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In silico investigation of possible caffeine interactions with common inflammation-related targets

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ABSTRACT

Caffeine (CA) is a methylxanthine alkaloid widely used in anti-inflammatory drug associations due to its vasoconstricting properties. Although CA is acknowledged to interact with a plethora of macromolecules in human organism, there was to the best of our knowledge, no survey regarding its possible interactions with common inflammation-related targets. Henceforth, this work was concerned in the investigation of CA possible interactions with cyclooxygenases-1 and -2 (COX-1 and COX-2), as well as prostaglandin H2 synthase-1 and leukotriene A4 hydrolase through *in silico* approaches. CA molecule was studied as a ligand whereas the ligand-macromolecules docking models were created through AutoDock Vina tools. Results showcased that, although the thermodynamic features of the best scoring models did not render enough information to affirm stable interaction between CA and the analyzed macromolecules, more studies are needed to shed light on the possible role of methylxanthines towards inflammation targets.

1. INTRODUCTION

Caffeine (CA) is a methylxanthine alkaloid whose stimulating activities find numerous uses in human therapeutics. This compound is usually associated with non-steroidal anti-inflammatory drugs due to its vasoconstricting properties, which are promoted through CA antagonistic features over diverse cellular receptors. Nonetheless, the methylxanthine moiety (Fig. 1A and B) present in CA allows its binding with adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3) due to structural similarities with the physiological ligand. However, this molecule is known to also bind antagonistically with inositol triphosphate, glycine, ryanodine, and other receptors, which outlines the variety of targets prone to bound with CA [1–4].

Although literature reports concerning CA binding to the aforementioned receptors are numerous, there is a significant lack of reports regarding CA binding studies with inflammatory-response targets, which evidences the importance of further investigating this molecule in order to elucidate its therapeutic potential [5–10].

Considering studies regarding ligand-receptor binding kinetics and thermodynamics, *in silico* approaches offer a cheap and valuable alternative for preliminary screenings concerning chemical compounds bioactivity, moreover, these methods are also heavily used for drug discovery. In this context, molecules such as CA might be freely studied under computational strategies without the need of *in vivo* or *in vitro* assays in the first investigational steps. Nonetheless, semi-empirical approaches, such as molecular mechanics, are valuable *in silico* tools, which further increase their appeal in docking analysis. Under this light, the assessment of a small molecule proneness to interact with selected receptors is easily feasible by docking studies and has low computational cost [11–13].

Considering the importance of better understanding ligand-receptor features and its implications on the therapeutic applicability of small molecules, this report is aimed to explore CA interaction kinetics and thermodynamics toward the most common targets related to inflammatory response in humans. Henceforth, *in silico* methods based on semi-empirical approaches were used

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to investigate CA interaction to cyclooxygenase (COX) isoforms (COX-1 and COX-2), as well as prostaglandin H2 synthase-1 and leukotriene A4 hydrolase.

2. EXPERIMENTAL

2.1. *In Silico* Methods

CA (1,3,7-trimethylpurine-2,6-dione) structure was minimized through the software Chimera version 1.13 coupled to *Molecular Modeling Toolkit* and AMBER *toolkit* 4.0 prior docking studies. The same software was used to edit protein units retrieved from *Protein DataBank* (PDB). Moreover, the software *Python Molecular Viewer* version 1.5.6 was used to evaluate torsion-prone regions in CA molecule, and the docking models were conducted using *AutoDock Vina* and *AutoDock Tools* version 1.5.6. The docking model herein employed is based on a flexible ligand and a rigid receptor, therefore configuring itself in a semi-flexible model [14,15].

2.1. COXs Structures

Human COX-1 (PDB entry: 3N8X), COX-2 (PDB entry: 5F19), prostaglandin H2 synthase-1 (PDB entry: 1CQE), and leukotriene A4 hydrolase (PDB entry: 3FTS) were used in this study.

3. RESULTS AND DISCUSSION

3.1. CA and COX-1 Interaction

In order to explore possible CA and COX-1 interactions, a docking study was performed. Figure 2 evidence the highest scoring model.

Table 1: Table of thermodynamical properties calculated for the lowest energy conformation in the docking of CA-1CQE, CA-3FTS, CA-3N8X, and CA-5F19.

Receptor	Affinity ($kcal.mol^{-1}$)	Ki ($cal.mol^{-1}.K^{-1})10^{-5}$	HBonds (ligand)	HBonds (receptor)
1CQE	−6.1	3.60	1	1
3FTS	−5.9	5.03	1	1
3N8X	−5.7	7.04	0	0
5F19	−5.1	19.26	0	0

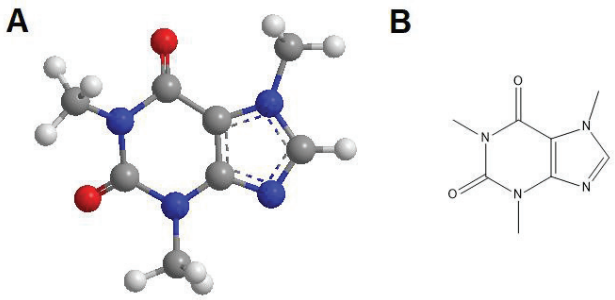

Figure 1: (A) Tri-dimensional representation of CA chemical structure. (B) CA chemical structure. Data processed in Chem3D Pro® software.

Results evidenced that CA highest scoring docking model presented no hydrogen bonds; however, the above than narrow distances found between CA and COX-1 electron-donor and electron-accepting moieties suggest possible intermolecular interaction [16–20].

3.2. CA and COX-2 Interaction

Concerning possible CA and COX-2 interactions, Figure 3 depicts the highest scoring model.

Regarding COX-2, CA highest scoring model did not present any hydrogen bonds (Figure 3). Although hydrogen bonds are nonetheless responsible for stable interactions between molecules, as well as intramolecular cohesion, their presence alone is not an indication of effective docking. In this context, other aspects such as torsional energies related to electronegative moieties, as well as molecular packaging, steric hindrance, and thermodynamic unbalance may turn hydrogen bond-rich models unfeasible. Henceforth, the first model presented highest score despite no strong bonds being detected [21–24].

3.3. CA and Prostaglandin H2 Synthase-1 Interaction

CA possible interaction with prostaglandin H2 synthase-1 had its highest scoring model presented in Figure 4.

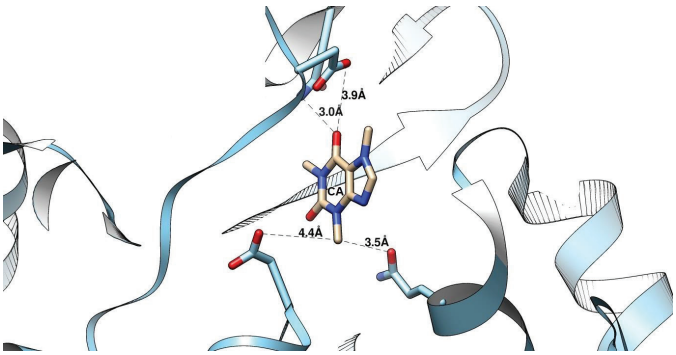

Figure 2: Docking depiction of the highest scoring model for CA-COX-1 interaction. All data gathered through Chimera software version 1.13.

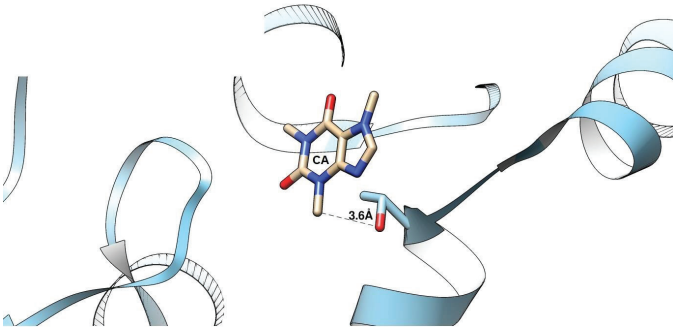

Figure 3: Docking depiction of the highest scoring model for CA-COX-2 interaction. All data gathered through Chimera software version 1.13.

Prostaglandin H2 synthase-1 and CA highest scoring model evidenced that two ligand sites are hydrogen bond donors to one acceptor site in the macromolecule (Fig. 4). This result is remarkable since the energy values for the depicted model when

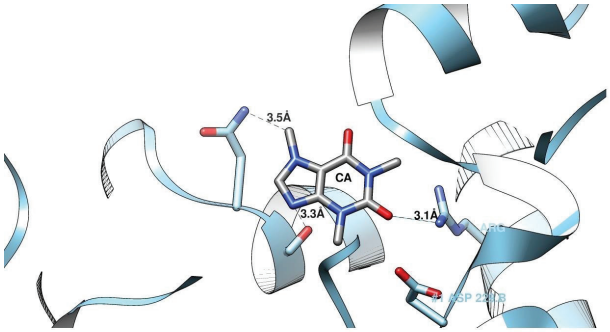

Figure 4: Docking depiction of the highest scoring model for CA-Prostaglandin H2 synthase-1 interaction. All data gathered through Chimera software version 1.13.

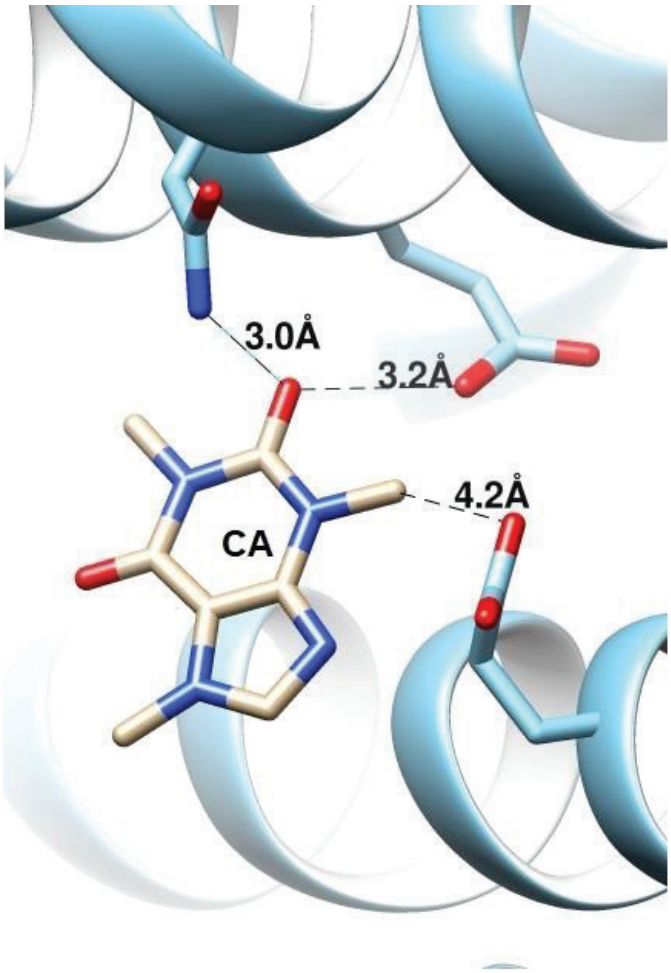

Figure 5: Docking depiction of the highest scoring model for CA-Leukotriene A4 hydrolase interaction. All data gathered through Chimera software version 1.13.

associated to hydrogen bond multiplicity imply nonetheless thermodynamic feasibility of ligand-macromolecule interaction. To the best of our knowledge, there was no report concerning the possible interaction of CA and prostaglandin H2 synthase-1, henceforth, the data herein depicted, although premature, may direct further investigations [21–24].

3.4. CA and Leukotriene A4 Hydrolase Interaction

The possible interaction of CA and leukotriene A4 hydrolase was also investigated. Figure 5 depicts the highest scoring model.

Results evidenced that leukotriene A4 hydrolase and CA may possibly interact through 3 hydrogen bond donor sites in the ligand and 2 receptor sites in the macromolecule (Figure 5). Results herein depicted are nonetheless relevant, since to the best of our knowledge, no similar study concerning CA docking models with the aforementioned receptors was performed. Moreover, the amount of hydrogen bonds associated to the thermodynamic feasibility of docking may imply possible interaction between CA and leukotriene A4 hydrolase. Furthermore, other reports evidence the relevance of hydrogen bonds abundance to successful models [16–20].

3.5. Interaction Constants

Gibbs free energy values give insights about the proneness of an interaction between ligand-receptor when comparing different receptors to a common ligand. Thermodynamics postulates that an interaction constant is directly linked to the interactions affinity through the following equation:

$$\Delta G = RTlnKb \quad (1)$$

Where ΔG is the interaction affinity, R is the gas constant, and T is the temperature. This equation can be derived in order to yield the interaction constant Ki.

$$Ki = e^{\frac{\Delta G}{RT}} \quad (2)$$

Where e is the Euler's number.

When considering ΔG values in molecular docking poses, higher scoring models possess smaller values of this parameter, while their Ki follow the same trend. In this sense, Ki values did corroborate to ΔG in the calculated models. However, since molecular docking is prone to many false positives, more studies are needed to further investigate the findings of this work.

4. CONCLUSION

The present work reported an investigation of CA potential interaction with macromolecules usually involved in inflammation. Although the thermodynamic features of the best scoring models did not render enough information to affirm stable interaction between CA and the analyzed macromolecules, more studies are needed to shed light on the possible role of methylxanthines towards inflammation targets.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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