Lab-in-Silico
https://lab-in-silico.com
eISSN: 2717-1922

ORIGINAL RESEARCH

Lab-in-Silico. 2020;1(1):3-6. DOI: 10.22034/labinsilico20011003

In Silico Interactions of Steviol with Monoamine Oxidase Enzymes

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Received: 06 June 2020 / *Accepted*: 19 June 2020 / *Published Online*: 30 June 2020

ABSTRACT. Interactions of steviol with each of monoamine oxidase A and B (MAO-A and MAO-B) enzymes were investigated by the *in silico* approach. Molecular Docking simulations (MDs) were performed explore the interacting ligand…target complex formations of steviol…MAO-A and steviol…MAO-B complex systems. The results indicated better formation of steviol…MAO-A complex than steviol…MAO-B complex in both of quantitative and qualitative aspects. The values of binding energy (BE) and inhibition constant (KI) indicated stronger steviol…MAO-A complex than steviol…MAO-B complex. Moreover, MAO enzyme contains Flavin group in the active site, in which steviol interacted with the Flavin of MAO-A only not with that of MAO-B proposing steviol as a possible inhibitor of MAO-A enzyme activity. Based on the employed *in silico* approach, the mechanism of action of steviol…MAO interactions were clarified very well.

KEYWORDS. Steviol; Monoamine oxidase; Enzyme; Docking; Simulation.

INTRODUCTION. Monoamine oxidases (MAO) enzyme belongs to the Flavin-containing amine oxidoreductases family of proteins, which are found outside of mitochondria membrane of cells.[1] There are two types of MAO in human cells; MAO-A and MAO-B.[2] The levels of activity of both enzymes are important to arise mood and mental disorders, in which their over-expression could yield problems for humans.[3] Therefore, development of novel inhibitors for blocking upper activity of MAO is an important task.[4] Earlier works indicated that the inhibitors are mostly specific for each of MAO-A and MAO-B enzymes, in which the mechanism of actions of these two enzyme are different. MAO-A is mainly incorporated with depression disorder whereas MAO-B is mainly incorporated with Parkinson's disease.[5, 6] In both case, these mental disorder and disease should be controlled for better human life.

Steviol (Fig. 1), obtained from *Stevia rebaudiana*, is a diterpene sweet compound as a sugar substitute.[7-10] Previous works indicated the enzyme inhibitory activity of steviol as an important step of pharmacotherapy.[11] Moreover, further explorations are still required to show various features of this favorite sweet especially for diabetic patients, who are dealing with serious health problems.[12] To this point, it is important to work on its impact on mental related disease and disorders.

Within this work, interactions of steviol with each of MAO-A and MAO-B enzymes were investigated by examining formation of ligand…target complexes including steviol…MAO-A and steviol…MAO-B. To this aim, *in silico* approach was used to simulate molecular

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systems to evaluate required quantitative and qualitative information regarding the purpose of this work. It is an advantage of *in silico* approach to provide an environment for molecular studies to reveal details of mechanism of interactions for the complicated biological systems.[13-15] Although the experimental material characterization approaches have been developing for years, but computational works could still clarify details of complicated systems as predictive part of complementary part of obtained results.[16-18] Based on this advantage, details of interactions of steviol with each of MAO-A and MAO-B enzymes were investigated in this work.

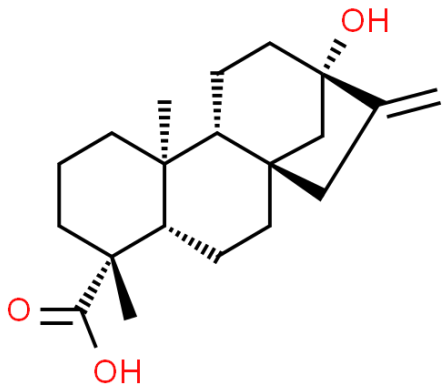

Fig. 1: Steviol; $C_{20}H_{30}O_3$; from ChemSpider ID: 398979.

METHODOLOGY. This work was done to see the interactions of steviol (Fig. 1) with each of MAO-A and MAO-B enzymes employing the *in silico* approach.[19] The 3D structural model of steviol (ID: 398979) was obtained from ChemSpider[20] and it was prepared as the ligand structure of this work. For preparing the target structures, the 3D structural models of each of MAO-A (2Z5X) and MAO-B (2XFU) were obtained from Protein Data Bank.[21] The required files for Molecular Docking simulation (MDs) were prepared using the AutoDock-Tools.[22] The Grid Box size was set to 70*70*70 with 100 numbers of Genetic Algorithm conformational search as implemented in the AutoDock program.[22] The MDs processes were performed to examine the formation of ligand…target complex systems between steviol and each of MAO-A and MAO-B enzymes. The output results including binding energy (BE), inhibition constant (KI), and interacting amino acids (AA) through hydrogen bond (HB) and non-HB interactions were all summarized in Table 1. Moreover, the graphical representations were exhibited in Fig. 2. It is important to note that *in silico* approach could provide insightful information for the complicated biological systems besides the experimental achievements.[23-26]

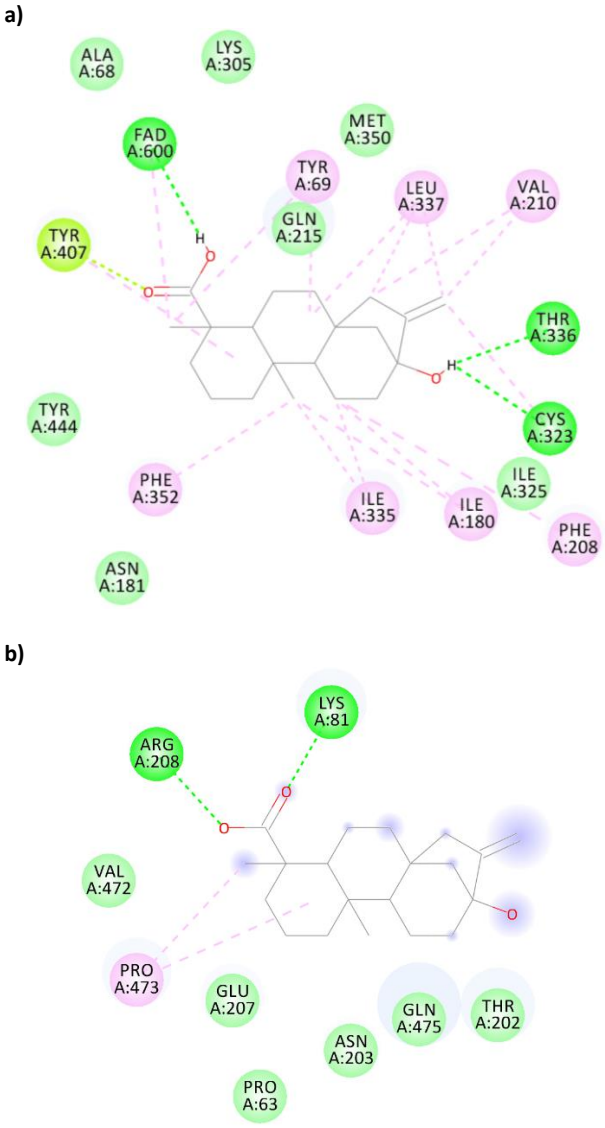

Fig. 2: Representations of interactions for **a)** Steviol…MAO-A complex, **b)** Steviol…MAO-B complex.

RESULTS & DISCUSSION. This work was done based on the *in silico* approach to investigate the interacting ligand…target complex systems of each of steviol…MAO-A and steviol…MAO-B (Fig. 2). The obtained results (Table 1) indicated that the investigated interacting complexes detected different environments by comparing the quantitative and qualitative results. The strength of steviol…MAO-A was more than steviol…MAO-B, which could mean better interaction of steviol with MAO-A than MAO-B. The values of ΔBE indicated that the steviol…MAO-A complex was 0.8 kcal/mol stronger than the steviol…MAO-B complex. The values of KI also indicated that the complex formation was better for

the steviol…MAO-A complex than the steviol…MAO-B complex with smaller value of KI for the MAO-A complex. Based on the quantitative results, it could be concluded that the steviol ligand could be more specific in interactions with MAO-A than MAO-B, in which the obtained values of both of BE and KI approved the trend of such ligand…target complex formation favorability.

Table 1: Molecular docking results*

Enzyme	BE	ΔBE	KI	HB AA	Non-HB AA
MAO-A	-6.98	0	7.65	CYS323; THR336; FAD600	ALA68; TYR69; ILE180; ASN181; PHE208; VAL210; GLN215; LYS305; ILE325; ILE335; LEU337; MET350; PHE352; TYR407; TYR444
MAO-B	-6.18	0.8	29.63	LYS81; ARG208	PRO63; THR202; ASN203; GLU207; VAL472; PRO473; GLN475

*See Figs. 1 and 2 for details. BE and ΔBE values are in kcal/mol and KI values are in uM.

In addition to the quantitative results, the qualitative achievements could yield insightful information about the details action of interacting ligand…target complex systems. A quick look at the content of Table 1 could reveal that the numbers of interacting amino acids with steviol was larger for MAO-A than MAO-B. The details of interactions were also exhibited in Fig. 2, in which various types of interactions could be seen for the MAO-A and MAO-B related complex systems. It is an important note than the MAO enzyme is a Flavin-containing enzyme, in which the Flavin is placed in the active site. Therefore, efficacy of steviol ligand for inhibiting each of MAO-A and MAO-B enzymes could be very much dependent on interaction with Flavin component of enzyme. Examining the results indicated that steviol interacted with Flavin in MAO-A only not in MAO-B. Therefore, in addition to quantitative achievements for better interacting steviol…MAO-A complex formation than steviol…MAO-B, the qualitative results also approved such achievement. Fig. 2 could also represent such trend by the visual condition of ligand…target interacting complex systems for interaction population of steviol…MAO-A complex in comparison with steviol…MAO-B complex.

As a concluding remark of this part, steviol is a ligand with better activity for MAO-A than MAO-B enzyme.

CONCLUSION. The ligand…target interacting complex formations of steviol…MAO-A and steviol…MAO-B complexes were investigated by *in silico* approach. The MAO enzyme contains Flavin in the active site, steviol interacted with Flavin of MAO-A only. The point could reveal favorability of steviol for inhibiting the activity of MAO-A but not MAO-B enzyme. Larger numbers of AA of MAO-A interacted with steviol in comparison with fewer numbers of AA of MAO-B. The trend was shown by the obtained BE values indicating stronger steviol…MAO-A complex than steviol…MAO-B complex. The values of KI also indicated that the steviol…MAO-A complex formation was more favorable than the steviol…MAO-B complex formation. As a conclusion, steviol could be proposed for further investigations on MAO-A enzyme inhibition.

ACKNOWLEDGEMENTS. This work was evaluated as a part of registered project (No. 50774) to the research council of Isfahan University of Medical Sciences, in which the supports are acknowledged.

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How to Cite: Harismah K, Mirzaei M. *In Silico* Interactions of Steviol with Monoamine Oxidase Enzymes. Lab-in-Silico. 2020;1(1):3-6.
DOI: https://doi.org/10.22034/labinsilico20011003
URL: https://sciengpub.com/lab-in-silico/article/view/labinsilico20011003