

## Bioprospecting Mangrove Plants for Novel Anticancer Compounds

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### ABSTRACT

Plant based phytoactive compounds are attracting the worldwide attention due to their natural origin, and curative potential. The tremendously diversified, and extreme environmental conditions of mangroves make them novel sources of various phytochemicals that have immense potential to cure a range of diseases, and dreadful cancer too. Especially endophytes of mangroves are treasure chests for bio-prospecting novel anti-cancer agents. Bio-prospecting for new anti-cancer agents is the need of hour to overcome the problem of drug resistance raised by the cancer cells. The present review is mainly focused on various bioactive compounds obtained from mangrove ecosystems.

**Keywords** Mangroves, Phytochemicals, Bio-prospecting, Anti-cancer agents.

### INTRODUCTION

Mangroves, the halophytic plants owing to their extreme environmental conditions have always gained special attention of researchers. They come under salt-tolerant ecosystems and are mainly found in tropical and subtropical regions along coastal margins (Bandaranayake 2002). Around one quarter of the world's coastline is occupied by the mangrove ecosystems spreading in more than 100 nations covering a stretch of 69,884 square miles across the world (Spalding *et al.* 1997). They are highly productive and diversified ecosystems among other kinds of ecosystems (Twilley *et al.* 1996, Chanda *et al.* 2016, Kumar *et al.* 2014) and acts as bridges between fresh and marine ecosystems (Chapman 1976). The extreme environmental conditions prevailing in the mangrove ecosystems allow them to survive under stressful environments viz., high salinity, high moisture content and tidal upsurges. There are different classifications of mangroves such as true mangroves and semi-mangroves (Wu *et al.* 2008), other classification includes major and minor mangrove sp., and mangrove associates (Tomlinson 1986). The major mangrove sp. and true mangroves are one and the same. The semi mangrove varieties are localized at earthbound marginal areas that are exposed to irregular flood tides (Wu *et al.* 2008).

The diverse plant species of the mangrove ecosystems have been used for therapeutic purposes for ages, owing to their rich wealth of bioactive compounds. In recent years, plant-based curative agents have gained greater significance in the field

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of medicine for their ability to treat several disorders along with diseases of chronic nature. Mangroves, because of their unique environs, develop specialized physiological processes for their survival, and for propagation. Such processes results in the production of various secondary metabolites in mangrove plants which can have therapeutic potential. Many of the mangrove plants found to use in traditional medicine (ethnomedicine) as they proved to have strong inhibitory activities over a range of pathogens (Saranraj and Sujitha 2015, Prabhu and Devaraj 2016). Metabolites from mangroves and their associates that belong to various classes have been isolated, identified, and studied for their efficacy. These can be obtained from different mangrove plant parts such as leaves, bark, stem, roots, flowers, and include alkaloids, flavonoids, carotenoids, carbohydrates, amino acids, alcohols, various fatty acids, phenolic compounds, hydrocarbons, saponins, terpenes, tannins (Bandaranayake 2002, Reddy and Grace 2016). Wu *et al.* (2008) reported that mangrove species produce around 349 different metabolites, of which 200 are reported from true mangroves. These are secondary metabolites with pharmacological, ecological and toxicological importance (Bandaranayake 2002). Different mangrove species harbor different bioactive principles. *Acrosticum aureum* and *Rhizophora apiculata* are rich in terpenoids and steroids. Long-chain alcohols and triterpenes are obtained from *Acanthus ilicifolius*, a mangrove species found to have analgesic and anti-inflammatory properties, and found applications in curing asthma, paralysis, rheumatic pains. Tannins were found to be active components in the family's Avicenniaceae, Sonneratiaceae and Rhizophoraceae (Bandaranayake 1995). An alkaloid named rhizophorin is obtained from the species *Rhizophora mucronata*. Naphthoquinones are the active components of *Avicennia alba*. The bark extracts of a *Bruguiera sexangular* rich in alkaloids found to be active against Sarcoma and Lewis Lung Carcinoma (Loder and Russell 1969). The alkaloid namely brugin is extracted from *Bruguiera sexangular*. Another mangrove species, *Excoecaria agallocha* secretes Latex which has biocidal effects on various marine organisms and phytoplanktons (Bandaranayake 2002, Reddy *et al.* 1991). *Acanthus ilicifolius* produces a steroid, Stigmasterol that shows hypercholesterolemic effects (Kokpol *et al.* 1984, Kokpol *et al.* 1990, Peng and

Long 1994, Firdaus *et al.* 2013). The plant species also produces a compound namely 2- Benzoxazolin that had the potential to use as CNS (central nervous system) depressants (Bandaranayake 2002).

Cancer is the most dreadful disease and found to be a major cause of death worldwide and is mainly caused by the mutations in genes leading to genetic alterations (Kooti *et al.* 2017, Valastyan and Weinberg 2011). As cancer is a more painful and dreadful disease, effective therapeutic measures are important to fight against this disease. The advancements in phytochemical research resulted in the isolation of bioactive compounds from various plants that proved to be effective in cancer treatment. The natural products owing to their biodegradable nature and safety gained more preference over their synthetic analogues (Ahmad *et al.* 2016). Plant based Vinca alkaloids such as vincristine and vinblastine, Paclitaxel, Docetaxel, Camptothecin, etoposide, irinotecan and topotecan have already proven their efficacy in the treatment of different types of cancers (Azam *et al.* 2016). In recent years, researchers have focused their attention on mangrove plants for screening novel bioactive compounds. These phytochemicals produced by the mangroves have already proven their efficacy in treating various disorders (Piyusha *et al.* 2012, Philip *et al.* 2009). Recent reports clearly indicate the antioxidant and anticancer activities of a number of mangrove species (Das *et al.* 2015, Samarakoon *et al.* 2016, Satyavani *et al.* 2015, Miranti *et al.* 2018). With this we can say that compounds isolated from mangrove plants have therapeutic importance and further research is needed to explore more diverse metabolites from this diverse ecosystem. The current review mainly focuses on various phytoactive compounds from mangrove sp. that have potential anti-cancer properties.

## MATERIALS AND METHODS

The literature collected from different databases viz., PubMed, Google Scholar, web of science Scopus, and science direct were reviewed using the keywords 'Bioprospecting', 'Mangrove ecosystem', 'Bioactive compounds', 'Separation', 'Isolation', 'Extraction' 'Pharmacological importance', 'Antimicrobial', 'Anti-cancer activity'.

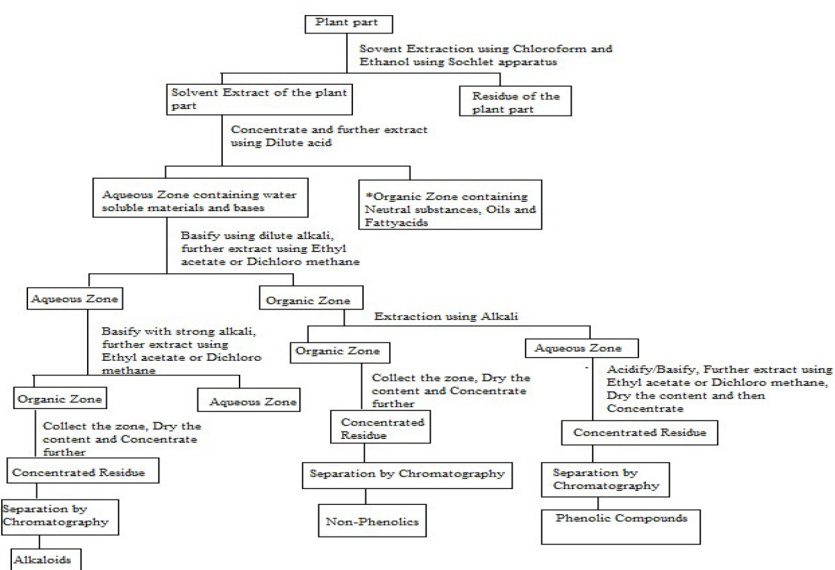


Fig. 1. Extraction of plant material in a generalized scheme (Modified scheme from Talapatra and Talapatra 2015).

### Derivation of phytochemicals from mangroves

Mangrove species are rich in phytochemicals that found have pharmaceutical importance and hence beneficial to treat various human diseases. The drug discovery is mainly based on the use of proper extraction methods to extract natural products from

different plant parts. Usage of correct extraction procedures plays an immense role in phytoactive compound research (Smith 2003, Sasidharan *et al.* 2011). Figs 1- 2 show the extraction methods applied to mangrove species.

### Anti-cancer agent from mangrove species

Worldwide cancer results in the death of 8.8 million

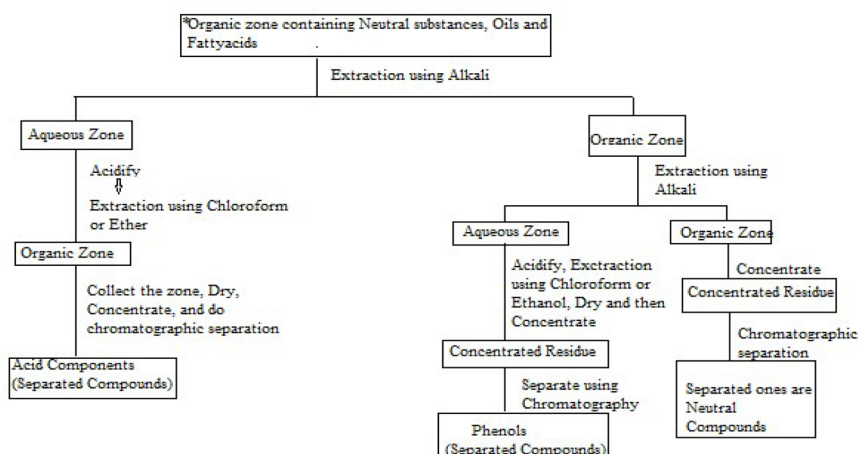


Fig. 2. Plant material extraction, continued from organic zone containing Neutral substances, Oils and Fatty acids of Fig. 1 (Modified scheme from Talapatra and Talapatra 2015).

individuals as per the reports of WHO 2016. This dreadful disease is mainly due to genetic abnormalities emerging during the process of cell division, alterations in the tumor suppressor genes, growth factor encoding genes, and genes that encode various transcription factors. Such changes result in the conversion of normal cells into dreadful cancer cells which evade apoptosis, immune surveillance, and as exhibit uncontrolled replication (Cavallo *et al.* 2011, Hanahan and Weinberg 2011, Akhtar and Swamy 2018). The traditional therapies to cure cancer such as chemo, and radiation therapies hold many disadvantages, there by replacing them with natural products. Many medicinal plants proved to be potential for their anti-inflammatory and anticancer properties. Of them, mangroves gained importance owing to their potential to tolerate harsher environmental conditions. The highly unique secondary metabolites produced by mangroves proved to have significant anti-cancer potentialities. To name a few, tetranor triterpenoids (Xylogranatins A-D), isolated from *Xylocarpus granatum*, were found to be exhibit cytotoxicity against different cell lines. In addition, granaxylocarpins A and B, the limonoids, showed cytotoxicity towards

P-388 cells (leukaemia cells) (Das *et al.* 2015, Yin *et al.* 2006). The *in vitro* cytotoxic assay with a flavones (3', 4', 5, 7- Tetrahydroxy flavone) extracted from *Sonneratia caseolaris* reported inhibitory action towards proliferation of SMMC-7721 cells (human hepatoma cells) (Tian *et al.* 2009). The methanol extracts of leaves of *Sonneratia apetala* showed anti-cancer potential towards EAC cell lines (Patra and Thatoi 2013). Polyisoprenoids isolated from *Nypa fruticans* exhibited significant anti-cancer potentialities (Sari *et al.* 2018). In mice model, *Rhizophora apiculata* methanolic extracts proved to contain 4-pyrrolidiny, pyrazole, and ketone derivatives, showed anti-inflammatory, and anti-cancer potential towards B16F10 cells (melanoma cells) (Prabhu and Guruvayoorappan 2012a). The extracts of *Avicennia marina* found to enhance apoptotic death in human hepatic and breast cancer cells, due to their rich phenolic and flavonoid content (Huang *et al.* 2016). The bark extracts from the mangrove species, *Excoecaria agallocha* exhibited cytotoxicity towards pancreatic cell lines (Patil *et al.* 2011). Batsa and Periyasami (Batsa and Periyasami 2013) reported the anti-cancer potential of *Excoecaria agallocha* leaf extracts. Table 1 show

**Table 1.** Anti-cancer activities of compounds isolated from mangrove plants.

Mangrove species	Phytoactive compounds and their Cytotoxic/Anti-cancer activities	References
<i>Acanthus</i> sp. ( <i>A. ilicifolius</i> )	The compound, Benzoxaxoline showed anticancer activity against HeLa and KB cell lines, Anti-tumor growth	(Das <i>et al.</i> 2015, Boopathy <i>et al.</i> 2011, Khajure and Rathod 2011)
<i>Avicennia</i> sp. ( <i>A. officinalis</i> )	The compounds, Triterpene, Betulinic acid, showed activity towards Ehrlich ascites carcinoma (EAC) cells	(Das <i>et al.</i> 2015, Sumithra <i>et al.</i> 2011)
<i>Avicennia germinans</i>	The compound, Tetracosane exhibited anticancer property towards MDA-MB-231, AGS, NIH 3T3, and HT-2918 cell lines	(Subathra and Mohideen 2018).
<i>Avicennia</i> sp. ( <i>A. marina</i> )	The compounds, Stenocarpoquinone, Naphthoquinones, Iridoid glycosides, and Avicequinones, showed cytotoxic and antitumor, anticancer and anti-mutagenic activities on HL-60 cell lines	(Das <i>et al.</i> 2015, Khafagi <i>et al.</i> 2003, Karami <i>et al.</i> 2012, Sukhramani and Patel 2013)
<i>Avicennia</i> sp. ( <i>A. alba</i> )	The compounds, Naphthoquinolines, Avicequinones, Phenolic compounds showed Anticancer, cytotoxicity on MCF 7 and HeLa cell lines	(Das <i>et al.</i> 2015, Ito <i>et al.</i> 2000, Eswaraiiah <i>et al.</i> 2020)
<i>Bruguiera</i> sp. ( <i>B. gymnorhiza</i> )	The compound, Brugin exhibited activity against Lung carcinoma, and antitumor activity towards Sarcoma 180	(Das <i>et al.</i> 2015, Bunyapraphatsara <i>et al.</i> 2003).
<i>Bruguiera</i> sp. ( <i>B. sexangula</i> )	The compounds, Tropine, Brugin, and Benzoic acid, exhibited activity towards Sarcoma 180 and Lexis lung carcinoma	(Das <i>et al.</i> 2015, Kathiresan <i>et al.</i> 2006, Govindasamy and Kannan 2012)
<i>Ceriops</i> sp. ( <i>C. decandra</i> )	The compounds, Quinine, triterpenes, Clionasterol, Stigmast-5-en-3-ol, Lupeol, and Diolein exhibited anticancer and anti-tumor activities towards Malignant ulcers, and Buccal pouch carcinogenesis	(Das <i>et al.</i> 2015, Govindasamy and Kannan 2012, Bandaranayake 1998, Kumar <i>et al.</i> 2013)

Table 1. Continued.

Mangrove species	Phytoactive compounds and their Cytotoxic/Anti-cancer activities	References
<i>Excoecaria</i> sp. ( <i>E. agallocha</i> )	The compounds, Tannins, Diterpenes, and Excoecarin showed antitumor activity, gastroprotective, Antinociceptive and also acted as Central nervous system depressants	(Das <i>et al.</i> 2015, Subhan <i>et al.</i> 2008a, Subhan <i>et al.</i> 2008b, Subhan <i>et al.</i> 2008c)
<i>Heritiera</i> sp. ( <i>H. fomes</i> )	The Phenolic compounds from this species exhibited anticancer and cytotoxic effects	(Das <i>et al.</i> 2015, Patra and Thatoi 2013)
<i>Rhizophora</i> sp. ( <i>R. apiculata</i> )	The Phenolic compounds from this species showed anticancer activity (A549, lung cancer cells)	(Ramalingam and Rajaram 2018).
<i>Rhizophora</i> sp. ( <i>R. mucronata</i> )	The phytol from this species exhibited cytotoxicity against Human gastric adenocarcinoma (AGS) cells	(Panjaitan and Suprajitnob 2018)
<i>Xylocarpus</i> sp. ( <i>X. granatum</i> )	The compounds, Flavonoids and Phenolic compounds exhibited activity towards Hela (cervical cancer) and MCF-7 (breast cancer) cell lines	(Darmadi <i>et al.</i> 2021)

different active compounds from mangrove species that exhibit anticancer activity.

## RESULTS AND DISCUSSION

Nature has provided us with plants that harbor novel bioactive compounds with significant therapeutic potential. Mangroves being located at habitats that exhibit extreme environmental conditions produce certain metabolites with unique properties that made them to tolerate the harsh conditions prevailed in those ecosystems. In recent times, the entire research community focused their attention on sustainable green resources. Compared to other plants, mangroves still remained as unexploited areas and hence extensive and exhaustive surveys regarding secondary metabolites of mangrove varieties is the need of the hour to screen potential bioactive compounds. Studies have already proved the potential of mangrove plants for their antimicrobial activities against various plant, human, and animal pathogens. Sufficient reports also signify their antioxidant activities. Anti-cancer potential of mangroves is gaining attention of researchers to screen these unique ecosystems for novel drugs. Scientists should focus their investigations on the separation of the bioactive components from plant extracts followed by proper characterization. Proper measures have to be taken as most of the bioactive principles are thermolabile, get denatured easily, and pressure-sensitive. The correct choice of solvents plays an immense role for any extraction procedure. The most widely employed solvents include meth-

anol, ethyl acetate, ethanol, water, and chloroform. Once solvent extraction is done, separation of bioactive constituents can be performed by using either TLC (thin layer chromatography), or by employing column chromatography. Now a day, these traditional techniques are replaced by LC-MS, HPLC-MS, and GC-MS. Once compounds are separated, their identification, and structural elucidations are another important tasks that can be done shown by various techniques viz., UV, NMR, FTIR, and MS. From the Table 1, it is clear that compounds such as benzoxaxoline obtained from *A. ilicifolius*; betulinic acid from *A. officinalis*; avicequinones from *A. marina*, and *A. alba*, brugin from *B. sexangular* and *B. gymnorrhiza*; quinine from *C. decandra*, and excoecarin from *E. agallocha* exhibit significant anti-cancer potentialities. Apart from anticancer activities, the mangrove extracts also showed anti-oxidative properties.

## CONCLUSION

The mangrove ecosystems can be considered as the most productive ecosystems with immense pharmacological importance because of their ability to withstand harsh environmental conditions such as greater salinity, varied temperatures, pressure, and tidal zones, which may provoke these plants to produce unique chemicals that make them to tolerate such harsh conditions. Yet these ecosystems have not been fully explored. Still more attention and effort is needed to explore these unique ecosystems which may help in the elucidation of novel therapeutic agents.

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