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Structure based virtual screening of anticanerous polyphenolic phytocompounds against G-protein coupled receptor and identification of potent antagonist ligand(s) through molecular docking

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Abstract:
Design of potential drug-like candidates for cancer is of interest in recent years. We used 60 compounds which are known to have the potential to down regulate Nuclear Factor kappaB (NFκB) for this study. The compounds were assessed for Lipinski's RO5 and ADMET properties. Allixin, anethole, capsaicin, linearol and syringic acid satisfied both Lipinski's RO5 and ADMET properties. These compounds showed strong molecular interaction with receptor GPCR55 indicating they have ability to block GPCR55. Thus, their role in anticellular proliferation and induction of apoptosis is implied.

Keywords: Cancer, GPCR55, polyphenolic phytocompounds, NFκB, anticellular proliferation, apoptosis, Lipinski's RO5 and ADMET properties.

Background:
Cancer is now a serious global health problem. Cancer is caused by a complex, poorly understood interplay of genetic, molecular and environmental factors **[1]**. Some conventional systems such as surgery, chemotherapy, radiation therapy, immunotherapy, monoclonal antibody therapy or other methods are being used for cancer treatment. Most of the agents are known to be mutagenic and or carcinogenic, and are highly toxic for normal cells **[2]**. Due to the toxic and adverse side effects caused by synthetic medicine, herbal medicines are alternatives to treatment **[3]**. Plant extracts and natural compounds purified from plants have been used by humans for many centuries for the treatment of a variety of inflammation-related diseases, including cancer **[4]**. Computer aided drug design have gained popularity and have become an integral part of the industrial and academic research for drug development **[5]**. Transforming ligands into active compounds with non-promiscuous-binding behaviour, known as hits; and then refining them into a structure or series of structures with relevant biological and drug-like activity, known as leads; are the key starting points for drug discovery programs **[6-7]**. Tumorogenesis is a multistep process that can be activated by any of various environmental carcinogens (such as cigarette smoke, industrial emissions, gasoline vapors), inflammatory agents (such as tumor necrosis factor (TNF) and H_2O_2), and tumor promoters (such as phorbol esters and okadaic acid). These carcinogens are known to modulate the transcription factors (e.g., NF-kB, AP-1, STAT3), anti-apoptotic proteins (e.g., Akt, Bcl-2, Bcl-XL), proapoptotic proteins (e.g., caspases, PARP), protein kinases (e.g., IKK, EGFR, HER2, JNK, MAPK), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), cell adhesion molecules, COX-2 and growth factor signalling pathways **[8]**. Many ligands acting via GPCRs, including thrombin, bombesin, radykinin, substance P, endothelin, serotonin, acetylcholine, gastrin, prostaglandin F_2alpha, and lysophosphatidic acid are known to elicit a mitogenic response in a variety of cell types **[9]**. We used compounds which have potential to downregulate Nuclear Factor kappaB as reviewed elsewhere **[4]** and show their ability to induce apoptosis and inhibit cell proliferation by blocking G-protein coupled receptor 55 (GPCR55) using computer aided screening studies.

Methodology:
Polyphenolic phytocompounds:
We used 60 compounds which are known to have the potential to down regulate Nuclear Factor kappaB (NFκB) for this study **[4]**. These compounds were already established as possible inhibitors of the NFκB pathway on animal and cancer cell line models.

T-cell receptor structure:
We used the T-cell receptor structure with PDB ID: 2X70 from protein databank (PDB) for this study.

Software and tools:
We used ACD/Chemsketch version 12 **[10]** to draw molecular structures and calculate chemical properties. The ADMET (Absorbtion, Distribution,

Excretion, Metabolism, Toxicology) properties were calculated for the phytocompounds using Accord for excel an Accelry's product **[11]**. The docking module in Discovery Studio, an Accelrys Software Inc (2.1) is used for docking studies **[12]**.

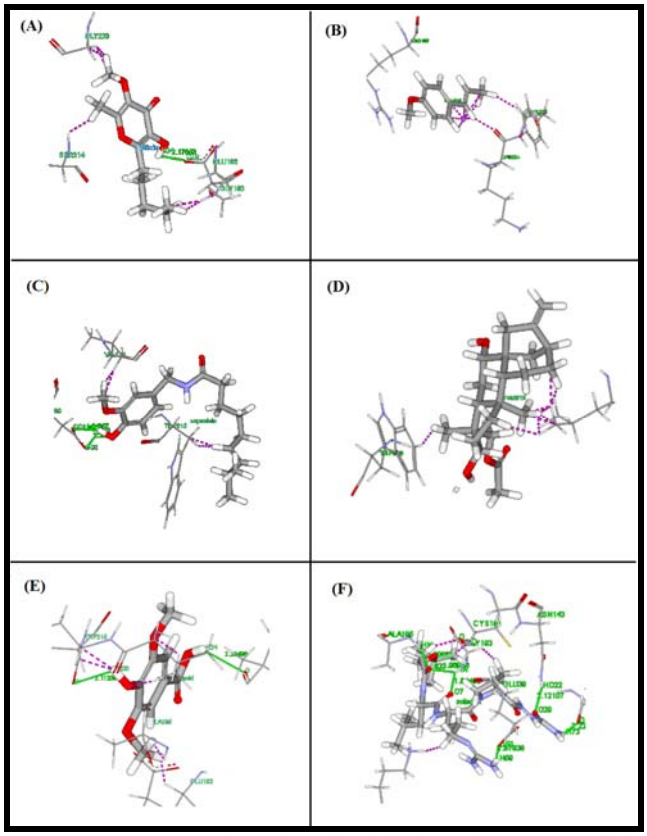

Figure 1: Drug-Receptor interaction. The docked complexes are **(A)** allixin; **(B)** anethole; **(C)** capsaicin; **(D)** linearol; **(E)** syringic acid; **(F)** Zoladex (Reference drug) with G-protein coupled receptor 55.

Results:

Figure 1 shows the interaction of GPCR55 domain with allixin, anethole, capsaicin, linearol, syringic acid and Zoladex. The results of drug-receptor interaction for compounds are given in **Table 1 (see Supplementary material)**. These compounds were selected from 12 out of the 36 compounds in the original list of 60 compounds which satisfied Lipinski's RO5 and ADMET properties.

Discussion:

The aim in drug design is the identification of novel small molecular scaffold exhibiting high binding affinity and selectivity for the target together with a reasonable absorption, distribution, metabolism, excretion and toxicity (ADMET) profile **[13]**. The simplest ADME-concerned filter is the Lipinski RO5 **[14-15]**. We used the 60 compounds which are known to have the potential to down regulate Nuclear Factor kappaB (NFκB) for this study **[4]**. It has been suggested that the predictable reactions typically are dose-related. Hence, there is a need to predict the toxic nature of these compounds **[16]**. Thus, these compounds were tested for Lipinski RO5 and ADMET properties. Analysis suggests that 36 of the 60 compounds satisfied Lipinski RO5 and ADMET properties analysis.

The computer aided toxicity screening was performed using Accord for Excel **[11]** and thus, 12 compounds with hepatotoxicity value '0' indicating non-toxic effect. Thus, these 12 compounds have satisfied both the Lipinski's rule of five and ADMET, achieving the status of 'oral drug-likeness' and are chosen for docking against the receptor GPCR55. Zoladex (low logP and high molecular weight), a commonly used reference molecule violated criteria for consideration as oral drug-likeness in Lipinski RO5 and ADMET analysis. Thus, the need to design compounds satisfying Lipinski RO5 and ADMET properties is important. A good docking interaction implies the prediction of ligand confirmation and orientation within targeted binding site and their lower interactions energies **[17-18]**. Docking results **(Figure 1; Table 1)** show that 5 compounds (allixin, anethole, capsaicin, linearol and syringic acid) have good molecular interactions with the receptor GPCR55.

Zoladex is being used alone or in combination with tamoxifen as a cytotoxic chemotherapy in patients with hormone receptor-positive tumours and is found to be effective when used after adjuvant chemotherapy **[19]**. It is also widely used in the treatment of advanced prostate cancer as well as for breast cancer **[20]**. However, it should be noted that Zoladex violates some of the molecular properties. Nonetheless, polyphenolic phytocompounds namely allixin, anethole, capsaicin, linearol and syringic acid satisfy both Lipinski's rule of five and ADMET properties. They also have produced good results for molecular interaction with the receptor GPCR55 in docking models. Thus, the role of these compounds in inhibiting GPCR55 activity is implied for consideration in cancer related illness.

Conclusion:

The compounds allixin, anethole, capsaicin, linearol and syringic acid satisfied Lipinski's RO5 and ADMET properties. The interactions of these compounds with GPCR55 were found to be strong in docking models. Thus, their potential ability to block GPCR55 is implied for consideration in drug design and development for cancer associated illness.

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References:

[1] Pandey G & Madhuri S. *Phytomedica* 2006 **7**: 99
[2] Hecker E. *Cancer Research* 1968 **28**: 2338 [PMID: 5723975]
[3] Harun-ur-Rashid M *et al. Pakistan Journal of Biological Science.* 2002 **5**(9): 968
[4] http://216.14.220.164/Prevention_and_therapeutic_effects_of_plant_polyphenols_through_suppression_of_nuclear_factor-kap.pdf
[5] Kalyanaraman C *et al. Biochemistry*. 2005 **44**: 2059 [PMID: 15697231]
[6] Kenakin T. *Nat Rev Drug Discov.* 2003 **2**: 429 [PMID: 12776218]
[7] Hubbard RE. 3D structure and the drug discovery process. 1960 Chapter 1: 1-31.
[8] Bharat B *et al. Biochemical pharmacology*. 2006 **71**: 1397
[9] Van Biesen T. *Endocr Rev.* 1996 **17**: 698 [PMID: 8969974]
[10] http://www.brothersoft.com/acd-chemsketch-133131.html
[11] Dixon SL & Villar HO. *J Comput Aided Mol Des.* 1999 **13**: 533 [PMID: 10483533]
[12] Massova I *et al. Perspectives in Drug Discovery and Design.* 2000 **18**: 113
[13] Lipinski CA *et al. Advanced Drug Delivery Review*. 1997 **23**: 3
[14] Lipinski CA. Strategies for optimizing oral drug delivery. Kobe 1999
[15] Lipinski CA. *J Pharmacol Toxicology Methods.* 2000 **44**(1): 235 [PMID: 11274893]
[16] Zimmerman HJ. Hepatotoxicity. Appleton-Century Crofts, New York. 1978 Page: 353
[17] Ing HR. *Transactions of the Faraday Society Articles.*1943 **39**: 372
[18] Srinivasan P *et al. Journal of Pharmacy Research.* 2011 **4**(1): 136
[19] Jonat W. *British Journal of Cancer.* 2001 **87**(12): 1480
[20] Moul JW & Chodak G. *Prostate cancer prostatic dis.* 2004 **7** Suppl 1: S2 [PMID: 15365575]

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Supplementary material:

Table 1: Results of Drug-Receptor Interactions

Compounds	Docking pose	Docking Scores		Receptor- ligand Hydrogen bonds				
	Absolute energy	Libdock score/ No. of Hot spots	Total no. of H bonds/ No. of contacts	Amino acid	Position	Atom in amino acid	Atom in Ligand	Bond length
Allixin	37.052	106.496/ "4.59,8.01,6.95,A,57,5-2.39,-7.81,10.95,P,59,90.81,7.21,10.15,A,67,15 "	1/ 6	GLU	192	OE2	H34	2.17653
Anethole	27.785	90.911/ "5.01,- 6.41,15.55,A,88,1 8.01,-5.61,19.15,A,97,5 6.81,-3.81,18.35,A,96,9"	0/ 11	-	-	-	-	-
Capsaicin	35.705	141.365/ "-4.19,- 13.01,5.35,A,48,7-1.79,-8.21,9.95,A,66,181.81,-6.41,7.35,A,60,22"	2/ 5	ASP ASP	189 189	OD1 OD2	H46 H46	1.84857 2.38704
Linearol	57.072	101.382/ "-4.59,- 8.01,6.95,A,57,1 -4.99,-14.01,4.35,A,38,8 0.21,-16.01,5.15,A,46,17"	0/ 9	-	-	-	-	-
Syringic acid	34.445	68.893/ "1.81,-6.41,7.35,A,60,1 -4.59,-8.01,6.95,A,57,11 0.41,-7.61,11.75,P,63,14"	2/ 6	ALA TRP	190 215	O O	H24 H20	2.28496 2.11200
Zoladex	64.012	146.95/ "-4.19,-13.01,5.35,A,48,3 -4.59,-8.01,6.95,A,57,34 -1.79,-8.21,9.95,A,66,39"	6/ 6	ALA GLY GLY ASN THR GLU	195 193 193 143 147 39	HN HN HN HD22 O OE1	O33 O33 O7 O29 H73 H59	1.69827 1.96936 1.64495 2.12107 2.22932 1.87838