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DOPA DECARBOXYLASE INHIBITION BY CHLOROGENIC ACID: EXPLORING THE POTENTIAL OF A NATURAL PRODUCT

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Abstract: Dopa decarboxylase is a key enzyme in the synthesis of neurotransmitters such as dopamine and is directly implicated in the pathophysiology of Parkinson's disease. In this study, a molecular docking analysis was performed to evaluate the inhibitory potential of isochlorogenic acid compared to other natural compounds, including caffeic acid, chlorogenic acid, quinic acid, and caffeine, as well as the known inhibitor carbidopa. Isochlorogenic acid displayed the highest binding affinity (-8.9 kcal/mol), surpassing even carbidopa (-7.1 kcal/mol). Chlorogenic acid also showed strong affinity (-8.0 kcal/mol), while quinic acid had the lowest (-5.7 kcal/mol). Isochlorogenic acid formed numerous hydrogen bonds and hydrophobic interactions with residues critical to the enzyme's catalytic function, such as HIS192, SER194, and LYS303. These results suggest that isochlorogenic acid may act as a potent competitive inhibitor of Dopa decarboxylase and holds promise for further investigation as a therapeutic agent in the treatment of Parkinson's disease.
Keywords: Dopa decarboxylase inhibition; Isochlorogenic acid; Chlorogenic acid; Molecular docking; Parkinson's disease; Natural polyphenols.

INTRODUCTION

In the United States of America, approximately 1.04 million persons were diagnosed with Parkinson's disease, PD, in 2017. (Yang et al., 2020). In this regard, L-carbidopa and L-dopa have been used to treat Parkinson's disease. Also, chinese traditional medicine revealed herbs with anti-Parkinson properties. Numerous polyphenols have been implicated in the treatment of Parkinson's; for example, verbascoside, has been implicated in the treatment of Parkinson's disease due to its capacity to regenerate tyrosine hydroxylase-inmunoreactive neurons (Liang et al., 2016). Although ***1*** has been detected in several plants, in Mexico was also identified in Buddleja chordata (Avila Acevedo et al., 2005), (Santos-Cruz et al., 2012).

Other natural compounds were evaluated against Parkinson's disease (Jha & Kumar, 2017); nevertheless, K_i values range between 2.67 μM and 221.78 μM. Whereas virtual screening of dopa decarboxylase revealed a K_i value of 500 nM (Daidone et al., 2012). Additionally, the benefits of another plant, *Ilex paraguarinensis*, more commonly referred to as yerba mate, have been examined, with results indicating that it provides neuroprotective support for dopaminergic neurons (Bernardi et al., 2019). In this regard, docking studies have demonstrated that chlorogenic acid ***2*** inhibits monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), which have been investigated as potential targets for natural chemicals in the treatment of PD (Engelbrecht et al., 2019). (Sivaraman & Srikanth, 2016). However, another therapy option for Parkinson's disease is tied to the Dopa decarboxylase conversion of L-dopa to dopamine. Due to the release of synaptic chemicals, dopa decarboxylase is a critical special in Parkinson's disease. Previous research on verbascoside's activity in Parkinson's disease has been also published (Daidone et al., 2012). In this study we report the inhibition of dopa decarboxylase by some of the main compounds found in Ilex paraguarinensis. Dopa decarboxylase is seen as a possible therapeutic target for developing treatments for Parkinson's disease. Carbidopa is a medical compouns which inhibits dopa decarboxylase for Parkinson's disease.

MATERIALS AND METHODS

The structure of the enzyme Dopa decarboxylase (DDC) was obtained from the Protein Data Bank (PDB), specifically the crystal structure 1JS3, in which the enzyme is co-crystallized with the inhibitor carbidopa. All water molecules, ions, and heteroatoms were removed from the structure prior to preparation for molecular docking. To further ensure

structural accuracy, homology modeling of the enzyme was also conducted using YASARA software (Krieger, 2002).

A virtual screening was performed using a set of natural and synthetic compounds including caffeic acid, chlorogenic acid, isochlorogenic acid, quinic acid, caffeine, and carbidopa (Ding, 2023). The atomic coordinates of the compounds were retrieved from PubChem. Their geometry was optimized, and Gasteiger partial charges were calculated using Gaussian 19 (Frisch, Trucks, Schlegel, et al., 2016), applying the B3LYP functional (Becke, 1993; Lee & Yang, 1988), which is widely used for geometry optimization in molecular modeling.

Molecular docking simulations were carried out with AMdock software (Valdés-Tresanco, 2020), which incorporates AutoDock Vina as the docking engine (Trott & Olson, 2010). The docking grid was centered on the crystallized carbidopa ligand by using the "center on hetero" option, which places the search space at the geometric center of the defined receptor. This approach is advantageous because several of the tested ligands, particularly isochlorogenic and chlorogenic acids, resemble the catechol structure of carbidopa, suggesting potentially similar binding modes.

The dimensions of the search space were set to 19 × 19 × 19 Å, determined based on the radius of gyration of the ligands as implemented in AMDock (Feinstein & Brylinski, 2015). Virtual screening was focused exclusively on ligands exhibiting negative binding affinities, indicative of stable interactions within the active site of DDC. Visualizations of the ligand--protein interactions were produced using the PyMOL Molecular Graphics System, version 2.0 (Schrödinger, LLC).

RESULTS

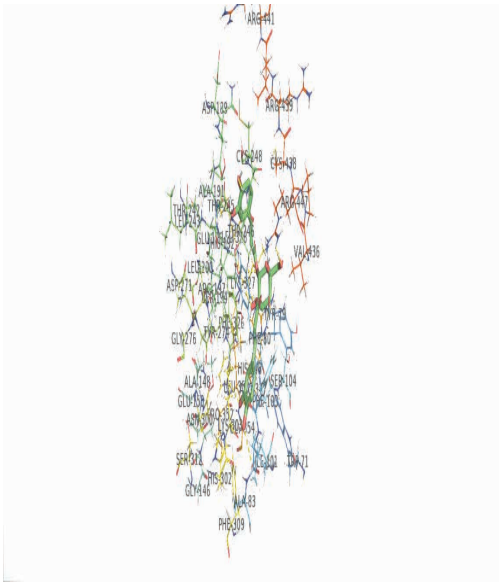

Figure 1. Ligand interaction diagram of isochlorogenic acid with dopa decarboxylase. The picture was generated by PyMOL (The PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC).

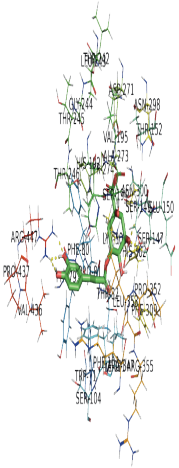

Figure 2. Ligand interaction diagram for chlorogenic acid with dopa decarboxylase residues. The picture was generated by PyMOL (The PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC).

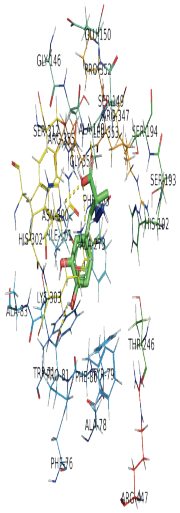

Figure 3. Ligand interaction diagram for carbidopa with dopa decarboxylase residues. The picture was generated by PyMOL (The PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC).

Hydrogen bond	Hydrophobic interactions
THR82	GLU150
LYS303	PRO352
HIS192	LEU353
SER193	PHE103
SER247	SER194
ARG447	SER193
THR246	SER104
	GLU196
	ARG97
	ILE101
	PHE309
	ASP139
	ALA272
	ASP271
	LEU243
	TYR274
	THR245
	GLN190
	ASP189
	LEU440
	ARG441
	ARG439
	PRO437
	VAL436
	TRP71
	TYR79
	CYS248
	SER247
	ASP189
	THR246
	SER247
	THR242
	LEU200
	LEU328
	LYS327
	PHE326
	HIS348
	ARG347
	PHE103
	PHE309
	ALA83
	THR82
	PHE80
	GLY276

Table 1. Docking interactions with isochlorogenic acid.

Hydrogen bond	Hydrophobic interaction
Ser147	THR152
Ser149	VAL195
Ser194	ASN298
Arg447	ASP271
	THR242
	LEU243
	ALA273
	GLY244
	THR245
	THR246
	THR82
	PRO81
	TYR79
	PHE80
	VAL436
	PRO437
	PHE103
	SER104
	ARG437
	ARG355
	LEU353

	PRO352
	HIS192
	TRP71
	TYR274
	ASN300
	ILE101
	PHE309
	HIS302
	GLU150
	LYS303

Table 2. Docking interactions with chlorogenic acid.

Hydrogen bond	Hydrophobic interaction
HIS302	ALA83
LYS303	TRP71
PRO81	PHE76
GLY354	ALA78
LEU353	TYR79
	ARG447
	THR246
	PHE80
	ASN300
	SER312
	GLY146
	GLU150
	PRO352
	ALA148
	SER149
	SER194
	SER193
	HIS192
	ALA273
	PHE103
	ARG347
	ILE101
	ARG355

Table 3. Docking interactions with carbidopa.

DISCUSSION

The interactions of the compounds with Dopa decarboxylase are as follows:

Caffeic acid exhibits an affinity energy of -6.6 kcal/mol; isochlorogenic acid, -8.9 kcal/mol; quinic acid, -5.7 kcal/mol; caffeine, -6.6 kcal/mol; and chlorogenic acid, -8.0 kcal/mol. In comparison, carbidopa shows an affinity energy of -7.1 kcal/mol. These results indicate that isochlorogenic acid has the highest affinity among all the compounds analyzed in this study. Chlorogenic acid also displays a strong affinity, followed by carbidopa. Caffeic acid has a slightly lower affinity, but it is comparable to that of caffeine, both with -6.6 kcal/mol. Quinic acid presents the lowest affinity energy.

As shown in (Table 1), numerous hydrogen bonds and hydrophobic interactions contribute to the binding of isochlorogenic acid with the Dopa decarboxylase enzyme. This abundance of interactions likely accounts for the ligand's high binding affinity. For the chlorogenic acid a similar behavior is observed, as described in (Table 2). Based on these results, it is noteworthy that isochlorogenic acid demonstrates a higher affinity than even the typical inhibitor, carbidopa. Isochlorogenic acid forms several interactions, as summarized in (Table 3).

Additionally, it is evident that isochlorogenic acid, chlorogenic acid, and carbidopa consistently interact with residues involved in the enzyme's catalytic activity. Notably, some of these residues include HIS192 (Bertoldi, 2001), SER194 (Lindén, 1982), and LYS303 (Dominici, 1991).

Furthermore, the three compounds, isochlorogenic acid, chlorogenic acid and carbidopa posses aromatic regions which can be involved in π-π stacking interactions with residues such as PHE103, TRP71 and PHE309 (Rhaman, 2015).

Remarkably, the isochlorogenic acid possses a higher number of total interactions with at least seven hydrogen bonds and more than 30 hydriphobic interactions which is directly

related to its high affinity energy to carbidopa decarboxylase. For example the interactions with LYS303, HIS192, SER193 and ARG447 are important as these residues are implied in the catalytic mechanism of stabilization of L-DOPA (Page, 1984).

CONCLUSION

In conclusion, in this work we have identified isochlorogeni acid and chlorogenic acid as possible inhibitors of the dopa decarboxylase enzyme, as their affinity energy values are higher in comparison with carbidopa. Isochlorogenic acid is a possible lead compound for PD and may be responsible for the observed positive effects of yerba mate use. As a possible lead compound, chlorogenic acid is suceptible to further structural changes in its molecular structure to enhance its inhibitory activity against dopa decarboxylase.

THE AUTHOR DECLARES NO CONFLICT OF INTEREST

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REFERENCES.

Avila Acevedo, J. G., Castañeda, C. M. C., Benitez, F. J. C., Durán, D. A., Barroso, V. R., Martínez, C. G., Muñoz, L. J. L., Martínez, C. A., & Romo De Vivar, A. (2005). Photoprotective activity of Buddleja scordioides. *Fitoterapia*, *76*(3–4), 301–309. https://doi.org/10.1016/j.fitote.2005.03.009

Becke, A. D. (1993). No Title. *J. Chem. Phys.*, *98*, 5648–5652.

Bernardi, A., Ballestero, P., Schenk, M., Ferrario, M., Gómez, G., Rivero, R., Avale, E., Taravini, I., Gershanik, O., Guerrero, S., & Ferrario, J. E. (2019). Yerba mate (Ilex paraguariensis) favors survival and growth of dopaminergic neurons in culture. *Movement Disorders*, *34*(6), 920–922. https://doi.org/10.1002/mds.27667

Bertoldi, M., Castellani, S., & Voltattorni, C. (2001). Mutation of residues in the coenzyme binding pocket of dopa decarboxylase. European Journal of Biochemistry, 268(10), 2975-2981. https://doi.org/10.1046/j.1432-1327.2001.02187.x C. Lee, W.Yang, R. G. P. (1988). No Title. *Phys. Rev. B*, *37*, 785–789.

Daidone, F., Montioli, R., Paiardini, A., Cellini, B., Macchiarulo, A., Giardina, G., Bossa, F., & Borri Voltattorni, C. (2012). Identification by virtual screening and in vitro testing of human DOPA decarboxylase inhibitors. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0031610

Ding, J., Tang, S., Mei, Z., Wang, L., Huang, Q., Hu, H., ... & Wu, J. (2023). Vina-GPU 2.0: further accelerating AutoDock Vina and its derivatives with graphics processing units. Journal of Chemical Information and Modeling, 63, 1982-1998.

Dominici, P., Maras, B., Mei, G., & Voltattorni, C. (1991). Affinity labeling of pig kidney 3,4-dihydroxyphenylalanine (dopa) decarboxylase withn-(bromoacetyl)pyridoxamine 5′-phosphate. European Journal of Biochemistry, 201(2), 393-397. https://doi.org/10.1111/j.1432-1033.1991.tb16296.x

Engelbrecht, I., Petzer, J. P., & Petzer, A. (2019). Evaluation of Selected Natural Compounds as Dual Inhibitors of Catechol-O--Methyltransferase and Monoamine Oxidase. *Central Nervous System Agents in Medicinal Chemistry*, *19*(2), 133–145. https://doi.org/10.2174/1871524919666190619090852

Feinstein, W. P., & Brylinski, M. (2015). Calculating an optimal box size for ligand docking and virtual screening against experimental and predicted binding pockets. *Journal of Cheminformatics*, *7*(1). https://doi.org/10.1186/s13321-015-0067-5

Jha, S. K., & Kumar, P. (2017). MOLECULAR DOCKING STUDY OF NEUROPROTECTIVEPLANT-DERIVED BIOMOLECULES IN PARKINSON'S DISEASE. *International Journal of Pharmacy and Pharmaceutical Sciences*, *9*(9), 149. https://doi.org/10.22159/ijpps.2017v9i9.20445

Krieger, E., Koraimann, G., & Vriend, G. (2002). Increasing the precision of the comparative models using YASARA NOVA—a self-parameterizing force field. Proteins: Structure, Function, and Bioinformatics, 47, 393-402.

Liang, J. Q., Wang, L., He, J. C., & Hua, X. D. (2016). Verbascoside promotes the regeneration of tyrosine hydroxylase-immunoreactive neurons in the substantia nigra. *Neural Regeneration Research*, *11*(1), 101–106. https://doi.org/10.4103/1673-5374.175053

Lindén, I., Neuvonen, P., & Vapaatalo, H. (1982). Effects of 3,4-dihydroxyphenylpyruvic acid and its triacetylated derivative on dopa decarboxylase. Acta Pharmacologica Et Toxicologica, 51(3), 266-269. https://doi.org/10.1111/j.1600-0773.1982.tb01024.x

M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. S., M. A. Robb, J. R. Cheeseman, G. Scalmani, V. B., G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. M., J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. H., J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. W.-Y., F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. P., T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. R., G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. F., J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. N., T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. P., F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. K., V. N. Staroverov, T. A. Keith, R. Kobayashi, J. N., K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. I., J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. C., J. W. Ochterski, R. L. Martin, K. Morokuma, O. F., & J. B. Foresman, and D. J. F. (2016). *Gaussian 16* (Revision A.03). Gaussian, Inc.

Page, M. I. (1984). Chapter 7 The mechanisms of chemical catalysis used by enzymes (Vol. 6, pp. 229–269). Elsevier. https://doi.org/10.1016/S0167-7306(08)60378-6

Rahman, M. M., Muhseen, Z. T., Junaid, M., & Zhang, H. (2015). The aromatic stacking interactions between proteins and their macromolecular ligands. *Current Protein & Peptide Science*, *16*(6), 502–512. https://doi.org/10.2174/1389203716061507021316

Santos-Cruz, L. F., Ávila-Acevedo, J. G., Ortega-Capitaine, D., Ojeda-Duplancher, J. C., Perdigón-Moya, J. L., Hernández-Portilla, L. B., López-Dionicio, H., Durán-Díaz, Á., Dueñas-García, I. E., Castañeda-Partida, L., García-Bores, A. M., & Heres-Pulido, M. E. (2012). Verbascoside is not genotoxic in the ST and HB crosses of the Drosophila wing spot test, and its constituent, caffeic acid, decreases the spontaneous mutation rate in the ST cross. *Food and Chemical Toxicology*, *50*(3–4), 1082–1090. https://doi.org/10.1016/j.fct.2011.12.006

Sivaraman, D., & Srikanth, J. (2016). Discovery of novel monoamine oxidase-b inhibitors by molecular docking approach for alzheimer's and parkinson's disease treatment. *International Journal of Pharmaceutical Sciences Review and Research*, *40*(1), 245–250.

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry, 31*(2), 455–461. https://doi.org/10.1002/jcc.21334

Valdés-Tresanco, M. S., Valdés-Tresanco, M. E., Valiente, P. A., & Moreno, E. (2020). AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. *Biology Direct*, *15*(1), 1–12. https://doi.org/10.1186/s13062-020-00267-2

Yang, W., Hamilton, J. L., Kopil, C., Beck, J. C., Tanner, C. M., Albin, R. L., Ray Dorsey, E., Dahodwala, N., Cintina, I., Hogan, P., & Thompson, T. (2020). Current and projected future economic burden of Parkinson's disease in the U.S. *Npj Parkinson's Disease*, *6*(1), 1–9. https://doi.org/10.1038/s41531-020-0117-1