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SHORT REVIEW

An Overview of the Phytochemical and Pharmacological Profile of the Spurred Mangrove *Ceriops tagal* (Perr.) C. B. Rob

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Abstract

Plant-based natural compounds have played a significant role in developing a variety of clinically useful therapeutic agents. Mangroves are special salt-tolerant plant communities which are known to produce a range of natural products with unique pharmacological activities. An attempt has been made to review such properties in the mangrove plant *Ceriops tagal* (Perr.) C. B. Rob. belonging to the Rhizophoraceae family. This species is widely spread across the coastal lines of African, Asian and Australian continents and is also commonly found in India. Traditional healers have been using this plant and its extracts to treat ailments such as ulcers, diabetes and malaria. The plant is a rich source of phytochemicals such as tannins, flavonoids, terpenes, terpenoids, phytosterols and many more novel metabolites which have conferred remarkable pharmacological activities. Reports of antibacterial, antiviral, antioxidant, antifeedant, antifouling and anticancer activities from different parts of this plant highlight its importance as a natural remedy and the need to perform more investigations to discover novel bioactive compounds to further exploit its therapeutic potential.

Keywords: Anticancer, Drug Discovery, Ethnomedicine, Pharmacology, Phytochemistry, Tangal

1. Introduction

Plants have been used for treating many ailments by mankind for ages. They are considered to be a storehouse of raw materials in the form of phytoconstituents that can be used in modern medicines and there are relentless global efforts to discover such untapped resources. Plants, therefore, undoubtedly hold a prominent place in drug discovery programmes as a source of lead molecules. Since a large proportion of the human population still relies on the traditional, natural product-based healing system of medicine, Ethno-botany studies tend to provide vital clues in these challenging endeavours[1,2].

Mangroves are a group of halophytic plants that form communities along the coastal intertidal zones of more than 123 tropical and subtropical region countries[3]. They are of special interest since they perform crucial ecological (by providing wind and tidal breaks and protecting from natural calamities like floods and cyclones) and economical roles (as a source of timber, dyes, ethnomedicines, and natural products). They have specially adapted to live and thrive in extremely harsh saline conditions. To ensure their survival in such an abiotically stressful environment, they are known to produce many secondary metabolites with unique properties[4]. Mangrove plants can be classified into three categories viz. true mangroves, mangrove minors and mangal associates[5].

Ceriops tagal (Perr.) C. B. Rob. is a medium-sized, true mangrove species that belongs to the family Rhizophoraceae. Being a hardy and salt-tolerant species,

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it can be found distributed prolifically in different geographical regions such as along the coastal lines of Africa, Asia, Australia and the Pacific region[6].

The mainland of India is reported to have 40 species of mangroves of which 22 are reported from the state of Maharashtra[7]. Maharashtra state is present on the western side of India and is blessed with 720 km of coastline, bordered by the Arabian Sea. The mangrove forest ecosystem observed in the state is of the riverine fringe type. The state has successfully implemented a scientific program for the conservation of its mangroves and as per the report of the Forest Survey of India, has been able to increase the mangrove area from 186 sq. km in 2013 to 320 sq. km in 2019[8].

C. tagal is one of the most predominant mangrove species that is found along both the eastern and western coasts of India, as well as along all the coastal districts of Maharashtra state. Locals are known to use this mangrove mainly as a source of firewood, for building fences, and frames and for setting fish traps. The species is also said to be used in traditional folklore medicine to treat ulcers, heal wounds, and control hemorrhage[9].

The pharmacological significance of mangroves is well documented and these plants are known to have antimicrobial, piscicidal, insecticidal, cytotoxic, antioxidant, DNA damage protective, antiviral, antidiabetic, anti-reverse transcriptase, anti-inflammatory, analgesic, and antiulcer activities[5,10–16].

Considering the extensive occurrence as well as the ecological and economical significance of *C. tagal*, this article is written to stack the information which concerns the various phytochemical classes and compounds isolated from this plant along with the reported bioactivities to showcase its potential medicinal and therapeutic value.

1.1 Description

C. tagal normally grows to a height of around 2 to 6 m and has greyish brown coloured bark with stilt roots originating from the lower parts of the stem. Even though in extremely suitable environmental conditions, the species has been rarely found to reach a height of up to 15 m, the plant is largely categorized as a shrub or a small tree[6].

C. tagal is characterized by rounded, slightly elliptic, oblong shaped, glassy-green leaves and the white coloured, small-sized pendulous flowers which appear in clusters of 5-10 terminally (Figure 1). Flowering is generally observed from August to March. Fruits are small in size, club-shaped or ovoid, viviparous, and green in colour from

Figure 1. Photograph of *C. tagal* showing various parts **A)** fruits with protruding hypocotyl; **B)** flowering branches with leaves; **C)** small, white flowers which soon turn brown.

which first a seedling and then a warty, smooth hypocotyl grow while still on the tree and maturity, drops onto the muddy habitat to germinate and produce roots[17,18].

It does not grow well in water-logged soils and prefers aerobic muddy lands with good drainage. An interesting association has been observed between this mangrove and crabs. Older leaves of *C. tagal* dropped on muddy ground are usually fed by crabs. While doing so, they make small holes in the muddy ground to have a safe shelter which indirectly creates aeration in the mud helping the plant to proliferate efficiently[18,19].

1.2 Taxonomy and Common names

C. tagal has been scientifically classified as follows:
Kingdom: Plantae
Subkingdom: Viridiplantae
Infrakingdom: Streptophyta
Phylum: Tracheophyta
Subphylum: Spermatophytina
Class: Magnoliopsida
Superorder: Rosanae
Order: Malphigiales
Family: Rhizophoraceae
Genus: *Ceriops*
Species: *Ceriops tagal*

The genus got its name *Ceriops* from the Greek word *keros* which mean 'wax' and *–ops which means* 'resembling'. These two words are combined to describe the shiny wax-like thick substance present at the base of the stipules. This species *tagal* has its origin after its vernacular name in the Tagalog language of the Philippines where it is abundantly found[17,18].

Since the species has a widespread distribution along the East African, Southeast Asian Northern Australian and Western Pacific countries, it is known by numerous common names such as Tagal mangrove, Spurred mangrove, Indian mangrove, Chinese mangrove, Yellow mangrove, as well as by the region-specific vernacular names (Table 1).

This species has been listed by the International Union for Conservation of Nature as Least Concern[27]. However, it is uncommon in southern China and is considered endangered in Singapore. Being an important member of the mangroves, it is a protected plant by forest acts of many countries such as India and South Africa[18].

1.3 Local Uses

Since the wood of *C. tagal* shows hardly any permeability to water, it is extremely hard and resistant to boring pests. This wood is a good source of timber for constructing huts, boats, fences, railway sleeper berths, and paving blocks and is used as firewood fuel[6,20]. Charcoal is also manufactured from wood[10]. In the production process of particle boards, the bark extract is sometimes used to bind and hold the ingredients. The bark is a rich source of tannins and often finds its application in dyeing and tanning and for making batik prints; and is still a popular practice in Southeast Asian countries like Indonesia, Malaysia and the Philippines[27]. The concentrations of these natural dyes are manipulated to dye cotton clothes in various shades of yellow, brown and orange. It is also used as a natural coloring and flavoring agent while cooking the rice[28]. Attempts have been made to extract natural dyes from *C. tagal* that could have applications in textile industries[29]. To preserve the taste, to delay the fermentation of the wine or toddy prepared from coconut and also to impart a flavor, pieces of the dried bark of *C. tagal* are added in the Philippines. It is also believed to prevent the growth of spoilage microbes helping in food preservation[11]. The nutritional richness and high energy

Table 1. Vernacular names of *C. tagal*

Name of the Country	Local/vernacular Name(s)
Kenya, Tanzania, Mozambique (East African countries)	*Mkandaa*[20]
India Maharashtra state (Marathi language) West Bengal state (Bengali language) Gujarat state (Gujarati language) Andhra Pradesh state (Telugu language) Karnataka state (Kannada language) Kerala state (Malayalam language) Tamilnadu state (Tamil language) Odisha state (Odia language)	 *Kirkiri, Kirrari, Chauri*[21-23] *Math garan, Mat goran*[22,24] *Kanari*[23] *Gedara*[23] *Chowri, Kiraari*[23] *Kantal, Annakkantal, Mannakkantal*[22,23] *Pandikutti*[22] *Gari Goran*[22]
Myanmar	*Madame*[6]
Thailand	*Prong, Prong daeng, Samae*[6]
China	*Jiao guo mu, Hai jia zi, Jian zi shu*[25]
Malaysia	*Tengar, Tengah*[6,26]
Singapore	*Tengar putih*[6,26]
Philippines	*Magtongod, Pakat, Rungon, Tagasa, Tangal, Tanggal, Tangal lalaki, Tigasan, Tungod*[6]
Indonesia	*Tangar, Tanggala tutu, Tingih, Tingi, Palun, Parun, Bido-bido*[6,26]
Brunei	*Tengar*[26]
Vietnam	*Da voi*[6]
Cambodia	*Smerkrohorm, Same*[6,26]

contents of fruits and hypocotyls of *C. tagal* have been reported suggesting their use as a supplement in animal feed[30]. Fishermen in Africa, often apply a coat of an extract prepared from the bark of *C. tagal* to their fishing nets and sails to delay their decay. The tannin content is directly proportional to the age of the plant. Few Indian markets sell blocks and powders that are processed and prepared from the tannins extracted from *C. tagal*[18,19].

1.4 Traditional Ethnomedicinal Uses

Just like most other mangroves, *C. tagal* has also been used in traditional medicines. The bark of *C. tagal* finds its use as an astringent. As an alternative to quinine, its decoction is used for curing malaria and its decoction has also been used to treat hepatitis and diabetes in African as well as Asian countries such as Madagascar, Kenya, China, Thailand, and Philippines[30,31]. In Malaysia, a decoction prepared from the bark is administered to women during childbirth. It is believed to have haemostatic and obstetrical properties and therefore helps in wound healing[5]. Externally, it is used in lotions to treat malignant ulcers, eczema and abdominal ailments[24,32,33].

2. Phytochemical Reports

Owing to its widespread distribution, *C. tagal* has attracted the attention of scientists from various countries and there are several reports about the presence of numerous primary and secondary metabolites in this mangrove plant. Some researchers conducted only preliminary qualitative analysis to identify the phytoconstituent class, whereas others were successful in isolating and structurally characterizing pure molecules from various parts of this plant.

Sudheer, *et al.*, carried out a preliminary phytochemical analysis of the aqueous extracts of *C. tagal* and reported the presence of alkaloids, flavonoids, polyphenolics, cardiac glycosides, saponins, and sterols. Researchers also separated these classes using High Performance Layer Chromatography (HPLC) and generated a fingerprint[34].

80% methanol extracts from leaves and stems of *C. tagal* (from Mandavi River, Goa) were prepared using the soxhlet apparatus and were subjected to qualitative and quantitative detection of various classes of secondary metabolites. Relatively more phytochemicals were observed in extracts prepared from the leaves. The highest numbers of peaks were recorded for flavonoids and bitter principles. Essential oils and saponins were intermediate, while anthraglycosides and terpenoids were present in the least amounts. Alkaloids and phenol carboxylic acids were not detected[35].

Healthy leaves of *C. tagal* from the Bhavanapadu creek area, Tekkali, Andhra Pradesh, were used to prepare methanol extracts which were screened for qualitative and quantitative phytochemical analysis. Phenols were found to be the most abundant phytoconstituent, followed closely by flavonoids. Tannins and alkaloids were recorded in relatively lower concentrations[36].

The presence of phytochemical groups in C. *tagal* extracts prepared in nine different solvents was analyzed from samples from a forest in Kakinada, Andhra Pradesh[37]. Qualitative analysis indicated the presence of all nine phytochemicals viz. alkaloids, anthraquinones, phenols, tannins, saponins, steroids, glycosides, flavonoids, and terpenoids in the extracts prepared in methanol. This was followed by water, acetone, and chloroform extracts which were able to extract seven phytochemical classes.

Basco, *et al.*, carried out a qualitative analysis of eight phytoconstituents present in the ethanol extract prepared from the bark of *C. tagal* collected from the Philippines. Out of the eight classes investigated, flavonoids, tannins, and cardiac glycosides were the three classes detected in the extract[28].

Methanol extract prepared from the leaves of *C. tagal* (Sundarban forest, Bangladesh) was fractionated and three different extracts (hexane, chloroform and aqueous) were analyzed for the existence of phytoconstituents[38]. Results showed the presence of carbohydrates, reducing sugar, and glycosides in all three extracts whereas saponins and alkaloids could be observed in the majority of the studied extracts. Anthraquinone glycosides, cardiac glycosides and resins were detected in the aqueous extract. Only chloroform extract indicated the presence of tannins.

Ranjana and Jadhav studied the phytochemicals present in the soxhlet-prepared methanol extract of leaves of three mangrove plants viz. *C. tagal, Bruguiera cylindrica*, and *Salvadora persica*. The place of collection was Gorai Creek, near Mumbai, India. The result showed that *C. tagal* did contain all the twelve phytoconstituents analyzed suggesting the richness of secondary metabolites in this plant[39].

Tongco, *et al.*, prepared extracts from the wood and bark of Philippine *C. tagal* using acetone and water mixture as a solvent in the soxhlet apparatus and analyzed the Total Phenolic Content (TPC) in these extracts using spectrophotometric analysis. Researchers reported a TPC

of 141.86 mg gallic acid equivalent/100 g in the wood extracts and 181.91 mg gallic acid equivalent/100 g in the bark extracts of *C. tagal*[40].

Several novel compounds such as tagalsins, dolichol, cerioptins, tagalons, cereotagalols, lupeol, betulin etc. have been isolated and characterized from various parts of *C. tagal* by researchers from countries such as China, Thailand, Indonesia, and India as summarized in Table 2[41-64]. A perusal of the literature indicates that *C. tagal* is rich in metabolites structurally related to the classes of tannins, terpenoids, steroids (phytosterols), and flavonoids like phenolic compounds[65] . *C. tagal* has been especially rich in Dolabrane which is a sub-type of diterpenoids and reports indicate the isolation of forty-five unique dolabranes from this plant, many of which are having novel bioactivities[46]. The chemical structures of a few important bioactive molecules reported from *C. tagal* have been shown in Figure 2.

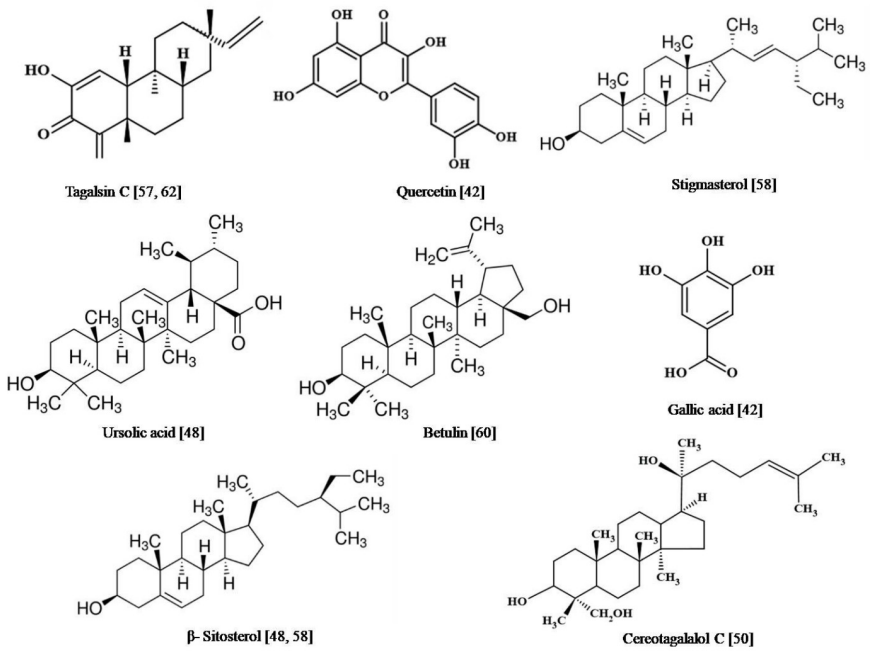

Figure 2. Representative compounds of pharmacological significance isolated from *C. tagal*.

Table 2. Molecules and phytochemical classes reported from *C. tagal*

Sr. No.	Compound Isolated and Class	Part Used	Place	Reference
1.	Dolichol (polyisoprenoid)	Leaves	N. Sumatra Province, Indonesia	41
2.	Gallic acid and quercetin (phenolic compounds)	Aerial leaves	Middle Andaman island, India	42
3.	Tagalphenylpropanoidins A and B (phenylpropanoids), 2,3,6-tri methoxy-5-(1-propenyl) phenol (first time from *C. tagal*)	Stems and twigs	Hainan Island, China	43
4.	Tagalenes J and K (dolabrane diterpenes), plus eleven known analogues (like Tagalene I, tagalsins P, Q, T, S, X etc.)	Stems and twigs	Hainan Island, China	44
5.	Two novel compounds, cerioptins A-B, plus seven known compounds (mainly di- and tetraterpenoids)	Stems	Nizampatnam sea coast,	45
6.	Tagalide A and tagalol A (dolabrane type diterpenes)	Stems, twigs	Hainan island, China	46
7.	Tagalons A-D (diterpenes), tagalene I, 4-epitagalene I and tagalsins A- B (dolabrane type diterpenes)	Stems and twigs	Hainan island, China	47

(*Continued*)

Table 2. (Continued)

Sr. No.	Compound Isolated and Class	Part Used	Place	Reference
8.	Twelve compounds - Stearic acid, betulin, β-hydroxy betulinic acid, ursolic acid, palmitic acid, β-sitosterol, upeol (mainly terpenes, triterpenoids)	Leaves	South Andaman, India	48
9.	Three new dolabranes, tagalenes G-I, plus five known analogues (like tagalsin Q, tagalsin S etc.)	Twigs	Hainan Island, China	49
10.	Cereotagalol C and D (dammarane triterpenes)	Leaves	Hainan, China	50
11.	Tagalsine X, plus five known analogues like tagalsin P, tagalsin Q etc.(dolabrane dinorditerpene)	Leaves	Haikou City, Hainan Province, China	51
12.	Two new dolabranes, tagalsins V and W, plus 10 known terpenes	Aerial parts	Hainan Island, China	52
13.	Proanthocyanidins (tannins)	Mature leaves	Dongzhai harbor, Hainan, China	53
14.	Dolabr-4(17),15(16)-dien-3-one, isopimar-8(14)-en-15,16-diol, isopimar-8(14)-en-16-hydroxy-15-one, lupeol, and lup-20(29)-en-3β,28-diol and lup-20(29)-en-3β-hydroxy-28-oic acid (Terpenoids)	Roots	Zanzibar, Tanzania	54
15.	3a-O-transferuloylbetulinic acid, 3a-O-transcoumaroylbetulinic acid, and 3b-Ocis-feruloylbetulin (lupane-type triterpenes) plus 10 known triterpenes	Aerial parts	Wenchang City, Hainan Province, China	55
16.	Tagalsins P-U (novel dolabranes), plus seven structurally pre-known dolabranes, along with an abietane, and a pimarane	Stems and twigs	Hainan Island, China	56
17.	Tagalsin O (a novel dolabrane), plus six known molecules tagalsins A-C, E-G (diterpenes)	Aerial parts	Wenchang City, Hainan Province	57
18.	Diterpene methoxy-ent-8(14)-pimarenely-15-one plus three pre-known molecules, ent-8(14)-pimarene-15R,16-diol, stigmasterol and β-sitosterol (Steroids)	Roots	Hainan Province, China	58
19.	Isopimar-8(14)-en-16-hydroxy-15-one, isopimar-8(14)-en-15,16-diol, and erythroxyl-4(17),15(16)-diene-3-one (diterpenes)	Roots	Maruhubi Mangrove Reserve, Zanzibar, Tanzania	59
19.	Betulin, 3-epi-butulinic acid, 3-epi-betulinic acid acetate, and 3 *β*(E)- feruloyllupeol (novel pentacyclic triterpenes)	Embryo	Sanya city, Hannan province, China	60
20.	tagalsin F (diterpenoid)	Roots	Nakhon Si Thammarat province, Thailand	61
21.	Seven novel dolabranes, Tagalsins A-G (diterpenes) and a nor-diterpene - tagalsin H	Stems and twigs	Hainan Island, China	62
22.	Tagalsins I and J (bisdolabrane-type tetraterpenoids)	Stems, twigs	Hainan Island, China	63
23.	Cereotagaloperoxide, cereotagalol A, and cereotagalol B (dammarane triterpenes), plus four pre-known dammarane type triterpenoids, an oleanane type triterpene, and 13 known lupane type triterpenes	Hypocotyls and fruits	Nakhon Si Thammarat Province, Thailand	64

Indian scientists have primarily been involved in qualitative analyses of various classes of phytochemicals derived from local mangroves, including *C. tagal*. However, there are a few investigations that report the isolation and characterization of unique compounds from this plant.

Sachithanandam, *et al.,* isolated two pure compounds viz. gallic acid and quercetin from the leaves of *C. tagal* collected from the middle Andaman islands, India. Gallic acid belongs to the class of phenolic compounds whereas quercetin is a well-known flavonoid. Both the molecules

have also been previously reported from a few other species of mangroves and are well documented for their diverse range of bioactivities[42].

Two novel metabolites viz. cerioptins A and B were reported from the stems of *C. tagal* collected from the Nizampatnam coastal area, Andhra Pradesh. Researchers also isolated seven other metabolites which were structurally already known and mainly belonged to diterpenes and triterpenoid classes[45].

Lakshmi, *et al.,* subjected the leaves of *C. tagal* (from the south Andaman Islands, India) to ethanol extraction followed by repeated chromatographic solvent fractionation (hexane and chloroform) and purification to characterize twelve compounds. These compounds mainly belonged to the classes of terpenes, terpenoids, triterpenoids, steroids, and steroid glycosides[48].

3. Pharmacological Importance

Clear evidence supports the proposition of considering *C. tagal* for isolating and characterizing novel bioactive molecules of pharmacological significance.

3.1 Antimicrobial Activity

Infections caused by different types of microorganisms such as bacteria, viruses, fungi, etc. result in millions of deaths worldwide and pose a serious threat. Despite the availability of hundreds of synthetic drugs against such pathogens, the development of resistance to such antimicrobial agents (especially against antibiotics) has been making the matter worse. Plant-derived products have emerged as a promising answer to these challenges.

Diterpenes isolated from the root extracts of *C. tagal* prepared in chloroform exhibited significant antibacterial activity against four of the ten bacterial strains screened. Gram-positive bacteria were more sensitive to diterpenes than Gram-negative bacteria[59].

During the trials carried out under cultured conditions in Cochin (India), the aqueous extract of *C. tagal* exhibited a prophylactic effect on the giant tiger shrimp *Penaeus monodon* against the White Spot Syndrome Virus (WSSV). Shrimps which were administered with the extract under study were observed to be devoid of the deadly virions. Out of the seven mangrove species investigated, since only *C. tagal* was found to be effective, it suggests that this mangrove plant could act as a promising candidate for discovering novel antiviral compounds[34]. Researchers corroborated these findings using gene expression and histological studies[66].

Arivuselvan, *et al.,* evaluated the antibacterial effects of aqueous, acetone, methanol, and ethanol extracts of *C. tagal* on five different human pathogens[67]. Results indicated a promising antimicrobial activity against the studied pathogens. Methanol extracts were shown to exhibit better inhibition suggesting that methanol could be the preferred solvent for extracting the active ingredient for future bioactivity studies.

The antimicrobial activity of leaf and bark extracts of *C. tagal* was investigated against five different bacterial species belonging to the *Aeromonas* and *Vibrio* genera. All were known pathogens of fish and shrimp species[68] . The efficacy of methanol extract was found to be the highest whereas acetone extracts exhibited the least potency against the test bacteria. The activity against *V. alginolyticus* was found to be at par with the standard antibiotic drug streptomycin which was used as a control for comparison purposes.

Extracts were prepared using the stem of *C. tagal* in seven different solvents and studied for their possible antibacterial effects on five drug-resistant and three drug-sensitive bacterial strains. Encouraging antibacterial activity was reported against the chosen clinical pathogens. Gram-positive bacteria were observed to be more susceptible to the crude extracts. Methanol extract was found to be the most potent in this study as well, followed by ethanol, aqueous, and acetone extract[37].

Lotlikar and Naik - Samant screened the crude extracts prepared from the leaves of *C. tagal* in distilled water, ethanol, and methanol against four human pathogens (two Gram-positive and two Gram-negative bacterial species). Extracts prepared in distilled water failed to exhibit any inhibitory activity whereas methanol extracts were found to be most effective followed by ethanol extracts. *Staphylococcus aureus* and *Bacillus subtilis* (Gram-positive) were highly susceptible while *Klebsiella pneumonia* (Gram-negative) was found to be highly resistant[69].

The antibacterial and antifungal potential of the methanolic extract of *C. tagal* leaves fractionated into hexane, water and chloroform were evaluated by Bulbul, *et al*[38]. However, surprisingly, the extracts failed to show any zone of inhibition against the eleven bacterial and three fungal strains selected as the test organism. The reasons could be attributed to the possibly low concentration of the bioactive compounds or the inefficiency of the selected

solvents to dissolve and extract the active secondary metabolite.

Tongco, *et al.,* reported promising antifungal activities of bark and wood soxhlet extracts of *C. tagal*. Researchers reported that the extract prepared from the bark was more potent against the tested fungal pathogen i.e., *Lasiodyplodia theobromae* and suggested that this activity was attributed to the phenolic compounds which were found in those samples. This study is of significance since it indicated that *C. tagal* extracts could be processed and natural wood preservative agents could be prepared from them[40].

3.2 Anti-diabetic Activity

Diabetes mellitus is a disorder caused by metabolic malfunction and is characterized by hyperglycemia arising mainly due to a deficiency of the hormone insulin. It is one of the most common diseases worldwide, affecting more than a billion individuals. It is projected to be one of the deadliest slow-killer diseases in the coming years[70]. Mangrove plants are well known for their anti-diabetic potential and *C. tagal* is no exception. It is already in use in traditional medicines to treat elevated blood sugar levels in diabetes[71]. There are few scientific investigations which highlight its possible role in treating diabetes[16,72].

Extract prepared from the leaves of *C. tagal* in ethanol was administered *in vivo* to normoglycemic rats and it was observed that the tolerance to glucose, post the sucrose load improved significantly. The extract was then orally administered to STZ-induced diabetic rats at a dosage of 250 mg/kg and was also found to be effective in controlling blood sugar levels. The extract was further fractionated and the hexane fraction exhibited potent anti-hyperglycemic activity comparable with a standard drug[73].

In another study, a similar n-hexane fraction isolated from processing the ethanol leaf extract stimulated the uptake efficiency of glucose molecules in L6 muscle cells in a dose-dependent manner, which was at par with the drug metformin used regularly to treat hyperglycemia suggesting novel anti-hyperglycemic agents could be isolated from *C. tagal*[74].

Lawag, *et al.,* evaluated the α-glucosidase inhibitory effect of six Philippine plants including *C. tagal*[75]. *α*-glucosidase inhibitory molecules are important in fighting diabetes as they delay the liberation of glucose post meal, retarding the glucose assimilation and thus help in reducing the postprandial plasma glucose levels. Researchers reported that the aqueous ethanolic extracts prepared from *C. tagal* bark, have *α*-glucosidase inhibitors and therefore exhibit anti-hyperglycemic activity.

Since Protein Tyrosine Phosphatase enzymes (better known as PTPases) are believed to be involved in the etiology of diabetes mellitus, their inhibition can give insights into the anti-diabetic activity of the test compounds. Lakshmi, *et al.,* evaluated the PTPase inhibitory activity of the crude extract, fractions prepared in three solvents, and twelve different compounds isolated from the hexane fraction. All the extracts, fractions, and molecules showed promising inhibitory activity. Four compounds showed more than 90% inhibition, clearly indicating that *C. tagal* has potential in the field of anti-diabetic drug discovery[48].

Ranjana and Jadhav prepared the extracts using leaves of three different mangroves in four solvents and assays were carried out to check the Inhibition of α-amylase and α-glucosidase. The results were used to interpret the anti-diabetic potential. Among the chosen mangrove species, *C. tagal* leaf extracts exhibited highly potent anti-diabetic activity with the highest percent inhibition and lowest IC_{50} values for both assays[39].

3.3 Anti-oxidant Activity

Free radicals can damage the human body by playing a role in various health ailments such as cancer, cardiovascular diseases, stroke, and other aging-related diseases. Anti-oxidants are substances that protect our cells and thereby our body from the potential damage of such harmful free radicals. Antioxidant activity is generally analyzed in terms of 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity wherein the anti-oxidants present in the sample react with DPPH and cause a change in colour which can be spectrophotometrically detected and correlated quantitatively.

Pharmacological studies carried out in a mangrove forest in Thailand reported that the young pods of *C. tagal* exhibited promising antioxidant activity with ED_{50} of 6.67 µg/ml. This has an added significance since the young pods are edible and therefore can be consumed as a cheaper and easily available source of antioxidants[76].

Jadhav, *et al.,* studied the DPPH free radical scavenging activity of the methanol extract of *C. tagal* prepared using soxhlet apparatus[35]. Results showed that both the stem and leaf extracts possess antioxidant activity. The stem extract exhibited superior DPPH scavenging activity (IC_{50} of 19.98 µg/ml) than the leaf extract (IC_{50} 29.97

µg/ml). However, since a crude extract was used in the investigation, both these values were much lower than the standard ascorbic acid which showed an IC_{50} of 11.65 µg/ml. A reducing power assay was also carried out to find the presence of possible reductant in the extracts that can break the free radical chain and exhibit antioxidant activity. The reducing assay for the transformation of Fe^{3+} – Fe^{2+} s showed an increase in absorbance with the increasing concentration confirming the presence of reducing agents with anti-oxidative activities.

Kiran Kumar, *et al.,* undertook various enzymatic assays (viz. superoxide dismutase, catalase, peroxidase, and glutathione reductase) to investigate the anti-oxidative potential of the leaf extracts of eight different mangrove plants[36]. These enzymes are believed to be produced by plants to protect the cellular oxidative damage by controlling the Reactive Oxygen Species (ROS). Encouraging superoxide dismutase and catalase activities were shown by the *C. tagal* extracts with 1.75 ± 0.01 units per mg of proteins and 2.10 ± 0.01 H_2O_2 decomposed per mg of protein per min respectively. These values were at par with the extracts of other mangrove species analyzed indicating that *C. tagal* has an anti-oxidant activity which can be further improved by purifying the crude extracts.

Zhou, *et al.,* fractionated and purified tannins present in the leaves of *C. tagal* and tested the isolated procyanidins for their antioxidant activities using DPPH scavenging capacity and Ferric Reducing Antioxidant Power (FRAP) assay. All thirteen sub-fractions exhibited highly potent antioxidant activities, indicating that purification of specific phytoconstituents from the crude extracts could increase the activity several folds[53].

Promising anti-oxidant activity of *C. tagal* bark extract was reported in terms of 93% DPPH scavenging activity at an effective concentration (EC_{50}) of 7.05 ppm as compared to that with the standard ascorbic acid at an effective concentration (EC_{50}) of 2.55 ppm[28].

Septiana, *et al.,* analyzed the certain phytochemicals present in the leaves of *C. tagal* collected from the RAWN mangroves Park, Indonesia and correlated them as a source of antioxidants. The leaves of *C. tagal* were found to contain an anthocyanin content of 0.068%, alkaloid content of 0.046%, a tannin content of 23.53% and the vitamin C content of 21,682 mg/100g. Researchers suggested that the high content of tannin and vitamin C in *C. tagal* leaves could serve as a food source and thereby as a habitat for the endemic buffalo *Bubalus* sp[77].

3.4 Antifeedant activity

There are a couple of reports that suggest that compounds isolated from *C. tagal* have encouraging effects against the pest insects which can dissuade these pests from feeding on their target plant hosts.

Brontispa longissima is a type of leaf beetle that feeds on young leaves and also causes significant damage to seedlings and mature coconuts and other palms. Hu, *et al.,* have reported that unique dolabrane-type molecules from *C. tagal* possess moderate antifeedant effects against the larvae of this pest beetle[56]. So such molecules could be used to deter the pest insects and prevent huge economic losses.

Similarly, three diterpenoids were characterized from the ethanol extract of stems of *C. tagal* which showed their capabilities of deterring the red floor beetle from feeding and spoiling the stored grains and cereals. Tagalsin A, B, and H showed strong feeding deterrent activity against the destructive adults of *Tribolium castaneum* beetles[78].

3.5 Anti-fouling Activity

Biological fouling is a major nuisance which results from the accumulation of various microorganisms, algae, plants or smaller animals on unwanted objects and places such as water inlets, pipes, roots and stems of marine plants, ponds, and rivers. Marine organisms cause fouling by accumulating and growing on materials that are submerged in seawater. Barnacle (*Balanus albicostatus)* infestation is a serious concern in the marine waters of East Asian countries and need timely attention. The majority of commercial synthetic anti-fouling compounds suffer from their toxic side effects which could be addressed by plant-based natural products.

Novel diterpenes and steroids isolated and characterized from the roots of *C. tagal* collected from Hainan Province, China were tested against the cyprid larvae of *B. albicostatus* by settlement inhibition assay. The results were highly promising as all four molecules showed anti-fouling activity. Terpene-based molecules were much more potent than their steroid partners. At the same time, they showed negligible toxicity against the sub-adult cyprids suggesting they were more effective against the larvae of the fouling crustaceans[58].

Forest departments of various nations have been carrying out mass plantations of mangrove plants for conservation and eco-restoration purposes. However, such mangrove seedlings planted in saline soils are known

to be facing the problem of barnacle infestation[27]. So it is recommended that more of such anti-fouling agents could be discovered from *C. tagal*.

It is therefore suggested that *C. tagal* extracts could be further purified to discover novel molecules that can deter feeding and destruction caused by herbivorous pests and fouling organisms.

3.6 Cytotoxic and Anticancer Activity

Since the last decade, *C. tagal* has fascinated researchers for its cytotoxic and anti-cancer properties and there are many reports involving both the crude extracts as well as the unique compounds that highlight these activities as summarized in Table 3.

Table 3. Anticancer/cytotoxicity studies of novel compounds/extracts of *C. tagal*

Active Compound / extract tested	Type of model cell lines/ organisms and method used	Result	Reference
Dolichol	Human colon cancer cell culture (WiDr cells) Flow Cytometry, RT-PCR	Induction of G0/G1 arrest Upregulation of p53 gene expression, downregulation of EGFR, PI3K, Akt, and mTOR gene expression. Growth inhibition of WiDr	41
Gallic acid and Quercetin	HeLa (human Cervical carcinoma cell line) and MDA-MB-231 (human Breast carcinoma Cell line) MTT Assay	IC_{50} of gallic acid (HeLa: 4.18 ± 0.45 mg/ml; MDA-MB-231: 80.04 ± 0.19 mg/ml at 24 h) and quercetin (HeLa: 99.9 ± 0.18 mg/ml; MDA-MB-231: 18.29 ± 0.12 mg/ml at 24 h)	42
Tagalenes I, J and K, ent-5α,3,15-dioxodoIabr-1,4(18)-diene-2,16-diol (4), Tagalsin P, T, S, Q	SW480, MCF-7, HepG2, Hela, and PANC-1 carcinoma cell lines MTT assay	IC_{50} values of ent-5α,3,15-dioxodoIabr-1,4(18)-diene-2,16-diol in SW480, HeLa and PANC-1 were 27.7, 22.2, and 17.6 μM, respectively.	44
Tagalide A, tagalol A (Dolabrane-type diterpenoids)	human breast carcinoma cell lines MTT Assay	Tagalide A IC_{50} values were 1.73, 8.12, 2.45, 12.03, 3.75, and 1.97 μM respectively in MDA-MB- 453, MDA-MB-231, SK-BR-3, MCF-7, MT-1, and ZR-75-1 cells. Induced G2/M arrest and apoptosis in a dose- and time-dependent manner. Tagalog A was inactive.	46
Polyisoprenoids	WiDr colon adenocarcinoma cell line MTT Assay, Cell cycle analysis by Flow Cytometry, Immunocytochemistry studies	IC_{50} 276±9.54 μg/ml A dose-dependent inhibitory effect on WiDr cells was observed after 24 h of treatment. G0/G1 arrest in cells treated with poly isoprenoids Polyisoprenoids also downregulated Bcl-2 and cyclin D1 expression in WiDr cells	79
Tagalons A and B, Tagalons C and D, tagalene I	human ovarian carcinoma cell line A2780, hepatoma BEL7402, two colon cancer cell lines, six human breast carcinoma cell lines MTT Assay	Tagalons C and D IC_{50} values of 3.75 and 8.07 μM in human breast cancer cell line MT-1; tagalene I IC_{50} values 8.97, 8.97, 4.62, and 3.93 μM in human breast cancer cell lines, MDA-MB-453, MDA-MB-231, SK-BR-3, and MT-1 respectively	47
Crude methanol -soxhlet extract from the fruits	MDA-MB-231(breast carcinoma) HCT116 (colon carcinoma) MTT assay	IC_{50} of 50.57μg/ml and 38.51μg/ml in MDA-MB-231 and HCT-116 respectively.	80
Cereotagalol C and D (dammarane type triterpenes)	A549, HepG2, HCT-116 and CNE-2 cell lines MTT assay	Cereotagalol C and D IC_{50} values of 29.7 and 37.2 μM in HCT-116 and CNE-2 respectively.	50

(*Continued*)

Table 3. (Continued)

Tagalsine X, Tagalsin P and Q, plus (5*S**, 8*S**, 9*S**, 10*R**, 13*S**)-2-hydroxy-16-nor-3-oxodolabr-1,4(18)-dien-15-oic acid	Human cancer cell lines (CNE-2, HCT-116, HepG2and A549) MTT assay	only (5*S**, 8*S**, 9*S**, 10*R**, 13*S**)-2-hydroxy-16-nor-3-oxodolabr-1,4(18)-dien-15-oic acid showed significant cytotoxicity against CNE-2, HCT-116, HepG2 and A549 cell lines with IC_{50} values of 13.57, 42.32, 11.21 and 15.23 μM, respectively	51
Crude Ethanol extract from the bark	Nauplii of brine shrimp (*Artemia salina*) Brine shrimp lethality test	Moderate cytotoxicity against *A. salina* at 425 ppm.	28
Tagalenes A–F plus 10 known analogues like Tagalsins A, C–H, Tagalsin O	A549 (human lung adenocarcinoma cell line), A2780 (human ovarian cancer cell line), HCT-8 (human colorectal carcinoma cell line), Bel7402 (human hepatoma cell line) and BGC823 (human gastric carcinoma cell line) MTT assay	Seven compounds showed potent cytotoxicity. Tagalsin C was the most potent molecule with IC_{50} of 3.51 - 13.57 (μM) against A549/T: taxol-resistant human lung adenocarcinoma cells, KB/VCR: vincristine-resistant human oral squamous carcinoma cells, K562/Adr: adriamycin-resistant human leukemic cells, MCF/Adr: adriamycin-resistant human breast cancer cells, HCT-8/V: vincristine-resistant human colorectal carcinoma cells, PATU-8988/FU: 5-fluorouracil-resistant human pancreatic cancer cells.	81
Eleven different Tagalsins	acute T cell leukemia cell lines Jurkat, SupT1, Molt-4 and CEM, the human myeloma cell lines U-266 and RPMI-8266, and the Hodgkin lymphoma cell lines L1236 and KM-H2 Flow cytometry, Comet assay, Western blotting	Tagalsin C EC_{50} at around 1 μM in all the cell lines Tagalsins TA, TB, TE, TF, and T10 EC_{50} on Jurkat T cells at 10-20 μM Tagalsin C induced S-G2 arrest in leukemic cells	82
Dolabr-4(17),15(16)-dien-3-one, isopimar-8(14)-en-15,16-diol, isopimar-8(14)-en-16-hydroxy-15-one, lupeol, lup-20(29)-en-3β,28-diol, lup-20(29)-en-3β-hydroxy-28-oic acid	Caspase-3 enzyme-based Colorimetric Assay	All compounds activated Caspase-3, suggesting all have apoptosis-inducing potential.	54
Tagalsin O, Tagalsin A - G	human cervical cancer cell line HeLa Microculture Tetrazolium Assay	Tagalsin O IC_{50} - 27.3 μM, tagalsin E IC_{50} - 30.5 μM, tagalsin G IC_{50} -22.3 μM. tagalsin C IC_{50} - 5.0 μM	57
Betulin , 3-epi-butulinic acid, 3-epi-betulinic acid acetate and 3β-(E)-feruloyllupeol (tripterpenes)	human liver carcinoma cell line (H-7402), human B-lymphoblastoid cell line (Raji), and human cervical carcinoma cell (Hela) MTT assay	Betulin and 3-epi-betulinic acid acetate inhibited cell proliferation in H-7402 (IC_{50} 14.42 mg/ml and 9.97 mg/ml respectively) and Hela (IC_{50} 11.84 mg/ml and 11.32 mg/ml). No compound inhibited the cell proliferation of Raji.	60
Cereotagalol A-B , 3β-*E*-feruloylbetulinic acid, dammarane - oleanane and 13 known lupane triterpenes	human oral epidermoid carcinoma cell line (BC), human breast cancer cell line (KB), and human small cell lung cancer cell lines (NCIH187) Colorimetric method	3β-*E*-feruloylbetulinic acid IC_{50} of 3.8, 3.0, and 1.8 μg/ml in KB, BC, and NIC-H187 cell lines respectively	64

As seen in Table 3, compounds isolated from C. *tagal* have been found to have anti-cancer effects in many cancer cell lines such as cervical, breast, colon, ovarian, colorectal, hepatoma, leukaemia, myeloma, small cell lung cancer, oral epidermoid carcinoma, Hodgkin lymphoma and a few more, indicating the broad spectrum anticancer activity displayed by the *C. tagal* derived extracts and compounds[41,42,44,46,47,50,51,54,57,60,64,79-82]. The majority of the research articles report only the cytotoxic potential (in terms of % inhibition) of the compounds and extracts of *C. tagal* and very few have identified their mechanism of action in cancer cells.

There are a few studies using animal xenograft models wherein mice were administered with the molecule tagalsin isolated from *C. tagal*. Tagalsin C administered at a dose of 50 mg/kg via the intraperitoneal route in mice, significantly reduced the *in vivo* tumor growth of human CEM T cell leukaemia xenografts[82]. Reports indicate that the molecule significantly inhibited the growth of H22 hepatoma cells in mice. RT-PCR and other studies suggested that the mechanism of this anti-tumor effect of tagalsin could be attributed to the up-regulation of p53 / caspase-3expression and down-regulation of the Survivin/ BCL-2 gene expression[83,84].

Artemia salina (commonly called brine shrimp) is a small marine crustacean that is considered a model organism for preliminary cytotoxicity studies. These are performed by the Brine Shrimp Lethality Assay (BSLA). These models are useful as they provide a general indication of the cytotoxic potential of the test compound (crude extract or the isolated molecule) and therefore BSLA is recommended for a quick initial screening[85]. There are many studies which report the toxicity of mangrove extracts against brine shrimps[86-88]. However, surprisingly, only a single study has been done using *C. tagal* extract[28]. Researchers in the Philippines, calculated the LC_{50} of *C. tagal* extracts as 425 ppm based on the mortality rate of *A. salina* nauplii exposed to different concentrations of *C. tagal* extracts and based on the value, reported this crude extract to be moderately toxic. As this assay is easy to perform, rapid and cost-effective, it is recommended that it could be carried out using a variety of mangrove extracts including *C. tagal*. This will give a better understanding of the cytotoxic potential of the extracts prepared in various solvents which will help in the identification of the solvent or extract that shows better potency for undertaking actual cytotoxicity studies using cancer cell lines.

A correlation between the presence of plant-based secondary compounds such as terpenoids, phytosterols, flavonoids and related phenolic compounds and a range of bioactivities has been well documented. There are numerous reports which highlight their potential pharmaceutical applications[89-94]. The pharmacological activities of *C. tagal* extracts can therefore be attributed to the presence of these phytochemicals in *C. tagal*.

4. Conclusion and Future Directions

This review indicates that the spurred mangrove species, *Ceriops tagal*, possesses tremendous potential for extracting pharmacologically novel compounds.

Various classes of phytochemicals such as di-, tri- and tetra-terpenoids, tannins, steroids, flavonoids, etc., have been already structurally characterized from this plant, many of which novel secondary metabolites and compounds have been reported to exhibit an array of biological activities.

The bioactivity of these molecules can be further enhanced by coupling them with synthetic analogues to develop new derivatives which can then be used as the lead molecules in future drug discovery and screening processes.

More efforts and initiatives to study ethnobotany and ethnopharmacology, by interacting and gathering information from the locals are required to create a traditional knowledge-based database which can be evaluated further with scientific screening methods.

Since this mangrove has been routinely used for healing wounds and treating ulcers, *in vivo* studies in animal models are warranted to corroborate the claim made by traditional knowledge healers.

There is a dearth of information about the isolation, structural elucidation and biological activity of mangrove-based natural products from the state of Maharashtra, India. Current global trends indicate that nanoparticle formulations using mangrove extracts as well as the endophytic bacteria and fungi isolated from mangroves exhibit promising bioactivity. Hence, such studies are warranted on mangroves, especially from Maharashtra.

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