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Chapter- 5

Role of mangroves in pharmacotherapy

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Abstract:

Mangroves are very unique, bridging salt and freshwater ecosystems and exhibiting a wide variety of flora exclusive to halophytic conditions. Local populations have relied upon the medicinal benefits of multiple parts of various trees and plants for the treatment of diseases and infections like nausea, asthma, leprosy, rheumatic pain, arthritis, skin infections etc. These bioactive and medicinal properties have developed in the plants from secondary metabolites and chemicals present in them, like saponins, tannins, flavonoids, polyphenols, glucosides etc. The essential properties of these chemicals have made them viable alternatives to chemical pharmaceutics. Although chemically manufactured medicines are more suitable for treating multiple diseases at a lower cost of production, large-scale mismanaged applications have given rise to bacterial populations which are unsusceptible to their effects and the development of antibacterial resistance in the human body. Traditional medicines have emerged as an answer to this problem by not showing any side effects of application, and with newer natural molecules being discovered progressively, they might have a big role to play in the pharmaceuticals of tomorrow.

Introduction:

The word "mangrove" originates from the Portuguese words "*mangue*" meaning tree and "grove" meaning garden. As of now, 16 families and 70 species of mangrove plants have been identified (Sengupta, 2010), and all of them generally refer to a group of salt-tolerant, evergreen woody plants which are genetically, morphologically and physiologically adapted to the extreme salt concentrations of the mangrove ecosystem (Abdel-Aziz et al., 2016). Because of the rampant use of antibiotics and the resulting development of resistance in the human body to these

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pharmaceuticals, alternative sources of medicine, such as plant extracts, have come to the forefront of medical research. Because of their application versatility, plant extracts have been used for years among the traditional folk to treat injuries and heal ailments without suffering side effects or increased resistance to antibiotic drugs. The medicinal property of mangroves is a result of high concentrations of phytochemicals like terpenoids, tannins, flavonoids, alkaloids, saponins and antimicrobial peptides, which have all been found to have antimicrobial and antifungal properties along with therapeutic properties (Panda et al., 2012) Phytochemicals are non-nutritive chemicals found in plants which are produced by the system for protection and disease prevention and sometimes even have a protective effect on the user against said diseases. Rheumatism, ulcers, smallpox, leprosy, hepatitis, asthma, toothache and other ailments can be treated with extracts from these plants (Ravindran et al., 2005), while some extracts can be used for anti-diabetic effects and even as mosquito larvicides (Thangam and Kathiresan, 1991).

Mangroves are very special in their adaptation because they are found in areas of extreme salt concentrations and unique soil-water dynamics. The high concentrations of moisture, salt, salt-tolerant microbes and low tides make them capable of growing in areas other vascular plants will be unable to thrive and as a result, they are ideal representatives of ecotonal species between fresh and marine water ecosystems (Smith et al., 2013). The most diverse mangroves are found in the region between Malaysia and New Guinea, with 80% of the total mangroves found in the Indo-pacific region, 9% in east Africa, 6% in west Africa, 5% in the Caribbean and South Americas respectively (Michel, 2014). Mangroves can be classified into three categories:

- The true mangroves, which are restricted to intertidal areas between high water levels and neap tides. Around 20 different families of plants are found here, with 80 species already recognized.
- Minor species are those which are distinguished by their inability to form conspicuous elements of vegetation and rarely form communities.
- The mangal associates are salt tolerant but not located exclusively in the mangrove regions of backwaters but can also appear in transitional zones (Bandaranayake, 2002).

Collectively, mangroves, minor mangroves and associates are very productive both economically and environmentally. In addition to providing benefits to humans by providing alternatives to therapeutics (Rangasamy et al., 2019), they provide ecological functions like controlling the coastline (Gijsman et al., 2021), stabilizing the sediments and soil structure (Völkel et al., 2018), purification of the coastal waters by phytoremediation (Moreira et al., 2011) and providing a habitat for crabs, shrimps, oysters, fishes etc. (Situmorang and Barus, 2015). As a buffer, it reduces soil erosion and maintains water quality. Because it is situated between a terrestrial and a marine ecosystem, it effectively traps sediments, nutrients and contaminated runoff which maintains the overall health of the marine ecosystem (Wagabi, 2015). In reverse, mangroves protect the land cover by absorbing the energy from tidal waves and currents directed at the land mass by creating a natural windbreak against the direction of strong winds, which has protected the in-lands of West Bengal in many instances within a very short period (Daniary, 2020).

Medicinal importance of mangrove plants:

Widespread use of antibiotics has given rise to multidrug-resistant diseases, like those caused by *Clostridium difficile*, the treatment of which has become increasingly difficult on account of the side effects of antibiotic use. Allergies have been a common side effect from the very start of application in human communities, and even when sulfonamides were considered to be very effective, the risk of skin infections was always present from the use of the drug. Chloramphenicol was widely used because of its ability to penetrate the blood-brain barrier but at the expense of a serious risk of developing aplastic anaemia (Mohsen et al., 2020). It is to be noted that the development of resistance is not only on a community level but also on an individual level. As reported quite recently, individuals prone to taking high amounts of antibiotics are also prone to developing other infections and have more resistant bacterial flora by the time they are on the verge of taking their next dosage (Malik et al., 2018). Adverse effects of use are dependent on the dose applied to the body and the duration of application or the presence of the chemical in the system. Common effects of use, like nausea or vomiting, are often masked by the original illness and often go undetected in the patient. Furthermore, because many adverse effects occur at relatively low rates and are identified in large trials, it becomes difficult to recognize them early and attribute their occurrence directly to a drug (U.S Food and Drug Administration, 2019). In response to this rapid development of antibiotic ineffectiveness, mangrove plants have been suggested as an alternative because of their efficacy among traditional folk for hundreds of years (Abeysinghe, 2010). Mangroves are the richest source of phytochemicals, and of the plants' carbohydrate, amino acid, fatty acid, lipids, phenols, sterols etc content. Steroids, saponins, flavonoids, alkaloids, and tannins are abundantly found in vegetation, functioning as their secondary metabolites. A study of only 5 species of plants revealed an abundance of the useful chemicals present, some of which have pharmacological and economic importance (Abeysinghe, 2010) (*Table 1*).

Table 1. Chemical composition of some mangrove plants (Abeysinghe, 2010).

Specie	Chemicals present
Acanthus ilicifolius	Long-chain alcohols, benzoxazoline, triterpenes, steroids, acanthicofolin, triterpenoidal saponinsalkaloid,
Aegiceras corniculatum	Carotenoids, coumarins, benzoquinones, flavonoids, saponins, triterpenes, tannins, polyphenols,
Avicennia marina	Terpenoids, flavones, glucosides, steroidsnaphthalene derivatives,
Excoecaria agallocha	Phorbol ester, lignin, tannins, pentosan, phenols, flavanone, glycoside,
Rhizophora apiculata	Triterpenes, steroids, esters

Phytochemicals such as triterpenoids, alkaloids, and flavonoids mentioned here are the major classes of antimicrobials and antioxidants found in plants and are indicative of their use beyond the scope of ecological stability and self-sustainability (Shamsuzzaman et al., 2021). The medicinal effect of the materials arises from the synergistic effect of the various phytochemicals and as such, the isolated effectiveness of each chemical is comparatively much less potent. These products also play a major role in maintaining the plant's defence system against foreign pathogens through cytotoxicity against microbial invaders (Sarkar et al., 2016; Patra and Mohanta, 2014) (*Table 2*).

Table 2. Biological role of phytochemicals.

Phytochemical	Biological role
Phenolic-flavonoids	Reaction with free radicals for prevention or treatment of skin ageing (Podda and Grundmann-Kollmann, 2001).
Alkaloids	Antitumor, antihypertensive, muscle relaxant, antiprotozoal (von Linné, 2007).
Steroids	Antioxidants and maintaining hormonal balance (Moss, 1989)
Flavonoids	Antioxidants (Toudert et al., 2009)
Tannins	Metal ion chelating property enables it to function as an antioxidant and antimicrobial agent (Tukiran, 2013).
Terpenoids	Purgative for cough treatment and asthma (Edeoga et al., 2005)
Cardiac glycosides	Used in the treatment of arrhythmia and congestive heart failure (McMurray and Pfeffer, 2005)

A study of a few more species reveal the multitudes of therapeutic properties of these plants (Rangasamy et al., 2019) (*Table 3*).

Table 3. Therapeutic use of mangrove plants.

Specie	Therapeutic use
Acanthus ilicifolius	Treatment of asthma, paralysis, hepatitis, dyspepsia, leprosy, rheumatic pain and is leishmanicidal
Aegiceras corniculatum	Asthma, hepatitis, diabetes, rheumatism and fish poison
Avicennia marina	Skin diseases

Avicennia officinalis	Aphrodisiac, leprosy, diuretic, hepatitis
Bruguiera gymnorhiza	Eye diseases
Bruguiera parviflora	Antitumor
Bruguiera cylindrical	Stopping haemorrhage, applied to malignant ulcers, antioxidants
Ceriops decandra	Hepatitis, ulcer
Lumnitzera racemosa	Antifertility, asthma, diabetes, treatment of snake bite
Rhizophora mangle	Angina, boils, many antifungal infections, malaria, diarrhoea, dysentery, elephantiasis, fever, leprosy, tuberculosis and is antisceptic
Rhizophora mucronata	Elephantiasis, febrifuge, haematoma, hepatitis, ulcers
Salicornia brachiate	Hepatitis
Sesuvium portulacastrum	Hepatitis
Sueda maritima	Hepatitis
Sueda monoica	Hepatitis

Anti-diabetic property:

For a long time, *Excoecaria agallocha* has been traditionally used for the treatment of epilepsy, conjunctivitis, hematuria, dermatitis, toothache, leprosy etc because of the presence of phorbol esters, flavanone, glycoside, dichloromethane, lignin, pentosan, saponins, tannins and phenols as confirmed by phytochemical screening. Pharmacological investigation of the various extracts containing these phytochemicals has shown that they are capable of being used as anti-diabetics, antioxidants and antibacterial effectively without showing any signs of development of resistance in the user (Zou et al., 2006; Kar et al., 2022). The edible viviparous seeds of *Rhizophora apiculata* are useful for the treatment of diarrhoea, nausea and vomiting, while the wood is a source of tannin and used as a substitute for petroleum coke, mosquito repellent, cure for typhoid fever and phytochemical screening showed the availability of triterpenes, steroids and novel triterpenoid esters which are effective against diabetes too (Rangasamy et al., 2019).

Antioxidant property:

The barks of *Bruguiera cylindrical* and *Ceriops decandra* have been shown to possess an appreciable quantity of polyphenols, with *C. decandra* showing a higher content when compared to other species. Already shown to possess tannins previously (Ravi and Kathiresan, 1990), newer tests show elevated levels of polyphenols which are the most active radical scavengers and hence a better option as antioxidants. There is also strong evidence which shows phenolics to be useful in age-related chronic diseases (Kroon and Williamson, 2005). DPPH assay (2,2-Diphenyl-1-picrylhydrazyl), which is the most commonly used test for antioxidant properties of plant extracts (Nagarajan et al., 2017), showed both these plants to possess a concentration-dependent antiradical activity. The scavenging activity of the extracts from both barks was high and decolourization of $ABTS^+$ cation reflected the capacity of the extracts to act as electron donors, which made it evident they act as antioxidants (Krishnamoorthy et al., 2011).

Anticancer activity:

Bioactive compounds have been isolated from mangrove plants, like *Xylocarpus granatum*, which show cytotoxic effects against cancer cell lines like tetranor triterpenoids, while limonoids granaxylocarpins A and B are cytotoxic against P-388 leukaemia cells (Yin et al., 2006). Naphtoquinones 3-chlorodeoxylapachol and stenocarpoquinone B isolated from *Avicennia germinans* and *A.* marina respectively have shown strong cytotoxic activity against cancer cell lines K562 and HeLa (Jones et al., 2005) (Table 4).

Antibacterial activity:

Plant extracts have been used for treating common diseases for centuries and were the first medicines to be used by humans (Petrovska, 2012). With the increasing complexity and virulence of diseases, chemical pharmaceutics started being used as more clinically efficient alternatives, cheaper to manufacture and could be administered orally and thus improving patient compliance (Wang et al., 2022). However, with increasing self-diagnosis and heightened use of these chemical therapeutics, the development of resistance has become rapid in human systems (Rather et al., 2017), giving rise to The Antibiotic Resistance Crisis (Ventola, 2015). Although chemically manufactured therapeutics possess greater efficacy against diseases because of their specificity, better membrane permeability and stability (Wang et al., 2022), the world is being forced to look at alternatives to stop the development of resistance which can be passed on to the future generations and thereby bringing about a global crisis (MacLean et al., 2010). One of the earlier research into medicinal properties of mangrove plants revealed that *A. ilicifolius*, *A. marina* and *E. agallocha* possess significant analgesic activity (Kokpol et al., 2004). Later, seventy-five extracts from various mangrove plants in various solvents like chloroform, ethyl acetate, petroleum ether, ethanol and water reveled that they inhibit the growth of *S. aureus* and *S. proteus* (Abeysinghe, 2010), the former being the most widely used bacterial strain for testing antibacterial activities (Chassagne et al., 2021). Increasing scientific developments lead to the World Health Organisation acknowledging mangroves have sufficient ability to combat disease, having proven antimicrobial, antifungal and antiviral properties (Nascimento et al., 2000). Research has already revealed the multitudes of bioactive compounds found in many mangrove plants and their pharmaceutical importance (Bandaranayake, 2002) and it is now about optimizing their yields and overcoming drawbacks such as the stability of organic peptides (Wang et al., 2022), specificity of organic molecules and standardizing synergism between antibiotics and natural compounds which is holding back large-scale production of natural medicines for the diseased.

Table 4. Mangrove plants and anticancer compounds.

Plant	Isolated compound	Effective against
Acanthus ilicifolius	Benzoxazoline	Anticancer and antiviral activities, tumours
Agiceras corniculatum	Hydroquinone	Antiproliferative activity against human tumour cell lines
Avicennia alba	Naphthoquinolines, avicequinone	Anticancer
Avicennia marina	Naphthoquinones, avicequinone, stenocarpoquinone, iridoid, glycosides	Used for cytotoxicity against tumour cells
Avicennia officinalis	Triterpine, betulinic acid	Ehrlich ascites carcinoma cells, human leukaemia cell line HL-60
Bauhinia variegate	Steroids, triterpenoids, flavonoids	Ehlrich ascites carcinoma cells
Bruguiera gymnorrhiza	Brugine	Anti-tumour activity against Sarcoma 180 and Lewis
Bruguiera sexangula	Tropine, isobutyric, benzoic acid, brugine	Sacroma 180, Lexis lung carcinoma
Calophylum inophylum	Biflavonoids, neoflavonoids, xanthone, benzophenones	Antitumor, anticancer and lipid peroxidation
Ceriops decandra	Quinine	Malignant ulcers, buccal pouch carcinogenesis
Excoecaria agallocha	Diterpenes, tannins, excoecarin	Enhancing antitumor activity
Heritieria fomes	Phenolic compounds	Cytotoxicity against cancer cells
Pongamia pinnata	Lanceolatin B, chalcone, flavonoid, polyhydroxylates	Development of cancer
Xylocarpus mekongenesis	Xylomolin, xyloccensin	Cytotoxic activity

Conclusion:

Traditionally, mangroves have always been a source of necessities for the area's local population. Apart from providing materials for living and food for sustenance, plants have been known to be a source of ethnobotanical medicines which do not possess the negative side effects of antibiotic use over a sustained period. With the progress of scientific research, phytochemical compounds began to be newly discovered, found and identified from various parts of these plants, many of which are responsible for imparting medicinal properties to the plants associated with them. Classes of flavonoids, polyphenols, tannins, essential oils, alkaloids, phorbol esters, terpenoids, derivatives of quinones, and steroids have all been discovered from various plants and identified as agents of pharmacological importance. Antimicrobial properties were among the first uses of these plant extracts as populations in and around mangrove areas have always been of the lower economic class for whom the availability of commercial medicines has always been a cause for concern. Other common uses like cures for nausea, vomiting, haemorrhage or snake bite have been met by selecting appropriate plant varieties and extracting its metabolites or using the biomass directly on the skin or consuming it in concentrated proportions to aid the natural immunity of the body. As mangroves started being recognised as a very unique ecosystem possessing ecotonal varieties of flora with adaptations to the extreme conditions of salinity, humidity, temperature and microbial population of the soil, exploring other applications of the flora became a scientific endeavour which is being proven to be successful, with advanced medical issues like diabetes, development of tumour, cytotoxicity of cells, cancer started coming within the scope of application of mangrove extracts. However, plant extracts cannot be substitutes for pharmaceuticals as the potency of activity is yet to be equated fully against established medications. Certain activities are less than effective compared to their chemical counterparts. When used on a wide scale, systemic and local toxicity have emerged as problems which need addressing, along with modifications to drug design, predicting biological activity and calculating the stability of peptides when antimicrobial peptides are in question. The biggest problem with establishing natural medicines as permanent alternatives to pharmaceuticals, especially when mangrove plants are considered, is the global distribution of these plants, which is extremely localized and adapted to a very unique and extreme set of abiotic conditions. The cost of production of such medication will go up unless an alternative to the lack of widespread availability is found.

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Conflicts of Interest:

The authors Chiradeep Basu, Subarna Bhattacharyya, Punarbasu Chaudhuri have no financial, commercial, legal or professional conflict of interest with any other parties with the submission of this manuscript.

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