Identification of Anti-prostate Cancer Targets for Resveratrol: an Inverse Screening Approach

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***Abstract*--Chemoprevention of cancer through phytochemicals has become a powerful weapon against cancer. The intake of bioactive components in our diet reduces the risk of cancer. Resveratrol has proved as one of the promising phytochemical derived from grape skin against cancer. In the present study the role of resveratrol in prostate cancer prevention was taken into consideration. The putative therapeutic targets for resveratrol were obtained from the PharmMapper Server with their fit scores. The targets obtained were classified as anti-prostate cancer, anti-inflammatory, Signal transducing modulators, anti-oxidant, anti-proliferative and anti-angiogenesis based on their therapeutic action using TTD (Therapeutic Target Database) and PDTD (Potential Drug Target Database). Our component resveratrol showed to be an important molecule which can be helpful in the drug discovery against prostate cancer.**

***Index Terms*-- inverse screening, molecular targets, prostate cancer, resveratrol**

I. INTRODUCTION

Dietary phytochemicals present in fruits and vegetables have proved to be protective against cancer and other diseases from the last decade. The bioactive components present in some of the major dietary agents are curcumin, genistien, resveratrol, lycopene, selenium, flavonoids, elagic acid, catechins, and isoflavones. These agents suppress inflammation which is responsible for the hyperproliferation and initiation of carcinogenesis. Angiogenesis and metastasis may also be suppressed which are the final steps of carcinogenesis [1].

Prostate cancer in men is one of the major cause of cancer mortality. Approximately 29,720 men will die from this cancer in 2013 according to The American Cancer Society statistics [2]. Elderly age, genetics, race, dietary habits and inflammation are the risk factors for Prostate cancer[3]. Early prostate cancer can be detected with the help of PSA(Prostate- specific antigen)[4]. Radical prostatectomy and radiation therapy are the current treatments for prostate cancer which has resulted in side effects such as erectile dysfunction and urinary incontinence [5].

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Resveratrol found in grapes, peanuts, berries, and red wine belongs to the stilbene family. Among the two isoforms of resveratrol the trans-isomer is more stable than the cis-isomer[6],[7]. This polyphenol has the ability to hinder carcinogenesis by modulating signal transduction pathways, inflammation, angiogenesis, apoptosis, and metastasis.

It has proved to inhibit cell proliferation in an ample variety of human tumor cells in-*vitro* [8].

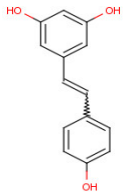

Fig 1**.** Resveratrol (3,4',5-trihydroxy-*trans*stilbene)

In-vitro studies have showed that resveratrol inhibits cell cycle regulators, cyclin-dependent kinases, cyclins, inhibitor proteins, such as p21WAF1 and p27KIP1. It has p53 and Rb tumor suppressors, matrix metalloproteinases (MMPs) which inhibit tumor metastasis and subsequently angiogenesis. Resveratrol affect cancer progression by directly inhibiting COX-2 activity and also the transcription factor nuclear factor-kappa B (NF-κB) is modulated by resveratrol [9] . It has reported that in transgenic adenocarcinoma mouse prostate (TRAMP) mice, resveratrol has suppressed prostate cancer progression [10].

In the present study we have identified the other molecular targets for resveratrol which may be helpful in understanding the role of resveratrol in the prostate cancer treatment or in cancer pathogenesis. This study utilized *in-silico* method like "Inverse Screening" to identify the potential molecular targets for resveratrol. Similar studies have been undertaken to find the putative targets for Tea polyphenols [11], Rosemary [12], and Saffron [13].

II. MATERIALS AND METHODS

A. Resveratrol 3D structure retrieval from PubChem

PubChem database was used to retrieve the three dimensional structure of resveratrol with the PubChem ID: 445154. Further

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MarvinSketch was used to convert the sdf file to .mol2 file as PharmMapper only supports tripose mol2 and mdl sdf formats. The resveratrol mol2 file was then submitted to PharmMapper server for the prediction of the molecular targets for resveratrol.

A. Target Screening Using PharmMapper

PharmMapper server **(http://59.78.96.61/pharmmapper)** is a freely accessed web server designed to identify potential target candidates for the given small molecules using pharmacophore mapping approach. Pharmacophore is the spatial arrangement of features essential for a molecule to interact with a specific target receptor, which is an alternative method for achieving this goal apart from molecular docking method. Human target set were considered to perform Genetic Algorithm (GA). And a maximum of 300 conformations generations were preferred prior to submission. On the basis of the fit score the resveratrol targets were analyzed

B. Classification of Targets

The potential targets obtained by the PharmMapper server were further classified based on their therapeutic action and disease involvement into anti-inflammatory, anti-angiogenesis, anti-proliferative, anti-mutagenic, signal transducing modulators and anti-oxidants. This was performed by referring to other target databases like UniProt, TTD Database (Therapeutic Drug Target Database) [14] , PDTD (Potential Drug Target Database)[15] etc.

C. Target Screening based on Ligand Pharmacophore Alignment

PharmaGist (http://lilab.ecust.edu.cn/pharmmapper/index.php) is a freely available web server for pharmacophore detection which employees ligand based method. It computes candidate pharmacophores by multiple flexible alignments of the input ligands. The innovative approach is of this server is that the flexibility of the input ligands is handled clearly and in deterministic manner within the alignment process. The advantage of this method is the ability of detecting pharmacophores shared by different subsets of input molecules. This ability is a key advantage when the ligands belong to different binding modes. The results of the PharmMapper had multiple entries for the same protein. Hence the ligands of the PDB entries were structurally aligned with resveratrol using PharmaGist. The mol2 files of the resveratrol and the ligands were submitted to PharmaGist and resveratrol was set as a key molecule for alignment with 5 features. Based on the PharmaGist score the target whose ligand showed highest score with resveratrol were considered for further study.

III. RESULTS AND DISCUSSION

The phytochemical taken for the present study was resveratrol as shown in figure 1. The submission of resveratrol to PharmMapper yielded nearly 300 targets with multiple PDB entries. This was further screened using the PharmaGist which utilizes ligand based pharmacophore screening. The list of putative targets after Inverse and Ligand based Pharmacophore screening are given in TABLE I. with their PDB Id and Fit scores. From this one can infer that resveratrol can inhibit prostate cancer. Among these, vitamin D3 receptor can be considered as one of the prominent targets for combating prostate cancer, as it shows highest fit score.

Table I

SCREENED TARGETS OF RESVERATROL FROM PHARMMAPPER SERVER WITH A THERAPEUTIC POTENTIAL AGAINST PROSTATE CANCER.

SI No	Target Name	Therapeutic action	PDB Id	Fit score
1	Neprilysin	Anti-Prostate cancer	1R1H	2.94
2	Androgen receptor	Anti-Prostate cancer	3B5R	2.95
3	Vitamin D3 receptor	Anti-Prostate cancer	1DB1	4.92
4	Hepatocyte growth factor receptor	Anti-Prostate cancer	1R0P	2.96
5	Macrophage metalloelastase	Anti-Prostate cancer	1ROS	2.93
6	Dual specificity mitogen-activated protein kinase kinase 1	Anti-Prostate cancer	1S9J	2.94
7	Retinoic acid receptor RXR-alpha	Anti-Prostate cancer	1FBY	2.88
8	Stromelysin-1	Anti-Prostate cancer	1HY7	2.94
9	Vascular endothelial growth factor receptor 2	Anti-Angiogenesis	1YWN	2.98
10	Dihydroorotate dehydrogenase, mitochondrial	Anti-Inflammatory	1D3H	3.41
11	Serum albumin	Anti-Inflammatory	1HA2	2.96
12	Mitogen-activated protein kinase 14	Anti-Inflammatory	2RG6	3.08
13	Mitogen-activated protein kinase 1	Anti-Proliferative	2OJJ	2.91
14	Neutrophil collagenase	Anti-Inflammatory	1MMB	2.87
15	Tyrosine-protein kinase SYK	Anti-Inflammatory	1XBB	2.90
16	Peroxisome proliferator-activated receptor gamma	Anti-Inflammatory	1FM6	2.94
17	Nitric oxide synthase, endothelial	Anti-Inflammatory	1M9J	2.99

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The Table I thus show that *in-silico* methods are helpful in screening targets for small molecules form plant origin. Targets for resveratrol belong to anti-prostate cancer targets, anti-inflammatory, anti-angiogenesis, anti-proliferative, and signal transducing modulators which are already proven to be drug targets against cancers. Inverse screening helped us to identify that resveratrol can play a vital role in prostate cancer suppression. Therefore resveratrol can be considered as a potential component for the chemoprevention of prostate cancer.

IV. CONCLUSION

This study of *in-silico* inverse target screening using PharmMapper and ligand pharmacophore screening with PharmaGist is done to find out the putative therapeutic targets for resveratrol. The targets identified using in-silico method like neprilysin, androgen receptor, vitamin D3receptor, hepatocyte growth factor receptor, macrophage metalloelastase etc, are already well established as anti-prostate cancer in experimental settings. Hence, further *in-vitro* and *in-silico* bioassays may reveal concrete evidence about the binding potential of resveratrol to a novel set of identified targets. Thus the present approach can be used as alternative computational method to rapidly identify therapeutic targets of chemicals from plant origin.

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