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Short Communication

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A Preliminary Review on the Importance of Colombian Mangroves as a Source of Endophytic Microorganisms Relevant in Pharmaceutical Industry

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Global Mangroves Forests Distribution

Mangroves' forests are one of the most productive natural ecosystems on the planet due to their ecological and socioeconomic importance and their coastal protection function especially in a scenario of sea level rise and increase of extreme energetic events [1-3]. They are plant species with morphological, physiological and reproductive characteristics that allow them to develop on saline soils in a critical interface between terrestrial, estuarine and near-shore marine ecosystems in tropical and subtropical regions [4]. Mangrove forests, due to their great biomass and capacity of accumulation of sediments, are able to store high concentrations of carbon, making them one of the most carbon-rich ecosystems in the tropics, with an estimated value of USD 194,000 ha.year^{-1} [5]. Mangroves' forests occupy approximately 14 million hectares, of which more than two thirds are located in eighteen countries: Indonesia, Brazil, Australia, Mexico, Nigeria, Malaysia, Myanmar, Bangladesh, Cuba, India, Papua New Guinea, Colombia, Guinea Bissau, Mozambique, Madagascar, Philippines, Thailand and Vietnam [3,6]. In Latin America and the Caribbean, which own 26% of the total world mangrove surface, they are essentially located in six countries: Brazil, Mexico, Cuba, Colombia, Venezuela and Honduras [7]. Although the loss of mangrove forests has been reduced in the last two decades, there are still rates of up to 3.1% per year in some countries, which would lead to a loss of their functionality in less than 100 years [3,8].

Mangroves Forests in Colombia

South America, on both Atlantic and Pacific coasts, has approximately 11% (≈2 million hectares) of the world's reported mangroves' forests [9] and only 10 out of the 70 species worldwide reported [9,10], which are: *Acrostichum aureum, Avicennia bicolor, A. germinans, A. schaueriana, Conocarpus erectus, Laguncularia racemosa, Pelliciera rhizophorae, Rhizophora harrisonii, R. mangle* and *R. racemosa* [9]. More than 90% the mangroves' forests of South America is found in five countries, i.e. Brazil, Colombia, the Bolivarian Republic of Venezuela, Ecuador and Suriname [9].

Colombia's coastline extends on the Pacific Ocean and the Caribbean Sea with a total length of 3,000 km [11]. Differences in rainfall patterns on both coasts condition mangrove cover, with approximately 292,724 ha on the Pacific coast and 87,230 ha on the Caribbean coast, for a total of approximately 379,954 ha consisting of 9 mangrove species: *Acrostichum aureum, Avicennia bicolor, A. germinans, Conocarpus erectus, Laguncularia racemosa, Pelliciera rhizophorae, Rhizophora harrisonii, R. mangle* and *R. racemosa* [9,12]. However, it is estimated that in the last 30 years approximately 40,000 ha of mangrove forest in Colombia have been mainly altered by anthropogenic activities (construction of roads, tourist infrastructures, expansion of urban, agricultural and industrial frontiers, deforestation, etc.) [13-15]. In addition, climate change scenarios for the Colombian coastal zone project that this mangroves could be mainly affected by rising sea levels and coastal erosion [16]. The alteration and/or disappearance of the mangrove swamp will not only lead to the loss of this strategic ecosystem and the ecosystem services that provides, but will also cause a great loss of its associated microbial biodiversity, which is so far a little explored issue, especially in relation to the presence of endophytic microorganisms.

Mangrove Endophytes With Potential Use in the Pharmaceutical Industry

Endophytes are microorganisms found within plant tissues for, at least, a part of the cycle of the plant life. Such microorganisms do not cause any disease to the hosting plant but generally offer multiple benefits favoring phosphates solubilization, production of phytohormones, nitrogen fixation, production of secondary metabolites with antimicrobial activity [17,18]. All existing plant host one or more species of endophytic microorganisms, however, only a small number of them have been thoroughly studied [19,20]. The populations of these microorganisms depend on conditions such as the characteristics of each specie, the stage of growth of the plant and the environmental conditions in which the plant develops [21].

In South America, the largest number of studies on endophytic microorganisms of mangroves have only been conducted in Brazil, most of them aimed at studying biodiversity, bioremediation and the attaining of enzymes for industrial use [22-28]. Colombia is considered the second country in the world with the greatest diversity of plants, with 1,500 exclusive species [29]. Despite this immense wealth of flora, few plant species in Colombia have been studied from the point of view of their endophytic microbiota and little has been explored about their potential use in the pharmaceutical industry. Therefore, Colombia is considered a relevant potential source of these microorganisms and the secondary metabolites associated with them [30]. Endophytes synthesize a wide range of bioactive metabolites with different properties and a single strain has the capacity to produce multiple variants, which means that the search for new endophytes and their metabolites could increase the possibility of finding new natural bioactive products (Figure 1) [21,31,32]. Although mangrove endophytic microorganisms have been extensively studied in Southeast Asia, the endophytic microbiota of the extensive mangrove forests of the Americas and the Caribbean remain largely unexplored [33].

Figure 1: Mangrove endophytes as a source of bioactive molecules.

Although Colombia has mangroves on both coasts, no studies have been reported in which endophytes have been isolated from these plants and their metabolism studied to obtain molecules with potential use in the pharmaceutical industry. Different studies have shown that the endophytic microbiota of mangroves is a promising source of bioactive molecules with antimicrobial, anti-HIV and cytotoxic activities (Figure 2) [33]. As an example, Wang et al. carried out a very complete review on the natural compounds obtained from endophytes of mangrove fungi where secondary bioactive metabolites are described, among which are terpenes, chromones, coumarins, polyketides, alkaloids and peptides with diverse structural features, many of which present activities such as cytotoxicity against cancer cells, anti-HIV, antibacterial and antioxidants [34].

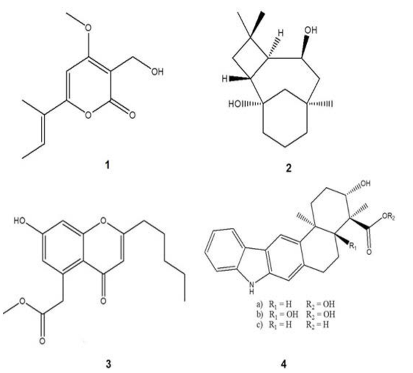

Figure 2: Compounds isolated from mangrove endophytes with antimicrobial, anti-HIV and cytotoxic activities against cancer cells: 1) Phomopyrone A 2) Bacaryolane B 3) Pestalotiopsone F and 4) Xiamycin A (a) and xiamycin B (b) and Xiamycin (c).

Demers *et al.* (2018) studied the capacity of endophytic fungi isolated from mangroves (*Rhizophora mangle, Avicennia germinans, Laguncularia racemosa*) and trees associated to mangroves (*Conocarpus erectus* and *Coccoloba uvifera*) in Florida (USA), demonstrating that extracts obtained from microorganisms presented activity against different microorganisms of clinical importance: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter cloacae, Mycobacterium tuberculosis, Naegleria fowleri* and *Leishmania donovani* [33]. Ding et al. (2015) isolated, from the species *Bruguiera gymnorrhiza,* a strain identified as *Streptomyces* sp. JMRC: ST027706 with the capacity of producing bacaryolane A-C, where bacaryo,ane B showed activity against *Bacillus subtilis* [35]. They also isolated from the mangrove's species *Kandelia candel* a strain identified as *Streptomyces* sp. HKI0595 that was able to produce three novel indolosquiterpenes, xiamycin B, indosespene and sespenine that presented moderate to strong antimicrobial activities against several bacteria of clinical interest, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* [36]. Cai et al. (2016) isolated from *Acanthus ilicifolius* the strain identified as *Phomopsis* sp. HNY29-2B that was able to produce the molecules identified as Acropyrone, Ampelanol and Phomopyrone A, the latter presenting antimicrobial activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* [37]. Moron et al. (2018) isolated from different mangrove species, i.e. *Avicennia officinalis, A. rumphiana, Aegiceras corniculatum, Bruguiera gymnorrhiza, Camptostemon philippinense, Excoecaria agallocha, Lumnitzera litorea, Rhizophora apiculata,* and *R. stylosa, Avicennia marina, Avicennia* sp., *A. corniculatum* and *Sonneratia alba* different strains of endophytic fungi identified as: *Arthrinium phaeospermum, Colletotrichum siamense, C. tropicale, Fusarium oxysporum, F. chlamydosporum, F. proliferatum, F. solani, Lasiodiplodia theobromae, Nodulisporium* sp., *Paecilomyces formosus, Penicillium citrinum*, and *Pestalotiopsis microspora* whose extracts showed greater or lesser activity against clinically important bacteria and fungi such as *Escherichia coli*, *Klebsiella pneumoniae, Serratia marcescens, Staphylococcus aureus* and *Candida albicans* [38]. Elavarasi et al. (2012) isolated from *Rhizophora annamalayana* the endophytic fungi identified as *Fusarium oxysporum* which has the ability to produce Taxol (paclitaxel), which is a compound recognized for its anticancer properties [39]. These investigations evidence that the microorganisms associated with the mangrove forest - especially the endophytes - represent a rich source of molecules with great interest in the pharmaceutical industry and this was not investigated in Colombia in spite of the fact that Colombia has a total area of approximately 379,954 ha of mangrove forests (with 9 species) on the Pacific and Caribbean coasts, which have great environmental differences and, hence, probably the presence of a wide diversity of endophytes. Unfortunately it should be noted that mangroves forest of Colombia are under strong anthropic pressure - this could put at risk the wide diversity contained in them, which makes it necessary the protection and conservation of this ecosystem but also the research of new molecules of pharmaceutical interest through the isolation, identification and study of secondary metabolism of microorganisms associated with them with special attention to endophytes.

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