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Research Paper

Comparison Docking Studies of Polydatin and Curcumin as therapeutic Targets on Several Protein and Enzymes

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Abstract— For the first time, we performed by Molecular Docking approach for six target proteins (DYRK-2, EGFR, COX-1-COV-2, MAPK-1 and MAK-3) the binding affinity of Polydatin and Curcumin respectively to evaluate their possible biological action. From all docking results, Curcumin has shown more binding affinity than Polydatin and also we noted that Curcumin has theoretically been able to bind mainly DYRK-2 and COX-1, showing excellent binding energy values of -10.15 kcal/mol and -9.59 kcal/mol respectively. As regards the case of Polydatin, it seems to have, among all the 6 targets investigated, only a good ability to bind with MAPK-1 with a binding energy value of approximately -9.11 kcal/mol. To achieve actual results, further molecular biological studies are necessary to understand both the mechanism of action of natural substances and their biological function with cells.

Keywords— Autodock Vina, Autodock 4, Polydatin, Curcumin

1. Introduction

The goal of this paper was to focus on the possible biological role of Polydatin and Curcumin respectively studying several computation methods on several proteins and enzymes. The approaches used are the classic Molecular Docking methods [1], through the Autodock Vina and Autodock 4 algorithms [2,3]. Several proteins and enzymes are screened with these computation analyses with Polydatin and Curcumin. Particular attention, we evaluated their role with the following proteins and enzymes targets:

- Dual specificity tyrosine phosphorylation regulated kinase 2 (or named DYRK2) [4,5].
DYRK2 has shown tyrosine autophosphorylation and catalyzed phosphorylation of histones H3 and H2B in vitro. Several studies reported that DYRK2 is as a tumor suppressor across various cancers triggering major antitumor and proapoptotic signals in breast, colon, liver, ovary, brain, and lung cancers, with lower DYRK2 expression correlated with poorer outcomes in patients [4,5].

- Mitogen-activated protein kinase kinase 1 (MAPK1). It is a dual-specificity kinase enzyme that phosphorylates mitogen-activated protein kinase (MAPK). General speaking, MAPKs is a group of serine/threonine protein kinases that play a role in regulating the response to external signals that reaches the cell [6].

-Mitogen-activated protein kinase kinase 3 (MAPK3). This kinase is activated by mitogenic and ecological stress, and participates in the MAP kinase-mediated signaling cascade [7].

- Epidermal growth factor receptor (EGFR). It is a transmembrane protein that is a receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligandsl [8].

- Prostaglandin-endoperoxide synthase (PTGS) ½ (or cyclooxygenase-1/2 or named COX-1 and COX-2). They are enzyme involved in inflammatory processes in the body[9]. Cyclooxygenase (COX) is the central enzyme in the biosynthetic path to prostaglandins from arachidonic acid [9]. Often the expression of these proteins or enzymes in inflammatory processes is altered or reduced, causing serious pathological processes.

For this reason, it is important to act promptly and diagnose symptoms early when possible. Among the various natural substances, in this work we have focused on Curcumin and Polydatin, both because there are several studies in the literature that demonstrate their role on cancer and inflammatory processes [10,11], but also due to their low side effects on humans.

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Figure 1. 3D representation of DYRK2 in Complex with Crystal Curcumin. The figure was reproduced by Chimera program.

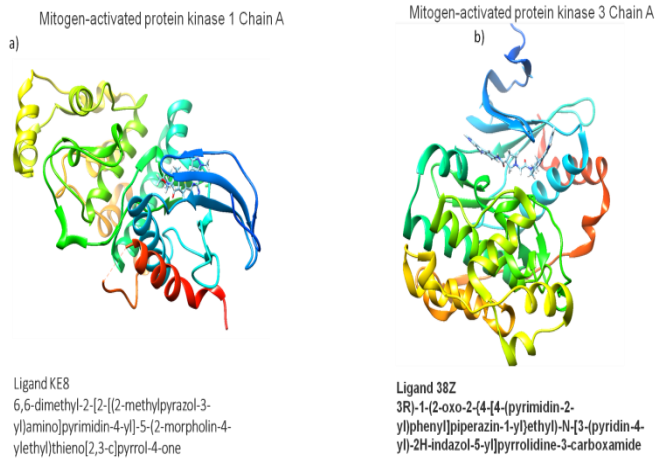

Figure 2. Comparison of 3D structures of a) MAPK-1 in complex with crystal ligand KE8 (6,6-dimethyl-2-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]-5-(2-morpholin-4-ylethyl)thieno[2,3-c]pyrrol-4-one) and MAPK-3 in complex with crystal ligand 38Z(3R)-1-(2-oxo-2-{4-[4-(pyrimidin-2-yl)phenyl]piperazin-1-yl}ethyl)-N-[3-(pyridin-4-yl)-2H-indazol-5-yl]pyrrolidine-3-carboxamide). The figure was reproduced by Chimera program.

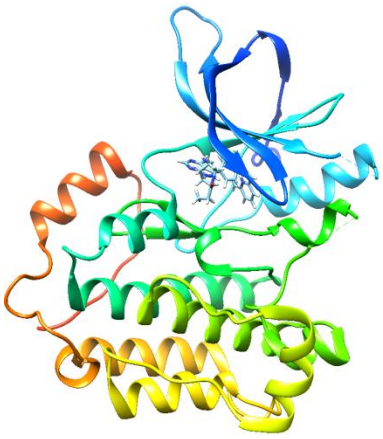

Figure 3. Comparison of 3D structures of a) MAPK-1 in complex with crystal ligand KE8 (6,6-dimethyl-2-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]-5-(2-morpholin-4-ylethyl)thieno[2,3-c]pyrrol-4-one) and MAPK-3 in complex with crystal ligand 38Z(3R)-1-(2-oxo-2-{4-[4-(pyrimidin-2-yl)phenyl]piperazin-1-yl}ethyl)-N-[3-(pyridin-4-yl)-2H-indazol-5-yl]pyrrolidine-3-carboxamide). The figure was reproduced by Chimera program.

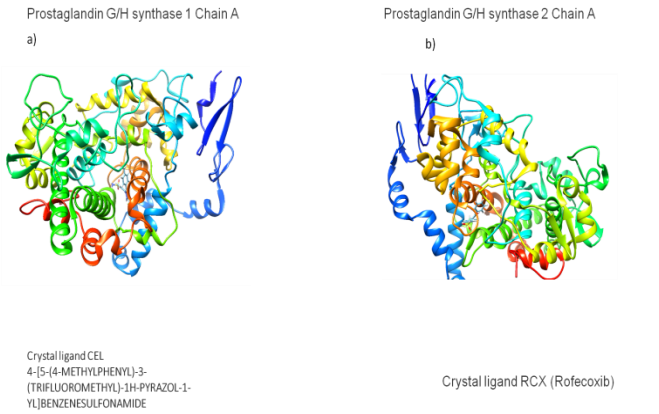

Figure 4. 3D structures of COX-1 in complex with crystal ligand CEL (4-[5-(4-METHYLPHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOL-1-YL]BENZENESULFONAMIDE) and COX-2 with crystal ligand RCX (Rofecoxib). The figure was reproduced by Chimera program.

2. Related Work

The approach applies in this communication was to investigate the computational analysis of Molecular Docking on as an tool investigation tool for medicine research.

3. Experimental Method/

All proteins were downloaded from the Protein Data bank (https://www.rcsb.org) and they are accurately prepared, and finally, they are saved in PDB format.

The first step, was the removal of ligands and crystallized water molecules and of Chain B from proteins, using Chimera software. [14] (https://www.cgl.ucsf.edu/chimera/). Later, Polar Hydrogens and Kollmann charges were added with MGL-Tool, or called AutoDockTools, (https://ccsb.scripps.edu/mgltools/downloads/) and converted to PDBQT format[12,13].

Regarding best compound preparation, (Curcumin and polydatin were manually downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in 3D Conformer SDF and they are minimized by Avogandro program with FFFF94 force field with Optimization Algorithm Decrescent and all Hydrogens and Gasteiger charges were added by Autodock Tools and finally, they are converted in pdbqt format, before to run Autodock 4 docking analysis [12,13].

4. Results and Discussion

This theoretical communication aims to identify for the first time the possible role of Polydatin and Curcumin respectively using several proteins and enzymes as targets, by bioinformatic approach, using Autodok 4 Algorithm [12,13] . Several proteins are evaluated for Docking analysis, for instance, the Crystal Structure of human Dual specificity tyrosine phosphorylation regulated kinase 2 (or named DYRK2); 3D Crystal Structure of Mitogen-activated protein kinase 1 (MAPK1), and the Mitogen-activated protein kinase 3 (MAPK3) respectively; 3D Crystal Structure of Epidermal growth factor receptor (EGFR) and human Crystal Structures of cyclooxygenase-1/2 or named COX-1 and COX-2). The aim of carrying out the Molecular Docking method by Autodock -4 with these targets evaluating the chemical-physical role of Polydatin and Curcumin. As is well known from the Scientific Literature, both natural substances have anti-inflammatory effects and they can be useful against various pathological processes [10,11].

In Table 1, we report the main docking results, comparing the binding energies scores (Kcal/mol in units) of Polydatin and Curcumin on Active Sites of DYRK-2 and EGFR respectively.

In Table 2, we summarized docking calculations Polydatin seems to have a better binding energy with MAPK-1 (-9.11 kcal/mol) than it binds with MAPK-3 (-8.22 kcal/mol).

Unfortunately, when Polydatin binds to the other targets investigated (DYRK-2, COX-1, COX-2, and EGFR) it did not show a high ability to bind to them. Instead, as regards the case of Curcumin, several targets have been shown to have an excellent binding affinity capacity.

Indeed to summarize our docking calculations Curcumin seems to have a better binding energy with MAPK-3 (-8.61 kcal/mol) than it binds in MAPK-1 (-8.01 kcal/mol). For more details see below Table 2.

In addition, Curcumin seems to have better binding energy with COX-1 (-9.59 kcal/mol) than it binds with COX-2(-8.93 kcal/mol). (See below Table 2).

Moreover, Curcumin reports a high Binding Energy value of -10.15 kcal/mol in DYRK-2 and a high Binding Energy value of -9.81 kcal/mol in EGFR (See below Table 1, Table 2, Table 3).

Considering all the kinases studied in this work, Curcumin appears to have a greater ability to bind to them than Polydatin and, furthermore, Curcumin has theoretically been shown to be the selective target of both COX-1 and DYRK-2 (See below Table 1, Table 2, Table 3).

Fig.5 shows a 2D plot of ligand-protein interactions (Crystal Curcumin and Docked Curcumin respectively with DYRK-2), using LigPlot + /LigPlus tool. As can be seen from the figure, both the Cur ligand crystal and itself, after the Docking analysis, are almost superimposable, with an RMSD value of 2.77 A°, demonstrating that the Molecular Docking analysis took place optimally. This can also be seen from the type of bond involved before and after docking with Curcumin.

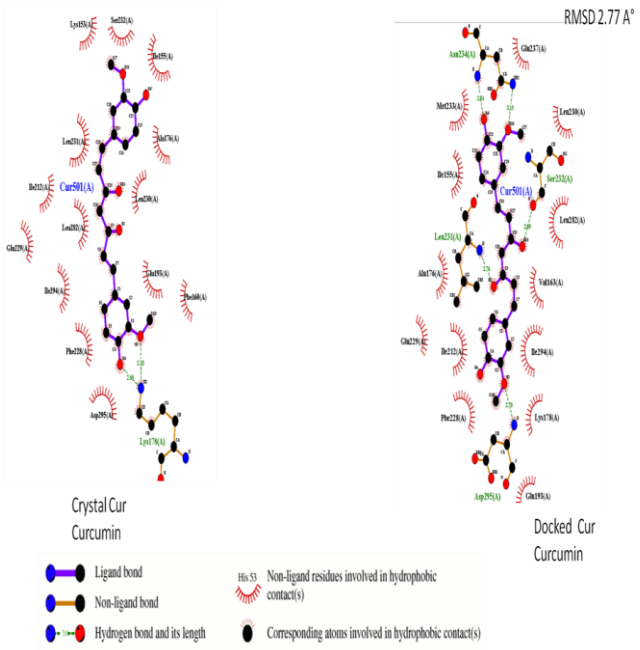

Figure 5. 2D plot interaction bonds of DYRK-2 in complex with Crystal Curcumin and docked Curcumin. The figure was reproduced by the LIGPLOT program.

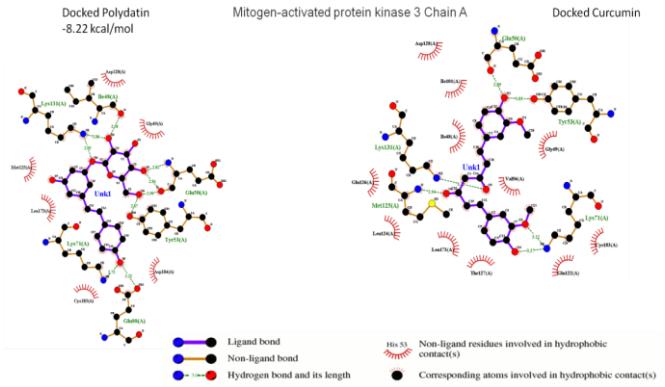

Figure 6. 2D plot interaction bonds of MAPK-3 in complex with docked Polydatin and docked Curcumin .The figure was reproduced by the LIGPLOT program.

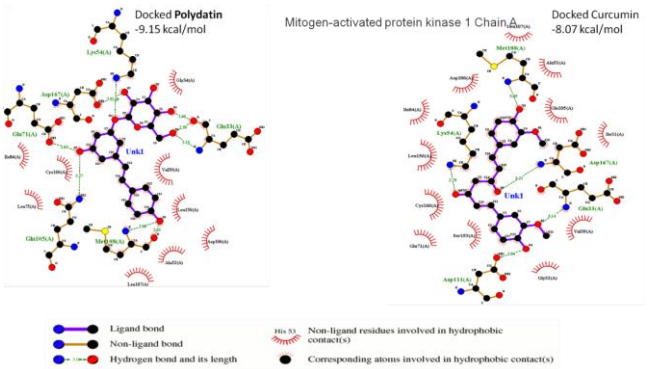

Figure 7. 2D plot interaction bonds of MAPK-1 in complex with docked Polydatin and docked Curcumin). The figure was reproduced by the LIGPLOT program.

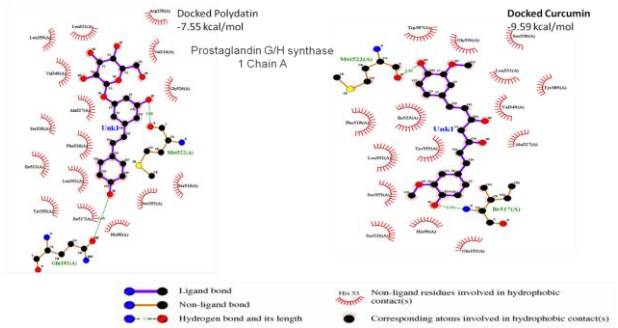

Figure 8. 2D plot interaction bonds of COX-1 in complex with docked Polydatin and docked Curcumin. The figure was reproduced by the LIGPLOT program.

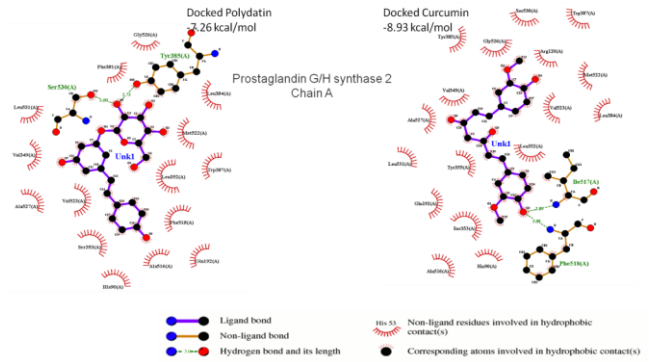

Figure 9. 2D plot interaction bonds of COX-2 in complex with docked Polydatin and docked Curcumin . The figure was reproduced by the LIGPLOT program.

Table 1. Comparison Binding energies scores (kcal mol-1) of docked Polydatin and docked Curcumin with DYRK-2 and EGFR respectively, calculated by Autodock -4 with MGL Tool.

Target	PDB 5ZTN (DYRK2)	PDB 5GTY (EGFR)
Polydatin	/	Binding Energy of -8.98 kcal/mol and Estimated Ki of (266.55 nM)
Curcumin	Binding Energy of -10.15 kcal/mol and Estimated Ki of (36.09 nM)	Binding Energy of -9.81 kcal/mol and Estimated Ki of (64.5 mM)

Table 2. Comparison Binding energies scores (kcal mol-1) of docked Polydatin and docked Curcumin with MAPK-1 with MAPK-3 respectively, calculated by Autodock -4 with MGL Tool. The binding energy of Crystal ligand 38Z *in complex with MAPK-3 is -16.87 kcal/mol.

Target	PDB 4QTB (MAPK-3)	PDB 6RQ4 (MAPK-1)
Polydatin	Binding Energy of -8.22 kcal/mol and Estimated Ki of (944.22 nM)	**Binding Energy of - 9.11 kcal/mol and Estimated Ki of (197.47nM)**
Curcumin	Binding Energy of -8.61 kcal/mol and Estimated Ki of (497.41 nM)	Binding Energy of -8.01 kcal/mol and Estimated Ki of (1.21 uM)

* (3R)-1-(2-oxo-2-{4-[4-(pyrimidin-2-yl)phenyl]piperazin-1-yl}ethyl)-N-[3-(pyridin-4-yl)-2H-indazol-5-yl]pyrrolidine-3-carboxamide)
The binding energy of Ligand KE8 * *in complex with MAPK-1 is -9.46 kcal/mol.
** 6,6-dimethyl-2-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]-5-(2-morpholin-4-ylethyl)thieno[2,3-c]pyrrol-4-one

Table 3. Comparison Binding energies scores (kcal mol-1) of docked Polydatin and docked Curcumin with COX-1 and COX-2 respectively , calculated by Autodock -4 with MGL Tool. The binding energy of Crystal ligand cel *in complex with MAPK-3 is -16.87 kcal/mol.

Target	PDB 3KK6 (COX1)	PDB 5KIR (COX2)
Polydatin	Binding Energy of -7.55 kcal/mol and Estimated Ki of (2.93 uM)	Binding Energy of -7.26 kcal/mol and Estimated Ki of (4.74 uM)
Curcumin	Binding Energy of -9.59 kcal/mol and Estimated Ki of (93.68 nM)	Binding Energy of -8.93 kcal/mol and Estimated Ki of (284.8 mM)

* 4-[5-(4-METHYLPHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOL-1-YL]BENZENESULFONAMIDE
The binding energy of Ligand RCX * *in complex with MAPK-1 is -9.82 kcal/mol.
* * Rofecoxib

6. Conclusion and Future Scope

For the first time, we performed by Molecular Docking approach for six target proteins (DYRK-2, EGFR, COX-1-COV-2, MAPK-1 and MAK-3) the binding affinity of Polydatin and Curcumin respectively to evaluate their possible biological action. The computational methods are performed by Autodock 4 with MGL Tool.

From all docking results, Curcumin has shown more binding affinity than Polydatin and also we noted that Curcumin has theoretically been able to bind mainly DYRK-2 and COX-1,

showing excellent binding energy values of -10.15 kcal/mol and -9.59 kcal/mol respectively. In addition, we characterized by the LIGPLOT program all targets with Polydatin and Curcumin, Several biological studies are needed to understand their biological role.

Data Availability
none

Conflict of Interest
Authors declare that they do not have any conflict of interest.

Funding source
none

Author's contribution
Ivan Vito Ferrari researched literature , involved in protocol development conceived the study. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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