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# Pharmacological potentials and toxicity effects of *Excoecaria agallocha*

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**ABSTRACT**

*Excoecaria agallocha* is commonly found on the landward side of mangroves. Belonging to the family Euphorbiaceae, trees are deciduous with leaves turning orange or red before shedding. The species produces white latex that is toxic, causing skin blistering and temporary blindness. The toxic *E. agallocha* latex which causes skin irritation and blistering has been attributed to three groups of diterpene esters of the daphnane and tigliane types. Classes of compounds of *E. agallocha* include diterpenoids, flavonoids, phenolic acids, sterols, tannins, and triterpenoids. The most common chemical constituents are diterpenoids which are of the labdane, artisane, beyerane, daphnane, tigliane, isopimarane and kaurane types. Commonly isolated diterpenoids include agallochaexcoerins, agallochaols, agallochins, excoeagallochaols, and excoecarins. Pharmacological properties of *E. agallocha* include antioxidant, antibacterial, antiviral, larvicidal, hedgehog signalling inhibition, anticancer, anti-inflammatory and analgesic activities. Other bioactivities include anti-ulcer, anti-diabetic, non-specific immunity, disease resistance, sedative, gastro-protective, anti-allergic and anti-hyperglycemic effects. A case report of a 15-year-old boy from Sri Lanka, splashed with a toxic latex of *E. agallocha* and admitted to the General Hospital in Matara, is presented.

## INTRODUCTION

The genus *Excoecaria* of the family Euphorbiaceae comprises 37 tree species with acceptable names (The Plant List, 2013). Trees are distributed throughout tropical Africa, Asia and Australia of which *E. agallocha* and *E. indica* occur in the mangroves (Duke, 2006; Yin *et al*., 2008). Several references are of direct relevance to the present review on *E. agallocha*. They are chemical constituents of plants from the genus *Excoecaria* (Yin *et al*., 2008); the chemistry and bioactivities of natural products from semi-mangrove flora (Li *et al*., 2009); *E. agallocha* (Euphorbiaceae): an overview (Rajeswari and Rao, 2015); an insight on *E. agallocha* (Kaliamurthi and Selvaraj, 2016); and ethnobotany, phytochemistry and pharmacology of *E. agallocha* (Mondal *et al*., 2016).

*Excoecaria agallocha* L. is a small deciduous tree up to 10–12 m tall (Duke, 2006; Giesen *et al*., 2007; Mondal *et al*., 2016). Trees are multi-stemmed and produce a copious amount of white latex, which is toxic, causing skin blistering and temporary blindness. The bark is greyish with vertical fissures and lenticels. Leaves are opposite, ovate or elliptic with a toothed margin and have two basal glands. They turn orange or red when old before shedding (Figure 1). The species is dioecious i.e. having male and female trees. Male flowers are larger than female flowers and scented (Figure 2). Fruits are a three-lobed capsule with dark brown or black seeds, resembling pepper corn. Commonly found at the landward side of mangroves, *E. agallocha* the species is distributed from South, Southeast and East Asia extending to Australia and the west Pacific (Duke, 2006; Giesen *et al*., 2007). In China, the species is widely distributed along the southern coast, stretching from Zhejiang to Guangxi and Hainan (Li *et al*., 2010). Trees of *E. agallocha* grow gregariously with abundance varying from 170 stems/ha at Tok Bali in Kelantan, Malaysia (Kasawani *et al*., 2007) to 533 stems/ha in the Sundarbans, Bangladesh (Kamruzzaman *et al*., 2018), and to 1294 stems/ha in Kerala, India (Vijayan *et al*., 2015). Closely related is *E. agallocha* is *E. indica*, which is monoecious i.e. having male and female flowers on the same tree (Ragavan *et al*., 2015).

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**Fig. 1:** Foliage of *Excoecaria agallocha* with old leaves turning orange or red.

**Fig. 2:** Male flowers (left) and female flowers (right) of *Excoecaria agallocha.*

Trees of *E. agallocha* have religious significance. At the Hindu temple of Chidambaram in India, the local community prays to the species as sacred plants (Kaliamurthi and Selvaraj, 2016; Agoramoorthy *et al*., 2007). The first newsprint mill in Bangladesh was located along the Bhairab river at Khalishpur in Khulna (Alam, 2006; Baba *et al*., 2013). The mill, which started operation in 1959, used *E. agallocha* (gewa) wood as raw material. The toxic latex of *E. agallocha* is known to cause skin irritation and blistering, and temporary blindness (Laith and Najiah, 2014). In countries of Southeast Asia, the latex has been used as fish poison. In Thailand, its bark and wood have been used as traditional medicine to treat flatulence (Karalai *et al*., 1994). The plant is traditionally used for the treatment of ulcers, rheumatism, leprosy, and paralysis in the coastal regions of South China (Li *et al*., 2012). In Okinawa, Japan, the resinous *E. agallocha* wood has been used to substitute agarwood (jinko) as incense (Konoshima *et al*., 2001).

## PHYTOCHEMISTRY

Classes and names of compounds isolated from various plant parts of *E. agallocha* are listed in Table 1. Classes of compounds include diterpenoids, flavonoids, phenolic acids, sterols, tannins, and triterpenoids. The most common chemical constituents of *E. agallocha* are diterpenoids, which have been isolated from the wood, bark, roots, leaves, and stems. Diterpenoids are of the labdane, artisane, beyerane, daphnane, tigliane, isopimarane and kaurane types (Yin *et al*., 2008; Li *et al*., 2009; Mondal *et al*., 2016). Commonly isolated diterpenoids include agallochaexcoerins, agallochaols, agallochins, excoeagallochaols, and excoecarins. From the leaves and stems of *E. agallocha*, triterpenoids, flavonoids, phenolic acids, sterols, and tannins have also been reported (Table 1). Triterpenoids are of the oleanane, taraxerane, friedelane, cycloartane and lupane types (Yin *et al*., 2008; Mondal *et al*., 2016). Flavonoids include catechin, kaempferol, myricetin and quercetin, and their derivatives. Recently, two new lasiodiplodins together with three known analogues, were isolated from *Lasiodiplodia* sp. 318, an endophytic fungus from *E. agallocha* (Huang *et al*., 2017). Lasiodiplodins are compounds with a resorcinol moiety fused to a 14/12-member macrocyclic lactone ring.

**Table 1:** Classes and names of compounds isolated from *Excoecaria agallocha.*

| Compound class and name (plant part) | (Reference) |
|---|---|
| **Diterpenoids** | |
| 2-Acetoxybeyera-1,15-diene-3,12-dione (root) | (Anjaneyulu *et al*., 2002) |
| Agallochaexcoerins D–F* (wood) | (Ponnapalli *et al*., 2013) |
| Agallochaols A, B, D–F, G–J, K–P, Q (leaf, stem, twig) | (Wang *et al*., 2004; 2005; 2006; Li *et al*., 2010) |
| Agallochaone A* (leaf, stem) | (Li *et al*., 2007) |
| Agallochins A–L, O* (root, leaf, stem) | (Anjaneyulu and Rao, 2000; 2003; Anjaneyulu *et al*, 2002; 2003; Wang *et al*., 2004; 2005; Li *et al*., 2010) |
| *ent*-Atisane-3β,16α-diol (bark) | (Wang *et al*., 2009) |
| *ent*-17-Caffeoyloxykaur-15-en-3-one (stem, twig) | (Li *et al*., 2010) |
| 7-Deoxogeayine (stem, twig) | (Li *et al*., 2010) |
| (13*R*,14*R*)-*ent*-8α,13,14,15-Diepoxy-13-*epi*-labda-3β-ol (wood) | (Konishi *et al*., 2003c) |
| *ent*-3α,11β-Dihydroxy-*ent*-isopimara-8(14),15-dien-2-one* (wood) | (Kang *et al*., 2005) |
| *ent*-3β,11α-Dihydroxyisopimara-8(14),15-dien-2-one (stem, twig) | (Li *et al*., 2010) |
| *ent*-15,18-Dihydroxylabd-8(17),13*E*-diene (stem, twig) | (Li *et al*., 2010) |
| *ent*-15,16-Epoxybeyeran-3α-ol (wood) | (Konishi *et al*., 2003b) |
| Excoagallochaols A–D* (leaf, stem) | (Wang *et al*., 2007; Liu *et al*., 2010) |
| Excoecarins A–F, G1, G2, H, K, M, N, R1, R2, S, T1, T2, V1–V3* (wood, leaf, stem) | (Konishi *et al*., 1996a; 1998a; 1998b; 1999; 2000a; 2000b; 2003a; 2003b; 2003c; Wang *et al*., 2005; Li *et al*., 2007) |
| Excolides A, B (stem) | (Annam *et al*., 2015) |
| 11-*epi*-Excolide A (stem) | (Annam *et al*., 2015) |
| 11,13-di-*epi*-Excolide A (stem) | (Annam *et al*., 2015) |
| *ent*-(14*S*)-8,13-Epoxy-14,15-dihydroxylabdan-3-one* (wood) | (Konishi *et al*., 1998a) |
| *ent*-8,13-Epoxy-2-hydroxy-13-epilabda-1,14-dien-3-one* (wood) | (Konishi *et al*., 1998a) |
| *ent*-(1*R*)-8,13-Epoxy-2-oxa-3-oxo-13-epilabd-14-ene-1- carboxylic acid* (wood) | (Konishi *et al*., 1998a) |
| *ent*-13-*epi*-8,13-Epoxy-2,3-secolabd-14-ene-2,3-dioic acid* (wood) | (Konishi *et al*., 1998a) |
| *ent*-13-*epi*-8,13-Epoxy-2,3-secolabd-14-ene-2,3-dioic acid 3-methyl ester* (wood) | (Konishi *et al*., 1998a) |
| 8,13-Epoxy-14-labden-3-one (leaf, stem) | (Li *et al*., 2007) |
| *ent*-16α-Hydroxy-atisane-3,4-lactone* (bark) | (Wang *et al*., 2009) |
| *ent*-16α-Hydroxy-atisane-3-one* (wood, bark) | (Kang *et al*., 2005; Wang *et al*., 2009) |
| *ent*-3,4-*seco*-16α-Hydroxyatis-4(19)-en-3-oic acid (bark) | (Wang *et al*., 2009) |
| 2-Hydroxybeyera-1,15-diene-3,12-dione (root) | (Anjaneyulu *et al*., 2002) |
| *ent*-3β-Hydroxybeyer-15-en-2-one (wood) | (Konishi *et al*., 2000b) |
| *ent*-3β-Hydroxybeyer-15-ene-2,12-dione (wood, stem, twig) | (Kang *et al*., 2005; Li *et al*., 2010) |
| *ent*-3β-Hydroxy-15-beyeren-2-one (wood) | (Konishi *et al*., 2003c) |
| *ent*-17-Hydroxykaur-15-en-3-one (stem, twig) | (Li *et al*., 2012) |
| *ent*-16-Hydroxykauran-3-one (root) | (Anjaneyulu *et al*., 2002) |
| *ent*-15-Hydroxy-labda-8(17),13*E*-dien-3-one (wood, stem, twig) | (Konishi *et al*., 1996a; Li *et al*., 2010) |
| *ent*-11α-Hydroxy-3-oxo-13-*epi*-manoyl oxide (wood) | (Konishi *et al*., 1996a) |
| *ent*-16-Hydroxy-3-oxo-13-*epi*-manoyl oxide (wood) | (Konishi *et al*., 1996a) |
| *ent*-Kaur-15-en-3β,17-diol (stem, twig) | (Li *et al*., 2010) |
| *ent*-13-*epi*-Manoyl oxide (wood) | (Konishi *et al*., 1996a) |
| *ent*-12-oxo-2,3-Secobeyer-15-ene-2,3-dioic acid (wood) | (Konishi *et al*., 2003b) |
| *ent*-2,3-Secobeyer-15-ene-2,3-dioic acid (stem) | (Konishi *et al*., 2003c) |
| Ribenol (wood) | (Konishi *et al*., 1996a) |
| Ribenone (wood) | (Konishi *et al*., 1996a) |
| Stachenol (wood) | (Konishi *et al*., 2000b) |
| Stachenone (wood) | (Konishi *et al*., 2000b) |
| **Flavonoids** | |
| Afzelin (leaf) | (Rifai *et al*., 2011) |
| (+)-Catechin (stem, twig) | (Li *et al*., 2012) |
| (+)-Catechin-3-*O*-β-D-glucopyranoside (stem, twig) | (Li *et al*., 2012) |
| (+)-Catechin-7-*O*-β-D-glucopyranoside (stem, twig) | (Li *et al*., 2012) |

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| Catechin hydrate (bark) | (Jahan *et al*., 2014) |
| (+)-Catechin-3-*O*-α-L-rhamnose (stem, twig) | (Li *et al*., 2012) |
| Compounds 1, 2 (flavonoid glycosides)* (leaf) | (Rifai *et al*., 2011) |
| Excoecariphenols A–D* (stem, twig) | (Li *et al*., 2012) |
| (2*R*,3*S*)-Gallocatechin (stem, twig) | (Li *et al*., 2012) |
| Isorhamnetin (leaf) | (Selvaraj *et al*., 2014) |
| Kaempferide 3-*O*-α-L-rhamnopyranoside (leaf) | (Rifai *et al*., 2011) |
| Kaempferol (leaf) | (Selvaraj *et al*., 2014) |
| Kaempferol-3-*O*-(2-*O*-acetyl-α-L-rhamnopyranoside (leaf) | (Rifai *et al*., 2011) |
| Kaempferol 3-*O*-α-L-arabinofuranoside (leaf) | (Rifai *et al*., 2011) |
| Luteolin (leaf) | (Selvaraj *et al*., 2014) |
| Myricetin (leaf) | (Selvaraj *et al*., 2014) |
| Myricetin-3-*O*-(6-*O*-galloyl)-β-glucopyranoside (stem, twig) | (Li *et al*., 2012) |
| (2*R*,3*R*)-3,5,7,3',5'-Pentahydroxyflavanonol-3- *O*-α-L-rhamno pyranoside* (stem) | (Konishi *et al*., 2003c) |
| Quercetin (leaf) | (Selvaraj *et al*., 2014) |
| Quercetin-3-*O*-(6-*O*-galloyl)-β-gallcopyranoside (stem, twig) | (Li *et al*., 2012) |
| Quercetin-3-*O*-(6-*O*-galloyl)-β-glucopyranoside (stem, twig) | (Li *et al*., 2012) |
| Quercetin-3-*O*-β-galactopyranoside (stem, twig) | (Li *et al*., 2012) |
| Quercetin-3-*O*-β-glucopyranoside (stem, twig) | (Li *et al*., 2012) |
| Quercitrin (leaf) | (Rifai *et al*., 2011) |
| Rutin (leaf) | (Rifai *et al*., 2011; Selvaraj *et al*., 2014) |
| **Phenolic acids** | |
| Ellagic acid (bark) | (Jahan *et al*., 2014) |
| Gallic acid (stem, twig, bark) | (Li *et al*., 2012; Jahan *et al*., 2014) |
| Vanillic acid (bark) | (Jahan *et al*., 2014) |
| **Sterols** | |
| (24*R*)-24-Ethylcholesta-4,22-dien-3-one (stem, twig) | (Tian *et al*., 2008) |
| β-Sitostenone (stem, twig) | (Tian *et al*., 2008) |
| β-Sitosterol (wood, stem, twig) | (Anjaneyulu *et al*., 1993; Tian *et al*., 2008) |
| **Tannins** | |
| Corilagin (stem, twig) | (Li *et al*., 2012) |
| Chebulagic acid (stem, twig) | (Li *et al*., 2012) |
| 3,4-Dihydroxybenzoic acid (stem, twig) | (Li *et al*., 2012) |
| Ellagic acid 4-*O*-xylopyranoside (stem, twig) | (Li *et al*., 2012) |
| Furosin (stem, twig) | (Li *et al*., 2012) |
| 1,2-di-*O*-Galloyl-3,6-(*R*)-HHDP-β-D-glucose (stem, twig) | (Li *et al*., 2012) |
| Geraniin (stem, twig) | (Li *et al*., 2012) |
| 1,2,3,4,6-Penta-*O*-galloyl-β-D-glucose (stem, twig) | (Li *et al*., 2012) |
| Tercatain (stem, twig) | (Li *et al*., 2012) |
| 1,3,4,6-Tetra-*O*-galloyl-β-D-glucose (stem, twig) | (Li *et al*., 2012) |
| 1,2,6-Tri-*O*-galloyl-β-D-glucose (stem, twig) | (Li *et al*., 2012) |
| 3,4,5-Trihydroxybenzoic acid ethyl ester (stem, twig) | (Li *et al*., 2012) |
| 3,4,5-Trimethoxyphenol 1-*O*-β-D-(6-galloyl) glucopyranoside (stem) | (Konishi *et al*., 2003c) |
| 4-*O*-Xylopyranoside (stem, twig) | (Li *et al*., 2012) |
| **Triterpenoids** | |
| 3β-Acetoxytaraxer-14-en-28-oic acid (wood) | (Anjaneyulu *et al*., 1993) |
| Acetylaleuritolic acid (stem, twig) | (Tian *et al*., 2008) |
| β-Amyrenone (latex) | (Kawashima *et al*., 1971) |
| β-Amyrin (wood, latex) | (Kawashima *et al*., 1971; Anjaneyulu *et al*., 1993) |
| *epi*-α-Amyrin (stem) | (Liu *et al*., 2010) |
| *epi*-β-Amyrin (wood, stem, latex) | (Kawashima *et al*., 1971; Anjaneyulu *et al*., 1993; Liu *et al*., 2010) |
| β-Amyrin acetate (leaf, stem, twig) | (Zou *et al*., 2006; Tian *et al*., 2008) |
| Betulin (stem) | (Liu *et al*., 2010) |

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|---|---|
| Betulinic acid (stem) | (Liu *et al*., 2010) |
| Betulone (stem) | (Liu *et al*., 2010) |
| Betulonic acid (stem) | (Liu *et al*., 2010) |
| Cycloart-22-ene-3β, 25-diol (stem, twig) | (Tian *et al*., 2008) |
| Cycloartenol (latex) | (Kawashima *et al*., 1971) |
| 3β-[(2*E*,4*E*)-6-oxo-Decadienoyloxy]-olean-12-ene (stem, twig) | (Tian *et al*., 2008) |
| 3β-[(2*E*,4*E*)-5-oxo-Deca-2,4-dienoyloxy]olean-12-ene* (leaf) | (Zou *et al*., 2006) |
| Epilupeol (leaf, stem) | (Zou *et al*., 2006; Liu *et al*., 2010) |
| Epitaraxerol (leaf, stem) | (Zou *et al*., 2006; Liu *et al*., 2010) |
| Friedelan-3α-ol (wood) | (Anjaneyulu *et al*., 1993) |
| Friedelan-3β-ol (wood) | (Anjaneyulu *et al*., 1993) |
| Friedelin (wood) | (Anjaneyulu *et al*., 1993) |
| (9*Z*,12*Z*)2,3-Dihydroxypropyl octadecadienoate (stem) | (Liu *et al*., 2010) |
| (9*Z*,12*Z*,15*Z*)2,3-Dihydroxypropyl octadecatrienoate (stem) | (Liu *et al*., 2010) |
| Taraxerol (wood, leaf, stem, twig) | (Anjaneyulu *et al*., 1993; Zou *et al*., 2006; Tian *et al*., 2008) |
| Taraxerone (leaf, stem, twig) | (Zou *et al*., 2006; Tian *et al*., 2008) |

* New to *Excoecaria agallocha.*

## PHARMACOLOGICAL POTENTIALS

### Antioxidant and antibacterial

Studies have shown that the leaf (Patra *et al*., 2009; Poorna *et al*., 2012; Deepa *et al*., 2015; Laith *et al*., 2016) and bark (Subhan *et al*., 2008a; Hossain *et al*., 2009) extracts of *E. agallocha* possess significant antioxidant activities when assessed using well-established assays. Based on 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging of different plant parts extracted with different solvents, the ranking was as follows: leaf > root > stem, and methanol > ethyl acetate > ethanol > chloroform (Sofia and Teresa, 2016). Similarly, studies have shown that leaf (Agoramoorthy *et al*., 2007; Vadlapudi *et al*., 2009; Raja *et al*., 2010; Laith and Najiah, 2014; Deepa *et al*., 2015; Laith *et al*., 2016) and bark (Subhan *et al*., 2008b) extracts of *E. agallocha* inhibited bacterial growth. Of interest was the inhibition of bacteria causing fish-related diseases (Laith and Najiah, 2014; Laith *et al*., 2016). One such study reported that the bark extract of *E. agallocha* (1−3 mg/ml) exhibited no antibacterial activity against bacteria from clinical isolates (Rajia *et al*., 2006). Recently, the antibacterial activity of *E. agallocha* bark extract (500 µg/disc) (Shanmugapriya and Ramanathan, 2015) and of silver nanoparticles of *E. agallocha* fruit extract have been reported (Nagababu and Rao, 2017). Another interesting study was on the anti-quorum sensing and anti-biofilm properties of *E. agallocha* leaf extract on *Pseudomonas aeruginosa* (Karuppiah and Thiruganasambandam, 2017). At 2 mg/ml, the leaf extract inhibited violacein production, biofilm formation including motility behaviour of *P. aeruginosa*.

### Antiviral

There was increasing research interest on *E. agallocha* when a novel phorbol ester (12-deoxyphorbol-13-[3*E*,5*E*]-deca-3,5-dienoate) isolated from its leaves and stems was found to be a potent inhibitor of HIV-1 replication with an $IC_{50}$ value of 6.0 nm (Erickson *et al*., 1995). Soon after, screening of mangrove plant extracts for anti-HIV activity in MT-4 cells showed that the ethanol leaf extract of *E. agallocha* displayed potent activity (Premanathan *et al*., 1996). Values were 7.3 and 30 µg/ml for 50% inhibition of HIV activity and for 100% inhibition of HIV adsorption, respectively. Recently, the active ethanol stem fraction of *E. agallocha* was reported to inhibit the reverse transcriptase enzyme which is responsible for the synthesis of proviral DNA (Patil *et al*., 2011). The fraction showed 34% of inhibition, comparable with the standard drug azidothymidine (36%). When screened for inhibition of Epstein-Barr virus (EBV) in TPA-activated Raji cells, diterpenoids isolated from the wood of *E. agallocha* displayed stronger inhibitory effects than glycyrrhetic acid, an anti-tumour agent (Konoshima *et al*., 2001; Konishi *et al*., 1998c). Among the diterpenoids, *ent*-3α-hydroxy-beyer-15-ene-2-one and excoecarin S exhibited the strongest anti-EBV activity. Polyphenols from the leaves of *E. agallocha* were evaluated for their inhibitory effects against hepatitis C virus (HCV) (Li *et al*., 2012). Results showed that excoecariphenol D and corilagin inhibited HCV NS3-4A protease with $IC_{50}$ values of 6.9 and 3.5 µM, and inhibited HCV RNA in Huh 7.5 cells with $EC_{50}$ values of 12.6 and 13.6 µM, respectively.

### HS inhibition and anticancer

Two new compounds (1 and 2) including six known flavonoid glycosides isolated from the leaves of *E. agallocha* were tested for hedgehog signalling (HS) inhibition, and for cytotoxicity against human pancreatic (PANC1) and prostate (DU145) cancer cells (Rifai *et al*., 2011). Compound 1 and kaempferol 3-*O*-α-L-arabinofuranoside displayed HS inhibition with $IC_{50}$ values of 0.5 and 2.0 µM, and cytotoxicity with $IC_{50}$ values of 0.7 and 1.8 µM against PANC1, and 0.8 and 2.4 µM against DU145 cancer cells, respectively. The HS pathway is known to control cell growth and proliferation, and abnormal activation has been implicated in the development of certain types of cancer (Abidi, 2014). Methanol and chloroform leaf extracts of *E. agallocha* have been reported to be cytotoxic against Hep-2 cancer cells (Batsa and Periyasamy, 2013). Earlier, six triterpenoids (β-amyrin acetate, epilupeol, epitaraxerol, 3β-[(2*E*,4*E*)-5-oxodeca-2,4-dienoyloxy]olean-12-ene, taraxerol, and taraxerone) isolated from the leaves of *E.*

*agallocha* were found to be inactive ($IC_{50}$ > 50 µg/ml) against human cancer cells of A549, BGC-823, MCF-7, Bel-7402 and HCT-8 (Zou *et al*., 2006). Recently, it was reported that the ethanol stem extract of *E. agallocha* exerted a significant cytotoxic effect on pancreatic cancer cells of Capan-1 and Miapaca-2 with $IC_{50}$ values of 4 and 7 µg/ml, respectively, but was inactive against cells of BxPC-3 and PANC-1 (Patil *et al*., 2011). When the five lasiodiplodins were evaluated for *in vitro* cytotoxic activities, 2,4-dihydroxy-6-nonylbenzoate was the most potent with $IC_{50}$ values of 5.3 and 13 µM against rat cancer cells of MMQ and GH3, respectively (Huang *et al*., 2017). Structural-activity analysis indicated that the resorcinol-3-OH functional group contributed greatly to their cytotoxic activities.

### Anti-inflammatory and analgesic

Diterpenoids including agallochaols isolated from stems and twigs of *E. agallocha* (Table 1) have been reported to possess anti-inflammatory activity (Li *et al*., 2010). They displayed potency in suppressing tumour necrosis factor (TNF)-α and interleukin (IL)-6 induced by lipopolysaccharide (LPS) in mouse macrophage RAW 264.7 cells by blocking NF-kB activation or AP-1 activation. In another study, *E. agallocha* was assessed for anti-inflammatory and analgesic effects (Babuselvam *et al*., 2012). The latex, leaf and seed extracts of *E. agallocha* (250 and 500 mg/kg) displayed significant inhibition of carrageenan-induced rat paw oedema after 3 hours. Inhibition was 63%, 62% and 70%, respectively. The seed extract also showed maximum inhibition of 57% in the cotton pellet-induced granuloma test. Using the acetic acid-induced writhing and tail immersion tests, the seed extract showed significant analgesic activity. Earlier, the bark extract of *E. agallocha* at 500 mg/kg was reported to show significant reduction of 54% in acetic acid-induced writhing of mice (Subhan *et al*., 2008c). Recently, the antinociceptive effect of *E. agallocha* leaf extract (alkaline chloroform fraction) was attributed to rutin (Selvaraj *et al*., 2014). Docking simulation demonstrated that rutin interacted strongly with cyclooxygenase, forming a number of specific hydrogen bonds.

### Other bioactivities

Leaf extracts of *E. agallocha* have anti-ulcer effect on NSAID-induced gastric ulcer rats (Thirunavukkarasu *et al*., 2009), anti-diabetic activity in alloxan-induced diabetic mice (Thirumurugan *et al*., 2009), enhance the non-specific immunity and disease resistance of fish (Laith *et al*., 2017), and inhibition of elastase and collagenase (Satyavani *et al*., 2018). The sedative effect on sodium thiopental injected mice (Subhan *et al*., 2008b), gastro-protective activity in albino mice (Subhan *et al*., 2008c), and anti-allergic activity in rat peritoneal exudate cells (Hossain *et al*., 2009) have been reported in the bark extracts of *E. agallocha*. Recently, the stem extract of *E. agallocha* has been reported to possess anti-hyperglycemic activity in glucose-loaded albino mice (Rahman *et al*., 2010).

## TOXIC EFFECTS

### Larvicidal

Of the different extracts of *E. agallocha* aerial parts (methanol, ethanol, hexane, chloroform and aqueous) evaluated for mosquito larvicidal activity, the methanol extract exhibited significant inhibition against *Aedes aegypti* and *Culex quinquefasciatus* larvae (Thirunavukkarasu *et al*., 2011; Pradeepa *et al*., 2015). Another recent study reported that 100% mortality of *A. aegypti*, *C. quinquefasciatus* and *Anopheles stephensi* larvae was observed at 1200, 300 and 300 ppm of *E. agallocha* latex after 24 h exposure (Mendhulkar *et al*., 2017). The methanol leaf extract of *E. agallocha* showed significant anti-filarial activity against the various stages of development of *Setaria digitata*, a metazoan filarial parasite (Patra *et al*., 2009). After 24 h of treatment with the extract at 10, 50 and 100 µg/ml, 30%, 75%, and 90% of the parasite were found dead, respectively. The bark extract of *E. agallocha* resulted in the lethality of brine shrimp larvae with $LC_{50}$ value of 504 µg/ml and $LC_{90}$ value of 800 µg/ml (Shanmugapriya and Ramanathan, 2015).

### Case report

A 15-year-old boy from the coastal suburb of southern Sri Lanka was splashed with toxic latex when cutting the branches of an *E. agallocha* tree (Kumarasinghe and Seneviratne, 1998). Within minutes, the boy experienced burning pain in the right eye, and in parts of the face, body and limbs contacted with the latex. He was admitted to the ophthalmology ward of the General Hospital in Matara. Ophthalmological examinations revealed superficial burns of the right eyelids, cornea and conjunctiva. Dermatological examination, two days later, showed erythema and oedema around the right eye and forehead, and blistering of the skin of the face, body, and limbs. On treatment with amoxycillin and paracetamol along with topical application of an antibiotic ointment containing neomycin, bacitracin, and polymyxin, the boy was discharged after five days. When reviewed after a month, the eye had normalized but the skin showed minor scarring and hypopigmentation. This case report on the toxic effects of *E. agallocha* latex was presented at the 19th World Congress of Dermatology held in June 1997, Sydney, Australia (Kumarasinghe and Seneviratne, 1998). In an earlier study, the toxic *E. agallocha* latex which causes skin irritation and blistering has been attributed to three groups of diterpene esters of the daphnane and tigliane types (Karalai *et al*., 1994). All three groups exhibited no irritant activity on the mouse ear but when trans-esterified with alkali, these cryptic irritants become highly toxic *Excoecaria* factors.

## CONCLUSION

In the mangroves, two species of *Excoecaria* occur. Information of the phytochemistry and pharmacological potentials of *E. agallocha* will serve as useful reference for *E. indica*, which is poorly studied. The latex of *E. agallocha* warrants further research before considering the beneficial pharmacological properties of the species. Notably are the toxic effects of the latex on humans, and on terrestrial and aquatic fauna of the mangroves.

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