C F, Wu X L and Huang W C, Casticin inhibits COX-2 and iNOS expression *via* suppression of NF-κB and MAPK signalling in lipopolysaccharide-stimulated mouse macrophages, *J Ethnopharmacol*, 2014, **158**, 310-316.

55 Zhou Y, Peng Y, Mao Q Q, Li X, Chen M W, Su J, Tian L, Mao N Q, Long L Z, Quan M F, Liu F, Zhou S F and Zhao Y X, Casticin induces caspase-mediated apoptosis *via* activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells, *Asian Pac J Trop Med*, 2013, **6**, 372-378.

56 Rasul A, Zhao B J, Liu J, Liu B, Sun J X, Li J and Li X M, Molecular mechanisms of casticin action: An update on its antitumor functions, *Asian Pac J Cancer Prev*, 2014, **15**, 9049-9058.

57 Arulanandam J P and Ghanthikumar S, Indirect organogenesis of *Vitex trifolia* Linn. – An important medicinal plant, *Nat Prod Rad*, 2001, **2**, 261-264.

58 Kathiresan K, Boopathy N S and Kavitha S, Coastal vegetation: An underexplored source of anticancer drugs, *Nat Prod Rad*, 2006, **5**, 115-119.

59 Manjunatha B K and Vidya S M, Hepatoprotective activity of *Vitex trifolia* against carbon tetrachloride-induced hepatic damage, *Indian J Pharm Sci*, 2008, **70**, 241-245.

60 Anandan R, Jayakar B, Karar B, Babuji S, Manavalan R and Kumar R S, Effect of ethanol extract of flowers of *Vitex trifolia* Linn. on CCl_4 induced hepatic injury in rats, *Pak J Pharm Sci*, 2009, **22**, 391-394.

61 Lin S, Zhang H, Han T, Wu J Z, Rahman K and Qin L P, *In vivo* effect of casticin on acute inflammation, *J Chin Integr Med*, 2007, **5**, 573-576.

62 Pfuzia A, Devi R K B, Sharatchandra K H, Debashree B N, Banylla S N and Monica K H S, Studies on the anti-inflammatory effect of the aqueous extract of the leaves of *Vitex trifolia* L. in albino rats, *Int J Pharm Biol Sci*, 2013, **4**, 588-593.

63 Lee C, Lee J W, Jin Q, Lee H J, Lee S J, Lee D, Lee M K, Lee C K, Hong J T, Lee M K and Hwang B Y, Anti-inflammatory constituents from the fruits of *Vitex rotundifolia*, *Bioorg Med Chem Lett*, 2013, **23**, 6010-6014.

64 Matsui M, Kumar-Roine S, Darius H T, Chinain M, Laurent D and Pauillac S, Characterisation of the anti-inflammatory potential of *Vitex trifolia* L. (Labiatae), a multipurpose plant of the Pacific traditional medicine, *J Ethnopharmacol*, 2009, **126**, 427-433.

65 Chowwanapoonpohn S and Baramee A, Antimalarial activity *in vitro* of some natural extracts from *Vitex trifolia*, *Chiang Mai J Sci*, 2000, **27**, 9-13.

66 Pothula V V S and Kanikaram S, *In vitro* antiplasmodial efficacy of mangrove plant, *Ipomoea pes-caprae* against *Plasmodium falciparum* (3D7 strain), *Asian Pac J Trop Dis*, 2015, **5**, 947-956.

67 Alam G, Gandjar I G, Hakim L, Timmerman H, Verpoorte R and Wahyuono S, Tracheo-spasmolytic activity of vitetrifolin-E isolated from the leaves of *Vitex trifolia* L., *Indon J Pharm*, 2003, **14**, 188-194.

68 Manjunatha B K, Vidya S M, Krishna V, Mankani K L, Singh S D and Manohara Y N, Comparative evaluation of wound healing potency of *Vitex trifolia* L. and *Vitex altissima* L., *Phytother Res*, 2007, **21**, 457-461.

69 Hu Y, Hou T T, Zhang Q Y, Xin H L, Zheng H C, Qin L P and Rahman K, Evaluation of the estrogenic activity of the constituents in the fruits of *Vitex rotundifolia* L. for the potential treatment of pre-menstrual syndrome, *J Pharm Pharmacol*, 2007, **59**, 1307-1312.

70 Hu Y, Xin H L, Zhang Q Y, Zheng H C, Rahman K and Qin L P, Antinociceptive and anti-hyperprolactinemia activities of fructus viticis and its effective fractions and chemical constituents, *Phytomedicine*, 2007, **14**, 668-674.

71 Tiwari N, Thakur J, Saikia D and Gupta M M, Anti-tubercular diterpenoids from *Vitex trifolia*, *Phytomedicine*, 2013, **20**, 605-610.

72 Thenmozhi S, Vibha K, Dhanalakshmi M, Manjuladevi K, Diwedi S and Subasini U, Evaluation of anthelmintic activity of *Vitex trifolia* Linn. leaves against *Pheretima posthuma*, *Int J Pharm Biol Arch*, 2013, **4**, 878-880.

73 Jangwan J S, Aquino R P, Mencherini T, Picerno P and Singh R, Chemical constituents of ethanol extract of leaves and molluscicidal activity of crude extracts from *Vitex trifolia* Linn., *Herba Polonic*, 2013, **59**, 19-32.

74 Arifin B, Nasution R, Saidi N, Marianne and Aprilia S, *Vitex trifolia* plant control of mice environmentally friendly, *Int J ChemTech Res*, 2014, **6**, 4595-4600.

75 Shin T Y, Kim S H, Lim J P, Suh E S, Jeong H J, Kim B D, Park E J, Hwang W J, Rye D G, Baek S H and An N H, Effect of *Vitex rotundifolia* on immediate-type allergic reaction, *J Ethnopharmacol*, 2000, **72**, 443-450.

76 Zhao K F and Feng L T, Resource of halophytic vegetation in China, Science Press, Beijing, 2001.

77 Wasuwat S, Extract of *Ipomoea pes-caprae* (Convolvulaceae) antagonistic to histamine and jelly-fish poison, *Nature*, 1970, **225**, 758.

78 Pongprayoon U, Bohlin L and Wasuwat S, Neutralization of toxic effects of different crude jellyfish venoms by an extract of *Ipomoea pes-caprae* (L.) R. Br., *J Ethnopharmacol*, 1991, **35**, 65-69.

79 Jacobsen N and Salguero C P, A compendium of traditional Thai herbal medicine. *In*: Thai herbal medicine, Findhorn Press, Scotland, UK, 2014, available online at http://www.thai-institute.net.

80 Manigauha A, Kharya M D and Ganesh N, *In vivo* antitumor potential of *Ipomoea pes-caprae* on melanoma cancer, *Pharmacogn Mag*, 2015, **11**, 426-433.

81 Venkataraman N D, Atlee W C, Muralidharan P, Prabhu T P P, Priya M S and Muthukumaran S. Assessment of acute dermal toxicity of ethanolic extracts from aerial parts of *Ipomoea pes-caprae* (L.) R. Br. on Wistar albino rats, *Res J Pharm Biol Chem Sci*, 2013, **4**, 769-776.

82 WHO, Medicinal plants of Papua New Guinea, World Health Organization, Regional Office for the Western Pacific, Manila, Philippines, 2009.

83 Marie D E P, Dejan B and Quetin-Leclercq J, GC-MS analysis of the leaf essential oil of *Ipomoea pes-caprae*, a traditional herbal medicine in Mauritius, *Nat Prod Comm*, 2007, **2**, 1225-1228.

84 Pereda-Miranda R, Escalante-Sanchez E and Escobedo-Martínez C, Characterization of lipophilic pentasaccharides from beach morning glory (*Ipomoea pes-caprae*), *J Nat Prod*, 2005, **68**, 226-230.

85 Escobedo-Martínez C and Pereda-Miranda R, Resin glycosides from *Ipomoea pes-caprae*, *J Nat Prod*, 2007, **70**, 974-978.

86 Tao H, Hao X, Liu J, Ding J, Fang Y, Gu Q and Zhu W, Resin glycoside constituents of *Ipomoea pes-caprae* (beach morning glory), *J Nat Prod*, 2008, **71**, 1998-2003.

87 Banerjee D, Hazra A K, Seal T, Sur T, Bhattacharya D, Ray J, Mukherjee A and Mukherjee B, Antioxidant and anti-inflammatory activities of different solvent extracts and isolated compounds of *Ipomoea pes-caprae* (L) Sweet of Sunderban mangrove eco-complex, *Asian J Chem*, 2013, **25**, 4997-5000.

88 Dutra D M, Barth C S, Block L C, Quintão N L M, Couto A G, Filho V C and Bresolin T M B, Simultaneous determination of four phenolic compounds in extracts of aerial parts of *Ipomoea pes-caprae* (L.) R. Br. (Convolvulaceae) by HPLC-UV, *Quím Nova*, 2014, **37**, 1510-1514.

89 Yu B W, Luo J G, Wang J S, Zhang D M, Yu S S and Kong L Y, Pentasaccharide resin glycosides from *Ipomoea pes-caprae*, *J Nat Prod*, 2011, **74**, 620-628.

90 Bragadeeswaran S, Prabhu K, Rani S S, Priyadharsini S and Vembu N, Biomedical application of beach morning glory *Ipomoea pes-caprae*, *Int J Trop Med*, 2010, **5**, 81-85.

91 Kumar A, Paul S, Kumari P, Somasundaram S T and Kathiresan K, Antibacterial and phytochemical assessment on various extracts of *Ipomoea pes-caprae* (L.) Br. through FTIR and GC-MS spectroscopic analysis, *Asian J Pharm Clin Res*, 2014, **7**, 134-138.

92 de Souza M M, Madeira A, Berti C, Krogh R, Yunes R A and Cechinel-Filho V, Antinociceptive properties of the methanolic extract from *Ipomoea pes-caprae* (L.) R. Br., *J Ethnopharmacol*, 2000, **69**, 85-90.

93 Krogh R, Kroth R, Berti C, Madeira A O, de Souza M M, Filho V C, Monache F D and Yunes R A, Isolation and identification of compounds with antinoceptive action from *Ipomoea pes-caprae* (L.) R. Br., *Die Pharm*, 1999, **54**, 464-466.

94 Vieira D, Padoani D, Soares J, Adriano J, Filho V C, de Souza M M, Bresolin T M B and Couto A G, Development of hydro-ethanolic extract of *Ipomoea pes-caprae* using factorial design followed by antinociceptive and anti-inflammatory evaluation, *Brazil J Pharmacogn*, 2013, **23**, 72-78.

95 Pongprayoon U, Bohlin L, Sandberg F and Wasuwat S, Inhibitory effect of extract of *Ipomoea pes-caprae* on guinea-pig ileal smooth muscle, *Acta Pharm Nordic*, 1989, **1**, 41-44.

96 Pongprayoon U, Baeckstrom P, Jacobsson U, Lindstrom M and Bohlin L, Antispasmodic activity of beta-damascenone and E-phytol isolated from *Ipomoea pes-caprae*, *Planta Med*, 1992, **58**, 19-21.

97 Pongprayoon U, Baeckstrom P, Jacobsson U, Lindstrom M and Bohlin L, Compounds inhibiting prostaglandin synthesis isolated from *Ipomoea pes-caprae*, *Planta Med*, 1991, **57**, 516-518.

98 Pongprayoon U, Bohlin L and Wasuwat S, Neutralization of toxic effects of different crude jellyfish venoms by an extract of *Ipomoea pes-caprae* (L.) R. Br., *J Ethnopharmacol*, 1991, **35**, 65-69.

99 Pongprayoon U, Bohlin L, Baeckstrom P, Jacobsson U, Lindstrom M, Soonthornsaratune P and Wasuwat S, Anti-inflammatory activity of *Ipomoea pes-caprae*, *Planta Med*, 1990, **56**, 661.

100 Pongprayoon U, Baeckstrom P, Jacobsson U, Lindstrom M and Bohlin L, Inhibition of ethyl phenylpropiolate-induced rat ear oedema by compounds isolated from *Ipomoea pes-caprae* (L.) R. Br., *Phytother Res*, 1992, **6**, 104-107.

101 Venkataraman N D, Atlee W C, Prabhu T P and Kannan R, Anti-inflammatory potential of ethanolic extracts from aerial parts of *Ipomoea pes-caprae* (L.) R. Br. using cotton pellet induced granuloma model, *J Appl Pharm Sci*, 2013, **3**, 61-63.

102 Kumar A, Paul S, Kumari P, Somasundaram S T and Kathiresan K, Antioxidant and free radical scavenging activities of *Ipomoea pes-caprae* (L.) R. Br. extracts, *Int J Curr Pharm Rev Res*, 2015, **5**, 91-109.

103 Khan M M, Ahmad F, Rastogi A K and Kidwai J R, Insulinogenic and hypoglycemic activities of *Ipomoea pes-caprae*, *Fitoterapia*, 1994, **65**, 231-234.

104 Suhasini S, Elanchezhiyan C and Babby A, Anti-hyperglycemic and anti-hyperlipidemic effect of *Ipomoea pes-caprae* plant extract in diabetic rats, *Int J Res Biochem Biophys*, 2014, **4**, 1-4.

105 Teramachi F, Koyano T, Kowithayakorn T, Hayashi M, Komiyama K and Ishibashi M, Collagenase inhibitory quinic acid esters from *Ipomoea pes-caprae*, *J Nat Prod*, 2005, **68**, 794-796.

106 Philippi M E, Duarte B M, da Silva C V, de Souza M T, Niero R, Filho V C and Bueno E C, Immuno-stimulatory activity of *Calophyllum brasiliense*, *Ipomoea pes-caprae* and *Matayba elaeagnoides* demonstrated by human peripheral blood mononuclear cells proliferation, *Acta Poloniae Pharm*, 2010, **67**, 69-73.

107 Fenner P J, Lippmann J and Gershwin L A, Fatal and non-fatal severe jellyfish stings in Thai waters, *J Travel Med*, 2010, **17**, 133-138.

108 Thaikruea L, Siriariyaporn P, Wutthanarungsan R and Smithsuwan P, Toxic jellyfish situation in Thailand, *Chiang Mai Med J*, 2012, **51**, 93-102.

109 Sunthon P and Wasuwat S, Jellyfish dermatitis treated by the extract of *Ipomoea pes-caprae*, *Siriraj Hosp Gazett*, 1985, **37**, 329-338.

110 Piyaphanee W, Choovichian V, Matsee W, Palakul K, Olanwijitwong J, Chinnarat N and Chaiyakul T, Efficacy of *Ipomoea pes-caprae* ointment as an add-on therapy in patients with jellyfish dermatitis, Poster presented at the 14th Conference of the International Society of Travel Medicine, Québec City, Canada, 24 to 28 May 2015, Available online at http://myistm.istm.org.