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CYTOTOXIC AND ANTIPROLIFERATIVE STUDIES OF ISOCORDOIN AND SOME DERIVATIVES AGAINST PROSTATE CANCER CELL LINES

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ABSTRACT: The proposed study was to evaluate the *in-vitro* cytotoxic and antiproliferative activities on prostate cancer cell lines of isocordoin (1) and 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone (2), chalcones isolated from roots of *Lonchocarpus xuul* Lundel, together with four analogues of 1. Isolation of compounds 1 and 2 from *L. xuul* roots and chemical modification were in accordance with previous works. All compounds were characterized by NMR spectroscopy and mass spectrometry. *In-vitro* cytotoxic and antiproliferative activities of compounds 1-6 against prostate cancer cell lines PC3, PC3M, DU145, and TRAMPC2, were evaluated using the MTT and sulforhodamine B method, respectively. Additionally, cytotoxic studies with HEK 293 cells were carried out, and a selective index was calculated. From them 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone (2), 2´,4´-diacetoxy-3´-(3-methylbut-2-enyl) chalcone (3), 2´-methoxy-3´-(3-methylbut-2-enyl) chalcone (5) together with isocordoin (1) showed the strongest cytotoxic activity on PC3M cell lines in the ranged of 2-3 μg/mL. Isocordoin showed the strongest activity also on TRAMPC2 cell lines (CC_{50}= 1.01 μg/mL). None of the compounds were cytotoxic (CC_{50} =14 to 667 μg/mL) on HEK293 cell line. Xanthohumol, a natural active chalcone, and docetaxel were used as positive controls. The modifications made to isocordoin (1) in all cases reduced the cytotoxicity of this metabolite on HEK 293 cell lines; however, no antiproliferative properties were detected on compounds 1-6.

INTRODUCTION: The term cancer encompasses a group of more than a hundred different types of the disease whose main characteristic is the rapid and disorganized growth of abnormal cells [1, 2]. At present, cancer is a major health problem in many developed countries and the leading cause of death worldwide [3].

Cancer therapy is based primarily on the association of surgical resection of tumors with radiotherapy, immunotherapy and/or chemo-therapy. The efficacy of cancer drugs is often limited by their insolubility and instability, the low rate at which the tissue absorbs them, and drug resistance [4].

Many studies have suggested that flavonoids exhibit anticancer properties, among others [5-7]. From then, chalcones (1, 3-diaryl-2-propen1-ones) are a type of flavonoids, which are abundant in most edible plants. Natural and synthetic chalcones display anticancer activity against various tumor cells lines *in-vitro* and *in-vivo* [8-11].

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From them, isocordoin (1), one of the main chalcone isolated from the root of *L. xuul*, together with a natural analogue of isocordoin, 2', 4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone has been pharmacologically studied [12-13]. Isocordoin (1) has been reported in some *Lonchocarpus* species and has many different biological activities. Isocordoin has demonstrated antiprotozoal activities when it was tested against *Leishmania braziliensis*, *L. donovani*, *L. amazonensis* and *Trypanosoma cruzi*[14-15]. Isocordoin (1) can inhibit the cell proliferation of ovarian cancer cells by competing with type II oestrogen binding sites [16]. However, there are no studies on the cytotoxic/ antiproliferative activities of this metabolite and its derivatives on different prostate cancer cell lines.

Here we described the isolation and derivatization of isocordoin (1) and their cytotoxic/ antiproliferative activities, together with the evaluation of its natural analogue, 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone (2). The *in-vitro* cytotoxic and antiproliferative activities were assessed against four prostate cancer cell lines: DU-145, PC3, PC3M and TRAMPC2. Parallelly, all derivatives were tested against HEK 293 cells to valorate the cytotoxicity of these metabolites.

MATERIALS AND METHODS:

General Procedures: Purification was performed using silica gel 60 (0.040-0.063 mm, Merck, Darmstadt, Germany) or Silica gel $60F_{254}$ (Merck) for thin-layer chromatography. Gel permeation column chromatography was carried out using Sephadex LH-20 from Pharmacia (Barcelona, Spain). Analytical TLC was performed on silica gel $60F_{254}$ aluminum plates (E.M. Merck, 0.2 mm thickness). Detection of the components under UV/Vis light at 254 nm and 365 nm was performed on a UV cabinet.

Visualization of components were done by using a solution of phosphomolybdic acid (20 g) and ceric sulfate (2.5 g) in 500 mL of sulfuric acid (5%), followed by heating. Reagents for derivatization together with xanthohumol were commercially obtained from Sigma-Aldrich and Fluka companies. Melting points were determined on a Thermocouple apparatus. IR spectra were recorded in KBr disc on a FT-IR Nicolet Protegé. ^{1}H- and the 13C-NMR spectrum was recorded on a Bruker Avance 400 NMR spectrometer at 400 MHZ and 100 MHz, respectively.

Plant Material: Roots of *Lonchocarpus xuul* Lundell (Leguminosae) were collected in Yaxcabá, Yucatan, Mexico, and identified by Dr Martha Mendez, Unidad de Recursos Naturales at CICY. A voucher specimen was deposited at the Herbarium "Roger Orellana" of the Centro de Investigación Científica de Yucatán (CICY) under the collection number MMéndez 2310.

Extraction and Isolation: Powdered roots (1 Kg) of *L. xuul* were extracted successively with *n*-hexane (3 × 6 L) at room temperature for 72 h. Evaporation of the solvent under reduced pressure provided 124 g of crude extract (12.43%).

Initial fractionation of the hexane extract (15 g) by VLC, eluting with 100% *n*-hexane and *n*-hexane: EtOAc 98:2 furnished six major fractions. Fraction four (2.43 g) was further purified by CC (benzene 100%), followed by gel permeation chromatography (100% MeOH) to afford 169 mg (0.13%) of solid yellow powder of isocordoin (1) and 25 mg of a pale yellow powder of 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone (2).

Isolates: 2',4'-dihydroxy-3'-(3-methylbut-2-enyl) chalcone (isocordoin) (1) (yellow amorphous solid) and 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl) dihydrochalcone (dihydroisocordoin) (2) (colorless oil), UV, IR and HR-EIMS in agreement with published data; ^{1}H- and ^{13}C-NMR are identical to those reported in a previous work.

Preparation of 2´, 4´-diacetoxy-3´-(3-methylbut-2-enyl) Chalcone (3): A mixture of 1 (8 mg), acetic anhydride (1 mL), and pyridine (2 mL) was allowed to stir overnight at room temperature. The reaction mixture was poured over water (30 mL) and the resulting suspension was extracted with ethyl acetate (3 times 1:1).

The organic layer was washed (1:1, v: v) successively in water, 5% HCl, 5% $NaHCO_3$ and a NaCl saturated solution. The treatment of the solvent with anhydrous Na_2SO_4 followed by filtration and evaporation yielded 10 mg of pure compound 3.

2´, 4´- diacetoxy - 3´- (3-methylbut – 2 - enyl) Chalcone (3): Yellow oil. Retention time (GC) = 13.92 min; IR ν_{max} (KBr): 1767, 1680, 1367, 1193 cm^{-1}. EI-MS (rel. Int.): m/z = 349 (90), 307 (100), 265 (90), 231 (10), 203 (60), 149 (70), 130 (55), 103 (42), 77 (20), 43 (55); HR-EIMS: m/z = 349.000 $[M+Na]^+$ (calcd. For $C_{24}H_{24}O_5$: 349.0101); ^{1}H NMR ($CDCl_3$):δ = 1.68 (3H, s), 1.74 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 3.25 (2H, *d*, *J*=6.8 Hz, H1¨), 5.03 (1H, *t*, *J*=6.8 Hz, H2¨), 6.98 (1H, *d*, *J*=8.8 Hz, H5´), 7.09 (1H, *d*, *J*=8.4 Hz, H6´), 7.17 (1H, *d*, *J*=16 Hz, Hα), 7.60 (1H, *d*, *J*=17.6 Hz, Hβ). ^{13}C NMR ($CDCl_3$, 100 MHz):192.7 (C, C=O), 169.4 (C, C=O), 169.0 (C, C=O),152.3 (C, C4'), 148.6 (C, C2'), 145.9 (CH, Cβ), 134.8 (C, C1), 132.9 (C, C3"), 131.2 (CH, C4), 129.4 (CH, C3, C5), 128.9 (CH, C2,C6), 128.3 (CH, C6'), 128.1 (C, C1', C3'), 125.3 (CH, Cα), 121.1 (CH, C2"), 120.6 (CH, C5'), 26.0 (CH_3, C3"), 24.5 (CH_2, C1"), 21.3 (CH_3), 21.2 (CH3), 18.3 (CH_3, C3").

Preparation of 2´, 4´-Dimethoxy-3´-(3-methyl-but-2-enyl) chalcone (4) and 2´-Hydroxy, 4´-methoxy-3´-(3-methylbut-2-enyl) chalcone (5): A mixture of 1 (30 mg), CH_3I (200 µl) and K_2CO_3 (100 mg) in 2 mL of acetone was left to stir overnight at room temperature and then diluted with 10 mL of water. The resulting solution was extracted with Ethyl Acetate (2× 20 mL). The crude reaction product presented two major components by TLC. The reaction mixture was purified by preparative TLC (*n*-hexane:acetone 8:2) to give metabolites 4 (24 mg) and 5 (4.5 mg).

2´, 4´- Dimethoxy - 3´- (3 – methylbut – 2 - enyl) chalcone (4): Pale yellow oil; Retention time (GC) = 13.38 min; IR ν_{max} (KBr) cm^{-1}: 1641 (C=O), 1286 (C-O-C). ^{1}H NMR (400 MHz, $CDCl_3$):δ 1.79 (s, 3H), 1.96 (s, 3H), 3.40 (2H, *d*, *J*=6.8 Hz, H1¨), 3.69 (s, 3H), 3.73 (s, 3H), 5.18 (1H, *t*, *J*=6.9 Hz, H2¨), 6.73 (1H, *d*, *J*=8.6 Hz, H5´), 7.45 (1H, *d*, *J*=15.8 Hz, Hα), 7.61 (1H, *d*, *J*=8.6 Hz, H6´), 7.73 (1H, *d*, *J*=15.8 Hz, Hβ). ^{13}C NMR and HR-EIMS in agreement with published data.

2´-Hydroxy, 4´-methoxy-3´-(3-methylbut-2-enyl) chalcone (5): Yellow powder; Retention time (GC) = 14.58 min; IR ν_{max} (KBr) cm^{-1}: 3385, 1659, 1337, 1275. ^{1}H NMR (400 MHz, $CDCl_3$):δ 1.69 (s, 3H), 1.81 (s, 3H), 3.39 (2H, *d*, *J*=6.8 Hz, H1¨), 3.93 (s, 3H, OMe), 5.23 (1H, *t*, *J*=7.2 Hz, H2¨), 6.51 (1H, *d*, *J*= 9.2 Hz, H5´), 7.61 (1H, *d*, *J*= 15.6 Hz, Hα), 7.81 (1H, *d*, *J*= 9.2 Hz, H6´), 7.88 (1H, d, J=15.6 Hz, Hβ), 13.37 (1H, s, 2´-OH).^{13}C NMR and HR-EIMS in agreement with published data.

Preparation of 2",2"-dimethypyran (5",6"3',4')-2'-hydroxy chalcone (6): 15 mg of chalcone 1 were heated under reflux for 24 h with 5 mL EtOH, 3 mL H_2O, and 0.5 mL conc. HCl. After the reaction mixture was complete (TLC monitoring) the contents were poured into ice water. The solid obtained was purified on gel permeation column chromatography using sephadex LH20 and eluting with MeOH to yield 6 mg of 5.

2",2"-dimethypyran (5", 6" 3', 4') - 2' - hydroxy chalcone (6): Yellow powder; Retention time (GC) = 13.92 min; IR (KBr): 2975, 1639, 1588, 1357, 1105; HR-EIMS, ^{1}H- and ^{13}C-NMR in agreement with published data.

Cytotoxicity Test: Cytotoxicity was performed by the MTT assay [27]. The cancer cell lines PC3 (human prostate), PC3M (cancer metastatic human prostate), DU154 (human prostate carcinoma), TRAMPC2 (mouse prostate cancer), and HEK 293 (Human embryonic kidney cell line) were cultured in DMEM medium supplemented with 10% fetal bovine serum (SFB), and then, it was added to the culture medium, 100 U/mL penicillin and 100 µg/mL streptomycin, to inhibit the growth of Gram-positive and negative bacteria.

To inhibit the growth of fungi it was also added amphotericin B and maintained it at 37°C in a 5% CO_2 atmosphere with 95% humidity. When cells reached >70% confluence, the medium was replaced and the cells were treated with different concentrations of the compounds dissolved in dimethyl sulfoxide (DMSO).

Docetaxel and xanthohumol were used as a positive control. The concentration of the compound that killed 50% of the cells (CC_{50}) was calculated by the formula: Percentage of cells killed = ($OD_{control}$ –OD_{sample}/$OD_{control}$) × 100. Results are expressed as the concentration of compound that killed 50% of the cells (CC_{50}), and they were calculated using the software GraphPad Prism 4. All determinations were performed in triplicate.

Antiproliferative Activity: To study cell proliferation, prostate cancer cells were cultured with DMEM medium until they reached >70% confluence in a microtiter plate. After this, the medium was replaced with DMEM 5% FBS. Cells (5×10^4 cells per well) were incubated with appropriate dilutions of the test compounds for 48 h. After 48 h, the medium was discarded, and cells were fixed by adding 50 µL of 10% trichloroacetic acid (TCA, Sigma-Aldrich Chemical, St Luis, MO, USA). The cells were incubated at 4 °C for 30 min; TCA was drained off, and the plates were left to dry. Then, 50 µL of sulforhodamine B stain (10 mg of 1% acetic acid, Sigma) were added to each well for 30 min [31]. Finally, the plates were washed four times with 1% acetic acid (100 µL). The OD was measured at 540 nm using and ELISA reader (Bio-Rad). The concentration of the compound that inhibits cell proliferation (IC_{50}) was calculated by the formula:

$$\text{Growth Inhibition (\%)} = (OD_{control} - OD_{sample}/OD_{control}) \times 100.$$

Results are expressed as the concentration of compound that reduced cell growth (IC_{50}) by 50%, and they were calculated using the software GrahPad Prism 4. All determinations were performed in triplicate.

RESULTS AND DISCUSSION: Successive chromatographic purifications of the hexane root extract of *L. xuul*, using a combination of VLC, gravity column chromatography, and gel filtration on sephadex LH-20 resulted in the isolation of metabolites 1 and 2 in pure form. The less polar metabolite 1, was obtained as a yellow amorphous solid. The parent ion peak at *m/z* 308 of its mass spectrum suggested a molecular formula $C_{20}H_{20}O_3$, which in turn indicated the presence of nine unsaturation sites in the structure. The ^{1}H NMR spectrum of 1 showed a number of signals that allowed to identify as 2',4'-dihydroxy-3'-(3-methylbut-2-enyl) chalcone, commonly named as isocordoin, previously reported from *Cordoa piaca*, *Adesmia balsamica*, *L. xuul*, and other Lonchocarpus species. Metabolite 2 was obtained as colorless oil. Its molecular formula ($C_{20}H_{22}O_3$) was determinated from the molecular ion peak at *m/z* 310 and consistent with ten degrees unsaturation. The ^{1}H NMR spectrum of 2 showed a number of signals that suggested an isocordoin-type structure, namely two one-proton signals at 6.35 (H-5', *d*, *J*= 8.8) and 7.54 (H-6', *d*, *J*= 8.8) corresponding to the two *ortho*-coupled protons of a 1,2,3,4 tetra substituted aromatic ring, and two multiples at 7.30 (2H and 7.25 (3H) corresponding to the five protons of a second monosubstituted aromatic ring. Additionally, the ^{1}H NMR of 2 displayed characteristic signals of two methylene groups (A_2B_2 system) at 3.04 (2H, *t*, *J*= 7.7) and 3.24 (2H, *t*, *J*= 7.7). Finally, the observed fragment ions at *m/z* 105 and 91 in the MS of 2 confirmed a dihydrochalcone-type structure. On the basis of its spectroscopic data, metabolite 2 was identified as 2', 4'- dihydroxy - 3' - (γ, γ - dimethylallyl) dihydrochalcone, commonly named as dihydro-isocordoin, previously reported from *L. xuul* and reported as erioschalcone B from *Eriosema glomerata*. Isocordoin (1) was first chemically modified at its phenolic hydroxyl position to get three different analogues (3-5). Compound 3 corresponds to the fully acetylated derivative of 1 named 2´,4´-diacetoxy-3´-(3-methylbut-2-enyl) chalcone. On the other hand, compounds 4 and 5 correspond to the dimethylated and monomethylated derivative of 1, named 2´, 4´-dimethoxy-3´-(3-methylbut-2-enyl) chalcone (4) and 2´-hydroxy-4´-methoxy-3´-(3-methylbut-2-enyl) chalcone (5), respectively. Modification of the prenyl chain of 1 allowed to obtain compound 6, named 2",2"-dimethypyran (5",6"3',4')-2'-hydroxy chalcone. Compound 7 corresponds to a commercially available xanthohumol (7). All compounds (1-7) **Fig. 1** were assayed for their cytotoxic and antiproliferative activities on four prostate cancer cell lines: DU-145, PC3, PC3M, and TRAMPC2, and the results are illustrated in **Table 1** and **2.**

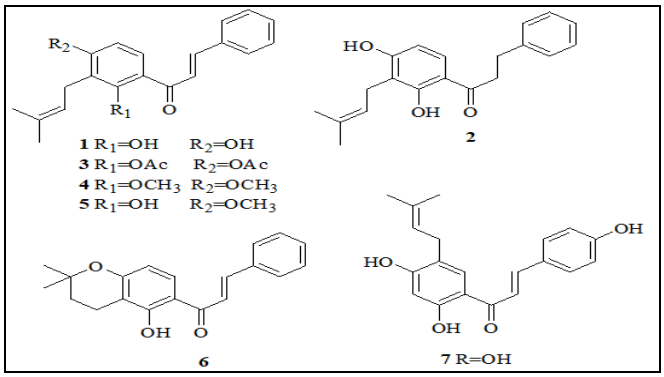

FIG. 1: CHEMICAL STRUCTURE OF ISOCORDOIN (1), ISOCORDOIN DERIVATIVES (2-6) AND XANTO-HUMOL (7)

The results obtained of the cytotoxic activity showed that almost all compounds, except compound 6, were active on the PC3M cell line with a CC_{50} of 1.76-3.52 µg/mL **Table 1**. Compound 4 showed a moderative activity against PC3M (CC_{50}=10.47 µg/mL). On the contrary, none of the derivatives 1, 4, 5, and 6 were active against DU-145 and PC3 (CC_{50}> 40 µg/mL), except xanthohumol, which means that the presence of the prenyl chain is important for the effectiveness of the cytotoxic activities of chalcones. Previous studies had been reported the importance of the prenyl chain in the biological activities of flavonoids. Some authors report that the presence of prenyl chain increases the hydrophobicity and pharmacological properties through enhanced affinity for the lipophilic membrane [16]. In addition, the cytotoxic activity of hydroxylated compounds 1, 2, and 7 are in accordance of previous studies on structure-activities relationships that demonstrated that the biological activities were determined by the number of oxygenated substituents (OH), an ability that is related to the collapse of mitochondrial membrane potential and increased oxygen uptake [17]. In the case of isocordoin derivatives, the cytotoxic activity increased slightly after esterification of both hydroxyl groups (3) on PC3M cancer cell lines (CC_{50}= 2.56 µg/mL). On the contrary, the dimethylated derivative (4) showed a minor cytotoxic activity in comparison with the monomethylated (5) derivative (CC_{50}=3.05 µg/mL) in the same cancer cell line. In order to confirm the selectivity of the analogues on prostatic cancer cell lines, the *in-vitro* cytotoxic evaluation against HEK 293 cell line was performed. According to the National Cancer Institute, one compound is considered cytotoxic when it has an IC_{50} value of ≤4 µg/mL. None of the compounds tested showed cytotoxic effects on HEK 293 cell line with a CC_{50} value between 14-667 µg/mL **Table 1.**

TABLE 1: *IN-VITRO* CYTOTOXIC ACTIVITIES (CC_{50}) OF ISOCORDOIN AND ITS ANALOGUES

Compound	Cell Lines CC_{50} ± SD µg/mL				
	HEK 293	DU-145	PC3	PC3M	TRAMPC2
1	14.56±2.64	7.12±2.45	18.58±2.30	2.65±1.06	1.01±0.97
2	27.65±4.17	>100	9.87±1.42	3.52±1.21	>100
3	29.83±4.36	6.52±1.23	10.18±1.32	2.56±0.97	13.44±4.03
4	167.9±4.21	>100	>100	10.47±2.64	39.48±2.12
5	667±7.32	40.28±3.85	>100	3.05±1.57	33.36±4.28
6	102.9±5.34	46.90±5.61	37.08±2.32	>100	27.03±2.15
7	3.45±1.32	1.64±0.95	0.79±0.24	1.76±0.78	6.65±2.42
Docetaxel	0.09±0.07	0.06±0.03	0.05±0.06	0.073±0.01	0.04±0.03

Data are expressed as mean standard deviations of three determinations.

While cytotoxicity determines the capacity of cells to survive or die in the presence of the compounds, cell proliferation allowed measuring the capacity of the compounds to affect cell division and proliferation, which is of special relevance in all types of cancer cells. As can be seen in **Table 2**, treatment with different concentrations of compounds 1-6 does not affect cell proliferation of almost all prostatic cancer cell lines. Compound 1 showed a moderate antiproliferative activity on PC3 (IC_{50}= 8.12 µg/mL) and PC3M (IC_{50}= 8.30 µg/mL) cell lines in comparison with compounds 2-6.

TABLE 2: *IN-VITRO* ANTIPROLIFERATIVE ACTIVITIES (IC_{50}) OF ISOCORDOIN AND ITS ANALOGUES

Compound	Cell Lines IC_{50} ± SD µg/mL				
	HEK 293	DU-145	PC3	PC3M	TRAMPC2
1	60.80±5.64	13.50±3.23	8.12±3.31	8.30±4.21	12.56±3.89
2	30.50±3.11	>100	29.04±8.12	44.89±7.24	36.68±6.02
3	64.87±4.78	48.93±4.16	20.46±4.21	13.23±5.21	11.61±3.81
4	194.20±5.34	>100	>100	43.20±7.01	16.78±6.23
5	221.70±5.34	>100	>100	36.89±5.71	14.44±2.98
6	143.00±7.34	>100	34.06±8.38	41.78±9.22	28.74±2.65
7	10.30±1.23	5.24±1.65	6.79±1.45	15.57±4.56	13.59±3.65
Docetaxel	0.02±0.04	0.014±0.013	0.005±0.001	0.002±0.001	0.02±0.004

Data are expressed as mean standard deviations of three determinations.

Recent studies made by Da Silva *et al*., (2019) demonstrated the antiproliferative action of a mixture of isocordoin (1), 2´,4´-dihydroxy-5´-prenylchalcone (2), prenylpinocembrin, lupeol, and lupenone contained in the hexanic extract of aerial part of *Lonchocarpus cultratus* against cells of chronic myeloid leukemia K562 (GI_{50}=0.71 µg/mL), breast MCF-7 (GI_{50}=2.53 µg/mL) and ovary multidrug resistance phenotype (GI_{50}=2.67 µg/mL) [18]. In addition, 2´,4´-dihydroxy-5´-prenylchalcone (8) has potent cytotoxic activities against breast (Hs578T), prostate (PC3), and liver (Hep G2) cancer cell lines with IC_{50} values 1.3,0.1 and 7.3 µg/mL, respectively. Therefore, it is not ruled out that the synergistic combination of isocordoin derivatives could potentiate the antiproliferative activity on prostate cancer cell lines. In summary, chalcones are important prototypes of anticancer drugs, mainly on ovarian and prostatic cancer cell lines. Strategies in the evaluation of the synergistic combination of derivatives 2-6, together with isocordoin (1) will be the subject of future work. This is the first report on the cytotoxic and antiproliferative activities of isocordoin derivatives on prostatic cancer cell lines.

CONCLUSION: We concluded that some modifications on isocordoin structure, especially the acetylation of both hydroxyl groups increasing the cytotoxic activity of this metabolite, and it has a better effect in PC3M cell lines.

The position of the substituents seems to be important for the effectiveness of the cytotoxic activity evaluated. The modifications made to isocordoin in all cases reduced the cytotoxicity of this metabolite on HEK 293 cell lines so far; however, no antiproliferative properties were detected on compounds 6-7.

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