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# In Silico Study of Phytochemical Chlorogenic Acid: A Semi-Empirical Quantum Study and Adme

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***Abstract* – Currently, bioprospection has been trying to identify new phytochemicals that have biological potential. Chlorogenic acid, found in several crops, being the highlight the coffee crop, has been showing great biological potential, being the targets of several studies. In this context, the present work has as objective to perform computational simulations at the semi-empirical quantum level that allowed to characterize the molecule of the chlorogenic acid, as well as to evaluate in silico its pharmacokinetic potential (absorption, distribution, metabolism, and excretion). Using the ADME descriptors, which enabled the electronic and structural characterization of the phytochemical chlorogenic acid, making it possible to identify its thermodynamically stable conformational structure, to identify its nucleophilic sites as well as to characterize the border orbitals, besides evaluating the pharmacokinetic potential, indicating this as a promising drug, being indicated for future in silico studies of drug desing, and molecular docking, which, together with the current in vivo studies being carried out, may explain the mechanism of action of this phytochemical.**

***Keywords* - Coffee.ADME.PM3.Theoretical chemistry.**

## I INTRODUCTION

Coffee is today one of the most consumed beverages in the world, belongs to the botanical family Rubiaceae, with about 500 genera and more than 6000 species [1] possessing a chemical constitution that varies according to species, being that its complex composition is based on a mixture of more than several components where caffeine is present, as the best known, however there are several biochemically active compounds, such as chlorogenic acid [2] [3], a phytochemical is eukaryotic metabolite produced during a metabolic reaction and has been used in trials studying the treatment of Advanced Cancer and Impaired Glucose Tolerance [4], being currently the target of several studies that are in the phase of clinical trials (table I).

Table 1

Clinical trials of chlorogenic acid

| Phase | Status | Purpose | Conditions |
|---|---|---|---|
| 1 | Completed | Treatment | Cancer, Advanced |
| 1 | Completed | Treatment | Glioblastomas |
| 1 | Terminated | Treatment | Cancer, Advanced |
| 1, 2 | Recruiting | Treatment | AdvancedLungCancer |
| 2 | Recruiting | Treatment | Impaired Glucose Tolerance (IGT) |

Source: drugbank (https://www.drugbank.ca/drugs/DB12029)

Currently, the advances in computational chemistry have been highlighting significantly in relation to the pharmaceutical market in the area of drug development. Recent advances in the computational field have demonstrated efficient quantum-chemistry algorithms providing molecular parameters of the ab-initio and semi-empirical methods, expressing geometric and electronic properties of the molecules and their interactions in a short time interval [5]. Molecular modeling is based on a set of tools that aims at the study of molecular

properties from structural design to virtual characterization, which involves visualization, analysis and storage of molecular systems [7-8].

In this context, the present work has as objective to perform computational simulations at semi-quantum quantum level that allowed to characterize the molecule of the chlorogenic acid, as well as to evaluate in silico its pharmacokinetic potential (absorption, distribution, metabolism, and excretion).

## II. METHODS AND MATERIALS

Obtaining chemical physical descriptors, identifiers and two-dimensional structure. The identification of two-dimensional structure of chlorogenic acid as well as its identifiers and physicochemical properties was carried out in DrugBank virtual repositories version 5.0 (https://www.drugbank.ca/drugs/DB12029) and CHEmBL (https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL284616/) [10]

According to Silva et al. [11], molecular descriptors are currently considered a very important tool in the prediction of molecular properties, by providing information about the physicochemical nature of the activity or properties under study in a mathematically quantified and computerized way [12] [ 13]. Following this context, the virtual simulation calculations were obtained through the semi-empirical method PM3 (Parametric Method 3), based on quantum mechanics, using a Hartree-Fock SFC approximation, with a maximum number of 500 interactions , which obtained the energy minimization and geometry optimization, frontier orbitals (HOMO and LUMO) and the electrostatic potential map (MEP). These calculations were performed in the ArgusLab® code [14].Prediction of absorption, distribution, metabolism, and excretion properties of the compounds were done using the freely available SwissADME software package. This was performed to enhance the success of drug discovery and development process. Using the Swissadme platform (http://www.swissadme.ch/index.php) to perform the parameters calculation of ADME [15-16].

## III. RESULTS AND DISCUSSIONS

Chlorogenic acid (https://www.drugbank.ca/drugs/DB12029),(1S, 3R, 4R, 5R) -3 - {[(2E) -3- (3,4-dihydroxyphenyl) prop-2-enoyl] oxy} -1,4,5-trihydroxycyclohexane- 1-carboxylic acid (Iupac name), has in its structure the carboxyl, hydroxyl and ester group (figure 1), thus belonging to Kingdom Organic compounds, super class organic oxygen, class organo oxygen compounds, sub class alcohols and polyols, direct parent quinic acids and derivatives (Figure 2). has an average weight of 354.3087, monoisotopic 354.095082174, chemical formula c16h18o9, xlogp3-aa-0.4, topological polar surface area 165 a ^ 2, heavy atom count 25, formal charge 0, complexity 534, isotope atom count 0, defined atom stereocenter count 4, undefined atom stereocenter count 0, defined bond stereocenter count 1, undefined bond stereocenter count 0, covalently-bonded unit count 1, melting point 205-209 ° c.

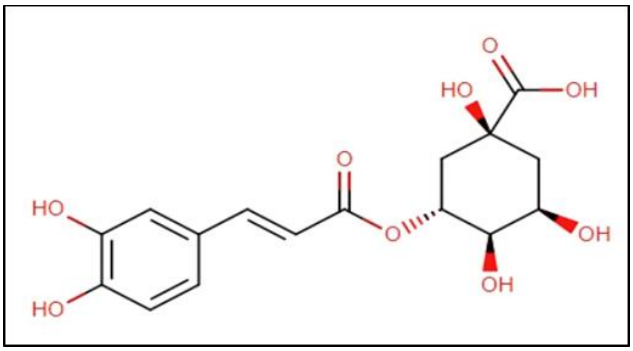


Fig. 1Two-dimensional structure of chlorogenic acid
Source:[https://www.drugbank.ca/drugs/DB01202]

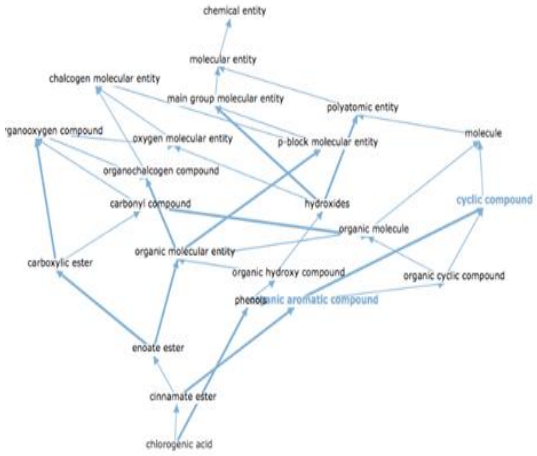


Fig. 2ChEbi Ontology of chlorogenic acid

Source:https://www.ebi.ac.uk/chebi/chebiOntology.do?chebiId=CHEBI:16112

The polarity and m of the fundamental descriptors in the characterization of a molecule for future studies of biological activity, because it directs the type of solvents to be used, as well as its behavior against future receptors [7]. The molecule of chlorogenic acid, because it has atoms as different electronegativity, has a resultant dipole momentum vector in the order of a polarity 11,59 debye, with vector decomposition in the x-axes in the order of -11.29 debye, y -1,28 debye and z 2,26 debye (figure 2), indicating a high polarity, being preferably soluble in polar solvents, solubility, so that the partition coefficients, called logp, are highlighted, which has the values (0.17; (3,33, -3,2), solubility in aqueous medium (3.44 mg / ml), and the presence of a high concentration , by means of the octanol system, thus defining the compound (polar or non-polar) found in precise experiments. the counting of receptor hydrogens is in the value of 8, and already the donor count is 6. It has a polarizability of 33.42 å3, and its polar surface area with 164.75 å2, and physiological charge -1. when subjected to simulations routines of admet (absorption, distribution, metabolism, and excretion), which describes the disposition of a pharmaceutical compound within an organism, it was possible to characterize the chlorogenic acid molecule as water soluble, with low lipophilicity (table 1), possessing a pharmacokinetic indicates a low intestinal gastrointestinal absorption, with skin permeation in the order of -8.76 cm / s (log kp), not inhibiting the enzymes cyp1a2, cyp2c19, cyp2c9, cyp2d6 and cyp3a4, having a lipinski (violation: nhoroh> 5) and of general form possessing good potential of oral biovailibility, as we can observe in the polygon of physicochemical space for oral bioavailability, in which we can the descriptors of lipophility (0 ≤ <xlogp3 <+0.50), size (150g mol -1 <mv <500g mol -1), polarity (20 å ^ 2 <tpsa<130 å ^ 2), insolubility (0 <log s (esol) <6), insaturation (0.25 <fraction csp3 <1) and flexibility (0 <num, rotatable bonds <9), were colored zone is the suitable physicochemical space for oral bioavailability (figure 3).

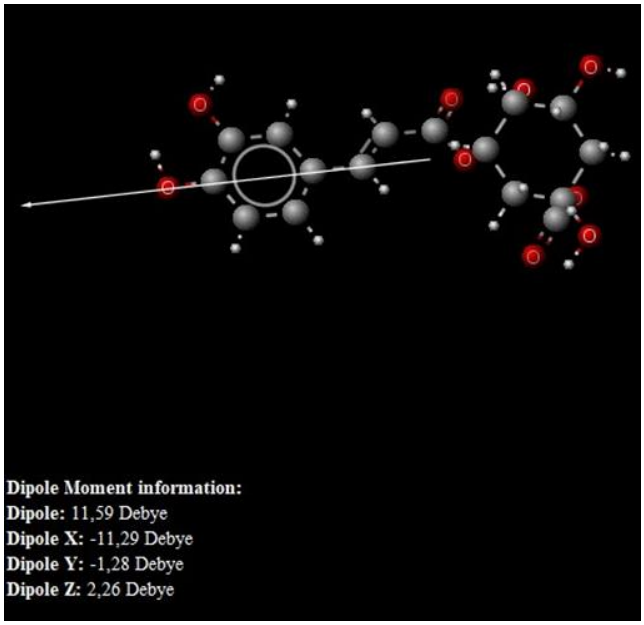


Fig.3 Calculated dipole moment of chlorogenic acid.

Table II

Descriptors generated by ADME of chlorogenic acid

| WaterSolubility | |
|---|---|
| Log *S* (ESOL) | -1.62 |
| Solubility | 8.50e+00 mg/ml; 2.40e-02 mol/l |
| Class | Verysoluble |
| Log *S* (Ali) | -2.58 |
| Solubility | 9.42e-01 mg/ml; 2.66e-03 mol/l |

| | |
|---|---|
| Class | Soluble |
| Log *S* (SILICOS-IT | 0.40 |
| Solubility | 8.94e+02 mg/ml;<br>2.52e+00 mol/l |
| Class | Soluble |
| Lipophilicity | |
| Log $P_{o/w}$ (iLOGP) | 0.87 |
| Log $P_{o/w}$ (XLOGP3) | -0.42 |
| Log $P_{o/w}$ (WLOGP) | -0.75 |
| Log $P_{o/w}$ (MLOGP) | -1.05 |
| Log $P_{o/w}$ (SILICOS-IT) | -0.61 |
| Consensus Log $P_{o/w}$ | -0.39 |

Source:Swissadmehttp://www.swissadme.ch/index.php

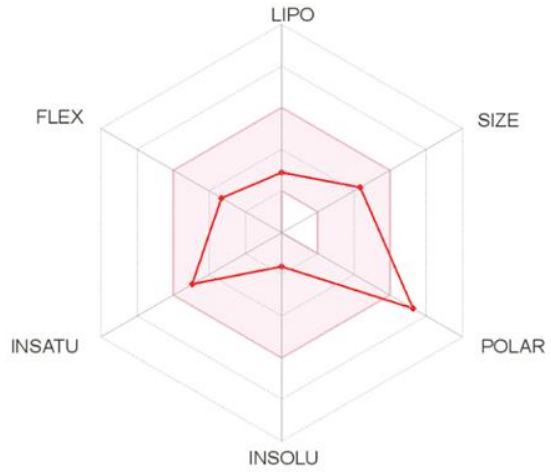


Fig. 4physico-chemical space for oral bioavailability of chlorogenic acid.

With respect to the dimensional structure available in several repositories, they have only fidelity in the connectivity of the atoms, often leaving gaps in the need with respect to the lengths of the connections and angles of torsion and dihedral, thus necessitating a mathematical treatment to characterize conformacionalmente the molecule, when using the parametric codes of the semi-empirical method, it was possible to optimize the structure, obtaining a 63092.53 kcal mol-1 energy, with formation heat of 167452.4 kcal mol -1.

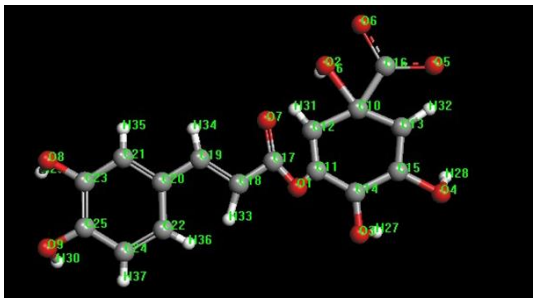

Fig. 5 optimized structure of chlorogenic acid.

According to Sant'Anna (2009) [19], electrostatic potential is established as the work to carry a positive unit charge from infinity to a certain point in space, to which these electrostatic potentials are represented by three-dimensional maps, intended for understanding the electrostatic contribution on the molecular surface through color differences, through computational resources from the molecular modeling. Following the context of Sant'Anna [19], the map of molecular electrostatic potential (MEP) is calculated through a grid of points detected in different layers, constructed as an overlap of Van Der Waals spheres in each atom around the molecule. The three-dimensional electrostatic maps allow us to predict the possible sites of nucleophilic and electrophilic bonds between biological molecules and their respective receptors [11], which confirms the theoretical concepts of the formation of bonds between atoms involving electrostatic forces between In this way, using the data of the optimization by means of theoretical semi-empirical calculations, it was possible to render the map of electrostatic potential of the molecule of the chlorogenic acid, that indicated the oxygen as I sit the regions with higher nucleophilic potential, thus distributing the sites at the ends of the molecule (Figure 6).

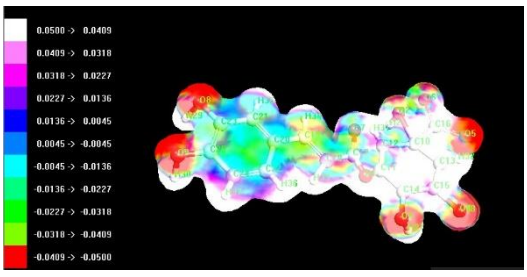


Fig.6 Potential surface map of chlorogenic acid.

Molecular orbitals contribute significantly to the advance of all research frontiers in the field of chemistry, especially the HOMO orbitals and the LUMO (Molecular Orbital Low Voltage Unbalanced Orbital). [20] These orbitals have arisen in analysis to the electron density in each atom of the border orbitals by a group of Japanese that investigated the reactivity of aromatic compounds. [21] The definition of these orbitals is related to two important characteristics, the HOMO energy having an electron donor character and the LUMO energy measures the electron-acceptor character [5] [22]. The data obtained in the geometric optimization, allowed to plot the border orbitals, where Homo (figure 7-A) has symmetry between the positive (blue) and negative phases ( red), being formed from the contribution of the carbon atoms of (C17, C18, C19, C20, C21, C22, C25) and oxygen (O9, O7). With respect to LUMO (Figure 7-B), it was possible to observe that it was formed from the carbon atoms (C15) and oxygen (O2, O5, 06), and also showed symmetry between the positive and negative phases.

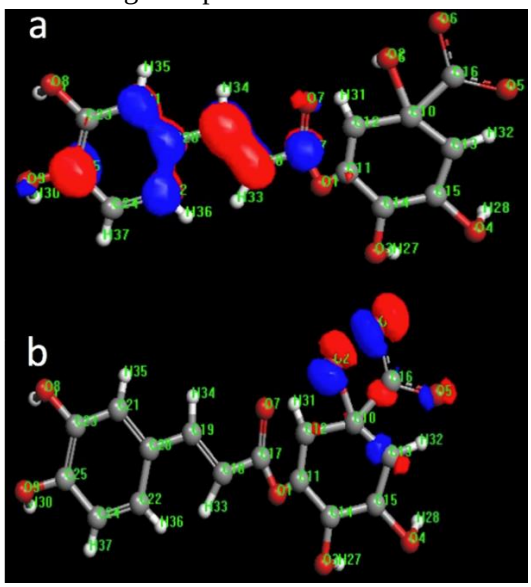


Fig. 7frontier orbitals of Chlorogenic acid: HOMO (A) and LUMO (B).

## IV. CONCLUSIONS

The present work allowed the electronic and structural characterization of the phytochemical Chlorogenic Acid, allowing to identify its thermodynamically stable conformational structure, to identify its nucleophilic site as well as to characterize the border orbitals, besides evaluating the pharmacokinetic potential, indicating this as a promising drug, being indicated for future in silico studies of drug desing, and molecular docking, which, together with the current in vivo studies being carried out, may explain the mechanism of action of this phytochemical.

## V. ACKNOWLEDGMENT

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## VI. REFERENCES

[1] J. Godos et al., “Coffee components and cardiovascular risk: Beneficial and detrimental effects,” International Journal of Food Sciences and Nutrition. 2014.

[2] S. A. Abrahão, R. G. F. A. Pereira, A. R. Lima, E. B. Ferreira, and M. R. Malta, “Compostos bioativos em café integral e descafeinado e qualidade sensorial da bebida,” Pesqui. Agropecu. Bras., 2008.

[3] M. M. Costa and L. C. Trugo, “Determinação de compostos bioativos em amostras comerciais de café torrado,” Quim. Nova, 2005.

[4] M. N. Clifford, “Chlorogenic acids and other cinnamates - nature, occurrence and dietary burden,” J. Sci. Food Agric., vol. 79, no. 3, pp. 362–372, Mar. 1999.

[5] A. Arroio, K. M. Honório, and A. B. F. Da Silva, “Propriedades químico-quânticas empregadas em estudos das relações estrutura-atividade,” Quimica Nova. 2010.

[6] A. Arroio, K. M. Honório, and A. B. F. Da Silva, “Propriedades químico-quânticas empregadas em estudos das relações estrutura-atividade,” Quim. Nova, vol. 33, no. 3, pp. 694–699, 2010.

[7] S. S. Carneiro, A. R. Lima, M. M. Marinho, and E. S. Marinho, “In silico Study Of The Therapeutic Agent In The Treatment Of Non-Hodgkin ’ s Lymphomas , Peripheral T- Cell Belinostat , A Semi-Empirical Approach,” Imp. J. Interdiscip. Res., no. 8, pp. 1645–1648, 2016.

[8] S. S. Carneiro, M. Marinho, and E. S. Marinho,

"ESTUDO IN SILICO DO FÁRMACO ANTI-LEISHMANIOSEMILTEFOSINA," JOIN, no. 1, 2017.
[9] D. S. Wishart, "DrugBank," in Principles of Pharmacogenetics and Pharmacogenomics, 2012.
[10] EMBL-EBI, "ChEMBL," ChEMBL. 2011.
[11] L. L. Bezerra and E. S. Marinho, "Caracterização eletrônico / estrutural do fármaco anti- hipertensivo Alprenolol : um estudo quântico semi-empírico," An. do XXIII Encontro Iniciac. aPesqui. -UNIFOR, 2017.
[12] E. S. Marinho, "UTILIZAÇÃO DO MÉTODO SEMI-EMPÍRICO PM7 PARA CARACTERIZAÇÃO DO FÁRMACO ATALURENO : HOMO ," Rev. Expressão Católica, vol. 1, no. 1, pp. 177–184, 2016.
[13] L. Paes, M. M. Marinho, and E. S. Marinho, "QUANTUM STUDY OF GEOMETRIC PROPERTIES OF THE ANTI- HIVCOUMARIN HERACLENOL : A STUDY OF DENSITY FUNCTIONAL," Int. J. Eng. Technol. Res. Manag., vol. 2, no. 02, pp. 27–37, 2018.
[14] M. A. Thompson, "ArgusLab 401. Planaria Software LLC, Seattle, WA. ArgusLab 4.0.1." Seattle, 2010.
[15] A. Daina, O. Michielin, and V. Zoete, "SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," Sci. Rep., 2017.
[16] A. Daina, O. Michielin, and V. Zoete, "ILOGP: A simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach," J. Chem. Inf. Model., 2014.
[17] A. Brexpiprazole, M. Nunes, M. M. Marinho, and E. S. Marinho, "Initial Studies of Electronic and Structural Characterization of," vol. XII, no. 1, pp. 11–20, 2020.
[18] A. K. Agrahari and C. George Priya Doss, "A Computational Approach to Identify a Potential Alternative Drug With Its Positive Impact Toward PMP22," J. Cell.Biochem.,2017.
[19] C. M. R. Sant'Anna, "Molecular modeling methods in the study and design of bioactive compounds: An introduction," Rev. Virtual Química, vol. 1, no. 1, 2009.
[20] P. W. Atkins, T. Overton, J. Rourke, M. Weller, F. Armstrong, and M. Hagerman, Shriver & Atkins' Inorganic Chemistry. 2010.
[21] G. Zhang and C. B. Musgrave, "Comparison of DFT methods for molecular orbital eigenvalue calculations," J. Phys. Chem.A, 2007.
[22] E. S. Marinho, "A DFT study of synthetic drug topiroxostat: MEP, HOMO, LUMO," Int. J. Sci. Eng. Res., vol. 7, no. July, pp. 1264–1270, 2016.