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Pentalinon andrieuxii, a Medicinal Plant with Antiviral Activity Against the Influenza A(H1N1pdm09) Virus

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Abstract. Respiratory viral infections, including influenza, continue to pose a significant global health challenge, leading to seasonal epidemics every year. The 2009 outbreak, triggered by a new strain of the influenza A(H1N1pdm09) virus, marked the first influenza pandemic of the 21st century that resulted in over 200,000 fatalities across more than 214 countries. Presently, and despite the availability of vaccines and antiviral medications, the ongoing mutations of these viruses necessitates continuing the search for new and more effective antiviral treatments.
Pentalinon andrieuxii, a vine native to the Yucatán Península, is traditionally used in Mayan medicine to treat snake bites and the skin lesions caused by cutaneous leishmaniasis. Current phytochemical knowledge of *P. andrieuxii* includes reports of tri-nor-sesquiterpenes, triterpenes, steroid derivatives, and sterols. However, to date, there are no reports on the antiviral activity of the extract or secondary metabolites from this plant. As part of our search for new antiviral metabolites from plants of the Apocynaceae family, we wish to report herein on the inhibition of the cytopathic effect of the semipurified fractions from the leaf extract of *P. adrieuxii*, when tested against the A/Yucatan/2370/09 (H1N1pdm09) strain of the influenza A virus, and the identification of polyphenolic metabolites in the bioactive fraction.

J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

Resumen. Las infecciones respiratorias causadas por virus, entre ellas la gripe, siguen siendo un importante reto sanitario a nivel mundial, cada año provocan epidemias estacionales. El brote de 2009, desencadenado por una nueva cepa del virus de la gripe A(H1N1pdm09), marcó la primera pandemia de gripe del siglo XXI y causó más de 200,000 víctimas mortales en más de 214 países. En la actualidad, pese a la disponibilidad de vacunas y medicamentos antivirales, las continuas mutaciones de estos virus obligan a seguir buscando tratamientos antivirales nuevos y más eficaces.
Pentalinon andrieuxii, una enredadera originaria de la Península de Yucatán, se utiliza tradicionalmente en la medicina maya para tratar las mordeduras de serpiente y las lesiones cutáneas causadas por la leishmaniasis cutánea. El conocimiento fitoquímico actual de *P. andrieuxii* incluye informes de tri-nor-sesquiterpenos, triterpenos, derivados de esteroides y esteroles. Sin embargo, hasta la fecha no existen informes sobre la actividad antiviral del extracto o los metabolitos secundarios de esta planta. Como parte de nuestra búsqueda de nuevos metabolitos antivirales de plantas de la familia Apocynaceae, deseamos reportar la inhibición del efecto citopático de fracciones semipurificadas del extracto de hoja de *P. andrieuxii*, evaluados contra la cepa A/Yucatan/2370/09 (H1N1pdm09) del virus de Influenza A, y la identificación de polifenoles en la fracción bioactiva.

Introduction

Currently, seasonal influenza infections are responsible for approximately 300,000 deaths annually worldwide.[1] International travel and migration are believed to have facilitated the spread of pathogenic strains of virus and microorganisms, with cities becoming important hubs for the transmission of infectious diseases. Several rural or wild pathogens have adapted to urban environments, while others have emerged or re-emerged in urban areas.[2-3]

Influenza A(H1N1) belongs to the Orthomyxoviridae family that includes seven genera and of these, influenza A, B and C can affect humans. These viruses are pleomorphic particles (80-120 nm), characterized by having a lipid coat covered of two important glycoproteins: hemaglutinin (HA) and neuraminidase (NA). Their genomes are segmented negative-strand RNAs and a complex of their own RNA-dependent polymerase. The natural reservoir of the influenza virus is wild waterfowl,[4] in humans it is transmitted via aerosols from the respiratory tract and the main symptoms of influenza are related to respiratory diseases which include headache, fever, muscle pain, nasal congestion, cough, and diarrhea. In the northern and southern hemispheres the presence of influenza is associated with the colder months, while in the tropics there is no association with the climatic time of the year.[5]

Presently, the overall share of antivirals developed for the treatment of influenza infections is only 4.6 %, with 10 % of these being antivirals approved for the treatment of acute infections [6]. Currently the antivirals used against influenza that are approved by the US Food and Drug Administration (FDA) include the neuraminidase (NA) inhibitors zanamivir, oseltamivir, and peramivir. While there are a number of antivirals being developed, including Baloxavir marboxyl (zofluza), VIS-410, MEDI-8852, Pimodivir, JNJ-5806, NT300, Fludase, Laminavivir Octanoate, Radavisen, and DAS181,[6] the existence of oseltamivir-resistant mutants emphasizes the urgent need to use known targets to search for new molecules with antiviral activity from different natural sources.[7]

To date, a number of natural products from plants have shown to posses antiviral activity,[8] particularly against the Influenza A virus (IAV),[9] The Apocynaceae family is known to be one of the most diverse angiosperm families, rich in alkaloids, flavonoids, carbohydrates, and terpenoids such as cardenolides and steroids.[10] A number of plants from this family have demonstrated antiviral activity, with cardenolides identified as the key bioactive metabolites contributing to these effects.[10] Recently, *Pentalinon andrieuxii* (Müll. Arg.) B.F. Hansen & Wunderlin (Apocynaceae) (Fig. 1) has been reported to contain cardenolides structurally-related to oleandrin, that are used by lepidopterans as part of their own defense mechanism against predators.[11] Even though there are limited reports on the biological activity of the phytochemicals identified from *P. andrieuxii*, sterols isolated from the roots have been reported to show immunomodulatory effect when treated with activated macrophages.[12] However, in view of the recent reports about the cardenolide oleandrin having antiviral activity against COVID-19,[13] and the fact that cardenolides structurally-related to oleandrin

J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

have been detected in the leaf extracts of *P. andrieuxii*,[11] we describe here the evaluation of the antiviral activity of the leaf crude extract and its semipurified fractions when tested against the A/Yucatan/2370/09 A(H1N1pdm09) strain of the influenza A virus.

Fig. 1. Flowering plant of *Pentalinon andrieuxii*.

Experimental

Plant material

Fresh leaves of *P. andrieuxii* were collected in Merida, Yucatan, Mexico in June 2018 from a population kept in the nursery of Centro de Investigación Científica de Yucatán. A voucher specimen was deposited at the Herbarium of CICY under collection number 68850.

Extraction, isolation and identification. The plant material (600 g) was dried at room temperature for three days, and then it was ground and extracted three times by maceration with methanol (20 L) at room temperature. The solvent was filtered, first through cheesecloth, then cotton, and evaporated under reduced pressure to yield 59 g (23 %) of crude methanolic extract (A1). A portion (15 g) of the crude extract (A1) was suspended in a mixture of H_2O/methanol (3:2, v/v) and the resulting suspension was successively partitioned with hexane (three times, 2:1, v/v,), dichloromethane (three times, 2:1, v/v,), and ethyl acetate (three times, 2:1, v/v,) to produce the corresponding low (1A, 8.75 g, 58 %), medium-low (1B, 0.42 g, 3 %) and medium (1C, 0.70 g, 5 %) polarity semipurified fractions, together with the aqueous residue or polar fraction which was frozen and freeze-dried (1D, 3.80 g, 25 %).

Quantification of in vitro antioxidant activity. 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was carried out following the methodology previously reported.[14] Briefly, a 20 µL aliquot of each sample, the medium polarity fraction of *P. andrieuxii* (100 µg/mL), the positive control, methanolic extract of *Camellia sinensis* (1000 µg/mL), or the blank (MeOH) was mixed with 180 µL of a 0.1 mM ethanolic solution of DPPH in a 96-well plate. After incubation in the dark for 30 minutes, the decrease in absorbance was measured at 517 nm using six replicates per sample. Antioxidant activity was calculated as milligrams of Trolox equivalents (TE) per gram of sample using a Trolox standard calibration curve (Fig. S1).

Determination of total phenol content (TPC). The total phenol content (TPC) was determined following the Folin-Ciocalteu methodology adapted to the 96-well plate assay, as described by Huber & Rupasinghe;[15] a stock solution of gallic acid (500 mM) was used to prepare serial dilutions (20 to 200 µg/mL) and a standard curve. The medium polarity fraction was evaluated at a concentration of 100 µg/mL (six replicates); the solvent and an the methanolic extract of *Camellia sinensis* (1000 µg/mL) were used as blank and positive controls, respectively. For the test, 100 µL of 0.2 N Folin-Ciocalteu´s reagent was combined with 20 µL of sample; after incubating for 5 min at room temperature (27±1 °C), 80 µL of a 75 % (w/v) solution of

J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

sodium carbonate was added to the mixture. The assay plate was incubated in the dark for two more hours under shake (100 rpm) conditions. The absorbance of the samples was recorded twice at 760 nm using a microplate reader (Cytation 3, BioTek Instrument Inc. USA). The results were expressed as mg of gallic acid equivalents (EAG) per gram of sample (Fig. S2).

Cells and virus strains. The influenza virus strain was provided by the Virology Laboratory of the Centro Regional de Investigaciones 'Dr. Hideyo Noguchi' (Universidad Autónoma de Yucatán). The virus, identified as A/Yucatan/2370/09 (H1N1pdm09) pdm (sensitive to oseltamivir carboxylate), was propagated in MDCK cells in the presence of 1 µg TPCK-trypsin (SIGMA) per ml and stored at -70 °C until use. Viral titre was determined in MDCK cells using a standard plaque assay protocol

Cytotoxicity assay

The cytotoxicity assay was performed using the MDCK (Madin-Darby Canine Kidney) cell line (donated by the Instituto de Diagnóstico y Referencia Epidemiologico InDRE/IRR FR-58); the MDCK cells were maintained in Dulbecco's minimal essential media (DMEM) enriched with 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 µg/mL streptomycin (GIBCO), and 1M HEPES, and incubated at 37 °C in a 5 % CO_2 environment. For the assay, MDCK cells were placed in 96-well plates at a density of 1×10^5 cells per well and incubated at 37 °C with 5 % CO_2 for 24 hours. After washing twice with phosphate-buffered saline (PBS) solution, each well received 100 µL of the extract or semipurified fractions at one of seven concentrations: 100, 50, 25, 12.5, 6.25, 3.125, and 1.56 µg/mL. Each concentration was replicated four times, with a control well containing only DMEM. The plates were incubated for an additional 72 hours under the same conditions. After removing the inoculum, the cells were washed once with PBS, stained with 0.4 % crystal violet in methanol for 30 min, then washed again with running tap water and allowed to dry. Absorbance was measured at 490 nm using a Multilabel Plate Reader (Victor 3x Perkin-Elmer). Cell viability was calculated as the ratio of the optical density (OD) of treated cells to that of the control cells, expressed as a percentage: Cell viability = (OD treated cells /OD cell control)*100

The concentration causing cell death in 50 % of the cells (CC_{50}) was determined by plotting extract concentration against cell viability percentage and performing regression curve analysis using the GraphPad Prism 7 software; for each sample tested, a cell blank control with only DMEM, together with 1% of DMSO as positive control, were included.

Cytopathic effect reduction assay in pre-treatment. MDCK cells were grown in DMEM supplemented with 10 % FBS for 24 h before washing with PBS and incubating for another 24 h with the extract or semipurified fractions in quadruplicate. After removing the inoculum, cells were exposed to virus at MOI: 0.001 A/Yucatan/2370/2009. After washing with PBS again, cells were incubated for 72 hours in DMEM containing 1µg/mL TPCK trypsin.

Cytopathic effect reduction assay in co-treatment. Cells were similarly prepared as described above, but combined with the extract or semipurifid fractions and the virus before incubation at room temperature for one hour. The mixtures were then added to the cells and incubated under standard conditions.

Cytopathic effect reduction assay in post-treatment. Cells were similarly prepared as described above, seeded until confluent and infected with the virus before being treated with various dilutions of the crude extract or semipurified fractions in DMEM supplemented with TPCK trypsin for 72 h.

Chromatographic analysis by UPLC-PDA-ESI-MS/MS

Chromatographic analysis was conducted using a Waters Acquity H-Class UPLC system (Milford, MA, USA) equipped with a quaternary pump, an automatic injector, and a photodiode array (PDA) detector. The separation was carried out using a Waters Acquity UPLC BEH C18 column (1.7 µm, 100 × 2.1 mm ID) and a mobile phase consisting of 0.1 % formic acid in ultrapure water (A) and 0.1 % formic acid in acetonitrile (B). The PDA detector recorded wavelengths in the 190–400 nm range, with absorbance measured at 290 nm. For mass spectrometry (MS/MS), a Waters Xevo TQ-S micro instrument was employed under previously reported but modified conditions.[16] The negative ion mode used a collision energy of 10 eV. Mass spectra were collected in full scan mode over a range of 50–700 m/z. Data acquisition and processing were performed using MassLynx V4.1 software. Tentative identification of components was achieved by comparing the chromatographic and MS experimental data with those in literature references and public databases such as the European Mass Bank (https://massbank.eu/MassBank/index.html) and ReSpect for phytochemicals (http://spectra.psc.riken.jp/menta.cgi/respect/index).

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J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

Statistical analyses

Data are presented as the mean (±) standard deviation of three independent experiments; statistical significance was calculated by a one-way ANOVA analysis and Dunnett´s test, with p-values < 0.05 considered as significant using the GraphPad Prism 7 software.

Results and discussion

Evaluation of the cytotoxicity of the crude leaf extract of *P. andrieuxii* and its semipurified fractions in MDCK cells showed that neither the extract, nor the semipurified fractions were cytotoxic (Fig. 2 and Fig. S3). These findings coincide with those previously reported about the leaf extract of *P. andruexii* not being toxic when tested in the Brine Shrimp lethality assay, commonly used as an indirect assay to detect cytotoxic metabolites im plant extracts.[17] Once it was established that none of the samples were cytotoxic, they were evaluated for their capacity to reduce the cytopathic effect, which refers to the ability of a particular sample or product to prevent the damage caused by viruses in infected cells, which can lead to cell death or alterations in cell function.[18] The crude extract and the semipurified fractions were tested using three different strategies to reduce the cytopathic effect, pre-treatment, co-treatment and post-treatment. Bioassay results showed the aqueous fraction of the *P. andrieuxii* best preventing the cytopathic effect, with a 100 % cell viability at all concentrations tested (50-1.56 µg/mL) using the co-treatment strategy (Fig. 2). Similarly, co-tretament with the medium polarity fraction also showed an important inhibition of the cytopathic effect, with over 80 % cell viability at all concentrations tested, and an SI value of >64 for both fractions. Interestingly, post-treatment with the aqueous fraction only showed moderate antiviral activity (58 % cell viability) at 50 µg/mL, with an IC_{50} of 46.27 µg/mL and an SI of 2.1, while post-treatment with the medium polarity fraction resulted in good antiviral activity (87 % cell viability) when tested in the post-treatment at 50 µg/mL, having an IC_{50} of 23.7 µg/mL and an SI of 4.2. The lack of antiviral activity when testing the extract and the semipurified fracions using the pre-treatment strategy suggests that the bioactive metabolites do not play a significant role in preventing the viral infection of the MDCK cells. However, the activity observed when testing the fractions using the co-treatment strategy implies that the bioactive metabolites act by either blocking the viral replication pathways, which reduces cell damage associated with infection, or by protecting the cells from virus-induced lysis, maintaining cell integrity and reduction of the cytopathic effect.[19-20] The fact that the leaf crude extract did not show a significant capacity to reduce the cytopathic effect, while its semipurified fractions did, demonstrate the importance of an early fractionation process to uncover metabolites with antiviral, or any other, activity.

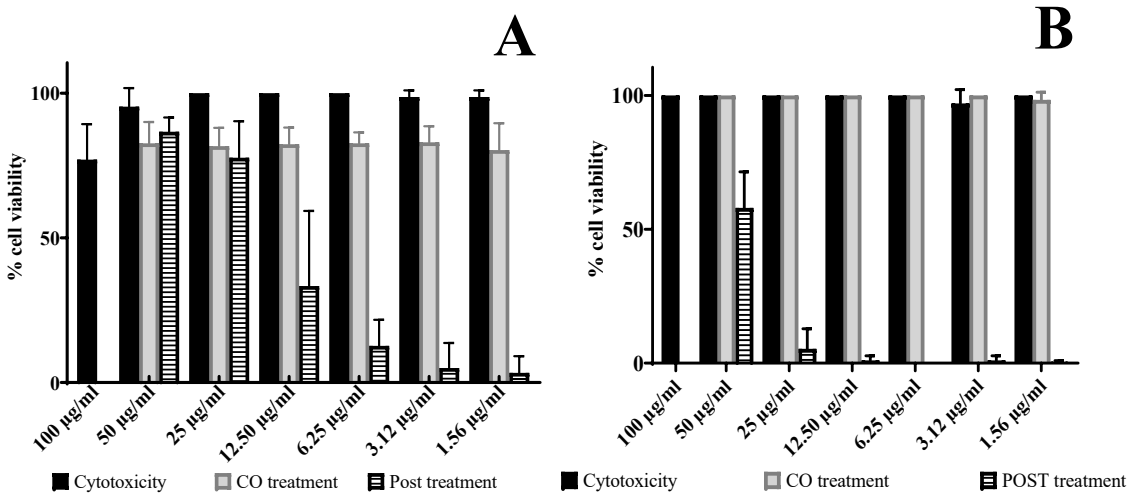

Fig. 2. Cytotoxicity against MDCK cells and reduction of the cytopathic effect in co-treatment and post-treatment of medium **(A)** and high **(B)** polarity semipurified fractions from the extract of *P. andrieuxii*.

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J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

While several studies have investigated the potential of plant extracts in the search for new antivirals against influenza A(H1N1),[21] the SI value (64) found for the medium polarity and aqueous fractions, is higher than that reported for the extract of *Fritillaria thunbergii* (Liliaceae) (SI 50.6), found to be less cytotoxic and more effective at inhibiting influenza infection A(H1N1) than oseltamivir, during its evaluation using the post-treatment strategy.[20] The fact that both fractions proved to be effective even at the lowest concentrations tested (1.56 µg/mL), with inhibition of the cytopathic effect of over 50 %, suggests that the SI of the fractions from *P. andrieuxii* could be higher.

A preliminary evaluation of the TLC chromatographic profiles of the medium and high polarity fractions showed a significant presence of antioxidant components in both fractions, detected when using the DPPH reduction reagent. However, quantification of the antioxidant activity and the total phenol content (TPC) of the two fractions showed that while the the TPC of the medium polarity fraction was higher than that of the aqueous fraction (1006.985 ± 239.9 vs 426.129 ± 0.8 mg EAG/g), the antioxidant activity of the medium polarity fraction was lower than that of the aqueous fraction (316.077± 35.7 mg vs 639.014± 38.7 mg TEAC/g extract). These values suggested that the medium polarity fraction was rich in polyphenolic metabolites and that, in this case, the TPC content of the two fractions is is not directly related to their antioxidant activity, even though a high content of polyphenols is commonly associated with antioxidant activity, known to be beneficial because its capacity to protect against oxidative stress.[22-23] However, these findings are in agreement with literature reports describing medium polarity fractions of plant extracts as containing a wide variety of polyphenolic metabolites such as flavonoids and catechins,[24-26] in comparison with aqueous fractions, where the presence of sugars, alkaloids and terpenoids, together with polyphenols, have been reported.[27-28] UHPLC-MS analysis of the aqueous and medium polarity fractions showed that the chromatographic profiles of both fractions were qualitatively similar, but quantitatively different (Fig. S4); analyses of the λmax absorption values, together with a comparison of the fragmentation patterns of the major components with those contained in the data base of the equipment, allowed the preliminary identification of the phenolic acids: neochlorogenic acid, chlorogenic acid and coumaroylquinic acid, in addition to the flavonoid rutin and the flavonoid glycosides kaempferol-3-O-rutinoside and kaempferol-N (Table 1, Fig. S3-S7). The presence of these metabolites in the medium polarity fraction is relevant since it has been reported that phenolic acids such as caffeic acid, gallic acid, ellagic acid, chlorogenic acid, and quinic acid, as well as flavonoids including quercetin, apigenin, luteolin, baicalin, naringenin, and kaempferol have demonstrated significant antiviral activity.[29-30]

Table 1. Polyphenolic metabolites detected in the medium polarity fraction from the extact of *P. andrieuxii.*

Metabolite number	t_R **(UHPLC-PDA)**	**λ max**	**Molecular ion ([M–H]$^-$)** *m/z*	**CV**	**Fragment ions** *m/z*	**Preliminary identification**
1	8.88	324, 214, 193	353	75	191, 179, 135	Neochlorogenic acid
2	9.29	325, 217, 194	353	75	191	Chlorogenic acid
3	9.89	312, 202	337	75	191, 173, 135	Coumaroylquinic acid
4	10.3	353, 255, 206	609	150	300, 271, 243	Rutin
5	10.87	347, 264, 210	593	150	285, 284, 255, 227	Kaempferol-3-O-rutinoside
6	11.19	345, 265, 213	593	150	284, 255, 227	Kaempferol-N*

*unidentified kaempferol glycoside

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While it has been established that structural features such as hydroxyl groups, substituents such as methyl groups and the position of functional groups can significantly influence the antiviral properties of polyphenols,[31] this study represents the first report of potential antiviral activity of neochlorogenic acid, coumaroylquinic acid and two glycosylated derivatives of kaempferol against the influenza virus A(H1N1pdm09).

Conclusions

Even though cardenolides are known to occur in plant species of the Apocynaceae family and have been reported to show antiviral activity, no presence of cardenolides was detected in the fractions with antiviral activity obtained from the leaf extract of *P. andrieuxii*. Instead, a number of polyphenols, some of which have been reported to show antiviral activity, were identified in the bioactive fractions. This study represents the first report on the potential of the leaf extract of *P. andrieuxii* as a potential source of therapeutic agents with antiviral activity *in vitro* against Influenza A(H1N1), where leaf extract fractions of medium and high polarity showed to inhibit virus replication. Further research is needed to identify the metabolite or metabolites responsible for the detected antiviral activity, as well as to elucidate the mechanism of action against influenza viruses, and to evaluate the potential broad-spectrum antiviral activity against other viral strains.

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J. Mex. Chem. Soc. **2026**, *70(1):e2494*
Regular Issue

ISSN-e 2594-0317

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