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Computational evaluation of certain flavonoids against poly (ADP-Ribose) Polymerase-1 using *in silico* docking studies

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Abstract

Poly (ADP-Ribose) Polymerase-1 (PARP-1) inhibitors may represent a class of chemotherapeutic mediators at cancers with defective DNA-damage repair. The objective of the present study is to examine the inhibitory affinity potential of the certain commercially available flavonoids such as acacatechin, catechin, daidzein, galangin, and kaempferol against PARP-1 enzyme using *in silico* docking studies. The *in silico* docking studies were performed using AutoDock 4.2. Olaparib, a known PARP-1 inhibitor was used as standard. In the docking studies, the conformational site analysis and the docking parameters were evaluated for the flavonoids against the PARP-1. The selected flavonoids showed excellent theoretical pharmacokinetic properties and no violations were described against Lipinski's Rule of 5. Further the flavonoids were subjected to molecular docking analyses. The docking energy and other parameters demonstrated that the flavonoids are highly conserved in nature. The top ranking molecule catechin has a minimum energy score of -6.55 kcal/mol. The amino acid residues responsible for the PARP-1 inhibition of the catechin were found to be Lys 15, Ser 108, and Gly 109. This compound is thus a good leading point for further development of strong inhibitors against PARP-1 enzyme, which might be attributed to the presence of benzopyran ring in its structure. Hence, further examination is required to develop novel chemical entities for the prevention and management of ovarian and breast cancer.

Keywords: Docking, Binding site, AutoDock 4.2, Intermolecular Energy, Inhibition constant.

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1. Introduction

Breast cancer is the most commonly occurring cancer in women worldwide, second most common gynaecological cancer is ovarian cancer in developed countries. Around 14,180 women die from ovarian cancer and 40,290 women die from breast cancer every year [1]. Poly (ADP-Ribose) Polymerase-1 (PARP-1) is an enormous protein comprised of 1014 amino acids and its molecular weight is 116 kDa. It has three domains: the auto modification domain (AMD), an amino-terminal DNA-binding domain (DBD), and the catalytic domain. At present, the third zinc-finger motif in the DBD assisted interdomain contact and assembly of the DNA-activated conformation of PARP-1, it was considered vital for DNA-dependent PARP-1 activity [2, 3].

The central AMD works as a regulatory segment and comprises of a breast cancer susceptibility protein C-terminus motif that is acquired in many other DNA repair and cell cycle targets [4]. The C-terminal region is the very important part of the PARP-1 enzyme. It comprises of an NAD^+-binding domain and performs the catalytic function of PARP-1, synthesizing PARs by consuming NAD^+ as a substrate. The highly preserved 50–amino acid PARP signature motif (NAD^+-binding site) has been recognised in all PARP family members [5, 6].

PARP-1 positively controls the transcription of MTUS1 and negatively controls the transcription of MTUS2/TIP150. With EEF1A1 and TXK, produces a complex that displays as a T-helper 1 (Th1) cell-specific transcription factor and attach to the promoter of IFN-

gamma to directly control its transcription, and is thus participated importantly in Th1 cytokine production [7]. Involved in the base excision repair (BER) pathway, by catalyzing the poly (ADP-ribosylation) of a partial number of acceptor proteins participated in chromatin architecture and in DNA metabolism. This alteration follows DNA damages and turns as an obligatory step in a signalling pathway directing to the reparation of DNA strand breaks [8, 9].

Flavonoids are subdivided into subclasses including flavones, flavanones, isoflavones, flavonols, flavan-3-ols, and anthocyanidins. Flavonoids have long been linked with a multiple pharmacological and biochemical properties, including antioxidant, anti-viral, and anti-inflammatory properties, and trusted to be valuable to human health. Epidemiological studies endorse that dietary intake of flavonoids may decrease the risk of tumors of the breast, lung, colon, pancreas, and prostate [10, 11]. A few intervention trials of flavonoids have documented for cancer preventative effects. Proposed anticancer mechanisms for flavonoids are inhibition of inflammation, proliferation, invasion, metastasis, and activation of apoptosis. Mechanistic studies are required to ascertain how flavonoid-rich diets influence gene adaptation for cancer prevention [12].

Hence, the objective of the current study is the computational drug discovery of the some commercially available flavonoids against poly (ADP-ribose)-polymerase-1 enzyme using *in silico* docking studies for the management of breast and ovarian cancer.

2. Materials and methods

2.1 Software required

Python 2.7 - language was downloaded from www.python.com, Cygwin was downloaded from www.cygwin.com, ChemSketch was downloaded from www.acdlabs.com, Molecular graphics laboratory (MGL) tools and AutoDock 4.2 was downloaded from www.scripps.edu, Discovery studio visualizer 2.5.5 was downloaded from www.accelrys.com. MedChem Designer was downloaded from https://simplus-downloads.com/. Online smiles translation was carried out using cactus.nci.nih.gov/translate/.

2.2 Docking Evaluation Methodology:

The Research Collaboratory For Structural Bioinformatics (RCSB) Protein Data Bank archive-information about the nucleic acids, three dimensional shapes of targets and its complex assemblies that assistance the researchers to recognize all aspects of biomedicine and agriculture, from target synthesis to the interpretation of health and disease. The crystal structure of poly (ADP-ribose) polymerase-1 enzyme (2COK) was procured from the RCSB protein data bank.

The refinement of the target protein was carried out using Accelrys studio viewer by removing heavy metal and adding hydrogen atoms to the target protein. The refined target was further used for the docking studies (Figure 1). An extended PDB format, termed as PDBQT file was utilized for coordinate the files which include atomic partial charges. ChemSketch is drawing software that permits to draw the chemical structures. In figure 2, the flavonoid ligands like acacatechin, catechin, daidzein, galangin, kaempferol and the standard were drawn using ChemSketch and optimized using “Prepare Ligands” in the AutoDock 4.2 for further docking studies. The optimized flavonoids were docked into refined target using the AutoDock 4.2 [13].

The working principle of the docking simulations was Lamarckian genetic algorithm (LGA). LGA is a hybrid of a genetic algorithm and a local search algorithm. The individual molecule with low resulting docking energy were shifted to the other generation and the method is then repeated [14]. 3D affinity grids of size 277 × 277 × 277 Å with 0.6 Å spacing were centred on the geometric centre of the enzyme and were computed for each of the following atom types: HD, C, A, N, OA, and SA, indicating all possible atom types in an enzyme [15].

In the AutoGrid procedure, the target was surrounded on a three dimensional grid point. The binding energy of each atom in the ligand molecule was encountered. The vital binding parameters for the LGA as follows: population size of 150 individuals, 2.5 million energy evaluations, maximum of 27000 generations, number of best individuals to spontaneously survive to next generation of 1, mutation rate of 0.02, crossover rate of 0.8, 10 docking runs, and random conformations were fixed. Rapid energy calculation was realised by pre calculating atomic affinity potentials for each atom in the flavonoids. The probability of performing local search on an individual molecule in the population was set to 0.06 [16].

AutoDock Tools offer multiple methods to examine the results of docking simulations such as, visualizing the binding site and its energy, conformational similarity, and additional parameters like inhibition constant and intermolecular energy. From the estimated free energy of flavonoid molecule binding energy (kcal/mol), the inhibition constant (*K*i) for each ligand was calculated [17].

3. Results

The original *Rule of 5* is extensively believed to be an important development in novel drug discovery. The *Rule of 5* takes on numeric values from 0 to 4 based on the potential difficulties of a compound might have with its pharmacokinetic characteristics. As such, *Rule of 5* is a

advantageous computational filter in drug candidate evaluation. In terms of ADMET Predictor models and descriptors, the *Rule of 5* models administrates can be expressed as follow the following set of environments, excessive lipophilicity (MlogP) > 4.15, Molecular weight (MWt) > 500, hydrogen bond donors (HBDH) > 5, hydrogen bond acceptors (M_NO) > 10 [18, 19].

The pharmacokinetic properties of the flavonoids were examined with the help of MedChem Designer (Table 1). All the examined flavonoids were exhibited excellent pharmacokinetic properties which indicate that these flavonoids have no violations in *Rule of 5*. Based on the results, the selected flavonoids may further screen for it's *in silico* biological activity against the PARP-1 inhibition.

In the present study, vital molecular docking aspects of the flavonoids against the PARP 1 inhibition were examined. Molecular docking studies were performed through AutoDock 4.2 which produced the binding energies of the selected flavonoids ranging between -6.55 kcal/mol to -6.27 kcal/mol (table 2). All the flavonoids had exhibited inhibitory binding energy against the PARP-1 enzyme. The standard showed potential binding energy of - 9.00 kcal/mol against the PARP-1.

In the current study the flavonoids revealed the potential interaction against PARP-1 along with the binding site confirmations. Amino acid residues of the catechin responsible for the PARP-1 inhibition was found to be, Lys 15, Asn 45, Lys 46, Lys 107, Ser 108, Gly 109, and Pro 110. Similarly for the standard olaparib was found that, Asn 13, Met 14, Lys 15, Ala 47, Ser 48, Arg 73, Gly 103, Ser 108, Gly 109, and Ser 111 (Figure 3). The amino acid residues such as Lys15, Ser 108, and Gly 109 are dynamically involved in the inhibition of PARP-1 in both the catechin and olaparib. This further clarifies that the catechin possesses the similar binding orientation sites when compared with the standard.

As shown in table 3, the selected flavonoids showed inhibition constant ranging from 15.76 µM to 25.30 µM. Flavonoids had showed inhibition constant at micro molar concentrations against the target molecule. The standard olaparib showed potential inhibition constant 253.36 nM against the PARP-1. From the docking study observations, the inhibition constant of the compounds is directly proportional to the binding energy. These results further strengthen the inhibitory affinity potential of the catechin against PARP-1.

Table 1: Pharmacokinetic properties for the selected flavonoids

Name	MWt	MlogP	S+logP	S+logD	T_PSA	HBDH	M_NO	Rule of 5
Acacatechin	290.274	0.757	0.664	0.634	110.38	5	6	0
Catechin	290.274	0.757	0.775	0.746	110.38	5	6	0
Daidzein	256.26	1.726	2.404	2.353	66.76	2	4	0
Galangin	272.259	1.45	2.238	1.961	86.99	3	5	0
Kaemperol	286.243	0.525	2.243	1.848	111.13	4	6	0
Olaparib	434.473	3.032	2.263	2.263	86.37	1	7	0

MWt - Molecular Weight; MlogP – Moriguchi octanol-water partition coefficient; S+logP - "StarList" of ion-corrected experimental logP values; S+logD - octanol-water distribution coefficient; T_PSA-Topological Polar Surface Area; HBDH - the count of HB donor protons; M_NO = total number of nitrogen and oxygen atoms (Ns and Os)

Table 2: Binding energies of the compounds based on their rank

Compounds	Binding energies of the compounds (Kcal/Mol)									
Acacatechin	-6.27	-6.21	-6.16	-5.54	-5.12	-4.97	-4.89	-4.81	-4.52	-4.40
Catechin	-6.55	-6.53	-6.50	-6.51	-5.74	-6.50	-6.38	-5.92	-5.87	-5.77
Daidzein	-6.40	-6.29	-6.28	-6.39	-6.31	-6.33	-6.05	-5.97	-5.97	-5.95
Galangin	-6.55	-5.86	-6.15	-6.07	-6.06	-5.99	-5.78	-5.66	-5.65	-5.26
Kaempferol	-6.36	-6.29	-5.93	-6.20	-5.35	-6.04	-6.01	-5.97	-5.91	-5.83
Olaparib	-9.00	-8.56	-8.33	-8.33	-8.20	-7.99	-7.96	-7.79	-7.48	-7.34

Table 3: Inhibition constant of the compounds based on their rank

Compounds	Inhibition Constant of the compounds based on their rank (*nM, **mM)									
Acacatechin	25.30	28.26	30.46	86.32	175.91	225.72	261.92	297.74	488.93	595.79
Catechin	15.76	16.46	17.25	17.02	62.53	17.05	20.92	45.88	49.64	59.12
Daidzein	20.29	24.46	24.91	20.67	23.87	22.73	36.82	41.85	41.88	43.23
Galangin	15.91	50.77	30.94	35.46	36.15	40.89	58.18	71.06	72.32	138.45
Kaempferol	21.72	24.56	44.63	28.58	119.51	37.49	39.01	42.05	46.27	53.00
Olaparib	253.36*	531.68*	785.70*	788.90*	970.20*	1.39	1.46	1.96	3.32	4.15

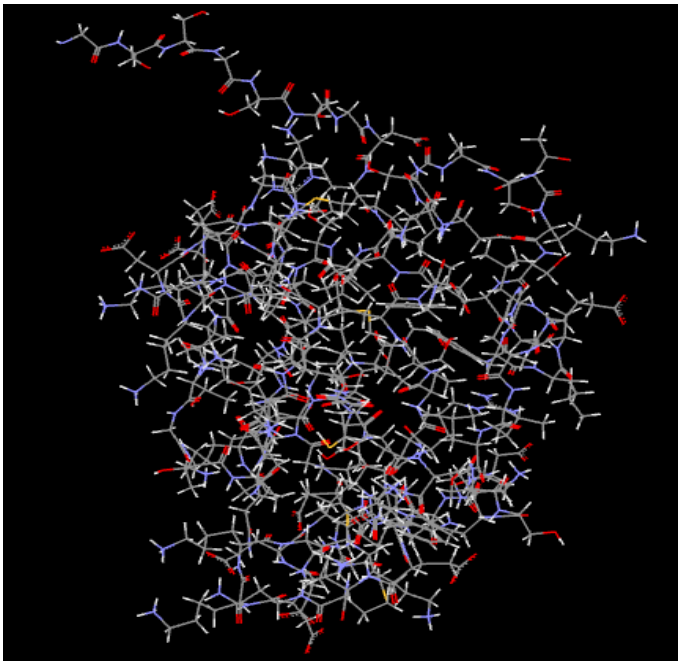

Figure 1: Refined structure of BRCT domain of poly (ADP-ribose) polymerase-1 (2COK)

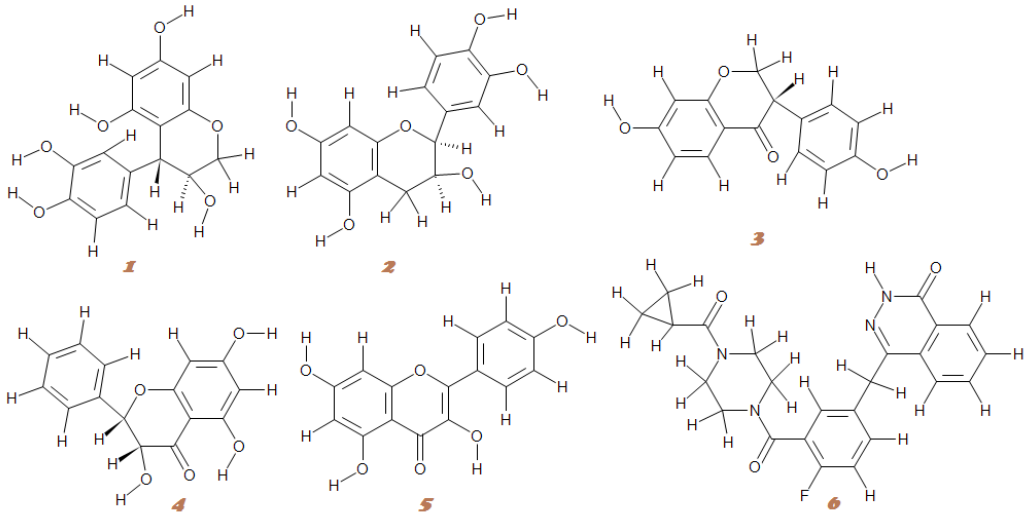

Figure 2: The optimized ligand molecules (1 acacatechin, 2 catechin, 3 daidzein, 4 galangin, 5 kaempferol, and 6 olaparib)

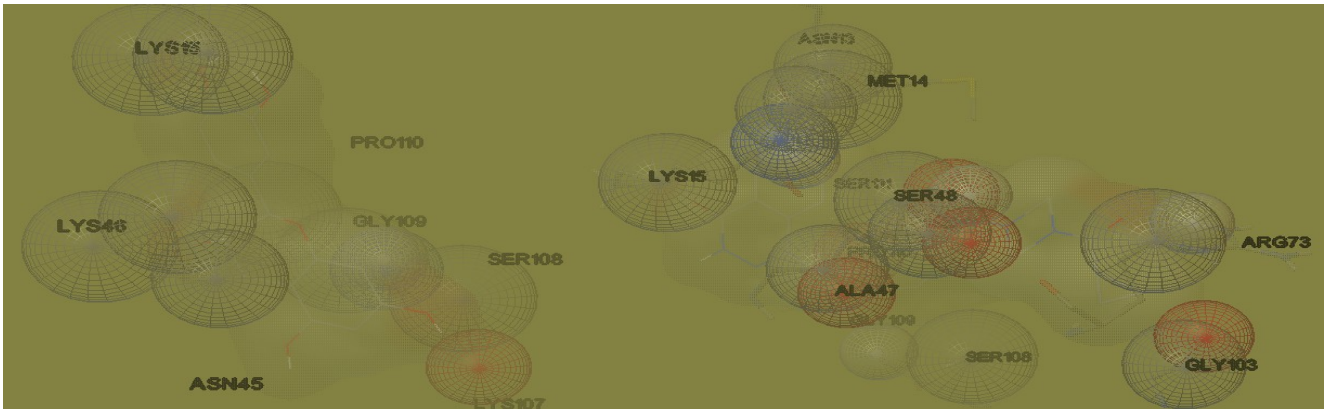

Figure 3: Conformational binding modes of catechin and olaparib with the human poly (ADP-ribose) polymerase-1

4. Discussion

Poly (ADP-ribose) polymerase-1 (PARP-1) is a subordinate of the PARP enzyme family consisting of PARP-1 and several newly recognized novel poly (ADP-ribosylating) enzymes. PARP-1 is an ample nuclear target functioning as a DNA nick-sensor target molecule. Upon binding to DNA breaks, triggered PARP separates NAD^+ into nicotinamide and ADP-ribose and polymerizes onto nuclear acceptor target including transcription factors, histones, and PARP itself. Similarly, oxidative stress-induced over activation of PARP employs NAD^+ and consequently ATP, culminating in dysfunction of cells. This mechanism has been linked in the diabetes, stroke, diabetes-associated cardiovascular dysfunction, myocardial ischemia, shock, arthritis, colitis, traumatic central nervous system injury, allergic encephalomyelitis, and several other forms of inflammation [20].

PARP is a constitutive constituent of the DNA damage surveillance network recognised by the eukaryotic cell to succeed with the numerous environmental and endogenous genotoxic mediators. This enzyme differentiates and generated by DNA strand breaks. The generation, by homologous recombination, of three distinct deficient mouse models has evidenced the function of PARP-1 in cells of mammalian under genotoxic prominence. Moreover, the enduring PARP effort found in defective cells of PARP-1 has been accredited to an innovative DNA damage-dependent PARP, substitute member of the expanding PARP family that achieves to be complex in the protection of genome [21].

The beneficial effect of PARP inhibitors in various animal models of several diseases endorses that PARP inhibitors can be demoralised to manage the human diseases. Potent PARP inhibitors can be expended in humans, fundamental safety matters must be addressed [22]. Because PARP has been alarmed in DNA repair and maintenance of genomic integrity, the major risk associated with long-term PARP inhibition might be distended mutation rate and production of cancer [23]. It is promising that PARP-deficient mice have not been labelled to have an improved occurrence of tumors. However, an increased number of tumors induced chemically have been supervised in PARP-deficient mice as associated with wild-type ones [24].

The computational drug discovery of potential flavonoids was examined in the present study for PARP-1 inhibitory activity of the flavonoids. Based on the current docking studies and conformational analysis, the PARP-1 inhibitory activity of the flavonoids was obtained to be decreased in the order of catechin, galangin, daidzein, kaempferol and acacatechin respectively.

Recent research into PARP inhibition has shown usefulness and the importance to act on DNA repair mechanisms. Based on the computational docking studies of the selected compounds, it has been further proven that the flavonoids possess the potential pharmacophore against PARP-1 inhibition and thereby it can be functioned in the management of cancer. Among the selected flavonoids catechin was found to be the successful drug pharmacophore in docking and conformational analysis against PARP-1 inhibition. This study will highlight the researchers in the design of a potential pharmacophore for the management of cancer. Therefore, *in vitro* and *in vivo* studies of the catechin molecule need to be perform to confirm the anti-cancer activity and thereby it can be act as a potential lead candidate.

Conflict of interest

The author declares that there are no conflicts of interest.

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