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RESEARCH PAPER

IDENTIFICATION OF PARP-1 INHIBITORS AGAINST BREAST CANCER USING *IN SILICO* REPURPOSING OF FDA APPROVED DRUGS: DOCKING BASED APPROACH, MM/GBSA AND ADME ANALYSIS

Aayushi Bhatnagar, Virendra Nath and Vipin Kumar*

Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer-305817, Rajasthan, India

**E-mail*: vipbhardwaj@rediffmail.com
Tel.: +91 8107742606.

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Drug discovery approaches have been time consuming and require huge monetary investments. The repurposing of already existing drugs is a promising approach for the faster and cost-effective drug discovery against various diseases. Cancer, being a heterogenous disease, requires special attention and breast cancer becomes a medical emergency, as it is the most diagnosed cancer among women associated with higher chances of relapse and recurrence. Targeted therapies overcome the toxic effects of conventional cancer therapies, and the development of new targeted therapies are the need of the hour due to the problems of acquired resistance, and deteriorating cancer scenario. PARP-1 emerges an attractive target for drug discovery against breast cancer due to its vital role in DNA repair. Therefore, the aim of the present work was to repurpose existing FDA approved drugs targeting PARP-1 inhibitors as anti-breast cancer agents. A three-tier virtual screening followed by binding energy analysis, was performed to find the FDA approved drugs exhibiting good and stable binding characteristics with PARP-1. Further, a comparative analysis of the *in silico* ADME profile of the drugs was carried out. Combined results of the *in silico* analysis were used for selecting best hits against PARP-1. Two best hits, Candesartan and Mycophenolic acid, were selected and the structural features of both the compounds matched with PARP-1 selective inhibitor, Olaparib. Further, *in vitro* and *in vivo* validation of the *in silico* results is warranted for assessing the potential of these compounds as repurposed PARP-1 inhibitors.

Key words: PARP-1 inhibitor, Breast cancer, *In silico* analysis, Virtual screening, Drug repurposing.

INTRODUCTION

Drug repurposing encompasses techniques for deciphering the utility of existing drugs for a new medical condition, other than the one for which it is indicated [1]. The approach can be used for testing existing drugs in pre-clinical animal models directly, while considerably saving time as well as money. The repurposing initiatives are appealing due to the already tested safety, efficacy and toxicity profile of the drug. As compared to the new drug applications, which account for 10% of the market approvals, the repurposed drugs take an upper hand as approximately 30% of them make up to the market [2]. Various drugs have been successfully repurposed for newer clinical indications, such as, the antihypertensive Minoxidil repurposed

for treating hair loss, the morning sickness drug Thalidomide, for symptomatic treatment of Leprosy, antidiabetic Metformin for cancer treatment, etc. Moreover, approximately 8000 drugs have been repurposed against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in COVID-19 pandemic [1, 3-5].

Although options for cancer cure are available through established drugs of synthetic or natural origin and many drugs are under investigation [6, 7] but still, cancer treatment remains a challenge for the scientists as well as the practitioners due to its heterogenous nature, the problem of acquired resistance against existing treatments, and toxicity profile of anti-cancer drugs [8]. Among all the cancers, breast cancer portrays to be a field of immediate medical emergency, because of being the most diagnosed cancer among women and a major reason for premature deaths, associated with high chances of relapse and recurrence post use of existing therapies [9]. Greater than 2.3 million new cases of breast cancer and 685,000 mortalities were reported for the year 2020. The burden of breast cancer is assumed to rise, as over 3 million new diagnoses and 1 million mortalities per year, are predicted by 2024 [10]. The cancer landscape has not improved significantly despite the progress in the discovery of novel anti-cancer agents since past two decades [8-11]. This calls for the fastening of the drug discovery pipeline, and drug repurposing has been identified among one of the most promising approaches for faster and cost-effective drug discovery [9-12].

Computational and Bioinformatics based tools have been found to be robust for drug repurposing endeavors. Structure-based virtual screening is an *in silico* approach used for drug repurposing, which helps to find binders, either functioning as activators or inhibitors of a particular target, based on the binding affinities [13, 14]. PARP-1, is the most familiar member of the Poly (ADP-ribose) Polymerase (PARP) family which governs essential cellular functions of replication, recombination, transcription and DNA repair by transferring ADP-ribose sugar to the target proteins [15, 16]. Some tumors having faulty homologous recombination mechanisms may rely on PARP mediated DNA repair for survival [16]. Thus, PARP-1 emerges as an attractive target for treatment of breast cancer. The inhibitors of PARP form a novel class of anti-cancer therapeutics which target the NAD^+ binding site, and are useful against tumors with homologous recombination deficiency such as, tumors with Breast Cancer Associated 1 and 2 (BRCA 1 and 2) mutations. The cessation of DNA repair machinery due to PARP inhibition has therapeutic implications in BRCA 1/2 mutated cancers, and the synergistic activity of these inhibitors with DNA damaging chemo-therapeutic agents has been beneficial against Triple Negative Breast Cancer [17].

PARP inhibitors Talazoparib and Olaparib have been approved as monotherapies for HER2-negative, deleterious or suspected detrimental germline BRCA-mutated breast cancer. Olaparib has been approved for metastatic breast cancer in the USA and locally advanced breast cancer in Europe. Talazoparib has been approved in the USA and Europe for locally advanced breast cancer. When compared with chemotherapy, Olaparib and Talazoparib monotherapies significantly improved progression-free survival in phase 3 trials. In a phase 3 trial, veliparib in conjunction with platinum-based chemotherapy demonstrated potential for treating locally advanced or metastatic breast cancer [18]. Thus, PARP inhibitors have a significant role in breast cancer clinical settings. However, emerging resistance to existing PARP-1 inhibitors and lack of selective inhibition warrant that novel inhibitors of PARP-1 be identified and evaluated for clinical efficacy [19].

Therefore, the aim of the present work was to reposition of existing FDA approved drugs as PARP-1 inhibitors against breast cancer. A library of FDA approved drugs was docked to the PARP-1 enzyme using three tier hierarchical docking-based screening. The obtained hits were subjected to binding energy calculations and in silico ADME analysis. Best hits repurposed as PARP-1 inhibitors were selected based on the combined results of docking based virtual screening, binding energy, interaction patterns and ADME analysis. Further, a chemo-structural feature analysis was also performed for understanding the pharmacophoric features for PARP-1 inhibition present in the repurposed drugs.

MATERIALS AND METHODS

Docking based virtual screening

Protein preparation and grid generation

For performing the docking based virtual screening, the three-dimensional X-ray crystallographic structure of the target protein, *i.e.* PARP-1 was obtained from the RCSB Protein Data Bank. PDB ID 5DS3 having resolution 2.60 Å, containing Olaparib as the co-crystallized

ligand was chosen for the virtual screening and prepared using the Protein Preparation Wizard of the Schrodinger Drug Discovery Suite 2017-2 [20]. During the protein preparation, missing loops and side chains were added, bond orders were assigned and disulphide bonds were created. The water molecules situated outside of 5 Å distance from the co-crystallized ligand were removed and hydrogen atoms were restrained using the OPLS3 force field. The active site was recognized as the co-crystallized ligand binding site and a three-dimensional grid was generated at the centroid of the bound ligand keeping the grid box dimensions to 20 × 20 × 20 Å [21].

Ligand preparation

A library of 1,123 FDA approved drugs was retrieved from the Enamine database and prepared using the Ligprep module of the Schrodinger Drug Discovery Suite 2017-2. During the ligand preparation, the compounds were desalted and specific chiralities were retained. Three dimensional structures of the compounds were generated and minimized using the OPLS-3 force field [22].

Hierarchical docking based virtual screening

Subsequent to the preparation of the protein and ligands, the compounds were subjected to three tier hierarchical screening on the generated grid using the High Throughput Virtual Screening (HTVS), Standard Precision (SP), and Extra Precision (XP) modes of docking using the Glide module of the Schrodinger Suite (2017-2). The screening criteria was set for retrieval of 50, 25 and 10 % of compounds from HTVS, SP and XP modes respectively [22].

Binding free energy analysis (MM/GBSA)

The structural information present in the protein-ligand complexes was used to calculate the relative energies of binding of the top hits obtained from docking-based screening. The Prime MM/GBSA (Molecular mechanics with generalized Born and surface area solvation) Module of the Schrodinger suite (2017-2) calculated the binding free energies of the top hits bound to PARP-1 using VSGB 2.0 implicit solvation model and OPLS3 force field. The binding site of the protein was set to adjust itself up to 10 Å distance from bound ligand [23, 24].

In silico ADME analysis

The pharmacological activity of a drug molecule is governed by the drug levels in blood and the tissue exposure. These aspects are controlled by four pharmacokinetic parameters, namely, Absorption, Distribution, Metabolism and Excretion (ADME). Though ADME profiling of the FDA approved drugs has been assessed clinically, an in silico ADME analysis of the hits retrieved from docking-based screening was performed. The Qikprop tool of Schrodinger software (2017-2) was used for the assessment of *in silico* ADME parameters such as the violations of the Lipinski rule of five, hERG channel liability, MDCK cell permeability, percentage oral absorption, etc. [25, 26].

Chemo-structural feature analysis

The structures of the selected hit molecules were compared with available PARP-1 inhibitor Olaparib to understand the structural similarities as well as the features essential for PARP-1 inhibition.

RESULTS AND DISCUSSION

Hierarchical docking based virtual screening

The prepared library of 1,123 FDA approved drugs, was subjected to hierarchical screening to retrieve 50, 25 and 10 % compounds respectively. The screening resulted in 12 compounds after the extra precision docking. All the obtained 12 compounds exhibited binding affinities in the range of -10.609 to -9.564 Kcal/mol. The co-crystallized ligand Olaparib, exhibited a slightly greater binding affinity, i.e., -12.469 Kcal/mol and interacted with Gly863, Ser904, Tyr896, Tyr889, His862 and Arg878 residues of the PARP-1 binding pocket. The orientation of the binding of the compounds and the interaction patterns resembled that of Olaparib, however, interactions other than those found with Olaparib were also present. The compounds also interacted with Gly894, Ala898, Gly888, Met890, Tyr907, Ala880, Glu988, Asn868 etc. present in the PARP-1 NAD+ binding pocket. The reference compound, Olaparib, and the screened hits formed hydrogen bonding (donor and acceptor) as well as π-π interactions within the PARP-1 active site.

Binding free energy analysis (MM/GBSA)

Subsequent to the docking-based screening, the MM/GBSA of prime module of Schrodinger Suite was used for calculation of binding energies of the compounds in the catalytic pocket of PARP-1. The compounds exhibited a stable fit in the protein active site, with free binding energies ranging from -98.281 to -52.895 Kcal/mol. The

binding energy of the reference compound, Olaparib, was found to be -98.893 Kcal/mol. The binding energy of Remdesivir was found to be the lowest (-98.281 Kcal/mol), and, comparable to the reference drug Olaparib (-98.893 Kcal/mol), followed by Candesartan (-79.643 Kcal/mol) and Mycophenolate (-76.473 Kcal/mol). The dock score, binding energy and the interaction patterns of the hits obtained from docking based screening are depicted in **Table 1**.

Table 1. Dock score, binding energy and interacting residues of the retrieved hits

Compound	Dock score (Kcal/mol)	Binding energy (Kcal/mol)	Interactions
Olaparib	-12.469	-98.893	Gly863, Ser904, Tyr907, Tyr896, Tyr889, Arg878, His862
Valacyclovir	-10.609	-68.603	Gly863, Ser904, Tyr907, Glu988, Phe897, Tyr896, Gly894, Ala898
Penciclovir	-10.498	-69.067	Gly863, Ser904, Tyr907, Gly888, Met890
Mitoxantrone	-10.495	-64.880	Gly863, Ser864, Ser904, Tyr907, Arg865, Ala880, Gly894
Zidovudine	-10.493	-52.895	Gly863, Ser904, Gly888, Met890
Mycophenolic Acid	-10.225	-66.976	Gly863, Ser904, Tyr896, Tyr907, Arg878
Inosine	-9.879	-60.639	Gly863, Ser904, Tyr907, Glu988, Gly888
Rebamipide	-9.833	-73.129	Gly863, Tyr907, Gly888, Met890
Demeclocycline	-9.817	-72.821	Gly863, Ser864, Tyr907, Arg865, Asn868, Glu988
Candesartan	-9.715	-79.643	Gly863, Ser904, Tyr907, His862, Arg878
Remdesivir	-9.625	-98.281	Ser904, Tyr907, Arg878, Glu888, Ala880
Mycophenolate	-9.613	-76.473	Gly863, Ser904, Arg878
Methotrexate	-9.564	-70.954	Gly863, Ser904, Tyr907, His862, Arg878, Gly876

In silico ADME analysis

The comparative study of the pharmacokinetic profile was carried out using the Qikprop tool of the Schrodinger Drug Discovery Suite. Rebamipide showed no violations of the ADME rules, moreover, Zidovudine, Candesartan, Mycophenolic acid, and Mycophenolate were found to be better than other compounds as they showed only single violation of ADME rules. However, the reference compound Olaparib showed optimum as well as better ADME characteristics as compared to the screened hits. The Caco-2 and MDCK cell permeabilities values were lower in most compounds, however, Candesartan and Mycophenolic acid had better values of Caco-2 and MDCK cell permeation among the hits, showing one violation of the ADME rules. Also, both Candesartan and Mycophenolic acid had better percentage oral absorption than the other hits. The results of *in silico* ADME prediction have been depicted in **Table 2**.

Table 2. Results of *in silico* ADME prediction

Compound	mol_MW	SASA	FOSA	DonorHB	accptHB	QPlogP o/w	QPlogHERG
Olaparib	434.469	746.225	303.616	1	8	2.88	-4.764
Valacyclovir	324.339	559.099	263.576	5	10.2	-1.126	-4.722
Penciclovir	253.26	489.041	142.603	5	8.9	-1.444	-4.118
Mitoxantrone	444.486	759.079	290.61	4	9.9	0.494	-7.286
Zidovudine	267.244	487.92	194.671	2	9.9	0.036	-3.769
Mycophenolic acid	433.5	761.443	583.241	0	9.2	2.32	-5.795
Inosine	268.229	454.926	93.628	4	11.8	-2.029	-3.758

Rebamipide	370.791	564.373	26.869	2.25	6.25	2.779	-2.874
Demeclocycline	464.858	644.842	168.697	3	9.2	0.025	-5.179
Candesartan	440.46	667.982	110.597	2	6.5	4.067	-3.961
Remdesivir	602.583	833.851	311.676	5	16.65	1.288	-5.891
Mycophenolate	320.341	577.201	341.293	1	5.5	2.526	-2.29
Methotrexate	454.444	735.186	156.162	6.25	11.75	-1.847	-2.009

Table 2 (cont). Results of *in silico* ADME prediction

Compound	% Human oral absorption	PSA	Rule of five	QPlogKhsa	QPPCaco	QPPMDCK
Olaparib	145.733	112.229	0	0.153	145.733	142.002
Valacyclovir	38.04	158.507	0	-0.769	9.733	3.662
Penciclovir	42.023	140.666	0	-0.911	20.644	7.462
Mitoxantrone	17.104	183.585	1	-0.34	1.029	0.357
Zidovudine	54.043	152.083	0	-0.892	31.793	11.9
Mycophenolic acid	75.7	118.721	0	-0.244	92.246	41.635
Inosine	42.198	143.419	0	-0.966	32.819	12.316
Rebamipide	68.891	122.616	0	-0.093	27.191	31.555
Demeclocycline	21.12	195.31	1	-0.121	2.457	1.691
Candesartan	80.01	125.406	0	0.326	43.1	21.029
Remdesivir	40.648	196.38	2	-0.657	62	24.494
Mycophenolate	67.504	120.124	0	-0.116	27.522	12.95
Methotrexate	0	234.553	2	-0.888	0.065	0.024

Scrutinization of best PARP-1 inhibiting hits

The selection of best PARP-1 inhibiting hits was done based on combined results of docking-based screening, binding energy, interaction pattern analysis and ADME prediction. The scrutinization resulted in two stably binding hits with admissible ADME, inhibiting PARP-1 in similar fashion to Olaparib. Candesartan exhibited a dock score of -9.715 Kcal/mol and binding energy of -79.643 Kcal/mol. It displayed interactions with Gly863, Ser904, Tyr907, His862, Arg878 and Tyr889 in the PARP-1 active site. Mycophenolic acid exhibited a dock score of -10.225 Kcal/mol and binding energy of -66.976 Kcal/mol. It displayed interactions with Gly863, Ser904, Tyr907, Tyr896 and Arg878 in the PARP-1 active site. Both the hits exhibited six and five interactions like Olaparib, which interacted with seven residues (Gly863, Ser904, Tyr896, Tyr889, His862 and Arg878) in the PARP-1 binding pocket. The binding interactions of Olaparib, Candesartan and Mycophenolic acid have been depicted in **Figures 1-3** respectively.

Both compounds had admissible ADME with only one violation. They showed oral absorption comparable to Olaparib and better MDCK and Caco-2 cell permeabilities as compared to other hits. Though Olaparib exhibited superior ADME and binding characteristics than Candesartan and Mycophenolic acid, they both hold promise as potential PARP-1 inhibitors due to optimal ADME and binding characteristics.

Chemo-structural feature analysis

The best hits share structural similarity with Olaparib, which is a PARP-1 inhibitor approved for both metastatic as well as locally advanced breast cancer. As evident from **Figure 4**, Candesartan is a benzimidazole carboxylic acid derivative and Mycophenolic acid is a 3-oxo-4-hydroxy-benzofuran derivative, where the cores of these compounds resemble the pthalazinone nucleus of Olaparib, shown in blue color. This is suggestive of the fact that a heterocyclic nucleus with hydrogen bond donor and acceptor atoms is necessary for PARP-1 inhibitory activity. Further, the pink colored region shows the presence of an aromatic or branched chain aliphatic linker, which should be hydrophobic in nature and a terminal appendage (green region) with groups capable of hydrogen bonding confer the compounds similarity with Olaparib. The structural similarity with Olaparib justify the results of the *in silico* repurposing of the FDA approved drugs as PARP-1 inhibitors. The repurposing endeavor brought forward anti-hypertensive Candesartan and immune-suppressant Mycophenolic acid as potential inhibitors of PARP-1. The benzimidazole and benzofuran nucleus present in the Candesartan and Mycophenolic acid respectively, have been known to possess anticancer activity [27, 28], which provide supporting evidence that the compounds may possess anticancer activity and may be repurposed as inhibitors of PARP-1

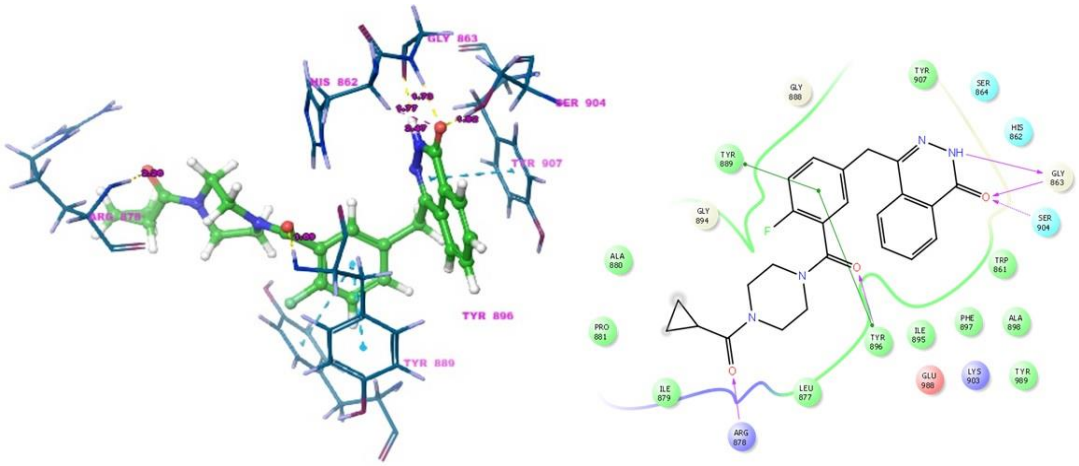

Fig. 1. 3D and 2D interaction pattern of Olaparib in PARP-1 cavity

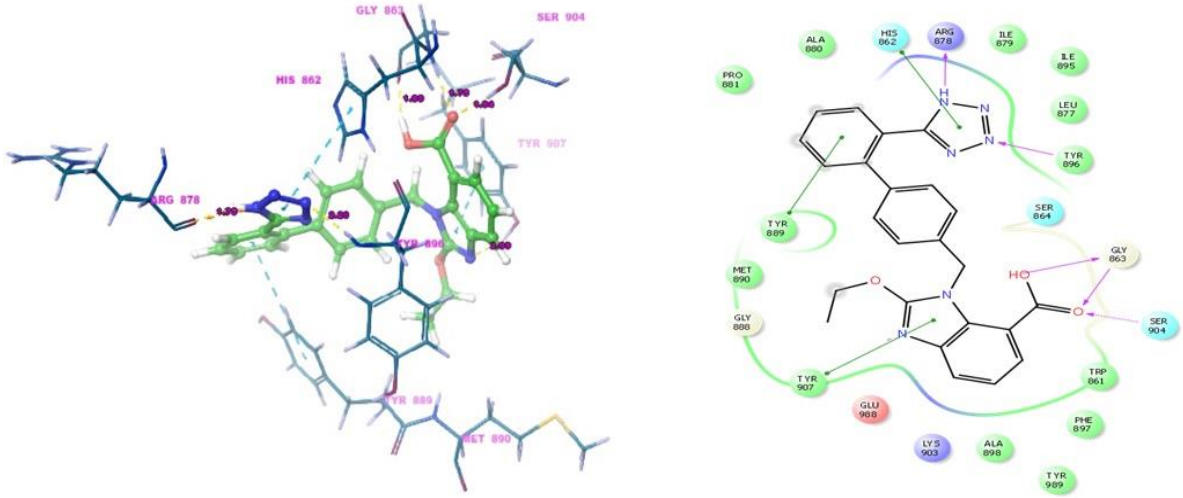

Fig. 2. 3D and 2D interaction pattern of Candesartan in PARP-1 cavity

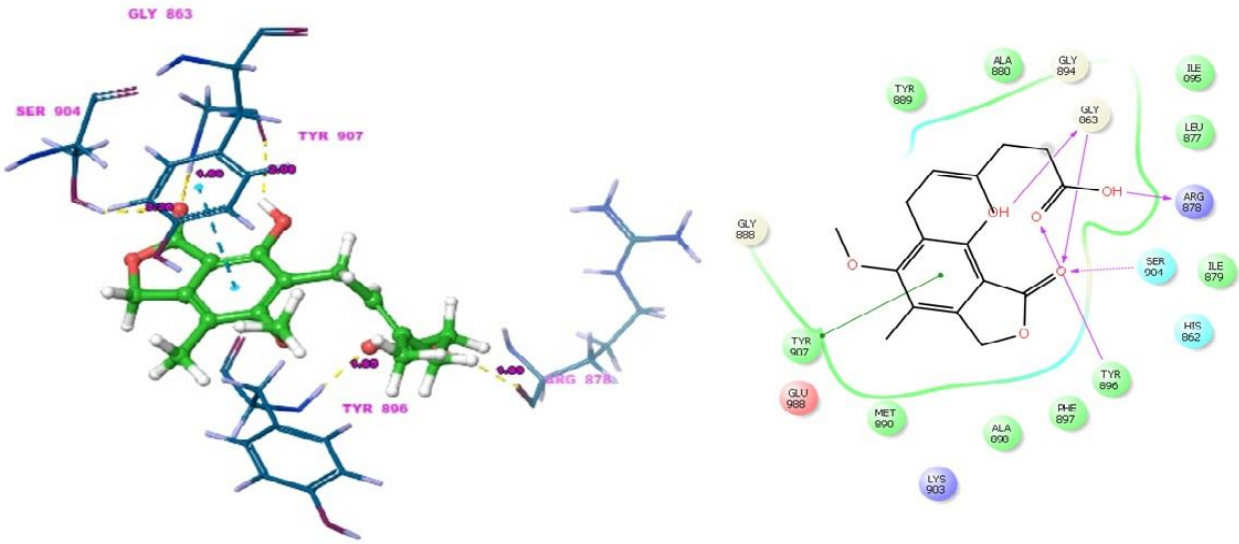

Fig. 3. 3D and 2D interaction pattern of Mycophenolic acid in PARP-1 cavity

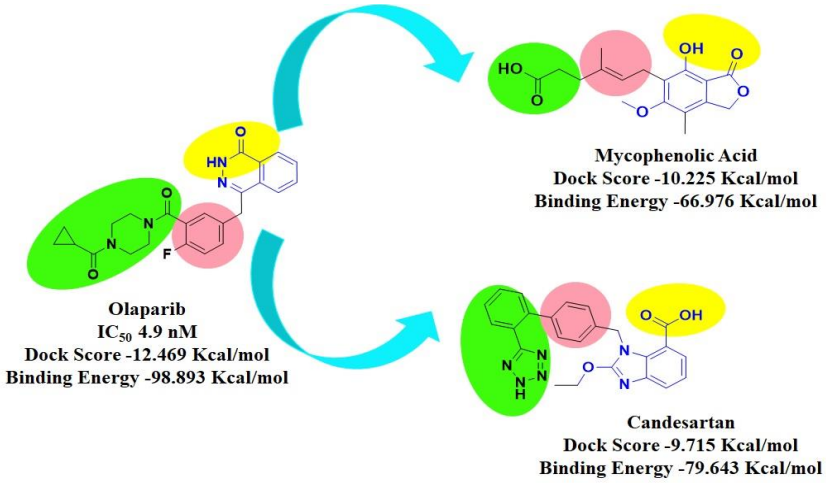

Fig. 4. Chemo-structural feature comparison of the best hits with Olaparib

against breast cancer. In a recent study, Candesartan was found to reduce tumor growth in colorectal cancer [29]. Also, the treatment with Candesartan has the potential to protect against cardiac damage associated with the conventional cancer treatment [30].

Mycophenolic acid is the active metabolite of Mycophenolate mofetil, an immunosuppressive drug that acts by inhibiting de novo purine synthesis, thus may act as anticancer agent. Several *in vitro* as well as *in vivo* experiments have validated the anticancer activity of Mycophenolic acid in various cell lines and murine models. However, the results of clinical trials have been unsatisfactory [31]. Further, experimental validation of the above results is warranted in support of the findings.

CONCLUSION

The studies represented in the present work are an example of *in silico* drug repurposing approach. The three-tier docking based screening approach gave 12 FDA approved drugs exhibiting good binding affinities towards PARP-1. Further, binding free energy analysis revealed that the 12 compounds exhibit stable binding in the PARP-1 pocket. A comparative study of the ADME profile along with the above parameters gave Candesartan, an anti-hypertensive drug and Mycophenolic acid, a metabolite of immune-suppressant Mycophenolate as potential PARP-1 inhibitors with chemical structure and binding characteristics almost similar to a selective PARP-1 inhibitor *i.e.* Olaparib. The anti-cancer potential of these compounds has been assessed experimentally. However, further experimental validation of the PARP-1 inhibitory potential against breast cancer should be assessed and the compounds should be taken forward in the drug discovery pipeline.

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