RESEARCH ARTICLE

Identification of Anti-Cancer Targets of Eco-Friendly Waste *Punica granatum* Peel by Dual Reverse Virtual Screening and Binding Analysis

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Abstract

Background: *Punica granatum* (family: Lythraceae) is mainly found in Iran, which is considered to be its primary centre of origin. Studies on pomegranate peel have revealed antioxidant, anti-inflammatory, anti-angiogenesis activities, with prevention of premature aging and reducing inflammation. In addition to this it is also useful in treating various diseases like diabetes, maintaining blood pressure and treatment of neoplasms such as prostate and breast cancer. Objectives: In this study we identified anti-cancer targets of active compounds like corilagin (tannins), quercetin (flavonoids) and pseudopelletierine (alkaloids) present in pomegranate peel by employing dual reverse screening and binding analysis. Materials and Methods: The potent targets of the pomegranate peel were annotated by the PharmMapper and ReverseScreen 3D, then compared with targets identified from different Bioassay databases (NPACT and HIT's). Docking was then further employed using AutoDock pyrx and validated through discovery studio for studying molecular interactions. Results: A number of potent anti-cancerous targets were attained from the PharmMapper server according to their fit score and from ReverseScreen 3D server according to decreasing 3D scores. Conclusion: The identified targets now need to be further validated through *in vitro* and *in vivo* studies.

Keywords: *Punica granatum* - ingredients - pharmMapper - reversescreen 3D - bioassay database - autodock pyrx

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Introduction

Punica granatum L., (family Lythraceae) (Pomegranate) is a shrub which attains a height of about 5-8 meters (Middha et al., 2013a). It is believed to have originated in Iran and is cultivated majorly in Mediterranean region, Indian subcontinent, Middle East, Central Asia, Northern Africa and tropical Africa (Akbarpour et al., 2009). The word pomegranate is derived from Latin word 'pomum' means 'apple' and '*granatum*' means 'seeded'. It is variously named thoroughout the globe like *grenadine* or *grantapfel* in German, *granatapple* in Swedish, *grenade* in French, *granda* in Spanish and *dadim*/*dadima* in India. Pomegranate is used widely in domestic as well as industrial purposes such as cooking, preparation of juice, baking, making of wine and other alcoholic beverages.

The fruit is round consisting a crown in the base rendered from the calyx. The texture of the peel is stringy and sturdy, with the colour ranging between yellow to red and is thick about 5 inches. The white spongy membrane inside form the compartments consisting sac like structure which is packed with pulp that is red or white in colour and juicy (Middha et al., 2013b).

Middha et al (2014) showed recently that the pomegranate peel or the rind (PP) which was earlier considered as an agricultural waste now should be removed has high potential for its medicinal and therapeutic values. It is evident that PP has better antioxidative properties than Musa paradisiaca and Citrus sinensis peel (Parmer et al., 2008). Several studies have also shown the presence of major active compounds such as tannins, flavonoids, and alkaloids in the pomegranate peel (Middha et al., 2013a). Due to the presence of these compounds the pomegranate peel has been focused by many researchers for the study of its incredible effects on human health. The pomegranate peel has been widely used for the treatment and prevention of several diseases like cancer (Hong et al., 2008; Dikmen et al., 2011; Middha et al., 2013a), diabetes (Middha et al., 2012; 2014), cardiovascular disease (Jurenka 2008),

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Alzheimer's disease, dental conditions (Middha et al., 2013), erectile dysfunction and male infertility (Kanatt et al., 2010). Though a number of clinical trials have been performed by various researchers to establish its therapeutic potential but still precise mechanism behind this is yet to be resolved. To findout its precise mechanism, the crude extract which is a store house of several phytochemicals have to be refined, to identify the most active ingredients responsible for its particular activity. In order to minimise the time and money, an alternative in *silico* approach would be more suitable to identify targets for various diseases like cancer. In this perspective, reverse screening approaches using Reverse docking system and Reverse pharmacophore mapping have gained importance in the recent past (Kinnings and Jackson, 2009). Thus keeping these in mind we used the active compounds such as corilagin (tannins), quercetin (flavonoids) and pseudopelletierine (alkaloids) previously reported by the authors (Middha et al., 2013b) in pomegranate peel for identifying the anti-cancerous targets by employing two *in silico* methods *viz*.-ReverseScreen 3D and PharmMapper.

Materials and Methods

Literature survey and annotation to the list of active compounds of pomegranate peel

Pomegranate peel is a rich source of various phytochemicals that have documented for its therapeutic activities. Therefore the literature survey was conducted to sort out the various active components of the pomegranate peel for finding the potent anti-cancerous targets.

The small molecules were confirmed using HPLC by authors in their previous studies from pomegranate peel *i.e*. corilagin, quercetin, pseudopelletierine (Figure 1)

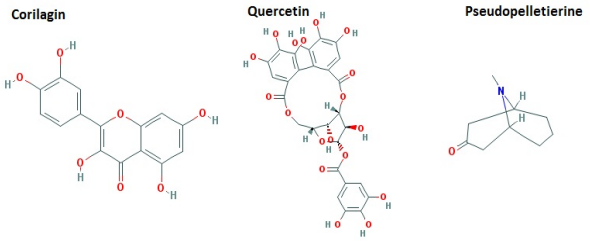

Figure 1. Small Molecules Selected for Study Using HPLC

were retrieved in *.sdf* format from the PubChem database.

Putative therapeutic target identification by dual inverse screening

By 2D fingerprint-based reverse virtual screening: It employs the use of online server ReverseScreen 3D that screens the potent targets for the given active components that searches against the biologically-significant ligands. Automatically-updated subset of ligands that were taken from the RSCB Protein Data Bank. Submission of the small molecule as an input to the server generated a list of about 25 conformers. Initially a 2D similarity search was carried out between the query compound and all the ligands in the database, from this a single ligand with highest 2D similarity was selected from each unique target binding site. It was then followed by a 3D structure based ligand matching based on which a LigMatch was carried out between the query compound and each of the previously selected database ligands. Only the top 10% of the ligand database that were prioritized by 2D scores were subjected to 3D structure based ligand matching (Kinnings and Jackson., 2011).

The sdf files of the active components of the pomegranate peel i.e., corilagin, quercetin and pseudopelletierine were submitted to the ReverseScreen 3D for 2D and 3D similarity searches. A list of potential targets were obtained which were further annotated to screen out the targets pertaining anti-cancerous activity.

By reverse pharmacophore mapping: This was carried out by employing the freely accessible online server PharmMapper which employs pharmacophore mapping strategy for the identification of the potential targets for the given small molecule that can be either drugs, natural products or other newly discovered compounds. It is a highly efficient robust mapping method. PharmMapper identifies the potential targets for the given molecule within few hours from the database. This server is supported by various databases such as the PDTD, BindingDB, DrugBank and TargetBank. Submission of a molecule to the PharmMapper finds the best targets by mapping the molecule against all the targets of the PharmMapper and as a result top N potential targets as well as the alignment of the molecule is outputted (Kinnings and Jackson, 2009; Bhattacharjee et al., 2012).

The sdf files of the active components of the pomegranate peel i.e., corilagin, quercetin and pseudopelletierine were submitted to the PharmMapper for mapping and identification of targets. A list of potential targets was obtained which were further annotated to screen out the targets pertaining anti-cancerous activity.

Therapeutic target identification from bioassay database

The potent targets of active compounds of pomegranate peel were then manually curated from different database such as NPACT (Naturally occurring Plant-based Anti-cancerous Compound-activity-Target database) and Herbal Ingredients' targets database.

NPACT database consists of natural compounds derived from plants that have anti-cancerous activity. It has about 1574 entries and each of the entry provides information of molecular targets, structure, properties, cancer type, inhibitory values, drug likeness commercial suppliers and cell lines (Mangal et al., 2013).

Herbal Ingredients' targets database is a widespread database that complements available protein targets of FDA approved. It consists of about 1,301 protein targets out of which 221 are direct targets. These are derived from several literatures and cover around 586 active compounds of more than 1,300 Chinese herbs (Hao et al., 2011).

Comparative analysis of in silico identified targets and bioassay findings

The targets sorted out from the in silico methods (ReverseScreen 3D and PharmMapper) were compared with targets identified from the bioassay database. This was done to evaluate the results obtained from the dual

virtual inverse screening.

ADME and toxicity predictions

ADME stands for Absorption, Distribution, Metabolism and Excretion studies which were performed in Accelrys Discovery studio 3.5 using ADME descriptors algorithm. ADME predicts the significant descriptors of drug likeness wherein various pharmacokinetic parameters like blood-brain-barrier penetration (BBB), hepatotoxicity levels, Human intestinal absorption, aqueous solubility and Plasma protein binding(PPB) are estimated for the ligand (Reddy et al., 2013; Usha et al., 2014). The results obtained from these were then verified with the standard levels.

Toxicity profiling of the ligand was carried out using the Toxicity prediction protocol of Accelrys Discovery Studio 3.5. This included screening of AMES mutagenecity, developmental toxicity potentials, aerobic biodegradability and carcinogenicity (Middha et al., 2013c).

Molecular docking simulation of therapeutic targets with active components

The macromolecular target structures were retrieved from RCSB-PDB and then subjected to docking with active components. Docking was performed using AutoDock Pyrx Vina to find out the mechanism of binding of the macromolecular targets to small active components. AutoDock performs a blind docking since the binding site is not known and hence predicts the protein-ligand complex structures with acceptable speed and accuracy. Here, the ligands were docked using the default settings of Lamarckian genetic algorithm (Lydia et al., 2014). The results were quantified in terms of free binding energy (ΔG).

Validation of docking poses

The macromolecular targets that showed least binding energy when docked in AutoDock Pyrx Vina were re-docked in order to validate using Discovery studio (DS) 3.5 accelrys tool. Prior to docking in DS the ligand was prepared in which the geometry of the ligand was cleaned and the uneven charges were distributed throughout using CHARMM force field (Middha et al., 2013; Sharma and Naik., 2013). Force field refers to the forces and energies on each particle of the system and also defines the positional relationships between atoms that determine their energy.

Results and Discussion

Pomegranate has been entitled as a "wonder fruit" due to the presence of its ample pharmacological properties. The pomegranate peel being the biological waste of the fruit have been in focus by various researchers due to the presence of its ethnomedical properties (Middha et al., 2013). These properties of pomegranate peel are due to the presence of several active constituents which include the major tannins, flavonoids and alkaloids as listed in Table 1 (Middha et al., 2013). In these studies we have made an effort to find the therapeutic targets for few active constituents of pomegranate peel i.e. quercetin, corilagin and pseudopelletierine.

Quercetin (Formula $C_{15}H_{10}O_7$; Mw 302.236g/mol) is one of the major flavonoid encountered in the peel of pomegranate that is ubiquitous in nature (Lamson and Brignale, 2000). This yellow coloured compound, is widely distributed in nature and is found in several fruits, vegetables, grains and leaves (Suri and Naik, 2012; Middha et al.,2013c; Usha et al., 2013; Aras et al., 2014). It is partially insoluble in water and soluble in aqueous alkaline solutions. Corilagin (Formula $C_{27}H_{22}O_{18}$; Mw 634.45g/mol), is one of the major tannins present in pomegranate peel and the leaves. Pseudopelletierine (Formula $C_9H_{15}NO$; Mw 153.22g/mol) is a colourless alkaloid found in the pomegranate peel and also in the bark of the tree.

Potential Targets of Quercetin identified from Dual Inverse Screening

The potent targets of quercetin were identified by employing PharmMapper and ReverseScreen3D screening tools which are freely accessible servers. A number of targets were obtained as shown in Table 2.

PharmMapper server enlisted a number of potential targets that were ranked based on their descending fit score which were further annotated to screen out anti-cancerous targets and gave away about 12 potential targets from PharmMapper. (Table 2). About 14 targets were obtained from ReverseScreen3D.

Potential Targets of corilagin and pseudopelletirene identified from Dual Inverse Screening

Eleven potential receptors for corilagin and two potent receptors for pseudopelletirene were identified after the dual inverse screening procedures by PharmMapper and ReverseScreen 3D as shown in Table 3.

ADMET predictions

ADMET properties are considered to be one of the most important criteria in order to determine true potential of the compound (Puzyn et al., 2010). About 50% of drugs are found to be unsuccessful due to the toxicity of compound during the clinical trials. Therefore in order to save the expenses at the clinical trial stage the *in silico*

Table 1. Major Tannins, Flavonoids and Alkaloids of the Pomegranate Peel (Middha et al., 2013)

Major tannins	Major flavonoids	Major alkaloids
Corilagin	Quercetin	Pseudopelletierine
Ellagic acid	Rutin	Valoneic acid
Gallic acid	Pelargonidin	Pelletierine
Grantin B	Flavan-3-ol	
Punicalin	Naringin	
Punicalagin	Luteolin	
Methyl gallate	Catechin	
Casuarinin	Luteolin-7-O-glucoside	
	Epigallocatechin 3-gallate	
	Epicatechin	
	Cyaniding	
	Kaempferol	
	Kaempferol-3-O-glucoside	
	Kaempferol-3-O-rhamnoglycoside	

Table 2. Potential Targets Of Quercetin Identified from Dual Inverse Screening

Target Name	PDB ID	PharmMapper	ReverseScreen3D	Fit Score	Binding energy (Kcal/mol)
GTPase HRas	5P21	✓		5.327	-2.62
Prot-oncogene tyrosine-kinase src	2BDJ	✓	✓	4.495	Found error
Tyrosine protein kinase HCK	1QCF	✓	✓	4.294	-3.77
HSP 90-alpha	2BSM	✓		4.131	-2.24
Cell division protein kinase-2	2BTS	✓		4.102	-4.01
Basic fibroblast growth factor receptor 1	3C4f	✓		3.964	-6.15
Cyclin A2	2IW8	✓		3.95	-3.41
Glycogen synthase kinase 3 beta	2JDR	✓	✓	3.87	2.54
Estradiol 17-beta-dehydrogenase 1	1I5R		✓	3.857	1.08
Leukotriene A-4 hydrolase	4DPR	✓		-	Found error
Lysozyme C	1JKB			-	-3.41
Death-associated protein kinase 1	2XZS	✓		-	-3.6
Vitamin D3 receptor	1KB2	✓		3.917	-10.97
Leukocyte elastase	1PPF	✓		3.806	-1.17
Apoptosis regulator BCL-X	1G5M		✓	-	-0.5
Proto-oncogene tyrosine-protein kinase LCK	3MPM		✓	-	-4.28
Serine/threonine-protein kinase PLK1	1UMW		✓	-	-3.65
Ser/thr protein kinase	3M9G		✓	-	-3.22
Cell division protein kinase 9	2YAC		✓	-	-4.19
Casein kinase II subunit alpha	4GUB		✓	-	-4.92
Cyclin-dependent kinase 6	1OIY		✓	-	-3.56
Prot-oncogene tyrosine-protein kinase receptor RET	2IVU		✓	-	-4.57
Androgen receptor	1GS4		✓	-	-5.36
NAD(P)H dehydrogenase [quinone] 1	1QRD		✓	-	-3.52

Table 4. Standard Levels of ADMET Descriptors from Discovery Studio

Aq. Solubility & Drug Likeness		BBB		CYP450		Hepatotoxicity		Intestinal Absorption	
level	Intensity	Level	Intensity	Level	Value	Level	Value	Level	Value
0	Extremely low	0	Very high	0	Non-inhibitor	0	Non-toxic	0	Good
1	No, very low	1	High	1	Inhibitor	1	toxic	1	moderate
2	Yes, low	2	Medium					2	Poor
3	Yes, good	3	Low	**PPB**				3	Very poor
				Level	% of binding				
5	No, too soluble			0	<90%				
				1	>90%				
6	Uknown			2	>95%				

Table 3. Potential Targets of Corilagin and Pseudopelletirene Identified from Dual Inverse Screening

Target Name	Corilagin	Pseudopelletierine
GTPase HRas	✓	-
Prot-oncogene tyrosine kinase HCK	✓	-
HSP 90-alpha	✓	-
Cell division protein kinase-2	✓	-
Death-associated protein kinase-1	✓	-
Vitamin D3 receptor	✓	-
Leukocyte elastase	✓	-
Galecitin-3	✓	-
Androgen receptor	✓	-
Estradiol 17-beta dehydrogenase-1	✓	-
NAD(P)H dehydrogenase[Quinone]-1	✓	-
Leukotriene A-4 hydrolase	-	✓
Lysozyme C	-	✓

toxicity prediction tools are used. The ADME values obtained for quercetin (Table 5) was compared with the standard levels (Table 4). It was found that quercetin is soluble in water and hence indicating good oral bio-availability. The BBB (Blood-Brain-Barrier) level was 4 showing low penetration across the CNS (Central Nervous System) therefore it minimizes the side effects related to CNS (Middha et al., 2013). Intestinal absorption level was found to be 1 indicating moderate absorption by the intestine. Hepatotoxicity is one of the major factors of ADME that has to be considered in order to ensure the toxicity of the drug. For quercetin, the hepatotoxic level was found to be 1 indicating it as toxic but studies have shown that when it is administered orally it is less toxic (Psahoulia et al., 2007). Studies on oral administration of quercetin have shown that there is as such no adverse effect on human health when about four grams of a single dose is taken or after one month of 500mg twice daily. If it is administrated intravenously then the kidney function

Table 5. Predicted ADME Properties of Quercetin

Aq.solubility level	BBB level	CPY2D6	Hepatototoxicity	Absorption level	PPB level
3	4	0	1	1	0

Table 6. Docking Scores of the Active Sites of Quercetin

Active site	C_docker_energy	C_docker_interaction_energy
Site 1	33.531	40.758
Site 2	26.749	29.493
Site 3	39.271	44.746
Site 4	10.554	24.928
Site 5	-18.318	-20.496
Site 6	30.862	39.239

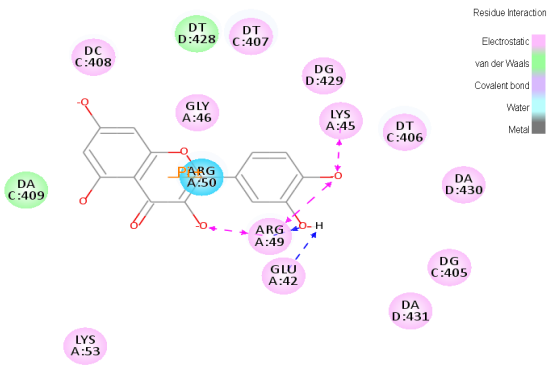

Figure 2. 2-D Diagram Showing the Interactions of Vitamin D-3 Receptor with Quercetin

test has to be carried out on a regular basis (Lamson and Brignale, 2000).

Docking results of quercetin with its potent targets

As quercetin showed maximum number of Hits (targets) compared to the other two ligands/active compounds, it was subjected to docking with its targets obtained from dual inverse screening procedures.

On docking, quercetin showed greater binding affinity to many of its receptors with least (negative) binding energy. Twenty one molecules out of twenty four molecules had negative binding energy. Three molecules i.e. Vitamin D-3 receptor, Basic fibroblast growth factor receptor-1 and Androgen receptor indicated the highest docking score of about -10.97kcal/mol, -6.15kcal/mol and -5.36kcal/mol respectively.

Validation of quercetin using Discovery studio (DS) 3.5 accelrys tool

The results obtained were re-docked in order to find out the binding site of quercetin and its interaction with the receptor. Since Vitamin D-3 receptor showed highest binding energy of -10.97kcal/mol when docked in autodock, it was subjected for validation in DS.

The effective binding site for quercetin was found to be in chain A of vitamin D-3 receptor. The active site was determined from the receptor's cavity in DS and about six active sites were obtained. These sites were docked with quercetin and analysed for its binding efficiency based on the least (negative) C_docker energy and C_docker interaction energy Table 6.

The docking scores obtained clearly indicated that quercetin was highly efficient when docked at fifth active site of the receptor (Table 6). The amino acid residues involved in interaction with quercetin are Arg:49, Glu:42 and Lys:45 which are involved in hydrogen bond formation. Pi interaction of quercetin was found with Arg:50 residue (Figure 2).

In conclusion, in our studies we have employed molecular docking in order to find the binding mechanism of the ligands. Quercetin have been majorly focused due to its effect on inhibiting several cancers such as in Lung cancer, gastric cancer, prostate cancer, breast cancer and liver cancers (Buckely, 2012). It was observed that quercetin had least binding energy with the Vitamin D-3 receptor when docked in autodock as well as when validated in DS. Vitamin D-3 receptor plays a major role in breast cancer (Welsh et al., 2003) and hence quercetin can be further useful for development of novel drug for better inhibitory effect on breast cancer.

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