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Short Communication

The antiproliferative potential of fungi associated with coral and algae collected from a Veracruz Reef System, Gulf of Mexico

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ABSTRACT. Coral reefs are ecosystems with great biodiversity and architectural complexity. Among these, marine fungi constitute one of the least studied groups, despite being potentially an inexhaustible source of bioactive metabolites. For this reason, in this research, we evaluate the antiproliferative activity of 52 fungal strains associated with marine organisms such as algae and coral collected from four islands located in the National Park Sistema Arrecifal Veracruzano, Mexico. One hundred four chloroform:methanol extracts corresponding to the culture broth, and biomass produced from each fungal strain was obtained from these. Subsequently, they were evaluated against six human solid tumor cell lines (HBL-100, HeLa, SW1573, T-47D, WiDr, and A549). The outcome was that six extracts showed activity against at least one cancer cell line. The identity of these fungi corresponded to the genera *Nigrospora*, *Pestalotiopsis*, *Cladosporium*, and *Ochroconis* according to their morphological and molecular analysis. In this sense, the strain found to have the highest antiproliferative potential [GI_{50} (μg mL^{-1}) 4.6, 2.5, 8.0, 5.6, 52.0, 4.0] grouped phylogenetically with a species of *Nigrospora* sp. The preceding confirms that ecosystems provide.

Keywords: *Nigrospora*; *Pestalotiopsis*; *Cladosporium*; *Ochroconis*; antiproliferative effect; marine fungi

Coral reefs are considered among the biomes with the greatest biodiversity and architectural complexity, which gives them great socio-economic value (Ban et al. 2014). An example of this is the National Park Sistema Arrecifal Veracruzano (PNSAV, Spanish acronym) of the Gulf of Mexico, a marine protected area with high marine biodiversity, including macroalgae which are known to maintain symbiotic relationships with microorganisms like fungi which are essential in the biological processes of the marine ecosystem (Galicia-García et al. 2013, Tisthammer et al. 2016). According to Jones et al. (2015), the classification of marine fungi includes 1112 species distributed in 472 genera, with the Halosphaeriaceae family of the Ascomycota being the most varied since it is considered to include 141 species in 59 genera. Endophytic fungi or those associated with marine invertebrates or algae are increasingly important sources of natural biologically active compounds due to their potential as compounds of medical interest. For example, some metabolites show antibacterial, antiviral, anti-inflammatory, antifungal, antioxidant, and antiproliferative activities (Schlingmann et al. 2002, Bhadury & Wright 2004, Debbab et al. 2011). In particular, compounds with antiproliferative activity have been of great biotechnological and pharmacological interest due to the rapid increase in different types of cancer (Zheng et al. 2013, Butler et al. 2014). Although some antiproliferative diterpenes produced by macroalgae are known (Chen et al. 2018), these reports are scarce and, compared to those produced by symbiont fungi, are more abundant and of a different che-

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mical nature (Jones 2011). Besides, being easy to grow in the laboratory allows non-invasive research to be carried out on the biome, thus favoring the maintenance and proper use of the environmental services provided by a marine ecosystem. Therefore, the objective of this study was to carry out a bioprospection of fungi associated with marine organisms in the northern zone of the PNSAV to evaluate their antiproliferative effect against six cancer cell lines.

The study and collection area was located on the islands located in the PNSAV (Fig. 1). A total of 11 samples of algae were collected. Three species (*Dictyota* sp., *Caulerpa sertularioides* and *Dictyota cervicornis*) from El Verde (19°11'50"N, 96°04'06"W), three species (*Halimeda opuntia*, *Galaxaura rugosa* and *Rhipocephalus phoenix*) from Arrecife Pájaros (19°11'18"N, 96°05'18"W) and five species (*Galaxaura rugosa*, *Caulerpa cupressoides*, *Dictyota cervicornis*, *Galaxaura obtusata* and *Caulerpa sertularioides*) from Isla Sacrificios (19°10'26"N, 96°05'32"W). *Acropora palmata* coral was collected from Anegada de Adentro (19°13'30"N, 96°03'18"W) at a depth of 1-2 m. The samples collected were transported in Ziplock bags with seawater from the sampling site, maintaining a temperature of 4°C. Later, they were washed, fragmented, disinfested, and seeded in culture media, following the method that Couttolenc et al. (2016) described. The development of fungal colonies was carried out by incubation under dark conditions at 25 ± 2ºC for 14 days. Finally, the pure cultures were obtained by reseeding the hyphal tip from each isolated colony (Lumbreras-Martínez et al. 2018).

Once the fungal strains were purified, small-scale liquid fermentations were conducted to homogenize and condition the strains in the marine culture medium (Kjer et al. 2010). The biomass and culture broth were separated after incubation, followed by a freezing and dehydration process by lyophilization. Finally, the lyophilized samples were extracted with a mixture of chloroform:methanol (1:1) and concentrated by distillation under reduced pressure. From each fungal extract, the antiproliferative effect was evaluated against cell lines derived from solid human tumors, HBL-100 and T-47D (breast cancer), HeLa (cervical cancer), A549 and SW1573 (lung cancer), and WiDr (colon cancer), following the protocols developed by the National Cancer Institute for the Sulforhodamine B assay (Skehan et al. 1990). The antiproliferative activity was expressed in terms of GI_{50}, which represents the amount of extract necessary to inhibit 50% of the growth of the cell lines tested (Couttolenc et al. 2016).

All isolated strains were identified by brightfield microscopy, using lactophenol blue as the fixation me-

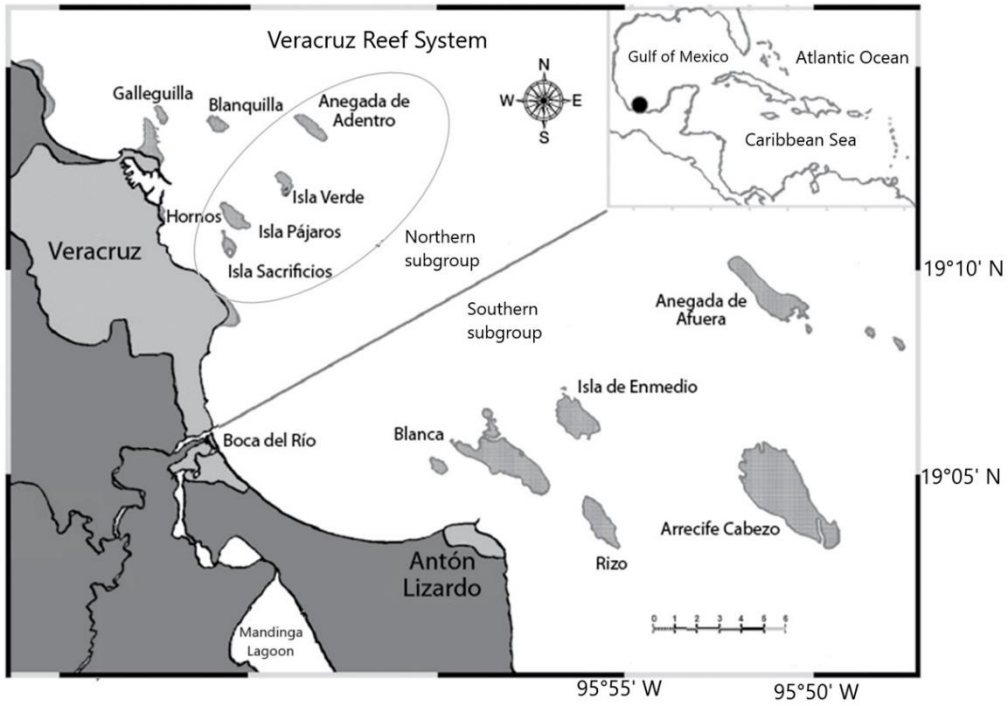

Figure 1. Study area, reefs located in the northern subgroup of the National Park Sistema Arrecifal Veracruzano. Isla Sacrificios, Isla Pájaros, Isla Verde and Anegada de Adentro (Arellano-Méndez et al. 2016).

medium and comparing them with taxonomic keys. DNA extractions were carried out to corroborate the identity of the bioactive fungal strains, and the ITS regions of the rDNA were amplified through the PCR reaction using primers ITS1 and ITS2. From the nucleotide, sequences obtained from the amplified products determined the percentage of species identity with the information from GenBank (www.ncbi.nlm.nih.gov). Finally, multiple alignments were performed using the Clustal W algorithm, and the cladogram was constructed using the maximum likelihood algorithm (K2 + G) of the MEGA7 software with a bootstrap analysis of 1000 repetitions (Lumbreras-Martínez et al. 2018).

Fifty-two fungal strains were isolated from 11 samples of algae and one of coral collected from islands located in the north group of the PNSAV (Table 1). From the coral, *A. palmata* 14 fungal isolates were obtained and classified into 10 genera according to their microscopic characteristics and comparison with taxonomic keys. The isolates of *Nigrospora* showed a frequency of 26.6%, followed by *Aspergillus* and *Penicillium* with 13.3%. In contrast, the rest of the isolated morphotypes corresponded to 6.6%. Concerning the fungi associated with the algae samples, 25 strains corresponding to 15 morphotypes were isolated, which presented morphological characteristics similar to the genera *Acremoniella*, *Acremonium*, *Alternaria*, *Aspergillus*, *Botrytis*, *Cladorrhinum*, *Cladosporium*, *Epicoccum*, *Fusarium*, *Nigrospora*, *Ochroconis*, *Paecilomyces*, *Pythium*, *Rhinocladiella*, and *Trichoderma*. Thirteen fungal strains did not present microscopic structures, which made it impossible to compare them taxonomically. There are few reports of fungi associated with the collected algae specimens. Thus, genera such as *Aspergillus*, *Chaetomium*, *Cladosporium*, *Fusarium*, *Myrothecium*, *Penicillium*, and *Phialophora* (Suryanarayanan 2012) have been reported from *Caulerpa sertularioides*, but only *Aspergillus versicolor* has been reported for *Halimeda opuntia* (Hawas et al. 2012). Our study adds *Paecilomyces* sp. in both species of algae. It should be noted that this is the first study on the fungi associated with algae *Dictyota* sp., *D. cervicornis*, *G. rugosa*, *R. phoenix*, *C. cupressoides*, and *G. obtusata*, and the species of coral *A. palmata*, of the latter identifying 10 genera of fungi, *Nigrospora* sp. being the most frequently isolated strain.

The bioactive strains' identity corroboration was carried out through molecular analysis based on ITS1 sequences located between the 18S and 5.8S rRNA genes, and ITS2 is reported as between 5.8S and 28S. From this data, in the corresponding cladogram (Fig. 2), it was observed that the CD1 strain grouped in the clade of *Nigrospora camellia-sinensis* shared 99% identity with the same species. Likewise, CD6 was located in a contiguous clade having 99% identity and presented similarity with *Nigrospora oryzae* and *Nigrospora* sp. Similarly, CD5 is grouped in the clade of *Pestalotiopsis* sp., *P. microspora* and *P. oxyanthi*. In the case of CD12 and CD44, both presented 98% identity CD12 grouped with sequences of the *Cladosporium oxysporum* and *C. cladosporioides* strains, while CD44 was related to *Ochroconis mirabilis* and *O. musae*, respectively. However, it is necessary to carry out more studies in regions other than the ITS to achieve greater homology and group our strains into specific species.

From the 52 isolated strains, 104 chloroform: methanol extracts (1:1) corresponding to the broth and biomass produced by small-scale fermentation were obtained. Only those extracts that presented a $GI_{50} \leq 50$ µg mL^{-1} were considered bioactive (Monks et al. 1991). According to this criterion, six extracts corresponding to four genera of fungi showed antiproliferative potential against at least one human solid tumor cell line tested (Table 2). In this sense, three biomass extracts showed a selective antiproliferative effect towards a specific cell line. Among them, we highlight CD1 *N. camelliae-sinensis* and CD12 *Cladosporium* sp., which showed activity against the lung cancer line SW1573 (GI_{50} 40 and 37 µg mL^{-1}, respectively). In addition, CD6 *Nigrospora* sp. was selective towards the cervical cancer line HeLa (GI_{50} 20 µg mL^{-1}). The remaining extracts exhibited a wide range of antiproliferative effects. Thus, the biomass extracts of CD5 *Pestalotiopsis* sp. and CD44 *Ochroconis* sp. showed GI_{50} values in the range of 20-87 and 39-63 µg mL^{-1}, respectively. The extract that presented the greatest antiproliferative potential was CD6 broth *Nigrospora* sp. against five cell lines with GI50 values in the range of 2.5-8.0 µg mL^{-1}. The effects of the extracts evaluated indicate that, apart from possessing the characteristic of inhibiting cell growth, they also show specificity on the lines of SW1573 and HeLa. Similarly, this effect has been presented in methanolic extracts of brown algae *Dictyota cilliolata* and *D. menstrualis* by inducing apoptosis in HeLa cells of human cervical adenocarcinoma (Moo-Puc et al. 2009, Gomes et al. 2015). However, the compounds described for the fungi isolated from this genus of algae and the others studied in this work are of a different chemical nature to those observed in host organisms (Jones 2011, Chen et al. 2018). In this sense, our bioactivity results coincide with those reported for species of the genus *Nigrospora*. An example of this is the endophytic marine strain *N. oryzae*, which produces diketopiperazines with antimicrobial, antioxidant, and

Table 1. Fungal isolates were obtained from coral and algae samples from the islands located in the northern group of the National Park Sistema Arrecifal Veracruzano. NP-ER: did not present reproduction structures.

Source	Host coral	Fungal isolation key	Fungal genus
Anegada de Adentro	*Acropora palmata*	CD (1, 4, 6)	*Nigrospora* sp.
		CD (2, 19)	*Aspergillus* sp.
		CD (3, 7)	*Penicillium* sp.
		CD5	*Pestalotiopsis* sp.
		CD20	*Alternaria* sp.
		CD21	*Cladosporium* sp.
		CD22	*Paecilomyces* sp.
		CD38	*Acremoniella* sp.
		CD39	*Gliocladium* sp.
		CD51	*Acremonium* sp.
		CD (8, 23, 50)	NP-ER
Isla Verde	Host algae		
	Dictyota sp.	CD24	*Trichoderma* sp.
		CD40	*Acremoniella* sp.
		CD42	*Cladorrhinum* sp.
		CD (9,41)	NP-ER
	Caulerpa sertularioides	CD (10, 12)	*Cladosporium* sp.
		CD11	*Fusarium* sp.
		CD25	*Paecilomyces* sp.
	Dictyota cervicornis	CD13	*Cladosporium* sp.
		CD27	*Alternaria* sp.
		CD43	*Pythium* sp.
		CD44	*Ochroconis* sp.
		CD (26, 28)	NP-ER
Arrecife Pájaros	*Halimeda opuntia*	CD29	*Paecilomyces* sp.
		CD30	NP-ER
	Galaxaura rugosa	CD49	*Aspergillus* sp.
	Rhipocephalus phoenix	CD14	*Nigrospora* sp.
		CD15	*Epicoccum* sp.
		CD16	*Cladosporium* sp.
		CD31	*Paecilomyces* sp.
Isla Sacrificios	*Galaxaura rugosa*	CD32	NP-ER
		CD (33, 34)	*Acremonium* sp.
		CD45	*Botrytis* sp.
	Caulerpa cupressoides	CD (17, 52)	NP-ER
	Dictyota cervicornis	CD48	*Rhinocladiella* sp.
	Galaxaura obtusata	CD35	*Aspergillus* sp.
		CD36	*Paecilomyces* sp.
		CD46	*Pythium* sp.
		CD (18, 47)	NP-ER
	Caulerpa sertularioides	CD37	*Cladosporium* sp.

antitumor activity, isolated from its liquid culture (Ding et al. 2016). Likewise, the genus *Pestalotiopsis* is also considered an endophyte isolated from extreme environments and capable of producing a great diversity of chemical compounds of biotechnological and pharmacological interest (Nadeem et al. 2002, Tejesvi et al. 2007, Maharachchikumbura et al. 2011). For example, pestalotiopsone F (5-carbomethoxymethy l-7-hydroxy-2-pentil chromone) with antiproliferative activity against the murine cancer cell line L5178Y, produced by the cultivation *Pestalotiopsis* sp. (Xu et al. 2009) and the metabolites pestaloficiol I, J, K, L showed cytotoxic activity against human solid tumor cell lines HeLa and MCF7, produced by *P. fici* (Liu et al. 2009). Finally, from the cultivation of a marine strain of *Cladosporium* sp. cladodionen was isolated, with cytotoxic activity against the human cancer cell lines MCF-7, HeLa, HCT-116 and HL-60 with values

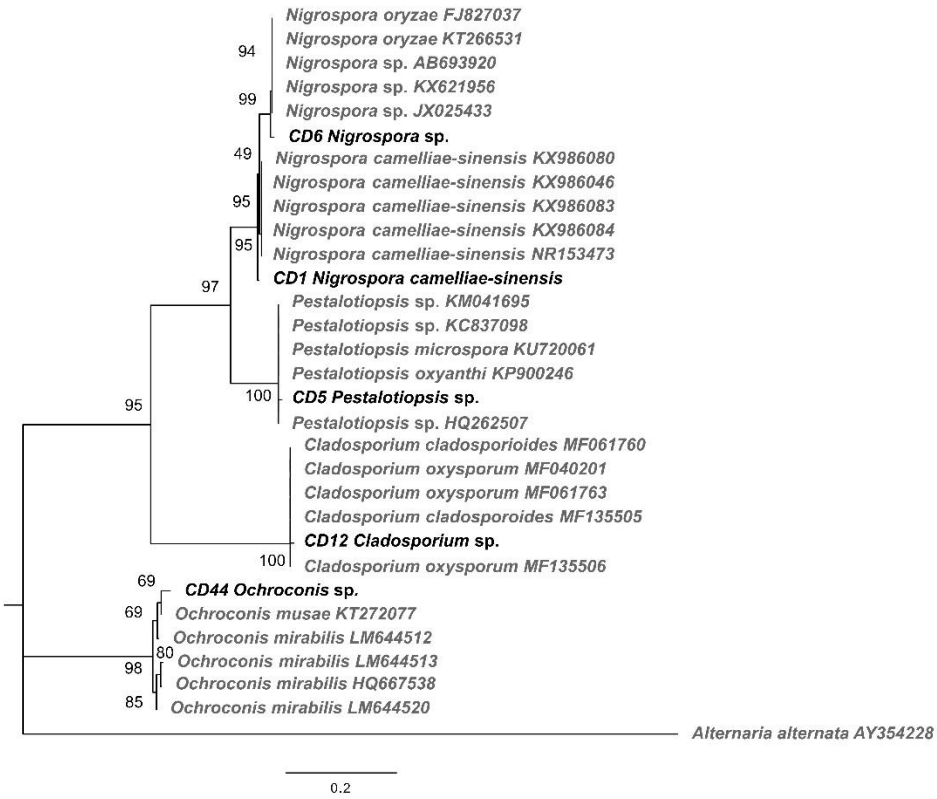

Figure 2. ITS-1 and ITS-2 regions of CD1, CD5, CD6, CD12 sequences, and CD44 strains phylogenetic relationships compared with the Genbank sequences. *Alternaria alternata* was used as the outgroup. A tree of maximum likelihood was generated with MEGA7 using the K2 model at 1000 bootstrap repetitions.

Table 2. Values of antiproliferative activity expressed in GI_{50} (≤ 50 µg mL^{-1}) from extracts of fungal strains isolated from the *Acropora palmata* coral and from the algae *Caulerpa sertularioides* and *Dictyota cervicornis* against at least one of the six tumor cell lines human solids tested. Higher antiproliferative potential values are shown in bold. HBL-100 and T-47D: breast cancer, HeLa: cervical cancer, A549 and SW1573: lung cancer, WiDr: colon cancer.

Key and fungal strain	Host	Extract type	Human solid tumor cell lines					
			HBL-100	HeLa	SW1573	T-47D	WiDr	A549
CD1 *Nigrospora camelliae-sinensis*	*Acropora palmata*	Biomass	250	250	**40**	250	250	250
CD5 *Pestalotiopsis* sp.	*Acropora palmata*	Biomass	87	**29**	**20**	63	**50**	**32**
CD6 *Nigrospora* sp.	*Acropora palmata*	Biomass	210	**20**	90	250	250	77
		Broth	**4.6**	**2.5**	**8.0**	**5.6**	52	**4.0**
CD12 *Cladosporium* sp.	*Caulerpa sertularioides*	Biomass	250	104	**37**	250	250	250
CD44 *Ochroconis* sp.	*Dictyota cervicornis*	Biomass	**47**	**40**	**45**	**47**	63	**39**

of IC_{50} of 18.7, 19.1, 17.9 and 9.1 µM, respectively (Zhu et al. 2018).

In conclusion, six fungal strains were found to show antiproliferative activity against at least one of the evaluated cancer cell lines, which corresponds to 11% of the total isolated strains, demonstrating the ability of marine fungi from PNSAV to inhibit cell growth of cancer cells. It should be noted that this is the first study on the fungi associated with the algae *Dictyota* sp., *D. cervicornis*, *G. rugosa*, *R. phoenix*, *C. cupressoides*, and *G. obtusata*, and the coral species *A. palmata*. Highlights of the latter are the isolation of *Nigrospora* sp., which presented the highest antiproliferative potential [GI_{50} (µg mL^{-1}) 4.6, 2.5, 8.0, 5.6, 52 and 4.0] against

the human solid tumor cell lines HBL-100, HeLa, SW1573, T-47D, WiDr, and A549, respectively. The preceding confirms that fungi associated with marine organisms prove to be a promising source of biologically active metabolites. Furthermore, it reinforces the importance of habitat conservation and the biotechnological use that these ecosystems provide.

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