Insight on *Excoecaria agallocha*: An Overview

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**Abstract**

*Excoecaria agallocha* is a milky mangrove widely distributed in Indian coastal regions. This review article explains chemical composition, pharmaceutical and environmental applications of *E. agallocha*. There are 20 different polyphenols, 15 terpenoids and more than 50 volatile derivatives were identified from leaves, stem, latex and root extract. Enormous number of compounds isolated from ethanolic extract of leaves. In conclusion, *E. agallocha* has huge amount of polyphenols and terpenoids, which was reported to have antidiabetic, anti-cancer and anti-diabetic agent.

**Keywords**: Mangroves; Thillai; Terpenoids; Rutin; Antidiabetic

**Background**

A mangrove is a tree, shrub, palm or ground fern, generally exceeding one half meter in height, that normally grows above mean sea level in the intertidal zone of marine coastal environments and estuarine margins. The term “Mangroves”, plants which exist in muddy, wet soil in tropical or subtropical tidal waters. *Excoecaria agallocha* L. (Euphorbiaceae) is an ancient mangrove species specified in “Thillai Lord Nataraja” temple, Chidambaram as “Tala virucham” in tamil. Common name of *Excoecaria agallocha*: Agallocha, blinding tree (General name); Thillai, Kampetti (in Tamil); Tilla, Tella and Chilla (in Telugu); Thelakiriya, Thaliala (in Singhalase) It is widely distributed in Pichavaram mangrove forest, Indian coastal regions, Australia from northern New South Wales, along the northern coastline around to Western Australia. According to Red list criteriat it is a least concern position [1] (Systematic classification) (Figure 1).

**Morphological characters identification**

Habitat - A dioecious tree to 15 m high with abundant white latex; Habitat - An evergreen shrub common along with higher estuarine banks, canals, tidal forest and mangrove swamps; Stem-bark grayish, lenticelate; Roots- Lateral roots spreading and intermingled with each other, supraterranean bandsproduce elbow-shaped pegs instead of pneumatophores; Leaves - leaves alternate, ovate-elliptic or orbicular, apex shortly acuminate, base narrowed, margin entire or sinuate-crenate, 3-8 × 1.5-3 cm, glabrous, petiolate; Flowers - Unisexual, Male flowers in catkin spikes, fragrant, yellow, 2-3 mm across; stamens 3, filaments free. Female flowers in axillary raceme, pale green, 2.5-3.5 mm across, pedicellate; calyx 3-lobed; ovary 3-celled, trifid style; Fruit - Capsule, globose 3-lobed, seeds sub-globose; Reproductive - Flowers are pollinated by insects; Regeneration - Epigeal or modified epigeal germination [2]. This evergreen mangrove species has traditionally been used to treat sores and stings from marine creatures, and ulcers, as a purgative and an emetic, and the smoke from the bark to treat leprosy [3]. They are well-known as extreme skin irritants and tumor promoter [4]. Recent ethnobotanical survey on Kodiyampalayam coastal village, Nagapatnam district, tamil nadu, India depicted the presence and traditional usage of *E. agallocha* to blood glucose level reduction and fish poison [5].

**Therapeutic Applications**

**Impact of *Excoecaria agallocha* on diabetes mellitus**

Type 2 diabetes mellitus (T2DM), is a prototype multi-factorial complex diseases that considered as one as one of the leading causes of morbidity and mortality around the world [6]. The pancreas plays a primary role in the metabolism of glucose by secreting the hormones insulin and glucagon. The islets of Langerhans secrete insulin and glucagon directly into the blood [7]. When the blood glucose level falls, glucagon secreted and increases blood glucose concentration partly by breaking down stored glycogen in the liver by a glycogenolysis pathway. Also, Gluconeogenesis is the production of glucose in the liver from non-carbohydrate precursors such as glycogenic amino acids [8]. Several studies was elaborated the risk factors responsible for Type 2 DM including obesity, hypertension, smoking, physical inactivity, low education, dietary patterns, family history and specific gene [9]. Recent years, researchers focused their interest to find out the potential anti-diabetic molecules from the medicinal plants to reduce the side effects caused by commercial drugs. Different type of alpha-glucosidase enzyme involved in the absorption of carbohydrate molecules such as glucose, sucrose and maltose in to small intestine, which leads to postprandial hyperglycemia. In previous studies we reported the alpha glucosidase inhibitory effect of coastal sand dunes and salt marshes from the southeast coast of India [10]. Aloxan and Streptozotocin is widely used in inducing hyperglycemia than compared to other toxins viz., vacor, 8-hydroxyquinolone dithizone and ferric nitrito triacetate. The agents can be administered using various methods such as intra-peritoneal, intravenous, or subcutaneous; however, the first route is the most popular in rodents [11]. The 500 mg/kg body weight of ethanolic extract of *E. agallocha* exhibited most significant anti-hyperglycemic (P<0.001) activity in alloxan induced wistar albino mice [12]. Also the 400 mg/kg body weight of methanolic stem extracts of *E. agallocha* orally administrated in to experimental mice showed significant reduction in serum glucose level (23 mg/dl) was observed [13]. Overall the anti-hyperglycemic effect of *E. agallocha* reflected in a dose dependent manner. The matrix metallato-proteinase activity of different extract of *E. agallocha* confirmed with collagenase and elastase inhibitory action [14].

**Impact of *Excoecaria agallocha* on cancer chemotherapy**

One of the major health issue all around the world is cancer. The major risk factors responsible causes of cancer are tobacco/alcohol consumption, preserved food products, family heredity, environmental...
pollution, sexual behaviour, medicines and its treatment procedures. Then compared to other factors, alcohol consumption increases the occurrence of cancer at oral, oesophagus, pharynx, stomach and liver region respectively. In India, the breast and cervical cancer are predominantly identified in women [15]. Cancer is the second leading disease factor cause more death in United states of America. Siegel et al. [16] estimated the death rate and various cancer sites (Oral cavity and pharynx, Digestive system, Respiratory system, Bones and joint, skin, breast, urinary system, eye, brain, endocrine system, lymphoma, myeloma) in both male and female subjects in United states of America.

Ethanolic stem extract of *E. agallocha* has a significant cytotoxic effect of different cell lines MiaPaca-2, BxPC-3, PANC-1 and Capan-1. IC50 values were higher (0.11 μg/ml) compared with the positive control flavopiridol by MTS assay. It might be action of cardiac glycosides and saponin in the bioactive fraction of *E. agallocha* confirmed by chromatographic fingerprint printing [17]. The higher concentration of methanolic and chloroform extracts of *E. agallocha* leaves showed lowest Hep-2 cells viability of 22 and 8% under *in vitro* conditions. Konoshima et al. [18] reported the diterpenoids isolated from *E. agallocha* wood showed their inhibitory action against induction of Epstein-Barr virus early antigen (EBV-EA) in Raji cells under *in vitro* conditions. Among these, the secolabdane-type diterpenoid showed anti-tumour promoting effect which analysed by *in vivo* Two-Stage Mouse Skin Carcinogenesis Test with promoter (12-O-tetradecanoylphorbol13-acetate) and an initiator 7,12-dimethylbenz[a]anthracene. The Flavonol glycosides of *E. agallocha* blocked the action of GLI-related protein is a transcriptional effector involved in tumour development which results inhibits the translocation of GLI1 in to nucleus. Therefore, it act as effective Hedgehog signaling inhibitor in cancer therapy [19,20]. Norhanom and Yadav [21] reported the long term continuous usage of the Euphorbiaceae family species like *E. agallocha* among rural Malays cause Epstein barr virus associated non-Hodgkin malignant lymphoma. Biotoxicity of *E. agallocha* reported by Kathiresan and Thangam [22].

**Impact of *Excoecaria agallocha* on pathogenic microbial strains**

Mangrove floral species play vital role in prevention of soil erosion, act as a sink for enormous amount of active metabolities. Apart from that, the mangroves serve as ahost for many endophytes which include parasitic, facultative saprobic, actinomycetes and majority of bacterial and fungal species. Especially in *E. agallocha*, ascomycete genus *Phomopsis* species belongs to diaportnaceae family and endophytic bacteria was identified [23]. The endophytes secreted Bacteriocins are act as promising antimicrobial agent [24]. The methanol, hexane and chloroform leaf extracts of *E. agallocha* were subjected to antimicrobial assay followed the standard agar well diffusion method. Nearly 50 μl of the samples with 100 mg/ml concentration was allowing to diffusion under *in vitro* conditions for 45 min. Among those strains, the ethanolic extract of *E. agallocha* exhibited potential antibacterial activity against *Acremonium strictum* and *Pnicellium expansum* then compared to others [25]. The chloroform and water extracts from leaves of *E. agallocha* showed potential activity against urinary tract pathogens, antibiotic sensitive ophthalmic bacterial pathogens, antibiotic resistant bacterial strains and fish pathogen [26]. *Staphylococcus aureus* is a multidrug resistant pathogenic bacterial strain. It showed resistant to commercially available antibiotics such as ceftazidime, gentamicin and kanamycin. Abeysinghe [27] reported the active ethyl acetate fractions from *E. agallocha* leaves showed highest inhibition to *Staphylococcus aureus* than *Proteus* sp. in the mean time the ethanolic extracts of *E. agallocha* pronounced for significant anti-bacterial activity against *Staphylococcus aureus*, *Shigella dysenteriae*, *Shigella sonnei* and *Enterococci* bacterial strains [28]. Also the methanolic, chloroform and DMSO extract of *E. agallocha* showed higher zone of inhibition.
against the soil born *Fusarium udum* fungal strains which cause wilt diseases on plants. The minimum zone of inhibition was absorbed in *Rhizoctonia solani* and *Sclerotium rossii* strains on potato dextrose agar medium [29]. *Chryseobacterium* spp. is a fish pathogen which resistant to commercial antibiotics such as erythromycin, tetracyclines and chloramphenicol [30]. Those antibiotics used in the fishers sectors to control the infectious diseases caused by the fish pathogens. The 500 mg/ml of methanolic extracts of *E. agallocha* showed the highest inhibition zone to *Chryseobacterium* gleum by disc diffusion and agar well diffusion assay. It also showed minimum values of minimum bactericidal concentrations and the minimum inhibitory concentration against the *Flavobacterium indicum*, *Chryseobacterium indologenes*, *Chryseobacterium gleum* and Elizabeth kingiameninoseptica [31]. Additionally, the ethanolic extract of *E. agallocha* showed higher inhibition to the fish pathogen *Aeromonas hydrophila*, which is a gram negative free living ubiquitous bacterial strain causes motile aeromonad septicaemia diseases [32]. Agoramooorthy et al. [33] reported the Fatty acid methyl esters extracts (FAME) from leaves of *E. agallocha* showed significant anti-bacterial and anti-fungal activity against *Bacillus subtilis*, *Bacillus pumilus*, *Candida albicans*, *Candida kruisi*, *Candida parapsilosis*, *Candida tropicalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Micrococcus luteus* and *Staphylococcus aureus*.

**Impact of *Excoecaria agallocha* on mosquito borne diseases**

Mosquitoes borne diseases are dangerous which causes endangered disease like malaria, dengue, filariasis and chikungunya were caused by the mosquito anthropods [34]. Guha-Spair and Schimme [35] reported the mosquito borne diseases causes two million infections, hemorrhagic fever, shock syndrome, impaired action of central nervous system and approximately 12,000 death rate per year. *Aedes aegypti* is a endemic viral species occurrence in the Southeast Asia, Africa including West africa, America and Pacific islands causes dengue fever [36]. Group of researchers evaluated the larvicidal activity of methanol, ethanol, hexane, chloroform and aqueous extracts of *E. agallocha* aerial parts. However the methanol extract exhibited significant inhibitory concentration against *Aedes aegypti* and *Culex quinquefasciatus* mosquito larvaees [37,38]. Secondary metabolities such as chyrosoriel and 4', 5', 7- trihydroxy 3',5- dimethoxy flavones reported the highest LD50 values and mortality against Mosquito Larvae [39]. Interestingly, the methanolic extracts of *E. agallocha* showed inhibition to developmental stages of female filarial worm *Setaria digitata* which is estimated by trypans blue dye and tunel staining for evaluating the fragmentation of chromosomal DNA [40].

**Impact of *Excoecaria agallocha* on pandemic diseases**

Acquired immunodeficiency syndrome is one the epidemic disease cased by the human immunodeficiency virus. Earlier, the phosphol ester bioactive compound isolated from the leaves and stem of *E. agallocha* from Northwest Australia reported to have anti-HIV potential [4]. Recently, Patil et al. [17] and his co-workers reported the reverse transcriptase (RT) enzyme inhibited by active stem ethanolic fraction of *E. agallocha* which is necessary for the synthesis of proviral DNA. The extract of *E. agallocha* showed 33% of inhibition than compared with the standard drug azidothymidine (35%).

**Impact of *Excoecaria agallocha* on anti-oxidant and free radical scavenging efficiency**

Cellular damage by free radicals causes a change of the net charge of cells, thus modifying their osmotic pressure and inducing their swelling and their death. The free radicals act also on the mediators of the inflammatory diseases and accelerate the tissue damage. Moreover, cells lesions lead to an increase in the production of the ROS which induces the consumption and depletion of the endogenous chelating agents. The hydroalcoholic extract of *E. agallocha* exhibited significant 2.2-diphenyl-1-picrylhydrazyl (IC50 179.16 µg/ml), hydrogen peroxide (IC50 120.24 µg/ml) and nitric oxide (IC50 134.29 µg/ml) free radical scavenging activity respectively [28]. Additionally the the lower concentration of alkaid rich fractions (10 ppm) of *E. agallocha* exhibited significant 88% of DPPH free radical scavenging activity [41].

**Impact of *Excoecaria agallocha* on anti-nociceptive effect**

The drug or compounds have the capacity to reduce the sensation of pain is called anti-nociceptive agents. Somatic/visceral and acute/chronical is the major classification of pain. Also it has been called as neuropathic or inflammatory pain. However the clinical veterinarians and researchers first understand the nociceptive nad antiinflammatory pathways which involved in the pathophysiology process of pain [42]. Commerically available non steroids anti-inflammatory or anti-nociceptive drugs causes few side effects includes gastric lesions induction in patients. The alkaline chloroform fraction of *E. agallocha* at 10, 15, 20 or 25 mg/kg was orally administrated into mice to evaluate its anti-nociceptive effect. The central and peripheral analgesic activity was determined using acetic Acid-induced Writhing and hot plate test. Alkaline chloroform fractions significantly reduced the writhing of mice in a dose dependent manner. Further HPLC-MS of Alk-CF confirmed the Rutin, Quercetin, Mycertin, Kaemferol, Luteolin, and Isorhamnetin might be responsible for its anti-nociceptive activity. In *silico* computational studies proved the higher binding affinity of rutin to COX-1 and 2 analgesic maker protein receptors [43]. Sodium thiopental-induced sleeping time, Open field, Hole cross and Hole-board test were used to determined the test samples potential on mice/rat behaviour changes such as sleeping time, number of square visited, number of entries through the hole and head dips time by using experimental animals. Oral administration of 200 mg/kg bw of ethanolic extract of EA revealed significant decline in sleeping time and gross behaviour of mice [28].

**Potential of *E. agallocha* in nanoparticles biosynthesis**

Nanobiotechnology and bionanotechnology are essentially synonyms refer to study materials and manipulated at nanometer scale (10-9 m scale) for various applications [44]. Advantages of silver nanoparticles has been increased every year in the field of opto electronics, biomolecular detection, diagnostics, antimicrobial, cancer treatment and environmental application [45-47]. Monodispersive spherical shaped silver nanoparticles synthesized from the leaf sample of *E. agallocha*. Transmission electron microscopy determined the nanoparticles were 15 to 45 nm in size. Phenol and functional group of proteins present in the leaf extracts provide stability to the biosynthesized silver nanoparticles [48]. Crystalline nature of silver nanoparticles observed by X-ray diffraction peak pattern at (111), (200), and (220). 100 µl of biologically synthesized nanoparticles has the potential to inhibit the nitrite formation in the reaction mixture compared with catechin standard [49]. Nanaencapsulated rutin from *Excoecaria agallocha* reported to have significant anti-diabetic and diabetic wound healing activity in streptozotocin induced diabetic rats [50,51].

**Impact of *Excoecaria agallocha* as a heavy metal bioindicator**

Due to industrialization, the ground water and soil content are highly polluted by the heavy metals like Zinc, copper, cadmium etc. A
A huge number of studies are in progress how to scavenge or remove the heavy metals from the polluted areas such as chemical and mechanical related industries, tourist area, fish landing and harbour respectively. In plant species, the zinc and copper metals played vital role in respiratory enzyme system activation phytohormones biosynthesis, photosynthetic process especially in photo system II and some protein, carbohydrates metabolites biosynthesis [52,53]. However those metals are required in minimal quantity for plant metabolism and biosynthesis process, but few mangrove species have the capacity to accumulate huge amount of heavy metals from the affect areas. Recently, Chakraborty et al. [54] examined the bioaccumulation of zinc, copper and lead heavy metals in the various part of E. agallocha including leaf, stem and root. They selected the 12 major stations such as Canning, Gosaba, Diamond harbour, Nayachar island, kolkata, Chemaguri, sagar south, Jambu island, Fraser gunge, Digha, Bali an dbagmara in the north east coast of bay of Bengal and Sunderbans indain mangrove ecosystem. As a result of this study, in the root and stem part of E. agallocha showed significant level of dissolved heavy metals and it proved its bioindicator potential.

**Chemical composition of E. agallocha**

Mangroves are rich sources of primary and secondary metabolities which are involved in many pharmaceutical and environmental applications. Numerous studies has been undertaked by various group of researchers to find out the pre liminary phytoconstituents and phenolic compounds present in different parts of E. agallocha. Previous phytochemical investigation studies of E. agallocha leaves revealed that the presence of diterpenoids, triterpenoids, flavonoids, alkaloids, anthraquinone, phytosterol, fixed oil, tannin, phlorobol esters, free amino acids, mucilage, glycosides, carbohydrates, and lignin [55,56]. Novel Excoecarin D, E and F diterpenoid from Leaves of E. agallocha and their structure depicted as 3α,18-dihydroxy-3β,20-epoxybeyer-15-ene, (15R,16S)-ent-15,16-epoxybeyeran-3-one and ent-3β-hydroxykaur-16-en-2-one using NMR and X-ray analytical techniques [57]. Additionally, 14-taxaren-3-one, dibutyl phthalate, phaehophytin A, betulin, beta roasterol, betulinic acid oleanolic and ursolic acid also identified from EA [58]. Fresh leaves of E. agallocha was extracted with mixture of petroleum ether, diethyl ether and ethanol by Likens-Nickerson distillation method up to 120 min. The concentrated fractions was analysed by GC-MS, it showed the presence of dodecanedioi, L-alanine-4-nitroanilide, benzene methanol, 1,1-diethoxyundecane, hexadecane, Metaraminol, 1,2-benzenediol, tetradeacne, hexadecane, benzyl alcohol, benzenemethanol, 4-trifluoroacet benzyl alcohol, L-alanine -4-nitroanilide, alanine, 2,6-Octadiene-4, undecane, Pentanoic acid, hydroxybenzenepranoic acid, diethyl methylphosphonate, acridine, triluuroacetic acid, triethyl (pentafluorophenyl)silane, N-giainone, N-1-Adanantyl-p-methylbenzalimine, pentachlorphenol, Isohumulone, Octadecanoic acid, decane, diethylphthahlate, benzamide, pentaneitrile, diacetate, clorvino and 1,2,5-trimethylpyhnyole by comparing the spectral data with NBS and IDENT dada base [59]. Latex contains alcohols - exocarol, agalocol, isoagalogol and mannotil; β-amyrin and its 3-epimer, β-amyrone and cycloartenol. Twigs and bark contain a piscidical compound which is toxic to Cryzias latipes. The leaf extract of E. agallocha used for rheumatism, paralysis, cutaneous infection and abortifacent. Several Preclinical trials carried out on Secondary metabolites of E. agallocha showed its potential as anti-HIV, anticancer, antibacterial, antidiabetic activities and antiviral agent. Alkaloids, carboxylic acid, Flavonoids, phenol, saponin, resins, steroids, tannin and sugars from seeds of E. agallocha exhibited anti-inflammatory and analgesic activity [60]. The crude hexane extraction of dried root of E. agallocha showed the presence of acyclic hydrocarbon and n-triacontane with mosquito larvicidal and insecticidal activity [61]. Other group of researchers found that the phytoconstituents in E. agallocha has been increased or decresed in their content with respect to salt availability conditions. The potential chemical structures of E. agallocha shown in Figure 2. Jenci and Natarajan [62] observed there was a increasing change in their starch and chlorophyll content of E. agallocha with respect to 300 mM sodıum chloride and 200 mM of potassium chloride. Dioecious nature of E. agallocha showed its potential as anti-HIV, anticancer, antibacterial, antidiabetic activities and antiviral agent. Alkaloids, carboxylic acid, Flavonoids, phenol, saponin, resins, steroids, tannin and sugars from seeds of E. agallocha exhibited anti-inflammatory and analgesic activity [60]. The crude hexane extraction of dried root of E. agallocha showed the presence of acyclic hydrocarbon and n-triacontane with mosquito larvicidal and insecticidal activity [61]. Other group of researchers found that the phytoconstituents in E. agallocha has been increased or decresed in their content with respect to salt availability conditions. The potential chemical structures of E. agallocha shown in Figure 2. Jenci and Natarajan [62] observed there was a increasing change in their starch and chlorophyll content of E. agallocha with respect to 300 mM sodıum chloride and 200 mM of potassium chloride. Dioecious nature of E. agallocha, the male trees are dominant then compared to female. Rao et al. [63] micro propagated the shoots and roots of E. agallocha under in vitro conditions using Murashige and Skoog, Woody Plant and a modified medium medium.

**Figure 2: Potential secondary metabolites in E. agallocha (a) Exoecarin D, (b) dibutyl phthalate, (c) phaehophytin A, (d) betulin, (e) Isorhamnetin, (f) trifluroacetic acid, (g) ursolic acid, (h) Rutin, (i) Kaemferol, (j) Luteolin and (k) pentachlorophenol**

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Table 1 indicates the chemical composition and biological activities of *Excoecaria agallocha*. In conclusion, this literature collections provide huge information about the traditional value, therapeutic impacts and phytoconstituents of *E. agallocha*. However fewer articles also examined the some toxic effects of *E. agallocha* latex part. Apart from that, the review shows the promising potential of *E. agallocha* to develop a drug molecules for epidemic, pandemic and chronic diseases like diabetes mellitus.

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