Title

*In silico* screening of natural products isolated from Mexican herbal medicines against COVID-19

Authors

*Gomez-Verjan JC† & Rivero-Segura NA†

Affiliations

†Dirección de Investigación, Instituto Nacional de Geriatría, México.

*Corresponding Author:* Dr. Juan Carlos Gomez-Verjan. Dirección de Investigación, Instituto Nacional de Geriatría (INGER). Av. Contreras 424, San Jerónimo Lídice, La Magdalena Contreras, 10200 Ciudad de México, CDMX, México. E-mail: jverjan@inger.gob.mx
ABSTRACT

COVID-19 caused by the SARS-CoV-2 has already taken the lives of more than 1 million people worldwide, causing several political and socio-economic disturbances in our daily life. To date, there are non-effective pharmacological treatments, and we are still expecting vaccines which represent a challenge for its distribution. Therefore, research for novel compounds becomes essential to develop pharmacological treatments. In this sense, natural products have proven to be quite useful for drug development. Moreover, it is estimated that from 1981 to 2002, almost 49% of new chemical entities were inspired on them. Mexico is one of the countries with the most biodiversity globally; therefore, in the present paper, we performed a cheminformatics screening, focused on 100 compounds isolated from the most widely used and studied Mexican natural products, to assess its activities in silico against SARS-CoV-2. We obtained ten compounds with leadlikeness profiles (Emodin anthrone, Kaempferol, Quercetin, Aesculin, Cichoriin, Luteolin, Matricin, Riolozatrione, Monocaffeoyl tartaric acid, Aucubin) from which the Cichoriin a coumarin glycoside, showed the most significant potential. Therefore, we evaluate its ADME properties and simulate this compound on a physiologically based pharmacokinetic model (PBPK). Interestingly, this compound seems to reach higher lung levels when administered intravenously at 100 mg/Kg (IV). In this sense, our results suggest Cichoriin may be considered for further experimental analysis, in the treatment or for the development of therapeutic tools versus SARS-CoV-2 or even to other similar viruses.

Keywords: COVID-19, drugs, cichoriin, natural products, chemoinformatics, drug development
Introduction

COVID-19 caused by the novel etiological agent SARS-CoV-2 has been diagnosed in more than 50 million people worldwide, causing the death of more than 1 million, and leading to a socio-economic crisis worldwide. At date, there are non-effective pharmacological treatments, and we are still expecting vaccines, from which its distribution will represent a challenge, due to its conditions for its transportation and storage representing a drawback in developing countries. In this context, according to Twomey et al.\textsuperscript{1}, there are two primary strategies to counteract against COVID-19, on one side develop novel biotechnological products, and on the other side, repurposing existing drugs. The last strategy becomes quite crucial for many reasons; the main is that repurposing drugs is more straightforward and saves time and money compared to the development of novel drugs. Also, the repurposing of compounds is more accurate than the development of biotechnological substances and could increase the development of therapeutic tools against the COVID-19.

On the other hand, natural products from plants, animals and microorganisms represent an essential chemical source. According to Cragg and Newman\textsuperscript{2,3} it is estimated that from 1981 to 2014 about 35\% of small molecules clinically used as antimicrobial and anticancer treatment were based on natural products directly or as derivatives (semi-synthetic or prototypes for leader molecules), most of which are mainly isolated from plants (~20\%)\textsuperscript{4}. In this sense, several efforts have been performed to identify whether herbal medicine possesses antiviral effects. For instance, Suwannarach et al.\textsuperscript{5} suggest that fungi are a source of natural bioactive compounds that are potentially useful for preventing viral infections and improving human immunomodulation. In this context, Mexico is the 4th country with
the most biodiversity globally; it has been estimated that there are more than 30 thousand species of plants six and more than 3 thousand vascular plants all over its geographical distribution. In this sense, Mexican plants have been studied phytochemically, pharmacologically and anthropologically for more than 100 years, by different national and international institutions. Several groups are dedicated to studying medicinal plants in Mexico\textsuperscript{7}, which may constitute an essential source of information for the development of drugs.

On the other hand, computational tools and novel algorithms have been implemented over the last years to accelerate and optimise the drug discovery process (estimated in 20 years and about 1.3 billion USD\textsuperscript{8}). Several methods have shown to reduce the cost of drug development up to 50%, such as chemoinformatics, quantitative-structure activity relation (QSAR), docking, molecular similarity, network pharmacology, and pharmacogenomics computational \textit{de novo} design, to mention a few examples\textsuperscript{9}. Moreover, the bioinformatic era has shown a significant increase in the development of computational and web tools that could be applied for novel drug design. For instance, systems pharmacology has enabled us to understand the dose-response relationships of novel compounds and perform physiologically-based pharmacokinetic (PBPK) models that make it easy to understand the pharmacokinetics properties of novel compounds. Additionally, chemoinformatic approaches allow us to analyse databases of compounds to obtain information about its potential as drugs. Hence, in an attempt to quickly propose the discovery of natural products that could be used against SARS-CoV-2, in the present study
we performed a chemoinformatic analysis with 100 compounds isolated from the most widely used and studied medicinal plants and marine products in Mexico $^{10,11}$.

**Methods**

*Chemical descriptors and computational screening*

We obtain a list of the 100 natural products isolated from the most traditionally used plants, as stated by $^{12}$ and $^{7}$. Additionally, we add essential marine products ten and already reported compounds with antiviral activities $^{10,13,11}$. From such compounds, we calculate the chemoinformatic properties using the Osiris DataWarrior (DataWarrior V4.7.2, Idorsia Pharmaceuticals Ltd., Allschwil, Switzerland), freeware software that calculates lipophilicity (expressed as compound logP), solubility in water (expressed as logS), molecular weight, druglikeness, leadlikeness, and toxicoinformatic properties of compounds. Additionally, we used the Swiss Bioinformatics Institute, which possesses a web server that calculates several ADME properties that could help to delve into compounds' pharmaceutical properties. The complete description of the computational medicinal chemistry algorithm for both was published $^{14}$. We use consensus Log P from 5 different predictions; LogS (Silicos-IT) is a fragmental method calculated; Ghose improvement for the Lipinski rule of Five $^{15}$, and synthetic accessibility from 1 very easy to 10 very difficult, implemented in the software. The most relevant compounds were selected according to its molecular descriptors and leadlikeness properties. A complete table of all descriptors could be seen in Table 1S.

*Docking*
Once we chose leader compounds from the previously mentioned list, we used the COVID-19 Docking Server ([https://ncov.schanglab.org.cn/](https://ncov.schanglab.org.cn/)), a web server that predicts the binding modes between different COVID-19 targets and the ligands. A complete description of the algorithm used for such could be found. We tested the targets: Main protease, Papain-like protease, Nsp3 (AMP site), Nsp3 (MES site), RdRp (RTP site), RdRp (RNA site), Helicase (ADP site), Helicase (NCB site), Nsp14 (ExoN), Nsp14 (N7-MTase), N protein (NCB site) with the selected ligands, accordingly to the best conformation (Emodin anthrone, Kaempferol, Quercetin, Aesculin, Cichoriin, Luteolin, Matricin, Riolozatrione, Monocaffeoyl tartaric acid, and Aucubin). Complete table of docking results could be seen in Table 2S.

*Pharmacokinetic assessment (PBPK model building and evaluation)*

Once that we chose the best compound according to docking results against SARS-CoV-2, we developed a PBPK model to predict the pharmacokinetic potential of such compounds in an individual. In this sense, the PBPK's models predict the concentration-time profile of compounds in the body, giving an idea of such compounds' performance in the body. The adult PBPK model was developed using PK-sim modelling software (version 8.0, 2017, [http://www.systems-biology.com/products/pk-sim.html](http://www.systems-biology.com/products/pk-sim.html)) and according to data from simulation from other coumarins and other variables included in the model could be seen in Table 3S.

*Results*

To establish which compounds are the most suitable for drug repurposing against SARS-CoV-2 targets, we calculated the molecular descriptors for each of the 100 compounds
(physicochemical features derived from the chemical structures at different dimensions), shown in Figure 1 and Table 1S. We also calculate the toxicoinformatic properties, such as LogP, bioavailability score, TPSA, the tumorigenic, mutagenic, reproductive effects and irritant potential (Figure 1B). In this sense, our results indicate that from the 100 compounds, only ten compounds (Emodin anthrone, Kaemferol, Quercetin, Aesculin, Cichoriin, Luteolin, Matricin, Riolozatrione and Monocaffeoyl tartaric acid, Figure 2) meet the lead-likeness and Lipinski's rules to continue the subsequent analyses against SARS-CoV-2 targets.
Figure 1. Chemoinformatic properties. A) Molecular descriptors calculated. A selection of some of the most important properties for selected compounds. According to the color code, red dots are the compounds with less leadlikeness while the blue dots are the compounds with the significant number of leadlikeness, meaning that blue dots may be
potential leaders for further analyses. B) Toxicoinformatic properties. Natural products according to their properties such as tumorigenic or irritant effect, Log P, bioavailability score TPSA and H-bonds acceptors.

Once we identify the compounds that meet the physicochemical criteria to become drug leaders, we evaluate its potential against the different targets of SARS-CoV-2. The results obtained from the COVID-19 Docking Server (Table 1 and Table 2S), demonstrate that among the ten leader compounds just three compounds (Quercetin, Riolozatrione and Cichoriin) achieve the most stable conformation against the main targets of SARS-Cov-2 (the more negative ΔG is, the more the equilibrium of the reaction in on the side of the resulting conformation 18). However, results from the toxicoinformatic analysis (Figure 1 and Table 1S) indicate that Riolozatrione could be irritant, mutagenic, tumorigenic, and with possible reproductive effects Quercetin may possess potential as mutagenic and tumorigenic such features compromises to continue the subsequent analysis with these compounds. Meanwhile, Cichoriin appeared as the safest compound according to its toxicoinformatic properties described in Figure 1 and Table 1S. Thus, we only show the conformations achieved by Cichoriin with the targets of SARS-CoV-2 in Figure 3. Accordingly, the best targets for Cichoriin binding are RdRp (RTP site), Nsp14 (ExoN), Nsp3 (207-379, AMP site) and papain-like protease (Table 1, 2S and Figure 3).
Figure 2. Compounds with chemical properties as leaders. According to the chemoinformatic analysis, we present the molecular structures of the ten compounds that meet the criteria for further analyses. A) Emodin anthrone, B) Kaempferol, C) Quercetin, D) Aesculin, E) Cichoriin, F) Luteolin, G) Matricin, H) Riolozatrione, I) Monocaffeoyl tartaric acid, J) Aucubin.

In our next step in the analysis, we aim to characterise whether Cichoriin had pharmacokinetic potential against COVID-19 since this issue stops several new compounds from going to clinics. However, since Cichoriin is not yet in human studies, required data to build the PBPK model simulations was constructed using data from other coumarins with
similar structure\textsuperscript{17} (complete simulation data could be found in Table 3S). We adjust the PBPK model parameters expecting that Cichoriin will be used in patients with COVID-19 in critical conditions. Thus, we simulate a 60-year-old male Mexican-American with three potential doses 1, 10, and 100 mg/Kg administered IV. The simulation results showed that Cichoriin reaches acceptable concentration in arterial, peripheral blood, and intracellularly (Figure 4). Additionally, Cichoriin reaches a higher concentration in the lungs intracellular than other compartments, suggesting that the best dose to treat COVID-19 maybe 100 mg/Kg since some of the targets are found once the virus is inside the cell.

Table 1. Docking results for leader compounds against the main targets of SARS-CoV-2.

|                | A   | C   | EA  | E   | K   | L   | M   | MTA  | Q   | R   |
|----------------|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|
| Protease       | -6.5| -7.4| -7.1| -7.7| -7.4| -7.3| -7.1| -6.7 | -7.3| -6.4|
| Papain-like protease | -7.7| -8.3| -7.9| -8.7| -8.2| -8.3| -8.5| -7.2 | -8.4| -9.4|
| Nsp3 (207-379, AMP site) | -7.7| -7.1| -7.5| -7.5| -7.8| -8.1| -7.1| -6.8 | -8.3| -8.3|
| Nsp3 (207-379, MES site) | -6.8| -8.4| -8.1| -7.8| -8.6| -7.9| -7.6| -7.7 | -8.6| -8.1|
| RdRp (RTP site)  | -9.4| -9.5| -9.2| -9.4| -10.2| -8.4| -7.5| -9  | -10.5| -8  |
| RdRp            | -6.6| -7.5| -6.7| -7.7| -7.4| -7.5| -7.2| -7   | -7.5| -7.5|
|                      | (RNA site) | Helicase (ADP site) | Helicase (NCB site) | Nsp14 (ExoN) | Nsp14 (N7-MTase) | Nsp15 (endoribonuclease) | Nsp16 (GTA site) | Nsp16 (MGP site) | Nsp16 (SAM site) | N protein (NCB site) |
|----------------------|-----------|---------------------|---------------------|-------------|-----------------|------------------------|------------------|-----------------|-----------------|------------------|
|                      |           | -6.3                | -6.7                | -6.3        | -6.6            | -6.6                   | -6.5             | -6              | -6.6            | -7.7             |
|                      |           | -7                  | -7.4                | -7          | -7.2            | -7.2                   | -7               | -7.1            | -7.1            | -7.2             |
|                      |           | -7.8                | -8.8                | -8.6        | -8.3            | -8.7                   | -8.7             | -8.1            | -8.1            | -8.7             |
|                      |           | -6.6                | -7.5                | -6.8        | -7.2            | -7.3                   | -7               | -6.1            | -6              | -7.4             |
|                      |           | -6.5                | -6.7                | -7          | -7.2            | -6.6                   | -6.4             | -6.8            | -7.3            |
|                      |           | -7.3                | -8.3                | -7.9        | -7.9            | -8.6                   | -8.8             | -7.5            | -7              | -8.7             |
|                      |           | -6                  | -7.2                | -7.1        | -7.2            | -7.2                   | -6.7             | -6.3            | -6.2            | -6.9             |
|                      |           | -7.5                | -8.1                | -7.5        | -8              | -8.7                   | -8.9             | -6.8            | -7.2            | -7.4             |
|                      |           | -6.6                | -7.7                | -8.7        | -7.8            | -8.1                   | -7.9             | -6.5            | -6.7            | -8.4             |
|                      |           |                     |                     |             |                 |                        |                  |                 |                 |                  |
Figure 3. Cichoriin dockings conformations against COVID-19 targets. Cichoriin (magenta) was docked to the main pharmaceutically attractive targets (rainbow ribbon 3D protein structure) of SARS-CoV-2 with the COVID-19 Docking Server. As depicted in this figure, Cichoriin achieves the most stable conformations with against the main protease, Papain-
like protease, Nsp3 (AMP site), Nsp3 (MES site), RdRp (RTP site), RdRp (RNA site), Helicase (ADP site), Helicase (NCB site), Nsp14 (ExoN), Nsp14 (N7-MTase) and N protein (NCB site).

Figure 4. PBPK simulation of Cichoriin IV at three concentrations. A) 1 mg/Kg, B) 10 mg/Kg C) 100 mg/Kg. D) Cichoriin kinetics in the lung with the three selected concentrations, suggesting that the best dose is 100 mg/Kg IV (pink).
Cichoriin is a glycoside member of coumarins and has been isolated in *dandelion* (*Taraxacum officinale*) and on *chicory* (*Cichorium intybus*) belong to the Asteraceae family. *Dandelion* distributes ubiquitously in all the geographical regions of Mexico, while *chicory* growth is restricted only to the central and northeast region of Mexico. In this sense, Cichoriin may be a promising molecule against COVID-19 not only due to its possible effects against SARS-CoV-2 targets, but also since its anti-inflammatory and antioxidant effects mediated via NF-κB, Akt, and the MAP-kinases MEK and ERK, which leads to suggest that this compound may target the chronic proinflammatory cytokine storm harmful for individuals with severe COVID-19. Additionally, Cichoriin has been reported to induce antifungal, antibacterial, and photoprotective effects and has an average synthetic accessibility score according to its chemical-nature as a natural product, suggesting that it may be easy to obtain and may be used for other targets.

**Conclusions**

COVID-19 has taken the lives of more than 1 million people worldwide, and to date, there is non-effective pharmacological treatment available for such disease. Therefore, in the present work, we performed a chemoinformatic screening with 100 compounds isolated from Mexican natural products to seek active molecules with the potential to be implemented in the pharmacological treatment of such disease (either as a drug itself or as an inspiring molecule to developed active compounds against SARS-CoV-2). In this sense, we found ten compounds isolated from natural products from Mexico with leadlikeness and Lipinski's potential. However, after the docking and toxicoinformatic analysis, only Cichoriin was safe and docked with high affinity to the main targets of SARS-CoV-2. Interestingly, the
PBPK simulation showed that this compound might reach acceptable levels in plasma and highest concentration in the lung when administered IV at 100 mg/Kg; suggesting that Cichoriin may be a potential candidate in treating severe COVID-19.

Nevertheless, despite these promising results, the present study's main drawback relies on the lack of experimental data and further experimental studies are urgently required to validate our results. However, Cichoriin is a glycoside member of coumarins, and in general, coumarins have shown important pharmacokinetic properties that make them easier to be implemented in clinics. Therefore, we propose that Cichoriin be considered for further experimental studies to generate active compounds that may be useful in treating COVID-19 critical cases.

Acknowledgements

None

References

(1) Twomey, J. D.; Luo, S.; Dean, A. Q.; Bozza, W. P.; Nalli, A.; Zhang, B. COVID-19 Update: The Race to Therapeutic Development. Drug Resist. Updat. 2020, 53, 100733.

(2) Mishra, B. B.; Tiwari, V. K. Natural Products: An Evolving Role in Future Drug Discovery. Eur. J. Med. Chem. 2011, 46 (10), 4769–4807.

(3) Cragg, G. M.; Newman, D. J. Natural Products: A Continuing Source of Novel Drug Leads. Biochim. Biophys. Acta 2013, 1830 (6), 3670–3695.

(4) Calixto, J. B. The Role of Natural Products in Modern Drug Discovery. An. Acad. Bras. Cienc. 2019, 91 Suppl 3, e20190105.
(5) Suwannarach, N.; Kumla, J.; Sujarit, K.; Pattananandecha, T.; Saenjum, C.; Lumyong, S. Natural Bioactive Compounds from Fungi as Potential Candidates for Protease Inhibitors and Immunomodulators to Apply for Coronaviruses. *Molecules* **2020**, *25* (8). https://doi.org/10.3390/molecules25081800.

(6) Barrero, A. G.; Gómez-Pompa, A.; Lissarrague, A. G. Successful Experiences in Promoting Scientific Research in Mexican Conservation Biology. *Mexican Natural Resources Management and Biodiversity Conservation*. 2018, pp 193–224. https://doi.org/10.1007/978-3-319-90584-6_10.

(7) Mata, R.; Figueroa, M.; Navarrete, A.; Rivero-Cruz, I. Chemistry and Biology of Selected Mexican Medicinal Plants. *Prog. Chem. Org. Nat. Prod.* **2019**, *108*, 1–142.

(8) Wouters, O. J.; McKee, M.; Luyten, J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 2020, p 844. https://doi.org/10.1001/jama.2020.1166.

(9) Ou-Yang, S.-S.; Lu, J.-Y.; Kong, X.-Q.; Liang, Z.-J.; Luo, C.; Jiang, H. Computational Drug Discovery. *Acta Pharmacol. Sin.* **2012**, *33* (9), 1131–1140.

(10) Pech-Puch, D.; Pérez-Povedano, M.; Lenis-Rojas, O. A.; Rodríguez, J.; Jiménez, C. Marine Natural Products from the Yucatan Peninsula. *Mar. Drugs* **2020**, *18* (1). https://doi.org/10.3390/md18010059.

(11) Gómez-Cansino, R.; Espitia-Pinzón, C. I.; Campos-Lara, M. G.; Guzmán-Gutiérrez, S. L.; Segura-Salinas, E.; Echeverría-Valencia, G.; Torras-Claveria, L.; Cuevas-Figueroa, X. M.; Reyes-Chilpa, R. Antimycobacterial and HIV-1 Reverse Transcriptase Activity of Julianaceae and Clusiaceae Plant Species from Mexico. *Evid. Based. Complement.*
Alternat. Med. 2015, 2015, 183036.

(12) Rodríguez-Fragoso, L.; Reyes-Esparza, J.; Burchiel, S. W.; Herrera-Ruiz, D.; Torres, E. Risks and Benefits of Commonly Used Herbal Medicines in Mexico. Toxicol. Appl. Pharmacol. 2008, 227 (1), 125–135.

(13) Silva-Mares, D.; Rivas-Galindo, V. M.; Salazar-Aranda, R.; Pérez-Lopez, L. A.; Waksman De Torres, N.; Pérez-Meseguer, J.; Torres-Lopez, E. Screening of North-East Mexico Medicinal Plants with Activities against Herpes Simplex Virus and Human Cancer Cell Line. Nat. Prod. Res. 2019, 33 (10), 1531–1534.

(14) Daina, A.; Zoete, V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. ChemMedChem 2016, 11 (11), 1117–1121.

(15) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterisation of Known Drug Databases. Journal of Combinatorial Chemistry. 1999, pp 55–68. https://doi.org/10.1021/cc9800071.

(16) Kong, R.; Yang, G.; Xue, R.; Liu, M.; Wang, F.; Hu, J.; Guo, X.; Chang, S. COVID-19 Docking Server: A Meta Server for Docking Small Molecules, Peptides and Antibodies against Potential Targets of COVID-19. Bioinformatics. 2020. https://doi.org/10.1093/bioinformatics/btaa645.

(17) Miura, T.; Kamiya, Y.; Hina, S.; Kobayashi, Y.; Murayama, N.; Shimizu, M.; Yamazaki, H. Metabolic Profiles of Coumarin in Human Plasma Extrapolated from a Rat Data Set with a Simplified Physiologically Based Pharmacokinetic Model. J. Toxicol. Sci. 2020, 45 (11), 695–700.
(18) Du, X.; Li, Y.; Xia, Y.-L.; Ai, S.-M.; Liang, J.; Sang, P.; Ji, X.-L.; Liu, S.-Q. Insights into Protein-Ligand Interactions: Mechanisms, Models, and Methods. *Int. J. Mol. Sci.* 2016, 17 (2). https://doi.org/10.3390/ijms17020144.

(19) Froese, N. T.; Van Acker, R. C. Distribution and Interference of Dandelion (Taraxacum Officinale) in Spring Canola. *Weed Science*. 2003, pp 435–442. https://doi.org/10.1614/0043-1745(2003)051[0435:daiodt]2.0.co;2.

(20) Ríos, J. L. V.; Espinosa García, F. J. *Catálogo de malezas de México*; Fondo De Cultura Economica USA, 1998.

(21) Villaseñor, J. L.; Espinosa-Garcia, F. J. The Alien Flowering Plants of Mexico. *Diversity and Distributions*. 2004, pp 113–123. https://doi.org/10.1111/j.1366-9516.2004.00059.x.

(22) Edwards, S. E.; da Costa Rocha, I.; Williamson, E. M.; Heinrich, M. *Phytopharmacy: An Evidence-Based Guide to Herbal Medicinal Products*; John Wiley & Sons, 2015.

(23) González-Castejón, M.; Visioli, F.; Rodríguez-Casado, A. Diverse Biological Activities of Dandelion. *Nutr. Rev.* 2012, 70 (9), 534–547.

(24) Del Valle, D. M.; Kim-Schulze, S.; Huang, H.-H.; Beckmann, N. D.; Nirenberg, S.; Wang, B.; Lavin, Y.; Swartz, T. H.; Madduri, D.; Stock, A.; Marron, T. U.; Xie, H.; Patel, M.; Tuballes, K.; Van Oekelen, O.; Rahman, A.; Kovatch, P.; Aberg, J. A.; Schadt, E.; Jagannath, S.; Mazumdar, M.; Charney, A. W.; Firpo-Betancourt, A.; Mendu, D. R.; Jhang, J.; Reich, D.; Sigel, K.; Cordon-Cardo, C.; Feldmann, M.; Parekh, S.; Merad, M.; Gnijatic, S. An Inflammatory Cytokine Signature Predicts COVID-19 Severity and Survival. *Nat. Med.* 2020, 26 (10), 1636–1643.
(25) Zhao, C.-N.; Yao, Z.-L.; Yang, D.; Ke, J.; Wu, Q.-L.; Li, J.-K.; Zhou, X.-D. Chemical Constituents from and Their Antifungal and Herbicidal Activities. *Biomolecules* **2020**, 10 (1). https://doi.org/10.3390/biom10010074.

(26) Seregheti, T. M. Q.; Pinto, A. P. R.; Gonçalves, M. da C.; Antunes, A. D. S.; Almeida, W. A. da S.; Machado, R. S.; Silva, J. N.; Ferreira, P. M. P.; Pessoa, C.; Santos, V. M. R. D.; Nascimento, A. M. do. Antiproliferative and Photoprotective Activities of the Extracts and Compounds from Calea Fruticosa. *Braz. J. Med. Biol. Res.* **2020**, 53 (9), e9375.

(27) Abdallah, H.; Farag, M.; Osman, S.; Kim, D. H.; Kang, K.; Pan, C.-H.; Abdel-Sattar, E. Isolation of Major Phenolics from Launaea Spinosa and Their Protective Effect on HepG2 Cells Damaged with T-BHP. *Pharm. Biol.* **2016**, 54 (3), 536–541.