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RESEARCH ARTICLE

IDENTIFICATION OF NATURAL PRODUCT LEADS AGAINST LIFE STYLE INDUCED PANCREATIC DUCTAL ADENOCARCINOMA

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ABSTRACT

Industrialization and westernization have influenced the life style including food habit and preferences of Indian population and this in turn resulted in dangerous health hazards such as pancreatic ductal adenocarcinoma (PDAC). ADAM8 is validated as a target for pancreatic ductal adenocarcinoma therapy. The HTVS of Zinc database obtained five prospective ligand molecules. Five molecules significantly satisfied the pharmacokinetic factors that are defined for human use and qualified as potential drug like molecules. The study concludes that five molecules could be successful molecules to be tested in *invitro* and *invivo* settings.

Key words: Pancreatic Cancer, ADAM8, Glide, ADME.

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INTRODUCTION

It is estimated that 75–85% of all chronic illnesses and diseases are linked to lifestyle and cannot be explained by differences in genetic makeup (Wong *et al.,* 2005). The role of diet takes special importance in countries like India which are fast moving towards industrialization and westernization. Descriptive epidemiological studies and international correlation studies have raised specific dietary hypothesis like meat consumption and colon (large intestine) cancer. In South India there is a trend towards increasing consumption of red meat and this can lead to increased risk for pancreatic cancer. Schlomann *et al.* (2015), have integrated ADAM8 in pancreatic cancer signalling and validated ADAM8 as a target for pancreatic ductal adenocarcinoma (PDAC) therapy. It is currently established that targeting protein molecule present inside the cancerous cell is the new fashion of therapeutic approach in cancer drug discovery programs (Preetha *et al.,* 2015). The present work is carried out to find inhibitors of ADAM8 (A disintegrin and metalloproteinase) by high throughput screening of a natural product database, ZINC (Irwinand Shoichet, 2005).

MATERIALS AND METHODS

Preparation of protein: The crystal structure of ADAM8 was obtained from proterin databank (PDB ID:4DD8) with a resolution factor 2.10Å.

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Before docking, the crystal structure of the protein was cleaned by removing the water molecules, added the hydrogen atom to the protein structure for tautomeric and ionization states of amino acid residues using OPLS-2005 force field. Finally the protein structure energy was minimized untill the average root mean square deviation of non bonded hydrogen atom is 0.30Å. The prepared protein was used as input file for molecular docking studies.

Preparation of Ligand Structure

1,15,000 natural compounds, mainly from plantsourceswere recovered from Zinc data base in the SDF file format. The ligand structures were further carried onto ligprep (ligprep version 2.7) for ligand preparation. Ligprep converted 2D structure to 3D structure, including different tautomers and ionized form at a pH range 7.0± 2.0. The prepared ligands were then used as input file for molecular docking studies.This study was carried out with the assistance of ubiquitous docking algorithm, glide version 6.0 for finding the binding preference of unknown ligands that are to be screened against the target. Initial docking analysis was done with the help of high throughput virtual screening (HTVS), secondly with standard precison (SP)mode and the molecules thus obtained were subjected to the Glide extra precision (XP) mode of docking, which performs extensive sampling and provides reasonable binding poses. The essence of efficacy of ligand molecules is determined by the behaviour of them in the human biological system, which is validated by several pharmacokinetic parameters. Absorption, distribution, metabolism, excretion

and toxicity (ADMET) properties of the promising ligands are calculated using QikProp version 3.7.

RESULTS AND DISCUSSION

The high throughput virtual screening (HTVS) and standard-precision mode, followed by Glide extra-precision mode yielded five molecule which posssesed better glide score when compared to cocrystal ligand. Five molecules significantly satisfied the pharmacokinetic factors also are defined for human use and qualified as potential drug like molecules.

Binding Mode Analysis

I) Binding mode of ZINC95485908 into ADAM8

Docking simulation of ZINC95485908 within the active site of the ADAM8 (Fig. 1) has been analyzed. The Glide Score and Glide Energy value observed were -8.936Kcal/mol and -58.715Kcal/mol. Upon the examination of docking features between ZINC95485908, eleven hydrogen bond interactions were formed between ZINC95485908 intoADAM8. The following aminoacid residues were mainly involved in hydrogen bond interaction with ADAM8, they are GLY 298, ASP 295, GLN 319, HIS 321, GLY 369, SER 367, ILE 368, VAL 301, SER 322 with bond length 1.810Å, 1.920Å, 2.541Å, 2.385Å, 2.552Å, 1.954Å, 2.053Å, 2.283Å, 2.541Å, 2.547Å and 2.241Å respectively.

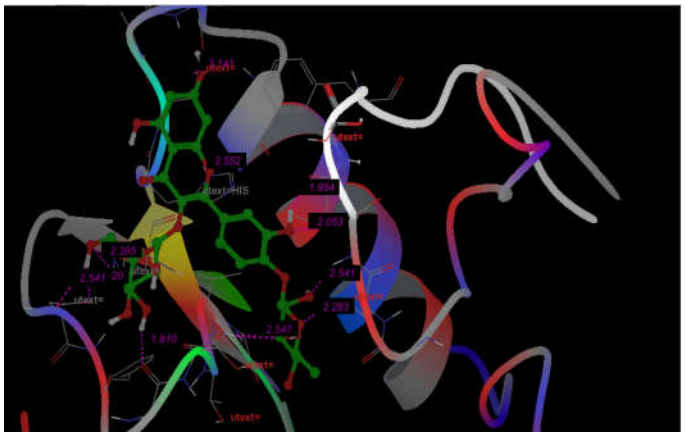


Fig. 1. Binding mode of ZINC95485908 into ADAM8

II. Binding mode of ZINC14952515 into ADAM8

Docking simulation of ZINC14952515 within the active site of the ADAM8 (Fig. 2) has been illustrated. The Glide Score and Glide Energy value obtained were -8.325Kcal/mol and -59.046Kcal/mol. Upon the examination of docking features between ZINC14952515 and into ADAM8 receptor only six hydrogen bond interactions were formed. First one is the side chain hydrogen atom of GLY 369 is strongly interacted with oxygen atom of the ligand with bond length (2.207Å), Second one is the side chain hydrogen atom of SER 367 was strongly interacted with oxygen atom of the ligand with bond length (2.015Å), Third, fourth, fifth one is oxygen atom of the THR 299 were well interacted with hydrogen atom of the ZINC14952515 with bond length (2.649Å, 2.243Å, 2.388Å), final one is backbone oxygen atom of the ALA 365 interacted with hydrogen atom of the ligand molecule with distance of 1.788Å.

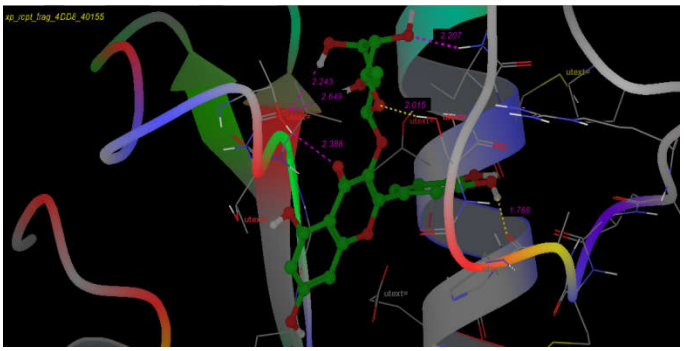


Fig. 2. Binding mode of ZINC14952515 into ADAM8

III) Binding mode of ZINC95486355 into ADAM8

Docking simulation of ZINC95486355 within the active site of the *ADAM8*has been demonstrated (Fig. 3). The Glide Score and Glide Energy value for ZINC95486355 were -7.963Kcal/mol and -60.760Kcal/mol. Upon the examination of docking features, only two hydrogen bond interactions were formed between ZINC95486355 into *ADAM8*. First one is backbone oxygen atom of the ALA 365 were interacted with hydrogen atom of the ligand molecule with distance of 1.711Å whereas thesecond one is the side chain hydrogen atom of SER 367 strongly interacted with oxygen atom of the ligand with bond length of 2.014Å.

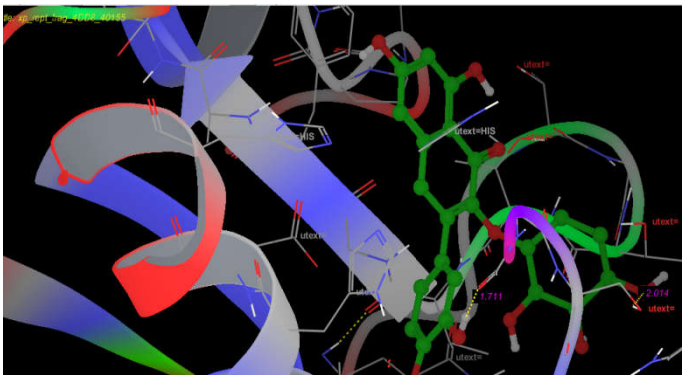


Fig. 3. Binding mode of ZINC95486355 into ADAM8

IV) Binding mode of ZINC95486346 into ADAM8.

Docking simulation of ZINC995486346 within the active site of the *ADAM8*has been demonstrated (Fig. 4). The Glide Score and Glide Energy value for ZINC995486346 were -8.705Kcal/mol and -55.631Kcal/mol. The docking features showed four hydrogen bond interactions between ZINC995486346and *ADAM8*. The GLU 335is interacted with hydrogen atom of the ligand molecule with distance of 1.737Å whereas the second one HIS 334is linked with a distance of 2.590Å strongly and GLY 366 and SER 367 are bonded with the receptor with bond length of 1.736Å and 1.795 Å respectively.

V) Binding mode of ZINC95485909 into ADAM8

Docking simulation of ZINC95485909within the active site of the *ADAM8* has been analyzed (Fig. 4). The Glide Score and Glide Energy value for ZINC95485909 were -8.705Kcal/mol and -55.631Kcal/mol. Upon the examination of docking features between ZINC95485909, only four hydrogen bond interactions were formed between ZINC95485909 into *ADAM8*. First one is the backbone oxygen atom of the GLU

335 were strongly interacted with hydrogen atom of the ligand with bond length (1.737Å), Second one is backbone oxygen atom of the HIS 334 was nicely interacted with hydrogen atom of ZINC95485909 with bond length (2.590Å),Third one is backbone oxygen atom of the GLY 366 was nicely interacted with hydrogen atom of ZINC95485909 with bond length (1.736Å), Fourth and final one is side chain hydrogen atom of the SER 367 was interacted with oxygen atom of the ligand molecule with distance (1.795Å).

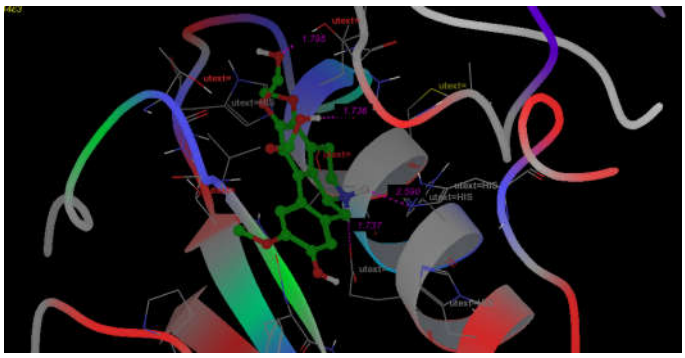


Fig. 4. Binding mode of ZINC95486355 into ADAM8

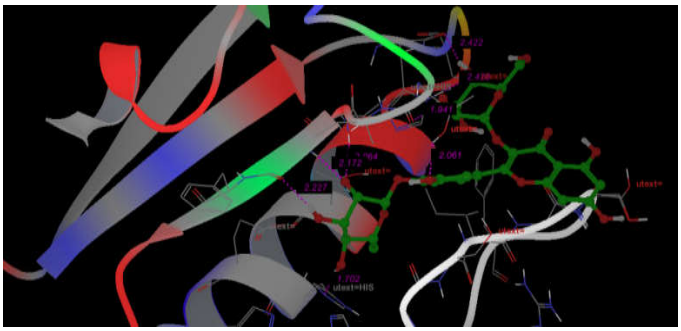


Fig 5 Binding mode of ZINC95485909 into ADAM8

ADME properties prediction of the five Natural Ligands: Prediction of the ADME properties of the five chemical compounds was performed using Qikprop module of the Schrödinger software. The ADME properties for the selected five compounds are presented in Table 2. Predicted ADME properties such as Total SASA, Log*P* (octanol/water), Log(B/B) Molecular weight (MW), (HBD), (HBA), Log*P* (hexadecane/gas), Log*P* (water/gas), Log*P* (octanol/gas), number of metabolites. The five chemical compounds are under acceptable range with predicted ADME properties were reported in table 2.

Table 1. Glide extra-precision (XP) results for five molecules by Schrodinger 9.5

Compound ID	Glide Score	Glide Energy	No of H bond interactions	Interacting Residue	Distance Å)
ZINC95485908	-8.936	-58.715	11	GLY 298	1.810
				ASP 295(2)	1.920
					2.541
				GLN 319	2.385
				HIS 321	2.552
				GLY 369(2)	1.954
					2.053
				SER 367	2.283
				ILE 368	2.541
				VAL 301	2.547
				SER 322	2.241
ZINC14952515	-8.325	-59.046	6	GLY 369	2.207
				SER 367	2.015
				THR 299(3)	2.649
					2.243
					2.388
				ALA 365	
					1.788
ZINC95486355	-7.963	-60.760	2	ALA 365	1.711
				SER 367	2.014
ZINC95486346	-8.705	-55.631	4	GLU 335	1.737
				HIS 334	2.590
				GLY 366	1.736
				SER 367	1.795
ZINC95485909	-8.434	-71.849	8	GLU 335 (2)	1.994
					1.827
				GLY 302 (2)	2.608
					2.539
				ALA 365	2.204
				ILE 368	2.077
				VAL 301	1.731

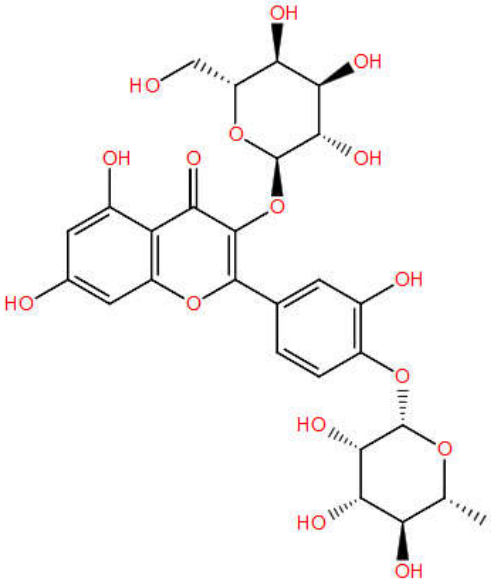
Table 2. The ADME properties of the five natural compounds were predicted using Qikprop.

Compound ID	MW	HB Donor	HB Acceptor	LogP (octanol/ water)	Total SASA	LogB/B	LogP (water/gas)	LogP (octanol/gas)	number of metabolites
ZINC95485908	610.524	9.000	20.550	-2.777	864.305	-5.646	36.298M	43.022M	10
ZINC14952515	448.382	6.000	12.050	-0.409	688.032	-3.306	23.747M	23.747M	7
ZINC95486355	430.410	6.000	9.850	0.130	649.971	-3.038	21.215M	28.296M	8
ZINC95486346	389.404	4.000	8.650	0.828	590.439	-0.924	15.051M	20.930M	6
ZINC95485909	770.696	10.000	22.550	-1.303	1020.687	-5.961M	40.071M	51.079M	16

Solute Molecular Weight = 368.385 (130.0 / 725.0); Solute Total SASA = 657.132 (300.0 /1000.0); Solute as Donor - Hydrogen Bonds = 3.000 (0.0 / 6.0); Solute as Acceptor - Hydrogen Bonds = 4.500 (2.0 / 20.0); QP log P for octanol/gas = 20.133M (8.0 / 35.0); QP log P for water/gas = 11.539M (4.0 / 45.0); QP log P for octanol/water = 3.073 (-2.0 / 6.5); QP log BB for brain/blood = -1.962 (-3.0 / 1.2); No. of Primary Metabolites = 8 (1.0 / 8.0).

2D structure of the top five natural compounds

ZINC95485908



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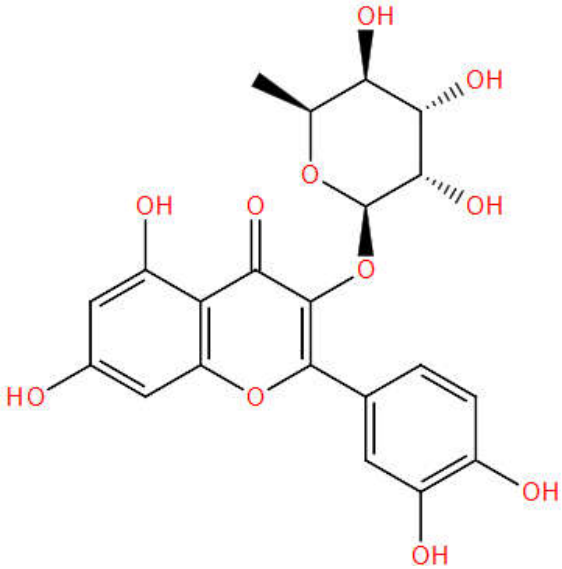

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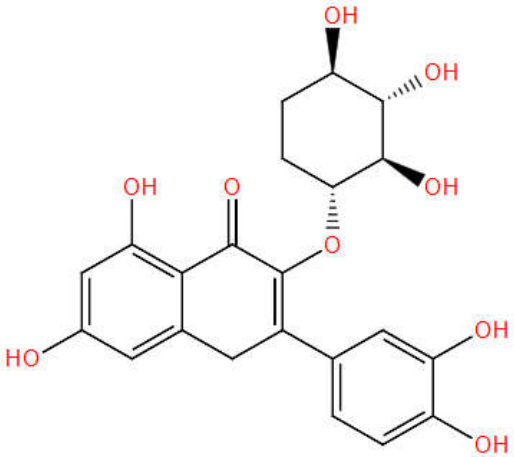

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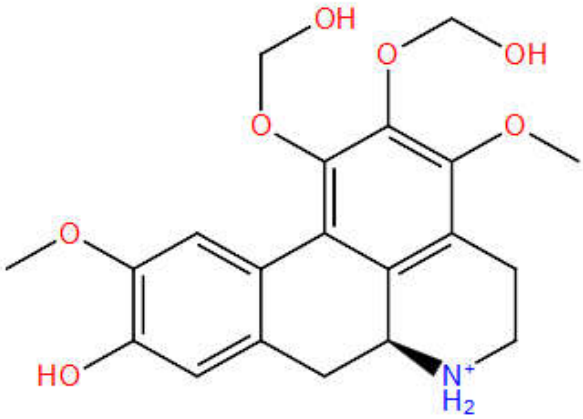
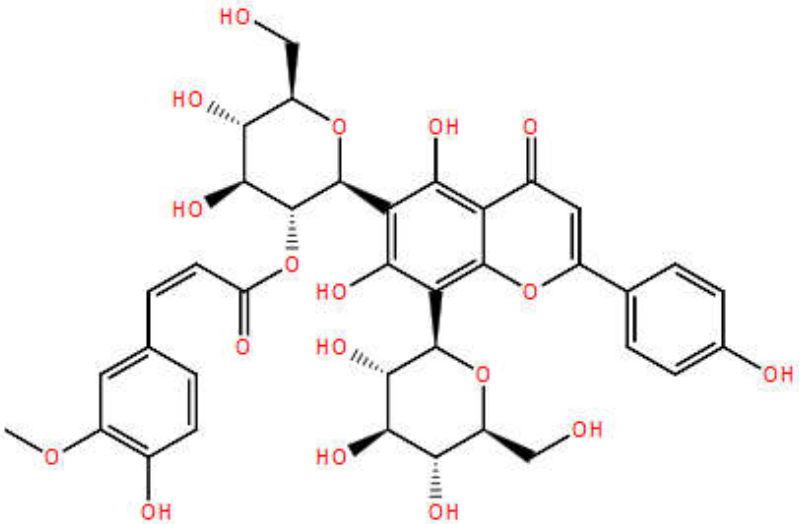


ZINC95485909



Conclusion

Pancreatic cancer is a leading cancer type induced by lifestyle changes. This study is an improvised and structured method where we can engage in using molecular docking tool and pharmacokinetics prediction to figure out lead- like molecules. The study was successful enough to find top five ADAM8 inhibitory molecules. This can be a lead for the ultimate objective of the study to further subject them to *invitro* and *invivo* analysis.

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