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Steviol and Iso-Steviol vs. Cyclooxygenase Enzymes: *In Silico* Approach

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ABSTRACT. Complex formations of each of steviol and iso-steviol, both originated from stevia, with two types of cyclooxygenase enzymes (COX-1 and COX-2) were investigated employing the *in silico* methodology. Molecular properties for singular ligands (steviol and iso-steviol) were examined in addition to their interaction with targets (COX-1 and COX-2) to yield complexes. The properties for singular ligand indicated their differences because of keto→enol change from steviol to iso-steviol, in which the corresponding interacting properties approved such different properties. Among the complex systems, steviol was assigned as better component than iso-steviol for contributing to interactions with both of COX-1 and COX-2 enzymes, in which it was very well specified for complex formation with COX enzymes. Quantum chemical computations and molecular docking simulations were performed to evaluate required properties, in addition to available properties, for examining the investigated systems of this work.

KEYWORDS. Steviol; Iso-steviol; Cyclooxygenase; *In silico*; Docking; Molecular simulation.

INTRODUCTION. Cyclooxygenase (COX) is the responsible enzyme for formation of prostanoids from arachidonic acid.[1] COX is also officially known as prostaglandin-endoperoxide synthase or prostaglandin G/H synthase, which is itself divided into two forms of COX-1 and COX-2.[2] COX specifically catalyzes the conversion from arachidonic acid to Prostaglandin H2 yielding inflammatory effects.[3] Therefore, inhibition of COX activity could help for moderating or eliminating inflammation and pain symptoms.[4] Considerable efforts on this purpose introduced nonsteroidal anti-inflammatory drugs (NSAIDs) as inhibitors of COX activity with the specifications for each of COX-1 and COX-2 enzymes.[5] NSAIDs are almost successful for COX inhibitions, but they have still side effects for the health quality of patients.[6] Therefore, exploring novel COX inhibitors is still an important task of research for providing better efficacies and higher health qualities for the patients.[7]

Steviol is a natural product obtained from Stevia rebaudiana, which is used as a sweet compound instead of sugar especially for diabetic patients.[8-11] Iso-Steviol is another isoform of steviol, in which one enol group is substituted by one keto group (Fig. 1). Biological activity of stevia has been already approved by enzyme inhibiting processes.[12, 13] The importance of steviol compounds has encouraged researchers to explore further features for this favorite sweet to

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improve life quality, especially for patients with diabetic and inflammatory symptoms.[14]

In current study, features of steviol and iso-steviol have been investigated versus each of COX-1 and COX-2 enzymes to explore possible formation of interacting ligand…target complexes (Fig. 2). To achieve this purpose, quantum chemical computations were performed for each of steviol and iso-steviol singulars and molecular simulations were performed to examine possible complex formations of ligands with each of COX-1 and COX-2. The obtained results were summarized in Tables 1 and 2 and they were exhibited in Figs. 1 and 2. Indeed, it is an advantage of such computer-based *in silico* approach to reveal useful information for complicated biochemical systems at the molecular scales in addition to critical experimental works.[15-23] This work was performed by the advantage of *in silico* approach for carful investigating complex formations of each of steviol and iso-steviol versus each of COX-1 and COX-2 enzymes.

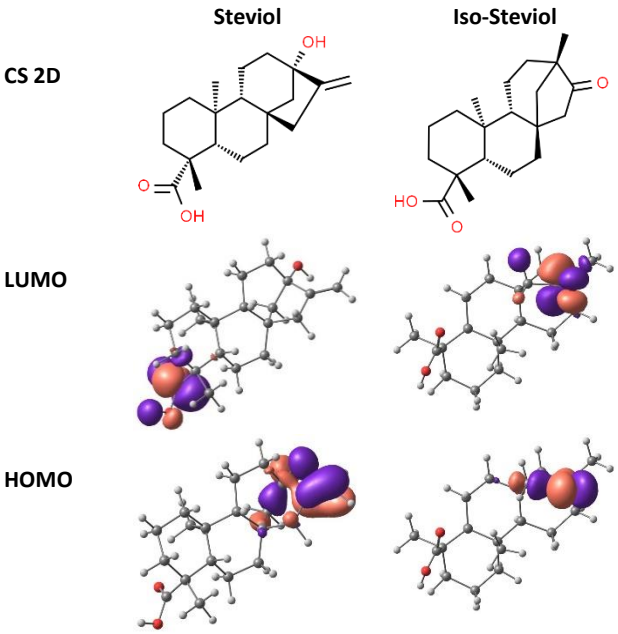

Fig. 1: Ligands schematic representations.

METHODOLOGY. Effects of each of steviol and iso-steviol on each of COX-1 and COX-2 enzymes were investigated in this work employing the computer-based *in silico* approach. To this aim, molecular structures of steviol (ID: 398979) and iso-steviol (ID: 89905) were obtained from ChemSpider[24] and they were considered for the ligand components (Fig. 1). The molecular properties (Table 1) were obtained from ChemSpider and quantum chemical computations at the B3LYP/3-21G* method of Gaussian program.[25] In the next step, 3D structural of COX-1 (6Y3C) and COX-2 (5IKQ) were obtained from Protein Data Bank[26] to consider for the target components in their pure amino acid containing biomolecules. Molecular docking simulations (MDS) processes were performed by submitting the ligand and target structures to SwissDock web server.[27] The MDs processes were performed to examine possibilities of complex formations for each of ligand…target interacting systems between each of steviol and iso-steviol and each of COX-1 and COX-2 enzymes (Table 2 and Fig. 2). It is worth noting that insightful information for the complicated biological systems could be provided very well employing the *in silico* approach in addition to other practical experiments.[28-30]

Table 1: Ligand properties.

Property	Steviol	Iso-Steviol
CSID	398979	89905
MF	$C_{20}H_{30}O_3$	$C_{20}H_{30}O_3$
MW	318	318
MV	272	276
D	1.2	1.2
LogP	4.44	4.13
HBA	3	3
HBD	2	1
LUMO	-0.34	0.02
HOMO	-6.26	-5.87
EG	5.92	5.85
DM	3.64	6.61

CSID (ChemSpider ID), MF (Molecular Formula), MW (Molecular Weight in Da), MV (Molar Volume in cm^3), D (Density in g/cm^3), LogP (Partition coefficient), HBA (Hydrogen Bond Acceptor), HBD (Hydrogen Bond Donor), LUMO (Lowest Unoccupied Molecular Orbital in eV), HOMO (Highest Occupied Molecular Orbital in eV), EG (Energy Gap in eV), and DM (Dipole Moment in Debye). See Fig. 1 for ligands schematic representations.

Table 2: SwissDock results.

Target	Result	Steviol	Iso-Steviol
COX-1	**ΔG_B**	-7.07	-6.87
	RMS	56.56	54.71
COX-2	**ΔG_B**	-6.95	-6.76
	RMS	69.71	54.22

ΔG_B (Delta-Energy of Binding kcal/mol) and RMS (Root Mean Square of ligand conformation fluctuation). See Figs. 1 and 2 for the corresponding schematic representations.

RESULTS & DISCUSSION. Computer-based *in silico* methodology was employed to investigate the

effects of each of stviol and iso-steviol on each of COX-1 and COX-2 enzymes. The results of molecular properties of singular ligands and complexes of each of ligand…target interacting systems were summarized in Tables 1 and 2 and Figs. 1 and 2. Examining the properties for singular ligands (table 1 and Fig. 1) could indicate that the slight change of enol-keto in structure could yield notable effects on the corresponding properties. The values of molecular weight (MW) were the same for both of steviol and iso-steviol with equivalent structural formulas; however, values of molar volume (MV) showed slight changes but without notable effects on density (D). The values of partition coefficient (LogP), as a ratio of oil/water solubility, detected the effects of enol-keto structural change in steviol and iso-steviol, in which the solubility system was changed for steviol and iso-steviol. The numbers of hydrogen bond acceptor (HBA) sites were similar for both ligands whereas the numbers of hydrogen bond donor (HBD) sites were reduced by enol→keto change in iso-steviol. Generally, the numbers of HBA and HBD were nor very much suitable for contributions of steviol and iso-steviol to HB interactions. The values of quantum calculated highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) detected the effects of enol→keto from steviol to iso-steviol, in which both levels were changed in addition to their differences as indicated by energy gap (EG). Furthermore, different HOMO and LUMO distribution patterns (Fig. 1) indicated different values of dipole moment (DM) for the ligand structures. It is important to mention here that the HOMO-LUMO distribution patterns are very useful here to interpret such significant change of DM values for steviol and iso-steviol. By careful examining the properties of singular ligands, it could be concluded here that the structural modifications, even slight modifications, could yield significant changes to their evaluated molecular properties, as seen for very much similar steviol and iso-steviol by a quick look but with different properties by deep in silico molecular analysis. The singular properties could also influence on the complex formation of ligand…target interacting system, which would be examined by further following discussion.

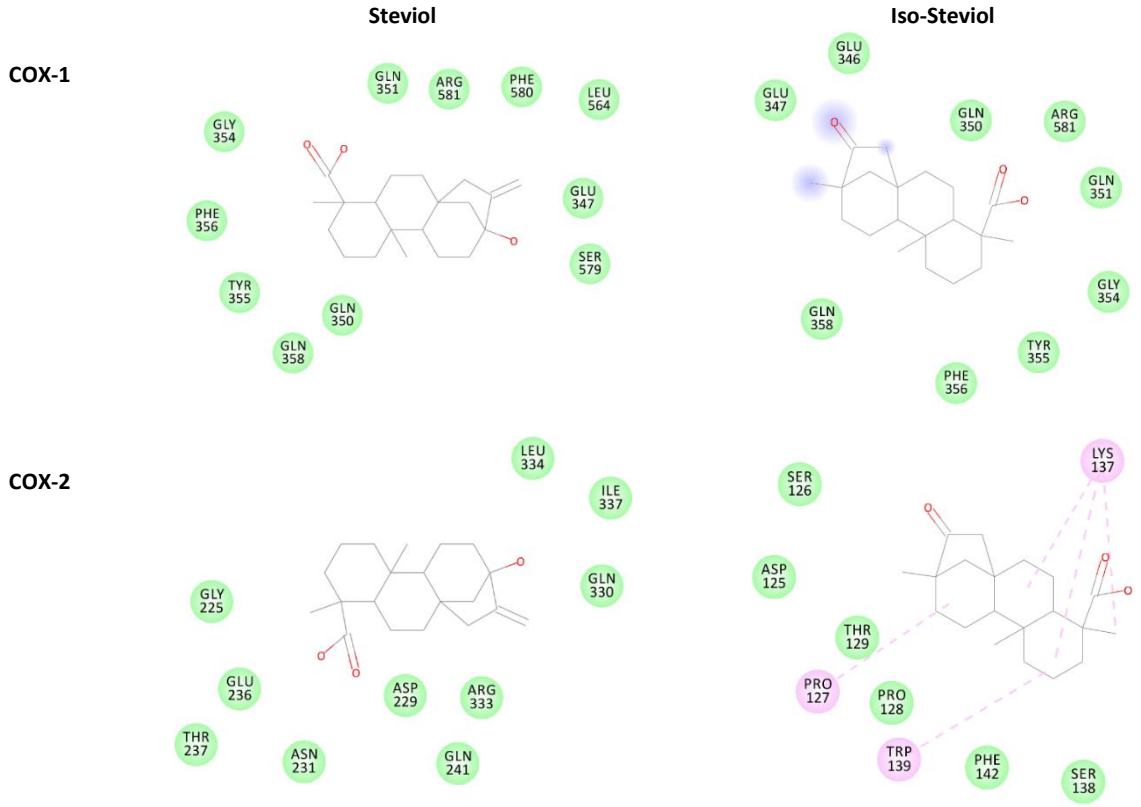

Fig. 2: Interacting ligand…target complexes representations.

Complex formations of each of steviol and iso-steviol ligands with each of COX-1 and COX-2 enzymes (Table 2 and Fig. 2) were investigated by performing MDs processes of SwissDock web server.[27] The results indicated different complex formation possibilities for each of ligand…target interacting systems by

evaluating different values of energies of binding (ΔGB) for the investigated complexes. By the molecular properties, the ligands were not significantly able to contribute to HB interactions, in which the schematic representations of complexes showed no HB interactions (Fig. 2). It could be noted that the non-HB interactions played dominant role for interactions of both of steviol and iso-steviol with each of COX-1 and COX-2, which were assigned before by low numbers of HBA and HBD and considerable value of LogP. Steviol could work better than iso-steviol for interactions with each of COX-1 and COX-2; the steviol…COX-1 complex could be assigned as the best complex formation (ΔGB = -7.07 kcal/mol). The obtained values of root mean square (RMS) for steviol was more significant than iso-steviol, in which steviol reached to complex formation with COX-1 earlier than COX-2 by lower value of RMS. However, this case is more favorable for iso-steviol versus COX-2 than COX-1. Additionally, the schematic representation could show the basket of amino acids in direct interaction with the centralized ligand structure. As a concluding remark of this part, steviol could work better than iso-steviol for interacting with both of COX-1 and COX-2 enzymes.

CONCLUSION. Within this work, the ligand…target complex formations of each of steviol and iso-steviol with each of COX-1 and COX-2 enzymes were investigated by employing the *in silico* methodology. The properties for singular ligands indicated that the enol→keto change from steviol to iso-steviol could arise significant changes to molecular features, in which different interactions were expected. The molecular properties did not propose the ligands for contributing to HB interactions, in which the results of ligand…target complexes approved such expectation. Additionally, binding strength values of complex formation were different introducing steviol better than iso-steviol for interacting with both of COX-1 and COX-2 enzymes. The final concluding remark, steviol could be applicable for COX enzymes and further studies would be still required to optimize such systems for specific applications in both computational and experimental aspects.

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