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Repurposing of potential bioactive compounds from various database to study their effects on MMP-7 by virtual screening.

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Abstract

Matrix metalloproteinase-7 (MMP7), a member of the matrix metalloproteinase (MMP) family, is involved in the mediation of both agonist-induced vascular tone and cardiac remodelling. We aimed to study the effect of a few bioactive molecules on (MMP-7) by in silico analysis. Data of bioactive molecules were collected from Pubchem and NPACT databases. PDB database was used for the generation of the 3D structure of protein MMP-7.

ADME/T properties showed 5 bioactive molecules obeying Lipkin's rule. Based on molecular docking, β-Sitosetrol and calyxin B are the top two compounds possessing higher ligand efficiency and interactive with higher number of amino acids while targeting MMP-7. The findings of this in silico study indicate 5 bioactive molecules obeying Lipkin's rule and out of these, two molecules may be considered as possible inhibitors of MMP-7.

Keywords: Bioactive molecules, MMP-7, ADME, Molecular Docking.

Introduction

Using bioactive compounds approved for one clinical use in another disease or syndrome is referred to as 'repurposing'. Most of the drive for repurposing is the high cost of developing a drug and the very long time it takes to determine the safety and specificity of a completely new drug[1].

Drug repositioning (DR) utilizes computational and experimental approaches to explore new clinical indications of existing drugs on a rational basis. Repurposing has investigated the clinical usefulness of many existing drugs as depicted above including some of the natural products such as ivermectin, colchicine etc. as prophylactic agents. FDA approved and clinical candidates, phytomedicine-derived bioactive compounds (or simply called phytochemicals such as curcumin, quercetin, epigallocatechin gallate EGCG and many others) have also been extensively investigated in search for potential lead molecules/drug candidates[2]. MMP-7 is a smallest protein member of MMP family. Matrix metalloproteinase (MMPs) are a family of proteolytic enzymes that regulate remodelling of the left ventricle (LV). MMP-7, also called matrilysin, is secreted as a 28 kDa proenzyme and is activated upon the removal of the pro-domain to generate a 19 kDa active enzyme[3]. Macrophages and cardiomyocytes are rich sources of MMP-7, 3, 4 and increased MMP-7 levels are detected in both the remote and infarct regions cardiovascular system. Naturally occurring bioactive compounds are ubiquitous in maximum nutritional better flora for human beings and livestock[4,5]. In systemic hypertension, the bioactive molecules may be explored for their function in modulating MMP-7, thereby regulating systemic hypertension[6, 7].

As *in sillico* screening of phytochemical database has gained tremendous interest in drug discovery research for the identification of new drugs, hence the present study was aimed to assess the effects of screened bioactive molecules on MMP-7 by *in silico* analysis.

Martial and Methods

Protein preparation: The crystal structure of human MMP-7 protein (PDB ID -2DDY) was obtained from the Protein Data Bank[8,9]. The protein structure was processed using Accelrys Discovery Studio by removing all non-receptor atoms including water, ion and various compounds. The refined and processed structure was saved as a "pdb" file format and viewed in Discovery studio[10]. The binding site for the inhibitor was searched based on a structural association of template with experimental evidence by using PDB-sum supported by a literature survey[11].

Ligand Preparation: A total of 130 biologically active plant-derived compounds (phytochemicals) with a wide range of structural diversity belonging to different phytochemical classes were selected based on their potential medicinal/biological interests as reported in traditional as well as modern phytomedicines. The 3D structures of compounds were downloaded from the PubChem database and saved in "sdf" files. Ligands were energetically minimized using the CHARMm-based minimizer on Biovia Discovery Studio (DS 2020)[12].

Pharmacokinetic Parameters: ADMET study is an essential step of drug screening for pharmacokinetic properties. The SWISS ADME tool analysed the properties including structural analogues; it predicts significant physical descriptors and pharmaceutically relevant properties. It consists of principle descriptors and physicochemical properties with a detailed analysis of the

logP (Octanol/Water), log S, molecular weight etc. It also calculates the analogues depending on Lipinski's rule of 5, an essential parameter for rational drug design[13].

Molecular Docking Studies: Maestro Schrödinger and molecular docking[14] 4.2 were used for selected 30 compounds (Table 1). Using genetic algorithm, extra precision docking was performed with the prepared protein and the ligands. Structures of ligands were kept flexible to generate different conformations. Receptor grid generation work flow was used to define a grid (box) around the ligand and to keep all the functional residues in the grid. Docking was performed on Intel® Core™ i3-7th gen laptop with 8 GB RAMS, Windows 10 system. All the results were visualized in Discovery studio.

Results

Structure of protein: The crystal structure of MMP-7 protein (PDB ID: 2ddy) was retrieved from PDB[15]. The MMP-7 protein is composed of 173 residues with molecular weight of 19 kDa and single motif. It is made of single A chain, contains 1 beta alpha beta unit, 1 beta hairpin, 1 psi loop, 7 strands, 3 helices, 22 beta turns and 2 gamma turns (Figure 1).

Binding site prediction: As per literature survey binding site information of target protein was predicted by performing PDBsum[16]. The ligand plot obtained from PDBsum showed binding site region of MMP-7 receptor containing 15 amino acid residues of chain A (Figure 2), viz. His 120, His 124, Glu 121, His 130, Leu 82, Ala 83, Ala 117, Thr 81, Pro 140, Tyr 116, Tyr 142, Thr 141, Ile 112 and MDW 178. These residues possess higher ligand efficiency and interaction with higher number of amino acids which are used for setting the grid of molecular docking.

Prediction of pharmacokinetic properties: *In silico* predictions of pharmacokinetic based on criteria via absorption, distribution metabolism and excretion (ADME)[17] properties have become important in drug selection and to determine their success for human therapeutic use.

Table 1
30 bioactive compounds selected for docking based on pharmacokinetics parameters

S.N.	Compound Name	Family	Molecular Weight
1	Calyxins B	Flavonoid	582.6
2	Artoindonesianin B	Flavonoid	468.5
3	Calyxins F	Flavonoid	582.6
4	Artoindonesianins V	Flavonoid	570.7
5	β- Sitosetrol	Flavonoid	414.7
6	Butein	Flavonoid	272.25
7	Calyxins A	Flavonoid	582.6
8	Calyxins C	Flavonoid	582.6
9	Calyxins D	Flavonoid	582.6
10	Calyxins E	Flavonoid	582.6
11	Calyxins G	Flavonoid	582.6
12	Calyxins H	Flavonoid	582.6
13	Calyxins J	Flavonoid	582.6
14	Artoindonesianin P	Flavonoid	368.3
15	Artoindonesianins A	Flavonoid	570.7
16	Artoindonesianins G	Flavonoid	570.7
17	Artoindonesianins H	Flavonoid	368.3
18	Artoindonesianins I	Flavonoid	368.3
19	Artoindonesianins U	Flavonoid	570.7
20	Baicalein	Flavonoid	270.24
21	Cajanol	Flavonoid	316.30
22	Biochanin A	Flavonoid	284.26
23	Blepharocalyxins A	Flavonoid	879.0
24	Blepharocalyxins B	Flavonoid	879.0
25	Blepharocalyxins C	Flavonoid	879.0
26	Blepharocalyxins D	Flavonoid	592.7
27	Blepharocalyxins E	Flavonoid	879.0
28	Burttinone	Flavonoid	438.5
29	Artoindonesianins V	Flavonoid	570.7
30	Apigenin	Flavonoid	270.24

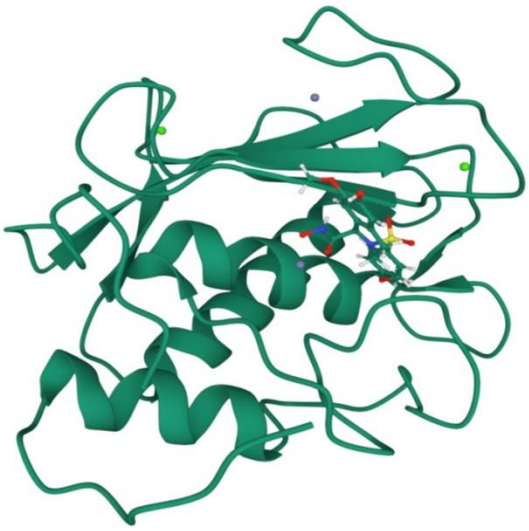

Figure 1: 2D structures of MMP-7

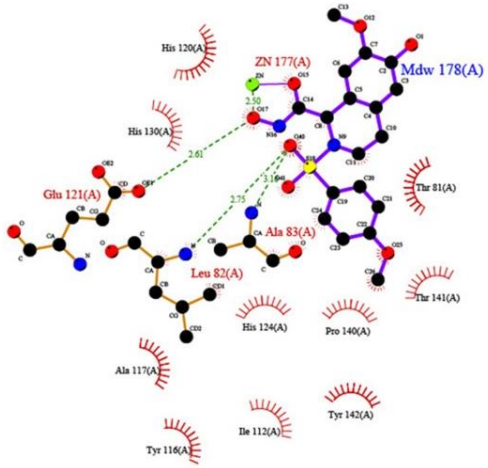

Figure 2: Amino acid residues lining higher ligand efficiency site of MMP-7.

Table 2
Top five compounds of ADME/T properties

S.N.	Compound Name	Molecular Weight (g / mole)	Rotatable Bonds	Hydrogen Bond Acceptor	Hydrogen Bond Donor	Lipinski Rule	Violation
01	Calyxins B	468.5	5	8	3	Yes	0
02	Artoindonesianin B	570.67	6	7	4	Yes	1
03	Calyxins F	582.64	12	8	6	No	2
04	Artoindonesianins V	582.64	9	8	5	Yes	1
05	β- Sitosetrol	414.7	6	1	1	Yes	1

So, these physiochemical properties were calculated to determine the ADME properties of the drugs. Bioactive molecules selected for present study were based on Lipinski's rule of five. All five ligands (Calyxins B, Artoindonesianin B, Calyxins F, Artoindonesianins V, β-Sitosetrol) have shown strong higher binding energy efficiency with target protein MMP-7 (-3.04 to -2.69 Kcal/mol). The said compounds followed the Lipinski's rule in table 2 of five without any violation with respect to molecular weight (≤ 600KDa), number of H-bond acceptors (≤ 8) and number of H-bond donors (≤ 6). The Lipinski's screening is an essential filter that determines if a compound is suitable for drug designing and their chemical structures had shown (Figure 3).

Molecular Docking Study: The human MMP-7 showed higher ligand efficiency (-3.04, -5.17, -5.89, -3.7 and -2.69) and interaction with amino acids as shown in table 3 and

figure 4. Finally, comparing the higher ligand efficiency (-3.04 to -2.69) and interaction with amino acids scores of all five known inhibitors of human MMP-7. β-sitosterol and calyxins B were proposed in the study as possible inhibitors for the human MMP-7[18].

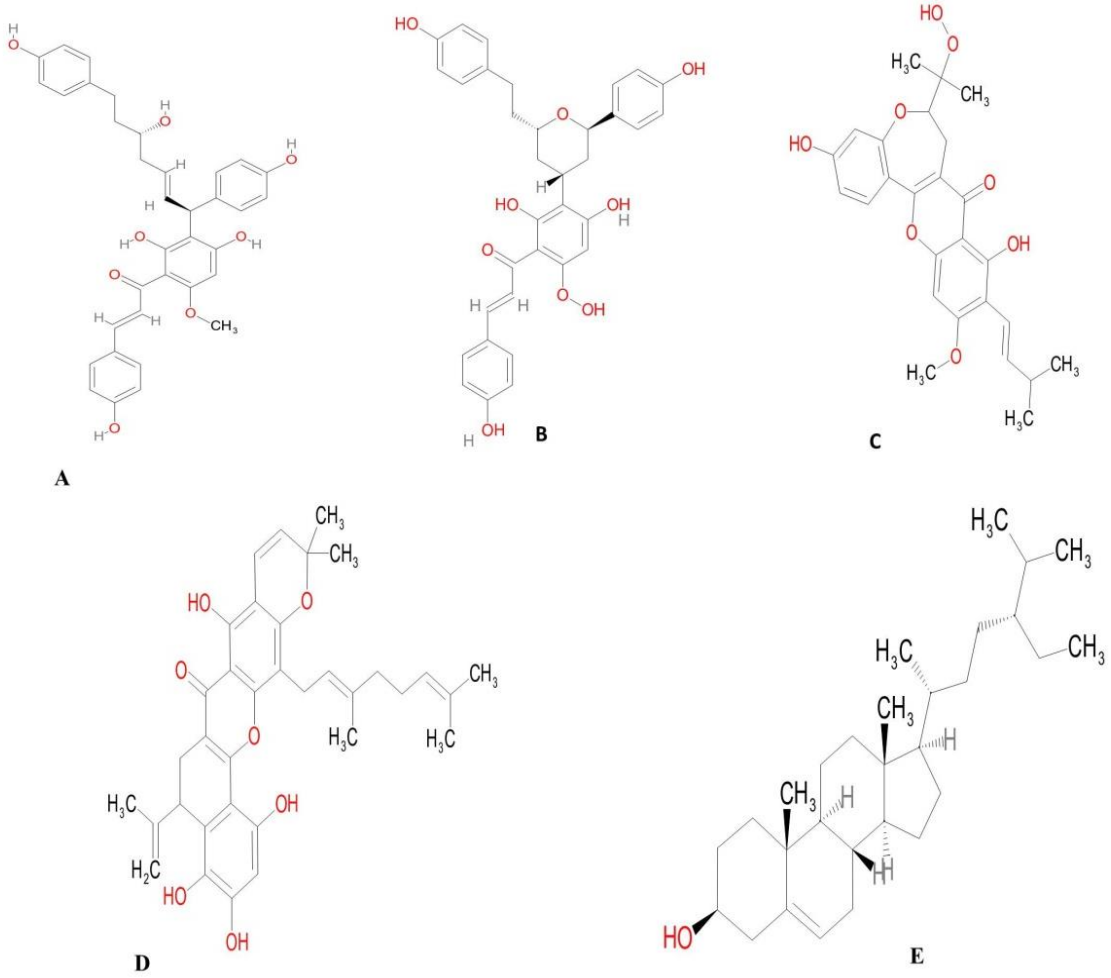

Figure 3: (A) Calyxins B (B) Calyxins F (C) Artoindonesianin B (D) Artoindonesianins V and (E) β- Sitosetrol

Table 3
Molecular Docking score

Molecules Name	Binding Energy (Kcal/mole)	Ligand Efficiency	Inhibition Constant	Interacting amino acid
Calyxins B	-3.04	-0.14	5.92	LYS 125, TYR 65,ALA 65, GLU 3, LYS 22, GLY 23,ASN 25
β- Sitosetrol	-2.69	-0.15	6.34	His 120, His 124, Glu 121, His130, Leu 82, Ala 83, Ala 117, Thr 81, Pro 140, Tyr 116, Tyr 142
Calyxins F	-5.89	-0.93	8.54	ARG103, VAL77, ALA105, ASN8, MET88, ALA86, PRO11, LYS113, ARG110, GLU118
Artoindonesianins V	-3.7	-0.18	1.94	ASN9, THR7, GLU63, ALA64, ALA63, ASN9, TYR67
Artoindonesianin B	-5.17	-0.25	10.29	ASN9, GLU8, GLU98, ASN70, LEU69,

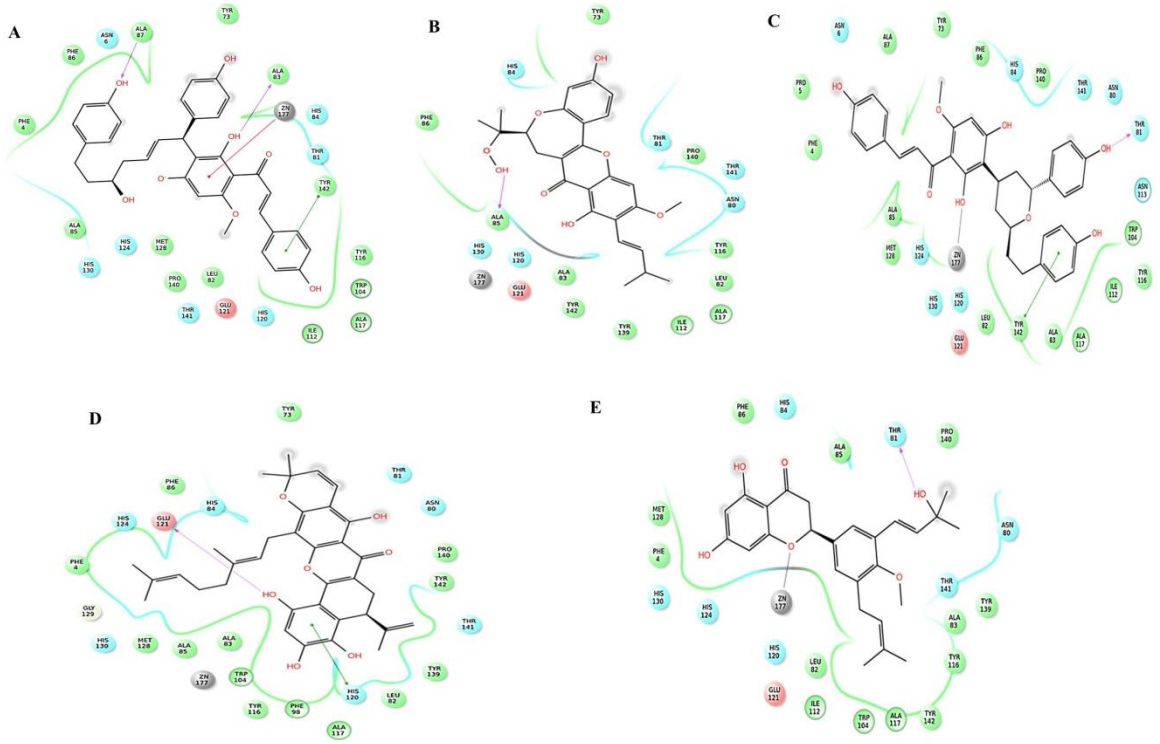

Figure 4: (A) Calyxins B (B) Calyxins F (C) Artoindonesianin B (D) Artoindonesianins V and (E) β- Sitosetrol

Discussion

Higher binding affinities were observed for docked compounds as compared to the co-crystal inhibitor. The more negative is the binding energy, the stronger will be the interaction. Affinity therefore depends on the energy of interaction. Thus negative binding energy depicts the strength of interactions as well as the affinity of a ligand molecule for its receptor molecule. Formation of stable complexes with well-defined interaction details predicts the significance of molecular docking and further molecular modelling studies[19].

From docking and drug-likeness/ADMET studies, five phytochemicals were found to exhibit remarkable inhibitory activities (best hit compounds), particularly against MMP-7. These phytochemicals are found in traditional Ayurvedic and Chinese medicines from plant sources such as neem, ashwagandha, ginseng soybean etc. All the identified compounds are basically tri-tetra-terpenoids, saponins or steroids with their wide natural abundance in traditional Ayurveda and Chinese medicines[19].

In the current work, ligands against the MMP-7 protein were selected from various phytochemical databases. Molecular docking was applied to explore the binding mechanism and correlate its docking score with the activity of the thirty (30) selected bioactive compounds. It has displayed good five (5) bioactive compounds with higher ligand efficiency and greater interaction with higher number of amino acids while targeting MMP-7. Molecular docking results further showed that calyxin B and β-sitosetrol are the best among the five (5) bioactive compounds with highest binding ligand efficiency and the maximum number of interactive amino acids. This present study can be useful for the design and development of novel compounds having better inhibitory activity against several diseases.

Conclusion

The results of the study indicate out of 30 selected bioactive compounds, 5 compounds were having higher ligand efficiency and interactivity with higher number of amino acids targeting MMP-7. Further out of 5 bioactive compounds, calyxin B and β-sitosetrol possesses the maximum ligand efficiency and interactivity with higher number of amino acids.

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