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A SYSTEMATIC REVIEW ON CHEMICAL AND PHARMACOLOGICAL ACTIVITIES OF EXCOECARIA AGALLOCHA: A POTENTIAL SUNDARBAN PLANT

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Abstract

Among various plants in the Mangrove Forest of the tropical and subtropical region, *Excoecaria agallocha* is notable for possessing multifarious pharmacological activity. As *Excoecaria agallocha* belongs to the Euphoriaceae family, this plant is rich in many classes of phytochemicals that are therapeutically potent such as Diterpenoids, Triterpenoids, Alkaloids, Polyphenol, Sterol, Flavonoids, Tanine, Flavanone, etc. Its ancient use in the treatment of disorders such as epilepsy, rheumatism, ulcer, leprosy, and others has attracted the interest of researchers, who are now studying different parts of the plant. Plant parts have been studied for reducing inflammation, and anti-microbial, anti-epileptic, and cytotoxic effects in several research. Phytoconstituents responsible for pharmacological activities have been distinguished and their possible mechanism of action along with IC_{50} value has been presented. From wood, roots, and stems of the plant physiologically active constituents such as Agallochin, ent-kauran-16â-ol-3-one, Chebulagic acid, Betulinic acid, Betulonic acid, Corilagin, Geraniin, Excoecarin, Agallochaexcoerin, Vanillic acid are described as pharmacologically potent molecules as they interact with certain biomolecules and precipitate changes in the physiological state of the body. This review elucidates the likely mechanism of action of each of these plant compounds that provide particular biological activity.

Keywords: Anti-epileptic property, Diterpenoids, Anti-inflammatory, Cytotoxic, *Excoecaria agallocha*

Introduction

People have been searching for natural cures for their illnesses since the dawn of time. No matter how far we have come as a civilization, mankind must turn toward nature for its needs. Humans, like animals, began employing medicinal plants for disease treatment as an innate behavior (Stojanoski & Art, 1999). Be it a wound on the skin or a critical internal injury, it is nature that has given us the ray of treatment. Most people in the world rely entirely or partially on the traditional medicinal system to meet their essential medical needs. The worldwide herbal medicines market was valued at USD 170 billion in 2022 and is expected to reach USD 600 billion by 2033, growing 15% from 2023 to 2033 (Silveira & Boylan, 2023). As a result, it's clear that people need plants in order to become well and stay well. One of the most common tree species in the mangrove forest, *Excoecaria agallocha*, has been put to many different uses over the years (Table 1). Numerous phytochemicals have been isolated from different parts of the plant with the intention of finding a physiologically active phytochemical. Multiple plant metabolites, including alkaloids, flavonoids, diterpenoids, triterpenoids, polyphenols, and others, have been linked to the plant's pharmacological effect. The physiologically active component composition of medicinal plants varies substantially depending on the plant species, soil type, and connection to microorganisms (Zhao et al., 2011). Anti-inflammatory, cytotoxic, and anti-microbial effects along with potential neuropharmacological activities based on its use in the traditional use of *Excoecaria agallocha*

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and the potential phytochemicals discovered give us the lead to further study of this plant. This review article focuses on the accumulation of phytochemicals, isolated from *Excoecaria agallocha* and its potential biological activity, as well as its likely cellular method of action, which may be useful in the identification of novel medications.

Materials and Methods

Searching-process

Interdisciplinary research on *Excoecaria agallocha* was being conducted on the 15th of March, 2023. Using keywords such as *Excoecaria agallocha*, phytoconstituents, pharmacological activity, bioactivity, mangrove plants, diterpenoids, triterpenoids, myrictin, rhamnoside, corilagic acid, chebulagic acid, betulinic acid, betulonic acid, lupenone, geraniin, afzelin, and corilagin; a literature survey was processed in Google Scholar and PubMed. In this review, the surveys included (i) in-vivo and in-vitro studies from various extracts and pure phytochemicals of *E. agallocha,* (ii) possible mechanism of action of the isolated phytoconstituents (iii) studies concerning the concentrations, doses, and route of administration of extracts and its phytochemicals.

Data extraction

A thorough literature investigation resulted in 587 records of which 88 studies were found relevant to our objective of the review. The data from the sources had been selected based on the surname of the author, publication date, pharmacological activity, observations, results, concentrations tested, and possible mechanism of action at a molecular level.

Table 1. Traditional medicinal uses of *Excoecaria agallocha*

Plant parts used	Traditional Use	Reference
Bark, Bark oil, Milky sap, leaves, Root	Treat sores and stings from marine creatures, ulcers, purgative, emetic, Anti-leprosy	(Ghani, 2003)
	Anti-rheumatism, Paralysis treatment.	(Subhan et al., 2008)
	Anti-HIV, anticancer, antibacterial and antiviral	(Peter et al., 1999)
	Epilepsy, ulcers, leprosy, rheumatism, and paralysis, flatulence, antioxidant, antimicrobial, anti-inflammatory, analgesic, antiulcer, anticancer, anti-reverse transcriptase, antihistamine-release, anti-filarial, DNA damage protective, antidiabetic, and antitumor protecting activities, abortifacient	(Mondal et al., 2016)
Leaves	Dart poison, fish poison	(A. S. Anjaneyulu & Rao, 2000)
Latex	Purgative, Abortifacient	

Phytoconstituents

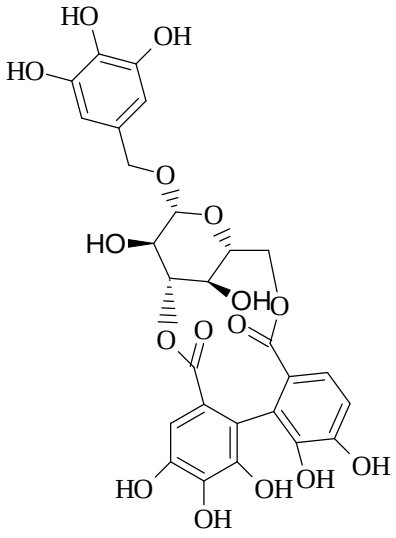
Excoecaria agallocha, as a very common mangrove plant has been evaluated for multiple pharmacological activities. Several phytoconstituents (Table 2) have already been isolated form different parts of the plant but their exact bioactivity hasn't been demonstrated yet of now. Prominent biologically active class of phytochemicals including Diterpenoids such as agallochin, excoecarin, and stachenone; Triterpenoids, flavonoids, tanins, alkaloids, etc. are assumed to be attributed for the potential pharmacologic activity of the plant.

Table 2. Reported phytoconstituents from different parts of *Excoecaria agallocha*

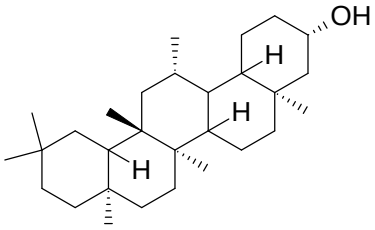
Plant Parts	Class of metabolites	Molecules	Reference
Root	Diterpenoids	3-oxo-ent-13-epi-8(13)-epoxy-15-chloro-14-hydroxy labdane; ent-15- chloro -13,14 -dihydroxylabd -8(9) ene -3 -one; ent-15 - chloro-labd-8(9) ene-3a,13,14-triol; ent-11β-hydroxy-8(14),15-isopimaradien-3-one; 8,13-epoxy-3- nor -2,3- seco-14-epilabden-2,4-olide; ent-3-oxo-13-epi-manoyl oxide (Ribenone); ent-3β-hydroxy-13-epi-manoyl oxide (Ribenol); ent-16-hydroxy-3-oxo-13-epi-manoyl oxide; ent-15-hydroxylabda-8 (17), 13E-dien-3-one; labda- 8 (17),13E- a 3β,15-diol; Ent-11α-hydroxy-3-oco-13-epi-manonyl-oxide; Agallochin A; Agallochin B; Agallochin C; Agallochin D; Agallochin E	(A. S. Anjaneyulu & Rao, 2000)
		ent-3 beta,20-epoxy-3 alpha,6 alpha-dihydroxykaur-16-ene (Agallochin F); 3 beta,20-epoxy-3 alpha-hydroxybeyer-15-ene (Agallochin G); 3 beta,20:15R,16S-diepoxy-3 alpha-beyeranol; (Agallochin H); 3 beta,20-epoxy-3 alpha,6 alpha-dihydroxy-18-nor-beyer-15-ene (Agallochin I); 2-acetoxy-1,15-beyeradien-3,12-dione; 2-hydroxy-1,15-beyeradien-3,12-dione ent-kauran-16α-ol-3-one	(A. S. Anjaneyulu et al., 2002)
		11α,14α-dihydroxy-7,15-isopimaradien-3-one (Agallochin J); 3α,11α,14α-trihydroxyisopimara-7,15-diene (Agallochin K); 6α,14α,17-trihydroxy-7,15-isopimaradien-3-one (Agallochin L)	(A. S. Anjaneyulu et al., 2003)
		ent-13-epi-8,13-epoxy-4, hydroxy-3,4-secolabd- 14-en-3-oate (Agallochin M); Methyl ent-13- ere 2,3-secolabd- 14-en-2,11-olid-3-oate (Agallochin N); methyl ent-17-hydroxy-3,4- secokaura-4(19),15-dien-3-oate (Agallochin O)	(A. S. R.Anjaneyulu & Rao, 2003)
		3α,11β-dihydroxy-*ent*-isopimara-8(14),15-dien-2-one; 16β-hydroxy-*ent*-atisan-3-one; *ent*-labda-8(17),13*E*-diene-3β,15-diol; *ent*-3β-hydroxybeyer-15-ene-2,12-dione	(Kang et al., 2005)
		(13R,14R)-ent-8α,13;14,15-diepoxy-13-epi-labda-3-one (excoecarin A); (13R,14S)-ent-8a,13;14,15-diepoxy-13-epi-labda-3-one (excoecarin B); (13R,14R)-ent-8a,13;14,15-diepoxy-13-epi-labda-3β-ol (excoecarin C)	(Konishi et al., 1996)
Wood	Diterpenoids	3α,18-dihydroxy-3β,20-epoxybeyer-15-ene (excoecarin D); (15R,16S)-ent-15,16-epoxybeyeran-3-one (excoecarin E); ent-3β-hydroxykaur-16-en-2-one (excoecarin K)	(Konishi et al., 2000)
		Excoecarin F; Excoecarin G1; Excoecarin G2	(Konishi et al., 1999)
		Excoecarin H	(Konishi et al., 1998)
		Excoecarin M; Excoecarin N	(Konishi et al., 2000)
		Excoecarin RI; Excoecarin R2	(T. Konishi et al., 2003)
		Excoecarin S; Excoecarin T1; Excoecarin T2	(Konishi et al., 2003)
		2α,3α,18-trihydroxy-3β,20-epoxybeyer-15-ene(Excoecarin V1); ent-2,3-secokaur-16-en-2,3-dioic acid (excoecarin V2); ent-3,4-seco-16a-hydroxyatis-4 (19)-en-3-oic acid (excoecarin V3)	(Konishi et al., 2003)
		ent-8,13-epoxy-4-Hydroxy-3,4-seco-13-epi-labd-14-en-3,11-olide (Agallochaexcoerin A); ent-8,13-epoxy-3β-hydroxy-13-epi-labd-14-	(Gowri et al., 2009)

		en-2-one (Agallochaexcoerin B); ent-8,13-epoxy-3β,11α-dihydroxy-3-oxo-13-epilabd-14-ene-2-one (Agallochaexcoerin C)	
		ent-11alpha-Hydroxy-3-oxo-13-epi-manoyl oxide; ent-16-hydroxy-3-oxo-13-epi-manoyl oxide; ent-13-epi-manoyl oxide	(Konishi et al., 2010)
		Ent-13-epi-8,13-epoxy-2-hydroxylabda-1,14-diene-3-one; ent-13-epi-8,13-epoxy-14S,15-dihydroxylabdane-3-one; ent-13-epi-8,13-epoxy-2,3-secolabd-14-ene-2,3-dioic acid; ent-13-epi-8,13-epoxy-2,3-secolabd-14-ene-2,3-dioic acid 3-methyl ester; ent-13-epi-8,13-epoxy-2-oxa-3-oxolabd-14-ene-1R-carboxylic acid"	(Konishi et al., 1996)
		8,13-epoxy-14-labden-3-one	(Li et al., 2007)
		Stachenol; Stachenone	(Konishi et al., 2000)
	Triterpenoids	Friedelan-3α-ol; Friedelan-3β-ol; Friedelin	(Anjaneyulu et al., 1993)
Bark	Diterpenoids	ent-Atisane-3β,16α-diol; ent-3,4-seco-16α-Hydroxyatis-4(19)-en-3-oic acid; ent-16α-Hydroxy-atisane-3,4-lactone	(Wang et al., 2009)
	Flavonoids	Catechin hydrate	(Jahan et al., 2014)
	Phenolic Acids	Ellagic acid; Gallic acid; Vanillic acid	(Jahan et al., 2014)
Latex	Diterpenoids	Excoecaria factor A_1; Excoecaria factor A_2; Excoecaria factor A_3; Excoecaria factor A_4; Excoecaria factor A_5; Excoecaria factor A_6; Excoecaria factor A_7; Excoecaria factor A_8; Excoecaria factor A_9	(Karalai et al., 1994)
	Flavanone Glycoside	28-nor-olean-2α,3β-dihydroxy-14,17-diene-16-one; β-amyrin; α-amyrin; 3α-O-trans-coumaroyl-betulinic acid; 3-acetyl-aleuritolic acid	(Mo et al., 2018)
Stem and/or Twigs	Diterpenoids	ent-17-Caffeoyloxykaur-15-en-3-one; 7-Deoxogeayine; ent-3β,11α-Dihydroxyisopimara-8(14),15-dien-2-one; ent-15,18-Dihydroxylabd-8(17),13E-diene; 8,13-Epoxy-14-labden-3-one; ent-Kaur-15-en-3β,17-diol; (9Z,12Z)2,3-Dihydroxypropyl octadecadienoate; (9Z,12Z,15Z)2,3-Dihydroxypropyl octadecatrienoate	(Li et al., 2010)
		ent-17-Hydroxykaur-15-en-3-one	(Li et al., 2012)
	Tannins	Corilagin; Chebulagic acid; 3,4-Dihydroxybenzoic acid; Ellagic acid 4-O-xylopyranoside; Furosin; 1,2-di-O-Galloyl-3,6-(R)-HHDP-β-D-glucose; Geraniin; 1,2,3,4,6-Penta-O-galloyl-β-D-glucose; Tercatain; 1,3,4,6-Tetra-O-galloyl-β-D-glucose; 1,2,6-Tri-O-galloyl-β-D-glucose;p 3,4,5-Trihydroxybenzoic acid ethyl ester	(Li et al., 2012)
	Triterpenoids	Betulin; Betulinic acid; Betulone; Betulonic acid; Epilupeol; Epitaraxerol	(Li et al., 2010)
		(9Z,12Z)2,3-Dihydroxypropyl octadecadienoate; (9Z,12Z,15Z)2,3-Dihydroxypropyl octadecatrienoate	(Liu et al., 2010)
		Taraxerol; Taraxerone	(Tian et al., 2008)
	Flavonoids	(+)-Catechin; (+)-Catechin-3-O-β-D-glucopyranoside; (+)-Catechin-7-O-β-D-glucopyranoside; (+)-Catechin-3-O-α-L-rhamnos;	(Li et al., 2012)

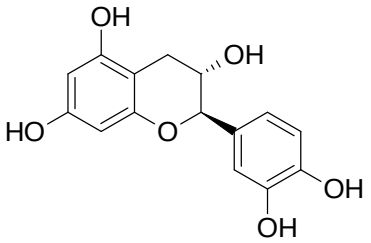
		Excoecariphenols A; Excoecariphenols B; Excoecariphenols C; Excoecariphenols D; (2R,3S)-Gallocatechin; Myricetin-3-O-(6-O-galloyl)-β-glucopyranoside; Quercetin-3-O-(6-O-galloyl)-β-glucopyranoside; Quercetin-3-O-β-galactopyranoside; Quercetin-3-O-β-glucopyranoside	
	Sterols	(24R)-24-Ethylcholesta-4,22-dien-3-one; β-Sitostenone; β-Sitosterol	(Tian et al., 2008)
Leaves	Flavonoids	Afzelin; Kaempferide 3-O-α-L-rhamnopyranoside; Kaempferol-3-O-(2-O-acetyl-α-L-rhamnopyranoside; Kaempferol 3-O-α-L-arabinofuranoside	(Rifai et al., 2011)
		Rutin	(Rifai et al., 2011; Selvaraj et al., 2014)
		Luteolin; Quercitrin; Myricetin; Isorhamnetin	(Selvaraj et al., 2014)
	Polyphenols	Excoecariphenols A; Excoecariphenols B; Excoecariphenols C; Excoecariphenols D	(Li et al., 2012)
	Alkaloids	2,4-dimethoxy-3-ψ,ψ-dimethylallyl-trans-cinnamoylpiperidide	(Prakash et al., 1983)
	Diterpenoids	Agallochanin A; Agallochanin B; Agallochanin C; Agallochanin D; Agallochanin E; Agallochanin F; Agallochanin G; Agallochanin H; Agallochanin I; Agallochanin J; Agallochanin K	(Jiang et al., 2019)



Corilagin



Fridelan-3-alpha-ol



(+)-Catechin

Figure 1(a): Structures of Flavonoids

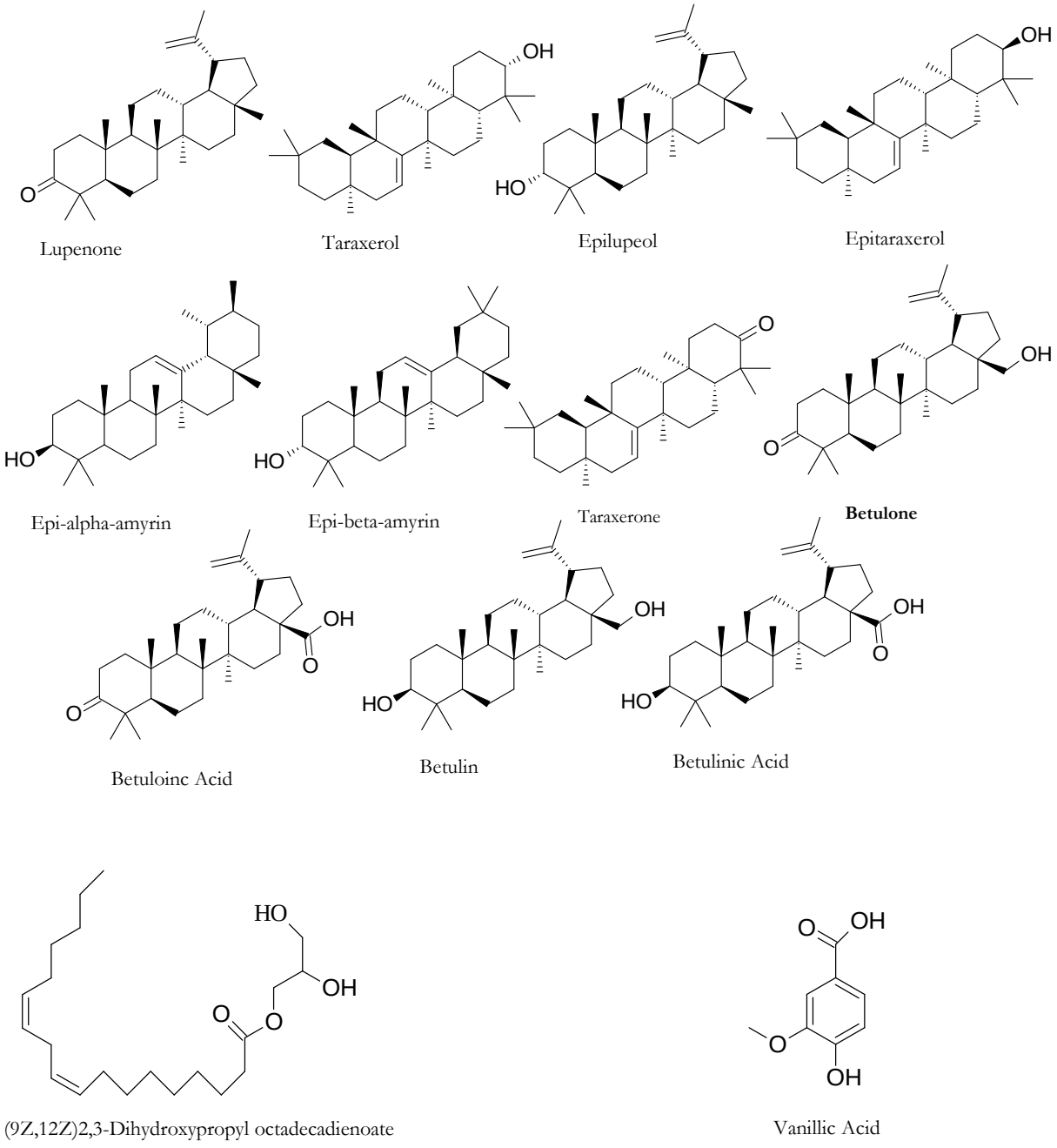
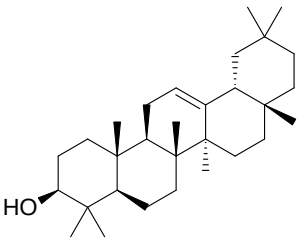
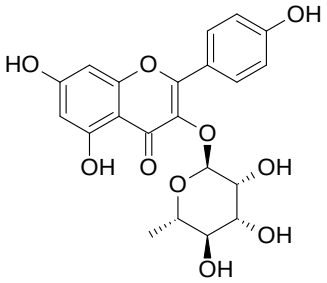


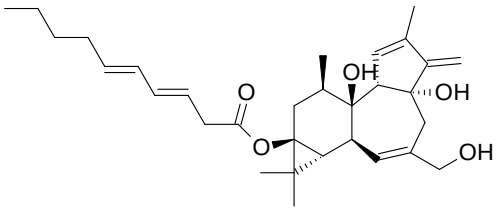
Figure 1(b): Structures of Diterpenoids



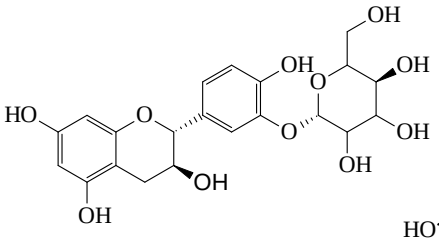
Beta-amyrin



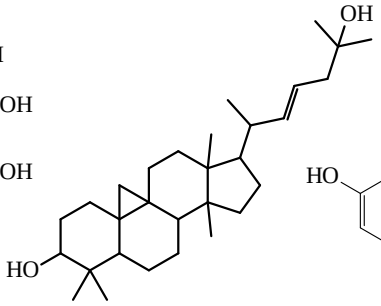
Afzelin



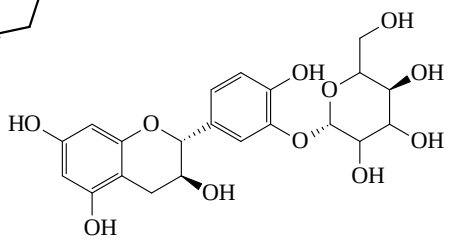
12-Deoxyphorbol-13-(3E,5E-decadienoate)



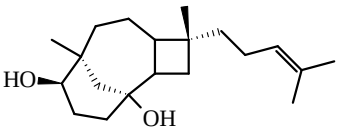
Chebulagic Acid



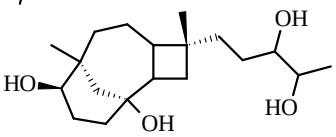
Cycloart-22-ene-3-beta,25-diol



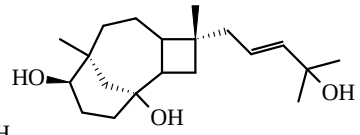
(+)-Catechin-3-beta-O-D-glucopyranoside



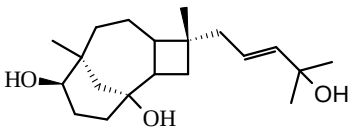
Excoagallochaol A



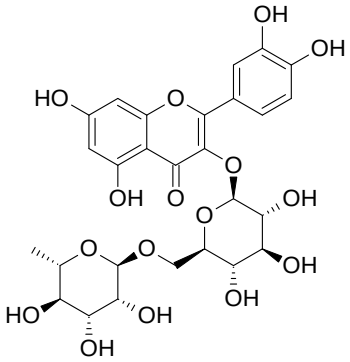
Excoagallochaol B



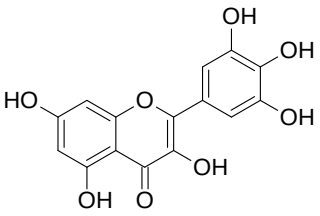
Excoagallochaol C



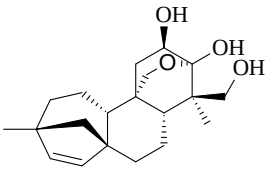
Excoagallochaol D



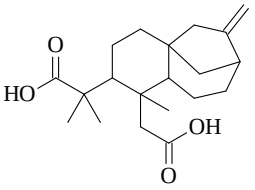
Rutin



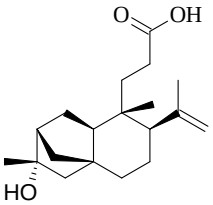
Myricetin



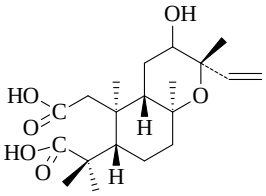
Excoecarin V1



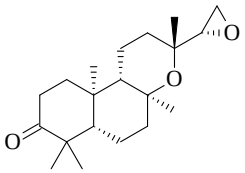
Excoecarin V2



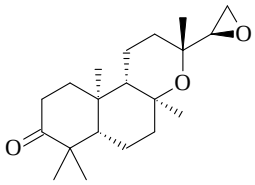
Excoecarin V3



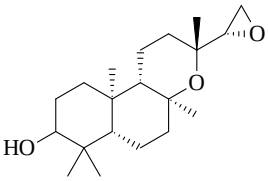
Excoecarin S



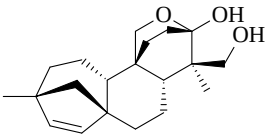
Excoecarin A



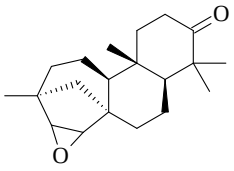
Excoecarin B



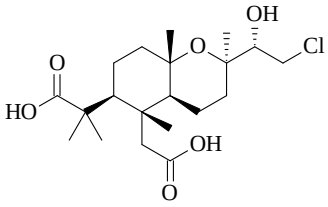
Excoecarin C



Excoecarin D



Excoecarin E



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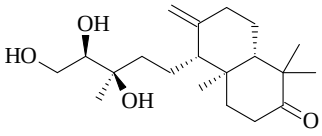

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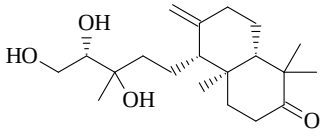

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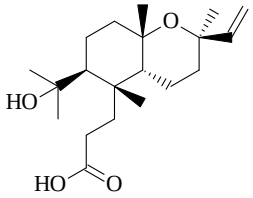
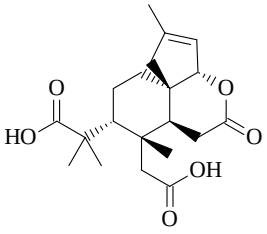
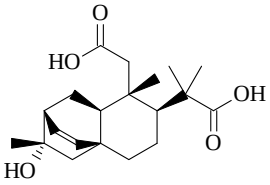


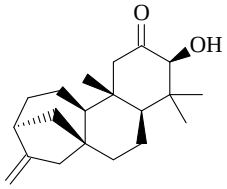
Excoecarin H



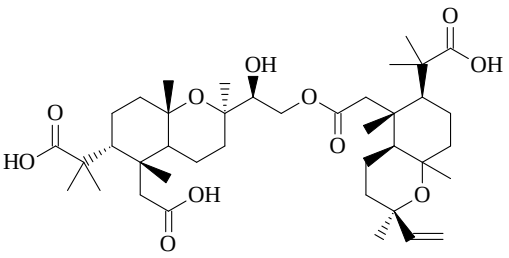
Excoecarin M



Excoecarin N



Excoecarin K



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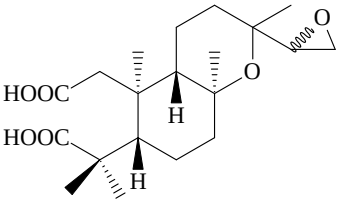
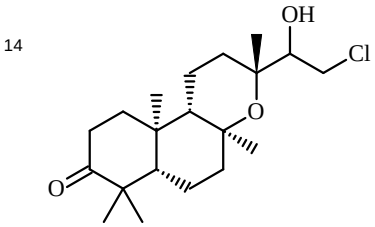
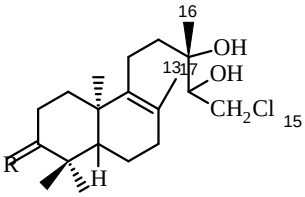


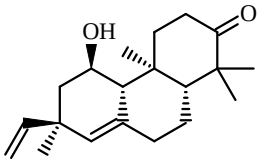
Excoecarin T1(14S)
Excoecarin T2(14R)



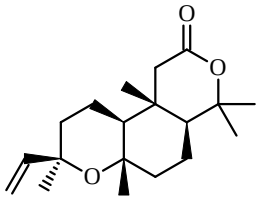
Agallochin A



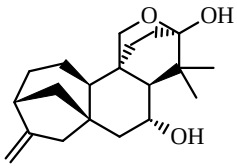
Agallochin B(R=O)
Agallochin C(R=OH)



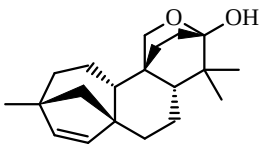
Agallochin D



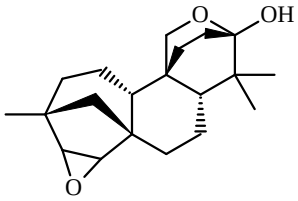
Agallochin E



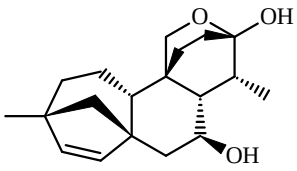
Agallochin F



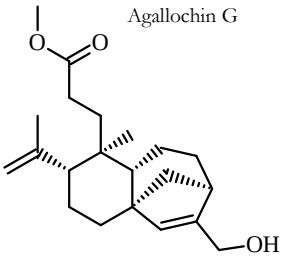
Agallochin G



Agallochin H



Agallochin I



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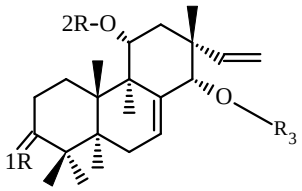
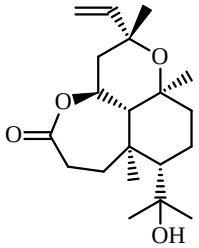
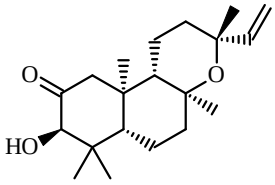


Agallochin J:; R_1=O; R_2=H; R_3 =H
Agallochin K; R_1 =  R_2=H, R_3=H



Agallochaexcoerin A



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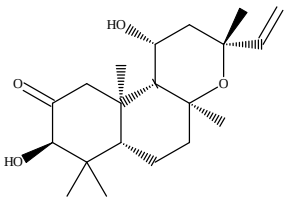

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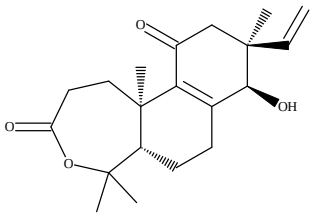
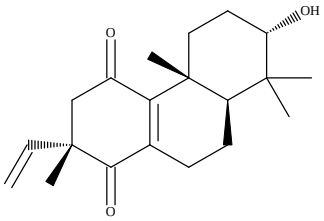
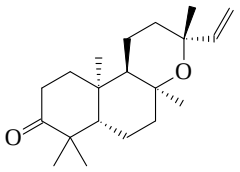


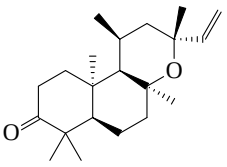
Agallochaexcoerin E



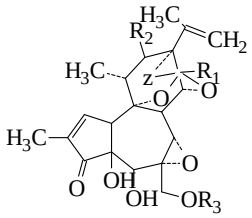
Agallochaexcoerin F



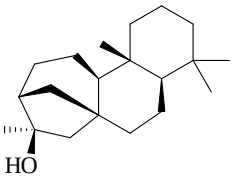
Ribenone



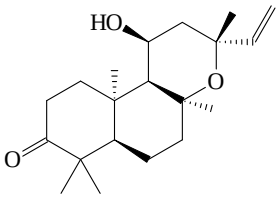
Ent-11-alpha-hydroxy-3-oxo-13-epi-manonyl-oxide



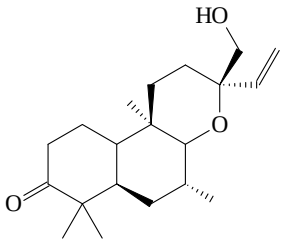
Excoecaria factor A1-9



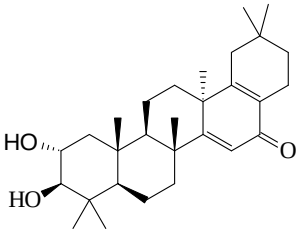
Ent-kauran-16-alpha-ol-3-one



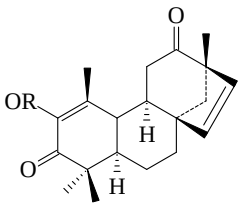
Ent-11-alpha-Hydroxy-3-oxo-13-epi-manoyl oxide



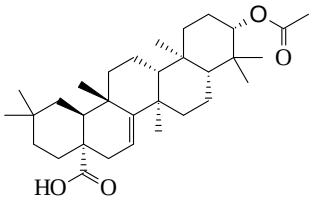
Ent-16-hydroxy- 3-oxo-13-epi-manoyl oxide



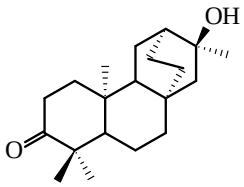
28-nor-olean-2a,3b-dihydroxy1-4,17-diene-16-one



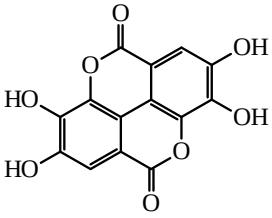
2-Acetoxy-1,15-beyeradiene-3,12-dione(R=Ac)
2-hydroxy-1,15-beyeradiene-3,12-dione(R=H)



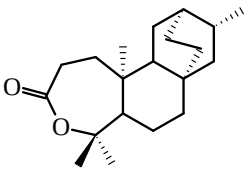
3-acetyl-aleuritolic acid



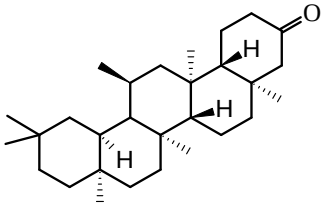
16- beta-hydroxy-ent-atisan-3-one



Ellagic Acid

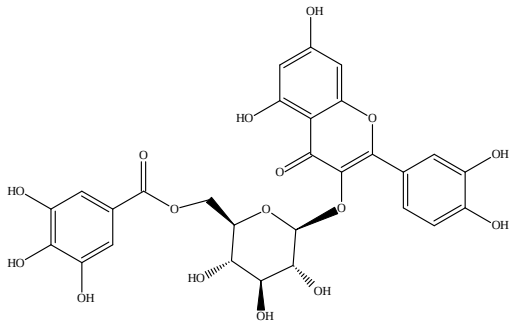


Ent-16-alpha-Hydroxy-atisane-3,4-lactone

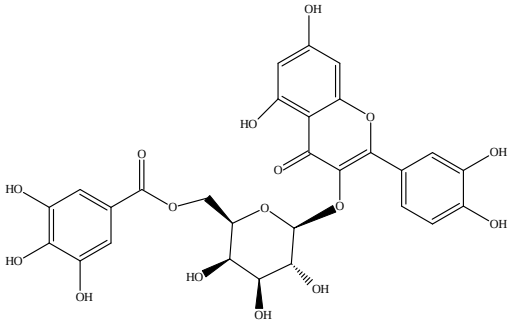


Friedelin

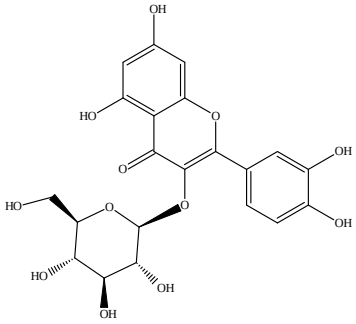
Figure 1(c): Structures of Triterpenoids



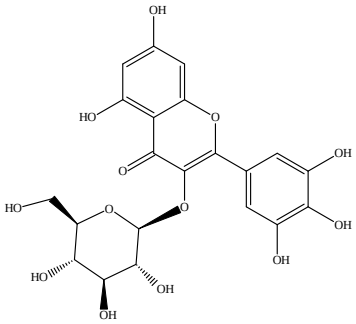
Quercetin-3-O-(6-O-galloyl)-b-glucopyranoside



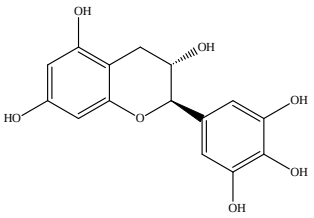
Quercetin-3-O-b-galactopyranoside



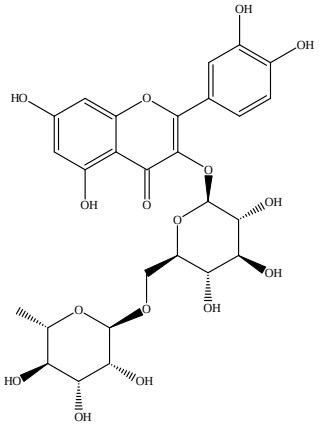
Quercetin-3-O-b-glucopyranoside



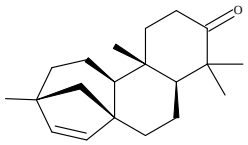
Myricetin-3-O-(6-O-galloyl)-b-glucopyranoside



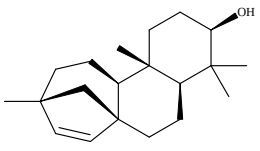
(2R,3S)-Gallocatechin



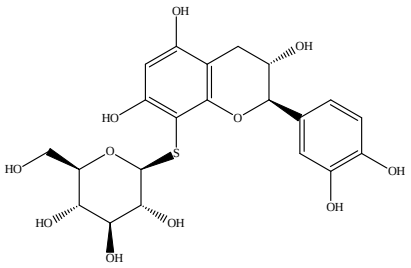
Rutin



Stachenone



Stachenol



Excoecariphenol A

Figure 1(d): Structure of other phytoconstituents

Table 3. Reported pharmacological activity and possible mechanism of action responsible for the activity

Pharmacological activity	**Test Model**	**Extract and dose (mg/kg)**	**Route of administration**	**Effect**	**Mechanism of Action**	**Reference**
Neuropharmacological	Sodium thiopental-induced sleeping time Swiss Albino Mice	100 and 200 mg/kg	Intraperitoneal	Prolonged the amount of time needed to fall asleep after taking sodium thiopental.	$GABA_a$ receptor complex	(Subhan et al., 2008)
	open field test	100 and 200 mg/kg	Orally	From zero to 240 minutes, there was a noticeably smaller movement.		
	Hole cross test	100 and 200 mg/kg	Orally	Movement from its starting value of 0 to 240 min has significantly decreased.		
	Hole board test	100 and 200 mg/kg	Orally	Movement from its starting value of 0 to 240 min has significantly decreased.		
Antimicrobial activity	Disk Diffusion method	(0.2 mg/disc)	In vitro	Zones of inhibition ranging from 11 to 15 mm and no activity against *Shigella flexneri* and *Staphylococcus epidermis*	N/A	
Anti-ulcer activity	In vivo NSAID induced ulcer test	125 mg/kg bdwt	Orally	N/A	Due to their role as peroxidase co-substrates, phenols promote the production of PGE.	(Thirunavukkarasu et al., 2009)
Cytotoxic activity	Brine shrimp lethality test	N/A	In vitro	High nauplii death rate increases with concentration.		(Sabu et al., 2022)
Anti-convulsant activity	Maximal Electroshock Model	N/A	Orally	Dose-dependent delay in the onset of seizures	Significant glycinergic and GABAergic potentiating processes are at work which is an inhibitory neurotransmitter that prevents convulsions.	(Shelar et al., 2018)
	Lithium Pilocarpine induced convulsion	N/A	Intraperitoneal	Lowered seizure frequency.		
Anti-diabetic activity	Acute hypoglycemic activity by blood glucose meter	Ethanolic 50% extract and Aquous extract at 500mg/kg body wt	Orally	Significant reduction in blood glucose level (FBGL) drop at 3 and 5 hour intervals.	N/A	(Thirumurugan et al., 2010)
Anti-inflammatory activity	Acute inflammation test by Carrageenin-induced paw oedema in rats	Ethanol and water mixture of seeds, Leaves and latex at 250 and 500mg/kg	Orally	Carrageenin-induced paw swelling was significantly inhibited.	Inhibition of the production of prostaglandins.	(Babuselvam et al., 2012)

Discussions

Based on traditional evidence, several research has been conducted to elucidate the scientific ground of using *Excoecaria agallocha* plant parts in different treatments. A significant number of pharmacological activities has been documented till now and possible mechanisms owing to these effects are demonstrated (Table 3). The many phytochemicals previously found are assumed to be responsible for the most prominent pharmacological effects (Table 4) associated with plants, according to a review of the relevant literature. Chemical structures of different phytochemicals present in *Excoecaria agallocha* have been drawn and documented here according to the class of compounds. (Figure 1,2,3,4)

Anti-microbial Activity

Among enormous amount of diterpenoids (Figure 1a) isolated from the plant parts, ent-3α-hydroxy-beyer-15-ene-2-one and excoecarin S were found to pose the strongest anti-EBV activity (Chan et al., 2018). Besides, inhibitory effects against hepatitis C virus (HCV) can be a attributed to the polyphenols Excoecariphenols A, Excoecariphenols B, Excoecariphenols C, Excoecariphenols D present (Figure1) in the leaves of *Excoecaria agallocha* (Li et al., 2012). It has been found that HCV NS3-4A protease enzyme is inhibited by Excoecariphenol D and corilagin 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 (Chan et al., 2018). Moreover, other compounds like saponins also have antifungal properties (Patra et al., 2009) and phenolic compounds that are toxic to microbial pathogens (Aboaba et al., 2006). The methanolic extract of the leaves had a minimum inhibitory concentration (MIC) of 3.12 mg/ml and a minimum bactericidal concentration of 6.25 mg/ml, respectively against a number of fish pathogens including *Flavobacterium meningosepticum, Chryseobacterium indologenes, Flavobacterium indicum, Chryseobacterium gleum, and Elizabethkingia meningoseptica* where the zone of inhibition varied significantly (P 0.05) for the crude extract doses of 100, 300, and 500 mg/ml and the recorded maximum activity (LC_{50}) was 94.19 mg/ml(Laith et al., 2014). To evaluate the antibacterial activity against *Bacillus cereus, Bacillus subtilis, Klebsiella pneumoniae, Proteus vulgaris, S. aureus,* and *Salmonella typhi*, 80% methanolic extracts of callus derived from leaves had more antibacterial activity (Table 2) (Arumugam et al., 2012).

Cytotoxic Activity

When *Excoecaria agallocha* flavonoid glycosides (Figure 1b) were tested for their capacity to decrease hedgehog signaling (HS) and cytotoxicity against human pancreatic (PANC1) and prostate (DU145) cancer cells, positive results were obtained (Rifai et al., 2011). When tested against PANC1 and DU145 cancer cells, kaempferol, 3-O-L-arabino-furanoside showed HS inhibition with IC_{50} values of 0.5 and 2.0 M and cytotoxicity with IC values at 0.7 and 1.8 M and 0.8 and 2.4 M, respectively. The abnormal activation of the HS pathway, which controls cell growth and proliferation, has been associated with the development of cancer (Abidi, 2014). 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). In *Excoecaria agallocha*, which has been shown to have an anticancer effect on SiHa cells, LC-MS data revealed the presence of Bergenin, also known as Cuscutin, Ardisic acid B, and Vakerin (Sultana et al., 2022). It has been discovered to produce G0/G1 cell cycle arrest in HeLa cervical cancer cells in a dose-dependent manner, as well as to block the STAT3 signaling pathway (Shi et al., 2019).

Chebulagic acid has an anti-tumor action via controlling apoptosis and introducing checkpoints at crucial periods in the tumor's development, which stops the growth of the tumors. Inhibition of NF-B expression results in increased expression of apoptotic proteins (Bax) and decreased expression of antiapoptotic proteins (Bcl-2 and Bcl-xL) (Prathiba et al., 2021). By triggering ROS-regulated apoptosis and autophagy, corilagin reduces the growth of cancerous cells. Corilagin decreased levels of Procaspase-3, Procaspase-8, Procaspase-9, PARP, and Bcl-2 in MCF-7 and SK-BR3 breast cancer cell lines while increasing levels of Caspase-8, Caspase-9, Bax, and elevated cleaved PARP, which led to apoptosis, autophagic cell death, and necroptosis (Tong et al., 2018). An increase in caspase-3, p-Akt and pErk1/2 and decreased Bcl-2 by Corilagin in cholangiocarcinoma showed antiproliferation and G_2/M arrest in cell cycle. (Gu et al., 2016). Corilagin is proposed to have promising anticancer activity in Esophageal squamous cell carcinoma (ESCC), Gastric carcinoma, Glioblastoma multiforme, Hepatocellular carcinoma, Lung cancer and Ovarian cancer with hypothetical mechanisms (Qiu et al., 2019); (Xu et al., 2019), (Milani et al., 2018), (Deng et al., 2018); (Ming et al., 2013), (Bai et al, 2019), (Jia et al., 2013). Betulinic acid is potent DNA Topo II inhibitor along with inhibitory activity on the growth of K562 tumor cell line (Moghaddam, 2012) and Myrecitin has been proven as an inhibitor of phosphatidylinositol 3-kinase (Phillips et al., 2011), serine/threonine kinase PIM1(Holder et al., 2007), cyclin-dependent kinase 1 (Zhang et al., 2011), MKK4 (Kim et al., 2009), Hsp70 ATPase (Koren et al., 2010),

metalloproteinase-2 (Ko et al., 2005). Geraniin from *G. thunbergii* extracts inhibited BACE1 activity in a concentration-dependent manner (4 μM IC_{50}) and nearly completely (97% inhibition) at 30 μM. It was more effective in inhibiting BACE1 than resveratrol, which required a greater dose of 15 μM to reach IC_{50} (Table 4). The inhibitor may bind to β-secretase subsites, as it is noncompetitive with the substrate (Youn & Jun, 2013). Isorhamnetin, a compound found in this plant, reduce the risk of skin and colon cancer (Kim et al., 2011; Li et al., 2014). Thus, these compounds can serve as leads for novel drug in the treatment of cancer.

Anti-inflammatory Activity

Inflammatory responses are mainly provided by various mediators such as COX, LOX Prostaglandins, leukotrienes etc. Agallochaol has been shown to have anti-inflammatory properties through the inhibition of 5-lipoxygenase (5-LOX), whereas betulinic acid has been seen to inhibit cyclooxygenase-2 (COX-2). α-amyrin is extensively studied for it/s numerous pharmacological actions, including antinociception, anti-inflammatory, antipruritic, hepatoprotective, and antihyperglycemic characteristics. Additionally, it's topical anti-inflammatory action is attributed to decreasing COX-2 expression, which inhibits prostaglandin E_2 (PGE_2) levels (Medeiros et al., 2007); (Otuki et al., 2005); (Romero-Estrada et al., 2016). Though it's anti-inflammatory, antitubercular, and cytotoxic actions have been reported, epilupeol has still received little research (Guzman et al., 2012); (Puapairoj et al., 2005); (Yasukawa et al., 1995). Six ent-kaurane diterpenoids, namely agallochaols K-P, as well as an atisane-type diterpenoid and agallochaol Q, were isolated from the stems and twigs of the mangrove *Excoecaria agallocha*. These drugs inhibit TNF- and IL-6 production in lipopolysaccharide (LPS)-stimulated murine macrophages (raw 264.7 cells), as well as altering the expression of NF-KB and AP-1 target genes (Rajeswari & Bhaskara-Rao, 2015). These results provide scientific credibility to the anti-inflammatory claims made by traditional users of this herb.

Neuropharmacological Activity

The traditional usage of *Excoecaria agallocha* to treat epilepsy is what has piqued the interest of the scientific community. In order to provide an explanation for this impact, a mechanism of action is sketched (Figure 2). Both geraniin and myricetin inhibited BACE1, the enzyme responsible for catalyzing Amyloid Precursor Protein to manufacture Amyloid protein, in a concentration-dependent manner (Park et al., 2016); (Youn & Jun, 2013). Isorhamnetin has the ability to counteract the morphological alterations generated by Amyloid β in human neuroblastoma SH-SY5Y cells, disrupt the stability of Aβ aggregates, and safeguard cells from Amyloid β-triggered cytotoxicity (Iida et al., 2015). In a preclinical investigation involving live rats administered with PTZ, corilagin has demonstrated promising antiepileptic characteristics (Yu et al., 2018).

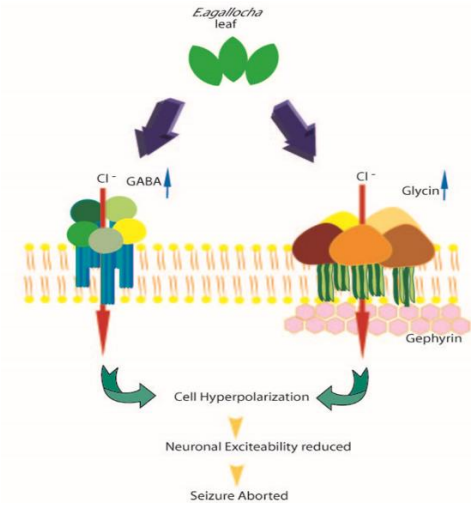


Figure 2. Possible anti-epileptic mechanism of *Excoecaria agallocha extract*

Table 4. Pharmacological activities of reported phytochemicals that isolated from *Excoecaria agallocha* extract

Name of Phytochemical	Activity	Mechanism	Reference
friedelan-3α-ol	Anti-microbial agsinst *Staphylococcus aureus*	N/A	(Chama et al., 2023)
Ribenone	Leishmania	N/A	
	Anti-cancer	Inhibitory effects on EBV-EA activation.	(Konishi et al., 1998)
friedelan-3β-ol	Anti-cancer	Induction of cell cycle arrest at the S-phase in HN22 cells.	(Wongprayoon et al., 2022)
Ellagic Acid	Anti-inflammatory	Binds with cysteine residues to prevent binding of Keap1 to Nrf2 and also Decreasing the expression of proinflammatory and pro-fibrinogenic cytokines like interleukins (IL-1α, IL-6, IL-8), tumor necrosis factor alpha (TNF-α) and TGF-β).	(García-Niño & Zazueta, 2015)
	Hepatoprotective	By regulating the activity of cytochrome P450 (CYP450	
	Antisteatotic	Enhanced peroxisome proliferator–activated receptor-alpha (PPAR-α), that upregulates the expression of genes responsible in fatty acid synthesis, cholesterol synthesis/transport and fatty acid-oxidation.	
	Antimicrobial activity	Causes change in hydrophobicity, negative surface charge decreased by pore formation in the cell membranes.	
	Cyto-toxic	Up-regulates Bax and down-regulates Bcl-2, resulting in the apoptosis of human laryngeal carcinoma cell line Hep-2 and gastric carcinoma cell line SGC-7901.	
Gallic Acid	Anti-microbial activity	Inhibits DNA polymerase of Epstein-Barr virus.	(Borges et al., 2013) e
Corilagin	Anti-epileptic	Provides anti-epileptic effect by reducing TNF-α and increasing IL-10 in the brain tissues.	(Yu et al., 2018)
	Anti-microbial	Abrogate interaction with host cell and penetration into HCMV, HCV, DENV-2, MV, and RSV during entry process in the cell.	(Lin et al., 2013)
	Neuroprotective	Induces autophagy via suppression of mTOR function.	(Kim et al., 2014)
Chebulagic acid	Anti-microbial activity	N/A	(Abdel-Raouf et al., 2015)

Conclusion

Excoecaria agallocha has been found to possess medicinal potential from many perspectives. Numerous studies have examined several components of plants, including leaves, roots, bark, stems, and twigs. Various pharmacologically active phytoconstituents have been identified in distinct anatomical components of the plant. Numerous biological activities, including anti-inflammatory, analgesic, anti-epileptic, and anti-cancer properties, have been extensively studied and documented. Various diterpenoids, such as kaurene, artisane, labdane, and agallochin, have been extracted and identified, among other phytoconstituent categories such as phenols, triterpenoids, alkaloids, tannins, flavonoids, and sterols. These compounds have been associated with distinct biological activities. Furthermore, our study has

successfully revealed the potential mechanism behind the anti-epileptic properties of the leaves of these plants. Additional research is necessary to elucidate the significance of natural products in various therapeutic interventions.

Abbreviation: SOD-Superoxide Dismutase, Keap 1- Kelch-like ECH-associated protein 1, Nrf2- nuclear erythroid 2-related factor 2, GPx- glutathione peroxidase, (HO-1)-heme oxygenase- 1, NQO1- ADPH: quinone oxidoreductase 1.

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Conflict of Interest
There is no conflict of interest.

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