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# Mycelial Secondary Metabolites with Anti-proliferative Potential from the Sediment-associated Fungus *Acremonium persicinum*

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**Abstract.** Fungi associated with marine organisms, sediments and the mangrove rhizosphere are a promising source of bioactive compounds. However, lagoon-craters-associated fungi have been little explored. Therefore, this work reports on the mycelial secondary metabolites of the liquid culture of *Acremonium persicinum* CF25 isolated from the sediment of an alkaline lagoon-crater as having an anti-proliferative potential. In this way, from the biomass generated in 50 L of *A. persicinum* CF25 culture, 4 extracts of intermediate polarity were obtained, of which fractions F3 and F4 showed anti-proliferative potential with values of [$GI_{50}$=µg/mL] equal to F3 (7.8, 13.0, 9.6, 11.0, 8.9, 21.0) and F4 (21.0, 35.0, 27.0, 27.0, 18.0, 27.0) against human solid tumor cell lines [A549, HBL-100, HeLa, SW1573, T-47D, WiDr], respectively. From the purification of F3, the sterols ergosterol, ergosterol peroxide and cerevisterol were isolated, while from F4 the anthraquinone known as questin

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was obtained. Questin presented a greater anti-proliferative effect against the A549 lung cancer and HeLa cervical cancer cell lines [$GI_{50}$=µM] of 27.0 and 31.0, respectively. In addition, questin was shown to induce cell death by apoptosis, with a high selectivity index in SW1573 and T-47D tumor cells. Finally, these results support the importance of bioprospecting studies in ecosystems such as alkaline lagoon-craters, since they are a good source of microorganisms from which it is possible to obtain bioactive compounds.

**Resumen.** Los hongos asociados a organismos marinos, los sedimentos y la rizosfera de manglares son una fuente prometedora de compuestos bioactivos. Sin embargo, los hongos asociados lagunas cráter han sido poco explorados. Por ello, en este trabajo se reportan los metabolitos secundarios con potencial antiproliferativo obtenidos a partir del cultivo líquido miceliar de *Acremonium persicinum* CF25 aislado del sedimento de una laguna cráter alcalina. De esta manera, a partir de la biomasa generada en 50 L de cultivo de *A. persicinum* CF25, se obtuvieron 4 extractos de polaridad intermedia, de los cuales las fracciones F3 y F4 mostraron potencial antiproliferativo con valores de [$GI_{50}$=µg/mL] correspondientes para F3 (7.8, 13.0, 9.6, 11.0, 8.9, 21.0) y F4 (21.0, 35.0, 27.0, 27.0, 18.0, 27.0) contra líneas celulares de tumores sólidos humanos [A549, HBL-100, HeLa, SW1573, T-47D, WiDr], respectivamente. De la purificación de F3 se aislaron los esteroles ergosterol, peróxido de ergosterol y cerevisterol, mientras que de F4 se obtuvo la antraquinona conocida como questina. Esta presentó mayor efecto antiproliferativo frente a las líneas celulares de cáncer de pulmón A549 y cáncer de cérvix HeLa [$GI_{50}$=µM] de 27.0 y 31.0, respectivamente. Además, se demostró que questina induce muerte celular por apoptosis, con un índice alto de selectividad en células tumorales SW1573 y T-47D. Finalmente, estos resultados respaldan la importancia de los estudios de bioprospección en ecosistemas como lagunas-cráter alcalinos, ya que son una fuente potencial de microorganismos de los que es posible obtener compuestos bioactivos.

## Introduction

Fungal biodiversity associated with marine organisms, sediments and the rhizosphere of mangroves, are a promising source of bioactive compounds; [1] Therefore, it is not surprising that between 2020-2022, 184 new natural products were reported isolated from 46 fungi associated with deep waters.[2] Microscopic fungi associated with these ecological niches have been able to adapt and tolerate salinity conditions, low temperature, changes of hydrostatic pressure and pH values. They have also developed the ability to produce biologically active secondary metabolites. [3,4]

In this sense, from the association of the genus *Acremonium* with algae, secondary metabolites have been reported, such as chlorinated polyketides and hydroquinone derivatives with antioxidant properties. Regarding the association of *Acremonium* sp. with marine sponges, alkaloids, peptides, oxygenated metabolites, among others, have been reported. Particularly from *A. persicinum*, 2 chloroacremines, 7 acremines (A, F, N, O, P, Q, R), meroterpenes, benzofuran derivatives, 2 cyclopeptides, 6 cyclohexapeptides including acremonpeptides E and F, a cyclic pentapeptolide and aselaycins C and D have been reported. [5–7]

Bisacremins A–D, acremin T, acremotins A–D, acremonpeptides A–D and a siderophore with antifungal properties are known from the association of *A. persicinum* with marine sediments. [8–11] Likewise, eremophilane-type sesquiterpenoids and the compound NGA0187 were isolated from Acremonium sp., associated with marine sediments and decayed leaf samples, respectively. [12,13] Therefore, it is recognized that Acremonium species from marine habitats are mainly associated with sediments, corals and sponges, and the metabolites that these species produce present chemical structures of terpenoid type (42 %), peptides (29 %), polyketides (20 %) and others (9 %), highlighting that these compounds have antibacterial, anti-inflammatory and cytotoxic effects. [14]

However, fungi associated with lagoon-craters have been little explored. Therefore, this work reports on the secondary metabolites of the liquid culture of *A. persicinum* CF25 isolated from the sediment of an alkaline lagoon-crater with anti-proliferative potential.

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## Experimental

### Collection and isolation of the strain

The *Acremonium persicinum* CF25 strain was isolated from sediment of the alkaline lagoon of Alchichica (19°25'0" N, 97°24'0" E, ~2,389 m.a.s.l.), belonging to the eastern basin of the Mexican highlands specifically from samples collected in the western area near the mountain system with larger calcareous deposits and less human activity. It was purified from hyphal tip reseeding methods in Petri dishes containing a modified A-culture medium (pH 8.5), useful for isolating fungi from marine macro-organisms and mangrove plants. [15-17] This way, pure subcultures were incubated at 25 ± 2 °C for 7 days.

### Liquid culture and extraction

*Acremonium persicinum* CF25 was cultured by submerged fermentation in a total volume of 50 L, using 500 mL Erlenmeyer flasks with 100 mL of modified Wickerham medium at pH 8.5, under shaking conditions of 150 rpm at 25 ± 2 °C for 7 days following the same period under static conditions. Once the incubation period was over, the culture broth and the biomass produced were separated by filtration using a Whatman No. 1 filter attached to a Kitasato flask, to continue with the freezing and lyophilization processes. [17] The biomass was then extracted with ethanol ($CH_3CH_2OH \geq 99.5$ %, Sigma Aldrich). Subsequently, the ethanolic extract and its solid residues were re-extracted with chloroform ($CHCl_3 \geq 99.5$ %, Sigma-Aldrich) until exhaustion, removing the solvent by distillation at reduced pressure. This generated 4 fractions of intermediate polarity, which were evaluated for their anti-proliferative potential.

### Bioguided purification of compounds

Chromatographic purification of the sub-extracts was based on their anti-proliferative capability. Thus, the extracts with the highest bioactive potential were purified by column chromatography using Merck 60 silica gel (0.2-0.5 mm and 0.040-0.063 mm) as the stationary phase and an ascending polarity gradient using Hexane:Ethyl acetate (Hx:EtOAc) mixtures as the mobile phase. The monitoring of the fractions and metabolites separated in this process was carried out by Merck 60 $GF_{254}$ thin-layer chromatography with a thickness of 0.2 mm, using iodine vapors, ultraviolet light ($\lambda$= 254 nm) and phosphomolybdic acid as developing agents. Once the presence of pure fractions was determined, washings were carried out with cold hexane to promote the crystallization of these compounds.

### Characterization and structural elucidation of metabolites

One and two-dimensional nuclear magnetic resonance experiments (NMR: $^{1}H$, $^{13}C$, COSY, HSQC and HMBC) and analyses in negative ion mode mass spectrometry (ESI-MS) are used to identify the isolated metabolites. The spectroscopic data (Ergosterol, Ergosterol peroxide, Cerevisterol and Questin) coincide with what is reported in the literature. [18-19]

### Anti-proliferative activity assays

According to the methodology proposed by the NCI, [20] six human solid tumor cell lines, A549, SW1573 (lung), HBL-100, T-47D (breast), HeLa (cervix) and WiDr (colon) were cultured in RPMI 1640 culture medium supplemented with 5 % fetal bovine serum, 100 U/mL penicillin G and 0.1 mg/mL streptomycin and 2 mM L-glutamine, incubated at 37 ºC, with 5 % $CO_2$ and 95 % relative humidity. They were then seeded in 96-well microplates using an RPMI medium to obtain a concentration of $10^4$ cells/100 µL. Each cell line was exposed for 48 h to three serial dilutions of the medium polarity fractions and pure compounds obtained from the *A. persicinum* CF25 extract, having a maximum test concentration of 250 µg/mL for fractions and 100 µM for pure compounds. Once the incubation period was over, the anti-proliferative activity was determined by a sulforhodamine B (SRB) colorimetric assay, measuring the optical density at 530 and 620 nm. The anti-proliferative activity was expressed as 50 % of growth inhibition ($GI_{50}$) caused by the fraction (µg/mL) or pure compound (µM); in this sense, fractions with a $GI_{50}$ value ≤ 50 µg/mL were considered as bioactive. [21]

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### Determination of the selectivity index (SI)

The SI of the compound to be tested was determined by the ratio of the cytotoxicity obtained in cells and non-transformed cells. If the value is (> 1) it suggests that the compound is more cytotoxic for tumor cells than for normal cells. [22] The formula used was the following: SI= $CC_{50}$ healthy cells/ $EC_{50}$ tumor cells.

### Apoptosis and effect on the cell cycle

Cancer-derived cell lines were incubated with a medium without stimulus (S/E), with dexamethasone (24 µg/mL) as a positive apoptosis control and with the test compound at the half effective concentration ($EC_{50}$). Cells were incubated at 37 °C in a 5 % $CO_2$ atmosphere for 24 h. The assay was performed according to the specifications of the Alexa Fluor® 488 annexin V/Dead Cell Apoptosis Kit with Alexa® Fluor 488 annexin V and PI for Flow Cytometry (Molecular Probes). The cells were analyzed by flow cytometry (Applied Biosystems, Atunne model), measuring fluorescence at 530 and 575 nm, using a 488 nm filter.

## Results and discussion

### Anti-proliferative activity

From the liquid culture of 50 L of A. *persicinum* CF25, 160 g of dry biomass was obtained, which was extracted with ethanol. After evaporating the solvent, two phases were generated, a liquid phase and a precipitate (F1 and F2), respectively. Subsequently, F1 and F2 were re-extracted with chloroform to generate fractions F3 (18 g) and F4 (12 g). The 4 fractions obtained in the ethanolic-chloroformic extraction stage of the biomass produced by *A. persicinum* CF25 were subjected to the determination of the anti-proliferative potential against the human solid tumor cell lines tested in this study. Thus, the fractions with the greatest anti-proliferative activity ($GI_{50}$ ≤50 µg/mL) against the six human solid tumor cell lines were those obtained by re-extraction with chloroform (F3 and F4), meanwhile fractions F1 and F2 were inactive ($GI_{50}$ >250 µg/mL), see Table 1.

**Table 1.** Growth inhibition values ($GI_{50}$) of ethanolic-chloroformic extraction fractions of *A. persicinum* CF25 biomass against six human solid tumor cell lines.

| **Biomass fractions** | **Human solid tumor cell lines ($GI_{50}$ µg/mL)** | | | | | |
|---|---|---|---|---|---|---|
| | **A549** | **HBL-100** | **HeLa** | **SW1573** | **T-47D** | **WiDr** |
| F1 | >250 | >250 | >250 | >250 | >250 | >250 |
| F2 | >250 | >250 | >250 | >250 | >250 | >250 |
| F3 | 7.8 | 13.0 | 9.6 | 11.0 | 8.9 | 21.0 |
| F4 | 21.0 | 35.0 | 27.0 | 27.0 | 18.0 | 27.0 |

Bio-directed purification of compounds was carried out on bioactive fractions F3 and F4 using conventional chromatographic techniques of normal phase column chromatography, preparative thin layer chromatography, as well as recrystallization of pure fractions. Thus, three characteristic mushroom sterols such as ergosterol (**1**), ergosterol peroxide (**2**) and cerevisterol (**3**) were isolated from fraction (F3). They were identified by thin layer analysis, comparison against authentic sample and by NMR spectroscopic data. [18] **1** was isolated in a 95:5 polarity (Hx:EtOAc), it was presented in the form of white needles with a melting point of 166 to 168 °C and Rf=0.55 (Hx:EtOAc 8:2), revealed with UV light (254 nm) and iodine vapors. **2** was isolated as a white crystalline compound with a melting point of 166-167 °C, purified from a 60:40 polarity (Hx:EtOAc), presenting an Rf=0.3 (Hx:EtOAc 7:3) revealed with UV light (254 nm) and iodine vapor. **3**

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crystallized as a white solid, with a melting point of 205-208 °C, obtained in a 50:50 polarity (Hx:EtOAc) and Rf=0.4 (EtOAc) revealed with phosphomolybdic acid.

Similarly, from fraction (F4), questin (**4**) was isolated in the form of orange crystals (3.4 mg), with a melting point of 296-298 °C, obtained in a 50:50 polarity (Hx:EtOAc) presenting an Rf = 0.4 (Hx:EtOAc 1: 1). The chemical shifts of the $^{1}H$ and $^{13}C$ NMR experiments coincided with those described previously. [4,19,23] However, we corroborated the structural identification through two-dimensional NMR experiments, which are summarized in Fig. 1. In addition, an ESI-MS analysis in negative ion mode = 283.1 m/z[M-H]$^{-}$ was performed, corroborating the molecular weight of 283 and molecular formula: $C_{16}H_{11}O_5$.

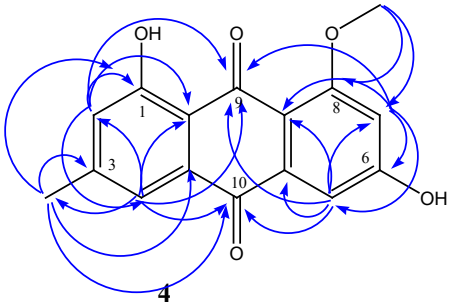


**Fig. 1.** HMBC correlations of questin (**4**). Blue arrows from proton to carbon HMBC correlations.

Once **4** was isolated and identified, its anti-proliferative activity was evaluated, showing growth inhibition values ($GI_{50}$=µM) of 27, 67, 31, 89, 100 and 93 in five of the six human solid tumor cell lines tested, A549, HBL-100, HeLa, SW1573, T-47D and WiDr, respectively. Particularly, a greater effect was observed against the lung cancer cell line A549 and the cervical cancer cell line HeLa.

In this sense, our results coincide with those reported by other fungal metabolites with a potential inhibitory effect for A549 and HeLa cell lines. An example of this is mentioned by Deng *et al*. who isolated 3*β*,5*α*-dihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6-one, inhibiting A549 and HeLa cell lines ($IC_{50}$= 4.98 and 1.95 µM), respectively, likewise, lithocarpinol A exhibited a moderate inhibition effect towards A549 cell line ($IC_{50}$ values of 10.9 µmol/L) from deep-sea derived fungus *Phomopsis lithocarpus* FS508. [24] Similarly, compounds isolated from the mangrove endophyte fungus *Pestalotiopsis* sp. demethylincisterol A3, ergosta-5,7,22-trien-3-ol, stigmastan-3-one, stigmast-4-en-3-one, stigmast-4-en-6-ol-3-one and flufuran, showed significant cytotoxicity against Hela, A549 and HepG2 (Zhou *et al*., 2018). [25] Also, acremotins A-D isolated from *A. persicinum* SC0105 showed anti-tumor activity against A549, HeLa, HepG2; $IC_{50}$: 1.2–21.6 µM. [10]

Meanwhile, Franceschy *et al*. reported antiproliferative activity for ergosta-8(14),22-dien-3,5,6,7-tetraol against A549 and HeLa, with values of ($GI_{50}$=16 and 18 µM), respectively. [17] Likewise, other fungal sterols were reported as active against cancer cell lines as the three new ergosterols, cholethosterols A-C from *Colletotrichum magnisporum* showed notable cytotoxic activity against A549 and HeLa, with values of $IC_{50}$ = 3.76-11.18 µM. [26] The metabolites phychaetoglobin D, chaetoglobosin C, chaetoglobosin E, chaetoglobosin G, chaetoglobosin V isolated from *Chaetomium globosum* kz-19 presented cytotoxic activities against A549 and HeLa with $IC_{50}$ = 3.8 to 13.7 µM. [7] From the AcOEt extract of the endophytic fungus *Penicillium herquei*, nine oxidized ergosterols known as penicisterols were isolated, of which penicisterols B and C showed cytotoxic activity against 4T1, A549 and HeLa cell lines, with values ranging from $IC_{50}$ = 17.22 to 31.35 µM. [27]

The evaluation of the cytotoxic effect on cancer cell lines of **4** showed a cytotoxic concentration of 50 % cell viability ($CC_{50}$) with good effectiveness, being cytotoxic at concentrations [µg/mL] A549 (59.45), HBL100 (57.59), HeLa (60.06), SW1573 (10.26), WiDr (4.71), NIH/3T3 (30.37), J774A.1 (1,103.00). The J774A.1 cell line showed peaks of proliferative activity at 50 µg/mL so it was not considered as a control to establish the selectivity index.

In this way, it was demonstrated that questin (**4**) exerts a cytotoxic effect at different concentrations against each cell line evaluated. This allowed establishing the $CC_{50}$ in the transformed or tumor cell line and the non-transformed epithelial cell line NIH/3T3 and thus calculating the selectivity index. In this sense, **4**

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presented an excellent SI against SW1573 and T-47D tumor cells, showing SI values = 2.96 and 6.44, respectively (Table 2).

**Table 2.** $CC_{50}$ of questin (**4**) tested on transformed cell lines and selectivity index with respect to the non-transformed cell line NIH/3T3.

| Cell line | $CC_{50}$ | SI NIH/3T3 |
|---|---|---|
| A549 | 59.45 | 0.51 |
| HBL-100 | 57.49 | 0.52 |
| HeLa | 60.06 | 0.50 |
| SW 1573 | 10.26 | 2.96 |
| T-47D | 4.71 | 6.44 |
| NIH/3T3 | 30.37 | 1.00 |

After obtaining the SI, the induction of apoptosis after the interaction of **4** with the SW1573 and T-47D cell lines was evaluated using propidium iodide and annexin V staining to determine their viability or their progress to apoptosis or necrosis through differences in the integrity of the plasma membrane and the increase in its permeability. In Figure 2, positivity is observed for SW1573 and T-47D with values of 6.65 and 15%, respectively. The above allows to establish that **4** induces cell death by apoptosis, with a high selectivity index in SW1573 and T-47D cells.

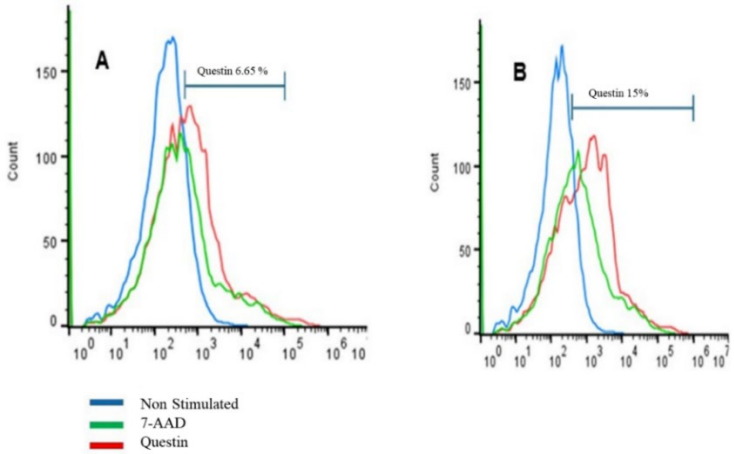


**Figure 2.** Effect of questin (**4**) on apoptosis of A) SW-1573 and B) T-47D. $1x10^5$ cells were incubated without stimulation (S/E) as a negative control; cells stimulated with 10 mM 7-AAD as a positive control and four concentrations according to their $CC_{50}$. Subsequently, they were stained with annexin V for evaluation of cell death by apoptosis.

During apoptosis, PS is translocated to the outer leaflet of the plasma membrane, which can be detected by annexin V due to its strong affinity for PS. [28] The translocation of phosphotidylserine (PS) residues from the inner face of the plasma membrane to the cell surface is an event that occurs in the early stages of apoptosis and can therefore be used to detect and measure this process. Annexin V has a strong $Ca^{2+}$ dependent affinity

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and can therefore be used as a probe for the detection of apoptosis. [29-30] Understanding the mechanisms of cell death and survival can be a critical aspect for the description of new drugs and their toxicological aspect. [31-32] Same studies suggest that cytotoxic effects of chemical products in different mammal cells and microorganisms are mediated through mechanisms involving cell wall disruption, actin cytoskeleton remodeling, autophagy induction, and perforin-1 and fas-based pathways. [33-35]

Thus, **4** induces cell death by apoptosis, with a high selectivity index in SW1573 and T-47D cells. Likewise, **4** presented cytotoxic activity at lower concentrations than ergosterol on transformed MCF-7 breast cancer cell lines. [36] These effects of **4** are also observed in other cytotoxic metabolites of the genus *Acremonium*, such as fusidione isolated from *A. fusidioides* RZ01, against (HL-60; $IC_{50}$: 44.9 μM), triacremoniate isolated from the marine-fungus *A. citrinum* MMF4 against (HeLa $IC_{50}$: 30.46 ± 1.99 μM), acremochlorins (A, E-G, K-M) against (MDA-MB-231 and MDA-MB-468, $IC_{50}$: 0.48–45 μM), respectively. [37–39] Also, anti-tumor metabolites are known, Wang *et al*. reported acremotins A-D isolated from *A. persicinum* SC0105 with anti-tumor activity against (A549, HeLa, HepG2; $IC_{50}$: 1.2–21.6 μM). [10] Similarly, Alfatah *et al*. isolated hypoculine from *Acremonium* sp. F2434 (LUNG, PAAD; $IC_{50}$: 9–14 μM) and Pulat *et al*. isolated marinobazzanan with anti-tumor activity isolated from *Acremonium* sp. CNQ-049. [13, 40]

The above suggests that **4** is a good candidate that could help in the treatment of cancer and the observed selectivity could be related to its activity as a metabolic modulator. This same activity has been observed in different compounds derived from fungi. Currently, 270 species of mushrooms are known to be potentially useful for human health, due to their known action against neoplasia and belong to the genera: *Agaricus, Albatrellus, Antrodia, Calvatia, Clitocybe, Cordyceps, Flammulina, Fomes, Funlia, Ganoderma, Inocybe, Inonotus, Lactarius, Laetiporus, Phellinus, Pleurotus, Russula, Schizophyllum, Suillus, Trametes* and *Xerocomus*, and the compounds isolated from these mushrooms present cytotoxic and antitumor activity. [41-44]

## Conclusions

Fractions F3 and F4 of the biomass extract of *Acremonium persicinum* CF25 showed an antiproliferative effect against human solid tumor cell lines (A549, HBL-100, HeLa, SW1573, T-47D and WiDr). Three bioactive sterols were isolated from the bioguided purification of F3. The anthraquinone questin (4) was isolated from F4, presenting a greater antiproliferative effect against the A549 lung and HeLa cervical cancer cell line. In addition, 4 was shown to induce cell death by apoptosis with a high selectivity index in SW1573 and T-47D tumor cells. Finally, these results support the importance of bioprospecting studies in ecosystems such as alkaline lagoon craters, since they are a good source of microorganisms from which it is possible to obtain bioactive compounds.

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