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Research Paper

Focus on Polydatin Interaction with Sirtuins Family: a Comparative Computational Analysis

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Abstract— Sirtuins (SIRTs), a family of NAD^+-dependent deacetylases, are involved in the regulation of physiological functions such as aging and inflammation. They are able to catalyze metabolic reactions, thus regulating several cellular processes, such as energy metabolism, stress response, cell survival and apoptosis, DNA repair, tissue regeneration and neuronal signaling. The present article examines the interaction of three polyphenols, as Resveratrol, Polydatin and Curcumin, with Sirtuins family. The data obtained through a computational analysis, by Molecular Docking and Molecular Dynamics approaches, shows that these natural compounds are able to bind the active site of Sirtuins involved in numerous biochemical signaling. Moreover, the results highlight that Polydatin bind all the considered SIRT proteins showing an excellent docking capability in terms of Binding Energies scores and estimation of Inhibition Constant Ki. Moreover, by the study of Dynamic Simulation (RMSF, RMSD, protein-ligand interactions, timeline simulation in the range of 100 ns) and Repeatability Docking tests, Polydatin appear more stable than Curcumin when binds SIRT-3 rather than SIRT-5 protein.

Keywords— Polydatin, Curcumin, Docking analysis and Sirtuins proteins

1. Introduction

Sirtuins (SIRTs) are a family of signaling proteins involved in metabolic regulation in prokaryotes and eukaryotes. Chemically, SIRTs possess either mono-ADP-ribosyltransferase or (NAD+)-dependent protein lysine deacylase activity [1,2]. They are a group of proteins that regulate cellular health and homeostasis, support energy metabolism, enhance brain health, help cellular repair, and support healthy aging. [3–7] SIRTs are involved in chemical reverse of acetyl-lysine modifications of cellular proteins. The most biologically relevant of the reactions catalyzed by sirtuin enzymes is the deacetylation of proteins [8–10] Deacetylation catalyzed by sirtuins is involved in regulating diverse biological processes, including energy homeostasis.[10,11] Mammals possess seven Sirtuin (SIRTs 1-7) which differ in their localization in subcellular compartments. SIRTs are present in the nucleus, SIRT-1 [12–14], SIRT-6 [15,16], and SIRT-7 [17]; in mitochondria, SIRT-3 [18] SIRT-4 [19]and SIRT-5 [20]or in the cytoplasm, SIRT-2 [21]. They are catalysts for several metabolic reactions regulating numerous physiological functions, such as energy metabolism, stress response, cell survival, DNA repair, tissue regeneration, inflammation, neuronal signaling and resistance to oxidative stress [6,7,11]. Moreover, these proteins are involved in cancer carcinogenesis [22,23] and neurodegenerative diseases[24–27]. The search of new drugs for the treatment of various pathologies includes the study of natural products, which may provide innovative therapeutic opportunities both used as single agents or in combination with other drugs. [28,29]. In this work we focused on three natural compounds: Resveratrol, Polydatin and Curcumin respectively with Sirtuins.

Resveratrol (RES; 3,4,5-trihydroxy-trans-stilbene), (Figure **1**A) a phytoalexin produced as a stress-signaling molecule by plants is one of the most studied polyphenols. Many studies have provided evidence of antioxidant, anti-free radical, anti-inflammatory, anticancer, neuroprotective and anti-aging properties of RES. Both in vitro and in vivo studies showed

positive health outcomes with the use of RES. [30–34]. Polydatin (PD or Piceid, 3,4′,5-trihydroxystilbene-3-β-D-glucoside) is the glycosylated form of RES in which the glucoside group substitutes a hydroxyl group (Fig. 1B). PD and RES are the main bioactive ingredients of Polygonum cuspidatum. These polyphenols belong to the class of organic compounds known as stilbene glycosides. [35] The glycosidic moiety present in Polydatin confers greater conformational freedom than the precursor Resveratrol. PD is more resistant to enzymatic oxidation than RES, soluble in water and, unlike RES, which penetrates the cell passively, it penetrates the cell via an active carrier mechanism using glucose carriers. This property gives the PD molecule greater bioavailability, furthermore, PD has a stronger antioxidant activity and higher stability than RES ([36–38]. Likewise, RES, PD possess antioxidant, anti-free radical, anti-inflammatory, anticancer, neuroprotective and anti-aging activity [31,36]. Respect to RES, PD has a stronger anti-inflammatory effect on reducing the production of pro-inflammatory cytokine interleukin-17 in human peripheral blood mononuclear cells [39]. In addition, Wang et al. 2015, recently found that PD and RES maintain balance through mutual transformation after oral administration; ultimately, PD is the main substance in serum (70%) [40].

Curcumin (CUR 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), a polyphenolic derivative is the main constituent of Curcuma longa rhizome that contain Curcumin (77%) (Figure.1C) followed by desmethoxycurcumin (17%) and bisdemethoxycurcumin (3%). It can positively influence numerous physio-pathological processes, preventing cardiovascular, malignant and neurological damage [41–43]. Indeed, CUR possesses various medicinal properties, including antibacterial, anti-inflammatory, antiviral, antioxidant, antifungal, anti-ischemic, anti-cancer, and antimutagenic .[44–46] Polyphenols have been described to possess many positive effects favorable for human health [47–49], while relatively less research has been reported on their functions as SIRT modulation mechanism. Polyphenols interact with the gut microbiota [50] ,where they undergo extensive metabolism to produce small molecules active on transcription factors (Nrf2, PGC1-α, FoXO3, AMPK, SIRT-1) involved in several cellular functions, including mitochondrial biogenesis, antioxidant systems, glucose and lipid homeostasis, DNA repair, and immune homeostasis [47,49] . We reported the work by Zhao et al. 2017, where they studied the role of Polyphenols as activators of Sirtuin-1 protein in obesity and associated inflammation in rats via the AMPKα1/SIRT1 signaling pathway [51]. It is well known that RES, PD and CUR exert their pharmacological effects by regulating multiple targets and metabolic pathways [40,46]. The literature review from 2006 to 2021 pointed out that flavonoids frequently interact with SIRT-1 [52,53] and SIRT-3[54] , followed by SIRT-6 [55].RES is the most widely studied natural product that can activate AMPK by multiple mechanisms, such as the activation of SIRT-1. Preliminary studies show that RES by activating (SIRT-1), can protect against the detrimental effects of oxidative stress and promotes neuronal development [56] .Likewise, RES, PD is usually considered a potential SIRT-1 activator and the pharmacological mechanisms of PD could involve members of the SIRT protein family, among which SIRT-1 plays a prevalent role [57,58] .CUR can modulate the activity of Sirtuins and facilitate adaptation to certain cellular settings, including stress factors. CUR has been shown to increase SIRT-1, this up regulation confers it protective effects against a range of neurological disorders. Moreover, the activation of AMPK and SIRT-1 by CUR has also been noted to mediate the protective effects of CUR against ischemia/reperfusion injury, cardiac fibrosis, diabetes, and lipid metabolism abnormalities [59].

2. Related Work

This work aims to provide, by Molecular Docking Simulation, (Lamarckian Genetic Algorithm with Autodock Tool) [60,61] predictive information on the potential interaction between Resveratrol, Polydatin and Curcumin respectively in Sirtuins proteins.

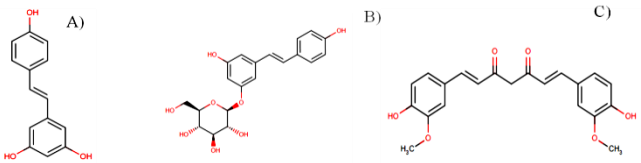

Figure. 1 The Structural formula a) Resveratrol (on the left side) b) Polydatin (on the center) and c) Curcumin (on the right side)respectively are shown

3. Calculation

Autodock Vina and Autodock 4 Algorithms are used in this work to discover best binding energies score of Resveratrol, Polydatin and Curcumin respectively in Sirtuins proteins.

4. Experimental Method

Target Receptor preparation

The 3D structures of our target protein human SIRT-1, SIRT-2, SIRT-3, SIRT-4, SIRT-5, SIRT-6 and SIRT-7, respectively (PDB 4KXQ, PDB 5D7P, PDB 4BN4, PDB 5OJN, PDB 2NYR, PDB 3K35 and PDB 5IQZ respectively) were downloaded from Protein Data Bank (RCSB PDB) and they are accurately prepared, and finally they are saved in PDB format before to run Docking Simulation by Autodock Vina (Trott et al.2010) with Pyrx program (Dallakyan et al.2015) and by Autodock 4 with MGL Tool. In Silico Molecular docking with the help of Autodock vina (The Scripps Research Institute, La Jolla, CA, USA) and Autodock4 was used to find the suitable binding modes and conformations of the ligand with the target proteins. This is necessary for the calculation of the ligands preferred orientations with the highest binding affinities for protein in active sites, which are related with pockets and structural cavities. In our work we performed both bioinformatic methodology, with particularly attention with Autodock 4.The PD and CUR binding to specific amino acid residues have been displayed in the LIGPLOT Program after molecular docking by Autodock Vina and Autodock 4. AutoDock-4 algorithm was used to

dock the isolated compounds into the active site of SIRT proteins. The first step preparation before perform docking analysis was the removal of crystal ligands and crystal water molecules from crystal SIRTs proteins, using Chimera software (https://www.cgl.ucsf.edu/chimera/) in order to make the protein as "clean" as possible, close to its 3D conformation in the human organism. Later, Polar Hydrogens and Kollmann charges were added into the SIRTs macromolecules with MGL-Tool, (https://ccsb.scripps.edu/mgltools/downloads/) and finally, all Sirtuins proteins were saved and converted to PDBQT format before to run Docking simulation. The main parameters chosen to Autodock 4 were: Grid Point Spacing (0.375 Å), Number of User-specified Grid Points (NPTS): X(40) Y (52) Z(40); Population size: 150, Number of energy evaluations: 2500000 and number of runs:1-10.

Ligand Preparation workflow for Docking
RES, PD and CUR were manually taken from the PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) in 3D Conformer SDF and they were minimized by Avogadro program with MMFF94 force field with Steepest Descent Optimization Algorithm. All Hydrogens and Gasteiger charges were added by Autodock Tools and finally the structures were converted in PDBQT format, before to run Autodock 4 docking analysis.

Predicted Pharmaceutical and Molecular properties of Polydatin by Pharmacology Database and Analysis Properties of TCMSP
Lipinski's rule of Five states that, in general, an orally active drug has:
-Not more than 5 hydrogen bonds donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
-Not more than 10 Hydrogen Bond Acceptors (nitrogen or oxygen atoms)
-A molecular weight under 500 g / mol
-A partition coefficient logP less than 5

Molecular Dynamic Simulation
The Desmond Molecular Dynamic (MD) simulation package [62] was used to perform the simulation study of the best ligand-protein complex of SIRT-3 and SIRT-5 with Docked PD and Docked CUR respectively, to assess their safety. Indeed, Polydatin has various pharmacological activities such as anti-inflammatory, antioxidant, protecting multiple tissues and organs from injury as reported by many articles in scientific literature. General workflows were used to solvate the complex using a system builder and to add counter ions to neutralize the system. Before the MD simulation, steepest descent steps were used to minimize the system. Furthermore, the system was gradually heated from 0 to 310 K before the production run, using the thermostat setting method and pressure relaxing method for 5 ns each, respectively. Overall, a simulation of 100 ns was performed, and 5000 frames were generated every 10 ps. In short, with default protocols, Desmond was used for the MD simulation (Chow, et al., 2008). The TIP3P water model in Desmond System Builder was used to solvate the protein (Srivastava et al., 2019). Periodic boundary conditions with 10 orthorhombic boxes were used, and the simulation system was neutralized with 0.15 M NaCl. The simulation was run for 100 ns at a temperature of 310 K and a pressure of 1.013 bar. Desmond, VMD (Visual Molecular Dynamics) and PyMOL were used to analyze the trajectory [62].

5. Results and Discussion

As is well known by the Scientific Community, a first important step before carrying out in Vitro and In Vivo studies could be the In-Silico study, through different software now available., For example, UCSF Chimera (Pettersen et al.,2004) and Pyrx [61](Dallakyan et al., 2015) are internally interfaced with Autodock Vina Algorithm[63] (Trott et al., 2010). Through these approaches it is possible to build large virtual libraries of compounds and to take into consideration only those that show excellent affinity to the target of interest. The Molecular Docking method based on Autodock Vina [63,64], a popular molecular docking program, allows us to estimate the Binding Energy (kcal/mol) between a compound that we want to investigate and the active site of a target receptor.

In general, predicting the Binding Free Energy between a ligand and a protein is an important component in the virtual screening and lead optimization of ligands for drug discovery.

The goal of our work was to collect information on a possible interaction between PD, RES and CUR in a complex with 7 different SIRTs., In particular, we focused on mitochondrial SIRT-3 and SIRT-5.Initially, we investigated with Molecular Docking analysis by Autodock Vina and Autodock 4, the best Binding Energies of PD and CUR with SIRT proteins and the diagram plot of the interactions (H-bonds and Hydrophobic bonds) with SIRTs residues. In this way with LIGPLOT program[65] it is possible to visualize all hydrophobic and Hydrogen bonds between the SIRTs proteins and docked PD, docked CUR and docked RES, in the Ligand Binding Site pocket. In turn, we evaluated the interaction of PD, RES and CUR in a complex with 7 different SIRTs by measuring theoretically their Binding Energies scores with a Molecular Docking analysis. As mentioned earlier, PD and CUR, which were screened against the human SIRT-1, SIRT-2, SIRT-3, SIRT-4, SIRT-5, SIRT-6 and SIRT-7 show excellent binding affinity to their targets (a docking score about -10 and -9.5 kcal/mol, respectively). From our analysis, these natural compounds show therefore excellent docking results, in terms of Binding Energies scores (kcal/mol) and estimation of Inhibition Constant Ki (nMolar units), with all SIRT proteins (SIRT1- SIRT 7). In general there is a correlation between Binding Energy Value (G) and Ki. Ki values were obtained automatically by Autodock Tool using the following formula:

$$G^{\circ} = -RT\ln Ki \quad (1)$$

The results, illustrated in Table **1**, indicate that PD has an ability to bind very well to all 7 SIRTs examined with approximate Binding Energies values in the order of about -

10 kcal mol-1. In particular, for PD Autodock 4 Algorithm reported a Binding Energy value of ca -10.47 kcal mol-1 in Human Sirtuin- 1; ca -10.49 kcal mol-1 in Human Sirtuin -2; ca -10.43 kcal mol-1 in Human Sirtuin- 3, ca -11.49 kcal mol-1 in Xenopus tropicalis Sirtuin- 4, ca -10.05 kcal mol-1 in Human Sirtuin 5, ca -10.72 kcal mol-1 in Human Sirtuin- 6, ca -9.17 kcal mol-1 in Human Sirtuin -7. CUR reaches similar values only with SIRT-4, SIRT-5, and SIRT-6. In particular, Curcumin has obtained excellent Binding Energy values about ca -9.97 kcal mol^{-1} in Xenopus tropicalis Sirtuin- 4, ca -10.16 kcal mol-1 in Human Sirtuin 5 and ca -10.40 kcal mol-1 in Human Sirtuin- 6.

Conversely, RES shows worse Binding Energies values with respect to those obtained with both PD and CUR.

Based on results illustrated in Table **1**, in Table **2** in Table **3** , it is possible to hypothesize that PD, although it is a precursor of RES and is similar from the point of view of the chemical structure, except for the introduction of glucose, is more effective in binding the active site of the SIRT family. In order to confirm and improve the pharmacological and molecular properties of PD we evaluated this compound using the Pharmacology Database and Analysis Platform (tcmsp-e.com), as illustrated in Table **4** The database used suggested some important drug screening criteria, such as OB (Oral bioavailability) > 20% and DL (Drug likeness) > 0.1%; BBB (non-penetrating blood-brain barrier) <-0.3 , HL (Drug half-life, t1/2) ≤4 hours (fast-elimination group) and TPSA (Polar surface area) less than 60Å2. Taken together these data confirm that PD has an effective pharmacological and biological activity. Many scientific studies have shown indeed that PD plays a role in activating SIRTs [66].

Table 1. Predicted Binding Energies Scores (kcal mol-1), Estimated Inhibition Constant Ki and Estimated Ligand Efficiency (kcal/mol) of Polydatin, in complex with SIRT-1, SIRT-2, SIRT-3, SIRT-4, SIRT-5, SIRT-6 and SIRT-7 proteins, evaluated by Autodock4 Algorithm with Autodock Tool. Among the considered ligands, Polydatin was found to show the highest Binding Energy values.

Binding Energies (kcal mol^{-1})	Estimated Ki (nM)	Ligand Efficiency (kcal mol^{-1})
SIRT1: -10,47	SIRT1: 21,33	SIRT1: -0,37
SIRT2: -10,49	SIRT2: 20,37	SIRT2: -0,37
SIRT3: -10,43	SIRT3: 22,49	SIRT3: -0,37
SIRT4*: -11,49	SIRT4: 2,28	SIRT4: -0,42
SIRT5: -10,05	SIRT5: 43,13	SIRT5: -0,36
SIRT6: -10,72	SIRT6: 13,87	SIRT6: -0,38
SIRT7: -9,17	SIRT7: 191,01	SIRT7: -0,33

* Xenopus tropicalis

Table 2. Predicted Binding Energies Scores (kcal mol-1), Estimated Inhibition Constant Ki and Estimated Ligand Efficiency (kcal/mol) of Resveratrol, in complex with SIRT-1, SIRT-2, SIRT-3, SIRT-4, SIRT-5, SIRT-6 and SIRT-7 proteins, evaluated by Autodock4 Algorithm with Autodock Tool.

Binding Energies (kcal mol^{-1})	Estimated Ki (nM)	Ligand Efficiency (kcal mol^{-1})
SIRT1: -7,94	SIRT1: 1520	SIRT1: 0,47
SIRT2: -7,72	SIRT2: 2190	SIRT2: -0,45
SIRT3: -8,36	SIRT3: 745,04	SIRT3: -0,49
SIRT4*: -8,79	SIRT4: 359,54	SIRT4: -0,52
SIRT5-7,75	SIRT5: 2080	SIRT5: -0,46
SIRT6: -8,47	SIRT6: 619,4	SIRT6: -0,5
SIRT7: -7,16	SIRT7: 5690	SIRT7: -0,42

* Xenopus tropicalis

Table 3. Predicted Binding Energies Scores (kcal mol-1), Estimated Inhibition Constant Ki and Estimated Ligand Efficiency (kcal/mol) of Curcumin, in complex with SIRT-1, SIRT-2, SIRT-3, SIRT-4, SIRT-5, SIRT-6 and SIRT-7 proteins, evaluated by Autodock4 Algorithm with Autodock Tool.

Binding Energies (kcal mol^{-1})	Estimated Ki (nM)	Ligand Efficiency (kcal mol^{-1})
SIRT1: -9,28	SIRT1: 157,82	SIRT1-0,34
SIRT2: -9,0	SIRT2: 254,1	SIRT2: -0,33
SIRT3: -9,44	SIRT3: 119,48	SIRT3: -0,35
SIRT4*: -9,97	SIRT4: 49,2	SIRT4: -0,37
SIRT5: -10,16	SIRT5: 35,91	SIRT5: -0,38
SIRT6: -10,43	SIRT6: 23,88	SIRT6: -0,39
SIRT7: -8,51	SIRT7: 582,12	SIRT7: -0,32

* Xenopus tropicalis

Docking Repeatability tests for Results Validation

After having carried out an accurate docking analysis of PD, RES and CUR with all the SIRTs proteins, we decided to focus only on the mitochondrial ones, to understand the actual role of these natural substances. We have chosen to investigate SIRT-3 and SIRT-5, two important proteins responsible for different biological processes. They are members of the Sirtuins family of protein deacetylases preferentially localized in mitochondria. Although it is very difficult to understand the biological role of PD and CUR in these two mitochondrial proteins, we have chosen to follow two theoretical tests to validate the results obtained previously: Docking repeatability measures through Autodock 4 with the Lamarckian Genetic Algorithm (LGA) and Molecular Dynamics simulations which will be explained in detail below. In figure 2, we report the comparison of the 3D structures of the SIRT-3 protein and SIRT-5 protein, complexed with its crystal ligand (ADP-Ribose and Suramin respectively) or with the PD and CUR docked in the active site. Table 2 shows the docking repeatability calculations of the two Sirtuins, demonstrating that the value of the Binding Energies of both PD and CUR are very good, if compared to the re-docked crystal ligands

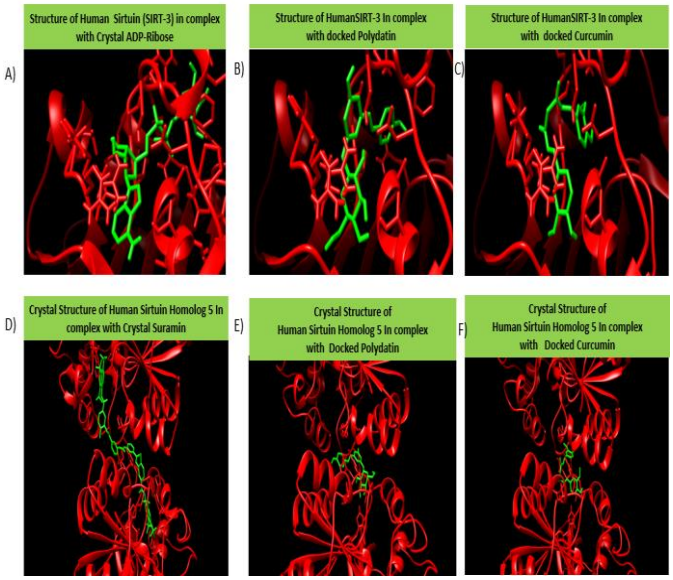

Figure. 2 Comparison of 3D structures of SIRT-3 (upper panels) and SIRT-5 (lower panels) in complex with a,d) Crystal Ligand, b,e) Docked Polydatin and c,f) docked Curcumin respectively. The figure was reproduced by Chimera program.

Table 4. Comparison results of Binding energies scores, estimation of Inhibition constant Ki and Ligand efficiency of crystal ligand AR6 (ADP Ribose), Polydatin and Curcumin respectively in complex with SIRT-3 . Docking analysis was performed by Autodock 4.

Binding Energies (kcal mol^{-1})	Estimated Ki (nM)	Ligand Efficiency (kcal mol^{-1})
AR6*: -11,27	SIRT1: 5,47	SIRT1-0,31
Polydatin: -10,43	SIRT2: 22,49	SIRT2: -0,37
Curcumin: -9,44	SIRT3: 119,48	SIRT3: -0,35

- Crystal ligand called ADP Ribose

Table 5. Comparison results of Binding energies scores, estimation of Inhibition constant Ki and Ligand efficiency of crystal ligand AR6 (ADP Ribose), Polydatin and Curcumin respectively in complex with SIRT-5 . Docking analysis was performed by Autodock 4.

Binding Energies (kcal mol^{-1})	Estimated Ki (nM)	Ligand Efficiency (kcal mol^{-1})
Sur*: +18,72	SIRT1: /	SIRT1/
Polydatin: -10,05	SIRT2: 43,13	SIRT2: -0,36
Curcumin: -10,16	SIRT3: 35,91	SIRT3: -0,38

* Crystal ligand named Suramin

Molecular Dynamics (MD) Stability Analysis Studies

RMSD and RMSF analysis and Type interactions

We have also investigated through the Molecular Dynamics simulation, a possible interaction capability with these Mitochondria proteins, as such SIRT-3 and SIRT-5 proteins.

The stability of ligand-protein interactions was investigated considering an MD trajectory of 100 ns (Figure. 3), and the interactions were analyzed using RMSD (Root-mean-square deviation) and RMSF (Root mean square fluctuation) data. In general, RMSD measures the alterations in the displacement of atoms for a particular frame with respect to a reference frame for all snapshots. The protein RMSD is good when it is less than 3Å. For the human SIRT-3- SIRT-5–Polydatin and Curcumin complex respectively, the protein RMSD was stable for most of the duration, and at around 20 ns a fluctuation of 1.8 Å was observed, but the ligand was found to fluctuate throughout the duration of the simulation.

For SIRT5, Curcumin and Polydatin reach 14 and 9 angstrom RMSD, respectively In our simulation of proteins-Polydatin and Curcumin complexes, the protein and ligand RMSD values were throughout the 100 ns trajectory, showing a good interaction. In a particular way from RMSD results, Polydatin is more stable than Curcumin, in both SIRTs proteins, mainly when it binds with SIRT-3. (See below figure. 3).The holo-form (un- liganded) SIRT-3 and SIRT-5 were simulated for 100 ns. Its RMSD graph is shown in Fig.3 (left side panel), where the protein C-alpha backbone did not fluctuate much and was stable throughout the simulation time. The RMSD fluctuation was at a range of 2 Å, which is fairly stable, and it remained stable form until the end. The RMSF values were also stable. In addition, molecular dynamics simulation studies of these complex (SIRT-3 and SIRT-5 with Curcumin (CUR) and Polydatin (PD), respectively, revealed that they were stable during the 100 ns virtual simulation time. Moreover, the trajectory analysis of these complexes for the interaction of these ligands (PD and CUR respectively) with the allosteric site showed that these compounds had various type of contacts during the 100 ns simulation. The most prominent interaction was the water-bridged assisted hydrogen bond , followed by the direct hydrogen bond with surrounding amino acids. This situation is presented mainly between CUR and SIRT-3 protein. Figure. 5 shows protein-ligand interactions. In particular case PD engages more water-bridged assisted hydrogen bonds than direct hydrogen bond compared to CUR, when PD is hosted into SIRT-3 and SIRT-5 proteins. Generally speaking, the four major types of non-covalent interactions, i.e., ionic interactions, hydrophobic interactions, water bridges and hydrogen bonds were considered to analyze the protein-ligands contacts. For the SIRT-3-CUR adduct, THR 320, GLU 323, ASN 344, VAL 348, LEU351 are mainly involved via hydrogen bond interactions; ILE 317, LEU 322, LEU 342, PRO 350, TRP 353, PRO 355, ALA 361, LEU 363 establish weak hydrophobic interactions) and GLY 121,LYS 122, VAL 144, ARG 158, SER 321 participate in the formation of water-bridges hydrogen bonds. When PD is bound to Sirtuin-3, it interacts via hydrogen bond to GLY 121, ASN 344, ASP 346 and through hydrophobic interactions with ILE 317, LEU 342, PRO 355, LEU 363. Additionally, water molecules assist the interactions with SER 321, GLU 322, LEU 351, ARG 356, ASP 359 residues For the CUR-SIRT-5 case, VAL 221, TRP 222, THR 87, PHE 91 are mainly involved in hydrogen bonds interaction, five residues (ALA 86, PHE 70, LEU 161, PHE 223 VAL 254) establish hydrophobic interactions and ARG 71, GLY 72, TYR 255, ASP 236, ARG 267 interact with the ligand through a bridged water molecule. Regarding PD complexed in SIRT-5 the major amino acids involved in the interactions using H-bonds are ALA 73, ARG 106, GLN 140, HIS 158, VAL 221, ASN 226; ALA 86 ILE 142, VAL 220, PHE 223 are involved in hydrophobic interactions and finally the weak interactions with PRO 68, THR 69, GLY 72, ASN 141, TRP 222, GLY 224, GLU 225, GLU 233 aminoacids are mediated by a water molecule .

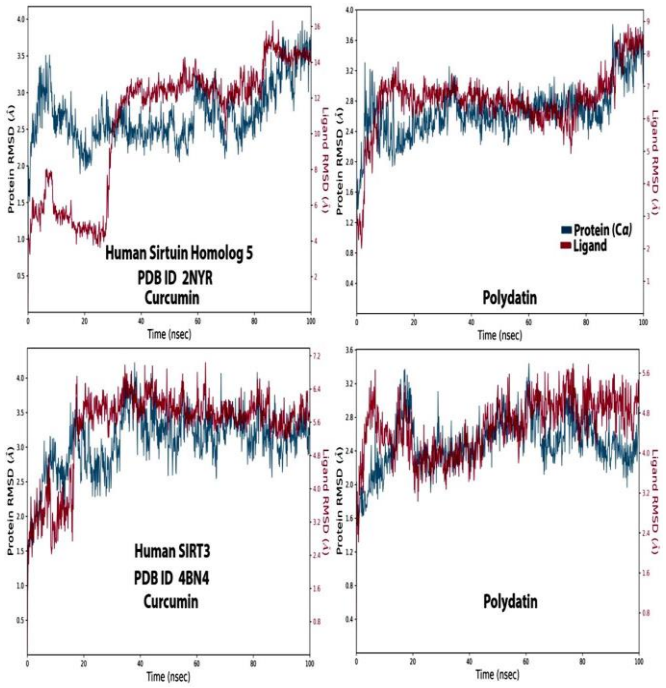

Figure. 3 Comparison of Protein Cα RMSD, Ligand RMSD (simply root-mean-square deviation) of Human Sirtuin Homolog 5 and Human SIRT-3 in complex with docked Polydatin and docked Curcumin respectively, in the selected 100 ns MD trajectory. Figure was reproduced by Desmond program.

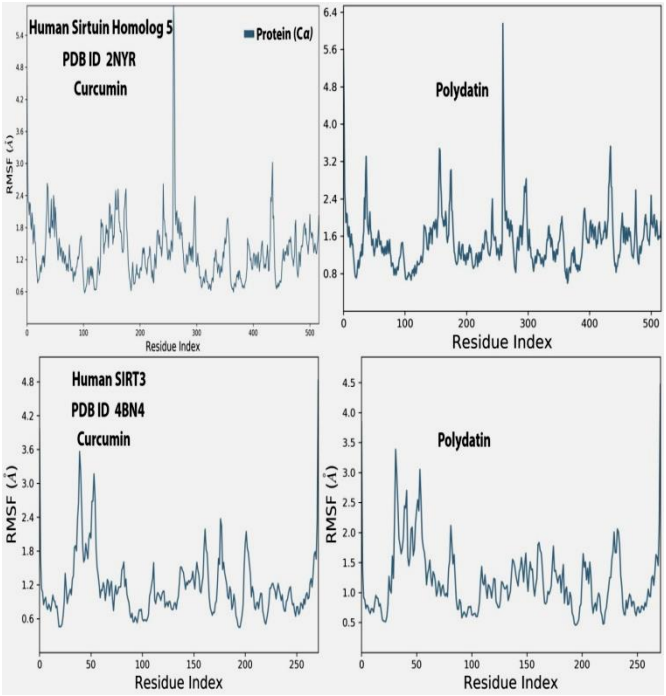

Figure. 4 Comparison of RMSF (root mean square fluctuation) a of Human Sirtuin Homolog 5 and Human SIRT-3 in complex with docked Polydatin and docked Curcumin respectively, in the selected 100 ns MD trajectory. Figure was reproduced by Desmond program.

Prediction of Pharmaceutical and Molecular properties of Polydatin by TCMSP Pharmacology Database and Analysis Platform

The traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) was used to calculate the ADME (absorption, distribution, metabolism, and excretion) properties of phytochemicals, as the predictions of physical-chemical significant descriptors and pharmacokinetically relevant properties can be important for the development of drugs. This platform evaluates such properties relying on one of the most important rules in pharmacology, Lipinski's rule, for defining a drug's molecular properties as significant in evaluating a drug's pharmaco-kinetics. ADME properties have a tremendous impact on the success of drug candidates and they can be affected by physical conditions in vivo, such as solubility, permeability, stability and metabolism.

Table 6. Predicted Pharmaceutical and Molecular properties of Polydatin by TCMSP Pharmacology Database and Analysis Platform (https://old.tcmsp-e.com/).

Molecular properties)	AlogP	HBD	HBA	OB(%)
390,42	11,1	6	8	21,44

*Note: molecular weight (MW), hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD); Oral bioavailability (OB)

6. Conclusion and Future Scope

This paper aims to understand the role of three natural molecules in the biological functions of the SIRTs family, widely studied in Literature. In our case, we considered Resveratrol, Polydatin, and Curcumin. We used Autodock Vina and Autodock4 Algorithms by Molecular Docking analysis. Resveratrol, Polydatin, and Curcumin are compared and evaluated concerning their binding energy score interaction with the SIRT family. The Binding Energy scores suggest that Polydatin is more active than Resveratrol with the SIRTs Family. Therefore, Polydatin could play a key role in SIRT's biochemical signaling pathways. Moreover, by the analysis of 100 ns–long MD trajectory in terms of RMSF, RMSD, protein-ligand interactions and Repeatability Docking tests, Polydatin seem to have a particular affinity with Sirtuins proteins than Curcumin . In addition, Polydatin has several interacting sites (both H-bonds and hydrophobic interactions) in all sirtuins. Currently, there are several biological tests on Polydatin involved in various biological processes, but how Piceid acts at the metabolic and biochemical level is still littles studied. Our computational study provides a first set of useful insights about the role of PD and Curcumin on Sirtuins protein family but further validation studies are needed.

Conflict of Interest

Authors declare that they do not have any conflict of interest

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None

Authors' Contributions

Protocol designed by IVF . Monitoring the execution of work IVF and MA. Methodology performed by IVF and MA. Manuscript was written and reviewed by IVF,MPF,ADE,MA,GR, FP and FC. All authors read and approved the final manuscript.

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